

## Update on the Role of Interleukin 2 and Other Cytokines in the Treatment of Patients with Stage IV Renal Carcinoma

Michael B. Atkins, Meredith Regan and David McDermott

*Clin Cancer Res* 2004;10:6342S-6346S.

<b>Updated version</b>	Access the most recent version of this article at: <a href="http://clincancerres.aacrjournals.org/content/10/18/6342S">http://clincancerres.aacrjournals.org/content/10/18/6342S</a>
------------------------	---

<b>Cited Articles</b>	This article cites by 33 articles, 13 of which you can access for free at: <a href="http://clincancerres.aacrjournals.org/content/10/18/6342S.full.html#ref-list-1">http://clincancerres.aacrjournals.org/content/10/18/6342S.full.html#ref-list-1</a>
-----------------------	---

<b>Citing articles</b>	This article has been cited by 10 HighWire-hosted articles. Access the articles at: <a href="http://clincancerres.aacrjournals.org/content/10/18/6342S.full.html#related-urls">http://clincancerres.aacrjournals.org/content/10/18/6342S.full.html#related-urls</a>
------------------------	--

<b>E-mail alerts</b>	<a href="#">Sign up to receive free email-alerts</a> related to this article or journal.
----------------------	--

<b>Reprints and Subscriptions</b>	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at <a href="mailto:pubs@aacr.org">pubs@aacr.org</a> .
-----------------------------------	--

<b>Permissions</b>	To request permission to re-use all or part of this article, contact the AACR Publications Department at <a href="mailto:permissions@aacr.org">permissions@aacr.org</a> .
--------------------	---

# Update on the Role of Interleukin 2 and Other Cytokines in the Treatment of Patients with Stage IV Renal Carcinoma

Michael B. Atkins,<sup>1,3</sup> Meredith Regan,<sup>2,3</sup> and David McDermott<sup>1,3</sup>

<sup>1</sup>Beth Israel Deaconess Medical Center, <sup>2</sup>Dana-Farber Cancer Institute; and <sup>3</sup>Dana-Farber/Harvard Cancer Center Renal Cancer Program, Boston, Massachusetts

## ABSTRACT

Immunoreactive cytokines have been the mainstay of treatment of renal cancer for the past 15 years. Most research has focused on interferon alpha (IFN- $\alpha$ ) and interleukin 2 (IL-2). IFN- $\alpha$  has been shown in Phase III studies to produce a modest survival advantage over inactive or non-IFN-containing regimens. Its general tolerability, multiple proposed mechanisms of action, and familiarity have prompted IFN- $\alpha$  to be studied in combination with a variety of agents with potential activity against renal cell carcinoma. These various studies may justify an increased role for IFN- $\alpha$  in the treatment of renal cancer in the foreseeable future. High-dose bolus IL-2 remains the only treatment for stage IV renal cancer approved by the United States Food and Drug Administration. Food and Drug Administration approval was granted in 1992 based on the ability of this agent to produce durable complete responses in a small number of patients. Unfortunately, the toxicity, expense, and restricted accessibility of high-dose IL-2 make it a poor standard. Regimens involving lower doses of IL-2 either alone or in combination with IFN- $\alpha$  have generally produced fewer tumor regressions of less overall quality. Recent efforts have focused on trying to identify factors predictive of response to IL-2 therapy so that this treatment could be limited to those most likely to benefit.

## INTRODUCTION

Renal cell carcinoma evokes an immune response, which occasionally results in spontaneous and significant remissions (1, 2). In an attempt to reproduce or accentuate this response, various immunotherapeutic strategies have been used, including nonspecific stimulators of the immune system, specific antitumor immunotherapy, adoptive immunotherapy, the induction of a graft-versus-tumor response via allogeneic hematopoietic stem

cell transplantation, and the administration of partially purified or recombinant cytokines (3–6). Although many such therapies display antitumor activity, research during the past 2 decades has tended to focus on various cytokines of which the protein structure and biological properties are more clearly defined.

A number of cytokines have shown antitumor activity in renal cell carcinoma; however, the most consistent results have been reported with interferon  $\alpha$  (IFN- $\alpha$ ) and interleukin 2 (IL-2). Although the mechanism of action of these cytokines remains to be fully elucidated, antitumor effects in murine models have been linked to the direct killing of tumor cells by activated T cells and natural killer cells, as well as to antiangiogenic effects. Given the limitations of these agents, recent research has focused on the use of IFN in combination with other agents and in identifying predictive factors that might enable IL-2 therapy to be applied more selectively to patients who are most likely to benefit.

## INTERFERON $\alpha$

IFN- $\alpha$  has undergone extensive clinical evaluation during the past 2 decades in metastatic renal cell carcinoma. Results of these investigations are thoroughly described in several reviews (7, 8). Despite the use of a variety of preparations, doses, and schedules, most studies have shown modest antitumor activity, with the overall response rate being  $\sim 10\%$  to  $15\%$ . Responses are often delayed in onset, with median time to response being  $\sim 4$  months. Most responses are partial and short-lived (median response duration, 6 to 7 months). Approximately 2% of patients have had complete responses, with only an occasional patient having a response persistence in excess of 1 year after therapy (9). Although no clear dose-response relationship exists, thrice weekly doses in the 5- to 10-MU/M<sup>2</sup> range appear to have the highest therapeutic index. The toxic effects of IFN include flu-like symptoms, such as fever, chills, myalgias, and fatigue, as well as weight loss, altered taste, depression, anemia, leukopenia, and elevated liver function test results. Most adverse effects, especially the flu-like symptoms, tend to diminish with time during long-term therapy.

Recent studies have suggested that IFN- $\alpha$ , despite having limited antitumor activity, may produce a modest impact on survival. For example, a Phase III trial comparing IFN- $\alpha$ 2a plus vinblastine chemotherapy to vinblastine alone reported a median survival of 67.6 weeks for the combination arm compared with 37.8 weeks for patients receiving vinblastine alone ( $P = 0.0049$ ; (10). In another trial which randomized patients with advanced disease to either IFN- $\alpha$  or medroxyprogesterone, there was a 28% reduction in the risk of death in the IFN- $\alpha$  group ( $P = 0.017$ ) and an improvement in median survival of 2.5 months (11). Despite its long track record of modest clinical activity, IFN- $\alpha$  continues to be actively investigated in patients with advanced renal cancer. Its excellent safety profile, multiple potential mechanisms of action, outpatient administration

Presented at the First International Conference on Innovations and Challenges in Renal Cancer, March 19–20, 2004, Cambridge, Massachusetts.

**Grant support:** Dana-Farber/Harvard Cancer Center Renal Cancer Specialized Programs of Research Excellence: P50 CA101942–01

**Requests for reprints:** Michael B. Atkins, Kirstein Room 153, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215. Phone: 617-667-1930; Fax: 617-975- 8030; E-mail: Matkins@bidmc.harvard.edu.

©2004 American Association for Cancer Research.

schedule, and familiarity to the community oncologist has prompted it to be used as the control arm in many cooperative group and industry-sponsored Phase III trials of novel agents and to be readily combined with other potentially active agents in renal cancer, including IL-2, 13-*cis*-retinoic acid, thalidomide, CCI-779, and bevacizumab. Although the addition of *cis*-retinoic acid to IFN- $\alpha$  produced no significant benefit (12), and combinations of IL-2 and IFN have produced mixed results (see below), studies that involve other combinations have only recently been initiated and, thus, results have yet to be fully reported.

## INTERLEUKIN 2

Inpatient high-dose bolus IL-2 received Food and Drug Administration approval for the treatment of patients with stage IV renal cell carcinoma in 1992 based on data presented on 255 patients who were entered onto 7 Phase II clinical trials (13, 14). In these studies, patients received 600,000 to 720,000 IU/kg of recombinant human IL-2 by 15-minute infusion every 8 hours during two 5-day courses (maximum, 14 doses per course) separated by 5 to 9 days of rest. Stable or responding patients received two to five courses of therapy at 8- to 12-week intervals and then were observed while not receiving any additional therapy. Objective responses were seen in 37 (15%) of the 255 patients, including 17 complete responses (7%) and 20 partial responses (8%). The median duration of response was 54 months for all of the responders, 20 months for partial responders and has not yet been reached for complete responders. The median survival was 16 months for all 255 patients. Follow-up data on these patients accumulated through June 2002 (median follow-up of >10 years) confirm the remarkable durability of these responses (3). Although some late relapses have been observed, the response duration curve appears to have leveled off after the 30-month time point, and 60% of complete responders remain in remission. In addition, 4 partial responders who underwent surgical resection of residual disease while still in response remain alive and disease-free at a minimum of 65 months. Therefore, most patients who achieved a complete response that lasted >30 months and those individuals with partial responses resected to "no evidence of disease" after a response to high-dose IL-2 were unlikely to progress and may actually be cured.

Although the inpatient high-dose bolus IL-2 regimen produces favorable outcomes in a handful of patients, it is also associated with significant toxic effects and cost and is not universally available, making it an unpalatable standard. Low-dose IL-2 regimens (with or without IFN- $\alpha$ ) have produced similar response rates and survival in nonrandomized Phase II trials, but responses appeared to be less durable than those seen with high-dose IL-2 (15-18). For example, in a series of Phase II trials performed sequentially by the Cytokine Working Group, 3-year progression-free survival was 9%, and median response duration was 53 months for patients who received high-dose IL-2 compared with 2% to 3% and 12 months for lower-dose IL-2 and IFN regimens. Although these trials involved the same treating physicians, relatively constant referral patterns, and identical response assessment and patient eligibility criteria, it was impossible to exclude selection bias or chance as an expla-

nation for the apparent superiority of the high-dose IL-2 regimen in terms of response quality.

In an effort to determine the value of outpatient subcutaneous IL-2 and IFN- $\alpha$  relative to high-dose IL-2, the Cytokine Working Group performed a prospectively randomized Phase III trial (19, 20). Patients were randomized to receive either outpatient IL-2 (5 MIU/m<sup>2</sup> s.c. every 8 hours for three doses on day 1 then daily 5 days per week for 4 weeks) and IFN- $\alpha$  2B (5 MIU/m<sup>2</sup> s.c., thrice weekly for 4 weeks) every 6 weeks or high-dose inpatient IL-2 (600,000 IU/kg per dose i.v. every 8 hours, days 1-5 and 15-19; maximum, 28 doses) every 12 weeks. Tumor responses were assessed at weeks 6 and 12 then every 12 weeks. Responding patients taking IL-2 and IFN- $\alpha$  received up to six cycles at 6-week intervals, whereas responding patients receiving high-dose IL-2 received up to three cycles at 12-week intervals.

One hundred ninety-two patients were enrolled between April 1997 and July 2000. Ages ranged from 21 to 75 years (median, 54 years); 70% were male. Ninety-six patients were assigned to each treatment arm. Patients were stratified for bone or liver metastases, primary in place, and a performance status of 0 or 1. Treatment arms were balanced for the following characteristics, as well as other factors: bone or liver metastases (44% *versus* 46%), primary in place (32% *versus* 30%), and performance status 0 (61% *versus* 59%), respectively. Toxic effects seen were typical for these regimens, including 1 treatment-related death from progressive disease and acute respiratory distress syndrome in a patient taking IL-2 and IFN- $\alpha$  and 1 death from capillary leak syndrome in a patient taking high-dose IL-2. Six patients (5 assigned to IL-2 and IFN- $\alpha$  and 1 assigned to high-dose IL-2) refused their assigned therapy after randomization and were, thus, inevaluable for tumor response or progression-free survival. Efficacy results were audited by two independent radiologists in April 2002.

The response rate for high-dose IL-2 was 23% (22 of 96) *versus* 9% (9 of 96) for IL-2 and IFN- $\alpha$  ( $P = 0.018$ ). Eight patients achieved a complete response while taking high-dose IL-2 *versus* 3 patients taking low-dose IL-2 and IFN- $\alpha$ . The median response durations were 14 months for high-dose IL-2 (range, 3-50+ months) and 7 months for IL-2 and IFN- $\alpha$  (range, 4-38+ months;  $P = 0.18$ ). Median overall survivals were 17 and 13 months ( $P = 0.12$ ), favoring high-dose IL-2. Median progression-free survival was 3 months for both treatments. The primary end point of the study was 3-year progression-free survival. Nine patients taking high-dose IL-2 were progression free at 3 years *versus* 2 patients taking IL-2 and IFN- $\alpha$  ( $P = 0.06$ ).

Responses to high-dose IL-2 were seen with equal frequency across the stratification criteria, whereas low-dose IL-2 and IFN- $\alpha$  appeared to produce more responses in patients without liver and/or bone metastases and in those who had undergone nephrectomy to remove the primary tumor. For patients with bone or liver metastases ( $P = 0.002$ ) or primary tumor in place ( $P = 0.54$ ), survival was superior with high-dose IL-2 compared with IL-2 and IFN- $\alpha$ , whereas no significant survival differences between the two treatments were noted for patients who had undergone prior nephrectomy or who were without bone or liver metastases. Furthermore, patients who had undergone a recent nephrectomy (debulking nephrectomy in the

setting of stage IV disease) appeared to fare as well with IL-2 and IFN- $\alpha$  as high-dose IL-2 (21).

Quality of life was assessed using the European Organization for Research on the Treatment of Cancer Quality-of-Life C30 questionnaire at seven time points during therapy. Six functional and 9 symptom scales were evaluated. Compared with IL-2 and IFN- $\alpha$ , patients receiving high-dose IL-2 noted diminished quality of life on some symptom scales early in therapy but experienced overall improved functional and symptomatic quality of life during treatment (22). Similar response, response duration, and quality-of-life data were observed by Yang *et al.* (23) in a recently published Phase III trial comparing high-dose IL-2 to either intermediate-dose i.v. IL-2 or outpatient-administered s.c. IL-2.

Taken in aggregate, these data suggest that high-dose IL-2 produces significantly more responses of apparent better quality and a borderline significant difference in number of patients progression free at 3 years relative to low-dose outpatient IL-2 and IFN- $\alpha$ . The benefit of high-dose IL-2 is particularly evident in patients with primary tumors in place or with liver or bone metastases. Quality of life during the treatment was also better for patients who received high-dose IL-2 relative to those who received lower-dose IL-2 and IFN- $\alpha$ . Consequently, high-dose IL-2 should remain the preferred therapy for appropriately selected patients with access to such therapy. Appropriate selection criteria for high-dose IL-2 need to be reevaluated and additionally refined.

## OTHER CYTOKINES

Clinical trials with other cytokines, such as IL-4 and IL-6, produced only occasional minor responses (24, 25). A few durable responses have been observed in Phase I trials of recombinant human IL-12 administered either i.v. or s.c.; however, in general, antitumor activity in these studies has been less than predicted by preclinical models (26). Subsequent clinical investigations have been plagued by the discovery of a peculiar schedule dependency for IL-12 whereby a single "test dose" of IL-12 has been shown to increase patient tolerance to subsequent therapy and possibly reduce antitumor effects (27). Novel schedules of IL-12 and combinations of IL-12 with IL-2 have been explored in an effort to sustain the biological activity of IL-12 (28, 29). These studies have shown some ability to restore IFN- $\gamma$  production in response to IL-12 and have produced some encouraging responses. Unfortunately, the lack of availability of IL-12 has greatly hindered additional exploration of this promising cytokine.

## CLINICAL PREDICTORS OF BENEFIT FROM CYTOKINE-BASED THERAPY

Many groups have attempted to determine reliable predictors of response and survival for patients with metastatic renal cell carcinoma who were receiving immunotherapy. Factors that have been variably associated with response include performance status, number of organs with metastases (1 *versus* 2 or more), absence of bone metastases, prior nephrectomy, degree of treatment-related thrombocytopenia, absence of prior IFN- $\alpha$  therapy, thyroid dysfunction, rebound lymphocytosis, erythro-

poietin production, and post-treatment elevations of blood tumor necrosis factor (TNF)  $\alpha$  and IL-1 levels (3).

Motzer *et al.* (30) have shown in patients receiving IFN- $\alpha$  that poor survival is associated with low Karnofsky performance status, high serum lactate dehydrogenase level, low hemoglobin, high "corrected" serum calcium level, and time from initial renal cell carcinoma diagnosis to start of therapy of <1 year. In a cohort of 453 patients who received IFN- $\alpha$  as initial therapy, the median survival for the favorable (no risk factors), intermediate (1 or 2 risk factors), and poor (3 or more risk factors) risk groups were 30, 14, and 5 months, respectively. Negrier *et al.* (18) also identified independent predictors of rapid disease progression, defined as progression within 10 weeks of initiation of therapy. These included >1 metastatic site, disease-free interval of <1 year, presence of liver metastases or mediastinal nodes, and type of immunotherapy used. Patients with liver metastases, >1 site of disease, and disease-free interval of <1 year had a lower response rate and a median survival of only 6 months, even while receiving combination IL-2 and IFN- $\alpha$  therapy. Figlin *et al.* (31) identified prior nephrectomy and time from nephrectomy to relapse as important predictors of survival in patients receiving IL-2-based therapy. In their series, patients who received systemic immunotherapy for metastatic disease >6 months after nephrectomy had the best median survival and had a 3-year survival rate of 46%. A recent multivariate analysis by the same group of investigators that was confined to patients who received IL-2 therapy after nephrectomy revealed survival to be inversely associated with lymph node involvement, constitutional symptoms, sarcomatoid histology, metastases that involved sites other than bone or lung or multiple sites, and a thyrotropin level of >2 mIU/L (32). They proposed a scoring algorithm based on these features in which survival at 1 year was predicted to vary from 1% to 92%. Recent data from the Cytokine Working Group Phase III trial, mentioned above, suggested that disease site factors, such as primary in-place or hepatic or bone metastases, may be more predictive of a poor response to low-dose IL-2 and IFN- $\alpha$  regimens than to high-dose IL-2 (3, 20, 21). Furthermore, this study suggested the greatest benefit from high-dose IL-2 relative to lower-dose regimens might be seen in patients with primaries in place and/or liver and bone metastases. These data call into question some of the prior studies and suggest that additional predictors of response and survival in patients receiving cytokine-based immunotherapy are necessary.

## PATHOLOGICAL AND MOLECULAR PREDICTORS OF RESPONSE TO IL-2

We performed recently a large-scale reanalysis of pathology specimens from patients who received IL-2-based therapy as part of Cytokine Working Group trials (33). We determined that response to IL-2 was significantly associated with clear cell histology with alveolar features and the absence of papillary or significant granular features. Patients with these features in their kidney tumor specimens had a 25% response rate (29 of 115) compared with a 4% response rate (2 of 50) for patients with papillary features, >50% granular features, or no alveolar features. The results in the kidney tumor specimens were confirmed in a separate analysis of metastatic lesions. In the metastatic



setting, responses were limited to patients with clear cell tumors with the favorable histologic patterns described in the primary tumor specimens.

Carbonic anhydrase IX has been identified recently as a molecular marker that is potentially predictive of response to IL-2. Carbonic anhydrase IX expression is mediated by the hypoxia-inducible factor 1 $\alpha$  transcriptional complex and induced in many tumor types, but is absent in most normal tissues. Bui *et al.* (34) used a monoclonal antibody designed to detect carbonic anhydrase IX expression to perform an immunohistochemical analysis of paraffin-embedded renal cell carcinoma specimens. They showed that >90% of renal cell carcinomas express carbonic anhydrase IX and that its expression decreases with advancing stage. In their analysis, high carbonic anhydrase IX expression in primary tumors was seen in 79% of patients and was associated with improved overall survival and possibly response to IL-2–based therapy. In addition, all of the long-term responders to IL-2–based treatment had high carbonic anhydrase IX expression.

Building on this work, we performed a nested case-control study within the larger cohort of patients whose pathological findings were reanalyzed (35). Carbonic anhydrase IX expression levels were correlated with response to IL-2, pathological risk categorization, and survival. As in the report by Bui *et al.* (34), the percentage of carbonic anhydrase IX–positive tumor cells was used to separate high (>85%) and low ( $\leq$ 85%) expressors. Twenty-seven (41%) of 66 selected patients had responded to IL-2–based regimens, with 20 (30%) remaining alive at a median follow-up of 2.6 years. Twenty-four (36%), 31 (47%), and 11 (17%) were classified into good-, intermediate-, or poor-risk groups according to the pathology model described above. Forty-one specimens (62%) had high carbonic anhydrase IX expression. Twenty-one (78%) of 27 responding patients had high carbonic anhydrase IX expression compared with 20 (51%) of 39 nonresponders (odds ratio = 3.3,  $P = 0.04$ ). Median survivals were 3 years and 1 year for high and low carbonic anhydrase IX expressors, respectively ( $P = 0.04$ ). Survival >5 years was only seen in the high-carbonic anhydrase IX-expressing group. High carbonic anhydrase IX staining was associated with better pathological features but remained an independent predictor of response. For example, in patients in the intermediate pathological features group, 9 of 9 responders had high carbonic anhydrase IX expression *versus* 11 of 22 nonresponders. A two-compartment model was proposed in which one group of patients with either good pathological features or intermediate pathological features and high carbonic anhydrase IX expression contained 26 of 27 responders (96%) compared with only 18 of 39 nonresponders (46%, odds ratio = 3.0,  $P < 0.01$ ). Significant survival benefit was also seen for this group ( $P < 0.01$ ).

Although this model requires prospective validation, it highlights the potential for using pathological and molecular features of the tumor to identify optimal patients to receive IL-2 therapy. Additional studies to explain these preliminary observations and correlate results with clinical features described previously are necessary. In addition, gene expression profiling of tumor specimens to identify new proteins or patterns of gene expression that might be associated with IL-2 responsiveness may eventually help to further narrow the application of IL-2 therapy to those who will benefit the most.

## OPEN DISCUSSION

**Dr. James Yang:** How was the 85% of positive cells picked as a cutoff? It does not capture all of the responders. It certainly does not even capture all of the complete responders in your study.

**Dr. Michael Atkins:** It was based on the UCLA data.

**Dr. Robert Figlin:** It's a statistical bootstrapping technique. In retrospect, we looked at the range between positive and negative. Our study by itself was nothing more than a hypothesis until Mike came along and was able to confirm it in another data set.

**Dr. Yang:** You have to be careful to use that clinically, because that may not be the best boundary to determine who can benefit from IL-2 *versus* which grouping gave the best correlation.

**Dr. Ronald Bukowski:** Is there a full description of the methodology for these studies?

**Dr. Atkins:** All these studies were done on paraffin tissue. One caveat is that they were done for the most part on the primary tumors when we were treating the metastatic disease. The CA-IX (carbonic anhydrase IX) expression in the metastases is probably less than in the primary, and it is possible that the correlation might even be stronger if you looked at the metastatic disease, although that is something that needs to be studied.

**Dr. Yang:** Did you ever see an objective regression of a primary tumor?

**Dr. Atkins:** Yes, we have seen primary tumors that have gotten smaller with IL-2 therapy. We have seen patients who had regressions, including some patients who had complete regression of their primary tumor without surgery, but a lot of the patients who had responses in their distant disease would require surgery to remove residual disease in their primary tumor.

**Dr. W. Marston Linehan:** Did you see complete response in primaries?

**Dr. Atkins:** Yes. Bob, could you comment on what the availability of the CA-IX antibody will be for future studies?

**Dr. Figlin:** Egbert Oosterwick in the Netherlands and Eric Stanbridge at the University of California, Irvine, are basically the people who have access to the antibody.

**Dr. Allan Lipton:** In your study of CA-IX and IL-2 therapy, was the CA-IX staining the same in both treatment groups?

**Dr. Atkins:** We have not collected all of the tissue. You have to realize what a task it was to even get the tissue to do the pathology reinterpretation, because the tissue does not reside in our institutions. It resides in the institutions where the patients had their surgery. So we collected as much as we could. Nonetheless, CA-IX staining seemed to be relatively balanced. In our group of patients, there were 66 patients; 32 had received low-dose IL-2 and interferon, and 34 had high-dose IL-2.

**Dr. Lipton:** Do you think it really is a drug effect or is there an imbalance in the two groups that would explain the difference?

**Dr. Atkins:** I think it is a treatment effect. I would also add that CA-IX may be a predictive marker of response to IL-2 and survival in patients treated with IL-2, but we have no idea

what the predictive value would be if the patients were treated with another agent or not treated at all.

**Dr. Figlin:** It may be that CA-IX would do the same thing for interferon-treated patients. It has just never been tested.

**Dr. Atkins:** We now have a reason for trying to collect tissue blocks as part of these various studies or at least to have a few unstained slides sent to a central place (Pathology Core) for potential later analysis.

## REFERENCES

- Gleave ME, Elhilali M, Fradet Y, et al. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. *N Engl J Med* 1998;338:1265-71.
- Vogelzang NJ, Priest ER, Borden L. Spontaneous regression of histologically proved pulmonary metastases from renal cell carcinoma: a case with 5-year followup. *J Urol* 1992;148:1247-8.
- McDermott DF, Atkins MB. Application of IL-2 and other cytokines in renal cancer. *Expert Opin Biol Ther*. 2004;4:455-68.
- Marten A, Flieger D, Renoth S, et al. Therapeutic vaccination against metastatic renal cell carcinoma by autologous dendritic cells: preclinical results and outcome of a first clinical phase I/II trial. *Cancer Immunol Immunother* 2002;51:637-44.
- Fishman M, Seigne J. Immunotherapy of metastatic renal cell cancer. *Cancer Control* 2002;9:293-304.
- Gitlitz BJ, Belldegrun AS, Figlin RA. Vaccine and gene therapy of renal cell carcinoma. *Semin Urol Oncol* 2001;19:141-7.
- Muss HB. Interferon therapy for renal cell carcinoma. *Semin Oncol* 1987;14:36-42.
- Neidhart JA. Interferon therapy for the treatment of renal cancer. *Cancer* 1986;57:1696-9.
- Muss HB, Costanzi JJ, Leavitt R, et al. Recombinant alfa interferon in renal cell carcinoma: a randomized trial of two routes of administration. *J Clin Oncol* 1987;5:286-91.
- Pyrhonen S, Salminen E, Ruutu M, Lehtonen T, Nurmi M, Tammela T, Juusela H, Rintala E, Hietanen P, Kellokumpu-Lehtinen PL. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. *J Clin Oncol* 1999;17:2859-67.
- Collaborators MRC. a. Interferon alfa and survival in metastatic renal carcinoma: Early results of a randomized controlled trial. *Lancet* 1999;353:14-7.
- Motzer RJ, Murphy BA, 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;18:2972-80.
- Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol* 1995;13:688-96.
- Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. *Cancer J Sci Am* 2000;6 Suppl 1:S55-7.
- Dutcher JP, Atkins MB, Fisher R, et al. Interleukin-2 based therapy for metastatic renal cell cancer: The Cytokine Working Group Experience. *Can J Sci Am* 1997;3:S73-8.
- Dutcher JP, Fisher RI, 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;3:157-62.
- Dutcher JP, Logan T, Gordon M, et al. Phase II trial of interleukin 2, interferon alpha, and 5-fluorouracil in metastatic renal cell cancer: a cytokine working group study. *Clin Cancer Res* 2000;6:3442-50.
- Negrier S, Caty A, Lesimple T, et al. Treatment of patients with metastatic renal carcinoma with a combination of subcutaneous interleukin-2 and interferon alfa with or without fluorouracil. *Groupe Francais d'Immunotherapie, Federation Nationale des Centres de Lutte Contre le Cancer. J Clin Oncol* 2000;18:4009-15.
- McDermott D, Flaherty L, Clark J, et al. A randomized phase III trial of high-dose interleukin-2 (HD IL2) versus subcutaneous (SC) IL2/interferon (IFN) in patients with metastatic renal cell carcinoma (RCC). A Cytokine Working Group Study. *Proc Am Soc Clin Oncol* 2001;2072a.
- Atkins MB, McDermott DF. Results of the Cytokine Working Group phase III trial of high dose IL-2 vs. low dose IL-2 and IFN therapy in patients with metastatic renal cell carcinoma. *Cancer Invest* 2003 Suppl 1 21:S87-8.
- McDermott D, Parker R, Youmans A, Connolly C, Atkins M. The effect of recent nephrectomy on treatment with high-dose interleukin-2 (HD IL-2) or subcutaneous (SC) IL-2/interferon alfa-2b (IFN) in patients with metastatic renal cell carcinoma (RCC). *Proc Am Soc Clin Oncol* 2003;22:385A.
- Cole B, McDermott D, Parker R, Youmans A, Connolly C, Ernstoff M, Atkins M. The impact of treatment with high-dose interleukin-2 (HD IL-2) or subcutaneous (SC) IL-2/interferon alfa-2b (IFN) on quality of life (QOL) in patients with metastatic renal cell carcinoma (mRCC). *Proc Am Soc Clin Oncol* 2003;22:387A.
- Yang JC, Sherry RM, Steinberg SM, et al. A three-arm randomized comparison of high and low dose intravenous and subcutaneous interleukin-2 in the treatment of metastatic renal cancer. *J Clin Oncol* 2003;21:3127-32.
- Margolin K, Aronson FR, Sznol M, Atkins MB, Dutcher J, Fisher RI, Weiss GR, Stewart M, Doroshow JH. Phase II evaluation of thrice-daily intravenous bolus interleukin-4 in advanced renal cell and malignant melanoma. *J Immunother* 1994;15:147.
- Weiss GR, Margolin KA, Sznol M, et al. A phase II study of the continuous intravenous infusion of interleukin-6 for metastatic renal cell carcinoma. *J Immunother Emphasis Tumor Immunol* 1995;18:52-6.
- Atkins MB, Robertson MJ, Gordon M, et al. Phase I evaluation of intravenous recombinant human interleukin-12 (RHIL-12) in patients with advanced malignancies. *Clin Cancer Res* 1997;3:409-17.
- Leonard JP, Sherman ML, Fisher GL, et al. Effects of single-dose interleukin-12 exposure on interleukin-12-associated toxicity and interferon-gamma production. *Blood* 1997;90:2541-8.
- Gollob JA, Mier JW, Veenstra K, et al. Phase I trial of twice-weekly intravenous interleukin 12 in patients with metastatic renal cell cancer or malignant melanoma: ability to maintain IFN-gamma induction is associated with clinical response. *Clin Cancer Res* 2000;6:1678-92.
- Gollob JA, Veenstra KG, Parker RA, et al. Phase I trial of concurrent twice-weekly recombinant human interleukin-12 plus low-dose IL-2 in patients with melanoma or renal cell carcinoma. *J Clin Oncol* 2003;21:2564-73.
- Motzer RJ, Bacik J, Murphy BA, 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;20:289-96.
- Figlin R, Gitlitz B, Franklin J, et al. 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.
- Leibovich BC, Han KR, Bui MH, et al. Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma: a stratification tool for prospective clinical trials. *Cancer* 2003;98:2566-75.
- Upton MP, Parker RA, Youmans A, Connolly C, Atkins MB. Histologic predictors of renal cell carcinoma (RCC) response to interleukin-2 based therapy. *Proc Am Soc Clin Oncol* 2003;22:851A.
- Bui MH, Seligson D, Han KR, 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;9:802-11.
- Atkins M, McDermott D, Mier J, et al. Carbonic anhydrase IX (CAIX) expression predicts for renal cell cancer (RCC) patient response and survival to IL-2 therapy. *Proc Am Soc Clin Oncol* 2004;23:383A.