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First-line bevacizumab combined with reduced dose interferon-α2a is active in patients with metastatic renal cell carcinoma

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Background: In patients with untreated metastatic renal cell carcinoma (mRCC), progression-free survival (PFS) was longer with bevacizumab + interferon (IFN)-α than IFN + placebo (AVOREN trial). In this hypothesis-generating study, subgroup analysis was carried out to determine the effect of IFN dose reduction.

Patients and methods: A total of 649 patients received IFN 9 MIU s.c. three times weekly plus bevacizumab 10 mg/kg or placebo every 2 weeks until disease progression. The IFN dose was reduced to 6 or 3 MIU with the development of IFN-attributed toxicity. Differences between treatment arms in PFS, response rate and tolerability were analysed in the reduced-dose group.

Results: IFN dose was reduced in 131 patients in the bevacizumab + IFN arm and 97 patients in the IFN + placebo arm during the trial. PFS rates in the bevacizumab + reduced-dose IFN group were comparable with the total population (Kaplan–Meier estimates of event-free rate at 1 year: 0.524 versus 0.427). Bevacizumab + reduced-dose IFN was well tolerated, with substantial decreases in the rate of adverse events following dose reduction.

Conclusion: This retrospective subgroup analysis suggests that the dose of IFN can be reduced to manage side-effects while maintaining efficacy in patients with mRCC receiving bevacizumab + IFN.

Key words: antiangiogenic therapy, bevacizumab, interferon-α, renal cell carcinoma, vascular endothelial growth factor (VEGF)

introduction

Renal cell carcinoma (RCC) is the most common malignant tumour of the kidney, with >120 000 cases diagnosed in Europe and the USA each year [1]; clear-cell carcinoma is the most predominant form [2]. Surgery is potentially curative in patients with localised disease, but therapeutic options are limited in patients with distant metastases [metastatic renal cell carcinoma (mRCC)].

RCC is highly resistant to chemotherapy [3]. Until recently, the standard first-line treatment was cytokine therapy using interferon (IFN)-α or interleukin-2. The use of IFN in mRCC is on the basis of the results of randomised trials demonstrating a significant improvement of survival [4, 5], while the registration of interleukin-2 in mRCC is on the basis of the durable responses observed in a small proportion of patients [6]. However, these agents are associated with considerable toxicity and are effective only in limited numbers of patients [4–8]. Thus, there is a need for alternative therapies and/or agents that can be used in combination with cytokines to improve efficacy or increase the number of patients likely to benefit.

A majority of patients with clear-cell RCC have mutations or epigenetic changes in the *von Hippel–Lindau* tumour suppressor gene, leading to increased transcription of several hypoxia-inducible genes that play a central role in tumorigenesis [9]. One of these genes is vascular endothelial growth factor (VEGF), a key mediator of angiogenesis that has other important effects that contribute to tumour growth, including inhibition of the host antitumour response [10–12].

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Bevacizumab (Avastin®) is a humanised mAb that binds specifically to VEGF and inhibits VEGF activity. Bevacizumab has significant clinical benefits in patients with the most common solid tumours, including metastatic colorectal carcinoma [13], metastatic breast carcinoma [14] and non-small-cell lung carcinoma [15]. Phase II trials demonstrated that bevacizumab has activity and is well tolerated in patients with both therapy-naive and pretreated mRCC [16, 17]. In addition, experience from clinical trials indicates that bevacizumab does not increase the toxicity of concomitantly administered chemotherapy [13–15].

Bevacizumab and IFN suppress tumour growth by direct and indirect mechanisms, and these two agents may have complementary and synergistic effects when combined, including down-regulation of oncogenes responsible for tumour progression, up-regulation of tumour suppressor genes, inhibition of angiogenesis and reduced activity of VEGF. Both agents have stimulatory effects on the immune response. For example, VEGF blockade, similarly to IFN treatment, has been shown to improve the function of dendritic cells [18, 19], which is suppressed in advanced cancer as a result of VEGF-mediated inhibition [20]. Preclinical evidence also indicates that IFN has antiangiogenic activity [21, 22] that is both dose and schedule dependent, with lower doses having greater antiangiogenic effects than 5- to 10-fold higher doses [23].

An optimal schedule of IFN in patients with mRCC has never been formally established. Most patients receive a dose of 9–18 MIU s.c. three times per week, but this regimen is associated with significant toxicity, most commonly fatigue and influenza-like symptoms, but also depression and asthenia [24]. Although some side-effects (e.g. depression) do not appear to be dose related, several studies have demonstrated that IFN dose reduction results in an improvement in overall tolerability and/or quality of life in patients with hepatitis C [25, 26] and mRCC [27, 28], but data indicate that efficacy may be impaired [29].

A phase III trial (AVOREN) has demonstrated that bevacizumab in combination with IFN 9 MIU three times weekly significantly improves response rate (31% versus 13%, $P = 0.0001$) and progression-free survival [PFS; 10.2 versus 5.4 months; hazard ratio (HR) = 0.63, $P = 0.0001$] compared with IFN + placebo [30]. This paper presents the results of a retrospective analysis of data from this trial, examining outcomes in patients in whom IFN dose was reduced to 6 or 3 MIU due to the occurrence of IFN-attributable toxicity.

patients and methods

design and patients

The AVOREN study was a randomised, double-blind, phase III study. The inclusion and exclusion criteria for this study are described in detail elsewhere [30]. Briefly, patients with predominantly (>50%) clear-cell mRCC were eligible for inclusion if they were aged ≥18 years, had a total or partial nephrectomy, had a Karnofsky performance status of ≥70% and had no central nervous system metastases and normal organ function.

The trial was approved by the institutional review board or ethics committee of each participating centre and was conducted in accordance with the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice. All patients provided written informed consent. The trial was sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

treatments and dose reduction for IFN

At study entry, patients were randomly assigned in a 1 : 1 ratio to receive IFN-α2a (Roferon®) s.c. for up to 1 year at a starting dose of 9 MIU three times per week plus either bevacizumab 10 mg/kg i.v. once every 2 weeks or placebo every 2 weeks. Bevacizumab and placebo were continued, with no modification of the dose or administration regimen, until disease progression, unacceptable toxicity or withdrawal of consent. Randomisation was stratified according to country and Memorial Sloan-Kettering Cancer Center (MSKCC) risk group.

A lower starting dose of IFN than 9 MIU was permitted as long as the 9 MIU dose was reached within the first 2 weeks of treatment. During treatment, IFN administration was withheld if the patient developed a grade 3 adverse event (AE) that was attributable to IFN. If that event resolved (to grade ≤1) within 28 days, IFN could be restarted at a dose of 6 MIU three times per week. If a patient on the 6 MIU dose developed a subsequent IFN-attributable grade 3 AE, a second dose reduction (to 3 MIU three times per week) was allowed if the event resolved within 28 days. Patients whose dose had been reduced could not have their dose increased during the study. Patients discontinued IFN if they had: grade 3 toxicity that did not resolve to grade ≤1 within 28 days; grade 3 toxicity after two dose reductions and unsuccessful schedule modification or any grade ≥4 toxicity. Bevacizumab was maintained at the starting dose irrespective of any IFN dose reduction (including discontinuation of IFN-α2a).

assessments

Tumour measurements and assessments using imaging techniques were carried out every 8 weeks until week 32 and every 12 weeks thereafter. Tumour response was assessed according to Response Evaluation Criteria in Solid Tumors. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 3.0 [31].

study end points and statistical analysis

Statistical considerations of sample size, study power and interim analyses and the analysis of end points in the total study population have been reported previously [30]. The end points for the present subgroup analysis were PFS, response rate and tolerability. PFS was defined as the time between randomisation and first documented disease progression or death due to any cause. Differences in efficacy and tolerability between the two treatments arms were analysed in those who received at least two doses of IFN 6 or 3 MIU after day 22 versus those who remained on IFN 9 MIU (full dose) and the total study population.

results

patient flow and baseline characteristics

From June 2004 to October 2005, 649 patients were randomised at 101 non-USA centres in 18 countries to receive bevacizumab + IFN ($n = 327$) or IFN + placebo ($n = 322$). In total, 322 patients in the bevacizumab + IFN arm and 314 in the IFN + placebo arm received at least one dose of IFN 9 MIU, which included 131 (41%) and 97 (31%) patients, respectively, who later received reduced doses of IFN (6 or 3 MIU) after day 22. Although the protocol specified that the dose of IFN should not increase after being reduced, a small number of patients ($n = 14$) increased back to 6 MIU after dose reduction to 3 MIU. Baseline patient characteristics,

Table 1. Patient demographics

	Reduced-dose group		Full-dose group		Total population[a]	
	Bevacizumab + IFN (n = 131)	IFN + placebo (n = 97)	Bevacizumab + IFN (n = 196)	IFN + placebo (n = 225)	Bevacizumab + IFN (n = 327)	IFN + placebo (n = 322)
Median age, years (range)	62 (34–82)	62 (28–81)	59 (30–81)	58 (18–80)	61 (30–82)	60 (18–81)
Sex, *n* (%)						
Male	90 (69)	69 (71)	132 (67)	165 (73)	222 (68)	234 (73)
Female	41 (31)	28 (29)	64 (33)	60 (27)	105 (32)	88 (27)
Tumour type, *n* (%)						
Clear cell	117 (89)	92 (95)	162 (83)	193 (86)	278 (88)	283 (88)
Mixed	14 (11)	5 (5)	34 (17)	32 (14)	39 (12)	39 (12)
Karnofsky performance status, *n* (%)						
100	60 (46)	39 (40)	84 (43)	85 (38)	144 (44)	124 (38)
90	38 (29)	36 (37)	67 (34)	90 (40)	105 (32)	126 (39)
80	24 (18)	17 (18)	34 (17)	33 (14)	58 (18)	50 (16)
70	9 (7)	5 (5)	11 (6)	17 (8)	20 (6)	22 (7)
MSKCC score, *n* (%)						
Favourable	34 (26)	33 (34)	53 (27)	60 (27)	87 (27)	93 (29)
Intermediate	70 (53)	52 (54)	113 (58)	128 (57)	183 (56)	180 (56)
Poor	14 (11)	5 (5)	15 (8)	20 (9)	29 (9)	25 (8)
Missing	13 (10)	7 (7)	15 (8)	17 (8)	28 (8)	24 (7)

[a]All randomised patients including those who did not receive study treatment within 22 days.
IFN, interferon; MSKCC, Memorial Sloan-Kettering Cancer Center.

including MSKCC score, were similar between the overall patient population, the reduced-dose group and the full-dose group (Table 1). Although IFN-related grade 3/4 toxicity was predefined as a requirement for IFN dose reduction, it was reported in only 44% and 41% of patients in the bevacizumab and placebo groups, respectively, in the 6 weeks before IFN dose reduction. In the majority of cases, IFN dose was reduced for reasons other than grade 3/4 IFN-related toxicity, including an accumulation of grade 2 IFN-related events or based on physician or patient preference.

dose reduction and duration

Of those patients who received reduced doses of IFN, 64% underwent one dose reduction (to 6 MIU), 31% underwent two dose reductions (to 6 MIU, then to 3 MIU) and 5% dose reduced directly to 3 MIU. These reduced doses were maintained while the patient remained on study therapy. The patients in the reduced-dose group spent on average 62% of the total IFN treatment duration at 6 or 3 MIU. The median duration of IFN treatment was longer in patients receiving bevacizumab + IFN than IFN + placebo in the reduced-dose group (9.9 versus 6.8 months), full-dose group (5.6 versus 3.6 months) and the total population (7.8 versus 4.6 months).

progression-free survival

Analysis of the total study population showed that the median duration of PFS in patients receiving bevacizumab + IFN was double that of patients receiving IFN + placebo (HR = 0.63, $P < 0.0001$) [30]. An exploratory analysis also showed a similar improvement in PFS with the addition of bevacizumab, both in patients who reduced IFN (HR = 0.63, $P = 0.0026$) (Figure 1) and those who maintained the full dose (HR = 0.69, $P = 0.0007$).

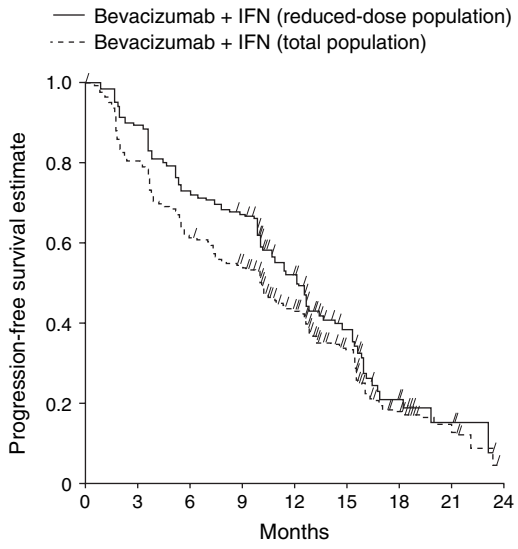

Figure 1. Kaplan–Meier analysis of PFS.

Kaplan–Meier estimates of PFS rates at 12 months in patients receiving bevacizumab + IFN were 0.524 [95% confidence

interval (CI) 0.436–0.613] in the reduced-dose group, 0.427 (95% CI 0.372–0.483) in the total population and 0.361 (95% CI 0.292–0.431) in the full-dose group. The 12-month PFS rate was consistent in patients who reduced to 3 MIU IFN [0.668 (95% CI 0.512–0.824)]. Furthermore, the 12-month PFS rates in patients who did not progress or die within 60 days of receiving their first dose of study medication (i.e. excluding those with early disease progression) were 0.554 (95% CI 0.463–0.645) and 0.465 (95% CI 0.383–0.547) in the reduced- and full-dose bevacizumab groups, respectively.

measurable tumour response and clinical benefit

The addition of bevacizumab to IFN provided a similar improvement in overall response rate in patients with measurable disease in the total study population (32% versus 13%) and the reduced- (34% versus 17%) and full-dose (31% versus 12%) groups (Table 2). The overall proportion of patients (both treatment arms) with stable disease was higher in the reduced-dose group, resulting in higher clinical benefit rates in this group (Table 2). The median duration of tumour response was similar when bevacizumab was combined with IFN in the reduced-dose group (13.6 months), full-dose group (13.5 months) and the total population (13.5 months); the corresponding median durations of response in patients who received IFN + placebo were 8.3, 14.0 and 11.1 months.

safety

The pattern of AE reporting showed that the majority of grade ≥3 AEs occurred during the first 3 months of treatment (data not shown). A marked reduction in grade 3/4 AEs was observed in the 6-week period after IFN dose reduction compared with the 6 weeks before reduction in patients receiving bevacizumab + reduced-dose IFN (44% versus 18%) and reduced-dose IFN + placebo (41% versus 10%). The trend towards improved safety 6 weeks after IFN dose reduction was consistent across the MSKCC risk categories.

Table 3 details the AEs that occurred within 6 weeks before and 6 weeks after IFN dose reduction, as well as those that occurred following IFN withdrawal in those patients in the bevacizumab + IFN arm who continued to receive bevacizumab for >30 days. These data indicate that both IFN dose reduction and withdrawal decrease the incidence of IFN-associated events, whereas the incidence of bevacizumab-associated events remains basically unchanged, as would be expected.

discussion

The results of the AVOREN trial have demonstrated that bevacizumab + IFN doubles the duration of median PFS compared with IFN + placebo in patients with mRCC [30]. The present retrospective analysis of data from this trial indicates that in patients with mRCC receiving bevacizumab + IFN, the dose of IFN can be reduced to manage the side-effects of this agent while maintaining a significant efficacy benefit over IFN + placebo that is similar to that observed in patients who received full-dose IFN.

The median response duration was longer in the placebo arm among patients who received full-dose IFN compared with those who received reduced-dose IFN (14.0 versus 8.3 months), but was similar in the bevacizumab arm regardless of the IFN dose (13.5 versus 13.6 months). All patients in the study received at least one dose of IFN 9 MIU (on average, 38% of the total IFN treatment duration was at this dose in patients who received reduced-dose IFN). Therefore, the trial design does not allow one to conclude that low-dose IFN alone is sufficient to induce tumour shrinkage. While reduced-dose IFN in combination with bevacizumab appears to be sufficient to sustain a tumour response, data currently indicate that reduced-dose IFN + placebo may be less effective in maintaining tumour response. To further examine this hypothesis, a prospective trial of bevacizumab + low-dose IFN is planned. The longer total duration of IFN therapy in the

Table 2. Measurable tumour response rates and clinical benefit

Parameter	Reduced-dose group		Full-dose group		Total population	
	Bevacizumab + IFN (n = 124[a])	IFN + placebo (n = 90[a])	Bevacizumab + IFN (n = 174[a])	IFN + placebo (n = 186[a])	Bevacizumab + IFN (n = 298[a])	IFN + placebo (n = 276[a])
Overall response, n (%)	42 (34)	15 (17)	54 (31)	22 (12)	96 (32)	37 (13)
	P = 0.0181		P < 0.0001		P < 0.0001	
Complete response	3 (2)	4 (4)	1 (1)	2 (1)	4 (1)	6 (2)
Partial response	39 (32)	11 (12)	53 (31)	20 (11)	92 (31)	31 (11)
	P = 0.0031		P < 0.0001		P < 0.0001	
Stable disease, n (%)	70 (57)	57 (63)	71 (41)	87 (47)	141 (47)	144 (52)
Clinical benefit, n (%)[b]	112 (90)	72 (80)	125 (72)	109 (59)	237 (79)	181 (65)
Progressive disease, n (%)	12 (10)	18 (20)	49 (28)	77 (41)	61 (21)	95 (34)
Median duration of tumour response (months)[c]	13.6	8.3	13.5	14.0	13.5	11.1

[a]Patients assessable.
[b]Clinical benefit = overall response rate + stable disease rate.
[c]Patients with measurable disease at baseline.
IFN, interferon.

Table 3. Overview of AEs in patients in whom IFN was reduced or withdrawn and bevacizumab was continued (events were collected in the 6 weeks before and the 6 weeks after IFN dose reduction and for patients in whom bevacizumab was continued for >30 days after IFN withdrawal)

Event, *n* (%)	Bevacizumab + IFN		
	Prior to IFN dose reduction (*n* = 136)	Post-IFN dose reduction (*n* = 136)	Post-IFN withdrawal (*n* = 87)
IFN-associated events			
Fatigue	28 (21)	11 (8)	1 (1)
Pyrexia	24 (18)	6 (4)	1 (1)
Anorexia	21 (15)	9 (7)	3 (3)
Nausea	17 (13)	10 (7)	3 (3)
Influenza-like illness	14 (10)	5 (4)	4 (5)
Asthenia	16 (12)	2 (1)	1 (1)
Neutropenia	12 (9)	5 (4)	2 (2)
Vomiting	9 (7)	8 (6)	3 (3)
Depression	9 (7)	5 (4)	1 (1)
Dyspnoea	7 (5)	3 (2)	2 (2)
Thrombocytopaenia	6 (4)	1 (<1)	1 (1)
Diarrhoea	6 (4)	7 (5)	7 (8)
Headache	6 (4)	5 (4)	1 (1)
Anaemia	3 (2)	2 (1)	1 (1)
Bevacizumab-associated events			
Hypertension	10 (7)	5 (4)	13 (15)
Bleeding	11 (8)	15 (11)	6 (7)
Proteinuria	4 (3)	2 (1)	13 (15)
Venous thromboembolic	1 (<1)	0 (0)	1 (1)
Arterial thromboembolic	0 (0)	0 (0)	3 (3)
Gastrointestinal perforation	0 (0)	0 (0)	0 (0)
Wound-healing complications	0 (0)	0 (0)	1 (1)
Other			
Congestive heart failure	0 (0)	0 (0)	0 (0)

AE, adverse event; IFN, interferon.

bevacizumab + IFN arm overall increased the probability that patients in this arm would need IFN dose reduction, which was reflected in the data (41% of patients in the bevacizumab + IFN arm and 31% in the IFN + placebo arm required dose reductions).

In the bevacizumab + IFN arm, the proportion of patients on reduced-dose IFN who were progression free at 12 months was greater than in those receiving full-dose IFN. A number of factors might have contributed to this. First, the duration of IFN treatment in those on a lower dose was longer, probably because this dose is better tolerated. Second, a selection effect might have occurred, with responding patients being treated for long enough to develop symptoms requiring IFN dose reduction; notably, excluding those with early disease progression reduced the difference in the percentages of patients progression free at 12 months between the reduced- and full-dose subgroups (55% and 47%). In addition, the existence of synergy between bevacizumab and lower doses of IFN cannot be excluded, as discussed below.

In clinical practice, the toxicity of IFN results in an inability to maintain IFN dose or withdrawal from therapy. Previous studies have reported a clear relationship between IFN dose and toxicity, and dose reductions led to decreased toxicity and better quality of life [24]. In the present study, we observed that the incidence of grade 3/4 events in the 6 weeks after IFN dose reduction was <20%, compared with at least 40% in the 6 weeks before dose reduction. This decrease appears largely to be due to a reduction in the incidence of IFN-associated events, in agreement with previous reports that reduced-dose IFN has a better safety profile than higher dose IFN. In many patients, IFN dose was reduced for reasons other than grade 3 or 4 adverse events, reflecting current medical practice. As this was not specified by the protocol, detailed information about the reason for IFN dose reduction in each case was not collected prospectively. Although grade 3 or 4 toxicity is relatively rare during IFN therapy, even grade 2 side-effects, especially if chronic, may have a profound impact on the quality of life of patients. Because of great interindividual differences in the tolerability of IFN therapy, a schedule that allows for individual dose modification would be of advantage for daily practice.

Data from this trial also indicate that bevacizumab + IFN does not induce cumulative toxicity, because the majority of AEs are observed early, within the first 3 months of therapy. However, while reduction of IFN dose has been consistently shown to result in the reduction of toxicity, it is widely believed that dose reduction could compromise efficacy. In an intrapatient trial of IFN dose escalation, objective responses were observed only in patients who attained a dose of 9 MU three times weekly or higher [29]. In contrast, the data from this analysis indicate that combining bevacizumab with reduced-dose IFN maintains the efficacy of the combination

regimen while allowing IFN-related toxicity to be effectively managed.

Based on its side-effects and limited efficacy as monotherapy [5, 32, 33], the advent of tyrosine kinase inhibitors has resulted in a decrease in the use of IFN. While the introduction of these new drugs represented substantial progress in therapy for mRCC, the list of drugs active in this tumour is still limited. For optimal management of mRCC, the concomitant or sequential utilisation of all available drugs may be required. In addition to demonstrating the activity of IFN with bevacizumab as first-line therapy for mRCC, the present data indicate that IFN dose may be tailored on the basis of tolerability in individual patients without compromising efficacy. Future studies should investigate the possibility of combining bevacizumab with other IFN regimens, including low-dose IFN or pegylated IFN.

Bevacizumab has been shown to be effective when given alone in patients with RCC (median PFS of 8.5 months) [16]. When combined with IFN, however, bevacizumab may induce complementary effects on tumour growth as well as the antitumour immune response. Local and systemic immune suppression is a fundamental mechanism by which tumour cells evade the host immune system. It has been demonstrated in experimental studies that tumour-derived VEGF is capable of inhibiting dendritic cell differentiation, maturation and function [20, 34]. When VEGF signalling is inhibited, differentiation of dendritic cells is improved, but not enough to induce an effective immune response [19]. IFN also induces the maturation of dendritic cells and increases their capacity to produce other cytokines, but this IFN effect is weaker at higher doses [18]. Thus, anti-VEGF therapy combined with IFN therapy may overcome the inhibitory effects of VEGF on dendritic cells, promoting their maturation, reversing immune suppression and stimulating cytokine production to further enhance antitumour activity. For example, preclinical evidence indicates that co-administered anti-VEGF therapy and immunotherapy provide greater antitumour activity than either agent alone in mice bearing established tumours [11]. Furthermore, preclinical evidence indicates that antiangiogenic activity of IFN is more pronounced at lower doses [23]. These putative mechanisms of synergy observed between bevacizumab and IFN offer a possible explanation not only for the improved outcome seen with bevacizumab + IFN compared with IFN + placebo in the total population but may also explain the observation that efficacy is maintained when the dose of IFN is reduced. Thus, these data indicate that the complementary and synergistic antiangiogenic and immunotherapeutic effects of bevacizumab and low-dose IFN are more pronounced when used in combination.

Analyses of reduced-dose IFN were not prospectively defined in the study protocol, and the reported retrospective analysis has obvious limitations. The study was randomised for the treatment arms, but not for IFN dose reduction strategies. The allocation of patients to these two strategies depended on a particular response to treatment (drug-related toxicity) in the original trial, introducing a patient selection bias. It also has to be noted that patients with early progressive disease were mostly included in the full-dose IFN group; exclusion of these patients improved the estimates of PFS in this group. Therefore, additional analyses designed to exclude the patients with early progression were carried out in an attempt to eliminate this bias. Finally, direct comparisons of the reduced-dose and full-dose patient populations are limited because there were fewer patients in the reduced-dose group than the full-dose group. Despite these limitations, the results indicate that IFN dose reduction is unlikely to impair the efficacy of the bevacizumab + IFN combination in the study.

In conclusion, this retrospective analysis indicates that the dose of IFN used in combination with bevacizumab can be reduced to manage IFN-related toxicity, enabling patients to remain on therapy, while maintaining efficacy. These data add to the evidence demonstrating that bevacizumab + IFN is an effective first-line treatment option for patients with mRCC. To examine this hypothesis further, a prospective trial of bevacizumab in combination with low-dose IFN in patients with mRCC will be carried out.

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