

## Update on the Application of Interleukin-2 in the Treatment of Renal Cell Carcinoma

David F. McDermott

*Clin Cancer Res* 2007;13:716s-720s.

**Updated version** Access the most recent version of this article at:  
<http://clincancerres.aacrjournals.org/content/13/2/716s>

**Cited Articles** This article cites by 24 articles, 15 of which you can access for free at:  
<http://clincancerres.aacrjournals.org/content/13/2/716s.full.html#ref-list-1>

**Citing articles** This article has been cited by 7 HighWire-hosted articles. Access the articles at:  
<http://clincancerres.aacrjournals.org/content/13/2/716s.full.html#related-urls>

**E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.

**Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at [pubs@aacr.org](mailto:pubs@aacr.org).

**Permissions** To request permission to re-use all or part of this article, contact the AACR Publications Department at [permissions@aacr.org](mailto:permissions@aacr.org).

# Update on the Application of Interleukin-2 in the Treatment of Renal Cell Carcinoma

David F. McDermott

**Abstract** High-dose bolus interleukin 2 (IL-2) was granted Food and Drug Administration approval based on its ability to produce durable complete responses in a small number of patients with metastatic renal cell carcinoma. Results from randomized phase 3 trials suggest that regimens involving lower doses of IL-2, either alone or in combination with IFN, produce fewer tumor regressions of less overall quality. Given the toxicity, expense, and limited efficacy of this treatment, recent studies have focused on identifying predictors of response (or resistance) to IL-2 therapy. This year, investigators launched a clinical trial designed to prospectively determine if patients who are more likely to respond to high-dose IL-2 can be identified before starting therapy. As the list of effective therapies for metastatic renal cell carcinoma grows, improvements in patient selection will be necessary to ensure that patients who might attain a durable remission with IL-2 will not miss this opportunity.

The prognosis for patients with recurrent and/or metastatic renal cell carcinoma (RCC) is poor, with median survival of 10 to 13 months (1–3). This outcome underscores the need for new effective systemic therapy in this disease. Recently, the application of molecularly targeted therapies has led to tumor shrinkage in the majority of patients with metastatic RCC but not to durable remissions (4, 5). In contrast, the administration of high-dose bolus interleukin-2 (IL-2) has consistently produced durable responses in a small percentage of patients with advanced RCC (6–8). However, the substantial toxicity and limited efficacy that is associated with IL-2 has narrowed its application to highly selected patients treated at specialized centers (9, 10). In an attempt to reduce toxicity, several investigators evaluated regimens that contained lower doses of IL-2 (11–13). Attempts were also made to improve treatment efficacy by adding IFN- $\alpha$ 2b and then fluorouracil to lower-dose IL-2 regimens (14, 15). These regimens were reported to produce response rates and survival comparable with those reported for high-dose IL-2 with much less toxicity but possibly less durable benefit (16–18). In recent years, the relative merits of these low- and high-dose IL-2 regimens have been clarified by the results of four randomized trials. More significantly, laboratory investigations associated with this clinical research suggest that the potential exists for identifying predictors of

response (or resistance) and limiting IL-2 therapy to those most likely to benefit. This article will summarize the recent investigation that has helped to define the appropriate application of IL-2 in patients with metastatic RCC.

## Randomized Trials with IL-2 with or without IFN

The French Immunotherapy Group conducted a large-scale, phase 3 randomized trial that compared intermediate-dose IL-2 given by continuous i.v. infusion plus s.c. IFN- $\alpha$  with either IL-2 or IFN- $\alpha$  given alone (16). Four hundred twenty-five patients were enrolled. The three treatment groups were well balanced for age and sex as well as known predictors of response and survival. The response rate and 1-year event-free survival were significantly greater for the combined IL-2 and IFN- $\alpha$  arm than for either of the single-agent arms, although there was no significant difference in overall survival among the three groups. Of note, responses were seen in only 6.5% and 7.5% of patients receiving IL-2 or IFN- $\alpha$  alone, respectively, with only 2.9% and 6.1% of these patients still responding at the week 25 evaluations. Although more antitumor activity was seen with the combination arm, this was largely due to the rather limited activity of the single-agent regimens. How an intermediate-dose combination of IL-2 and IFN- $\alpha$  would compare with high-dose IL-2 alone remained to be established.

The National Cancer Institute Surgery Branch investigators performed a randomized trial comparing standard high-dose i.v. bolus IL-2 and a low-dose i.v. bolus IL-2 regimen developed by Yang et al. (19). After randomizing 117 patients, a third arm was added that involved s.c. IL-2 given according to the regimen described by Sleijfer et al. (11). Results were analyzed and reported according to groups that were concurrently randomized. Among the 306 patients concurrently assigned to either high- or low-dose i.v. IL-2, the response rate was significantly higher with high-dose therapy (21% versus 13%), with a trend toward more durable responses. Duration of

**Author's Affiliation:** Beth Israel Deaconess Medical Center and the Dana-Farber/Harvard Cancer Center Renal Cancer Program, Boston, Massachusetts  
Received 7/27/06; revised 11/7/06; accepted 11/10/06.

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

Presented at the Second Cambridge Conference on Innovations and Challenges in Renal Cancer, March 24–25, 2006, Cambridge, Massachusetts.

**Financial Disclosures:** D.F. McDermott is a consultant for Genentech and Bayer/Onyx.

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

© 2007 American Association for Cancer Research.

doi:10.1158/1078-0432.CCR-06-1872

**Table 1.** Results of phase 3 trials with IL-2

Trial	Treatment regimens	N	Response rate	P	Durable complete response	Overall survival	Overall survival difference
FIG 1 (11)	CIV IL-2		6.5	<0.01	1	12	NS
	LD s.c. IFN		7.5		2	13	
	CIV IL-2 + IFN		18.6		5	17	
NCI SB (14)	HD i.v. IL-2	156	21%	0.05	8	NR	NS
	LD i.v. IL-2	150	13%		3	NR	
CWG (15)	HD i.v. IL-2	95	23%	0.02	7	17.5	NS
	LD s.c. IL-2/IFN	91	10%		0	13	
FIG 2 (16)	MPA	123	2.5%	NR	NR	14.9	NS
	IFN	122	4.4%		NR	15.2	
	IL-2	125	4.1%		NR	15.3	
	IL-2/IFN	122	10.9		NR	16.8	

Abbreviations: HD, high dose; LD, low dose; CIV, continuous i.v. infusion; NR, not reported; NS, not statistically significant; NCI SB, National Cancer Institute Surgery Branch; CWG, Cytokine Working Group; FIG, French Immunotherapy Group; MPA, medroxyprogesterone.

response was superior in patients who received the high-dose i.v. IL-2 compared with those who received the low-dose i.v. IL-2. There were no differences in overall survival. Although toxic effects were also significantly greater in the high-dose group (particularly hypotension), there were no deaths attributable to IL-2 in either arm, and patient assessments of quality of life were found to be roughly equivalent. Among the patients concurrently assigned to either s.c. IL-2 or high-dose i.v. IL-2, a higher response rate was seen with high-dose i.v. IL-2 (21% versus 10%), but the difference was of borderline statistical significance. Once again, there were no differences in overall survival.

In an effort to determine the value of outpatient s.c. IL-2 and IFN- $\alpha$  relative to high-dose i.v. IL-2, the Cytokine Working Group did a phase 3 trial in which patients were randomized to receive either outpatient IL-2 and IFN- $\alpha$  every 6 weeks or standard high-dose inpatient IL-2 every 12 weeks (20). One hundred ninety-three patients were enrolled, and 192 were evaluable for toxicity and tumor response.

The response rate for high-dose IL-2 was 23% (22 of 96) versus 10% (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 only three patients taking low-dose IL-2 and IFN- $\alpha$ . The median response durations were 24 months for high-dose IL-2 and 15 months for IL-2 and IFN- $\alpha$  ( $P = 0.18$ ). Median overall survivals were 17.5 and 13 months ( $P = 0.12$ ), favoring high-dose IL-2. Ten patients (nine major responders) who received high-dose IL-2 were progression free at 3 years versus three patients (two major responders) who received IL-2 and IFN- $\alpha$  ( $P = 0.08$ ). Of note, responses to high-dose IL-2 were seen with equal frequency across the stratification criteria, whereas low-dose IL-2 and IFN- $\alpha$  seemed to produce fewer responses in patients with liver and/or bone metastases and in those who had not undergone prior nephrectomy to remove the primary tumor. For patients with bone or liver metastases ( $P = 0.001$ ) or primary in place ( $P = 0.04$ ), 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.

In a subsequent phase 3 trial, the French Immunotherapy Group studied the effect of low-dose cytokine therapy on survival in patients with intermediate likelihood of response to IL-2 and IFN (21) as defined in prior studies with these cytokines (16). Untreated patients with Karnofsky performance status of  $\geq 80$  and with more than one site of metastatic disease were randomized to receive medroxyprogesterone (control group), s.c. IFN, s.c. IL-2, or the combination of IFN and IL-2. Four hundred ninety-two patients were randomized, and the treatment groups were well balanced for predictors of response and survival. Although significant toxicity was more common in the IL-2 and IFN arm, median overall survival did not differ between the arms. The investigators concluded that s.c. IFN and IL-2 should no longer be recommended in patients with metastatic RCC and intermediate prognosis.

Investigators from the Cytokine Working Group have reanalyzed the results of their phase 3 trial in the subset of patients who would have fallen into the "intermediate" prognosis group defined by the French Immunotherapy Group.<sup>1</sup> Most patients treated in the Cytokine Working Group study (80%) were in either the intermediate or poor prognosis group. In this subset, high-dose IL-2 continued to produce a significant improvement in response rate (25% versus 10%,  $P = 0.017$ ) and durable complete response (7 versus 0,  $P = 0.014$ ) compared with IL-2 and IFN- $\alpha$ . Furthermore, all 10 patients taking high-dose IL-2 were progression free at 3 years in this intermediate-risk group, whereas three intermediate-risk patients were progression free in the IL-2 and IFN- $\alpha$  group ( $P = 0.08$ ).

Taken together, these studies suggest that high-dose i.v. bolus IL-2 is superior in terms of response rate and possibly response quality to regimens that involve either low-dose IL-2 and IFN- $\alpha$ , intermediate- or low-dose IL-2 alone, or low-dose IFN- $\alpha$  alone (Table 1). The superiority of high-dose IL-2 is particularly apparent in patients with tumor metastases in immune sequestered sites, such as liver or bone, or who have their primary tumor in place, or who fall into the intermediate-risk or poor-risk groups defined by the French Immunotherapy

<sup>1</sup>M.B. Atkins, D.F. McDermott, M. Regan, unpublished data.

Group. Consequently, although low-dose cytokine therapy has a limited role in metastatic RCC, we must conclude that high-dose i.v. IL-2 should remain the preferred therapy for appropriately selected patients with access to such therapy. However, given the toxicity and limited efficacy of high-dose i.v. IL-2 therapy, additional efforts should be directed at better defining the patient population for whom this therapy is appropriate.

## Pathologic and Molecular Predictors of Response to IL-2

**Influence of histologic subtype.** Responses to immunotherapy are most frequently seen in patients with RCC of clear cell histology (22–24). This observation was detailed in a retrospective analysis of pathology specimens obtained from 231 patients (163 primary and 68 metastatic tumor specimens) who had received IL-2 therapy on Cytokine Working Group clinical trials (24). For patients with primary tumor specimens available for review, the response rate to IL-2 was 21% (30 of 146) for patients with clear cell histology primary tumors, compared with 6% for patients with non-clear cell histology (1 responder in 17 patients). Among the patients with clear cell carcinoma, response to IL-2 was also associated with the presence of alveolar features and the absence of papillary or granular features. The response rate in patients whose primary tumors had “good” predictive features (e.g., >50% alveolar and no granular or papillary features) was 39% (14 of 36). In addition, patients with primary tumors that contained “intermediate” predictive features (e.g., alveolar but not papillary features and <50% granular features) had a response rate of 19% (15 of 77). Patients with tumors that contained “poor” predictive features (e.g., >50% granular or any papillary features) had a response rate of 3% (1 of 33). When this model was then applied to the 68 patients with specimens from metastatic sites, those patients who were treated without resection of their primary tumors, five tumor responses were seen in the 20 patients with “good” predictive features, whereas no tumor responses were seen in the 16 patients in the poor predictive group, thus supporting the validity of the model developed from the primary kidney tumor specimens. Median survivals for all patients with clear cell tumors by risk group were 2.87, 1.36, and 0.87 years, respectively ( $P < 0.001$ ). As a result of these data, it may be appropriate for patients whose primary tumor is of non-clear cell histology or of clear cell histology but with “poor” predictive features to forgo IL-2–based treatment altogether. However, given that even in the most favorable predictive group >50% of patients failed to respond to IL-2 therapy, additional investigations into tumor-associated predictors of responsiveness to IL-2 are still necessary.

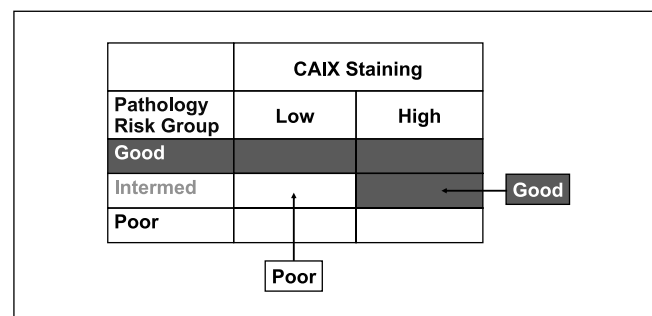
## Immunohistochemical Markers

Some investigators have begun to examine tumor tissue to identify immunohistochemical markers that might predict the outcomes of patients with RCC. Carbonic anhydrase IX (CAIX) has been identified as one potential marker. Bui et al. used a monoclonal antibody designed to detect CAIX expression to perform an immunohistochemical analysis of paraffin-embedded RCC specimens. They showed that >90% of RCC

expresses CAIX, and that its expression decreases with advancing stage (25). In their analysis, high CAIX expression in primary tumors was seen in 79% of patients and was associated with improved survival and possibly response to IL-2–based therapy. In addition, all long-term responders to IL-2–based treatment had high CAIX expression. In this study, low CAIX expression was associated with a worse outcome for patients with locally advanced RCC and was an independent predictor of outcome in patients with metastatic disease.

Building on this work, Atkins et al. performed a nested case-control study within the larger cohort of patients whose pathology was analyzed (26). CAIX expression levels were correlated with response to IL-2, pathologic risk categorization, and survival. As in the report by Bui et al., the percentage of CAIX-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-risk, intermediate-risk, or high-risk groups according to the pathology model described above. Forty-one specimens (62%) had high CAIX expression. Twenty-one (78%) of 27 responding patients had high CAIX 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 CAIX expressors, respectively ( $P = 0.04$ ). Although tumor response were seen in six patients with low CAIX staining, survival >5 years was only seen in the patients with high CAIX-expressing tumors. High CAIX staining was associated with better pathology features but remained an independent predictor of response. For example, in patients within the intermediate-pathology group, 9 of 9 responders had high CAIX expression versus only 11 of 22 nonresponders. A two-compartment model was proposed in which one group of patients with either good pathology or intermediate pathology and high CAIX expression contained 26 (96%) of 27 responders compared with only 18 (46%) of 39 nonresponders (odds ratio, 30;  $P < 0.01$ ; Fig. 1). Significant survival benefit was also seen for this group ( $P < 0.01$ ).

The fact that this analysis enriched for responding patients makes it inappropriate to report response rates. However, if this model were applied to an unselected population of renal cancer patients receiving IL-2 therapy, one would estimate that approximately half of patients would be in each risk group,



**Fig. 1.** The proposed new model for combining pathology predictive group with CAIX staining. Three pathologic risk groups previously reported by Upton et al. (24) can theoretically be collapsed into two groups having distinct response rates to IL-2 therapy and survivals.

and that the response rate would be 35% to 40% for the good-risk group and <5% for the poor-risk group. Although this model and these assumptions require prospective validation, it highlights the potential for using pathologic 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 previously described clinical features are necessary.

### Molecular Markers

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. Using this approach, Pantuck et al. were able to identify a set of 73 genes whose expression distinguished complete responders from nonresponders after IL-2 therapy (27). In their hands, complete responders to IL-2 have a signature gene and protein expression pattern that includes CAIX, PTEN, and CXCR4. Although this approach requires prospective validation, it may become a powerful aid for clinicians in selecting appropriate treatment options.

### Current Investigation

This year, the Cytokine Working Group launched the high-dose IL-2 "Select" Trial. The primary objective of this study is to determine, in a prospective fashion, if the predictive model proposed by Atkins et al. can identify a group of patients with advanced RCC who are significantly more likely to respond to high-dose IL-2-based therapy ("good" risk) than a historical, unselected patient population (26). New factors (including baseline immune function, immunohistochemical markers, and gene expression patterns) that might be associated with response to high-dose IL-2 therapy will also be explored in an attempt to more narrowly limit the application of IL-2 to those patients most likely to benefit.

### Conclusions

High-dose bolus IL-2 remains the only therapy for RCC capable of producing durable responses of metastatic disease and should be considered for appropriately selected patients with access to such treatment (28). Recent studies suggest that the potential exists for identifying predictors of response and therefore limiting therapy to those most likely to benefit. When attempting to determine initial therapy for a patient with metastatic RCC, the data currently available suggest that patients with good or intermediate prognosis clinical features, tumors with clear cell histology, and high CAIX expression are more likely to benefit from high-dose IL-2 therapy and should be presented with this treatment option (24–26). Those patients with poor clinical prognostic

features and tumors with non-clear cell histology and low CAIX expression do not benefit from IL-2 and should not receive it. For patients unlikely to benefit from, unable to receive, or who progress after IL-2, the emergence of molecularly targeted therapies offers hope for improved clinical outcome.

### Open Discussion

**Dr. Ernstoff:** Although the data for the targeted therapies have been on cytokine failures, it is clear that targeted therapies are moving to frontline therapy. Unless targeted therapies are curing patients, they will at some point fail. In that group of patients, have you thought about how you would potentially select interleukin-2 (IL-2) patients?

**Dr. McDermott:** In our practice, we are becoming increasingly concerned that patients who fail targeted therapy are not in good enough condition to receive HD IL-2. A study looking at the response rate in this group of patients would be of interest. Determining eligibility for IL-2 after targeted therapy would largely be influenced by performance status. I would assume that if patients were eligible to receive IL-2 in this setting, their likelihood of response would be influenced by the same criteria as those that have been developed for first-line patients. But this hypothesis remains to be tested.

**Dr. Flaherty:** Couldn't you pick the potential IL-2 patients based on their early course of sorafenib therapy? You could use the first 2 or 3 months of antiangiogenic therapy to prescreen the subset that is IL-2 responsive.

**Dr. McDermott:** You could argue that those patients also have HIF-driven CAIX-expressing tumors. However, once a patient begins to benefit from antiangiogenic treatment, it becomes much harder to convince them to stop.

**Dr. Flaherty:** How are you ever going to know who those patients are if you do not entertain that idea? You can stop and restart therapy as long as you are not allowing the emergence of a critical genetic event in their tumor that makes antiangiogenic therapy irrelevant for them in the future.

**Dr. Figlin:** Whether IL-2 monotherapy with this select trial is accomplished, it does not address whether we should be thinking about combination therapy with IL-2. What rational combinations could be envisioned?

**Dr. McDermott:** The Cytokine Working Group is currently studying bevacizumab at full dose given 2 weeks before and then through a course of IL-2 in an attempt to improve the frequency and duration of responses to IL-2. Some of the potential positive effects of this combination include improvements in immune function that may be seen with lower VEGF levels and a decrease in the incidence of hypotension. However, some data suggest that to get lymphocytes to leave the blood and enter the tumor you may need VEGF. So this combination could limit the efficacy of IL-2. We also talked about doing trials with sorafenib, but this agent might make T cells work less well. We need more preclinical data to guide us in this area.

### References

- Linehan WM, Bates SE, Yang JC. Cancers of the kidney. In: Cancer: principles and practice of oncology, 7th ed. In: DeVita VT, Jr., editor. Philadelphia: J. B. Lippincott Williams and Wilkins; 2005.
- Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med* 2005;353:2477–90.
- Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999; 17:2530.
- Yang JC, Haworth L, Sherry RM, et al. A Randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427–34.
- Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patient



- with metastatic renal cell carcinoma. *J Clin Oncol* 2006;24:16–24.
6. 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.
7. 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:S55–7.
8. Rosenberg SA, Yang JC, White DE, et al. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. *Ann Surg* 1998;228:307–19.
9. Beldegrun A, Webb DE, Austin HA III, et al. Renal toxicity of interleukin-2 administration in patients with metastatic renal cell cancer: effect of pre-therapy nephrectomy. *J Urol* 1989;141:499–503.
10. Margolin KA, Rayner AA, Hawkins MJ, et al. Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors: analysis of toxicity and management guidelines. *J Clin Oncol* 1989;7:486–98.
11. Sleijfer DT, Janssen RA, Buter J, et al. Phase II study of subcutaneous interleukin-2 in unselected patients with advanced renal cell cancer on an outpatient basis. *J Clin Oncol* 1992;10:1119–23.
12. Lopez Hanninen E, Kirchner H, Atzpodien J. Interleukin-2 based home therapy of metastatic renal cell carcinoma: risks and benefits in 215 consecutive single institution patients. *J Urol* 1996;155:19–25.
13. Yang JC, Topalian SL, Parkinson D, et al. Randomized comparison of high-dose and low-dose intravenous interleukin-2 for the therapy of metastatic renal cell carcinoma: an interim report. *J Clin Oncol* 1994;12:1572–6.
14. Atzpodien J, Lopez Hanninen E, Kirchner H, et al. Multi-institutional home-therapy trial of recombinant human interleukin-2 and interferon alfa-2 in progressive metastatic renal cell carcinoma. *J Clin Oncol* 1995;13:497–501.
15. Figlin RA, Beldegrun A, Moldawer N, et al. Concomitant administration of recombinant human interleukin-2 and recombinant interferon alfa-2A: an active outpatient regimen in metastatic renal cell carcinoma. *J Clin Oncol* 1992;10:414–21.
16. 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;338:1272–8.
17. Vogelzang NJ, Lipton A, Figlin RA. Subcutaneous interleukin-2 plus interferon alfa-2a in metastatic renal cancer: an outpatient multicenter trial. *J Clin Oncol* 1993;11:1809–16.
18. Atzpodien J, Kirchner H, Hanninen EL, et al. Interleukin-2 in combination with interferon alpha and 5-fluorouracil for metastatic renal cell cancer. *Eur J Cancer* 1993;29A:S6–8.
19. Yang JC, Sherry RM, Stienberg 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.
20. McDermott DF, Regan MM, Clark JI, et al. A 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;23:133–41.
21. Negrier S, Perol D, Ravaud C, et al. Do cytokines improve survival in patients with metastatic renal cell carcinoma of intermediate prognosis? results of the prospectively randomized PERCY Quattro trial. *Proc Am Soc Clin Oncol* 2005;4:511.
22. Cangiano T, Liao J, Naitoh J, et al. Sarcomatoid renal cell carcinoma: biologic behavior, prognosis, and response to combined surgical resection and immunotherapy. *J Clin Oncol* 1999;17:523.
23. Motzer RJ, Bacil J, Mariani T, et al. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. *J Clin Oncol* 2002;20:2376.
24. Upton MP, Parker RA, Youmans A, McDermott DF, Atkins MB. Renal cell carcinoma: histologic predictors of cytokine response. *J Immunother* 2005;28:488–95.
25. Bui MHT, Seligson D, Han K, et al. Carbonic anhydrase IX is an independent predictor of survival in advanced renal cell carcinoma: implications for prognosis and therapy. *Clin Cancer Res* 2003;9:802–11.
26. 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;11:3714–21.
27. Pantuck AJ, Fang Z, Liu X, et al. Gene expression and tissue microarray analysis of interleukin-2 complete responders in patients with metastatic renal cell carcinoma. *Proc Am Soc Clin Oncol* 2005;4:535.
28. Dutcher J. Current status of interleukin-2 therapy for metastatic renal cell carcinoma and metastatic melanoma. *Oncology* 2002;16:4.