Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial

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Summary

Background Vascular endothelial growth factor (VEGF) inhibition is a valid therapeutic approach in renal cell carcinoma. Therefore, an investigation of the combination treatment of the humanised anti-VEGF monoclonal antibody bevacizumab with interferon alfa was warranted.

Methods In a multicentre, randomised, double-blind, phase III trial, 649 patients with previously untreated metastatic renal cell carcinoma were randomised to receive interferon alfa-2a (9 MIU subcutaneously three times weekly) and bevacizumab (10 mg/kg every 2 weeks; n=327) or placebo and interferon alfa-2a (n=322). The primary endpoint was overall survival. Secondary endpoints included progression-free survival and safety. An interim analysis of overall survival was prespecified after 250 deaths. On the basis of new second-line therapies that became available while the trial was in progress, which could have confounded analyses of overall survival data, we agreed with regulatory agencies that the pre-planned final analysis of progression-free survival would be acceptable for regulatory submission. The protocol was amended to allow the study to be unblinded at this point. The final analysis of progression-free survival is reported here. Efficacy analyses were done by intention to treat. This trial is registered with centerwatch.com, number BO17705E.

Findings 325 patients in the bevacizumab plus interferon alfa group and 316 in the placebo plus interferon alfa group received at least one dose of study treatment. At the time of unblinding, 230 progression events had occurred in the bevacizumab plus interferon alfa group and 275 in the control group; there were 114 deaths in the bevacizumab plus interferon alfa group and 137 in the control group. Median duration of progression-free survival was significantly longer in the bevacizumab plus interferon alfa group than it was in the control group (10·2 months *vs* 5·4 months; HR 0·63, 95% CI 0·52–0·75; p=0·0001). Increases in progression-free survival were seen with bevacizumab plus interferon alfa irrespective of risk group or whether reduced-dose interferon alfa was received. Deaths due to adverse events were reported in eight (2%) patients who received one or more doses of bevacizumab and seven (2%) of those who did not receive the drug. Only three deaths in the bevacizumab arm were considered by investigators to be possibly related to bevacizumab. The most commonly reported grade 3 or worse adverse events were fatigue (40 [12%] patients in the bevacizumab group *vs* 25 [8%] in the control group) and asthenia (34 [10%] *vs* 20 [7%]).

Interpretation The combination of bevacizumab with interferon alfa as first-line treatment in patients with metastatic renal cell carcinoma results in a significant improvement in progression-free survival, compared with interferon alfa alone.

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Introduction

Renal cell carcinoma is diagnosed in more than 120 000 patients in Europe and the USA every year, and causes about 60 000 deaths.[1] Most of these cases are clear-cell carcinomas.[2] The 5-year survival rate for patients with stage IV renal cell carcinoma is 10–20%, and a third of patients have stage IV disease at presentation.[3,4] A further 20–30% of patients with initially localised disease relapse after nephrectomy.[5]

Most patients with clear-cell renal cell carcinoma have mutations of the von Hippel–Lindau tumour suppressor gene, leading to increased transcription of several hypoxia-inducible genes.[6] One of these factors is the vascular endothelial growth factor (VEGF), a potent proangiogenic molecule that inhibits dendritic cell maturation and tumour cell apoptosis, as well as stimulating tumour angiogenesis.[7–9] These findings stimulated the clinical assessment of strategies that inhibit the activity of VEGF.

Metastatic renal cell carcinoma is highly resistant to conventional treatment.[4] Until recently, the standard systemic treatment for metastatic renal cell carcinoma was immunotherapy with either interleukin 2 or interferon, both of which produce modest overall response rates (<20%) along with substantial toxicities, although occasional, durable complete responses are seen. Randomised trials have shown that interferon results in a median overall survival of 13 months[10] and high-dose interleukin 2 can achieve curative outcomes in 5–10% of patients.[11,12] The tyrosine kinase inhibitors sorafenib and sunitinib have also been approved for the treatment of advanced renal cell carcinoma. In patients

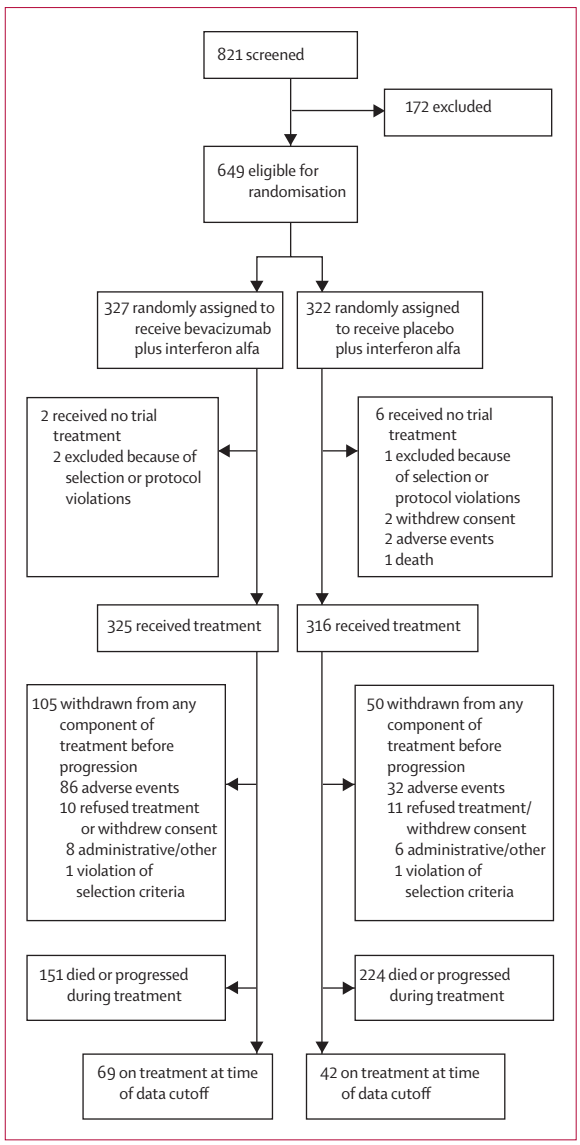

Figure 1: **Trial profile**

who have failed interferon or interleukin 2, sorafenib doubles progression-free survival compared with placebo[13,14] and sunitinib results in an overall response rate of 42%.[15,16] More recently, sunitinib has been shown to significantly increase progression-free survival compared with interferon (11 months *vs* 5 months; p<0·001) in previously untreated patients.[17] Despite this progress in the management of metastatic renal cell carcinoma over the past 2 years, only the mammalian target of rapamycin (mTOR) inhibitor temsirolimus has been shown to improve overall survival compared with interferon alone, in patients with poor prognosis and previously untreated non-clear-cell tumours.[18]

Bevacizumab is a humanised monoclonal antibody that inhibits VEGF. The drug has shown a clinical benefit in phase II studies of metastatic renal cell carcinoma: bevacizumab monotherapy resulted in a median progression-free survival of 8·5 months in previously untreated patients; monotherapy increased the median time to disease progression compared with placebo (4·8 months *vs* 2·5 months; hazard ratio [HR] 0·39, p<0·001) in patients with previously treated disease.[19,20] A number of patients have had durable responses lasting 3–5 years with continued bevacizumab therapy.[21] The efficacy and safety profiles of bevacizumab when administered in combination with a wide range of chemotherapeutic and targeted agents in several other tumour types are well defined.[20,22–26]

These data, together with the long-established role of immunotherapy as the first-line standard of care for metastatic renal cell carcinoma, formed a strong rationale to examine bevacizumab in combination with interferon. The aim of this study was to determine whether first-line bevacizumab plus interferon improves efficacy compared with interferon alone.

Methods

Patients

Patients were eligible for enrolment if they were aged 18 years or older, with measurable or non-measurable tumour (according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria[27]), had predominantly (>50%) clear-cell renal cell carcinoma (based on routine assessment of tumour histopathology by local pathologists with the American Joint Committee on Cancer/International Union Against Cancer [AJCC/UICC] classification[28]), and had undergone nephrectomy or partial nephrectomy (if resection margins were clearly negative of disease). Patients had to have a Karnofsky performance status of 70% or more and normal hepatic, haematopoietic, and renal function. Only minimal proteinuria at baseline was allowed (≤0·5 g of protein every 24 h). Exclusion criteria included prior systemic treatment for metastatic renal cell carcinoma, recent major surgical procedures, evidence of brain metastases, ongoing full-dose oral or parenteral anticoagulant or anti-platelet aggregation treatment, uncontrolled hypertension on medication, clinically significant cardiovascular disease, or chronic corticosteroid treatment.

The trial was approved by the institutional review board or ethics committee of each participating centre and was done in accordance with the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice. All patients provided written informed consent.

Procedures

In this international, multicentre, randomised, double-blind phase III trial, patients were randomised in a 1:1 fashion to receive bevacizumab plus interferon alfa or to receive placebo plus interferon alfa. Randomisation was done centrally with a block design procedure and stratified according to country and Memorial

Sloan-Kettering Cancer Center (MSKCC) risk group (favourable, intermediate, or poor). The patient randomisation list was kept in a secure location and was not available to any person directly involved in the study other than the interactive voice recognition system provider and the randomisation manager at Roche.

Bevacizumab (F Hoffmann-La Roche Ltd, Basel, Switzerland) 10 mg/kg or placebo was administered intravenously every 2 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. No dose reduction was permitted. Interferon alfa-2a (F Hoffmann-La Roche Ltd, Basel, Switzerland) 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. An initial dose of less than 9 MIU was permitted as long as the recommended dose was reached within the first 2 weeks of treatment. Dose reduction of interferon alfa to 6 MIU or 3 MIU was allowed to manage adverse events of grade 3 or worse that were attributable to interferon alfa according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[29] Other antineoplastic therapies were allowed subsequent to progression or toxicity.

The primary endpoint of the trial was overall survival, defined as the time between the date of randomisation and death due to any cause. Patients without an event were censored on the day of last follow-up assessment or the day of last study drug administration if no follow-up assessment was done. Secondary endpoints included progression-free survival (time between randomisation and first documented disease progression or death due to any cause), overall response rates, and safety. The dose intensity of bevacizumab/placebo and of interferon alfa was calculated as the amount of drug administered versus the amount that should have been administered over the course of treatment.

Tumour measurements and assessments with imaging studies were done every 8 weeks up to week 32 and every 12 weeks thereafter until disease progression. Tumour response was assessed by the investigator with RECIST.[27] Non-measurable lesions were used to define complete responses and disease progression only. Responses had to be confirmed by a second assessment 4 weeks or more after the first response was recorded.

Safety was assessed on an ongoing basis by documentation of adverse events (CTCAE version 3.0[29]), physical examination, electrocardiography, urinalysis, and measurement of blood pressure. Patients who developed grade 3/4 hypertension underwent weekly monitoring. Patients had 24 h urine collection if protein was observed with a dipstick analysis (≥1+ in first 80 patients; 2+ in subsequent patients).

Statistical analysis

The study was designed to have 80% power for the log rank test to detect an improvement in overall survival with an HR of 0·76, assuming an improvement of median survival from 13 months to 17 months, at a two-sided alpha level of 0·05. The planned sample size was 638 patients, with 445 deaths required for the final analysis. One interim analysis was planned, after about 250 deaths had been observed. To ensure that the overall significance level remained at 5%, the interim analysis followed a sequential alpha spending function approach, using an O'Brien-Fleming boundary.[30] With the planned interim analysis at 56% of the events, this approach resulted in a two-sided alpha level of 0·0056 for the interim analysis and 0·0482 for the final analysis.

During the trial, it became apparent that the results of a similar trial (CALGB 90206, open label) and new second-line therapies for renal cell carcinoma would become available while the trial was in progress.[13–16] We anticipated that the primary objective (overall survival) would be confounded by patients in the control group who progressed subsequently receiving these new second-line options or crossing over to receive bevacizumab, even though this scenario was not envisaged in the protocol. Therefore, an agreement with regulatory agencies was reached that presentation of the results of the pre-planned final analysis of progression-free survival before data for the primary

	Bevacizumab plus interferon alfa (N=327)	Placebo plus interferon alfa (N=322)
Sex		
Male	222 (68%)	234 (73%)
Female	105 (32%)	88 (27%)
Age (years)	61 (30–82)	60 (18–81)
Karnofsky performance status		
100	144 (44%)	124 (39%)
90	105 (32%)	126 (39%)
80	58 (18%)	50 (16%)
70	20 (6%)	22 (7%)
Sites of metastases*		
Lung†	192 (62%)	179 (59%)
Liver†	57 (18%)	56 (19%)
Lymph nodes†	107 (34%)	107 (36%)
Bone‡	58 (18%)	65 (20%)
Number of disease sites	2 (1–5)	2 (1–6)
MSKCC risk score		
Favourable	87 (27%)	93 (29%)
Intermediate	183 (56%)	180 (56%)
Poor	29 (9%)	25 (8%)
Not available	28 (9%)	24 (7%)
Metastatic renal cell carcinoma >12 months after nephrectomy	105 (32%)	104 (32%)

Data are n (%) or median (range). *n=312 in bevacizumab plus interferon alfa group; n=301 in placebo plus interferon alfa group. †Location of target lesions. ‡Location of non-target lesions.

Table 1: **Baseline demographic and clinical characteristics**

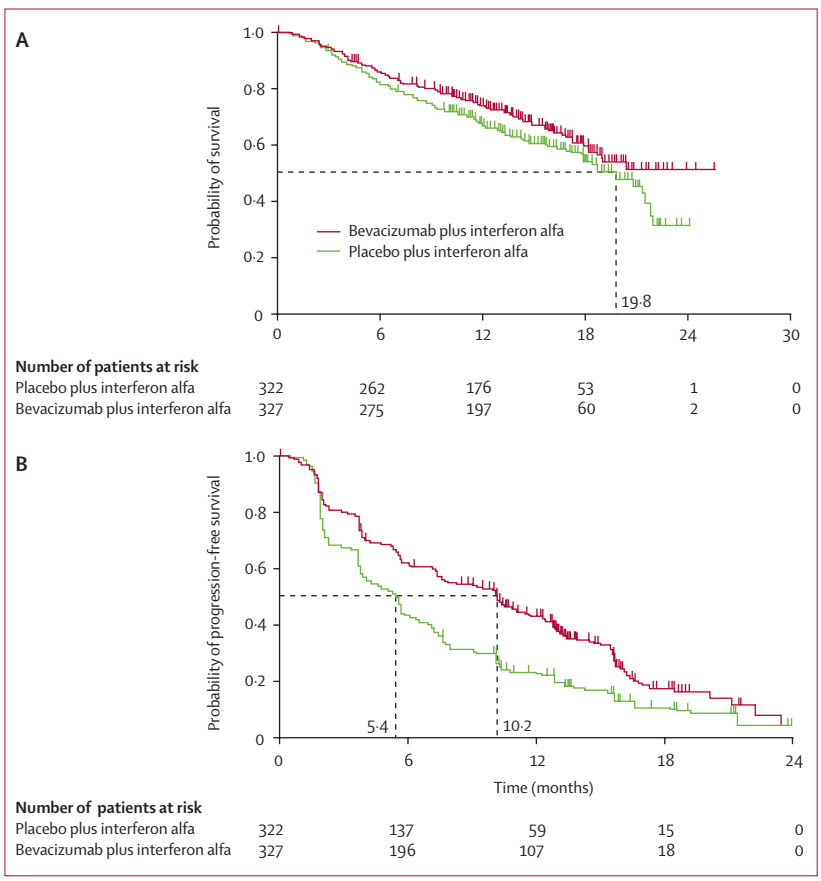

***Figure 2*: Kaplan-Meier estimates of (A) overall survival and (B) progression-free survival**
Interim analysis of overall survival based on 251 of 450 scheduled events. Median overall survival had not been reached in the bevacizumab plus interferon alfa group. Final analysis of progression-free survival based on 505 progression events.

endpoint were mature would be acceptable as the basis of the study to support regulatory submissions. The protocol was subsequently amended to unblind the study at the time of the final progression-free survival analysis, since it was anticipated that progression-free survival data would be mature at that time. The data and safety monitoring board had the responsibility for assessing the results of the interim analysis. After reviewing the final progression-free survival results and the interim overall survival results, the data and safety monitoring board recommended that patients in the control group who had not progressed should be crossed over to receive bevacizumab. Patients are still being followed for survival; mature overall survival data will be reported when the prespecified number of deaths has occurred.

Efficacy was assessed by intention to treat; all patients who were randomised and exposed to study medication were included in safety analyses. For the purposes of safety analysis, patients were assigned to treatment groups on the basis of what they actually received, with patients in the placebo arm receiving one or more doses of bevacizumab being assigned to the bevacizumab arm. SAS version 8.2 was used for statistical analysis.

This trial is registered with centerwatch.com with the number BO17705E.

Role of the funding source

The funding source contributed to the design, conduct, data collection, and data analysis. All authors had access to the primary data and take responsibility for the accuracy and completeness of the data reported. The corresponding author had final responsibility for the decision to submit for publication.

Results

821 patients were screened, of whom 649 were randomised to one of the two treatment groups between June, 2004, and October, 2005 (figure 1). Two (0·6%) patients in the bevacizumab plus interferon alfa group and six (2%) in the placebo plus interferon alfa group withdrew before treatment. All remaining patients (n=641) received at least one dose of study treatment. The arms were balanced with regard to baseline disease and demographic characteristics (table 1).

At the time of clinical data cutoff (Sept 8, 2006), 230 progression events had occurred in the bevacizumab plus interferon alfa group and 275 in the control group, with 114 and 137 deaths, respectively. Median follow-up at data cutoff was 13·3 (0–25·6) months in the bevacizumab plus interferon alfa group and 12·8 (0–24·2) months in the control group. After disease progression, 49 (15%) patients in the bevacizumab plus interferon alfa group and 64 (20%) in the control group received second-line therapy with tyrosine kinase inhibitors to date.

The median duration of bevacizumab treatment in the bevacizumab plus interferon alfa group was almost twice as long as that of placebo treatment in the control group (9·7 [range 0–24·4] months *vs* 5·1 [0–24·0] months). Similarly, the median duration of interferon alfa treatment in the bevacizumab plus interferon alfa group was longer than that in the control group (7·8 [0–13·9] months *vs* 4·6 [0·2–12·6] months). Median bevacizumab/placebo dose intensity was 92% (range 24–122; mean 88%) in the bevacizumab plus interferon alfa group and 96% (39–110; 91%) in the control group; the median dose intensity for interferon alfa was 91% (4–150; 83%) in the bevacizumab plus interferon alfa group and 96% (28–120; 89%) in the control group. 105 (31%) of the 337 patients who received one or more doses of bevacizumab and 43 (16%) of the 304 patients who did not receive bevacizumab remained on therapy for more than 1 year.

At the time of data cutoff, 251 (56%) of the 445 deaths required for the final analysis of overall survival to be powered adequately had occurred. Thus, the data presented for overall survival are not mature. Median overall survival has not yet been reached in the

bevacizumab plus interferon alfa group; median overall survival was 19·8 months in the control group (HR 0·79, 95% CI 0·62–1·02; unstratified log-rank test p=0·0670; figure 2). The pre-planned exploratory analysis of overall survival stratified by MSKCC risk group and region was similar to the unstratified analysis and showed an improvement in the bevacizumab plus interferon alfa group, relative to the control group (0·75, 0·58–0·97; p=0·0267).

Median progression-free survival was 10·2 months in the bevacizumab plus interferon alfa group, compared with 5·4 months in the control group (HR 0·63, 95% CI 0·52–0·75; p=0·0001; figure 2). An analysis stratified by MSKCC risk group and region confirmed these results (0·61, 0·51–0·73; p<0·0001). Furthermore, censoring patients on the day they received subsequent antineoplastic therapy had no apparent effect on the efficacy of bevacizumab, producing a comparable HR (0·62, 0·52–0·74). These findings were consistent with a significantly longer time to disease progression (median 10·2 months *vs* 5·5 months; HR 0·61, 95% CI 0·51–0·73; p=0·0001) and time to treatment failure (7·7 months *vs* 4·4 months; 0·73, 0·62–0·87; p=0·0003) in the bevacizumab plus interferon alfa group than in the control group.

The overall response rate was significantly higher with bevacizumab plus interferon alfa than with placebo plus interferon alfa (p=0·0001; table 2). Overall, 214 (70%) patients reported tumour shrinkage in the bevacizumab plus interferon alfa group, compared with 112 (39%) of those in the control group. The median duration of response was longer in the bevacizumab plus interferon alfa group than in the control group (table 2). Duration of stable disease was longer and time to response was shorter in the bevacizumab plus interferon alfa group than in the control group (table 2).

Progression-free survival was longer in the bevacizumab plus interferon alfa group than in the placebo plus interferon alfa group, irrespective of MSKCC risk group: 12·9 months versus 7·6 months in the favourable prognosis group, 10·2 months versus 4·5 months in the intermediate prognosis group, and 2·2 months versus 2·1 months in the poor prognosis group (figure 3); a test of interaction indicated that the treatment effect was consistent across the MSKCC risk groups (p=0·508). An improvement in progression-free survival in subgroups defined with other baseline or disease characteristics was also seen in the bevacizumab plus interferon alfa group (figure 3). Analysis of overall survival in these subgroups revealed HR of 0·69 (95% CI 0·36–1·33) in the favourable prognosis group, 0·74 (0·53–1·02) in the intermediate prognosis group, and 0·87 (0·48–1·56) in the poor prognosis group.

The recommended dose of interferon alfa was 9 MIU three times a week. During the course of treatment, the dose was reduced to 6 or 3 MIU in 124 (40%) patients in the bevacizumab plus interferon alfa group and 94 (30%) patients in the control group. An exploratory analysis indicated that patients who reduced their dose of interferon alfa at any time (n=131) and maintained a dose of 6 or 3 MIU thereafter, might also benefit from bevacizumab treatment (progression-free survival rate for patients in the bevacizumab group at 1 year was 43% compared with 52% in the dose-reduced patients).

Adverse events occurred in 328 (97%) of those patients who received at least one dose of bevacizumab and 287 (94%) of those who did not receive bevacizumab. Serious adverse events were reported in 98 (29%) patients who received bevacizumab and 50 (16%) of those who did not. The proportion of patients who experienced an adverse event that led to treatment discontinuation was higher in the bevacizumab plus interferon alfa group than in the control group (table 3). Median Karnofsky

	Bevacizumab plus interferon alfa (N=306)	Placebo plus interferon alfa (N=289)
Overall response*	96 (31%)	37 (13%)
Complete response	4 (1%)	6 (2%)
Partial response	92 (30%)	31 (11%)
Stable disease	141 (46%)	144 (50%)
Disease progression	61 (20%)	95 (33%)
Not assessable	8 (3%)	13 (5%)
Duration of response (months)	13·5 (1·8–20·3)	11·1 (3·7–19·5)
Duration of stable disease (months)	10·1 (2·1–23·5)	7·2 (2·3–24·0)
Time to response (months)	2·2 (2–14)	3·7 (1–10)

Data are median (range) or n (%). Only patients with measurable disease at baseline are included in the analysis of response rate. *p=0·0001 for comparison of overall response.

Table 2: **Tumour response***

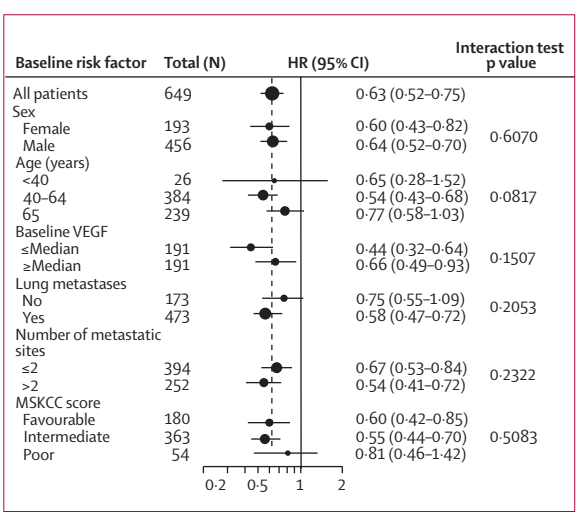

Figure 3: **Subgroup analysis of progression-free survival**

	All grades		Grade 3 or worse	
	Bevacizumab plus interferon alfa (N=337)	Placebo plus interferon alfa (N=304)	Bevacizumab plus interferon alfa (N=337)	Placebo plus interferon alfa (N=304)
Adverse events that occurred with a frequency of 2% or more				
Fatigue	110 (33%)	83 (27%)	40 (12%)	25 (8%)
Asthenia	109 (32%)	84 (28%)	34 (10%)	20 (7%)
Proteinuria	59 (18%)	8 (3%)	22 (7%)	0 (0%)
Neutropenia	24 (7%)	20 (7%)	15 (4%)	7 (2%)
Hypertension	88 (26%)	28 (9%)	11 (3%)	2 (<1%)
Bleeding	112 (33%)	28 (9%)	11 (3%)	1 (<1%)
Influenza-like illness	82 (24%)	77 (25%)	10 (3%)	6 (2%)
Anorexia	121 (36%)	92 (30%)	10 (3%)	8 (3%)
Depression	41 (12%)	31 (10%)	10 (3%)	4 (1%)
Anaemia	33 (10%)	41 (13%)	9 (3%)	17 (6%)
Pyrexia	152 (45%)	130 (43%)	8 (2%)	2 (<1%)
Thrombocytopenia	21 (6%)	12 (4%)	7 (2%)	3 (<1%)
Headache	79 (23%)	49 (16%)	7 (2%)	4 (1%)
Diarrhoea	69 (20%)	47 (15%)	7 (2%)	3 (<1%)
Venous thromboembolic event	10 (3%)	3 (<1%)	6 (2%)	2 (<1%)
Dyspnea	44 (13%)	38 (13%)	2 (<1%)	7 (2%)
Additional targeted adverse events				
Arterial thromboembolic event	5 (1%)	2 (<1%)	4 (1%)	1 (<1%)
Gastrointestinal perforation	5 (1%)	0 (0%)	4 (1%)	0 (0%)
Wound healing complications	5 (1%)	3 (1%)	2 (<1%)	0 (0%)
Congestive heart failure	1 (<1%)	1 (<1%)	1 (<1%)	0 (0%)
Adverse events leading to study discontinuation				
Any study drug	95 (28%)	37 (12%)	..	..
Bevacizumab/placebo	63 (19%)	17 (6%)	..	..
Interferon alfa	76 (23%)	35 (12%)	..	..
Death not due to disease progression	8 (2%)	7 (2%)	..	..

Data are n (%). *Adverse events were reported until up to 28 days after the last dose of study drug; deaths were reported irrespective of when they occurred.

Table 3*: Overview of adverse events

performance status did not deteriorate in either treatment arm during the study (median score at baseline and last day of treatment 90% in both groups) and the use of medication for pain relief (analgesics, corticosteroids, non-steroidal anti-inflammatory drugs, opioids) was similar in the two groups (data not shown).

There were 203 grade 3 or worse adverse events reported by patients who received one or more dose of bevacizumab, compared with 137 reported by those who did not receive the drug. In both groups the most commonly reported grade 3 or worse adverse events were established interferon-related toxicities (eg, fatigue, asthenia, and neutropenia). The incidence of interferon-related toxicities was 10% higher per patient-year in the bevacizumab plus interferon alfa group than in the control group (data not shown). An increase in bevacizumab-related toxicities (eg, proteinuria, bleeding, and hypertension) was seen in the bevacizumab plus interferon alfa group only.

Grade 3 and 4 adverse events in patients who received bevacizumab included four gastrointestinal perforations (1%; three grade 4) and 10 thromboembolic events (3%; four grade 4). Seven (2%) patients with hypertension of any severity discontinued treatment due to this event and 16 (5%) patients discontinued due to proteinuria of any severity. A higher proportion of patients were withdrawn from the bevacizumab or placebo treatment component in the bevacizumab plus interferon alfa group than in the control group (table 3); proteinuria, hypertension and gastrointestinal perforation were the most common reasons.

Deaths due to adverse events were reported in eight (2%) patients who received bevacizumab and in seven (2%) of those who did not receive the drug. Only three (<1%) deaths of the patients who received bevacizumab—two bleeding events and one gastrointestinal perforation—were deemed to be possibly related to bevacizumab: a gastric perforation in a 67-year-old woman with metastases to the colon who died 9 days after surgery for a gastroduodenocolonic fistula; haemoptysis in a 73-year-old woman with extensive lung metastases; and a rupture of a pre-existing abdominal aneurysm that was present at study entry in a 68-year-old man. The other causes of death of those who received the study drug were myocardial infarction, atrial fibrillation, pneumonia, hepatic failure in a patient with a 12-year history of active hepatitis B infection, and multiresistant staphylococcal sepsis.

Discussion

This multicentre, randomised, double-blind phase III study suggests that the combination of bevacizumab with interferon alfa in patients with metastatic clear-cell renal cell carcinoma produces significant and clinically meaningful improvements in progression-free survival and overall response rates compared with placebo plus interferon alfa. Since this report is based on the results of an interim analysis of overall survival and final analysis of progression-free survival, overall survival data are immature. Progression-free survival is a meaningful endpoint in this setting given the potential for subsequent treatments to reduce the effect of a new therapy on overall survival. Safety data are consistent with previous observations in patients with cancer treated with bevacizumab or interferon alfa alone. These data, in combination with previous phase II data for bevacizumab, indicate that bevacizumab plus interferon alfa is an option for first-line treatment for patients with metastatic renal cell carcinoma.

The current estimate of overall survival for the control group is considerably greater than that seen in previous trials.[10] On the basis of studies done in the 1990s and available at the time of initiation of this trial, median overall survival in the control group was anticipated to be around 13 months. Subsequently, supportive care and second-line therapies have improved, extending the

overall survival for this group of patients. This effect is supported by the results of this trial, as well as in a similar patient group in another recent phase III trial (median overall survival 17·7 months).[31]

Bevacizumab treatment until progression, recommended in this study, has been used in all bevacizumab trials to date, and has been shown to provide a survival benefit in phase III trials of metastatic colorectal cancer[23] and advanced non-small-cell lung cancer.[25] By contrast, the recommended duration of treatment with interferon alfa, to progression or for a maximum of 52 weeks, was based on the observation that few patients receive more than 12 months of treatment with interferon alfa. That the duration of bevacizumab therapy was significantly longer than that of placebo, and also that interferon alfa was administered for longer in the bevacizumab plus interferon alfa group than in the placebo plus interferon alfa group, is notable.

Treatment of metastatic renal cell carcinoma with interferon alfa in patients who are not in the good prognosis MSKCC risk group has become controversial, and the arrival of new tyrosine kinase inhibitors has led some to question its role.[32–34] The results of this study demand reassessment of this position. The improvement in progression-free survival was seen in all patients, irrespective of MSKCC risk group, including those in the intermediate prognosis MSKCC risk group, who derive moderate benefit from interferon alfa. Furthermore, the study applied a dose reduction scheme for interferon alfa to reduce the occurrence of recognised interferon-associated toxicities (eg, flu-like symptoms experienced by most patients).[35] Interestingly, bevacizumab provided an improvement in duration of progression-free survival in patients who received the recommended, as well as reduced doses of interferon alfa. Therefore, the combination of interferon alfa with bevacizumab could allow more flexible modification of the dose of interferon in some patients, which might translate into safety and tolerability benefits. This finding needs to be confirmed in future studies, not least in view of recent trials showing the clinical benefit of low-dose interferon alfa in melanoma, where patients were treated for 4–5 years.[36]

Bevacizumab has a well-defined safety profile, based on an extensive clinical trial programme that has included more than 10 000 patients to date.[19–26] The safety profile of the combination of bevacizumab and interferon alfa was consistent with toxicities seen with each of these agents; grade 3/4 events were manageable with standard therapies.

The overall occurrence of adverse events and events leading to withdrawal of study treatment was higher in the bevacizumab plus interferon alfa group than in the placebo plus interferon alfa group, which was in part due to the adverse events known to occur with bevacizumab therapy, as well as a small increase in interferon-related toxicities. The increase could also be a result of the longer duration on treatment (per protocol until progression) and lower dropout rate due to progressive disease in the bevacizumab plus interferon alfa group, compared with the control group. Since more patients in the bevacizumab plus interferon alfa group were not treated until progression, the analysis of progression-free survival is conservative for the activity of bevacizumab. This analysis could only be biased towards bevacizumab if patients in the bevacizumab plus interferon alfa group had gone on to receive other antineoplastic therapies when withdrawing for reasons other than progressive disease, which increased the time to progression. However, the use of second-line treatments has not confounded the results because censoring patients on the day they received subsequent antineoplastic therapy resulted in similar HR for progression-free survival in this patient group and the full population. On the basis of these results, second-line therapies did not affect the treatment effect of bevacizumab on progression-free survival, suggesting that these data are robust.

A bevacizumab monotherapy arm would have been useful to determine the respective roles of each drug when used in combination. However, at the time of trial design, bevacizumab monotherapy had not been examined extensively in a large clinical trial, and such an arm was considered unethical. The lack of independent radiological review could also be considered a limiting factor. However, due to the double-blind design, the likelihood that the results would have changed is very low, as was shown in another large trial in renal cell carcinoma.[13] Even in open-label trials, independent review has had little effect on the results.[17] Furthermore, the progression-free survival observed in the control group of our study is consistent with that reported in the open-label sunitinib trial,[17] suggesting that progression-free survival in the combination arm is unbiased.

The data presented here raise intriguing questions regarding the future of therapy for metastatic renal cell carcinoma. The availability of a variety of active agents provides increased treatment options and the opportunity to provide several lines of therapy and improved survival. In metastatic colorectal cancer, the use of all available active therapeutic agents is essential to maximise survival.[23,37] Available data indicate that sunitinib and sorafenib have activity when used after bevacizumab[38,39] or each other;[40] that sunitinib, temsirolimus, and sorafenib can be combined with bevacizumab;[41–43] and that interferon alfa alone is not an effective second-line treatment option. The best treatment strategy in metastatic renal cell carcinoma will probably be defined by ongoing and future trials, which are expected to assess combinations of the available novel agents.

Contributors

All authors have seen and approved the final version of the manuscript. BE, AP, PK, AR, SB, CS, CC, MF, BM, EB, VG JOB, IB, and AJG contributed patients to the trial. BE and NM contributed to the design and interpretation of the data. NM contributed to data management and statistical analysis.

AVOREN Trial investigators

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Conflict of interest statement

BE has consulted for and received honoraria from Roche, Bayer, Wyeth, Pfizer, Inate, and Antigenics. SB has consulted for Roche, Pfizer, Wyeth, and Bayer. AR has acted as an adviser for Bayer, Pfizer, GSK, Novartis, and Wyeth. NM is an employee of and owns stock of Roche. BM has received honoraria and research funding from Roche. All other authors declare that they have no conflict of interest.

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