

INTERFERON GAMMA-1b COMPARED WITH PLACEBO IN METASTATIC RENAL-CELL CARCINOMA

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ABSTRACT

Background Most trials of immunomodulators in metastatic renal-cell carcinoma have been uncontrolled and subject to selection bias. The objective of this blinded, placebo-controlled study was to compare overall response rates, time to disease progression, and survival of patients with metastatic renal-cell carcinoma treated with recombinant human interferon gamma-1b or placebo.

Methods Patients with biopsy-proved metastatic renal-cell carcinoma were randomly assigned to receive interferon gamma-1b (60 µg per square meter of body-surface area subcutaneously once weekly) or placebo. The primary tumor had been treated by nephrectomy or angioinfarction at least three weeks previously. Patients were evaluated for radiologic evidence of progression, and all responses were independently reviewed by a committee that was unaware of the treatment.

Results A total of 197 patients with metastatic renal-cell carcinoma were enrolled at 17 centers in Canada. One hundred eighty-one patients could be evaluated; of these, 91 were assigned to receive interferon gamma-1b and 90 were given placebo. The groups were well balanced in terms of prognostic factors. Two thirds of all patients had Karnofsky scores of 90 or 100, and more than half had two or more metastatic sites. Grade I and II toxicity, mostly chills, fever, asthenia, or headaches, was reported in 91 percent and 61 percent, respectively, of the patients in the interferon group, as compared with 76 percent and 63 percent in the placebo group. Life-threatening drug-related events were rare, occurring in 1 percent of patients in the interferon group. No significant differences between groups were observed in overall response rates, time to disease progression, or survival. The overall response rate was 4.4 percent (3.3 percent complete response and 1.1 percent partial response) in the interferon group and 6.6 percent (3.3 percent complete response and 3.3 percent partial response) in the placebo group ($P=0.54$), with a rate of durable complete response of 1 percent in both groups. The median time to disease progression was 1.9 months in both groups ($P=0.49$), and there was no significant difference in median survival (12.2 months with interferon vs. 15.7 months with placebo, $P=0.52$).

Conclusions No difference in outcome was observed in patients with metastatic renal-cell carcinoma who were treated with interferon gamma-1b as compared with placebo. These results emphasize the necessity of testing the efficacy of immunomodulators in randomized studies. (N Engl J Med 1998; 338:1265-71.)

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RENAL-CELL carcinoma is the 10th most common cancer in Western countries, with about 30,600 new cases diagnosed and 12,000 deaths from the disease in the United States during 1996.¹ Surgical resection of localized disease is the only curative treatment. Approximately one third of patients present with metastatic disease, which is incurable except in a few patients who undergo surgical excision of a solitary soft-tissue metastasis. The median duration of survival of patients with metastatic renal-cell carcinoma is about one year, and only 10 percent survive beyond two years.² The results remain poor because of resistance to conventional therapies, such as radiation, hormones, and chemotherapy.³⁻⁵

The natural history of metastatic renal-cell carcinoma is variable and may be marked by prolonged stabilization of metastatic disease,⁶ late relapses after nephrectomy,⁷ or occasional spontaneous regression of metastatic lesions.⁸ These clinical features suggest that the immune system has a role in controlling tumor progression and have aroused interest in the treatment of metastatic renal-cell carcinoma with immunomodulators such as interleukin-2 or interferon. In uncontrolled studies, metastatic renal-cell carcinoma responded to cytokine therapy, with interleukin-2 and interferon producing the best results. High-dose interleukin-2 was approved for treatment of metastatic renal-cell carcinoma by the Food and Drug Administration (FDA), despite the lack of placebo-controlled or randomized studies, on the basis of a rate of durable complete response of 4 per-

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cent in seven phase 1 studies.⁹⁻¹⁴ In these trials the median duration of survival was 16.3 months, almost double that in historical controls. However, the patients were selected on the basis of their good performance status, a method that can bias the results toward higher response rates and longer survival.

Interferons have diverse immunomodulatory effects and directly inhibit cell proliferation.¹⁵ Uncontrolled clinical trials of interferon alfa in patients with metastatic renal-cell carcinoma produced responses in 15 to 20 percent of patients and a complete-response rate of 2 percent.¹⁶⁻¹⁸ Phase 1 and 2 studies of recombinant human interferon gamma-1b reported average overall response rates of 11.5 percent.¹⁹⁻²³ Interpreting these data is difficult because of differences in patient populations, treatment regimens, and the various interferon products used. Early studies of interferon gamma-1b used doses that approached or equaled the maximal tolerated doses. Subsequent studies that used neopterin (a product of activated macrophages) and beta₂-microglobulin (the light chain of the HLA-A complex) as surrogate markers of immune activation found a gaussian relation between the dose of interferon gamma-1b and its biologic effects, which suggested that doses below the maximal tolerated dose can produce optimal biologic effects.²³⁻²⁶ A phase 1 study determined the optimal biologic dose of interferon gamma-1b (defined as the lowest dose inducing a maximal increase in neopterin and beta₂-microglobulin) to be 100 μg subcutaneously once a week.²⁷ Using this low-dose regimen, Aulitzky et al.²⁷ reported an overall response rate of 30 percent and a complete-response rate of 10 percent. A subsequent phase 2 trial reported a response rate of 15 percent and a rate of durable complete response of 3 percent.²⁸

The cumulative data from phase 2 trials with low-dose interferon gamma-1b, which showed a 22 percent response rate and a 7 percent complete-response rate, prompted this phase 3 study. This placebo-controlled study was designed to determine the overall response rates to low-dose interferon gamma-1b in patients with metastatic renal-cell carcinoma, and whether this treatment prolongs life or the time to disease progression. The placebo group was used to control for spontaneous regressions and provide information on the natural history of untreated metastatic renal-cell carcinoma, and the double-blind design was intended to eliminate bias in evaluating responses.

METHODS

Patients

We studied adults with histologically confirmed metastatic renal-cell carcinoma that was not curable by surgery. All patients had a life expectancy of at least 12 weeks, a performance score of

at least 70 on the Karnofsky scale, and measurable disease. The primary tumor was controlled by either nephrectomy or angiinfarction at least three weeks before entry into the study. Patients were excluded if they had metastases only to bone, known brain metastases, a seizure disorder, hypercalcemia (calcium level, >12 mg per deciliter [3 mmol per liter]), or previous cancer (except nonmelanoma skin cancer) or if they were receiving immunosuppressant medications (e.g., corticosteroids).

Study Design

Eligible patients were randomly assigned to receive either 60 μg of recombinant human interferon gamma-1b (Actimmune, Genentech, San Francisco) per square meter of body-surface area or a placebo consisting of the interferon gamma-1b vehicle (sterile water, mannitol, sodium succinate, and polysorbate 20). The medication was self-administered subcutaneously once every seven days. To help minimize side effects and maintain blinding, all patients received 650 mg of acetaminophen orally before the weekly subcutaneous injection and every 4 to 6 hours for 48 hours thereafter. Patients who had complete, partial, or minor responses or whose disease was stable continued to receive weekly doses of interferon gamma-1b or placebo through day 365 and then continued the interferon gamma-1b or placebo on a maintenance-treatment program. The treatment code was broken by the study monitors when radiologically documented disease progression was found. Under these circumstances, patients receiving placebo were given the option of receiving interferon gamma-1b in an open-label treatment program. Patients who had progression of disease while receiving interferon gamma-1b left the study and were treated at the discretion of the investigators until death.

Patient Monitoring

Screening tests to determine eligibility were completed less than 14 days before the initiation of therapy and included medical history taking and a physical examination, Karnofsky test, complete blood count, a battery of standard blood tests, coagulation profile, urinalysis, chest radiography, and electrocardiography. All patients underwent radionuclide bone scanning not more than four weeks before enrollment. The medical history, Karnofsky score, and results of physical examination and blood work were recorded every four weeks during the first year and every eight weeks during the maintenance program. Chest films and appropriate radiographic assessments of metastatic lesions were obtained every eight weeks. Adverse events included all adverse experiences, whether or not they were considered drug-related. Side effects, injuries, toxic reactions, sensitivity reactions, and intercurrent illnesses were counted as adverse events.

Radiographic Assessment of Metastatic Lesions

Radiographic tests were performed within 14 days of enrollment as clinically indicated to determine the size of all metastatic lesions. The tests included, but were not limited to, chest radiography, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography. Tumors were measured in two dimensions by the attending physician or radiologist at each participating center. Tumor size was recorded as the product of the largest diameter of the tumor and its perpendicular. The radiographs used to monitor responses or progression were reviewed by a committee of board-certified oncologists and radiologists who were unaware of the treatment and who did not otherwise participate in the trial. The open-label portion of the study was reviewed independently of the blinded portion. The consensus of this committee served as the official evaluation for the study.

Response Criteria

A complete response was defined as the disappearance of all radiographically or grossly apparent tumors. A durable complete response was defined as a complete response lasting more than 12 months. A partial response was defined as a reduction of at least

50 percent in the sum of the sizes of all lesions. A minor response was defined as a reduction of 25 to 49 percent in that sum. Patients in the above three categories had no new lesions, and none of the existing lesions increased in size by more than 25 percent. Stable disease was defined as no reduction, or a reduction of 25 percent or less, in the sum of the sizes of all lesions. Progressive disease was defined as an increase of more than 25 percent in the size of at least one lesion, or the appearance of any new lesion. The duration of response was defined as the time from the initial response to the onset of progressive disease.

Statistical Analysis

The primary end point was the overall response rate (complete responses plus partial responses). The first analysis (performed according to the intention-to-treat principle) included all patients who received any treatment, regardless of the duration of the therapy. The second analysis included only patients who could be evaluated (those who received at least one dose of a treatment and were evaluated for a response). Ninety-five percent confidence intervals were used to estimate response rates in each treatment group and the differences in response rates between the two groups. The null hypothesis of no difference between the treatments was tested against a two-sided alternative by Fisher's exact test.²⁹

The secondary end point was the time from entry into the study to disease progression. The Kaplan-Meier method was used to estimate time to disease progression, and the curves for the two groups were compared by the log-rank test.³⁰ Duration of response was measured from the time of initial response to the onset of progressive disease. All patients who received at least one dose of therapy were included in the safety analysis.

Estimates of the sample size required to demonstrate efficacy were based on an estimated rate of overall response of 1 percent for placebo and 15 percent for interferon gamma-1b. A two-tailed test was used to determine statistical significance (P<0.05). With these assumptions, statistical comparisons of 91 patients in each group would have a power of 90 percent to detect a difference in overall response rates between the two treatment groups.

RESULTS

Base-Line Characteristics

Between May 1993 and April 1995, 197 patients with metastatic renal-cell carcinoma were enrolled at 17 centers in Canada. Ninety-eight patients were randomly assigned to receive interferon gamma-1b, and 99 to receive placebo. Ninety-one patients in the interferon gamma-1b group and 90 in the placebo group could be evaluated. The patients were approximately equally distributed with respect to sex, age, and Karnofsky score (Table 1). Roughly two thirds of the patients had Karnofsky scores of at least 90, and over half had two or more metastatic sites. Table 2 shows the characteristics of the tumors in the interferon gamma-1b and placebo groups before treatment. In the group receiving interferon gamma-1b, the primary tumor was managed by nephrectomy in 86 percent of patients and angioinfarction in 14 percent; in the placebo group, 78 percent of patients underwent nephrectomy and 22 percent underwent angioinfarction. In both groups the median number of metastatic sites was two. The metastasis-free intervals and duration of metastatic disease before entry into the study were essentially the same in both groups.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	INTERFERON GAMMA-1b	PLACEBO
No. of patients		
Enrolled	98	99
Evaluated*	91	90
Mean (±SD) age (yr)	58±10.2	62±10.1
Sex (%)		
Male	74	72
Female	26	28
Karnofsky score (%)†		
100	38	36
90	32	27
80	13	28
70	11	7
60	0	2‡

*These patients received at least one dose of double-blind treatment and underwent tumor-response evaluation.

†Data on four patients in the interferon group were missing. Because of missing data and rounding, percentages do not total 100.

‡Two patients who enrolled with Karnofsky scores of less than 70 were subsequently determined to represent protocol deviations but were included in the analysis.

TABLE 2. BASE-LINE TUMOR CHARACTERISTICS.*

CHARACTERISTIC	INTERFERON GAMMA-1b (N=98)	PLACEBO (N=99)
Prior treatment (% of patients)		
Nephrectomy	86	78
Angioinfarction	14	22
Radiotherapy	8	12
Hormonal treatment	3	3
No. of metastatic sites		
1	42	44
2	35	37
≥3	23	18
Location of metastatic sites (% of patients)		
Lung	71	69
Lymph nodes	30	35
Bone	17	21
Liver	19	18
Lung only	28	28
Metastasis-free interval (mo)		
0-6	64	57
>6-24	14	21
>24	22	22
Duration of metastatic disease (mo)		
0-6	74	71
>6-24	13	19
>24	13	10

*Because of rounding, not all percentages total 100.

Responses**Response Rates**

The results of analyses of the primary end point (overall response rates) were the same regardless of whether all enrolled patients or all patients who could be evaluated were included. The overall response rate was 4.4 percent (3.3 percent for complete response and 1.1 percent for partial response; 95 percent confidence interval, 1.4 to 11.5 percent) in the interferon gamma-1b group and 6.6 percent (3.3 percent complete response and 3.3 percent partial response; 95 percent confidence interval, 2.7 to 14.5 percent) in the placebo group ($P=0.54$), with a rate of durable complete response of 1 percent in both groups (Table 3). Minor responses and stable disease were reported in 2 percent and 31 percent, respectively, of the interferon group, as compared with 0 and 29 percent of the placebo group. Progressive disease occurred in 63 percent of the patients treated with interferon gamma-1b and in 64 percent of the patients given placebo.

Responses occurred more often in patients 60 years of age or younger (6 percent for interferon gamma-1b and 15 percent for placebo) than in those more than 60 years of age (2 percent for interferon gamma-1b and 3 percent for placebo). The response rates were higher in patients who had been free of metastases for less than six months (7 percent for interferon gamma-1b and 11 percent for placebo) than in those who had been free of metastases for six months or less (0 for interferon gamma-1b and 2 percent for placebo). The response rates were also higher in patients who had had metastatic disease for six months or less before enrollment (6 per-

cent for interferon gamma-1b and 9 percent for placebo) than in those who had had metastatic disease for more than six months (0 for interferon gamma-1b and 0 for placebo). There were no significant differences in overall response rates between men and women. Most patients with responses in both groups had higher Karnofsky scores than patients without responses (data not shown).

Minor differences were noted between the response rates reported by the local investigators and those reported by the evaluation committee. On the basis of all available data, the overall response rate as assessed by the investigators was 6 percent for the interferon gamma-1b group and 9 percent for the placebo group, as compared with the committee's results of 4.4 percent for the interferon gamma-1b group and 6.6 percent for the placebo group.

Duration of Response

The durations of response in the four patients with responses in the interferon gamma-1b group were >5, 11, >11, and >18 months, as compared with 2, 5, 7, 8, >9, and 13 months for the six patients with responses in the placebo group (Table 3). The responses tended to be more durable in patients receiving interferon gamma-1b (median, >11 months) than in those receiving placebo (median, 7 months), but these differences were not statistically significant ($P=0.11$).

Time to Progression and Death

The median time to disease progression in the 181 patients who could be evaluated was 1.9 months in both groups ($P=0.49$) (Fig. 1A). The two groups did not differ significantly in median survival from

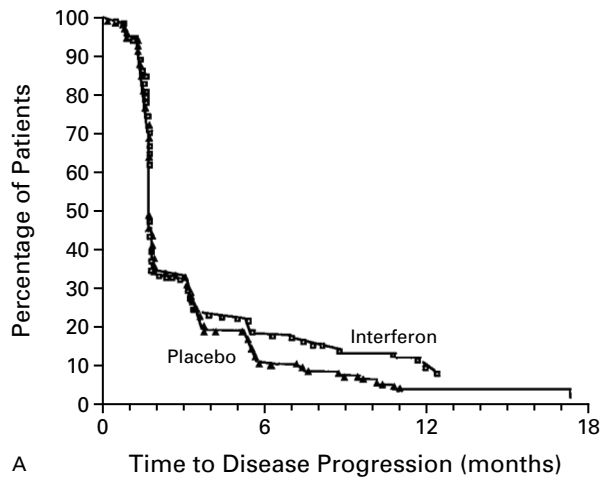
TABLE 3. COMPARISON OF RESPONSE RATES, TIMES TO DISEASE PROGRESSION, AND SURVIVAL ACCORDING TO STUDY GROUP, IN ALL PATIENTS WHO COULD BE EVALUATED.

VARIABLE	INTERFERON GAMMA-1b (N=91)	PLACEBO (N=90)	P VALUE
Response rates (%)*			
Overall response	4.4 (1.4 to 11.5)	6.6 (2.7 to 14.5)	0.54
Durable complete response	1 (0.1 to 6.8)	1 (0.1 to 6.9)	
Complete response	3.3	3.3	
Partial response	1.1	3.3	
Minor response	2	0	
Stable disease	31	29	
Progressive disease	63	64	
Median time to disease progression (mo)†			
Duration of response‡	>11	7	0.11
Time to progression	1.9 (1.7 to 3.9)	1.9 (1.7 to 3.8)	0.49
Median time to death (mo)†			
From first treatment	12.2 (5.2 to >19.3)	15.7 (6.5 to 18.5)	0.52
From metastatic diagnosis	18.1 (9.9 to 105.9)	21.4 (10.3 to 40.0)	0.99

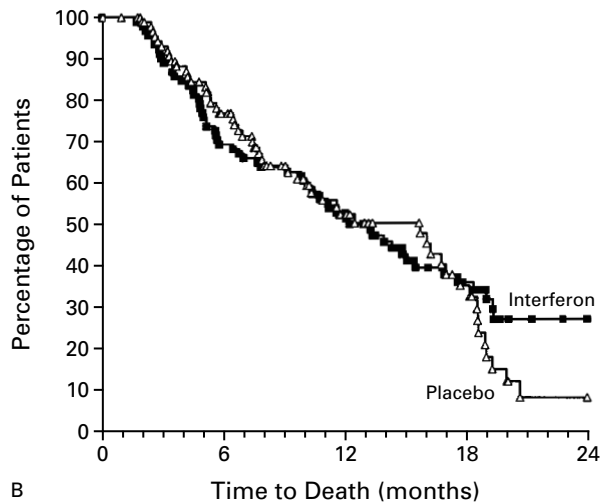
*Values in parentheses are 95 percent confidence intervals.

†Values in parentheses are interquartile ranges.

‡The analysis included only patients with a complete or partial response.



A Time to Disease Progression (months)



B Time to Death (months)

Figure 1. Time to Disease Progression (Panel A) and Time from First Treatment with the Study Drug to Death (Panel B) in 91 Patients Receiving Interferon Gamma-1b and 90 Patients Receiving Placebo.

When patients were stratified according to response, no significant differences were observed between the two groups in either measure according to Kaplan-Meier survival-curve analysis. The median time to disease progression was 1.9 months in both groups (Panel A). The median time to death was 12.2 months in the group receiving interferon gamma-1b and 15.7 months in the group receiving placebo (Panel B).

the time of first treatment with the study drug (12.2 months for interferon gamma-1b vs. 15.7 months for placebo, $P=0.52$) or from the time of the diagnosis of metastatic disease (18.1 months for interferon gamma-1b vs. 21.4 months for placebo, $P=0.99$) (Fig. 1B).

Adverse Events

Table 4 shows that, in general, toxic effects were minor in both groups. World Health Organization

TABLE 4. INCIDENCE OF ADVERSE EVENTS.*

GRADE OF TOXICITY†	ALL ADVERSE EVENTS		DRUG-RELATED ADVERSE EVENTS	
	INTERFERON GAMMA-1b	PLACEBO	INTERFERON GAMMA-1b	PLACEBO
	percentage of patients			
I	91	76	82	51
II	61	63	43	34
III	29	28	9	5
IV	5	4	1	0
Total	98	92	91	66

*Adverse events were reported during the blinded phase of the study (median follow-up, 1.9 months). The sample size was based on intention to treat: 98 in the interferon group and 99 in the placebo group.

†The World Health Organization system of classification was used.

grade I or II toxicity, mostly chills, fever, asthenia, or headaches, was reported in 91 percent and 61 percent, respectively, of the patients assigned to interferon gamma-1b and in 76 percent and 63 percent of the patients assigned to placebo. Life-threatening events were rare (1 percent in the group assigned to interferon gamma-1b). According to the investigators' reports, all deaths during the double-blind phase (5 in patients assigned to interferon gamma-1b and 5 in patients assigned to placebo) and the open-label phase (10 deaths) were probably related to metastatic renal-cell carcinoma.

DISCUSSION

The variable natural history of metastatic renal-cell carcinoma and the occasional occurrence of spontaneous remissions suggest a role for the immune system in the control of tumor progression and provide a rationale for treatment of this neoplasm with immunomodulators. Although reasonable rates of response to interferons and interleukin-2 have been reported in uncontrolled studies, the effects of such agents on the natural history of metastatic renal-cell carcinoma remain poorly defined. The assessment of the efficacy of interleukin-2 and interferon was based on rates of objective responses after treatment; although complete responses were durable in some patients and survival was prolonged in these few patients, survival was not improved in most patients with partial responses.

Despite the lack of placebo-controlled trials, interleukin-2 has become the central component of most immunotherapeutic strategies for metastatic renal-cell carcinoma.¹⁴ Initial phase 2 studies using high-dose interleukin-2 therapy reported response rates of 20 percent, with 7 percent of patients entering a complete remission.^{10,11} A multicenter, uncontrolled

study of 255 patients treated with interleukin-2 alone reported a 4 percent complete-response rate and an 8 percent partial-response rate.³¹ After reviewing clinical data from seven phase 2 studies (partial-response rate, 11 percent; complete-response rate, 4 percent), the FDA approved interleukin-2 for metastatic renal-cell carcinoma in 1992.¹¹ It is important to emphasize that the patients in these studies were selected for their good performance status, and the 4 percent complete-response rate with high-dose interleukin-2 must be balanced against considerable toxicity.

The problem of toxicity has led to the adoption of regimens with lower doses of interleukin-2. Combination therapy with lymphokine-activated killer cells or interferon alfa added no therapeutic benefit to interleukin-2 alone.³² The response rates with interferon alfa alone in uncontrolled studies of over 1000 patients averaged 12 percent, with a complete-response rate of 2 percent.¹⁵⁻¹⁸ A preliminary report of a recent phase 3 study comparing interferon alfa-2a plus vinblastine with vinblastine alone described improved response rates (16 percent vs. 2.5 percent), delayed time to progression (3.0 vs. 2.1 months), and prolonged survival (15.8 vs. 8.8 months) in the combination-therapy group.⁴ Interestingly, survival in that group was identical to the survival in both groups of our study.

Interferon gamma is produced by activated T cells and has antiviral, antiproliferative, and immunomodulatory activity. It is the predominant macrophage-activating factor and enhances cell-mediated immune responses, and for these reasons it was approved by the FDA for the treatment of chronic granulomatous disease.³³ Phase 1 and 2 trials of interferon gamma-1b in metastatic renal-cell carcinoma reported overall response rates ranging from 0 to 33 percent (mean, 11.5 percent), results similar to those with interleukin-2 and interferon alfa.¹⁹⁻²⁸ A clinical trial to define an immunologically active regimen of interferon gamma-1b by means of biologic markers (neopterin and beta₂-microglobulin) was reported in patients with malignant melanoma, and maximal increases in these markers were observed at a dose of 100 μ g once per week.^{8,34} A phase 1 study in patients with metastatic renal-cell carcinoma similarly found that the optimal biologic dose was 100 μ g subcutaneously once per week and reported a 30 percent overall response and 10 percent complete-response rate.²⁷ A subsequent phase 2 trial using the same regimen reported a 15 percent response rate and a rate of durable complete response of 3 percent.²⁸

These data with low-dose interferon gamma-1b provided the basis for our phase 3 study, which was designed to determine whether interferon gamma-1b prolongs the time to disease progression and prolongs survival. Unfortunately, no statistically signifi-

cant differences were observed between the interferon gamma-1b and placebo treatments. The overall response rate was 4 percent with interferon gamma-1b and 7 percent with placebo, and the rate of durable complete response was 1 percent in both groups. The median time to disease progression was 1.9 months in both groups, and there was no significant difference in median survival (12.2 months with interferon gamma-1b vs. 15.7 months with placebo). Despite the less stringent criteria for performance status in our study, survival in the placebo group was 15.7 months, almost identical to that reported in the phase 2 trials with interleukin-2.^{11,31}

Our study had adequate statistical power to compare the efficacy of a biologic response modifier with that of placebo in metastatic renal-cell carcinoma. The discrepancies between the phase 2 and phase 3 results may be attributed to differences in study design (open-label vs. randomized, placebo-controlled designs), patient selection, evaluation of responses (blinded vs. nonblinded), and number of treatment centers (single-center vs. multicenter). In addition, the primary end-point data were independently validated in this study, whereas the phase 2 data either were not available for validation²⁷ or were retrospectively reviewed.²⁸ Furthermore, the patients treated in phase 2 studies with interleukin-2 or interferon gamma-1b were selected for good performance status. The use of this criterion may bias the results, because patients with lower performance status are less likely to respond to therapy or have spontaneous regression.³⁴⁻³⁹

The acceptance of uncontrolled data from phase 2 studies has been defended because the studies included patients with progressive metastatic disease and because spontaneous regression rates are not believed to be high enough to account for the responses observed.¹¹ However, our placebo-controlled study found no benefit of recombinant human interferon gamma-1b in metastatic renal-cell carcinoma, as measured by the rate of overall response, the rate of durable complete response, time to disease progression, and survival. This result emphasizes the need for cautious interpretation of data from uncontrolled clinical studies and the importance of a control group when the efficacy of immunomodulators is tested.

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