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	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] June 2007.		
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 October 7, 2006 (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.

NUMBER OF PATIENTS

	Pl+CG	Bv7.5+CG	Bv15+CG
ITT	347	345	351
PPP	283	297	282
SAP	327	330	329

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

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EFFICACY RESULTS:

The addition of bevacizumab (at either dose level) to cisplatin/gemcitabine chemotherapy resulted in a clinically relevant and statistically significant improvement in both PFS (the primary efficacy parameter) and objective response rate. The duration of response was also improved by the addition of Bv to CG as compared to Pl+CG

Table 1: Summary of Overall Efficacy (Clinical Cut-Off October 7, 2006; ITT)

Parameter	**Pl+CG** **N = 347**	**Bv7.5+CG** **N = 345**	**Bv15+CG** **N = 351**
PFS HR (95%CI)		0.75 (0.62; 0.91) p = 0.0026	0.82 (0.68; 0.98) p = 0.0301
Overall Survival* HR (95% CI)		0.88 (0.68; 1.14)	1.02 (0.79; 1.31)
Overall Response Rate	20.1%	34.1%	30.4%
Complete Response	0%	0.9%	1.2%
Partial Response	20.1%	33.1%	29.2%
Stable Disease	49.7%	46.4%	40.4%
Progressive Disease	13.0%	4.6%	12.0%
Missing**	17.3%	14.9%	17.2%
Duration of Response (KM estimate – months)	4.7	6.1	6.1

* Exploratory analysis

** Missing: Includes pts with no post-baseline tumor assessments, pts who received antineoplastic therapy not defined in the protocol before first tumor assessment, and pts whose first tumor assessment occurred > 56 days after last dose of last component of study medication

None of the FACT-L, FACT-G, TOI, or LCS scores appeared to change meaningfully after baseline in any of the treatment arms, suggesting that the addition of bevacizumab to cisplatin/gemcitabine chemotherapy did not lead to a deterioration of QoL during trial treatment.

PHARMACODYNAMIC RESULTS:

In multivariate Cox and logistic regression, there was no evidence of a relationship between baseline VEGF value being above or below the median and duration of PFS or OR.

COAGULATION RESULTS

No conclusion can be drawn on a prothrombotic risk related to bevacizumab exposure.

PHARMACOKINETIC RESULTS:

The comparability of bevacizumab pharmacokinetics in patients with NSCLC and in oncology patients with different types of cancer was assessed using a Bayesian feedback analysis. No consistent difference was found in the pharmacokinetic parameters between NSCLC patients and oncology patients.

The results from the drug-drug interaction substudy indicated no effect of bevacizumab on the disposition of cisplatin, as measured by total platinum but did not allow firm conclusion to be drawn on the impact of

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bevacizumab on gemcitabine disposition.

SAFETY RESULTS:

Almost all patients in each study arm experienced at least one adverse event (see Table 2).

A higher incidence of adverse events of special interest was observed in the bevacizumab arms, with a higher incidence in the Bv15+CG arm. No clinically significant differences between the two bevacizumab arms were apparent.

The overall higher incidence of events of special interest in the bevacizumab arms was mostly driven by hypertension (all Grades) and certain bleeding events (e.g. epistaxis).

Slightly more patients prematurely discontinued treatment for safety reasons in the bevacizumab arms.

The incidence of death due to adverse events was comparable between the treatment arms.

Overall, bevacizumab did not seem to increase the known toxicities of cisplatin/gemcitabine and no new safety signal related to bevacizumab appeared.

Table 2: Overview of Adverse Events

	Pl+CG N = 327	**Bv7.5+CG N = 330**	**Bv15+CG N = 329**
	Number of Patients (%)		
Any AE	322 (98%)	326 (99%)	326 (99%)
Grade 3,4,5 AE	246 (75%)	252 (76%)	265 (81%)
Serious AE	116 (35%)	116 (35%)	145 (44%)
AE leading to Death	14 (4%)	13 (4%)	16 (5%)
AE leading to any component withdrawal	74 (23%)	86 (26%)	98 (30%)
AE of Special Interest	135 (41%)	189 (57%)	207 (63%)
Grade 3,4,5	48 (15%)	65 (20%)	76 (23%)
Bleeding	6 (2%)	14 (4%)	14 (4%)
Hypertension	6 (2%)	21 (6%)	29 (9%)
Venous Thromboembolic events	21 (6%)	24 (7%)	23 (7%)
Arterial Thromboembolic events	15 (5%)	8 (2%)	10 (3%)
Congestive Heart Failure	2 (< 1%)	4 (1%)	3 (< 1%)
Gastrointestinal Perforations	2 (< 1%)	0	1 (< 1%)
Proteinuria	0	1 (< 1%)	4 (1%)
Wound Complication	2 (< 1%)	0	0

CONCLUSIONS:

The combination of bevacizumab with cisplatin and gemcitabine for the treatment of NSCLC resulted in a clinically relevant and statistically significant improvement in both progression-free survival and objective response rate. The duration of response was also improved by the addition of bevacizumab. In addition, bevacizumab could be safely administered in combination with cisplatin/gemcitabine and the safety profile was consistent with prior bevacizumab studies in lung cancer.