SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BO17705)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	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. Final Report No. [redacted] March 2009.	
INVESTIGATORS / CENTERS AND COUNTRIES	101 centers in 18 countries (Australia, Belgium, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Netherlands, Norway, Poland, Russia, Singapore, Spain, Switzerland, Taiwan, United Kingdom)	
PUBLICATION (REFERENCE)	Escudier B, Pluzanska A, Koralewski P, et al. Lancet 2007; 370:2103-2111. Melichar B, Koralewski P, Ravaud A, et al. Annals Oncol 2008; 19:1470-1476.	
PERIOD OF TRIAL	June 29, 2004 to September 24, 2008 (first patient randomized to final data cut-off)	CLINICAL PHASE: III
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 renal cell carcinoma (mRCC), 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)	
STUDY DESIGN	Multicenter, randomized (2 treatment arms), double-blind	
NUMBER OF PATIENTS	Planned sample size: 638 patients (319 per treatment arm) Patients randomized (= intent-to-treat population): 649 (Bv + IFN: 327; Pl + IFN: 322)	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Metastatic renal cell carcinoma, majority component (> 50%) clear-cell type, documented nephrectomy, no prior systemic treatment for metastatic RCC, Karnofsky performance status ≥ 70%	

TRIAL DRUG / STROKE (BATCH) No.	Bevacizumab (Bv, batch numbers: [redacted] Interferon alfa-2a (IFN, batch numbers: [redacted] formulations [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Bevacizumab (10 mg/kg iv every 2 weeks) plus interferon alfa-2a (9 MIU sc 3 × weekly) for 52 weeks or until disease progression. In the absence of disease progression after 52 weeks, patients could continue with bevacizumab monotherapy.
REFERENCE DRUG / STROKE (BATCH) No.	Placebo (Pl, batch numbers: [redacted] formulation [redacted] Interferon alfa-2a (batch numbers as above)
DOSE / ROUTE / REGIMEN / DURATION	Placebo (iv every 2 weeks) plus interferon alfa-2a (9 MIU sc 3 × weekly) for 52 weeks or until disease progression. In the absence of disease progression after 52 weeks, patients could continue with bevacizumab-placebo monotherapy.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary:** Duration of overall survival (OS) **Secondary:** Duration of progression-free survival (PFS), time to progression, time to treatment failure, overall response rate (ORR), 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.
SAFETY:	Adverse events, laboratory tests (hematology, serum chemistry, urinalysis), vital signs, ECG, anti-bevacizumab antibodies
STATISTICAL METHODS	The difference in OS, PFS, time to progression, and time to treatment failure was tested with a 2-sided log-rank test at the 5% alpha level. The difference in ORR was tested with a chi-squared test (2-sided) with Schouten correction. The interim OS analysis (including the final PFS analysis, cut-off September 8, 2006, see report No [redacted]) followed a sequential alpha spending function approach using an O'Brien and Fleming boundary function, resulting in a 2-sided significance level of 0.0056 for the interim OS analysis and 0.0482 for the final OS analysis. Population PK: Empirical Bayes estimates were obtained from a reference population PK model.

METHODOLOGY:

Randomization was 1:1 and stratified according to country and Motzer score. Tumor assessments were made using modified RECIST criteria based on CT scans, MRI scans, X-ray, bone scan, and/or clinical examination. Adverse events were recorded on an ongoing basis. After the pre-planned interim OS analysis (including the final PFS analysis, cut-off September 8, 2006), the study was unblinded, and patients treated with placebo who had not progressed were allowed to switch to bevacizumab.

EFFICACY RESULTS:

The difference in overall survival in the Bv+IFN arm and the Pl+IFN arm did not reach statistical significance, see summary below. Of note, a high proportion of patients received subsequent non-study therapy for RCC (63% of Pl+IFN patients and 55% of Bv+IFN patients), which introduced an uncontrolled element into the primary analysis.

An unstratified multiple Cox regression model of best fit using backward selection indicated that several baseline prognostic factors were strongly associated with survival independent of treatment (eg, gender, number of metastatic sites, and Motzer score). Adjustment for these factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63;0.96], p-value = 0.0219).

Summary of Efficacy (Intent-to-Treat Population, Unstratified Analyses)

Parameter	**Pl + IFN N = 322**	**Bv + IFN N = 327**	**Hazard Ratio [95% CI]**	**p-Value [b]**
Median follow-up (months)	20.6	22.9	-	-
Overall survival (months) [a]				
Interim OS analysis (cut-off Sept 8, 2006)	19.8	n.r.	0.79 [0.62;1.02]	0.0670
Final OS analysis (cut-off Sept 24, 2008)	21.3	23.3	0.91 [0.76;1.10]	0.3360
Progression-free survival (months) [a]				
Final PFS analysis (cut-off Sept 8, 2006)	5.4	10.2	0.63 [0.52;0.75]	0.0001
PFS using cut-off Sept 24, 2008	5.5	10.2	0.75 [0.64;0.88]	0.0004
Time to progression (months) [a]	5.5	10.2	0.73 [0.62;0.86]	0.0002
Time to treatment failure (months) [a]	4.5	8.1	0.78 [0.66;0.92]	0.0023
Best Overall Response [d]	**Pl + IFN n = 289**	**Bv + IFN n = 306**	**Difference in Rates [95% CI]**	**p-Value [c]**
Overall response rate	12.5%	32.4%	19.9% [13.2%;26.6%]	< 0.0001

n.r.: not reached
[a] Medians were estimated from Kaplan-Meier curves.
[b] Log-rank test
[c] Chi-squared test
[d] Patients with measurable disease

PHARMACOKINETIC RESULTS:

The results of the population pharmacokinetic analyses were reported as part of the interim study report (report No [redacted]).

SAFETY RESULTS:

The safety findings were consistent with those presented in the interim study report (report No [redacted]) and with the known safety profiles of bevacizumab and interferon alfa-2a, see summary below. The median duration of treatment with bevacizumab was 295 days (42 weeks) in the Bv+IFN arm compared to a median duration of treatment with placebo of 155 days (22 weeks) in the Pl+IFN arm. The median duration of interferon treatment was 236 days and 140 days in the Bv+IFN and Pl+IFN arm, respectively.

Two fatal AEs were judged related to treatment, both in the Bv+IFN arm. There were no new findings in laboratory test results, assessments of vital signs, ECG parameters, Karnofsky performance status, or anti-bevacizumab antibodies.

Summary of Safety (Safety Population)

Adverse Event	Pl + IFN No. of Patients (%) n = 304	Bv + IFN No. of Patients (%) n = 337
NCI-CTC grade 3, 4, 5 adverse event	139 (46%)	211 (63%)
Serious adverse event	51 (17%)	103 (31%)
AE leading to discontinuation of at least one study drug	37 (12%)	105 (31%)
Deaths from causes other than disease progression	7 (2%)	12 (4%)
Bleeding AEs	28 (9%)	113 (34%)
Bleeding AEs excluding epistaxis	21 (7%)	46 (14%)
Hypertension	29 (10%)	98 (29%)
Proteinuria	9 (3%)	68 (20%)
Venous thromboembolic event	3 (<1%)	13 (4%)
Arterial thromboembolic event	2 (<1%)	7 (2%)
Wound healing complication	4 (1%)	5 (1%)
Gastrointestinal perforation	0	5 (1%)
Congestive heart failure	1 (<1%)	1 (<1%)

CONCLUSIONS:

In this study, treatment with bevacizumab in combination with interferon alfa-2a resulted in a median duration of overall survival of 23.3 months vs 21.3 months in the control arm and a hazard ratio of 0.91 (95% CI [0.76;1.10], unstratified analysis). This improvement of survival did not reach statistical significance (log-rank test p-value = 0.3360). The median duration of progression-free survival, a secondary endpoint, was almost 5 months longer in patients treated with bevacizumab. The improvement in duration of progression-free survival was clinically relevant and statistically significant. Treatment with bevacizumab also resulted in a longer time to disease progression, a longer time to treatment failure, and a more than 2-fold higher objective response rate.

The safety data were consistent with previous observations in cancer patients treated with bevacizumab or interferon alfa-2a. The safety profile of bevacizumab in combination with interferon alfa-2a in patients with RCC was considered acceptable.