Invented name/Name: **Avastin**
International non-proprietary name/Common name: bevacizumab

TYPE II VARIATION: EMEA/H/C/000582/II/0015

Extension of indication to include:

Avastin in combination with interferon alfa-2a for first line treatment of patients with advanced and/or metastatic renal cell cancer.

1. Introduction

Avastin (Bevacizumab) is a recombinant humanized monoclonal antibody. It inhibits angiogenesis by neutralizing all isoforms of human vascular endothelial growth factor-A (VEGF), and blocking their binding to VEGF receptors. Bevacizumab binds to vascular endothelial growth factor (VEGF) and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth.
Avastin is approved in the EU for the first-line treatment of patients with metastatic cancer of the colon or rectum (mCRC), in combination with intravenous 5- fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan, the treatment of locally recurrent and metastatic breast cancer (mBC) and in combination with platinum-based chemotherapy for first-line treatment of advanced non-squamous Non-Small-Cell Lung Cancer (NSCLC).

The data submitted in this application, support an extension of the indication to include the combination of bevacizumab and interferon alfa-2a in the treatment of patients with advanced and/or metastatic renal cell cancer (mRCC).

RCC is an adenocarcinoma originating in the renal cortex which accounts for about 2% of all solid tumours, and 90-95% of tumours arising from the kidney. The four main histological subtypes of RCC are, according to their degree of increasing aggressiveness, oncocytic, chromophobic, chromophilic and clear-cell. The latter, consisting of cells derived from the proximal tubule with cytoplasm that appears empty, accounts for 75% -80% of all cases of RCC. Commonly, RCC presents as a mixture of these different histological subtypes. The incidence of kidney cancer in Europe for males is about twice that for females (11.04 and 5.04 (per 100,000), respectively), with a mortality rate which is also twice that in males than in females (5.4 and 2.4 (per 100,000), respectively).

The current standard of care for RCC is nephrectomy, for local as well as for disseminated disease, followed by systemic therapy for metastatic disease. In general, patients who present with metastatic disease usually have a poor prognosis even when their primary and metastatic disease has been resected. The 5-year survival of patients with metastatic disease is 5 -15%. In some patients with metastatic disease, nephrectomy may be justified because removal of bulk disease can improve constitutional symptoms that are typical of mRCC, and in addition, local symptoms such as loin pain and haematuria can be alleviated if they exist. Conventional hormonal and chemotherapy treatments are generally regarded as having little or no effect against RCC, with response rates typically in the range of 4% – 6%. This apparent resistance may be due to the expression of a multidrug resistance transporter in the proximal tubule cells. Vinblastine, one of the most extensively studied, failed to show any antitumour activity in more recent trials, and responses to floxuridine are usually partial and relatively short lived.

Cytokines have been widely used as first-line therapy of metastatic disease, but are generally considered to be only modestly effective. IFN-alfa has been extensively investigated in randomized trials as monotherapy and in combination with interleukin-2 (IL-2), 5-fluorouracil (5-FU), gemcitabine and vinblastine. It is approved in Europe for advanced RCC, based on a randomised study

demonstrating an increase in overall survival (OS), when combined with vinblastine, from 37 to 68 weeks. In more recent studies however, IFN in combination with vinblastine has not been shown to improve response rates or OS compared to IFN alone.

Very rare long-term remissions of metastatic disease have been achieved only with high-dose IL-2, the currently approved standard of care in the United States. However, its toxicity profile, particularly the capillary leak syndrome associated with severe hypotension, pulmonary oedema and renal dysfunction, severely limits its broad use.

In 2005 and 2006, two oral protein kinase inhibitors, sorafenib and sunitinib, which inhibit tumour cell proliferation and vascularisation, were approved for the second-line treatment of advanced RCC. Sorafenib was shown to increase progression free survival (PFS) and OS compared to placebo, and sunitinib increased the overall response rate (ORR) in patients who had failed IFN-alfa or IL-2. More recently, sunitinib has been shown to significantly increase PFS compared to IFN-alfa (11 months versus 5 months, respectively; $p<0.001$) in previously untreated patients with mRCC. It has been approved in USA and Europe as first-line therapy in this indication. In spite of the fact that there is no OS benefit reported yet, sunitinib has, in the past six months, become a new standard of treatment in the USA. Sorafenib has however failed to show such a benefit in PFS over IFN-alfa in a randomised clinical trial in previously untreated patients with mRCC.

In November 2007, a selective inhibitor of mammalian target of rapamycin, temsirolimus, a serine/threonine kinase involved in controlling many cellular functions such as cell proliferation, cell survival, protein synthesis and transcription, was approved for the first-line treatment of advanced RCC. Temsirolimus has been shown to increase OS compared to IFN-alfa alone. For the comparison between the combination of temsirolimus and IFN-alfa with IFN-alfa alone, the difference in OS was not statistically significant.

Despite the availability of these newer compounds, the management of patients with mRCC still remains a major therapeutic challenge and highlights the high medical need for expanding new therapeutic choices in this indication. The benefit in OS from IFN-alfa, despite its limitation to few patients, has improved during the past decade. However, long-term survival for patients with mRCC remains modest. Hence, combining newer treatment modalities with this established standard appears to be a logical step forward in treating patients with mRCC.

2. Clinical aspects

The clinical programme investigating the use of bevacizumab in the treatment of advanced and/or mRCC, consists of one controlled pivotal Phase III study, ***BO17705***, of bevacizumab as first-line therapy in combination with interferon alfa-2a as first line treatment in patients with advanced and/or mRCC, and two supportive controlled Phase II studies, ***AVF0890s*** (second-line bevacizumab monotherapy), and ***AVF2938g*** (first-line bevacizumab monotherapy versus erlotinib combination).

2. 1. Clinical pharmacology

The results of the clinical pharmacology program for bevacizumab were extensively discussed in the original Marketing Authorisation Application for the first-line treatment of colorectal cancer EMEA/H/C/582, and in the Type II Variation applications for metastatic breast cancer EMEA/H/C/582/II/08 and non-small cell lung cancer EMEA/H/C/582/II/09. Therefore, this application summarizes the previously submitted data and the focuses on new information from three drug interaction studies and the population pharmacokinetic (PK) analysis from the Phase III study (BO17705) in patients with advanced and/or metastatic RCC.

In the present dossier, the applicant presents the results of two interaction studies (***AVF3135g*** and ***NP18587***) in which it is demonstrated that administration of bevacizumab does not affect the pharmacokinetics of either irinotecan/SN38 or capecitabine and oxaliplatin. AVF3135 has already been assessed once as FUM 016 and finalised at the January 2007 meeting.

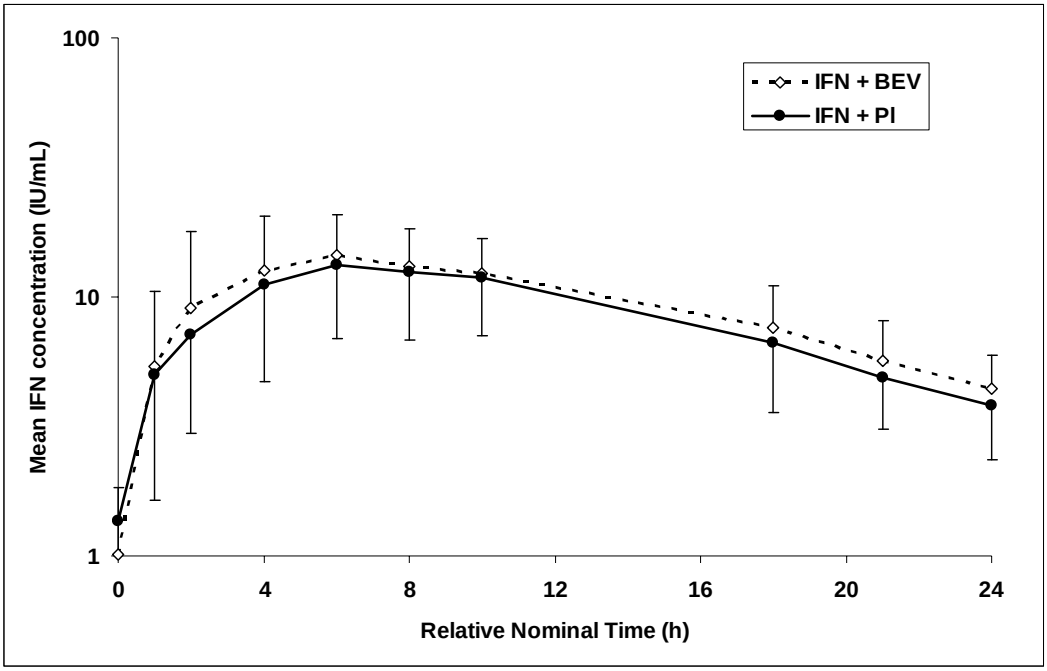
These results support the previously submitted data showing a lack of interaction between bevacizumab and co-administered anticancer therapies.
Furthermore, an interaction study with specific relevance for the RCC indication was presented:

A substudy was conducted within the Phase III study ***BO17705*** in patients with advanced and/or metastatic RCC with the purpose of assessing the potential effect of bevacizumab on interferon alfa-2a pharmacokinetics.
Patients and Methods: The pharmacokinetic assessments for interferon alfa-2a were performed in patients who were stable on bevacizumab from Week 7 onwards (4th bevacizumab infusion). Fourteen (14) patients were randomized to the interferon alfa-2a plus bevacizumab group (Bv + IFN), and 12 were randomized to the interferon alfa-2a plus placebo group (Pl + IFN). The primary parameter for the statistical analysis was the dose-normalized AUC0-last and secondarily the dose-normalized Cmax of interferon alfa-2a. Thirteen (13) patients were analyzed for AUC0-last, and 12 for Cmax in the Bv + IFN arm and 11 patients for AUC0-last and Cmax in the Pl + IFN arm.
Results: Interferon alfa-2a pharmacokinetic parameters were derived from the serum concentrations following the 4th or subsequent bevacizumab infusions. Results are summarized in **Table 1.** The mean concentration-time profiles were comparable for the Bv + IFN arm and the Pl + IFN arm (**Figure 1**).

Table 1 Pharmacokinetic Parameters of Interferon Alfa-2a Following an S.C. Administration of Interferon and After a ≥4th I.V. Infusion of Bevacizumab (10 mg/kg q2w) or Placebo in Patients with Metastatic Renal Cell Cancer

Pharmacokinetic Parameter	Treatment group	
	Bv + IFN	Pl + IFN
	n=13	n=11
Cmax/D (IU/mL)	16.5	13.8
	(CV=47.6)	(CV=44.8)
	n=13	n=11
tmax (h)	6.45	7.52
	(CV=39.9)	(CV=26.5)
	n=12	n=9
t1/2 (h)	9.44	8.59
	(CV=25.5)	(CV=25.6)
	n=13	n=11
AUC0-last/D (h*IU/mL)	230	211
	(CV=37.1)	(CV=41.2)
	n=13	n=11
CL/F (L/h)	3.78	4.27
	(CV=35.7)	(CV=35.8)
	n=12	n=9
Vss/F (L)	53.3	56.1
	(CV=60.8)	(CV=68.7)

Figure 1; Mean (+/-SD) Dose-Normalized Serum Concentrations-Time Profiles of Interferon Alfa-2a After an S.C. Injection and Following ≥4th I.V. Infusion of Bevacizumab (10 mg/kg q2w) or Placebo in Patients with Metastatic Renal Cell Cancer



The geometric mean ratio for dose-normalized $AUC_{0\text{-last}}$ was 1.089 (90% CI=0.816-1.453) and for dose-normalized C_{max} was 1.179 (90% CI=0.837-1.660).

In conclusion, there was no statistically significant effect of bevacizumab on the PK of interferon. There was a trend to an increased interferon ratio of 1.1 and 1.2 for AUC and Cmax. However, a clinically significant effect is very unlikely due to the small deviation of these ratios from 1.

Furthermore, the pharmacokinetics of bevacizumab were characterized in patients with mRCC. In conclusion, the PK parameters of bevacizumab were comparable to those previously reported for Avastin.

Finally, in study ***BO17705***, a **population pharmacokinetic substudy** was performed by Bayesian-feedback analysis of bevacizumab PK data. Individual bevacizumab concentration-time profiles and individual PK parameters were predicted based on empirical Bayes estimates obtained from a reference population PK model and the BO17705 data. The reference model was the population PK model used to describe the pharmacokinetics of bevacizumab in previously investigated populations (reference population), i.e. oncology patients with different types of cancer (4629 bevacizumab samples collected from 491 patients who received intravenous doses of bevacizumab ranging from 1 to 20 mg/kg at a dosing frequency ranging from every 1 to 3 weeks). The BO17705 pharmacokinetic population for Bayesian-feedback analysis was defined as all blood samples for the bevacizumab PK assessment (both sparse and rich sampling scheme) associated with a documented dosing history.

Table 2: Summary Statistics of Individual PK Parameters in the Population of Patients with Metastatic Renal Cancer and in the Reference Population

	Clearance (mL/day)			Central Volume (L)			Peripheral Volume (L)	
	mRCC	Reference		mRCC	Reference		mRCC	Reference*
Median	209	228		3.03	2.89		2.30	1.80
25th Percentile	200	200		2.70	2.50		1.90	1.40
75th Percentile	300	300		3.30	3.30		2.80	2.30
Min	70	82		1.36	1.64		0.34	1.04
Max	400	600		3.90	5.80		4.60	2.90

* The Peripheral Volume of patients of the reference population treated with bevacizumab alone

In conclusion the metrics used in this population PK analysis allow the conclusion that the pharmacokinetics of bevacizumab are comparable in patients with advanced and/or metastatic RCC and the previously investigated population consisting of oncology patients with different types of cancer.

The pharmacokinetics of bevacizumab have not been studied in children and adolescents, or in specific studies in patients with renal or hepatic impairment, and there are no new data for these patients groups.

2. 2. Clinical Efficacy

- Main studies and methods

The three studies supporting this MAA, the pivotal phase III study ***BO17705***, and the two phase II supportive studies, ***AVF0890s*** and ***AVF2938g***, were adequately controlled, randomized, double-blind, with a comparative parallel group design.

All three studies enrolled predominately nephrectomised patients who were at least 18 years of age with histologically or cytologically confirmed metastatic clear-cell RCC.

In general the key inclusion and exclusion criteria were similar among the three studies**.** These included the requirement that patients had adequate organ function as determined by laboratory tests, including haematology and tests for liver and renal function. In addition, at enrolment, patients were required to have no evidence of central nervous system metastases or spinal cord compression, bleeding diathesis or coagulopathy, or clinically significant cardiovascular disease, including cerebrovascular accidents (≤6 months), myocardial infarction (≤ 6 months), NYHA Class II or greater congestive heart failure and serious cardiac arrhythmias requiring medication. Patients with uncontrolled hypertension were excluded from participation in the studies.

Study BO17705 (pivotal):

Objective: This was a multicenter study recruiting in 101 centres in 18 countries in Eastern and Western Europe and Australasia. It compared bevacizumab in combination with interferon-alfa-2a (N = 327) to placebo plus interferon (N = 322) as first-line therapy of nephrectomised patients with advanced and/or mRCC. Patients were stratified to treatment according to country and to risk category according to Motzer score (favourable, intermediate and poor risk groups) in order to avoid an imbalance in prognostic factors between the two treatment arms.

Inclusion/exclusion: Patients were required to have a Karnofsky performance status of at least 70%. Patients with measurable and non-measurable disease were included as the objective response rate was only a secondary endpoint. Patients were excluded if they had received prior systemic or adjuvant therapy for RCC.

Dosing: Bevacizumab was given at a dose of 10 mg/kg of body weight every two weeks (q2w), and interferon alfa-2a at a target dose of 9 MIU three times weekly for 52 weeks in both treatment arms until disease progression or unmanageable toxicity was seen. Only a delay in bevacizumab

administration was allowed for toxicity reasons, while the dose of interferon alfa-2a could be reduced in two stages (6 MIU and 3 MIU) in case of interferon toxicity. Patients in the interferon alfa-2a control arm also received a placebo in fusion (q2w) to maintain the double-blind. At the time the study was unblinded, patients in the interferon alfa-2a arm were given the opportunity to receive bevacizumab monotherapy, as the one year IFN therapy period had been passed.
The choice of 10 mg/kg q2w bevacizumab as the dose to be tested in the pivotal study ***BO17705***, was based on the results of the dose finding study ***AVF0890s***, in which, compared to placebo, a statistically significant prolongation in the time to disease progression and an improved overall response rate was seen with 10 mg/kg q2w, but not with 3 mg/kg q2w. The safety profile of 10 mg/kg q2w was acceptable in the monotherapy setting.

Interferon alfa-2a has been used in RCC at doses ranging from 3 MIU to 18 MIU given three times a week. However, since no clear dose dependent efficacy has been shown over this dose range, and in view of the toxicity profile observed with interferon alfa-2a at the different dosages, the use of 9 MIU three times a week in study BO17705 was considered to be the preferred dose in terms of the required efficacy and acceptable toxicity with respect to the duration of treatment. It is also the most commonly used dosing regimen in this indication in Europe, and therefore the best experience exists with the management of its adverse effects. To further increase the tolerability, the initial doses of interferon in study BO17705 could be reduced and then escalated to the recommended dose level during the first two weeks of treatment. The duration of interferon dosing used in study BO17705 of one year is in line with the recommendation for responding patients. Dose reductions to 6 MIU or 3 MIU were allowed depending on the side effects observed. No dose reductions were allowed for bevacizumab although dose interruptions were permissible.
Endpoints: The primary efficacy endpoint in study ***BO17705*** was OS and the secondary endpoints were PFS, objective response rate, duration of response, time to disease progression and time to treatment failure.
Tumour burden was assessed every eight weeks until week 32, then every 12 weeks until week 56, within ± 7 days of the scheduled visit. Patients whose disease had not progressed at week 56 could continue in the trial and tumour assessments were performed at week 68, 12 weekly up to week 104, and thereafter every 6 months until disease progression.

Study AVF0890s (supportive):
Objective: 116 patients with metastatic clear-cell RCC who were previously treated with IL-2 (or in whom IL-2 was contraindicated) were randomized to treatment with bevacizumab, 3 mg/kg (N = 37) or 10 mg/kg (N = 39) of body weight q2w, or placebo q2w (N = 40). Patients were stratified according to whether or not they had previously received IL-2 therapy.
Inclusion/exclusion: This study included patients who had either failed previous IL-2 therapy or in whom IL-2 was contraindicated. Patients were required to have an ECOG performance score of 0 or 1.
Endpoints: The primary objective of this trial was time to disease progression and ORR. OS was a secondary objective, since patients who progressed on placebo were allowed to cross over and receive 3 mg/kg bevacizumab therapy or combination therapy with 3 mg/kg bevacizumab and thalidomide.
Tumour assessments were performed five weeks after therapy started, then every two months for the first year and every three months for the second year of therapy.

Study AVF2938g (supportive):
Objective: A multicenter study exploring the potential benefit of adding Tarceva® (erlotinib - 150 mg daily) to bevacizumab (10 mg/kg q2w) in a placebo controlled setting, in previously untreated patients with metastatic clear-cell RCC. 51 patients were randomised to treatment with bevacizumab plus erlotinib and 53 to bevacizumab plus placebo. The study consisted of a 24-month treatment phase and a follow-up phase.
Inclusion/exclusion: Only patients with measurable disease at baseline were included. Patients were required to have an ECOG performance score of 0 or 1.Patients were excluded if they had received prior systemic or adjuvant therapy for RCC.
Endpoints: PFS and ORR were the two co-primary efficacy endpoints. Secondary efficacy parameters were the duration of objective response, OS and time to symptom progression.
Tumour assessments were taken every two months (±4 days) during treatment.

Statistical analyses:
In studies ***BO17705*** and ***AVF0890s***, the primary population for the analysis of efficacy was the intent-to-treat (ITT) population which included all patients randomised into each study. Efficacy analyses in study ***AVF2938g*** were based on the efficacy evaluable population, which was defined as any patient who received any treatment during the study and who had at least one post-baseline tumour assessment. The data in all three studies was analysed using standard statistical methods (log rank tests), including Kaplan Meier curves with median survival estimates and confidence limits.
The primary analysis of OS and PFS in Study ***BO17705*** was based on an unstratified analysis. In addition, stratified Cox regression analyses, using region (Western Europe, Eastern Europe, other) and Motzer score at baseline as stratification factors, were performed to test the robustness of the results.

In summary, all three studies investigated the efficacy and safety of bevacizumab given at a dose of 10 mg/kg q2w, either alone (**AVF0890s, AVF2938g**), in combination with erlotinib (**AVF2938g**), or in combination with interferon alfa-2a (**BO17705**), and all studies had a standard design with no unusual features. The population of patients enrolled in all three studies was similar and representative of patients with advanced and/or mRCC. The main difference between the studies was that bevacizumab was given as first-line therapy in studies ***BO17705 (in addition to IFN)*** and ***AVF2938g (in addition to erlotinib)***, and as second-line therapy following treatment with IL-2 in study ***AVF0890s***.

- **Results**

Study BO17705 (pivotal):
Patients: This study enrolled a total of 649 patients with advanced and/or mRCC, of whom 327 were randomized to treatment with bevacizumab 10 mg/kg q2w plus interferon alfa-2a 9 MIU 3x/wk, and 322 to treatment with placebo q2w plus interferon alfa-2a 9 MIU 3x/wk.
Demographics: The demographic and baseline characteristics were generally comparable across the treatment arms. The mean age of the patients in the Bv + IFN arm (60.1 years) was similar to that in the Pl + IFN arm (59.4 years), the patients enrolled in both arms were predominantly male (73% and 68%, respectively), and the majority were white (97% and 95%, respectively). Most patients in both treatment arms had a Karnofsky performance status score of ≥ 90 at baseline, and a Motzer score which was intermediate. All patients were nephrectomized (or partially nephrectomized with clearly negative resection margins).
Results: The results of the analyses of the primary and secondary efficacy parameters are based on the intent-to-treat population of patients (all randomised patients) and include 327 patients in the BV+IFN arm and 322 patients in the Pl+IFN arm (Table 3).

Table 3 Summary of Efficacy Results in Study BO17705: Intent-To-Treat Analysis Population

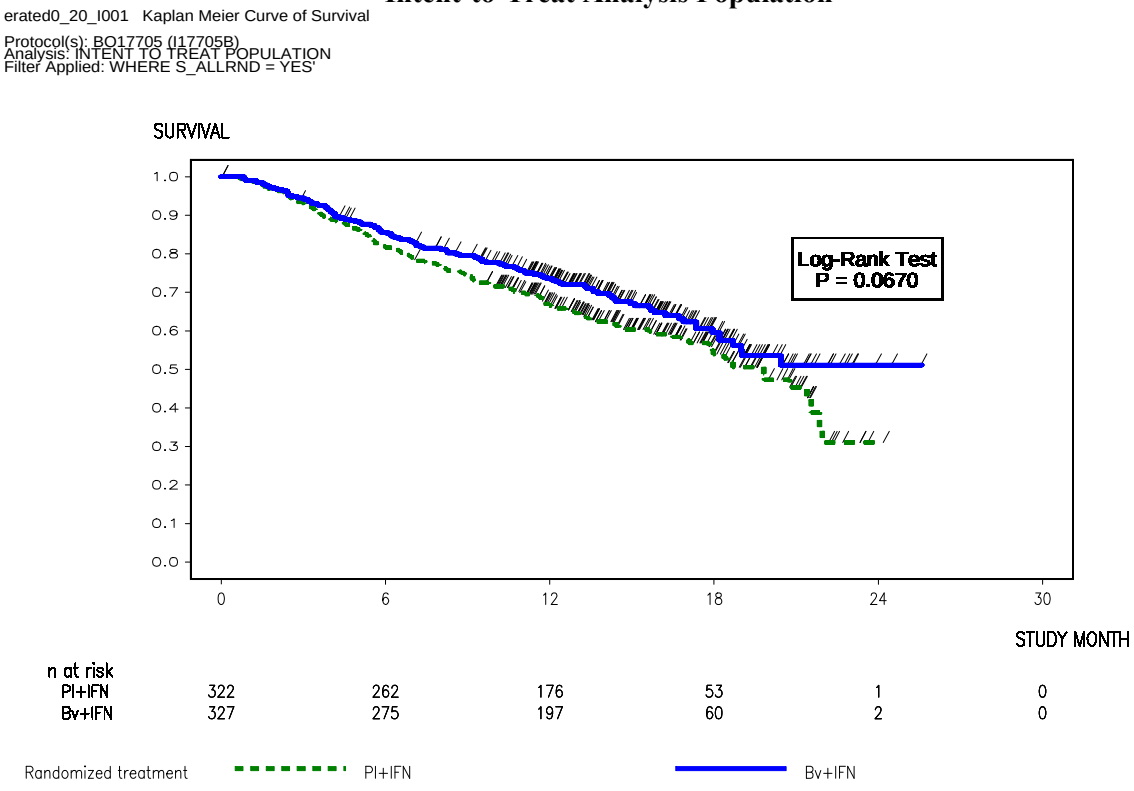
Parameter	Pl + IFN1 N = 322	Bv2 + IFN1 N = 327
Overall survival (months)		
Median	19.8	NR[a]
95% CI	17.8, 21.9	18.7, -
Unstratified analysis		
Hazard ratio	0.79	
95% CI	0.62, 1.02	
p-value (log-rank)	0.0670	
Progression-free survival (months)		
Median	5.4	10.2
95% CI	4.1, 5.7	7.8, 11.1
Unstratified analysis		
Hazard ratio	0.63	
95% CI	0.52, 0.75	
p-value (log-rank)	<0.0001	
Time to disease progression (months)		
Median	5.5	10.2
95% CI	4.1, 5.7	7.9, 11.5
Unstratified analysis		
Hazard ratio	0.61	
95% CI	0.51, 0.73	

p-value (log-rank)		**<0.0001**	
Time to treatment failure (months)			
Median	**4.4**		**7.7**
95% CI	**3.8, 5.6**		**6.5, 10.1**
Unstratified analysis			
Hazard ratio		**0.73**	
95% CI		**0.62, 0.87**	
p-value (log-rank)		**0.0003**	
Objective response rate[b] (%)	**12.8**		**31.4**
Difference in objective response rate (%)		**18.6**	
95% CI		**11.9, 25.2**	
p-value (Chi-squared test)		**<0.0001**	
Complete response (%)	**2.1**		**1.3**
Partial response (%)	**10.7**		**30.1**
Stable disease (%)	**49.8**		**46.1**
Progressive disease (%)	**32.9**		**19.9**
Duration of response (months)			
Median	**11.1**		**13.5**

[1] Interferon alfa-2a 9 MIU 3x/wk; [2] Bevacizumab 10 mg/kg q2w
[a] Median not reached; [b] CR + PR; Patients with measurable disease at baseline

Primary endpoint: There was a strong trend for an improvement in OS in favour of the Bv + IFN arm compared to the Pl + IFN arm, with a relative risk reduction of 21% in the Bv + IFN arm. However, the difference between the two treatments (unstratified HR 0.79; 95% CI 0.62, 1.02; p-value (log rank) 0.0670) did not reach the pre-specified level of statistical significance (p=0.0056) for this interim analysis .(Figure 2). The results represent the final analysis of PFS at this time point. The final analysis of OS will be performed after a sufficient number of events have been collected.

Figure 2: Kaplan Meier Estimates of Overall Survival at the Interim Analysis of Study BO17705:
Intent-to-Treat Analysis Population



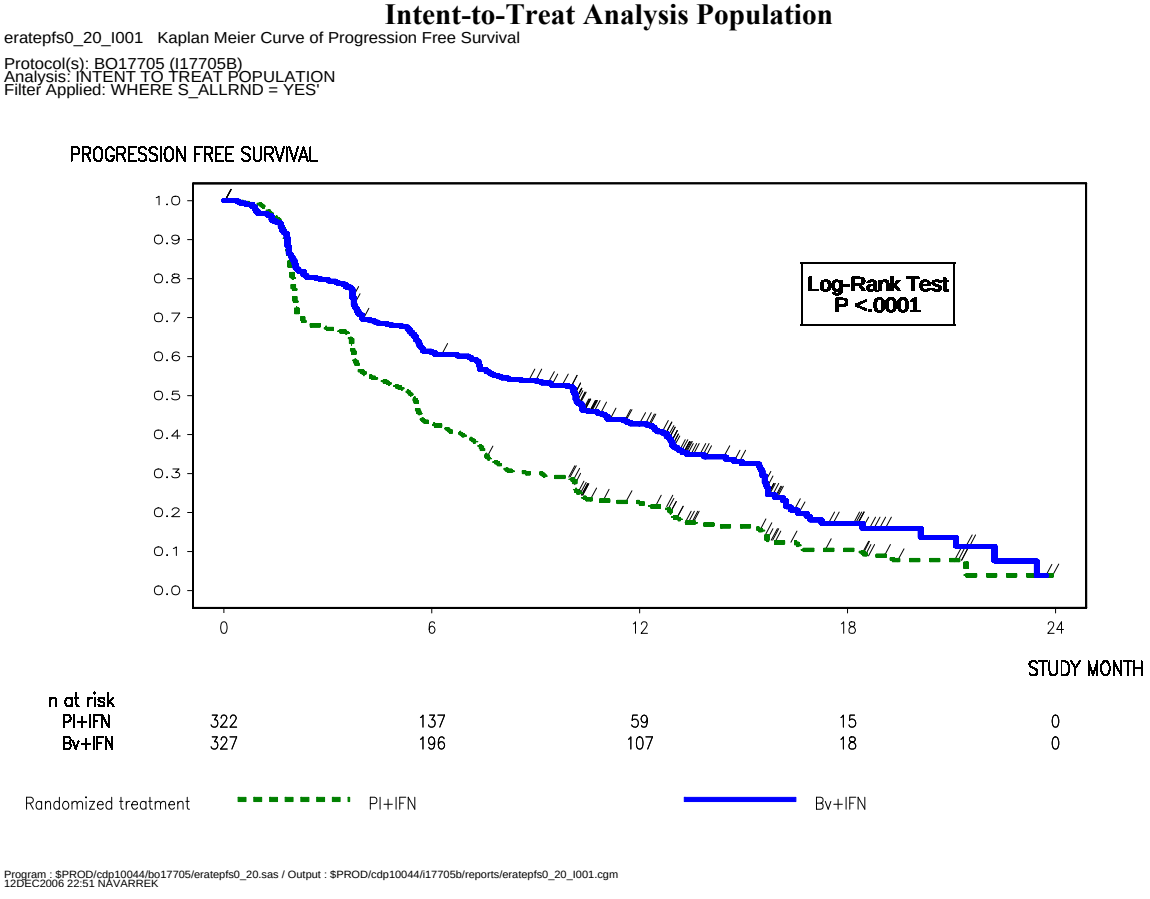
The stratified analysis, which took into account the country and baseline Motzer risk category, also showed a strong trend for an improvement in OS in the Bv + IFN arm (HR 0.75; 95% CI 0.58, 0.97; p-value (log-rank) 0.0267).

In the largest subgroup of patients with an intermediate prognosis for survival based on their Motzer score, which represented two thirds of the population, there was also a strong trend to an increase in OS in the Bv + IFN arm compared to the Pl + IFN arm HR 0.74; 95% CI 0.53, 1.02; p-value (log-rank) 0.0680.

Secondary endpoints:

PFS: Treatment with Bv + IFN resulted in a clinically meaningful and highly statistically significant increase in the median duration of PFS of almost five months compared to treatment with Pl + IFN (median: 10.2 versus 5.4 months; unstratified HR 0.63; 95% CI 0.52, 0.75; p-value (log-rank) <0.0001). The risk of an event was reduced by 27% in the Bv + IFN arm compared to the Pl + IFN arm **(Figure 3).**

Figure 3: Kaplan Meier Estimates of Progression-Free Survival in Study BO17705: Intent-to-Treat Analysis Population



The results of the stratified analysis also showed a statistically significant increase in PFS in patients in the Bv + IFN arm compared to those in the Pl + IFN arm (HR 0.61; 95% CI 0.51, 0.73; p-value (log-rank) <0.0001). Patients in the Bv + IFN arm who had an intermediate prognosis for survival based on their Motzer score also had a statistically significant increase in PFS (HR 0.55; 95% CI 0.44, 0.70; p-value (log-rank) <0.0001).

The increase in PFS was reflected in a statistically significant increase in the median **time to disease progression** in the Bv + IFN arm compared to the Pl + IFN arm (10.2 vs. 5.5 months; p<0.001) and the risk of an event in the Bv + IFN arm was reduced by 39% compared to the Pl + IFN arm.
The median time to treatment failure of 7.7 months in the Bv + IFN arm was statistically significantly longer than the 4.4 months seen in the Pl + IFN arm (p=0.0003).

Objective Response Rate (ORR): The incidence of patients with a best overall response of CR + PR was more than double in patients treated with Bv + IFN (31.4%) compared to those receiving treatment with Pl + IFN (12.8%), which was due to a substantial increase in the incidence of patients with a PR in the Bv + IFN arm (30.1% versus 10.7%). Slightly more patients in the Pl + IFN arm had a CR than in the Bv + IFN arm (6 versus 4 patients, respectively). Patients in the Bv + IFN arm had a slightly longer median **duration of response** (13.5 months) than those in the Pl + IFN arm (11.1 months). Thus, adding bevacizumab to interferon alfa-2a increased the response rate and slightly increased the median duration of the response.

Antineoplastic Therapy Given Following Disease Progression
In the intent-to-treat analysis population of patients, antineoplastic therapies following disease progression (i.e., second-line treatment) were reported in 39% of patients in the Pl + IFN arm and 28% of patients in the Bv + IFN arm in study BO17705. The most common of these are shown in Table 4:

Table 4: Subsequent Antineoplastic Therapy: Metastatic Renal Cell Cancer Study BO17705

Treatment Class	Pl + IFN[2] N = 322	Bv[1] + IFN[2] N = 327
All classes	**39%**	**28%**
Tyrosine kinase inhibitors	**20%**	**15%**
Surgical and medical procedures	**10%**	**6%**
Cytokines	**8%**	**5%**
Antimetabolites	**6%**	**3%**
Vinca alkaloids	**3%**	**3%**
Angiogenesis inhibitors	**3%**	**2%**
Antineoplastic agents	**4%**	**<1%**
Bisphosphonates	**2%**	**1%**

[1] **Bevacizumab 10 mg/kg q2w**
[2] **Interferon alfa-2a 9 MIU 3x/wk**

Treatment with sunitinib (Pl + IFN: 11%; Bv + IFN: 9%), sorafenib (Pl + IFN: 8%; Bv + IFN: 6%) and radiotherapy (Pl + IFN: 7%; Bv + IFN: 5%) were the most common antineoplastic treatments given to patients following discontinuation of trial treatment.

Study AVF0890s (supportive):
Objective: Patients with metastatic clear-cell RCC, who were previously treated with IL-2 (or in whom IL-2 was contraindicated), were randomized to treatment with bevacizumab, 3 mg/kg (N = 37) or 10 mg/kg (N = 39) of body weight q2w, or placebo q2w (N = 40). Patients were stratified according to whether or not they had previously received IL-2 therapy.
A total of 116 patients with clear-cell mRCC were randomized to the three treatment arms; 37 to low-dose (3 mg/kg q2w), 39 to high-dose bevacizumab (10 mg/kg q2w) and 40 to placebo (q2w).
Demographics: Taking into account the small number of patients enrolled in each treatment arm, the demographic and baseline characteristics of the patients enrolled were generally comparable across the three treatment arms. The median age of the patients in the three arms ranged from 53 – 54 years, and the majority of patients in each treatment arm were male (68% - 84%). Most patients had undergone a nephrectomy (>90%) prior to study entry, and the majority had received prior IL-2 therapy (>90%).
Results: Following the second pre-planned interim analysis, the NCI Data Safety and Monitoring Board recommended closing accrual into the study, as the difference in the primary endpoint of time to disease progression between the placebo and high dose bevacizumab arms was statistically significance. In the intent-to-treat analysis, the time to progression of disease in the 10 mg/kg q2w bevacizumab arm was significantly longer than in the placebo arm (4.8 vs., 2.5 months, respectively: $p<0.001$). The difference in the time to progression of disease in the bevacizumab 3 mg/kg q2w arm (3.0 months) compared to placebo was of borderline significance ($p=0.041$). Similar results were seen when an analysis from the five-week assessment was performed. At four months, the percentage of patients who had no tumour progression in 10 mg/kg q2w arm (64%) was greater than in the 3 mg/kg q2w arm (39%) and the placebo arm (20%), and at eight months was 30%, 14% and 5%, respectively.

Objective responses were seen in four patients, all of which were partial responses, and all occurred in the high dose arm. Overall survival was not significantly different between the three arms (p>0.20 for all comparisons).
The safety profile of bevacizumab in this study was generally similar in terms of the type and incidence of adverse events reported as that seen in other indications.

Study AVF2938g (supportive):
Objective: A multicenter study exploring the potential benefit of adding Tarceva (erlotinib - 150 mg daily) to bevacizumab (10 mg/kg q2w) in a placebo controlled setting, in previously untreated patients with metastatic clear-cell RCC. 51 patients were randomised to treatment with bevacizumab plus erlotinib and 53 to bevacizumab plus placebo. The study consisted of a 24-month treatment phase and a follow-up phase.
Patients: Overall, 104 patients with histologically confirmed mRCC were randomized to treatment in this study, 53 to bevacizumab 10 mg/kg q2w plus placebo and 51 to bevacizumab 10 mg/kg q2w plus erlotinib 150 mg daily.
Demographics: The demographic and baseline characteristics were generally similar across the treatment arms. The majority of the patients enrolled in both study arms were male (Bv + Erl:64.7%; Bv + Pl 75.5%), and the mean age was slightly higher in the Bv + Erl arm than in the Bv + Pl arm (59.9 vs. 65.0 years, respectively) which was due to the inclusion of more patients ≥ 65 years of age in the Bv + Erl arm. The ECOG performance status was balanced across the two treatment arms as were the baseline Motzer risk factors; all patients were of low or intermediate risk.
Results: Analysis of the primary endpoint PFS, showed no difference between the Bv + Pl arm and the Bv + Erl arm (median PFS 8.5 vs. 9.9 months, respectively. HR 0.858; p=0.5831). No improvement in the objective response rate was seen in the combination arm. Seven patients in each arm had an objective response, the majority of which were partial responses; one complete response occurred in the combination arm. Furthermore, the addition of erlotinib to bevacizumab did not result in an improvement in OS (HR 1.764; p=0.1789), duration of objective response (6.7 vs. 9.1 months) or time to symptom progression (HR 1.172; p=0.5076).
No new safety signals were seen with the addition of erlotinib to bevacizumab compared to those known for the two drugs separately.
Conclusions: The addition of erlotinib to bevacizumab as first-line treatment of patients with mRCC did not result in a clinically or statistically significant improvement in PFS, objective response rate, OS, duration of objective response or time to symptom progression. Nevertheless, a pooled analysis of the median PFS (8.6 months) compared favorably to historical data for interferon alfa (4.7 months), indicating that bevacizumab at a dose of 10 mg/kg q2w is active in mRCC.
Compared to the known safety profile of the two drugs, no new safety signals were seen.

- **Analyses performed across trials**

Table 5: Summary of Efficacy Results in Metastatic Renal Cell Cancer Studies with Bevacizumab

	BO17705[1]		**AVF0890s[1]**			**AVF2938g[2]**	
	Pl + IFN[4] N = 322	**Bv[3] + IFN[4] N = 327**	**Pl N = 40**	**Bv 3 mg/kg N = 37**	**Bv 10 mg/kg N = 39**	**Bv[3] + Pl N = 53**	**Bv[3] + Erl[5] N = 50**
Overall survival (months)							
Median	19.8	NR	NA	NA	NA	NR	20.0
Hazard ratio	0.79 (p=0.0670)		-	-	-	1.567 (p=0.1582)	
Progression-free survival (months)							
Median	5.4	10.2	NA	NA	NA	8.5	9.9
Hazard ratio	0.63 (p<0.0001)		-	-	-	0.86 (p=0.5831)	
Time to disease progression (months)							
Median	5.5	10.2	2.5	3.0	4.8	NA	NA
Hazard ratio	0.61 (p<0.0001)		-	1.26	2.55	-	
Time to treatment failure (months)							
Median	4.4	7.7	NA	NA	NA	NA	NA
Hazard ratio	0.73		-	-	-	-	

		(p=0.0003)					
Objective response rate							
Overall (%)	12.8	31.4	0.0	0.0	10.3	13.2	14.0
		(p<0.0001)				p=1.0000	
Complete response (%)	2.1	1.3	0.0	0.0	0.0	0.0	2.0
Partial response (%)	10.7	30.1	0.0	0.0	10.3	13.2	12.0
Duration of response (months)							
Median	11.1	13.5	NA	NA	NA	6.7	9.1
Hazard ratio		0.94		-	-	NA	
Time to symptom progression (months)							
Median	NA	NA	NA	NA	NA	3.7	1.9
Hazard ratio		-		-	-	1.172	
						(p=0.5076)	

[1] Intent-to-Treat (all randomized) population [2] Efficacy evaluable population
[3] Bevacizumab 10 mg/kg q2w [4] Interferon alfa-2a 9 MIU 3x/wk
[5] Erlotinib 150 mg daily Pl = Placebo; NA = Not available; NR = Not reached

Overall, the efficacy results were better in the BO17705 study than in either of the other two studies, both in terms of the magnitude of the increase in the duration of PFS or time to disease progression, and the increase in objective response rate when bevacizumab was given in combination with the recommended dose of interferon alfa-2a. Study BO17705 was larger than the other two studies, and was more statistically robust, which may, in part, account for this. All three studies were double-blind, so it is unlikely that the investigator assessed response and progression were biased and would have played a major role in contributing to the difference seen between the studies. Time to disease progression was somewhat lower in study AVF0890s than in study BO17705, which is expected given the fact that the patients in this study were treated with bevacizumab in the second-line setting after they had failed IL-2 therapy, and had a lower life expectancy.

Study ***AVF2938g*** did not demonstrate an advantage of adding erlotinib to bevacizumab. The median duration of PFS seen in this study for bevacizumab monotherapy in mRCC compares favourably with that previously reported with the use of interferon alfa. Study ***AVF0890s***, in which patients also received single agent bevacizumab, further supports the view that bevacizumab monotherapy has activity in mRCC which is independent of previous exposure to other therapy in this disease.

- **Efficacy in subgroups**

Pre-specified subgroup analyses for PFS and OS using the following factors were conducted for the Phase III study BO17705:

- Sex (male, female)
- Age (<65, ≥65 years)
- Baseline VEGF above median value, not above the median value
- Region (Western Europe, Eastern Europe, other)
- Lung metastases (yes, no)
- Number of metastatic sites (≤2, >2)
- Motzer score (poor, intermediate, favorable)
- Body weight loss in the six months before baseline (≤10%, >10%)

In study AVF2938g, analyses for PFS and objective response were performed in the following subgroups of patients:

- Age (<65, ≥65 years)
- Sex (male, female)
- Race (non-White, White)
- ECOG performance status (0, 1)

No subgroup analyses were conducted in study AVF0890s.

Progression-Free Survival in Subgroups – Study BO17705

The result of the PFS analysis in each subgroup analyzed was consistent with that seen in all patients. In all subgroups examined, the point estimate of the hazard ratio was below 1, indicating a consistent benefit in PFS of adding bevacizumab to interferon alfa-2a (Figure 4).

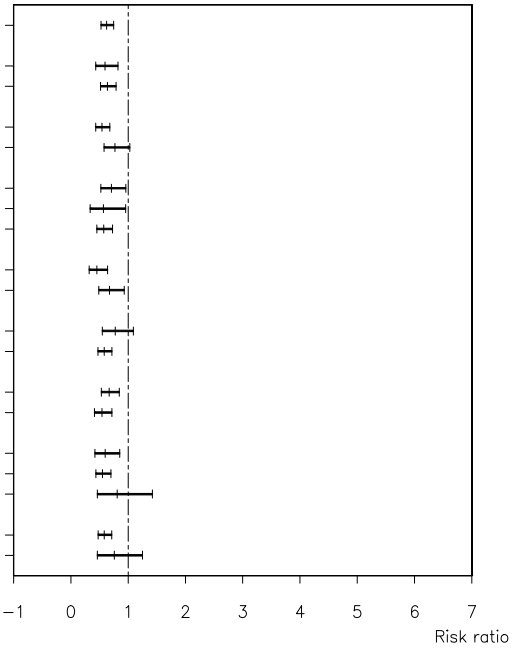
In the subgroup of patients who had an intermediate prognosis for survival based on their Motzer score at baseline, a significant increase in PFS was seen in the Bv + IFN arm compared to the Pl + IFN arm (HR 0.55; 95% CI 0.44, 0.70; p-value (log-rank) <0.0001).

Figure 4: Forest Plot of the Hazard Ratio for Progression-Free Survival in Subgroups: Metastatic Renal Cell Cancer Study BO17705 - Intent-to-Treat Analysis Population

escoxpfs1_20_l001 Forest Plot of Hazard Ratio for Progression Free Survival by Subgroup

Protocol(s): BO17705 (I17705B)
Analysis: INTENT TO TREAT POPULATION
Filter Applied: WHERE S_ALLRND = 'YES'

Category	Subgroup	N	Lower confidence limit	Estimate	Upper confidence limit
All		649	0.52	0.63	0.75
Sex	FEMALE	193	0.43	0.60	0.82
	MALE	456	0.52	0.64	0.79
Age Category	<65	410	0.43	0.54	0.68
	>=65	239	0.58	0.77	1.03
Region Classification	EASTERN EUROPE	218	0.52	0.71	0.96
	OTHER	74	0.34	0.57	0.96
	WESTERN EUROPE	357	0.45	0.57	0.73
Baseline VEGF above median?	NO	191	0.32	0.45	0.64
	YES	191	0.49	0.67	0.93
Lung metastases?	NO	173	0.55	0.77	1.09
	YES	473	0.47	0.58	0.72
Number of metastatic sites	<=2	394	0.53	0.67	0.84
	>2	252	0.41	0.54	0.72
Motzer score	Favorable	180	0.42	0.60	0.85
	Intermediate	363	0.44	0.55	0.70
	Poor	54	0.46	0.81	1.42
Percentage Body Weight Loss	<=10	501	0.48	0.58	0.71
	>10	81	0.46	0.76	1.25



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Overall survival in Subgroups – Study B017705

Since this was an interim analysis of OS that was performed when 251 (56%) of 445 deaths required for the final analysis had been observed, the data are currently not mature enough to make any firm conclusions on the efficacy of adding bevacizumab to interferon alfa-2a on OS.

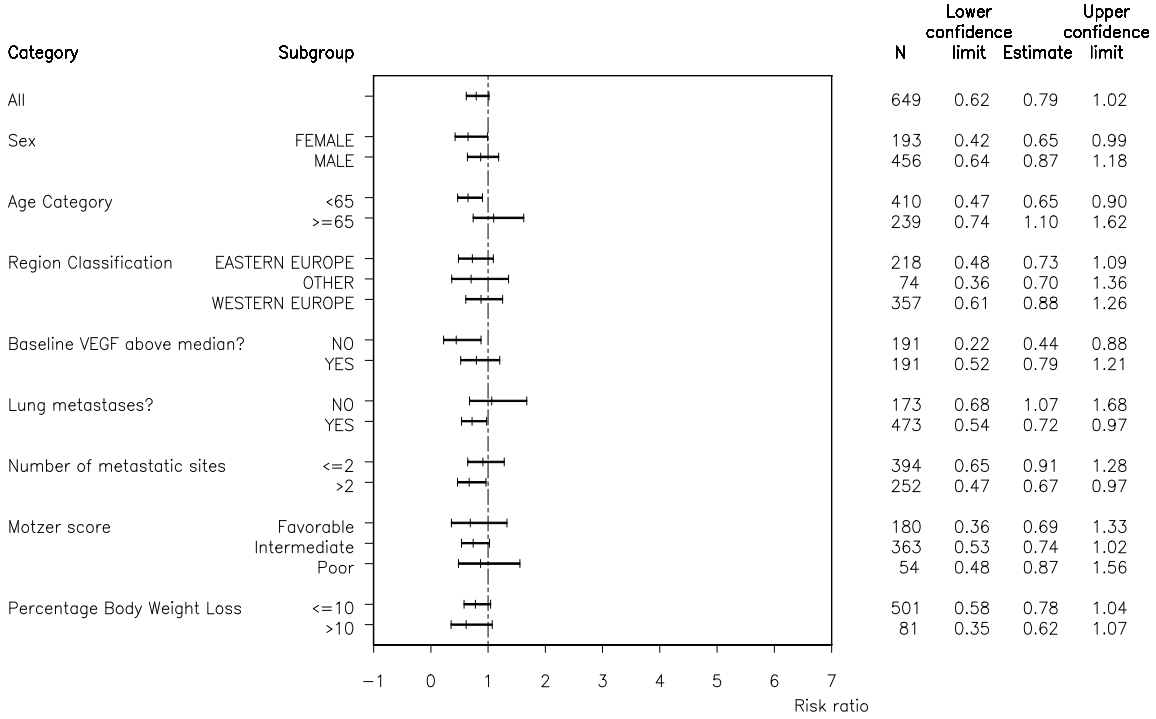
However, the results of each of the subgroup analyses for OS were generally consistent with those seen for all patients, and for the majority of subgroups, the point estimate of the hazard ratio was below 1 indicating a potential benefit in OS of adding bevacizumab to interferon alfa-2a (Figure 5).

In the subgroup of patients with an intermediate prognosis for survival based on their Motzer score at baseline, a strong trend for an increase in OS was seen in the Bv + IFN arm compared to the Pl + IFN arm. This analysis included 217 Pl + IFN patients, 96 of whom had an event, and 216 Bv + IFN patients, 67 of whom had an event (HR 0.74; 95% CI [0.53, 1.02], p=0.0056). The number of patients in the other two subgroups – patients with a poor or a favorable Motzer score – were relatively small and the same trend for longer OS was not seen.

Figure 5: Forest Plot of the Hazard Ratio for Overall Survival in Subgroups: Metastatic Renal Cell Cancer Study BO17705 - Intent-to-Treat Analysis Population

escoxd1_20_l001 Forest Plot of Hazard Ratio for Survival by Subgroup

Protocol(s): BO17705 (I17705B)
Analysis: INTENT TO TREAT POPULATION
Filter Applied: WHERE S_ALLRND = 'YES'



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Discussion on Clinical Efficacy

The BO17705 study demonstrated that the addition of bevacizumab to interferon alfa-2a as first-line therapy substantially improved the efficacy of interferon alfa-2a in patients with advanced and/or mRCC. This was shown by statistically significant and clinically relevant increases in progression free survival, time to treatment failure, time to disease progression and objective response rate, while maintaining the duration of the response. Moreover, there was a strong trend in the interim analysis for an increase in OS in patients treated with the combination therapy. The observed benefit in the median PFS is impressive, and almost doubled when bevacizumab was added to interferon alfa-2a. OS was not shown to be significantly different, but the immaturity of the data on the one hand, and the rather unpredicted high level of efficacy observed in the control arm (median OS of 19.8 months), considerably increased the hurdle to show a significant benefit in OS. With a p-value of 0.0670 for the unstratified analysis, and a p-value of 0.0263 for the stratified analysis, a strong trend in OS benefit has been demonstrated in this study.

The consistency in the subgroup analyses confirms the robustness of the results. It is noted that the benefit of bevacizumab on PFS is most striking in patients with an intermediate prognosis for survival (based on their Motzer score) who comprise the large majority of patients in the trial.
For the OS analysis, no specific subgroups seem to benefit from the treatment of bevacizumab.
All hazard ratios for both OS and PFS indicate a benefit in each Motzer score sub-group with the addition of bevacizumab to interferon alfa-2a.
The efficacy of bevacizumab in previously untreated mRCC is further supported by the limited monotherapy data (AVF2938g), confirming a very favourable efficacy profile as compared to the interferon arm in study BO17705 (PFS of 8.5 months compared to 5.4 months in study BO17705), and with historical data for interferon.

The efficacy of bevacizumab also appears to be independent of previous exposure to cytokines (IL-2) based on the results of study AVF0890s which showed a statistically significant increase in the time to

progression of the disease with bevacizumab monotherapy given as second-line treatment to patients with mRCC.

2.3. Clinical Safety

The safety of bevacizumab in combination with interferon alfa-2a as first-line therapy for patients with advanced and/or mRCC is derived from one Phase III, randomised, double-blind, placebo-controlled trial. In addition, an indication of the safety of bevacizumab as monotherapy comes from two Phase II studies which were both randomised, double-blind trials; one of bevacizumab monotherapy in previously untreated patients (first-line treatment) and one in previously treated patients (second-line setting). Additional data of bevacizumab in combination with erlotinib is also provided.

Safety Data Collection and Analysis
Full safety data were collected in study ***BO17705***, including adverse events of all NCI-CTCAE (version 3.0) grades up to at least 28 days post-treatment, serious adverse events (indefinite reporting), adverse events leading to treatment interruption or discontinuation, deaths, laboratory tests and vital signs. Progression or deterioration of mRCC (including new sites of metastasis and death due to disease progression) were considered to be part of the efficacy assessment and were not reported as adverse events.

In study ***AVF2938g***, only NCI-CTCAE (version 3.0) Grade 3 and 4 adverse events, serious adverse events, adverse events leading to study treatment interruption or discontinuation and deaths were recorded until 28−45 days after the last dose of study treatment. In addition, laboratory test results and blood pressure measurements were recorded in this study. Adverse events of all NCI-CTC (version 2.0) grades were collected in study ***AVF0890s***, but only those adverse events occurring in at least 10% of patients receiving bevacizumab and those that were more frequent than in patients receiving placebo were reported in the publication.
All three studies paid particular attention to the adverse events of hypertension and proteinuria which are known, from trials in other indications, to be associated with bevacizumab therapy. In addition, cases of wound healing complications, gastrointestinal perforation, arterial and venous thrombotic events, bleeding/haemorrhage, and congestive heart failure were followed closely in studies ***BO17705*** and ***AVF2938g***.

Patient exposure
A total of 517 patients with mRCC were exposed to at least one dose of bevacizumab in the three studies; 129 patients to monotherapy with either 3 mg/kg q2w (37 patients) or 10 mg/kg q2w (92 patients) bevacizumab, 51 patients to bevacizumab 10 mg/kg q2w in combination with erlotinib, and 337 patients to bevacizumab 10 mg/kg q2w in combination with IFN (Table 1). At the time of the BO17705 data cut-off for this Summary of Clinical Safety (September 8, 2006), which was approximately 1 year after the last patient was entered into the trial, 105 (31%) of the 337 patients in study BO17705 who received bevacizumab in combination with IFN had completed 52 weeks of combination therapy and had changed to bevacizumab monotherapy; however, separate data for this monotherapy period are not available.

Table Number of Patients Treated with Bevacizumab in mRCC

Bevacizumab Treatment	No. Patients Treated	Source Study
Bv 3 mg/kg q2w monotherapy	37	AVF0890s (low-dose arm)
Bv 10 mg/kg q2w monotherapy	92	AVF2938g (Bv+PL arm [53 patients]) + AVF0890s (high-dose arm [39 patients])
Bv 10 mg/kg q2w + erlotinib	51	AVF2938g (Bv+Erl arm)
Bv 10 mg/kg q2w + IFN	337	BO17705 (Bv+IFN arm)
TOTAL	**517**	

Bv, bevacizumab; IFN, interferon alfa-2a; Erl, erlotinib.

Adverse events

A comparison of adverse event data across the three studies is confounded by the differences in the reporting and grading of events, the different patient population sizes, and durations of treatment. Nevertheless, the available data indicate that the safety profile of bevacizumab at a dose of 10 mg/kg q2w in patients with advanced and/or mRCC is not different, whether administered as monotherapy or in combination with IFN or erlotinib.

The incidences of serious adverse events, Grade 3-4 adverse events, adverse events leading to modification and/or discontinuation of bevacizumab, and treatment-related deaths in bevacizumab-treated patients in study BO17705 were comparable to those observed in the bevacizumab monotherapy and Bv + Erl treatment arms of study AVF2938g.

Table 1 Overview of the Adverse Event Experience in Metastatic Renal Cell Cancer Studies

	BO17705		**AVF0890s**			**AVF2938g [6]**	
	Pla + IFN[2]	**Bv [1]+ IFN[2]**	**Placebo**	**Bv 3 mg/kg**	**Bv 10 mg/kg**	**Bv[1] + Pl**	**Bv[1] + Erl[3]**
	N = 304	**N = 337**	**N = 40**	**N = 37**	**N = 39**	**N = 53**	**N = 51**
Any AE	287 (94%)	328 (97%)	NR	NR	NR	NR	NR
Grade 3 AE	129 (42%)	192 (57%)	NR	NR	NR	31 (59%)[4]	33 (65%)[4]
Grade 4 AE	12 (4%)	21 (6%)	0 (0%)	0 (0%)	0 (0%)		
Related AE (any grade)	238 (78%)	293 (87%)	NR	NR	NR	NR	NR
Serious AE	50 (16%)	98 (29%)	NR	NR	NR	18 (34%)	14 (28%)
Targeted AE (Grade ≥ 3)							
Any [7]	6 (2%)	58 (17%)	NR	NR	NR	24 (45%)	26 (51%)
Proteinuria	0	22 (7%)	0 (0%)	2 (5%)	3 (8%)	3 (6%)	4 (8%)
Hypertension	2 (<1%)	13 (4%)	0 (0%)	0 (0%)	8 (21%)	14 (26%)	16 (31%)
Bleeding	1 (<1%)	11 (3%)	0	0	0	2 (4%)	3 (6%)
Arterial TE	1 (<1%)	4 (1%)	0	0	0	0	1 (2%)
Venous TE	2 (<1%)	6 (2%)	0	0	0	2 (4%)	0
GI Perforation	0	5 (1%)	0	0	0	0	1 (2%)
Wound healing comp.	0	2 (<1%)	0	0	0	2 (4%)	0
CHF	0	1 (<1%)	0	0	0	1 (2%)	1 (2%)
AE leading to:							
Bv/Pl discontinuation	17 (6%)	63 (19%)	NR	NR	NR	16 (30%)[6]	13 (26%)[6]
Bv/Pl modification	57 (19%)	109 (32%)	NR	NR	NR		
Death no due to PD [5]	7 (2%)	8 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)

1 Bevacizumab 10 mg/kg q2w
2 Interferon alfa-2a 9 MIU 3x/wk
3 Erlotinib 150 mg/day
4 Grade 3 and 4 adverse events combined.
5 BO17705: All adverse events reported with an outcome death (related and unrelated, no time limit);
AVF0890s: Deaths possibly related to bevacizumab; AVF2938g: Deaths considered to be possibly or probably related to trial treatment, and which occurred up to 45 days of last drug intake.
6 Adverse events leading to change, hold or discontinuation of bevacizumab.
7 Includes hypertension, proteinuria, wound healing complication, bleeding/haemorrhage, gastrointestinal perforation, thromboembolic event (TE), congestive heart failure.
NR, not reported; AE, adverse event

The incidence of Grade 3-4 proteinuria, a known toxicity associated with bevacizumab, was also similar in the two studies (6%-8%) as well as in the 10 mg/kg q2w bevacizumab treatment arm of study AVF0890s (8%). The only notable exception was Grade 3-5 hypertension, which occurred at a much lower incidence in patients who received Bv + IFN in study BO17705 (4%) compared to patients who received Bv + Pl or Bv + Erl in study AVF2938g (26%-31%) and 10 mg/kg q2w bevacizumab in study AVF0890s (21%). This may well be explained by a difference in the way the hypertension events were reported in study BO17705, as it is suspected that some investigators graded hypertension events as Grade 2 instead of Grade 3, as they did not fully take into account the additional antihypertensive medications given to the patients when assessing the grade of

hypertension. Furthermore, it is possible that Grade 1 and 2 hypertension was treated more aggressively and/or proactively in this study than in the earlier studies, as investigators were now better trained to take appropriate measures to control this side effect.

Grade 3 and 4 adverse events, treatment-related events (any grade), serious adverse events, and adverse events leading to discontinuation or modification of trial treatment (interferon with bevacizumab/ placebo) showed a higher incidence in the Bv + IFN arm compared to the Pl + IFN arm. This difference may be explained by a higher incidence of the adverse events known to be associated with bevacizumab treatment, as well as the longer duration of IFN treatment in the Bv + IFN arm (236 days [34 weeks]) compared to the Pl + IFN arm (140 days [20 weeks]). There is some evidence that side effects of interferon may increase with the increased duration of treatment. Overall, taking into consideration the longer duration of exposure in the Bv + IFN arm, the addition of bevacizumab to interferon alfa-2a did not appear to lead to any clinically significant exacerbation of the known toxicities of interferon.
In the Phase II study AVF2938g, the incidences of Grade 3 or 4 (combined) adverse events, Grade 3-5 targeted adverse events, and of adverse events leading to study discontinuation were slightly higher in patients who received combination therapy with Bv + Erl compared to those who received bevacizumab alone. As in the BO17705 study, this may be explained by the addition of an active drug, in this case erlotinib, to bevacizumab. The reverse was true for serious adverse events. Overall, the addition of erlotinib to bevacizumab did not appear to worsen the toxicities associated with bevacizumab treatment. This study provides a good idea of what toxicities can be expected when using bevacizumab as monotherapy in mRCC.
Adverse event data from study AVF0890s are limited to the toxic effects of any grade that occurred in at least 10% of patients receiving either dose of bevacizumab and that were more frequent than in patients receiving placebo. In this study, no life-threatening Grade 4 (major organ) events or deaths possibly related to bevacizumab occurred. This study also clearly showed the safety profile which can be expected under exposure to single agent bevacizumab.

- **Adverse events in the pivotal study B017705**

Virtually all patients in both treatment arms (94%-97%) experienced at least one adverse event (any grade) between the time of first drug administration and 28 days after the last drug administration. The most common adverse events, reported in at least 10% of patients in one or both treatment arms, were all known to be associated with either IFN and/or bevacizumab.

The adverse events most commonly reported in study BO17705, but with a rather limited difference between both treatment arms, were those toxicities known to be caused by IFN treatment, and included pyrexia (Bv + IFN 45% vs. Pl + IFN 43%), anorexia (36% vs. 30%), fatigue (33% vs. 27%), asthenia (32% vs. 28%), and nausea (28% vs. 26%). In each case, the incidence was higher in the Bv+IFN arm than in the Pl+IFN arm; however, the increase in incidence did not exceed the increase in median IFN exposure in the Bv+IFN arm (236 days vs. 140 days = factor of 1.7), indicating that the increase in incidence may be related to the longer median duration of IFN treatment in the Bv+IFN arm. A time to onset analysis supports this explanation, since the Kaplan Meier estimate of median time to the first occurrence of any of four common IFN-associated toxicities (pyrexia, fatigue, asthenia, and malaise) was similar in both treatment arms (Bv+IFN 12 days vs. Pl+IFN 15 days. Other frequently reported IFN associated toxicities with an incidence of at least 10% in one or both treatment arms were influenza-like illness, chills, diarrhoea, myalgia, back pain, depression, weight decrease, and anaemia. Most of these events occurred more frequently in the Bv + IFN arm than in the Pl + IFN arm.

Established bevacizumab-specific toxicities of all grades with an incidence of at least 10% in the Bv + IFN arm were epistaxis (27% vs. 4%), hypertension (26% vs. 9%), and proteinuria (18% vs. 3%), and, as expected, all showed a much higher incidence in the Bv + IFN arm compared to the Pl + IFN arm. Adverse events with an incidence of at least 5% and showing a clear increase in incidence in the Bv + IFN arm compared to the Pl + IFN arm were sinusitis (5% vs. 1%) and dysphonia (5% vs. 0%). Neither of these events are known to be associated with either bevacizumab or IFN treatment.

The most commonly reported Grade 3-5 adverse events that occurred with at least a 2% difference between the treatment arms were the established interferon toxicities, fatigue and asthenia. Both of these events occurred more frequently in patients receiving combination therapy with Bv + IFN. However, these events occurred throughout the treatment period in both arms, suggesting that the longer duration of treatment in the Bv + IFN arm, and hence the higher number of patients at risk at any time point, may have resulted in the increased frequency reported for both these adverse events (Table 8). Furthermore, since all events except one in each treatment arm were Grade 3, it can be concluded that the addition of bevacizumab to IFN did not result in a clinically significant exacerbation of these two relatively common IFN related toxicities.

Table 9; Grade ≥3 Adverse Events That Occurred With at Least a 2% Difference Between Treatment Arms in Study BO17705: Safety Analysis Population

Body System/ Adverse Event	Pl + IFN N=304 No. (%)	Bv + IFN N=337 No. (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	25 (8.2)	40 (11.9)
ASTHENIA	20 (6.6)	34 (10.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
ANAEMIA	17 (5.6)	9 (2.7)
NEUTROPENIA	7 (2.3)	15 (4.5)
RENAL AND URINARY DISORDERS		
PROTEINURIA	-	22 (6.5)
VASCULAR DISORDERS		
HYPERTENSION	2 (0.7)	11 (3.3)

Deaths: At the time of the data cut-off for the interim analysis (September 8, 2006), a total of 15 patients were reported as having died for reasons other than disease progression; 7/304 (2%) patients in the Pl+IFN arm and 8/337 (2%) patients in the Bv+IFN arm. No particular pattern or cluster of adverse events leading to death can be identified.
Of the eight deaths in the Bv+IFN arm, four were associated with targeted bevacizumab-associated adverse events; ruptured aneurysm on Day 23, haemoptysis on Day 148, gastric perforation on Day 170, and myocardial IFNarction on Day 487. The first two (ruptured aneurysm and hemoptysis) were assessed by the investigator as being related to treatment. However, as outlined below, it is possible that both deaths were in fact linked to the underlying mRCC. Note that four other gastrointestinal perforation adverse events resolved without sequelae.

Serious adverse events (SAEs): were reported almost twice as frequently in the Bv + IFN arm (29%) than in the Pl + IFN arm (16%). However, other than the known bevacizumab toxicities such as gastrointestinal haemorrhage and perforations, epistaxis and haemoptysis, and those commonly seen with interferon treatment such as fatigue and pyrexia (all of which occurred more frequently in the Bv + IFN arm possibly because of the longer treatment duration), the majority of events were sporadic occurrences in one or two patients only.

Discontinuations: For both bevacizumab/placebo and IFN components of trial treatment, the proportion of patients who experienced an adverse event leading to discontinuation of treatment was higher in the Bv+IFN arm than in the Pl+IFN arm. Nevertheless, the median duration of treatment for both bevacizumab/placebo and IFN components remained significantly longer in the Bv+IFN arm compared to the Pl+IFN arm.

The increase in incidence of adverse events leading to discontinuation of treatment in the Bv+IFN arm was approximately 3-fold for bevacizumab/placebo (Bv+IFN 63/337 [19%] vs. Pl+IFN 17/304 [6%]) and 2-fold for IFN (76/337 [23%] vs. 35/304 [12%]), with a higher proportion of patients stopping IFN than bevacizumab/placebo in both treatment arms. The increase in incidence of events leading to discontinuation of bevacizumab can be explained by the active (bevacizumab) vs. non-active (placebo) treatment whilst the increase in incidence of events leading to discontinuation of IFN may be explained, at least in part, by the longer duration of IFN treatment in the Bv+IFN arm. Overall, adverse events leading to discontinuation of at least one component of trial treatment (either component) were experienced by 2.3 times as many patients in the Bv+IFN arm as in the Pl+IFN arm (95/337 [28%] vs. 37/304 [12%] patients.

In the Bv+IFN arm, the most common adverse events leading to discontinuation of treatment (either component) were toxicities known to be associated with either IFN (asthenia 14/337 [4%]; fatigue (9/337 [3%]) or bevacizumab (proteinuria 16/337 [5%]; hypertension [including one case of hypertensive crisis] 7/337 [2%]). A variety of gastrointestinal disorders, including several gastrointestinal perforations, also led to the discontinuation of treatment in several patients (13/337 [4%]).

In the Pl+IFN arm, the most common adverse events leading to discontinuation of treatment (either component) were fatigue (5/304 [2%]), asthenia (4/304 [1%]) and depression (4/304 [1%]).

Serious adverse events leading to discontinuation of one or both components of treatment occurred in 32/337 (9%) patients in the Bv+IFN arm and in 15/304 (4%) patients in the Pl+IFN arm. The majority of events led to discontinuation of both components of treatment. Nine of 32 patients in the Bv+IFN arm discontinued treatment due to a bevacizumab-related event; gastrointestinal perforation (4 patients), hemorrhage (2 patients), cerebrovascular accident (1 patient), pulmonary embolism (1 patient) and hypertensive crisis (1 patient). One patient in the Pl+IFN arm also discontinued treatment due to intracranial hemorrhage, confirming that intracranial lesions are at very high risk of bleeding events. The serious adverse events leading to discontinuation in the remaining patients in the Bv+IFN arm, and in all patients in the Pl+IFN arm, did not show any particular clustering of events.

- **Adverse events in study AVF2938g**

In study AVF2938g, a total of 31/53 (59%) patients in the Bv+Pl arm and 33/51 (65%) patients in the Bv+Erl arm experienced a Grade 3 or 4 adverse event. This small difference in incidence is not considered to be of clinical relevance.
The most common type of adverse event in both treatment arms was hypertension (Bv+Pl 14/53 [26%] vs. Bv+Erl 16/51 [31%]), which is an expected event for bevacizumab. Other Grade 3 or 4 adverse events reported by at least 3 (6%) patients in one or both treatment groups included proteinuria, which is also known to be associated with bevacizumab, and rash and diarrhea, both of which are known to be associated with erlotinib. All other Grade 3 and 4 events were reported by ≤ 2 patients in one or both treatment arms, for which no clinical relevance can be established.

Table 12: Grade 3 and 4 Adverse Events occurring in at Least Two Patients in One or Both Treatment Arms (Study AVF2938g)

Adverse event	**Bv[1] + Pla N = 53**	**Bv[1] + Erl[3] N = 51**
Any adverse event	31 (58.5%)	33 (64.7%)
Adverse event occurring in ≥ 2 patients		
Hypertension	14 (26.4%)	16 (31.4%)
Rash	0 (0.0%)	5 (9.8%)
Diarrhea	0 (0.0%)	4 (7.8%)
Proteinuria	3 (5.7%)	3 (5.9%)
Weight decreased	1 (1.9%)	3 (5.9%)
Dermatitis acneiform	0 (0.0%)	3 (5.9%)
Back pain	3 (5.7%)	0 (0.0%)
Vomiting	1 (1.9%)	2 (3.9%)
Dehydration	1 (1.9%)	2 (3.9%)
Nephrotic syndrome	0 (0.0%)	2 (3.9%)
Hyponatremia	2 (3.8%)	0 (0.0%)
Mental status changes	2 (3.8%)	0 (0.0%)
Renal failure acute	2 (3.8%)	0 (0.0%)
Wound healing (fistula, wound complication)[1]	2 (3.8%)	0 (0.0%)
Venous thrombosis (DVT, pulmonary embolism)[1]	2 (3.8%)	0 (0.0%)
Bleeding (GI hemorrhage, duodenal ulcer hemorrhage, hemoptysis) [1]	2 (3.8%)	3 (5.9%)

1 Targeted adverse events. Individual events were experienced by only one patient, but by at least two patients when combined with other events in the same targeted adverse event category.

The majority of toxicities reported were CTC Grade 1 or 2. Bevacizumab-associated Grade 3 events occurring in more than one patient were hypertension, proteinuria and chest pain; all except two cases of Grade 3 proteinuria occurred in the 10 mg/kg bevacizumab arm. There was no Grade 4 or 5 adverse events in this study.

Adverse events (Grade 1 and 2) that have not previously been associated with bevacizumab and which showed an increase in incidence in one or both of the bevacizumab treatment arms compared to placebo were fever without infection, malaise, hyponatremia and elevated alanine aminotransferase (ALAT). The increases in incidence in these adverse events are in line with the suspected difference in duration of treatment, which suggests some link to the bevacizumab treatment.

- **Adverse events of special interest**

Bleeding/haemorrhage, thromboembolic events (arterial or venous), hypertension, proteinuria, wound healing complications, congestive heart failure and gastrointestinal perforation are safety signals that have been identified during treatment of cancer patients with bevacizumab in a variety of indications. Therefore, to better understand the underlying pathogenesis, define the at risk patient population and therefore better manage these events, enhanced reporting was put in place to collect and report these "targeted events".

Hypertension

Across the studies there was an increase in the incidence of hypertension in the bevacizumab containing arms as compared to the control arms.

In study BO17705, the incidence of patients who developed any grade of hypertension in the Bv + IFN arm was 26% compared to 9% in the Pl + IFN arm. Most occurrences were grade 1 or 2, and none resulted in death. Grade 3 and 4 hypertension was reported in 4% of patients in the Bv + IFN arm and in 1% of patients in the Pl + IFN arm, which is lower than previously reported, and also lower than that seen in the two other trials in RCC reported here (AVF0890s [21%] and AVF2938g [26% – 31%]). As explained previously, this may be due, at least in part, to the difference in the way the severity of hypertension was reported in the three studies. No grade 4 or 5 hypertension was reported in studies AVF0890s and AVF2938g.

Although a fairly substantial number of patients experienced hypertension, only seven (8%) of the 88 patients with hypertension in the Bv + IFN arm discontinued bevacizumab therapy compared to none in the Pl + IFN arm, and only two Grade 4 hypertension events were reported.

Thirty-two (36%) of the 88 patients who developed hypertension in the Bv + IFN arm also had proteinuria reported. For the majority of these patients (30/32; 94%), the hypertension was Grade 1-2 and the proteinuria Grade 1-3. Only two patients with Grade 3-4 hypertension also had proteinuria (one Grade 1, one Grade 3). One (4%) of the 28 patients in the Pl + IFN arm who had hypertension also had proteinuria (Grade 2 hypertension, Grade 2 proteinuria).
Blood pressure data collected throughout the BO17705 study confirmed the increased incidence of hypertension in patients treated with bevacizumab. Forty (12%) patients in the Bv + IFN arm and 10 (3%) patients in the Pl + IFN arm had at least one systolic and/or diastolic reading above 150/100 mmHg. Two of the patients in the Bv + IFN arm and one of the patients in the Pl + IFN had severe hypertension (>200/110 mmHg).

Proteinuria

The incidence of all grades of proteinuria was higher in the Bv + IFN arm (18%) than in the Pl + IFN arm (3%) in study BO17705. Of the 59 patients with proteinuria in the Bv + IFN arm, 27 (46%) had Grade 3 proteinuria, compared to none in the Pl + IFN arm. No Grade 4 proteinuria events were reported. Bevacizumab/placebo treatment was discontinued in 16 (27%) of the 59 patients in the Bv + IFN arm and in 1 (13%) of the eight patients in the Pl + IFN arm. The relatively low number of patients withdrawn from bevacizumab therapy because of proteinuria indicates that for many patients the proteinuria can be managed relatively quickly by withholding their dose of bevacizumab until values have returned to within acceptable limits to continue treatment (which was only allowed to take place within a 6 week time window).

Among all patients with an adverse event of proteinuria, 32/59 (54%) patients in the Bv + IFN arm and 1/8 (13%) patients in the Pl + IFN arm had an accompanying hypertension adverse event.

In study AVF2938g, Grade 3 proteinuria was reported in 3/53 (6%) patients in the Bv + Pl arm and in 2/51 (4%) patients in the Bv + Erl arm. In addition, two patients in the Bv + Erl arm had Grade 4 proteinuria; both events were reported as nephrotic syndrome and bevacizumab therapy was discontinued. This study also investigated whether there was a correlation between proteinuria and Grade 3 and 4 hypertension, however, the correlation between the two was not significant (p=0.529).

Three of the 39 (8%) patients treated with bevacizumab 10 mg/kg q2w in study AVF0890s, and 2/37 (5%) patients receiving 3 mg/kg q2w arm had Grade 3 proteinuria. There were no reports of Grade 3 proteinuria in the placebo arm, and no cases of Grade 4 or 5 proteinuria in any of the treatment arms. Of 13 patients with Grade 2 or 3 hypertension, 7 (54%) patients also had Grade 2 or 3 proteinuria. Of 63 patients with Grade 0 or 1 hypertension, 10 (16%) patients also had Grade 2 or 3 proteinuria (p=0.007 by Fischer's exact test).

Haemorrhage/Bleeding
The incidence of patients with bleeding events was higher in the Bv + IFN arm (33%) than in the Pl + IFN arm (9%) in study BO17705. The majority (>80%) of these events in both treatment arms were Grade 1 epistaxis and gingival bleeding, and only nine cases (3%) of Grade 3 bleeding, and no cases of Grade 4 bleeding were reported in the Bv + IFN arm.

Most of the increased incidence in bleeding events reported in the Bv + IFN arm can be accounted for by the higher incidence of epistaxis, which is a known toxicity associated with bevacizumab; 27% of patients in the Bv + IFN arm compared to 4% of patients in the Pl + IFN arm experienced epistaxis. Of the remaining bleeding events, gingival bleeding (4% vs. 0.3%), and to a certain extent mouth haemorrhage (0.9% vs. 0%), were increased in the Bv + IFN arm. These three types of bleeding event are considered to be of only minor clinical relevance. Cases of various bleeding or haemorrhage events in the gastrointestinal tract were rare, and occurred in only one to two patients.

Three patients in this study died as a result of their bleeding events; two patients in the Bv + IFN arm (haemoptysis in a patient with progressive pulmonary metastases, and a ruptured aneurysm in a patient with an underlying aneurysm) and one patient in the Pl + IFN arm (intracranial haemorrhage in a patient with cerebral metastases). All three bleeding events are likely to be related to the underlying disease.

The incidence of bleeding (Grade 3-4) adverse events in study AVF2938g (4%-6%) was similar to that seen in the Bv + IFN arm in study BO17705 (3%). There were no deaths due to haemorrhage in either treatment arm.

No cases of ≥ Grade 3 bleeding were reported in any of the treatment arms in study AVF0890s.
Gastrointestinal Perforation
Five (1%) cases of a gastrointestinal perforation were reported in study BO17705, and all occurred in patients receiving Bv + IFN therapy. All patients experiencing this event were withdrawn from treatment, all events were Grade 3 or 4 and all resolved without sequelae, except for one patient who died as a result of a gastric perforation. This patient's death was considered by the investigator to be due to the underlying renal cancer with gastrointestinal tumour involvement.

One occurrence of a gastrointestinal perforation was reported in the Bv + Erl arm in study AVF2938g which resulted in the death of the patient. This patient presented with abdominal pain and diarrhoea, and was diagnosed with an ischemic bowel.

No gastrointestinal perforations were reported in study AVF0890s.

Thromboembolic Events
In study BO17705, arterial and venous thromboembolic adverse events were experienced by slightly more patients in the Bv + IFN arm (4%) than in the Pl + IFN arm (2%). The difference between the

two arms was primarily due to venous events, which were reported in 3% of patients in the Bv + IFN arm compared to 1% of patients in the Pl + IFN arm.

Grade 4 venous thromboembolic events occurred in four patients in the Bv + IFN arm and in one patient in the Pl + IFN arm, and one patient in the Pl + IFN arm had an arterial thromboembolic event; all events were embolisms. One case of a pulmonary embolism required discontinuation of bevacizumab therapy, as did a further four thromboembolic events (portal vein thrombosis, cerebrovascular accident, myocardial infarction, transient ischemic attack). None of the thromboembolic events were fatal

One arterial thrombotic event (Grade 3 transient ischemic attack) in the Bv + Erl arm, and two venous thrombotic events (Grade 3 deep venous thrombosis and a Grade 4 pulmonary embolism) in the Bv + Pl were reported in study AVF2938g. No venous thrombotic events were reported in the Bv + Erl arm.

No thromboembolic events were reported in the publication for study AVF0890s.

Wound Healing Complications
Wound healing complications were rare in study BO17705, and well balanced between the two treatment arms (Bv + IFN arm [1.5%]; Pl + IFN arm [1.0%)]. Two of the six events in the Bv + IFN arm were Grade 3; a case of skin graft failure requiring interruption of bevacizumab therapy and a case of impaired healing which led to bevacizumab being discontinued.

Two Grade 4 wound healing events occurred in the Bv + Pl arm in study AVF2938g, a fistula (erosion into the bowel secondary to tumour progression) and a non-infectious wound complication (chylous leak after left modified radical neck dissection).

No wound healing complication adverse events were reported in the publication of study AVF0890s.

Congestive Heart Failure
Two cases of congestive heart failure were reported in study BO17705, one in the Bv + IFN arm (Grade 3 ventricular dysfunction) and one in the Pl + IFN arm (Grade 2 cardiac failure). One case of dyspnoea (Grade 3) in the Bv + Pl arm and one case of ventricular dysfunction (Grade 3) in the Bv + Erl arm were reported in study AVF2938g. No cases of congestive heart failure were reported in patients treated with bevacizumab monotherapy or placebo in study AVF0890s.

- **Laboratory findings**

No new safety signals associated with bevacizumab treatment were identified from the laboratory test results in studies BO17705 or AVF2938g. The majority of post-baseline abnormalities for all parameters were Grade 1 or 2. As expected from the adverse events reporting, Grade 3 proteinuria, measured either by dipstick or in a 24-hour urine sample, occurred more often in patients in the Bv + IFN arm than in the Pl + IFN arm.

Raised serum creatinine values (Grade 3 or 4) in study BO17705 were reported rarely (one patient in each treatment arm), indicating that adding bevacizumab to interferon did not adversely affect renal function.

- **Safety in special populations**

Not performed.

- **Safety conclusions**

Overall, bevacizumab was safe and well tolerated in patients with advanced and/or mRCC at the recommended dose of 10 mg/kg q2w in combination with 9 MIU interferon alfa-2a given three times weekly.

In particular, adding interferon to bevacizumab did not appear to increase the incidence of the targeted adverse events of hypertension, proteinuria, bleeding, gastrointestinal perforation, wound healing complications, thromboembolic events or congestive heart failure, all of which have been previously identified as being related to bevacizumab therapy. The incidence of these and other events seen with

Bv + IFN combination therapy was not greater that that seen in the two studies which had a bevacizumab monotherapy arm, or in studies with bevacizumab in other cancer indications.
No unexpected safety findings were identified.
The incidence of well-known AEs related to bevacizumab was not greater than seen in other studies with bevacizumab given as monotherapy. However, not surprisingly, more toxicity was reported in the Bv+IFN arm, and especially the rate of SAEs and discontinuations was almost doubled when adding bevacizumab to the IFN treatment.
In relation to the well-known safety profiles of bevacizumab and IFN, no synergistic adverse effects were induced by combining the treatments, but overall, it appears that the gain in PFS and ORR is at the expense of greater toxicity in some of the patients. iv.

3. OVERALL CONCLUSION AND Benefit-risk assessment

This application is based on one pivotal Phase III study (BO17795 - ongoing) which investigates the use of bevacizumab in combination with IFN in patients with advanced and/or metastatic renal cell cancer, and two supportive Phase II studies (AVF2938g and AVF0890s).

All three studies were multi-centre, randomized, double-blind, of a comparative parallel group design.
Study BO17705 evaluated the efficacy and safety of bevacizumab (10 mg/kg q2w) in combination with interferon alfa-2a (target dose of 9 MIU three times weekly) (Bv+IFN) versus placebo and interferon alfa-2a (Pl+IFN) as first line treatment administered to nephrectomised patients with advanced and/or metastatic renal cell cancer (mRCC). Study AVF2938g evaluated the efficacy and safety of bevacizumab (10 mg/kg q2w) in combination with erlotinib (150 mg daily) (Bv + Erl) compared with bevacizumab plus placebo (Bv + Pl) in patients with metastatic clear-cell RCC. Study AVF0890s evaluated the efficacy and safety of bevacizumab monotherapy (3.0 mg/kg and 10 mg/kg q2w) compared to placebo in patients with relapsing metastatic clear-cell RCC who had failed IL-2 therapy, or in whom IL-2 therapy was contraindicated. In all three studies bevacizumab was given until disease progression or unacceptable toxicity, and the maximum duration of treatment with bevacizumab was approximately 24 months. The dose selection and the dose-response question of bevacizumab have still not been resolved. As there's no evidence of an association between the baseline VEGF level and the efficacy of bevacizumab, the Applicant has not been able to justify why the highest dose of bevacizumab (10 mg/kg q2w) is required in RCC patients. Overall, the dose-finding study (AVF0890s) investigated the activity of 3.0 mg/kg and 10 mg/kg q2w bevacizumab as single-agent second-line treatment in RCC patients previously treated with IL-2. Therefore, the results can not directly be extrapolated to the proposed indication, as patients are expected to get a better response from first-line therapy plus additional benefit from IFN. Furthermore, the lack of investigations of a 5.0 mg/kg q2w bevacizumab arm seems obvious as it theoretically could convey corresponding efficacy but lower toxicity than the 10 mg/kg dose. No specific, predictive factors of toxicity have been identified. Possibility for further investigations on the 5 mg/kg q2w bevacizumab dose in combination with IFN for the first-line treatment of patients with metastatic renal cell cancer was discussed at the CHMP but it was finally accepted that investigation of potentially predictive biomarkers would be way to address such issues.

In the pivotal study IFN was given for 52 weeks or until disease progression or unacceptable toxicity. In the absence of disease progression, patients in study BO17705 could continue with bevacizumab/placebo treatment alone for maximally 52 weeks, while upon evidence of disease progression all study treatments were to be discontinued permanently. Patients who experienced protocol-defined toxicity to bevacizumab/placebo or interferon alfa-2a were required to discontinue treatment with the corresponding agent. In cases where bevacizumab/placebo was discontinued, continuation of IFN could be considered.

The pivotal study (BO17705) included 649 patients, 327 in the Bv+IFN arm and 322 in the Pl+IFN arm. The study was conducted in 101 centres in 18 countries (Eastern and Western Europe and Australasia). Originally, the primary endpoint was to assess overall survival (OS). However, in November 2006 the study was unblinded and the primary endpoint was changed to progression free survival (PFS), which was originally a secondary endpoint. Other secondary endpoints were time to disease progression (TTP), time to treatment failure (TTF), objective response rate (ORR) and

duration of response (DR). In the two treatment arms, the baseline data of the recruited patients were generally similar except for a small difference in gender (27% women in the Pl+IFN arm *vs.*32% women in the Bv+IFN arm). The Motzer score, Karnofsky performance status, median number of disease sites per patient as well as the target lesion sites were all comparable between the two treatment arms. The interim analysis indicated a weak tendency towards an improvement in OS for the bevacizumab arm (HR=0.79; p<0.067). There was a statistically and clinically significant increase in median PFS, which was almost doubled with Bv+IFN treatment (10.2 months) compared to Pl+IFN treatment (5.4 months) (HR=0.63 p<0.0001). There was also a statistically significant difference in median TTP (4.7 months; HR=0.61 p<0.0001) and TTF (3.3 months; HR=0.73 p=0.0003) in favour of the Bv+IFN treatment. The ORR was significantly increased in patients treated with Bv+IFN (31%) compared to those receiving treatment with Pl+IFN (13%) (p<0.0001), and the median duration of objective response was slightly longer in the Bv+IFN treated patients (13.5 months) compared to the Pl+IFN treated patients (11.1 months) (95% CI [0.55, 1.61]).

No significant change was observed in OS, but the data were not mature at the time of the data cut-off for the interim analysis, and the result may have been confounded by the introduction of new second-line therapies during the progress of the pivotal trial. Therefore, PFS is accepted as a valid primary endpoint with regulatory precedence. Furthermore, the MAH has presented data to support PFS as a surrogate for survival and has demonstrated that the addition of bevacizumab to IFN does not have a negative impact on patients' performance status before progression, the use of co-medication for pain relief or haemoglobin values.

In general, exploratory subgroup analyses of PFS in study BO17705 showed point estimates for the Hazard Ratio below 1 in all subgroups examined, indicating a consistent benefit in adding bevacizumab to interferon alfa-2a. No conclusions can be made at present for OS in subgroups by age as the data are currently immature. A possible, smaller benefit in the elderly subgroups across studies and indications, could be explained by a limited number of enrolled patients, higher variability and shorter life expectancy in the elderly population.

Pharmacokinetic data from study BO17705 are consistent with results from previous studies. The existing data suggest that bevacizumab has no major interaction on the pharmacokinetics of IFN. Furthermore, the MAH has demonstrated that neither renal nor hepatic function have an influence on bevacizumab exposure. An update of section 5.2 in the SmPC on the available information regarding the distribution, metabolism and excretion of bevacizumab is requested.

Comparison of data across the three studies BO17705, AVF0890s and AVF2938g, is complicated by differences in treatment regimens, patient populations, and durations of treatment. Nevertheless, the available data from the pivotal study BO17705 and the supportive study AVF0890s showed that the PFS was almost doubled for patients receiving bevacizumab treatment compared to patients in the placebo group. Furthermore, in study AVF2938g the PFS observed with bevacizumab as monotherapy was approximately 80% of the PFS in the Bv+IFN arm of the BO17705 study (8.5 and 10.2, respectively).
Thus, from the submitted documentation a prolongation of PFS and an improvement in objective response rate was observed for patients receiving bevacizumab treatment (10 mg/kg/q2w). This should, however, be confirmed by an independent review of tumour assessments.

The regimen of 10 mg/kg 2qw bevacizumab in combination with IFN has demonstrated clinically significant efficacy, and has proven an acceptable safety profile, whereas a lower dose of bevacizumab (3 mg/kg q2w) had not resulted in a clinically meaningful benefit. The MAH commits to investigate on modeling and simulation of the Dose – Tumor response over time. In particular, the MAH will evaluate the dose-tumor size response relationship using a mathematical model characterizing the dose effect of Avastin on Tumor progression. It is envisaged that this model can be build using the Phase II study (AVF0890s) data which investigates the placebo, 3 mg/kg 2qw and 10 mg/kg q2w and the Phase III study (BO17705) data which investigated IFN and 10 mg/kg q2w bevacizumab + IFN. It is anticipated that the model developed can be used to evaluate the expected tumour size response over time following 5 mg/kg 2qw bevacizumab + IFN.

The MAH has proposed an indication which includes both advanced and metastatic RCC. According to the inclusion criteria the patients should present with metastatic clear-cell RCC. In the study population, both patients with locally advanced disease and metastatic disease were analysed. It seems reasonable to include both advanced and metastatic disease in the indication. Furthermore, the indication should not be restricted to nephrectomised patients. Limited data and the mechanism of action of bevacizumab indicate that patients, who do not undergo nephrectomy, will also benefit from treatment with bevacizumab.

In conclusion, the pivotal study BO17705 demonstrated a substantial increase in median PFS (10.2 months versus 5.4 months) and ORR (31.4% versus 12.8%) when bevacizumab was added to IFN compared to placebo+IFN in the treatment of patients with mRCC. Thereby, bevacizumab+IFN offer a treatment effect that is better than IFN as single-agent therapy and in line with the effect of tyrosine kinase inhibitors in first-line therapy.

A total of 517 patients with mRCC were exposed to at least one dose of bevacizumab in the three studies; BO17705, AVF2938g and AVF0890s. Generally, there were no unexpected toxicities with the use of bevacizumab in combination with IFN in study BO17705. The principal risks shown to be associated with bevacizumab in the pivotal study were an increase in Grade ≥ 3 proteinuria, hypertension, bleeding, and gastrointestinal perforation. Other targeted adverse events which also showed an increased incidence in the Bv+IFN arm were arterial thromboembolic events, wound healing complications and CHF. However, in all three cases, the incidence in both study arms was ≤ 1%. Furthermore, other Grade ≥ 3 events with an increase in absolute incidence of > 1% in the bevacizumab arm compared to the control arm in study BO17705 were fatigue, asthenia, depression, neutropenia and venous thromboembolic events.

A total of five bevacizumab-treated patients died as a result of a targeted adverse event in the three studies; two patients due to GI perforation (studies BO17705 and AVF2938g), two patients due to bleeding (both BO17705), and one patient due to myocardial infarction (study BO17705).

In summary, the overall incidence of adverse events experienced in patients that were treated with bevacizumab+IFN was higher than in patients treated with placebo+IFN. The adverse events reported most often in the bevacizumab+IFN group were toxicities known to be caused by IFN treatment including pyrexia, anorexia, fatigue, asthenia, and nausea. Established bevacizumab-specific toxicities like bleeding (mainly epistaxis), hypertension, proteinuria, gastrointestinal perforations and thromboembolic events also showed a much higher incidence in the bevacizumab+IFN arm compared to the Pl + IFN arm, as expected, but they were no more frequent than previously reported from studies in other indications. Grade 3-4 adverse events were reported for IFN frequently, but the incidence of serious adverse events and discontinuations almost doubled in the bevacizumab+IFN arm compared to the control arm. Nevertheless, the median duration of treatment remained significantly longer in the Bv+IFN arm compared to the Pl+IFN arm. Deaths were mainly due to progressive disease. No new safety concerns were identified.

Overall, a clinical benefit to the patients has been established, why the benefit/risk balance of bevacizumab + IFN in the treatment of mRCC is considered positive. Although increased toxicity was observed when combining bevacizumab with IFN, the safety profiles of both drugs are well established and the combination regimen did not lead to unexpected safety findings.

The three key issues relevant for assessing similarity with orphan medicinal products approved in RCC setting are molecular structural features, mechanism of action and therapeutic indication. The conclusion of non-similarity regarding molecular structure and mechanism of action is supported.

In conclusion, a clear clinical benefit to the patients can be established and the benefit/risk balance of bevacizumab + IFN in the treatment of mRCC is overall considered positive, given the urgent need for additional treatment options in this population of cancer patients with a very poor prognosis. Although increased toxicity was observed when combining bevacizumab with IFN, the safety profiles of both drugs are well established and the combination regimen did not lead to unexpected safety findings.

The overall Benefit/Risk assessment of bevacizumab in combination with interferon alfa-2a is for the first line treatment of patients with advanced and/or metastatic renal cell cancer is positive. The MAH will also provide a survival update for study BO17705.

The MAH will perform an independent retrospective review of the tumour assessments done in study BO17705 with the objective to collect all images from all patients enrolled in the study. Due to the retrospective nature of this review, it is not expected that it will be possible to obtain all images; however, every effort will be made to obtain images from as many evaluable patients as possible.