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Phase III Trial of Bevacizumab Plus Interferon Alfa Versus Interferon Alfa Monotherapy in Patients With Metastatic Renal Cell Carcinoma: Final Results of CALGB 90206

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ABSTRACT

Purpose
Bevacizumab is an antibody that binds vascular endothelial growth factor and has activity in metastatic renal cell carcinoma (RCC). Interferon alfa (IFN-α) is the historic standard initial treatment for RCC. A prospective, randomized, phase III trial of bevacizumab plus IFN-α versus IFN-α monotherapy was conducted.

Patients and Methods
Patients with previously untreated, metastatic clear cell RCC were randomly assigned to receive either bevacizumab (10 mg/kg intravenously every 2 weeks) plus IFN-α (9 million units subcutaneously three times weekly) or the same dose and schedule of IFN-α monotherapy in a multicenter phase III trial. The primary end point was overall survival (OS). Secondary end points were progression-free survival (PFS), objective response rate, and safety.

Results
Seven hundred thirty-two patients were enrolled. The median OS time was 18.3 months (95% CI, 16.5 to 22.5 months) for bevacizumab plus IFN-α and 17.4 months (95% CI, 14.4 to 20.0 months) for IFN-α monotherapy (unstratified log-rank $P = .097$). Adjusting on stratification factors, the hazard ratio was 0.86 (95% CI, 0.73 to 1.01; stratified log-rank $P = .069$) favoring bevacizumab plus IFN-α. There was significantly more grade 3 to 4 hypertension (HTN), anorexia, fatigue, and proteinuria for bevacizumab plus IFN-α. Patients who developed HTN on bevacizumab plus IFN-α had a significantly improved PFS and OS versus patients without HTN.

Conclusion
OS favored the bevacizumab plus IFN-α arm but did not meet the predefined criteria for significance. HTN may be a biomarker of outcome with bevacizumab plus IFN-α.

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INTRODUCTION

Metastatic renal cell carcinoma (RCC) has historically been treated with interferon alfa (IFN-α), with a 10% to 15% objective response rate and a median survival time of 12 months.[1-3] IFN-α has also demonstrated a modest overall survival (OS) advantage over hormones and chemotherapy in randomized trials and a meta-analysis.[1,2,4] The addition of interleukin-2, hormones, or antiproliferative agents such as *cis*-retinoic acid has not demonstrated significant advantages over IFN-α monotherapy in randomized trials.[5-7] Thus, until the recent development of agents targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin pathways, IFN-α (and high-dose interleukin-2 in highly select patients

based on durable complete responses) has been the historic standard of care.

More recently, the pathogenesis of RCC has been further elucidated, resulting in identification of relevant therapeutic targets. RCC is characterized by inactivation of a tumor suppressor gene known as Von Hippel-Lindau (*VHL*), the downstream effect of which is activation of the hypoxia response pathway and transcription of several genes, including *VEGF*.[8-11] VEGF is a potent proangiogenic protein, acting through its cognate receptor and leading to increased vascular permeability and endothelial cell proliferation and migration.[12] Phase III trials have demonstrated substantial clinical benefit from blocking the VEGF receptor with the small-molecule inhibitors sunitinib and sorafenib.[13,14] Although a numerical OS advantage was

demonstrated, the trials failed to meet prespecified statistical criteria for benefit. For example, sunitinib-treated patients had a median OS time of 26.4 months compared with 21.8 months for IFN-treated patients ($P = .051$).[15] Sorafenib-treated patients had a median OS time of 17.8 months compared with 15.2 months for patients treated with placebo (hazard ratio [HR] = 0.88; 95% CI, 0.74 to 1.04; $P = .15$).[16] In both trials, there was substantial patient cross over to subsequent active therapy, likely contributing to the lack of a demonstrable survival advantage.

Bevacizumab (Avastin; Genentech, South San Francisco, CA), an antibody that binds to circulating VEGF protein, produced a significant prolongation of time to disease progression compared with placebo in patients with treatment-refractory metastatic RCC in a small randomized trial.[17] In addition, IFN has demonstrated antiangiogenic effects,[18] and antibody-mediated VEGF inhibition has antitumor effects through improvement in dendritic cell function.[19] Given these considerations, two phase III trials (a European study and the present study conducted by the Cancer and Leukemia Group B [CALGB]) were simultaneously undertaken and randomly assigned patients with metastatic RCC to IFN-α monotherapy or IFN-α plus bevacizumab. Both studies have previously reported significant advantages in objective response rate and progression-free survival (PFS) for bevacizumab plus IFN-α compared with IFN-α alone.[20,21] The final OS results, the primary end point of the CALGB trial, are now reported here.

PATIENTS AND METHODS

Patients

Patients with metastatic RCC, a clear cell histologic component, and no prior systemic therapy for RCC were enrolled as previously described.[21] Major eligibility criteria included a Karnofsky performance status of $\geq 70\%$; adequate end organ function; blood pressure less than 160/90 mmHg; and lack of CNS metastases, significant cardiac comorbidity, or recent history of bleeding or clotting. The protocol was approved by the central Institutional Review Board of the US National Cancer Institute (NCI) and by the institutional review board of each participating site, and all patients provided written informed consent.

Study Design

This study was conducted by the CALGB with the support of the Eastern Cooperative Oncology Group (ECOG), the National Cancer Institute of Canada Clinical Trials Group, and the NCI Cancer Trials Support Unit. Patients were randomly assigned with equal probability to receive either bevacizumab (10 mg/kg given intravenously every 2 weeks) plus IFN-α (9 million units [MU] subcutaneously three times a week) or the same dose and schedule of IFN-α as monotherapy. A stratified random block design was used, with random assignment stratified by nephrectomy status (yes v no) and number of adverse prognostic factors (zero, one to two, or $\geq$ three factors), which has been previously described for patients with metastatic RCC receiving IFN-based initial systemic therapy.[3] Dose modifications for toxicity were undertaken as previously described.[21]

Bevacizumab was provided by the NCI Cancer Therapy Evaluation Program and was administered at a dose of 10 mg/kg actual body weight intravenously on days 1 and 15 of each 28-day cycle. IFN-α-2b (Intron; Schering, Kenilworth, NJ) was provided by the Cancer Therapy Evaluation Program and administered identically in both arms (subcutaneously at a starting dose of 9 MU on 3 nonconsecutive days per week with dose reduction to 6 MU and 3 MU permitted for IFN-related toxicity). Treatment was continued until disease progression per investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST),[22] unacceptable toxicity, or withdrawal of consent.

Efficacy and Safety

Response and progression were assessed according to the RECIST criteria and were determined by investigator assessment of radiographs. Tumor assessments were performed at baseline and every 12 weeks. Adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events (version 3).

Statistical Design and Data Analysis

The primary end point was OS, which was defined as the time from registration to death as a result of any cause, with a target sample size of 700 patients. The following assumptions were made: an annual accrual rate of 233 patients accrued over a 3-year enrollment period (based on previous CALGB RCC trial accrual), a 2-year follow-up period, and survival time followed an exponential distribution. The trial was designed with 86% power to detect an HR of 0.76 (a 30% improvement in median survival in patients randomly assigned to bevacizumab plus IFN-α compared with patients assigned to IFN-α monotherapy) assuming a two-sided significance level of $P = .05$. The primary analysis of the OS end point was based on the stratified log-rank statistic. Secondary end points were PFS (defined from the date of random assignment to date of progression using RECIST criteria according to the first tumor assessment where disease progression was observed or death as a result of any cause, whichever occurred first), objective response rate using RECIST criteria, and safety. Patients who discontinued treatment for reasons other than progression were observed for disease progression or death.

The Lan and Demets analog of the O'Brien-Fleming sequential boundary was used to maintain the overall significance level of $\alpha = .05$ while conducting interim analyses of the OS end point. Under the alternative hypotheses, 588 deaths were expected at the end of the trial. An intent-to-treat approach was used in the analysis. In addition, the Kaplan-Meier product-limit method was used to estimate the PFS time and duration of response in the two arms. The analysis of the PFS end point was based on a two-sided stratified log-rank test comparing the two arms, and the threshold for significance was $P = .05$. The χ^2 test and Fisher's exact test were used to compare objective response rates and adverse events between the two treatment groups, respectively. All analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC).

CALGB Statistical Center personnel were responsible for patient registration, data collection, and quality assurance for all the data submitted by the participating institutions. Statistical analyses were performed by CALGB statisticians. As part of the quality assurance program of the CALGB, members of the Audit Committee visit all participating CALGB institutions at least once every 3 years to review source documents. The auditors verify compliance with federal regulations and protocol requirements, including those pertaining to eligibility, treatment, adverse events, tumor response, and outcome in a sample of protocols at each institution. Such on-site review of medical records was performed for a subgroup of 177 patients (24.2%) of the 732 patients enrolled onto this study, and no major problems or discrepancies were identified. The data presented here for clinical and safety parameters used a data cutoff date of March 24, 2009, representing 17 months of additional follow-up from the original report.[21]

RESULTS

Patient Characteristics

Between October 2003 and July 2005, 732 patients were enrolled. As previously reported, patients were predominantly male, 62% had ECOG performance status of 0, and 85% had prior nephrectomy. Twenty-six percent, 64%, and 10% of patients had good-risk, intermediate-risk, and poor-risk disease, respectively.[3]

Treatment Administration

Three hundred sixty-three patients were randomly assigned to IFN-α monotherapy, and 369 were assigned to combination therapy (Fig 1). Patients on IFN-α monotherapy received a median of 4.2
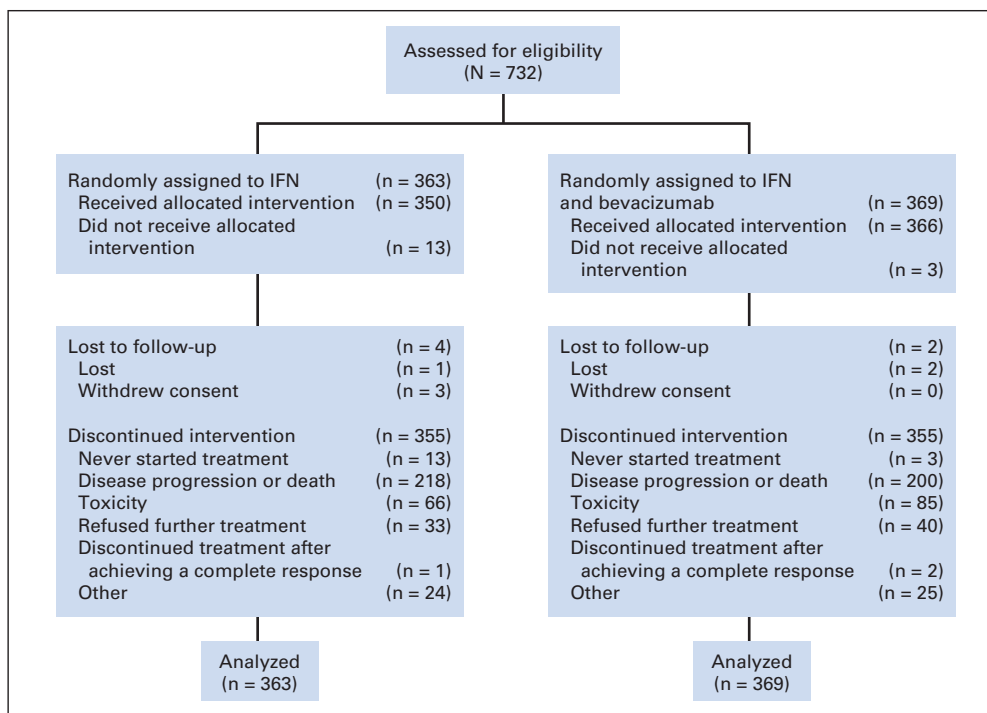
cycles of therapy (range, 0.2 to 57 cycles) compared with 8.2 cycles (range, one to 59 cycles) in patients receiving bevacizumab plus IFN-α. Dose reductions of IFN-α to 6 MU and 3 MU were undertaken in 136 patients (37%) and 37 patients (10%), respectively, on the IFN-α monotherapy arm and in 170 patients (46%) and 68 patients (18%), respectively, on the bevacizumab plus IFN-α arm. In aggregate, treatment delays occurred in 31.6% of patients receiving IFN-α and 61.7% of patients receiving IFN-α plus bevacizumab. The majority of IFN-α dose modifications and delays were caused by fatigue. The majority of patients discontinued treatment as a result of disease progression or death (Fig 1).

OS

The median OS time was 18.3 months (95% CI, 16.5 to 22.5 months) for bevacizumab plus IFN-α and 17.4 months (95% CI, 14.4 to 20.0 months) for IFN-α monotherapy (unstratified log-rank $P = .097$; Fig 2). Adjusting on stratification factors, the HR was 0.86 (95% CI, 0.73 to 1.01; stratified log-rank $P = .069$) for patients receiving bevacizumab plus IFN-α compared with patients receiving IFN-α. The median duration of follow-up among surviving patients was 46.2 months (interquartile range, 45.2 to 48.2 months). Using Clark's C,[23] the completeness of follow-up for this study is 95.7%. Applying Wu's modification to adjust for unreported deaths,[24] the completeness of follow-up is 96.9%. The median OS times in the bevacizumab plus IFN-α and IFN-α arms were 32.5 months (95% CI, 21.6 to 43.7 months) and 33.5 months (95% CI, 24.3 to 39.4 months; $P = .5189$) for Memorial Sloan-Kettering Cancer Center good-risk patients, respectively; 17.7 months (95% CI, 15.6 to 22.5 months) and 16.1 months (95% CI, 13.4 to 19.9 months; $P = .1688$) for intermediate-risk patients, respectively; and 6.6 months (95% CI, 5.9 to 8.9 months) and 5.7 months (95% CI, 4.4 to 9.2 months; $P = .2439$) for poor-risk patients, respectively. Noting the limitations of subgroup analysis, the

HRs for death for bevacizumab plus IFN-α versus IFN-α were 0.89, 0.87, and 0.76 for the good-, intermediate-, and poor-risk groups, respectively. There was no significant difference in OS when evaluated according to nephrectomy status, presence of liver metastases, age, or sex (Fig 3).

No cross over on trial was permitted for patients randomly assigned to IFN-α monotherapy. Nonetheless, a substantial percentage of patients on both arms received systemic anticancer therapy subsequent to progression (62% of patients on IFN-α monotherapy and 54% of patients on bevacizumab plus IFN-α). The majority of these patients received VEGF-targeted agents such as sunitinib and sorafenib, which became available during the conduct of this trial.
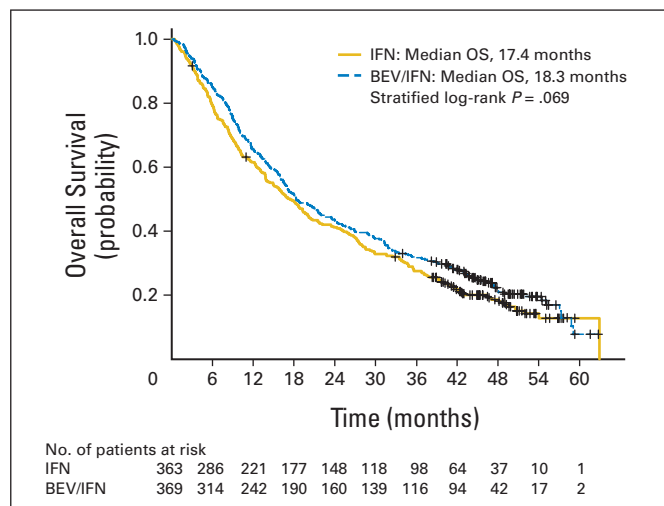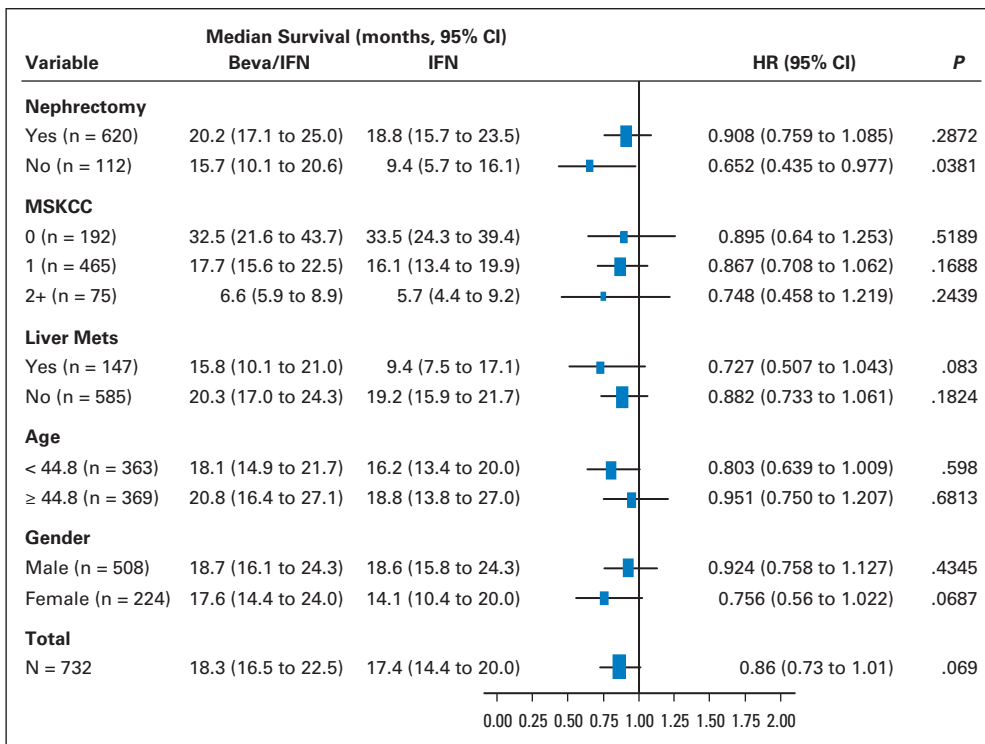

Fig 2. Overall survival (OS) according to treatment arm. IFN, interferon; BEV, bevacizumab.

Variable	Median Survival (months, 95% CI) Beva/IFN	IFN	HR (95% CI)	P
Nephrectomy				
Yes (n = 620)	20.2 (17.1 to 25.0)	18.8 (15.7 to 23.5)	0.908 (0.759 to 1.085)	.2872
No (n = 112)	15.7 (10.1 to 20.6)	9.4 (5.7 to 16.1)	0.652 (0.435 to 0.977)	.0381
MSKCC				
0 (n = 192)	32.5 (21.6 to 43.7)	33.5 (24.3 to 39.4)	0.895 (0.64 to 1.253)	.5189
1 (n = 465)	17.7 (15.6 to 22.5)	16.1 (13.4 to 19.9)	0.867 (0.708 to 1.062)	.1688
2+ (n = 75)	6.6 (5.9 to 8.9)	5.7 (4.4 to 9.2)	0.748 (0.458 to 1.219)	.2439
Liver Mets				
Yes (n = 147)	15.8 (10.1 to 21.0)	9.4 (7.5 to 17.1)	0.727 (0.507 to 1.043)	.083
No (n = 585)	20.3 (17.0 to 24.3)	19.2 (15.9 to 21.7)	0.882 (0.733 to 1.061)	.1824
Age				
< 44.8 (n = 363)	18.1 (14.9 to 21.7)	16.2 (13.4 to 20.0)	0.803 (0.639 to 1.009)	.598
≥ 44.8 (n = 369)	20.8 (16.4 to 27.1)	18.8 (13.8 to 27.0)	0.951 (0.750 to 1.207)	.6813
Gender				
Male (n = 508)	18.7 (16.1 to 24.3)	18.6 (15.8 to 24.3)	0.924 (0.758 to 1.127)	.4345
Female (n = 224)	17.6 (14.4 to 24.0)	14.1 (10.4 to 20.0)	0.756 (0.56 to 1.022)	.0687
Total				
N = 732	18.3 (16.5 to 22.5)	17.4 (14.4 to 20.0)	0.86 (0.73 to 1.01)	.069

0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

Fig 3. Forest plot of overall survival of selected subgroups. HR, hazard ratio; IFN, interferon; Beva, bevacizumab; MSKCC, Memorial Sloan-Kettering Cancer Center; Mets, metastases.

Given the potential confounding effects of subsequent anticancer therapy on OS, a post hoc analysis was performed on patients who did not receive treatment after discontinuation of protocol therapy (n = 324) and patients who received subsequent therapy (n = 408). Notably, patients who received subsequent therapy, compared with those who did not, had more favorable baseline prognostic features, including a significantly higher percentage of patients with ECOG performance status of 0 (67% *v* 56%, respectively; *P* = .012), a greater percentage of patients with prior nephrectomy (88% *v* 80%, respectively; *P* = .004), and significantly more good-risk patients (29% *v* 22%) and fewer poor-risk patients (6% *v* 15%, respectively; *P* < .001). As seen in Table 1, the median OS time was greater for patients who received subsequent therapy, regardless of treatment arm. Furthermore, the HR for OS was consistent, favoring the patients receiving bevacizumab plus IFN-α regardless of receipt of subsequent therapy.

Adverse Events

In patients evaluable for toxicity (n = 347 for IFN-α and n = 362 for bevacizumab plus IFN-α), 80% of patients receiving bevacizumab plus IFN-α experienced grade ≥ 3 toxicity compared with 63% of patients receiving IFN-α monotherapy (*P* < .001; Table 2). Noting that patients receiving combination therapy had a duration of treatment that averaged 4 months longer than IFN-α monotherapy, bevacizumab plus IFN-α resulted in significantly more grade ≥ 3 hypertension (HTN; 11% *v* 0%, respectively), anorexia (17% *v* 8%, respectively), fatigue (37% *v* 30%, respectively), and proteinuria (15% *v* < 1%, respectively). The incidence of grade 4 neutropenia and anemia was low in each arm, and there were no differences in the rate of febrile neutropenia or requirement for RBC transfusion (each < 1%). There were four treatment-related deaths on the IFN-α monotherapy arm and three on the bevacizumab plus IFN-α arm.

Table 1. OS According to Treatment Arm and Subsequent Therapy

		OS (months)									
		Bevacizumab + IFN-α (n = 369)		IFN-α (n = 363)		All Patients (N = 732)			Adjusted		
Subsequent Therapy	No. of Patients	Median	95% CI	Median	95% CI	Median	95% CI	P	HR*	95% CI	P
Received	408	31.4	25.6 to 37.8	26.8	21.5 to 29.4	28.2	25.6 to 32.3	.079	0.80	0.64 to 1.01	.055
Did not receive	324	13.1	10.0 to 15.7	9.1	7.8 to 10.2	10.2	9.1 to 13.0	.059	0.82	0.65 to 1.04	.108
Total	732	18.3	16.5 to 22.5	17.4	14.4 to 20.0	18.1	16.4 to 20.2	.097	0.86	0.73 to 1.01	.069

Abbreviations: OS, overall survival; IFN-α, interferon alfa; HR, hazard ratio.
*HR for death for patients treated with bevacizumab plus IFN-α compared with IFN-α monotherapy adjusted by nephrectomy status (yes *v* no) and number of adverse prognostic factors (zero, one to two, or ≥ three factors).

Table 2. Treatment-Related Adverse Events

Adverse Event	Bevacizumab + Interferon Alfa (n = 362)				Interferon Alfa Monotherapy (n = 347)			
	All Grades		Grade ≥ 3		All Grades		Grade ≥ 3	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Hematologic								
Anemia	59	16	14	4	76	20	13	4
Neutropenia	158	43	33	9	124	36	31	9
Thrombocytopenia	38	10	8	2	30	9	2	< 1
Nonhematologic								
Cardiovascular								
Cardiac ischemia/infarction	5	1	5	1	0	0	0	0
Left ventricular dysfunction	2	< 1	2	< 1	0	0	0	0
Hypertension	103	28	39	11	13	4	0	0
Thrombosis/embolism	14	4	6	2	6	2	3	< 1
Constitutional symptoms								
Fatigue	336	93	135	37	312	90	105	30
Weight loss	57	16	15	4	42	12	5	1
Endocrine								
Thyroid dysfunction	2	< 1	2	< 1	0	0	0	0
GI								
Anorexia	258	71	63	17	213	61	28	8
Nausea	210	58	26	7	204	59	17	5
Perforation, GI	0	0	1	< 1	0	0	0	0
Hemorrhage/bleeding								
Hemorrhage, genitourinary	3	< 1	0	0	1	< 1	0	0
Hemorrhage, GI	18	5	4	1	3	< 1	1	< 1
CNS								
CNS cerebrovascular ischemia	5	1	5	1	0	0	1	< 1
Pulmonary								
Dyspnea	53	15	23	6	32	9	12	3
Pneumonitis/pulmonary infiltrates	3	< 1	1	< 1	4	1	3	< 1
Renal								
Proteinuria	257	71	56	15	24	10	1	< 1
Maximum overall adverse events	360	99	290	80	340	98	217	63

HTN As a Biomarker of Clinical Outcome to Bevacizumab Plus IFN-α

Given the observation with bevacizumab-based therapy in breast cancer[25] and across solid tumors (including RCC) with a VEGF receptor inhibitor that treatment-induced HTN may be a biomarker of clinical outcome,[26] a retrospective analysis of the current trial was undertaken. Ten (3%) of 350 patients on IFN-α monotherapy and 75 (21%) of 366 patients on bevacizumab plus IFN-α who received therapy and had available blood pressure data developed grade ≥ 2 HTN. There was no difference in baseline prognostic factors between patients who did or did not develop HTN, with the possible exception of a higher percentage of prior nephrectomy in patients who developed HTN (92% v 83%, respectively; P = .049). Patients on bevacizumab plus IFN-α who developed grade ≥ 2 HTN of any relation to study therapy had a significantly greater PFS and OS compared with patients who did not develop HTN (Table 3, Fig 4). There was no significant difference in the objective response rate based on the development of HTN. Results were similar when the analysis was restricted to the development of grade ≥ 3 HTN; to patients with HTN possibly, probably, or definitely related to study therapy; or to a landmark analysis of the development of HTN at 2 or 3 months on study therapy. On multivariate analysis, the development of HTN at 2

months was an independent predictor of OS, with an HR of 0.622 (95% CI, 0.390 to 0.992; P = .046). An analysis of HTN as a biomarker in the IFN-α monotherapy arm was not possible because of the limited number of events.

Table 3. Clinical Outcome to Bevacizumab Plus Interferon Alfa According to the Development of Grade ≥ 2 Hypertension

Outcome	Patients With Grade ≥ 2 Hypertension* (n = 75)	Patients Without Grade ≥ 2 Hypertension (n = 291)
ORR, %	13.1	9.0
95% CI	9.7 to 16.7	6.3 to 18.9
P	.95	
PFS, months	13.2	8.0
95% CI	10.6 to 15.5	5.9 to 8.6
P	< .001	
OS, months	41.6	16.2
95% CI	26.3 to 55.1	14.2 to 18.7
P	< .001	

Abbreviations: ORR, objective response rate; PFS, progression-free survival; OS, overall survival.
*Any relation to therapy according to Common Terminology Criteria for Adverse Events (version 3).
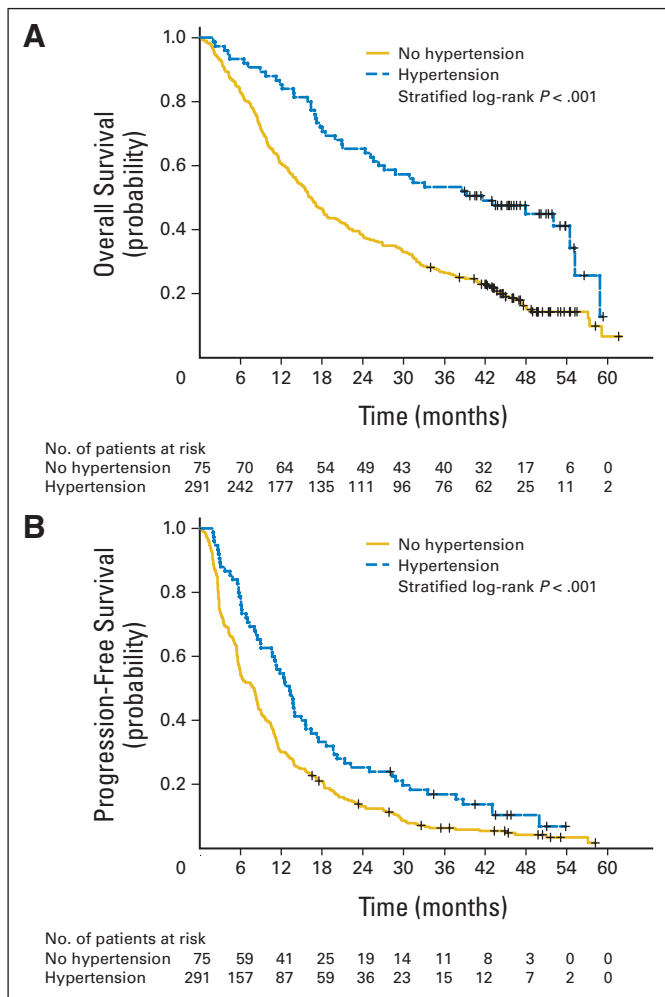
Fig 4. Kaplan-Meier (A) overall survival and (B) progression-free survival according to development of grade ≥ 2 hypertension on bevacizumab plus interferon alfa.

DISCUSSION

This prospective randomized trial demonstrated a greater OS time in patients with metastatic clear cell RCC receiving bevacizumab plus IFN-α as initial systemic therapy compared with IFN-α alone, but the difference did not meet predefined criteria for statistical significance. However, the clinical benefit derived from the addition of bevacizumab to IFN-α is evident in the statistically significantly prolonged PFS and increased objective response rate, as reported previously in this trial and in a similar phase III trial.[20,21]

Although precedent certainly exists for trials in which improvements in PFS and objective response rate do not translate into an improvement in OS, an alternative explanation for the results observed in this trial are the confounding effects of the emergence of multiple active therapeutic options during the conduct of this trial. The majority of patients on this trial received one or more active therapies on disease progression before death. Therefore, it is possible that the initial impact of more favorable disease control with bevacizumab plus IFN-α (as reflected by the PFS advantage) did not translate into a statistically significant OS advantage for this reason.

Although the HR for OS for bevacizumab plus IFN-α is preserved regardless of subsequent treatment, the most robust OS was achieved in patients who received initial bevacizumab-based therapy and then received subsequent therapy; in this case, the adjusted HR in favor of bevacizumab plus IFN-α approached significance with a $P = .055$. Indeed, the cohort of patients who received subsequent therapy after initial bevacizumab plus IFN-α had an OS time greater than 2.5 years.

These results are not surprising. First, baseline prognostic features such as performance status and risk group classification continue to influence outcome in metastatic RCC, even in the current era of active targeted therapy. Patients with the most favorable underlying disease biology will be fit enough at disease progression to receive further therapy. In addition, further therapy will include agents with proven antitumor activity in the treatment-refractory setting, extending control of tumor burden and thus OS.[13,27,28] The fact that other contemporary phase III trials, including trials investigating sunitinib and sorafenib and the other phase III investigation of IFN-α plus bevacizumab versus IFN-α, have also failed to demonstrate a statistically significant OS advantage suggests that the same confounding effect of subsequent active therapy is operative.[13,15] Indeed, the HRs for OS in favor of therapy containing VEGF-targeted treatment were identical across the current trial, a similar international trial comparing bevacizumab plus IFN-α to IFN-α monotherapy, and the phase III trial of sunitinib versus IFN-α. These similarities suggest a significant and consistent OS advantage of VEGF-targeted therapy compared with the historical standard of cytokine monotherapy. The numerical differences across trials in median OS likely reflect differences in patient selection. Furthermore, until new classes of active agents are developed, it is likely that clinical benefit in metastatic RCC trials will continue to be defined by a PFS end point. Indeed, the European and US regulatory authorities recently approved the combination of bevacizumab plus IFN-α for the treatment of metastatic RCC based on a PFS end point.

This study is limited by the lack of a placebo control arm and lack of independent review of radiographs. However, the objective response rate and HR for PFS demonstrated in this trial mirrored a similarly designed international trial that used both a placebo control and independent review of radiographs.[20]

Subset analysis failed to identify patient subgroups (according to baseline factors) with significantly better or significantly worse outcomes to bevacizumab plus IFN-α. Noting the limitations of retrospective subset analyses, these data highlight the fact that the current management of patients with metastatic RCC is empiric, based on data derived from clinical trials. Intriguingly, the development of HTN with bevacizumab plus IFN-α treatment identified a group of patients with superior clinical outcome, consistent with this observation across solid tumors and with multiple VEGF-targeted therapies. Further investigation of the underlying biology of this observation is warranted to maximally exploit this phenomenon for therapeutic benefit. The combination of IFN-α and bevacizumab is clearly a treatment option to be considered for patients with metastatic RCC. Perceived relative risks and benefits of each therapy, patient preference, availability in a given country including cost considerations, and physician experience all feed into the complex equation of individualized therapy. The development of patient- and/or tumor-specific characteristics to educate the risk-benefit ratio for a single patient should be a top research priority.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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