SYNOPSIS OF RESEARCH REPORT [redacted]

(PROTOCOL BO17704)

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	Clinical Study Report Addendum – BO17704 - A randomized, double-blind multicenter Phase III study of bevacizumab in combination with cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with advanced or recurrent non-squamous non-small cell lung cancer, who have not received prior chemotherapy. Report No. [redacted] September 2008.		
INVESTIGATORS / CENTERS AND COUNTRIES	150 centers in 20 countries (Argentina 7, Australia 12, Belgium 5, Brazil 2, Bulgaria 6, Canada 11, Czech Republic 4, France 11, Great Britain 6, Germany 14, Greece 4, Hong-Kong 3, Hungary 6, Israel 5, Italy 12, Poland 7, Russia 9, Spain 18, Taiwan 5, Thailand 3) Principal investigator: [redacted] Germany,		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	January 31, 2005 to November 30, 2007 (1st patient screened to data cut-off)	CLINICAL PHASE	III
OBJECTIVES	Primary: • To demonstrate superiority in progression-free survival (PFS), when bevacizumab was added to cisplatin (C) and gemcitabine (G) (Bv7.5+CG, Bv15+CG) compared to placebo plus cisplatin/gemcitabine (Pl+CG) Secondary: • To compare overall survival (OS). • To compare time to treatment failure • To compare response rate and assess duration of response. • To evaluate and compare the safety profile of patients treated with 2 different doses of Bv+CG versus Pl+CG. • To study coagulation parameters (in a subgroup of patients). • To characterize the pharmacokinetics (PK) of the combination of Bv, cisplatin and gemcitabine (PK drug-drug interaction and population PK substudies). • To evaluate the relationship between baseline VEGF and clinical outcome parameters. • To assess quality of life (QoL). • To analyze pharmacoeconomics in all treatment arms. • To analyze pharmacogenetics in all treatment arms (in accordance with protocol BO17704RG).		
STUDY DESIGN	Multi-center, randomized, double-blind Phase III study.		

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NUMBER OF PATIENTS		Pl+CG	Bv7.5+CG	Bv15+CG
	ITT	347	345	351
	PPP	291	307	285
	SAP	327	330	329
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients ≥ 18 years of age with histologically or cytologically documented inoperable, locally advanced (stage IIIB with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic (stage IV) or recurrent non-squamous NSCLC were eligible. Patients had to have adequate hepatic, renal and hematologic function with an ECOG performance status of 0 or 1.			
TRIAL DRUG / STROKE (BATCH) No. / DOSE / ROUTE / REGIMEN / DURATION	Bv+CG were administered every 3 weeks for a maximum of 6 cycles followed by Bv as single agent until disease progression. • Bv (7.5 or 15 mg/kg q3w IV, day 1) Batch No [redacted]			
REFERENCE DRUG / STROKE (BATCH) No. / DOSE / ROUTE / REGIMEN / DURATION	Pl+CG was administered every 3 weeks for a maximum of 6 cycles followed by placebo as single agent until disease progression. • Placebo (IV, day 1) Batch No [redacted] • Cisplatin (80 mg/m^2 IV, day 1) • Gemcitabine (1250 mg/m^2 IV, days 1 and 8)			
CRITERIA FOR EVALUATION	**Efficacy:** progression-free survival (primary endpoint), overall survival, time to treatment failure, response rate, duration of response, QoL (FACT-L, FACT-G, TOI, LCS). **Safety:** adverse events, vital signs, laboratory parameters. **Pharmacokinetics:** For the PK drug-drug interaction substudy $AUC_{0-\infty}$, AUC_{0-last}, C_{max}, T_{max}, CL, Vd and $t_{1/2}$ of cisplatin (total platinum) and gemcitabine. For the population PK substudy CL, central and peripheral Vd, $AUC_{0-\tau}$ of bevacizumab. **Coagulation**: D-dimer, Prothrombin fragment F1 and F2, von Willebrand factor and E-selectin			
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-square test with Schouten correction and 95% Hauck-Andersen confidence intervals for the difference in response rate between treatment arms **Population PK:** Empirical Bayes estimates were obtained from a reference population PK model **PK drug-drug interaction**: The geometric mean ratio of AUC_{0-last} or $AUC_{0-\infty}$ when appropriate were analyzed by an ANOVA with			

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fixed effect for treatment, day and random effect for patients.

EFFICACY RESULTS:

The purpose of this final CSR-addendum is to report the protocol-specified final analysis of overall survival (a secondary efficacy parameter of the trial). The clinical cut-off for this analysis was approximately 14 months after that for the analysis presented in the final CSR (clinical cut-off extended from October 7, 2006 to November 30, 2007). Further exploratory analysis of other efficacy parameters with this longer follow-up are presented for completeness. Additional safety data is also presented covering the period from the start of the trial until a clinical cut-off date of November 30, 2007, an additional 14 months from the clinical cut-off for safety data presented in the final CSR (Report No. [redacted] of June 2007).
This resulted in approximately an additional 5.5 months (median) survival follow-up compared to the final PFS analysis. The efficacy results remain comparable to those at the time of the final PFS analysis.

The results confirm that the addition of bevacizumab to cisplatin/gemcitabine chemotherapy adds a clinically relevant and statistically significant improvement in the duration of progression-free survival. However, this did not translate into an improvement in the duration of overall survival. The reason(s) why the increased response rate and progression-free survival benefit did not translate into a survival benefit remain unclear. However, post-progression subsequent NSCLC therapy was not specified in the protocol, which introduced an uncontrolled element to the overall survival analysis, and a large proportion of patients received NSCLC-therapy other than trial treatment, with many different types of therapy being used (approximately 66 different agents and modalities).

Parameter	Pl+CG N = 347	Bv7.5+CG N = 345	Bv15+CG N = 351
Primary Efficacy Parameter			
PFS Hazard Ratio (95% CI)		0.75 (0.64; 0.87)[a] p= 0.0003[b]	0.85 (0.73; 1.00)[a] p = 0.0456[b]
Secondary Efficacy Parameters			
Overall Survival Hazard Ratio (95% CI)		0.93 (0.78; 1.11)[a] p= 0.4203[b]	1.03 (0.86; 1.23)[a] p= 0.7613[b]
Objective Response Rate[c]	21.6%	37.8%	34.6%
Complete Response	0.3%	1.2%	0.9%
Partial Response	21.3%	36.5%	33.7%
Duration of Response (KM estimate - months)	NA	NA	NA

[a] Treatment effect: compared to Pl+CG arm: for time to event parameters, estimates were calculated by Cox regression. [b] Log-Rank p value (unstratified). [c] % of patients with measurable disease at baseline with complete or partial response as best response prior to next-line NSCLC therapy.

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PHARMACODYNAMIC RESULTS:

Please refer to the final CSR (Report No. [redacted] of June 2007).

COAGULATION RESULTS

Please refer to the final CSR (Report No. [redacted] of June 2007).

PHARMACOKINETIC RESULTS:

Please refer to the final CSR (Report No [redacted] of June 2007). For one patient, the incorrect gemcitabine Day 8 AUCinf data were used when calculating the ratio and confidence interval for gemcitabine, updated results are presented in this addendum. However, the conclusions did not change (the data did not allow firm conclusion to be drawn on the impact of bevacizumab on gemcitabine disposition).

SAFETY RESULTS:

At the time of the clinical cut-off (October 7, 2006) for the analysis presented in the final CSR, 211 of the 1043 randomised patients (54 (16%) Pl+CG, 79 (23%) Bv7.5+CG and 78 (22%) Bv15+CG) were continuing on at least one component of trial treatment. Compared to exposure displayed in the final CSR, the median duration of bevacizumab treatment increased from 4.0 to 4.9 months in the Bv7.5+CG arm, and from 3.8 to 4.3 months in the Bv15+CG arm. The maximum duration of bevacizumab therapy was extended to 28.5 months in the Bv7.5+CG arm and 23.4 months in the Bv15+CG arm.

The median duration of safety follow-up was longer in the bevacizumab-containing treatment groups (6.0 months Bv7.5+CG and 5.4 months Bv15+CG) compared to the placebo-containing arm (4.6 months Pl+CG). AEs in the following categories appeared to have a higher incidence rate in the bevacizumab-containing arms compared to the placebo-containing arm (in some cases there also being an indication of a dose dependency); SAEs, adverse events of special interest (including Grade 3 and above) and AEs leading to discontinuation. This was consistent with the safety findings presented in the final CSR.

On comparison of the adverse event preferred terms in the various adverse event categories, no new safety signals were observed and the adverse event profile was consistent with that previously established for bevacizumab, or the chemotherapy backbone. The incidence of all grade bleeding events (epistaxis and hemoptysis), hypertension, stomatitis and headache were higher in the Bv15+CG arm compared to both other treatment arms. However, several other AEs which had a higher incidence in the Bv-containing arms than the placebo-containing arm, were of highest incidence in the Bv7.5+CG arm compared to the Bv15+CG arm (eg. pulmonary embolism, dysphonia and peripheral sensory neuropathy)

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	Pl+CG N= 327	**Bv7.5+CG N= 330**	**Bv15+CG N= 329**
Exposure and safety observation period			
Number of patients (%) starting 6 cycles of Bv/Pl	178 (55)	219 (66)	195 (59)
Number of patients (%) starting 6 cycles of chemotherapy	178 (55)	203 (61)	194 (59)
Median duration of safety observation (months)[a]	4.63 (1.0-16.1)	5.98 (1.0-29.3)	5.39 (1.0-23.5)
Incidence rate % **(Number of patients with at least one event)**			
Death within 60 days of randomisation (ITT)	4%	3%	4%
AEs leading to death [b]	4%	4%	5%
AEs leading to any component of trial treatment discontinuation [b]	31%	32%	36%
SAEs [b]	36%	39%	45%
Grade ≥ 3 AEs [b]	77%	80%	83%
Grade ≥ 3 AEs of special interest[c]	15%	22%	26%
AEs of special interest[c]	44%	62%	66%
Any Grade AE [b]	99%	99%	99%

Data are unadjusted for time on treatment or duration of safety observation.
[a] Time between 1st dose of trial treatment and up to 28 days after the last dose of any component of trial treatment. [b] AEs that started after the 1st dose of trial treatment until up to 28 days after the last dose of trial treatment.[c] AEs that started after the 1st dose of trial treatment until up to 6 months after the last dose of trial treatment.

CONCLUSIONS:

At the time of the protocol-defined final analysis of overall survival, it was confirmed that the addition of bevacizumab to cisplatin/gemcitabine chemotherapy adds a clinically relevant and statistically significant improvement in the duration of progression-free survival (the protocol defined primary efficacy parameter). However, this did not translate into a statistically significant improvement in the duration of overall survival. The reason(s) for this remains unclear, but post-progression subsequent NSCLC therapy was not specified in the protocol, and there was a rapid adoption of active subsequent treatments during the conduct of the study. This introduced an uncontrolled element to the overall survival analysis.
With a clinical cut-off approximately 14 months after that for the analysis presented in the final CSR, it was confirmed that bevacizumab could be safely administered in combination with cisplatin/gemcitabine and the safety profile was consistent with previously reported bevacizumab studies in lung cancer.