SYNOPSIS OF RESEARCH REPORT [redacted]

(PROTOCOL BO19734)

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	An open label, non-controlled study of bevacizumab in combination with cisplatin-gemcitabine or carboplatin-paclitaxel, as first line treatment for patients with advanced or recurrent squamous non-small cell lung cancer (NSCLC). Report No. [redacted] August 2008		
INVESTIGATORS / CENTERS AND COUNTRIES	14 centers in 9 countries (Australia; Belgium; Czech Republic; Spain; France; Hungary; Israel; Poland; Russia Principal investigator: [redacted] France		
PUBLICATION (REFERENCE)	none		
PERIOD OF TRIAL	Sep 04, 2006 to July 11, 2007 (first patient screened to study termination)	CLINICAL PHASE	II
OBJECTIVES	Primary objective: To assess the feasibility of using bevacizumab with cisplatin-gemcitabine or carboplatin-paclitaxel in patients with squamous NSCLC considered to be at major risk for pulmonary hemorrhage, when using preventive measures designed to reduce the risk of pulmonary hemorrhage. Secondary objectives: To assess overall safety and tolerability To determine best overall response To determine the duration of response To evaluate progression free survival (PFS)		
STUDY DESIGN	Open-label, single-arm, multi-centre, phase II study to evaluate the feasibility of administering bevacizumab and cisplatin-gemcitabine or carboplatin-paclitaxel as first-line treatment for patients with stage IIIB (with pericardial or pleural effusion), stage IV or recurrent squamous NSCLC. Recruitment was suspended on May 18, 2007 due to occurrence of 2 cases of NCI-CTCAE grade ≥ 3 pulmonary hemorrhage within the first 30 evaluable patients (pre-specified as a reason to halt recruitment) and the study was prematurely terminated on July 11, 2007 due to a number of practical problems associated with the study conduct. These included the high drop-out rate of 40% and lack of compliance with respect to the selected eligibility criteria (patients with short life expectancy, involvement of blood vessels, lack of reporting of hemoptysis in timely manner).		

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NUMBER OF SUBJECTS	Treatment	Study Population	Exploratory Population	Safety Population
	Bv 15 + CG/CP	35*	2	20
	* Patients in the Study Population received 5 cycles of palliative radiotherapy (20 Gy) prior to receiving Bv + CG/CP			
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients ≥ 18 years with stage IIIB squamous NSCLC with malignant pleural or pericardial effusion (i.e. patients who were not candidates for radical combined modality therapy or high-dose consolidation radiotherapy) OR stage IV (metastatic) OR recurrent disease; ECOG Performance Status of 0 or 1.			
TRIAL DRUG / STROKE (BATCH) No.	Bevacizumab / Batch [redacted] Cisplatin-Gemcitabine / commercially available supply Carboplatin-Paclitaxel / commercially available supply			
DOSE / ROUTE / REGIMEN / DURATION	Bevacizumab: 15 mg/kg / i.v / q3w for 12 months until disease progression, unacceptable toxicity or patient withdrawal Cisplatin: 80 mg/m^2 i.v. for a maximum of 6 cycles Gemcitabine: 1250 mg/m^2 on days 1 and 8 of each cycle for a maximum of 6 cycles Carboplatin: AUC = 6 (based on the Calvert formula) for a maximum of 6 cycles Paclitaxel: 200 mg/m^2 for a maximum of 6 cycles			
REFERENCE DRUG / STROKE (BATCH) No.	N/A			
DOSE / ROUTE / REGIMEN / DURATION	N/A			
CRITERIA FOR EVALUATION				
EFFICACY:	Tumor assessments based on RECIST criteria using CT/MRI at baseline at the end of cycle 1 (week 6), 3 (week 12) and 6 (week 21) (Study Population) and at the end of cycle 3 (week 9), and 6 (week 18) (Exploratory Population) and every 12 weeks thereafter (all patients)			
PHARMACODYNAMICS:	N/A			
PHARMACOKINETICS:	N/A			
SAFETY:	Adverse events, laboratory tests, physical exam, vital signs, ECG			
STATISTICAL METHODS	Descriptive statistics and 95% confidence intervals (Pearson-Clopper estimates) are provided for efficacy variables. Kaplan-Meier estimates and 95% confidence intervals for time to event analyses. Safety variables are summarized descriptively.			
METHODOLOGY:				

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After undergoing screening assessments and providing their informed consent, patients in the Study Population received involved-field radiotherapy 4 Gy / day for 5 consecutive working days prior to receipt of their first cycle of chemotherapy with cisplatin-gemcitabine or carboplatin-paclitaxel. Patients in the Exploratory Population received no palliative radiotherapy. Bevacizumab 15 mg/kg iv was started on day 1 of cycle 1 of chemotherapy in the Exploratory Population and on day 1 of cycle 2 of chemotherapy in the Study Population and was to be given for a maximum of 12 months or stopped earlier for confirmed disease progression, unacceptable toxicity (requiring discontinuation of study treatment) or withdrawal at patient request. A maximum of five target lesions per organ and 10 lesions in total were to be identified, recorded, and measured at baseline. All other lesions were to be recorded as non-measurable disease. Tumor measurements/assessments were made using modified RECIST criteria based on CT scans or MRI scans until (confirmed) evidence of disease progression.
Adverse events were recorded on an ongoing basis. Adverse events of special interest (events described with bevacizumab treatment i.e. hypertension, proteinuria, GI perforation, wound healing complications, hemorrhage and thromboembolic (venous and arterial) events) were to be followed up until resolution or stabilization. Assessments including body weight, body temperature, pulse, blood chemistry, urinalysis and ECOG performance status were performed pre-dose and at each 3-weekly cycle after treatment start for the duration of study therapy. Hematology was assessed weekly during each 3-weekly cycle. ECG was to be performed at baseline and thereafter as clinically indicated. Blood biomarker assessment was performed at baseline and at cycle 4. In all patients, the following assessments were to be made 28 days and 60 days after end of treatment: tumour assessments, hematology, blood chemistry, urinalysis, concomitant treatments, ECOG PS and adverse events. Physical measurements including body weight, body temperature, pulse and blood pressure were assessed 28 days after end of treatment.

SAFETY RESULTS:

Primary Variable (Rate of Grade ≥ 3 Bv-related pulmonary hemorrhage):

Two patients experienced a Grade ≥ 3 Bv-related pulmonary hemorrhage during the trial. As a result of these 2 cases within the first 20 patients receiving at least one dose of bevacizumab, investigators were informed by Roche on May 18th, 2007 that recruitment and bevacizumab administration were not to be continued until further notice. Roche permanently terminated the study on July 11, 2007 due to a number of practical problems associated with the study conduct. These included the high drop-out rate of 40% and lack of compliance with respect to the selected eligibility criteria (patients with short life expectancy, involvement of blood vessels, lack of reporting of hemoptysis in timely manner)..

General Safety:

The bevacizumab-specific safety observations were generally consistent with observations in previous studies of bevacizumab in cancer patients. Most patients (≥ 80%) experienced one or more adverse events. The overall incidence of patients experiencing a grade 3, 4 or 5 adverse event was 65%.
The incidence of serious adverse events was 30%. Serious adverse events considered remotely, possibly or probably related to treatment were thrombocytopenia (2 patients), pulmonary hemorrhage (2 patients), anemia, granulocytopenia, leukopenia, neutropenia, pnemothorax, gastric ulcer (all 1 patient each).
The incidence of patients who discontinued any component of study treatment was 20%. Reasons for dose

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modification of any component of the study medication (bevacizumab and/or CG or CP) were neutropenia (5 patients), leukopenia, thrombocytopenia, vomiting (2 patients each), diarrhea, dysphagia, renal failure, renal impairment, bronchitis and hypertension (1 patient each).
Of those adverse events known to be associated with bevacizumab therapy (adverse events of special interest) the most common were thrombocytopenia, neutropenia, epistaxis and hypertension. NCI-CTCAE grade 3-5 AEs of special interest were mainly hematological such as thrombocytopenia (8 patients) and neutropenia (7 patients).
One patient died during the study as a result of causes other than disease progression, 12 days after having received their last dose of bevacizumab in combination with carboplatin-paclitaxel. The cause of death was pulmonary hemorrhage (Grade 5) which was considered possibly related to treatment by the investigator.
No clinically significant changes were seen in the laboratory parameters measured in this study.

Safety Parameter – Safety Population	**Bv 15 + CG/CP N = 20**
Number (%) of patients with:	
NCI-CTCAE grade ≥ 3 pulmonary hemorrhage	2 (10%)
at least one adverse event	16 (80%)
at least one NCI-CTC grade 3-5 adverse event	13 (65%)
at least one serious adverse event	6 (30%)
at least one AE leading to discontinuation of Bv	3 (15%)
at least one adverse event of special interest	14 (70%)
at least one NCI-CTCAE grade 3-5 AE of special interest	12 (60%)
AEs leading to death	1 (5%)
Number (%) of patients with:	
Bleeding events (all events)	6 (30%)
Pulmonary hemorrhage	2 (10%)
Neutropenia	9 (45%)
Hypertension	4 (20%)
Venous thromboembolic events	1 (5%)
Thrombocytopenia	9 (45%)

EFFICACY RESULTS:
This report presents the results of the final analysis of efficacy following premature termination on July 11, 2007. Efficacy analyses were limited by the very low number of patients who received treatment with bevacizumab (n = 20). In patients with measurable disease at baseline, 5/20 patients had a best objective response of CR + PR. Of the 5 patients with a response, 4 patients had a response which was ongoing at the time of the clinical cut-off for the analysis. At the time of the analysis of PFS, 6 progression events had occurred. For one of the 6 patients, the progression event was death. In the remaining 5 patients, the triggering event for the PFS analysis was progressive disease.

CONCLUSIONS:
Study BO19734 was prematurely terminated as a result of a number of practical problems associated with

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the study conduct including a high drop-out rate (40%) and lack of compliance with respect to selected eligibility criteria. At the time of termination, two bevacizumab related NCI-CTCAE grade ≥ 3 pulmonary hemorrhage events had occurred among the first 20 patients treated with bevacizumab. The incidence rate was 10% with a corresponding 95% CI 1.2 to 31.7% within this patient group. Therefore, this trial could not provide firm conclusions about the risk or guidance on mitigating the risk of pulmonary hemorrhage in patients with squamous NSCLC.
Within the limitations of a low patient recruitment and number of patients exposed to bevacizumab, the safety profile of the combination of bevacizumab with cisplatin-gemcitabine or carboplatin-paclitaxel was generally consistent with observations in previous studies of bevacizumab in cancer patients and did not reveal any excess in dose modifications or delays. There were no new safety signals observed in the study.