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ORIGINAL REPORT

Phase III Trial of Bevacizumab Plus Interferon Alfa-2a in Patients With Metastatic Renal Cell Carcinoma (AVOREN): Final Analysis of Overall Survival

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ABSTRACT

Purpose
A phase III trial of bevacizumab combined with interferon alfa-2a (IFN) showed significant improvements in progression-free survival (PFS) in metastatic renal cell carcinoma (mRCC). Here, we report overall survival (OS) data.

Patients and Methods
Six hundred forty-nine patients with previously untreated mRCC were randomly assigned to receive bevacizumab (10 mg/kg every 2 weeks) plus IFN (9 MIU subcutaneously three times a week; n = 327) or IFN plus placebo (n = 322) in a multicenter, randomized, double-blind, phase III trial. The primary end point was OS. Final analysis of the secondary end point (PFS) was reported earlier.

Results
Median OS was 23.3 months with bevacizumab plus IFN and 21.3 months with IFN plus placebo (unstratified hazard ratio [HR] = 0.91; 95% CI, 0.76 to 1.10; $P = .3360$; stratified HR = 0.86; 95% CI, 0.72 to 1.04; $P = .1291$). Patients (> 55%) in both arms received at least one postprotocol antineoplastic therapy, possibly confounding the OS analysis. Patients receiving postprotocol therapy including a tyrosine kinase inhibitor had longer median OS (bevacizumab plus IFN arm: 38.6 months; IFN plus placebo arm: 33.6 months; HR = 0.80; 95% CI, 0.56 to 1.13). Tolerability was similar to that reported previously.

Conclusion
Bevacizumab plus IFN is active as first-line treatment in patients with mRCC. Most patients with mRCC receive multiple lines of therapy, so considering the overall sequence of therapy when selecting first-line therapy may optimize patient benefit.

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INTRODUCTION

Over the last 4 years, the US Food and Drug Administration (FDA) and the European Medicines Agency have approved various novel agents for patients with metastatic renal cell carcinoma (mRCC). Bevacizumab plus interferon alfa-2a (IFN) and sunitinib are now standard first-line options for patients with previously untreated, good- or intermediate-prognosis (using Memorial Sloan-Kettering Cancer Center [MSKCC] criteria) mRCC, whereas temsirolimus is standard for patients with previously untreated poor-prognosis disease.[1] Sunitinib, sorafenib, and everolimus[2] are approved for use in patients who experience disease relapse.

Bevacizumab is a humanized monoclonal antibody that precisely inhibits the activity of vascular endothelial growth factor (VEGF), a key mediator of tumor angiogenesis.[3] The randomized, double-blind, phase III AVOREN trial compared bevacizumab 10 mg/kg every 2 weeks plus IFN 9 MIU three times a week with IFN plus placebo in patients with systemic therapy-naïve mRCC.[4] Although the primary end point of this trial was overall survival (OS), the preplanned final analysis of progression-free survival (PFS) conducted at the interim OS analysis showed clinically meaningful, statistically significant benefit (PFS, 10.2 months with bevacizumab plus IFN *v* 5.4 months with IFN plus placebo; hazard ratio [HR] = 0.63; $P < .001$, unstratified; overall response rate [ORR], 31% *v* 13%, respectively; $P < .001$, unstratified).[4] AVOREN was unblinded at this time, and the data safety monitoring board (DSMB) recommended that patients in the control group who had not experienced progression should

cross over to receive bevacizumab. PFS data were used to support regulatory applications because second-line therapies that became available while the trial was ongoing could confound OS analyses. Contrasting with other trials,[5] the robustness of investigator-assessed PFS and ORR in AVOREN has been verified by independent review, confirming the significance and extent of improvements (median PFS, 10.4 months with bevacizumab plus IFN *v* 5.5 months with IFN plus placebo; HR = 0.571; $P < .001$, stratified; ORR, 31% *v* 12%, respectively; $P < .001$, stratified).[6] The relative contributions of bevacizumab and IFN to the efficacy of this combination regimen were not evaluable in this trial but have been discussed elsewhere based on mechanisms of action and data for bevacizumab plus low-dose IFN.[7]

The open-label, phase III Cancer and Leukemia Group B (CALGB) 90206 trial comparing bevacizumab plus IFN with IFN monotherapy also showed significant PFS and ORR benefits for bevacizumab plus IFN (median PFS, 8.4 *v* 4.9 months, respectively; HR = 0.71; $P < .001$, stratified; ORR, 25.5% *v* 13.1%, respectively, stratified).[8,9] Differences in the patient populations of these trials do not allow direct comparisons with AVOREN. Median OS has also been reported for the CALGB 90206 trial (18.3 months for bevacizumab plus IFN *v* 17.4 months for IFN monotherapy; HR = 0.86; $P = .069$, stratified).[8] Reasons for the nonsignificant improvement in OS may include the impact of postprogression therapies.

At the time of reporting the interim analysis of AVOREN, OS data were not mature.[4] We report the final OS analysis and updated safety.

PATIENTS AND METHODS

Patients

Detailed patient eligibility criteria have been described previously.[4] In brief, eligible patients were aged ≥ 18 years and had confirmed mRCC with more than 50% clear cell histology, undergone radical nephrectomy or partial nephrectomy (if resection margins were clearly negative of disease), Karnofsky performance status ≥ 70%, minimal proteinuria at baseline (< 0.5 g/24 hours), measurable or nonmeasurable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST]), no prior systemic treatment for mRCC, no recent major surgical procedures, and no evidence of CNS metastases.

Procedures

Study procedures have also been described in detail previously.[4] AVOREN was an international, multicenter, randomized, double-blind, phase III trial comparing bevacizumab plus IFN with IFN plus placebo. Patients were randomly assigned 1:1 using a block design procedure and stratified according to country and MSKCC risk.

Bevacizumab (F. Hoffmann-La Roche, Basel, Switzerland) 10 mg/kg or placebo was administered intravenously every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. No bevacizumab dose reduction was permitted. IFN (F. Hoffmann-La Roche) 9 MIU was administered three times per week as a subcutaneous injection for a maximum of 52 weeks or until disease progression, unacceptable toxicity, or withdrawal of consent. Dose reduction of IFN to 6 or 3 MIU was allowed to manage grade ≥ 3 adverse events (AEs) attributable to IFN according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Other antineoplastic therapies were allowed subsequent to progression or toxicity.

The primary end point was OS. Secondary end points included PFS, time to disease progression, time to treatment failure, ORR, and safety. Tumor response was investigator assessed using RECIST. Nonmeasurable lesions were used to define complete responses and disease progression only. Responses were confirmed by a second assessment ≥ 4 weeks after the first response was recorded.

After reviewing the final PFS and interim OS results, the DSMB recommended that patients in the IFN plus placebo arm whose disease had not progressed should cross over to receive bevacizumab. Patients continued to be observed for the primary end point of OS. Efficacy was assessed on an intent-to-treat basis. All patients randomly assigned and exposed to study medication were included in safety analyses. For the safety analysis, patients were assigned to treatment groups based on treatment actually received, with patients in the IFN plus placebo arm who received ≥ one dose of bevacizumab before cross over being assigned to the bevacizumab arm. Patients on the IFN plus placebo arm who crossed over after unblinding of the study were assigned to the IFN plus placebo arm; events occurring after cross over were excluded and summarized separately for safety analyses.

Safety was assessed on an ongoing basis by documentation of AEs (Common Terminology Criteria for Adverse Events version 3.0), physical examination, electrocardiography, urinalysis, and blood pressure measurement.

Statistical Analysis

The study was designed to have 80% power for the log-rank test to detect an improvement in OS with an HR of 0.76, assuming an improvement in median survival from 13 to 17 months, at an overall two-sided $\alpha = .05$. The planned sample size was 638 patients, with 445 deaths required for the final analysis.

Preplanned unstratified and stratified analyses of OS and PFS were performed. Stratification factors were those used for patient random assignment (ie, country [grouped into region for analysis] and MSKCC risk category). AVOREN used unstratified and stratified analyses based on European and US FDA registrations, respectively. SAS version 8.2 (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

Between June 2004 and October 2005, 649 patients (intent-to-treat population) with previously untreated mRCC were randomly assigned to receive either bevacizumab plus IFN (n = 327) or IFN plus placebo (n = 322; Fig 1). Treatment arms were well balanced with regard to patient characteristics, as described previously.[4] After the DSMB recommendation to unblind the trial, 13 patients in the control arm crossed over to bevacizumab treatment before disease progression.

The clinical cutoff for the final analysis of OS was September 2008, when 220 deaths (67%) had occurred in the bevacizumab plus IFN arm and 224 deaths (70%) had occurred in the control arm. Median follow-up times were 23 and 21 months for patients receiving bevacizumab plus IFN and IFN plus placebo, respectively. Median duration of bevacizumab or placebo treatment was 42 and 22 weeks in the bevacizumab plus IFN and control arms, respectively; median duration of IFN treatment was 34 and 20 weeks, respectively. A total of 121 patients (36%) in the bevacizumab plus IFN arm and 54 patients (18%) in the control arm received bevacizumab or placebo treatment for more than 1 year. The median percentage of planned dose of bevacizumab or placebo was 92% (range, 24% to 104%) in the bevacizumab plus IFN arm and 95% (range, 39% to 109%) in the control arm; the median proportion of planned dose for IFN was 92% (range, 4% to 150%) in the bevacizumab plus IFN arm and 96% (range, 28% to 120%) in the control arm. Bevacizumab or placebo was withdrawn in 9% of patients in each arm as a result of treatment refusal/withdrawal of consent, administrative error, or protocol violation.

Final median OS in the intent-to-treat population was 23.3 months in the bevacizumab plus IFN arm compared with 21.3 months

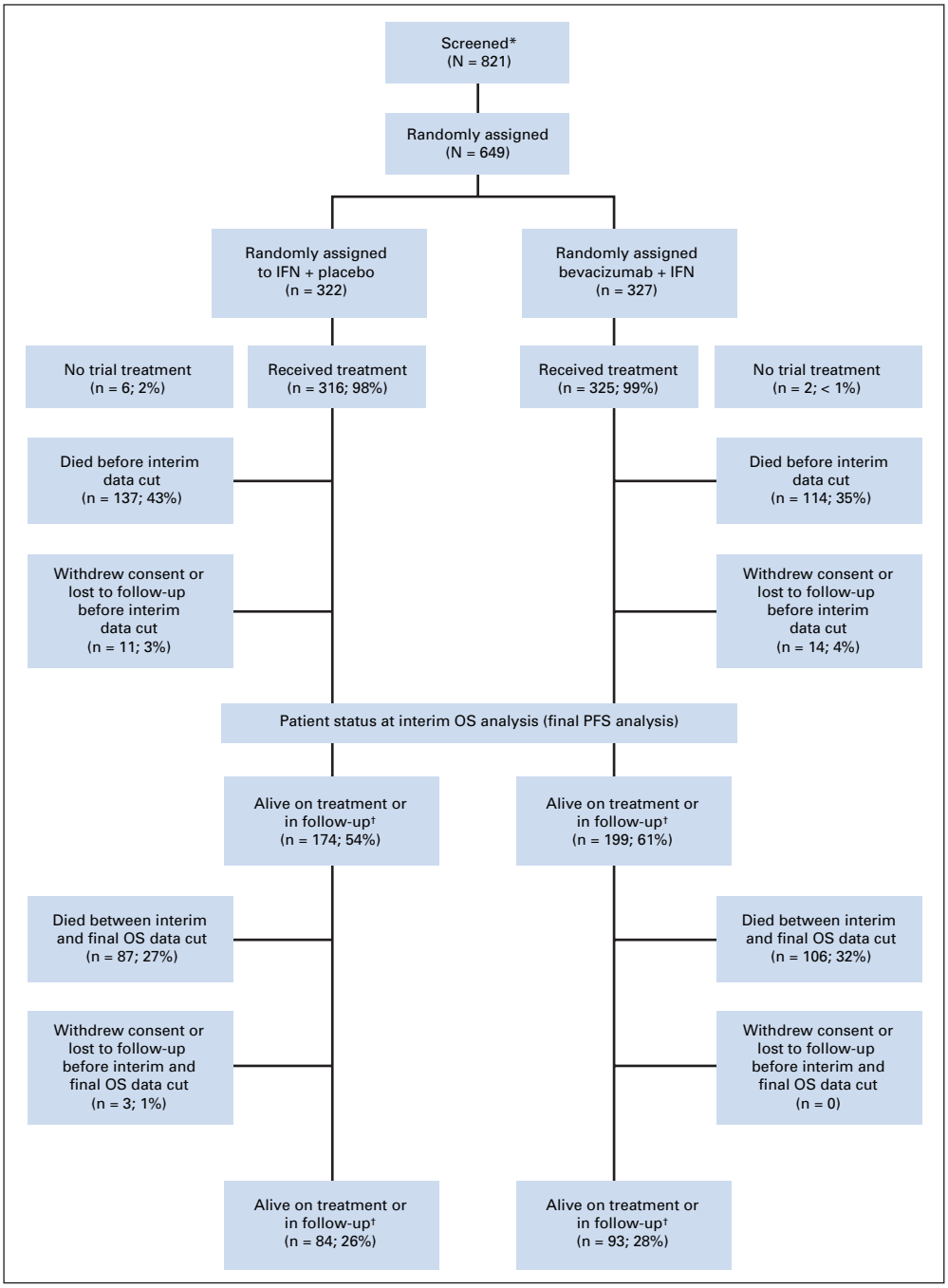

Fig 1. Study profile (CONSORT diagram). (*) Number of patients screened is not derived from the clinical database and is not validated. (†) Includes patients who were still receiving any of two components of trial drug or were in follow-up; percentages are shown based on number. IFN, interferon alfa-2a; OS, overall survival; PFS, progression-free survival.

in the control arm (unstratified HR = 0.91; 95% CI, 0.76 to 1.10; $P = .3360$; Fig 2A). The stratified analysis (stratified by MSKCC risk and region) showed a more pronounced improvement in OS in the bevacizumab plus IFN arm (HR = 0.86; 95% CI, 0.72 to 1.04; $P = .1291$). A similar HR was observed when patients in the control arm who crossed over to the bevacizumab plus IFN arm when the trial was unblinded (n = 13) were censored (stratified HR = 0.84; 95% CI, 0.70 to 1.02; $P = .0766$). In patients in whom IFN doses were reduced to 6 or 3 MIU three times a week to manage IFN-related AEs, the OS benefit of bevacizumab plus IFN was maintained (median OS, 26.0 months; Fig 2B).

A prespecified multiple Cox regression model indicated that several baseline prognostic factors were associated with survival independent of treatment (Table 1). Adjustment for these baseline factors resulted in a more pronounced treatment effect, with an HR of 0.78 (95% CI, 0.63 to 0.96; $P = .0219$), indicating a 22% reduction in the risk of death for patients in the bevacizumab plus IFN arm compared with the control arm.

An exploratory analysis of OS evaluated the treatment effect across different patient subgroups based on baseline disease characteristics (Fig 3). In most subgroups, HRs were consistent with the HR for the overall population. A reduction in the risk of death for patients in

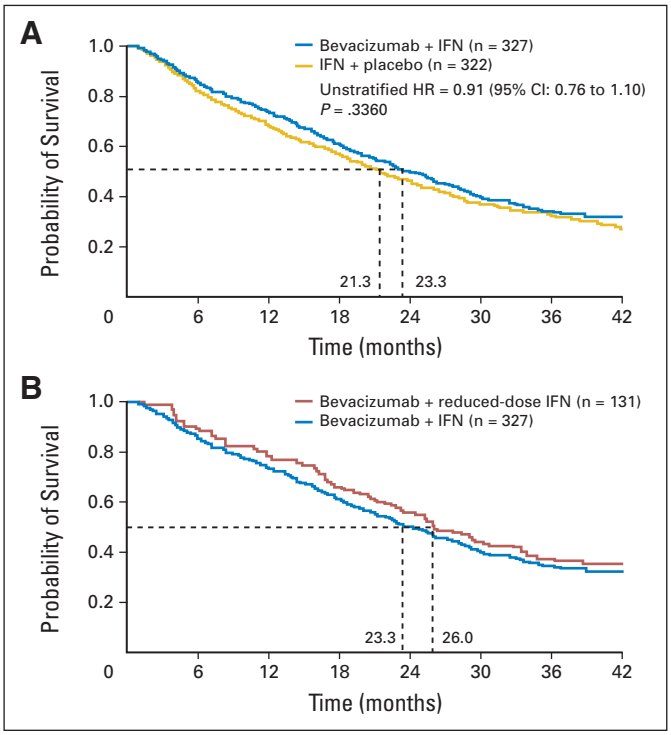

Fig 2. (A) Kaplan-Meier estimate of overall survival based on 444 of 445 required events. (B) Kaplan-Meier estimate of overall survival in patients who received bevacizumab plus reduced doses of interferon alfa-2a (IFN). HR, hazard ratio.

the bevacizumab plus IFN arm compared with the control arm was observed in each of the MSKCC risk groups (Table 2).

Postprotocol therapy, not limited to second-line therapy, was administered to patients with progressive disease or those in whom trial therapy was discontinued. A high proportion of patients received postprotocol anticancer therapies, including antineoplastic agents, which may have impacted on OS; of patients receiving bevacizumab plus IFN, 180 patients (55%) received at least one postprotocol therapy compared with 202 patients (63%) in the control arm. Tyrosine kinase inhibitors (TKIs; sunitinib and sorafenib) were the most common postprotocol therapies (35% in the bevacizumab plus IFN arm and 37% in the control arm). Baseline characteristics for patients receiving subsequent TKIs were well balanced between the treatment arms (data not shown).[10] An unplanned, exploratory analysis showed that median OS was longer in patients receiving subsequent TKI therapy after bevacizumab plus IFN (n = 113) compared with patients receiving TKIs after IFN plus placebo (n = 120; OS, 38.6 *v* 33.6 months, respectively; HR = 0.80; 95% CI, 0.56 to 1.13, unstratified; Table 3).

Table 1. Multivariate Cox Regression Analysis for Overall Survival

Variable	HR	95% CI	*P*
Randomly assigned treatment	0.78	0.63 to 0.96	.0219
Sex (male *v* female)	0.78	0.62 to 0.97	.0275
Baseline WBC count (≤ *v* > ULN)	0.71	0.52 to 0.96	.0250
Baseline platelets (≤ *v* > ULN)	0.73	0.54 to 0.99	.0397
Body weight loss (≤ *v* > 10%)	0.73	0.54 to 0.99	.0435
No. of sites (1 *v* > 1)	0.68	0.52 to 0.91	.0087
Baseline SLD (< *v* ≥ median)	0.64	0.51 to 0.80	< .001
Motzer score (intermediate *v* all other)	0.42	0.29 to 0.59	< .001
Motzer score (favorable *v* all other)	0.24	0.16 to 0.36	< .001

Abbreviations: HR, hazard ratio; ULN, upper limit of normal range; SLD, sum of the longest diameter of target lesions.

The incidence of AEs was consistent with that reported previously for this trial.[4] Fatigue (bevacizumab plus IFN, 13%; IFN plus placebo, 8%) and asthenia (bevacizumab plus IFN, 11%; IFN plus placebo, 7%), both IFN-related AEs, were the most commonly reported grade ≥ 3 AEs, irrespective of treatment arm; proteinuria (8%) and hypertension (6%) were the most common grade 3 or 4 AEs associated with bevacizumab treatment. Bevacizumab or placebo was discontinued as a result of AEs in 23% of patients receiving bevacizumab plus IFN and 5% of patients receiving IFN plus placebo; IFN was discontinued as a result of AEs in 22% and 12% of patients, respectively.

Progressive disease was the principal cause of death (62% of patients receiving bevacizumab plus IFN *v* 68% of patients receiving IFN plus placebo). Deaths as a result of causes other than disease progression included 12 patients (4%) in the bevacizumab plus IFN arm and seven patients (2%) in the control arm who died as a result of AEs.

DISCUSSION

The final analysis of OS in AVOREN showed an improvement with bevacizumab plus IFN compared with IFN plus placebo (HR = 0.91; *P* = .3360, unstratified), although this was not statistically significant. The improvement in OS seemed greater in a stratified analysis (HR = 0.86; *P* = .1291), which reduces variability between treatment arms even in cases such as this where there were no apparent imbalances in baseline factors; this is advocated as a better method for predicting patient-specific treatment benefit.[11] A similar magnitude of benefit was observed in the stratified analysis of OS data from CALGB 90206 (HR = 0.86; *P* = .069).[8] It is interesting to note the similarity in terms of observed treatment effect (HR values) between stratified analyses of OS in AVOREN and CALGB 90206 despite differences in absolute median OS values, which may have resulted from differences in patient characteristics (e.g., prior nephrectomy was required in AVOREN but not CALGB 90206) and treatment duration and exposure.[4]

Why a statistically significant OS benefit was not observed in AVOREN is unclear but could be a result of one or more potential confounding factors. Thirteen patients randomly assigned to IFN plus placebo crossed over to receive bevacizumab before progression; censoring these patients impacted on the final OS results. The most probable confounding factor for OS was the availability and extensive use of active anticancer therapies after disease progression, a factor not foreseen when the trial was designed and thus not incorporated into the study design. In AVOREN, more than 55% of patients received poststudy therapy, and more than 35% received the TKIs sunitinib and sorafenib, which became available for clinical use in Europe in July 2006. Evidence of the effect of postprogression therapy is provided by the performance of patients in the control arm; at 21.3 months, the observed median OS was considerably longer than the median OS of approximately 13 months[12] assumed for a patient population treated with IFN when the trial was designed and on which statistical assumptions were based. The most likely reasons for this difference are improved patient care and newly available treatments.

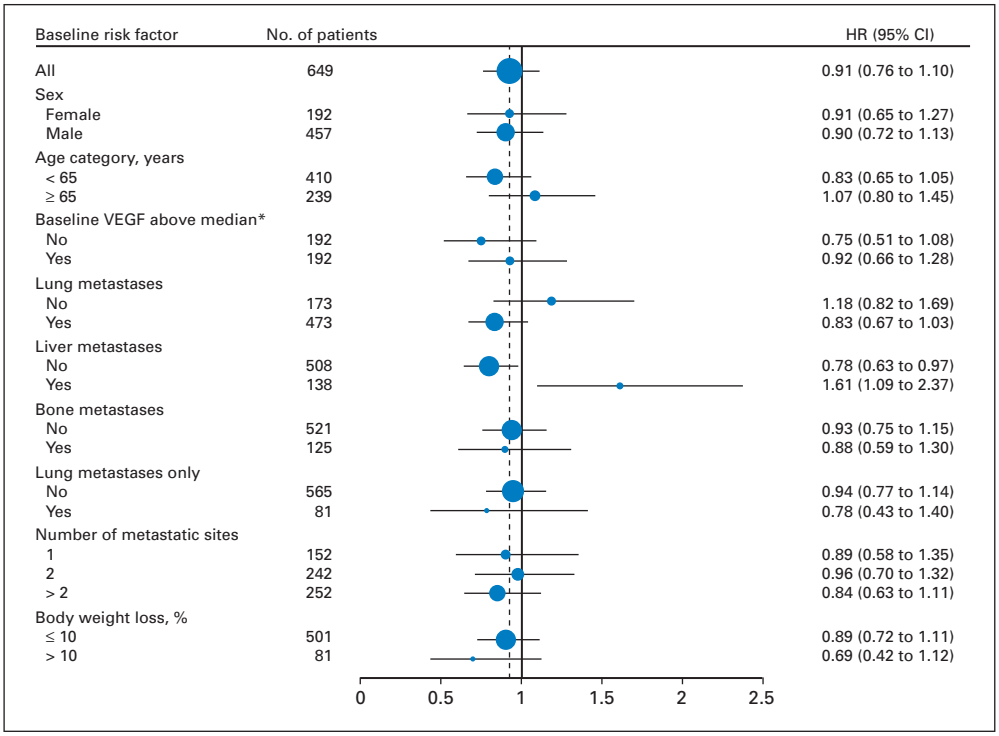

Fig 3. Subgroup analysis of overall survival (unstratified). (*) Median VEGF was 54.5 pg/mL. HR, hazard ratio; VEGF, vascular endothelial growth factor.

Data from AVOREN indicate that maximizing the use of available therapeutic agents is likely to maximize survival, although confirmation is required from prospective trials. In a post hoc exploratory analysis, median OS in patients who received bevacizumab plus IFN and then received poststudy TKIs was 38.6 months, increasing median OS to beyond 3 years. The availability of active, second-line therapies had a similar effect in CALGB 90206, with retrospective exploratory analysis showing extended OS benefit with first-line bevacizumab plus IFN (31.4 months).[8] The potential for subsequent lines of therapy to extend OS after first-line bevacizumab plus IFN was predicted based on theoretical models using median PFS data from studies of novel agents used in various lines of therapy.[13] Studies suggest that second-line sunitinib is feasible and highly active after other novel agents[14-17]; median PFS for sunitinib therapy after bevacizumab was 7.0 months.[16] Combination therapy, despite some encouraging phase I and II trials,[18-20] has yet to prove its role in mRCC. Until data from ongoing randomized trials are available, sequencing available therapy remains the more relevant treatment strategy.

Related to this discussion is the issue of whether OS is the most appropriate end point for trials in which patients may receive multiple lines of therapy. Future trials of novel agents in mRCC may encounter difficulties demonstrating significant OS benefit without controlling for the use of second and further lines of active therapy. This issue is highlighted in AVOREN, where median OS in the control arm was longer than expected, most likely because of the use of therapy after disease progression, impacting on the statistical assumptions used to design AVOREN. As a marker of efficacy, PFS may be adopted as a primary end point to assess the true efficacy of these therapies because the sensitivity of OS to subsequent therapy has become increasingly problematic as more therapies become available for advanced cancers such as colorectal cancer and renal cell carcinoma.[21] Both the US FDA[22] and the European Medicines Agency[23] accept PFS as a valid measure of clinical benefit, particularly when poststudy therapy is expected to confound analysis of OS benefit. Trials of sequential therapy will need to ensure that factors such as patient characteristics, prior

Table 2. OS by MSKCC Risk Category

	Favorable Risk		Intermediate Risk		Poor Risk	
OS	Bevacizumab + IFN (n = 87)	IFN + Placebo (n = 93)	Bevacizumab + IFN (n = 200)	IFN + Placebo (n = 192)	Bevacizumab + IFN (n = 30)	IFN + Placebo (n = 29)
Median, months	35.1	37.2	22.6	19.3	6.0	5.1
95% CI	25.0 to 45.6	25.0 to 47.7	18.3 to 25.8	14.8 to 22.8	2.8 to 11.8	2.6 to 10.5
HR	0.92		0.83		0.85	
95% CI	0.62 to 1.37		0.65 to 1.05		0.49 to 1.47	
P (log-rank test)	.6798		.1230		.5594	

Abbreviations: OS, overall survival; MSKCC, Memorial Sloan-Kettering Cancer Center; IFN, interferon alfa-2a; HR, hazard ratio.

Table 3. OS by Postprotocol Therapy

Therapy	No. of Patients		Median OS (months)		HR	95% CI
	Bevacizumab + IFN	IFN + Placebo	Bevacizumab + IFN	IFN + Placebo		
All patients	327	322	23.3	21.3	0.86	0.72 to 1.04
TKI*	113	120	38.6	33.6	0.80	0.56 to 1.13
Sunitinib*	83	92	43.6	39.7	0.88	0.58 to 1.35
Sorafenib*	60	50	38.6	30.7	0.73	0.44 to 1.20
Second-line TKI†	96	81	38.6	33.2	0.77	0.51 to 1.15

Abbreviations: OS, overall survival; IFN, interferon alfa-2a; HR, hazard ratio; TKI, tyrosine kinase inhibitor.
*Subsequent therapy was defined as more than one treatment given as postprotocol therapy, any line.
†Second-line TKI therapy was given for one line only immediately after study therapy.

response to therapy, and duration of first PFS are taken into account to ensure that results can be compared.

The phase III AVOREN and CALGB 90206 trials of bevacizumab are not the first to report statistically nonsignificant increases in OS despite significant PFS benefit. A phase III trial of sunitinib reported an improvement in OS that did not achieve statistical significance (median OS, 26.4 months for sunitinib *v* 21.8 months for IFN; HR = 0.82; $P = .051$, unstratified),[24] although PFS was the primary end point, in contrast to AVOREN and CALGB 90206. Comparison of HR values for OS in these trials may be more appropriate because they reflect the difference in OS over the duration of the trial rather than at one specific time point. On the basis of stratified analyses, outcomes seem similar (14% reduction in the risk of death with bevacizumab plus IFN compared with IFN plus placebo *v* 18% with sunitinib).

Although the most likely reason for the lack of significance was the availability and extensive use of anticancer therapies after progression, differences in study population, study design, and protocol-specified treatment duration may also be relevant. For instance, in the phase III sunitinib trial, both sunitinib and IFN treatment to progression was mandated, whereas in AVOREN, the intention was to administer bevacizumab until progression and IFN for 52 weeks. Thus, if IFN was stopped as a result of toxicity, bevacizumab could be continued; 125 patients continued bevacizumab for a median of 83 days (range, 1 to 399 days) after IFN withdrawal. On the basis of the biologic activity of VEGF throughout tumor progression and particularly in renal cell carcinoma where HIF overexpression is the main driver of tumor growth, continuous VEGF inhibition before and potentially after progression using bevacizumab and VEGF receptor TKIs may be a reasonable treatment approach.

Data from the preplanned exploratory analyses of the subgroups of patients without liver metastases, with lung metastases, or younger than 65 years of age apparently showing greater survival benefit are difficult to assess because the corresponding analyses of CALGB 90206 did not show similar results and were conflicting in the case of the analysis of the impact of liver metastases.

With increases in patient survival and long-term use of therapy, tolerability is an increasingly important consideration in selecting therapy for mRCC.[25] Although the toxicity of IFN has to be considered when using bevacizumab, its AEs seem to be manageable by dose reduction without affecting response rates, PFS, or OS when used in combination with bevacizumab.[7]

In conclusion, final data from the phase III AVOREN trial confirm that bevacizumab plus IFN remains a first-line standard of care for patients with mRCC. Considering the overall sequence of therapy when selecting first-line therapy for patients with mRCC may allow rational development of regimens to optimize patient benefit. Further well-designed, prospective trials are needed to indicate which therapies in which sequence provide greatest benefit in individual patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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