SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BO17705)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: Avastin® NAME OF ACTIVE SUBSTANCE(S): Bevacizumab	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Interim Analysis: A randomised, double-blind, phase III study to evaluate the efficacy and safety of bevacizumab in combination with interferon alfa-2a (Roferon) versus interferon alfa-2a and placebo as first line treatment administered to nephrectomised patients with metastatic clear cell renal cell carcinoma. Report No. [redacted] March 2007, amended version July 2007 (error in analysis of sub groups by Motzer score corrected)		
INVESTIGATORS / CENTERS AND COUNTRIES	101 centers in 18 countries (Australia 10, Belgium 4, Czech Republic 3, Finland 2, France 16, Germany 8, Hungary 2, Israel 5, Italy 9, Netherlands 2, Norway 4, Poland 6, Russia 10, Singapore 1, Spain 9, Switzerland 3, Taiwan 4, United Kingdom 3) Principal investigator: [redacted] France, [redacted]		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	June 29, 2004 to September 8, 2006 (first patient randomized to data cut-off)	CLINICAL PHASE	3

OBJECTIVES

Primary:

- To determine the efficacy of the combination of bevacizumab and interferon alfa-2a (Bv+IFN) compared to placebo and interferon alfa-2a (Pl+IFN) in patients with metastatic RCC, based on overall survival

Secondary:

- To determine the progression-free survival, time to disease progression, time to treatment failure and objective response rates of bevacizumab and IFN compared to placebo and IFN
- To characterize the safety profile of the combination of bevacizumab and IFN compared to placebo and IFN
- To explore the potential existence of anti-bevacizumab antibodies (HAHA)

A pharmacokinetic sub-study was conducted under a separate protocol (BO17705-PK).

- Primary objective: To evaluate the potential effect of bevacizumab on the pharmacokinetics of IFN
- Secondary objective: To assess the pharmacokinetics of bevacizumab

STUDY DESIGN: Multicenter, randomized (2 treatment arms), double-blind

NUMBER OF PATIENTS

	Bv + IFN	Pl + IFN
Randomized	327	322
Still on treatment/in follow-up	199	174

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Metastatic clear cell renal cell carcinoma

Inclusion criteria:

- No prior systemic treatment for metastatic RCC (including neo-adjuvant therapy)
- Age ≥ 18

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	• Patient was nephrectomized for primary renal cell carcinoma (clear cell type). Partial nephrectomy was allowed only if the resection margins were clearly negative. • Patient with renal cell carcinoma (RCC) for whom a majority component (> 50%) of conventional clear cell type was mandatory • If metastatic disease was diagnosed more than two years from the date of the initial diagnosis (of RCC), histological or cytological confirmation of renal cell carcinoma (clear cell type) origin of the metastatic lesion(s) was mandatory. • Karnofsky performance status ≥ 70% • If applicable: negative pregnancy test; effective contraceptive measures
TRIAL DRUG / STROKE (BATCH) No.	Bevacizumab (batch numbers: [redacted] formulation [redacted] Interferon alfa-2a (batch numbers: [redacted] formulations [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Bevacizumab (10 mg/kg iv every two weeks) plus interferon alfa-2a (9 MIU sc 3 times weekly) until disease progression
REFERENCE DRUG / STROKE (BATCH) No.	Placebo (batch numbers: [redacted] formulation [redacted] Interferon alfa-2a (batch numbers as above)
DOSE / ROUTE / REGIMEN / DURATION	Placebo (iv administration every two weeks) plus interferon alfa-2a (9 MIU sc 3 times weekly) until disease progression
CRITERIA FOR EVALUATION	
EFFICACY:	Primary: • Duration of overall survival (OS) Secondary: • Progression-free survival (PFS) • Time to progression • Time to treatment failure • Overall response rate (OR) • Performance status (Karnofsky score)
PHARMACOKINETICS:	Population PK: Primary parameters were clearance, central volume, and peripheral volume of bevacizumab. Secondary parameter was $AUC_{0-\tau}$ of bevacizumab at steady state. PK sub-study: Primary parameter was AUC_{0-last} of IFN in serum. Secondary parameters were C_{min}, C_{max}, $AUC_{0-\tau}$, $AUC_{0-\infty}$, CL_{ss}/F, V_z/F, terminal $t_{1/2}$, t_{max} of IFN and C_{min}, C_{max}, $AUC_{0-\tau}$, CL_{ss}, V_{ss}, and terminal $t_{1/2}$, t_{max} of bevacizumab.

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SAFETY:	Adverse events, laboratory tests (hematology, serum chemistry, urinalysis), vital signs, ECG, anti-bevacizumab antibodies
STATISTICAL METHODS	Efficacy: 2-sided log rank test at the 5% alpha level, Kaplan Meier curves, Cox regression analyses; difference in overall response rate was tested using a chi-squared test with Schouten correction. Population PK: Empirical Bayes estimates were obtained from a reference population PK model. For the PK sub-study the geometric mean ratio of $AUC_{0\text{-last}}$ and C_{max} of IFN were reported.

METHODOLOGY:

After undergoing screening assessments and providing their informed consent, patients were randomized to one of two treatment arms: IFN 9 MIU 3 times weekly plus bevacizumab 10 mg/kg every two weeks or IFN 9 MIU 3 times weekly plus placebo every two weeks. IFN was administered for a maximum duration of 52 weeks in the absence of disease progression or major toxicity. In case of permanent discontinuation of one of the two treatment components (IFN or bevacizumab/placebo) for safety reasons, the other treatment component could be continued.

Upon evidence of disease progression, all study treatments were to be discontinued permanently. In the absence of disease progression at week 57, the patient could continue with bevacizumab/placebo treatment until progression.

A maximum of 5 target lesions per organ and 10 lesions in total were to be identified, recorded, and measured at screening. All other lesions were to be recorded as non-measurable disease. Tumor measurements/assessments were made based on RECIST criteria based on CT scans, MRI scans, X-ray, bone scan, and/or clinical examination until (confirmed) evidence of disease progression. Post screening assessments were to be done every 8 weeks up to week 32 and every 12 weeks thereafter until disease progression. In cases of clinical evidence of progression before the next scheduled assessment, an unscheduled tumor assessment was to be performed.

Adverse events were recorded on an ongoing basis. Special guidelines were to be followed in case of hypertension, proteinuria, thrombosis, or hemorrhagic events. Assessments including body weight, body temperature, pulse, hematology, and blood chemistry were performed pre-dose, at weeks 1, 3, 5, 7 after treatment start, and every 4 weeks for the duration of study therapy. Urinalysis and blood pressure were to be assessed prior to each bevacizumab/placebo infusion.

For population PK analyses, blood samples were collected from a subset of 230 patients. Samples were collected before the first dose of bevacizumab/placebo, and pre-dose at week 3, week 5, week 11, and then 28 days after the last dose. Patients participating in the PK sub-study provided additional blood samples on a day when both bevacizumab/placebo and IFN were administered: within 15 minutes before the start of the bevacizumab infusion, at the end of the infusion, and at 1, 4, 8, and 24 hours after IFN injection; blood samples for bevacizumab were also drawn 5, 8, 11, and 15 days after the first PK sampling, with the last sample just before the next bevacizumab infusion. For IFN, blood samples were drawn within 15 minutes before injection and 1, 2, 4, 6, 8, 10, 18, 21 and 24 hours after administration.

In all patients, the following assessments were to be made 28 days after end of treatment: Karnofsky performance status, physical measurements including body weight, body temperature, pulse, hematology, blood chemistry, urinalysis, and blood pressure, blood samples for anti-bevacizumab antibodies (in case the patient was in the study up to and including week 11), concomitant treatments, adverse events.

Survival follow-up for all patients (either on completion of treatment or at discontinuation after 28 days

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safety follow-up) was to continue until study closure. Visits were scheduled every 3 months for the first year of the survival follow-up and 6 monthly thereafter.
The following assessments were requested:

- Patients without documented disease progression were to be followed for progression and survival.
- Patients with documented disease progression were to be followed for survival only.
- Subsequent anti-cancer therapy
- Follow-up of specific events at end of treatment: Hypertension, proteinuria, and wound healing
- Anti-bevacizumab antibodies (HAHA) at month 3 and 6 (only for patients who had been in the study up to and including week 11)
- Study drug related serious adverse events until the event had resolved
- Surgical procedures and major injuries which occurred up to 6 months after treatment

EFFICACY RESULTS:

This report summarizes the interim analysis of overall survival and final analysis of progression-free survival. The addition of bevacizumab to interferon alfa-2a as first-line therapy for patients with metastatic clear cell renal cell carcinoma resulted in:

- A clinically relevant and statistically significant increase in progression-free survival (median 10.2 vs 5.4 months; hazard ratio 0.63, 95% CI [0.52, 0.75], p<0.0001)
- A strong trend towards an increase in overall survival (hazard ratio 0.79, 95% CI [0.62, 1.02], p=0.0670)
- A statistically significant increase in time to disease progression (median 10.2 vs 5.5 months; hazard ratio 0.61, 95% CI [0.51, 0.73], p<0.0001)
- A statistically significant increase in the percentage of responders in the Bv+IFN arm (31%) compared to the Pl+IFN arm (13%); difference in response rates 18.57, 95% CI [11.9, 25.2], p-value <0.0001
- An increase in the duration of PFS and OS in most of the subgroups analyzed which was generally consistent with the overall treatment effect

PHARMACOKINETIC RESULTS:

A Bayesian feedback population PK analysis was performed. Based on the metrics used, the pharmacokinetic characteristics in patients with mRCC and previously treated populations comprised of patients with different types of cancer were comparable.
The PK characteristics of IFN and bevacizumab were consistent with previous observations. There was no statistically significant effect of bevacizumab treatment on the pharmacokinetics of interferon.

SAFETY RESULTS:

The safety data were generally in line with observations in previous studies of bevacizumab in cancer patients. The overall incidence of grade 3-5 adverse events, serious adverse events, and adverse events leading to withdrawals was 1.3-3.2-fold higher in the Bv+IFN arm compared to the Pl+IFN arm. This was due in part to the adverse events known to occur with bevacizumab therapy, including bleeding, hypertension, proteinuria, thromboembolic events, and gastrointestinal perforations, see table below.
The most common adverse events in both treatment arms were 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%). All 5 are established IFN-associated toxicities, although anorexia and nausea may also be linked to the underlying disease. Some of the imbalance in the incidence of these types of AEs may be due to the longer median duration of IFN treatment in the Bv+IFN arm (34 weeks vs 20 weeks).
There were 5 patients in the Pl+IFN arm and 7 in the Bv+IFN arm who died due to an adverse event during

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the time from first drug administration until 28 days after last study drug administration. Two more patients in the Pl+IFN arm and one in the Bv+IFN arm died due to an AE occurring later during follow-up. No particular pattern was seen in the types of events that resulted in death.
Laboratory tests did not show new clinically relevant safety signals. The incidence of shifts from baseline was comparable between study arms with the exception of increases in proteinuria and GGT, which were more common in the Bv+IFN arm, and a decrease in hemoglobin, which was more common in the Pl+IFN arm. The rate of other grade 3-4 laboratory abnormalities was comparable between study arms.
No notable changes in vital signs, ECG parameters, and Karnofsky performance status were observed during the study.
Two patients in the Bv+IFN arm had a negative human anti-human antibody (HAHA) titer at screening and a positive (but low) HAHA titer when measured 3-6 months after the end of treatment.

Safety Parameter	**Pl + IFN n = 304**	**Bv + IFN n = 337**
Any adverse event	287 (94%)	328 (97%)
NCI-CTC grade 3, 4, 5 adverse event	137 (45%)	203 (60%)
Adverse event leading to death	6 (2%)	8 (2%)
Serious adverse event	50 (16%)	98 (29%)
AE leading to discontinuation (any study drug)	37 (12%)	95 (28%)
AE of special interest (all categories)	66 (22%)	186 (55%)
Hypertension	28 (9%)	88 (26%)
Proteinuria	8 (3%)	59 (18%)
Gastrointestinal perforation	0	5 (1%)
Wound healing complication	3 (1%)	5 (1%)
Venous thromboembolic events	3 (<1%)	10 (3%)
Arterial thromboembolic events	2 (<1%)	5 (1%)
Bleeding (all events)	28 (9%)	112 (33%)
Congestive heart failure	1 (<1%)	1 (<1%)

CONCLUSIONS:

This study demonstrated that the addition of bevacizumab to interferon alfa-2a therapy provides substantial benefit to patients with advanced and/or metastatic renal cell cancer. This was shown by a statistically significant, 1.9-fold increase in the median duration of progression-free survival (10.2 months versus 5.4 months), a longer time to disease progression, a longer time to treatment failure, and a >2-fold higher objective response rate. Although data for overall survival are immature, there was a strong trend for an increase of overall survival (hazard ratio 0.79, p-value 0.067).
The safety data were consistent with previous observations in cancer patients treated with bevacizumab. The pattern of the incidence of common adverse events includes both the established side effects of IFN treatment (eg, asthenia and fatigue) as well as the known bevacizumab associated toxicities, such as bleeding/hemorrhage, hypertension, proteinuria, and thromboembolic events.
A population pharmacokinetic analysis was performed and showed that the pharmacokinetic characteristics of bevacizumab in mRCC patients were comparable to those observed previously in patients with different types of cancer. Results from the drug-drug interaction sub-study suggest that a clinically relevant effect of bevacizumab on interferon alf-2a pharmacokinetics is very unlikely.