London, 21 August 2007
Product Name: **Avastin**
EMEA/H/C/582/II/09

SCIENTIFIC DISCUSSION

Extension of the indication for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology, in addition to platinum-based chemotherapy.

1. Introduction

Over one million new cases of lung cancer are diagnosed each year worldwide, resulting in close to one million deaths. It is the second most common cancer in men as well as women, accounting for about 13% of cancer diagnoses, but it is the leading cause of cancer-related deaths in industrialized countries.

NSCLC represents about 80% of lung cancer. The most common histologies are epidermoid or squamous cell carcinoma (30-35%), adenocarcinoma (40-45%), and large cell carcinoma (<10%). The frequency of these different histological subsets varies across countries and over time, with a decrease in squamous cell histology in industrialised countries. These histologies are often classified together because approaches to diagnosis, staging, prognosis, and treatment are similar. In clinical practice, a high proportion of patients with NSCLC are diagnosed at an advanced stage of the disease (approximately 30% locally advanced and 40% metastatic disease) with the remainder (25-30%) presenting with early stage. Despite recent advances in treatment, the prognosis for patients with lung cancer remains poor. The 5-year survival rate for patients with NSCLC is still only about 15%.

Research over the past decades has proven that chemotherapy has a definite role in the treatment of advanced NSCLC with incremental advances mainly occurring during the last two decades. One-year survival rates in patients with advanced NSCLC have respectively increased from around 10% without chemotherapy, to 20% with an active single agent, and to 35% with the combination of two active drugs. Platinum-based chemotherapy emerged as the standard treatment for advanced NSCLC. In 1995, a large meta-analysis evaluated first- and second-generation platinum-based regimens (developed in the 1980s) and demonstrated a significant increase in median survival of 1.5 months and 1-year survival rate of 10%, the latter corresponding to a 27% reduction in the probability of death for cisplatin-based therapy, compared with best supportive care.

Two recent meta-analyses evaluated the benefit of single agent regimens vs. doublets and doublets vs. triplets in advanced, incurable NSCLC. The meta-analysis by Delbaldo established an increase in 1-year survival from 30% with a single agent regimen to 35% with a doublet regimen, but did not show any survival benefit of triplets over doublets and confirmed doublet regimens as the standard therapy in NSCLC. Overall, carboplatin/paclitaxel and cisplatin/gemcitabine became reference regimens for the treatment of advanced NSCLC based on their efficacy and manageable safety profiles demonstrated by the results of a randomized, comparative trial, Study E1594. Carboplatin/paclitaxel was established as the reference regimen for ECOG studies in the treatment of patients with locally advanced or metastatic NSCLC in the first-line setting and is most commonly used in the USA, whereas cisplatin/gemcitabine is popular in Europe.

Bevacizumab is a recombinant humanized monoclonal antibody. It recognizes and neutralizes all major isoforms of human VEGF. Bevacizumab potently neutralizes VEGF and blocks its signal transduction through both the VEGFR-1 and VEGFR-2 receptors. It inhibits angiogenesis by neutralizing all isoforms of human vascular endothelial growth factor-A (VEGF), and blocking their binding to VEGF receptors.

Although chemotherapy provides a meaningful survival benefit to patients with advanced NSCLC, it remains a rapidly fatal disease. It is clear that additions or alterations in the components or schedules of standard cytotoxic regimens are unlikely to result in major improvements in outcome in NSCLC. Thus, the development of drugs aimed at targeting pathways specific for cancer, such as angiogenesis, represents a way forward.

2. Clinical aspects

The MAH (Roche) in cooperation with Genentech Inc. (MAH in the US) and the National Cancer Institute (NCI) in the USA are conducting a global development program for bevacizumab in a variety of malignant diseases. Clinical pharmacological data for bevacizumab are currently available from 12clinical studies. Nine of these studies were submitted previously in the original Marketing Authorization Application (MAA) for colorectal cancer, and an additional study was submitted in the Variation Application for metastatic Breast Cancer..

The clinical program investigating the use of bevacizumab in addition to platinum-based chemotherapy in patients with locally advanced, metastatic or recurrent NSCLC consists of one pivotal Phase II/III study (E4599 – NCI-sponsored) and two supporting studies, one Phase III study (BO17704 – Roche-sponsored) and one Phase II study (AVF0757g – Genentech-sponsored). Data from these three studies forms the basis of this submission. All studies are completed for the primary endpoints and are adequately controlled, randomized, comparative parallel group design, but only study BO17704 is double-blind incorporating placebo in the comparative arm with platinum-based chemotherapy. A total of 1184 NSCLC patients (other than predominantly squamous cell histology) were allocated to bevacizumab in these three studies (817 patients to a bevacizumab dose of 15 mg/kg/q3w and 367 to 7.5 mg/kg/q3w).

In the initial bevacizumab study in patients with NSCLC (AVF0757g), life-threatening and fatal hemoptyses were identified as bevacizumab-related adverse events (AEs). In a retrospective exploratory multivariate analysis of these cases, only predominant squamous cell histology (4 of the 6 cases) was identified as a risk factor. A total of 20 of the 98 treated patients in the study had predominant squamous cell histology (13 of whom received bevacizumab). Subsequent NSCLC trials excluded patients with predominant squamous cell histology, patients with hemoptysis and patients with evidence of tumor invading or abutting a major blood vessel (the latter in BO17704 only). One study is ongoing which investigates the efficacy and safety of bevacizumab use in NSCLC of predominant squamous histology (AVF3744g).

Scientific advice was obtained from the Rapporteur and the Co-Rapporteur in March 2004 with regard to the design of the Roche-sponsored Phase III study BO17704 and was followed. Pre-submission meetings were held with the Rapporteur and Co-Rapporteur in July and August 2005 to discuss the content of this submission, and the impact of the publication of the E4599 study data on the feasibility and necessity of completing study BO17704. This discussion resulted in agreement on the content of the submission (as presented here) and amendment of the BO17704 protocol.

Study E4599 was conducted by the Eastern Cooperative Oncology Group (ECOG) under the National Cancer Institute's (NCI's) Investigational New Drug (IND 7921) in the USA according to the ECOG standard operating procedures and to all Department of Health and Human Services, Office of Human Research Protections, and U.S. Food and Drug Administration (FDA) regulations regarding the conduct of human research that gave their origins in the Declaration of Helsinki. The BO17704 study was conducted in accordance with the guidelines for Good Clinical Practice according to the Tripartite Guidelines (January 1997) and local ethical and legal requirements. The AVF0757g study was conducted in accordance with U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs) and local ethical and legal requirements.

2.1 Clinical efficacy

One large, randomized open-label **pivotal phase II/III trial** (E4599 – carried out by ECOG and sponsored by the US National Cancer Institute [NCI]) carried out mainly in the US included 878 patients and tested bevacizumab at a dose of 15 mg/kg/q3w in combination with six cycles of paclitaxel and carboplatin chemotherapy, followed by bevacizumab as a single-agent until disease progression or unacceptable toxicity. Patients were not permitted to receive bevacizumab after disease progression.

Two-drug chemotherapy regimens which combine a platinum agent with paclitaxel, docetaxel, vinorelbine, irinotecan and gemcitabine are universally accepted as "standard of care" for the treatment of advanced NSCLC. Literature indicates that the different platinum-based chemotherapy regimens currently used in the treatment of NSCLC are considered to have no clinically relevant differences in terms of efficacy. It is therefore acceptable to extrapolate the results of the combination of bevacizumab and paclitaxel/carboplatin to other platinum based chemotherapies.

Two supportive studies are:
One supportive **Phase II study** (**AVF0757g** – sponsored by Genentech) carried out in the US included 79 patients with non-squamous cell histology and tested bevacizumab at doses of 7.5 or 15 mg/kg/q3w in combination with six cycles of paclitaxel and carboplatin chemotherapy, followed by bevacizumab as a single-agent until disease progression or unacceptable toxicity (up to a maximum of 18 cycles). Patients in the control arm were eligible to cross-over to single-agent bevacizumab (15 mg/kg/q3w) after disease progression until further disease progression or for the remainder of the study (total of 378 days), whichever occurred first.

A **Phase III study** (**BO17704** - sponsored by Roche) carried out internationally outside the US included 1043 patients and is complete for the primary endpoint (progression free survival). The study tests bevacizumab at doses of 7.5 or 15 mg/kg/q3w in combination with six cycles of cisplatin and gemcitabine chemotherapy, followed by bevacizumab as a single-agent until disease progression or unacceptable toxicity. Patients were not permitted to receive bevacizumab after disease progression.

Table 1 summarises the studies submitted in this application

Table 1 Efficacy Studies with Bevacizumab in NSCLC

Study	Study Design	N	Patient Characteristics
E4599 NCI sponsored	Phase II/III, R, OL, C, PG Paclitaxel and carboplatin ± 15 mg/kg/q3w Bv. Completed	878	Histologically- or cytologically-confirmed advanced NSCLC (stage IIIB with malignant pleural effusion or Stage IV or recurrent disease) except predominantly squamous cell carcinoma; ECOG PS 0 or 1
AVF0757g Genentech-sponsored	Phase II, R, OL, C, PG Paclitaxel and carboplatin ± 7.5 or 15 mg/kg/q3w Bv Completed	79 [a]	Newly diagnosed stage IIIB (with pleural effusion), stage IV or recurrent NSCLC; ECOG PS 0, 1 or 2.
BO17704 (AVAIL) Roche-sponsored	Phase III, R, DB, PC, C, PG. Cisplatin and gemcitabine with placebo, 7.5 or 15 mg/kg/q3w Bv. Completed for primary endpoint.	1043[b]	Locally advanced (stage IIIB with supraclavicular lymph node metastases or malignant pleural or pericardial effusion), metastatic (stage IV) or recurrent non-squamous NSCLC; ECOG PS 0 or 1.

Bv, bevacizumab; C, comparative; DB, double-blind; OL, open label; PC, placebo controlled; PG, parallel-group; PS, performance status (ECOG); R, randomized. a Non-squamous population only. All randomized population: N = 99.

Main Study – E4599

The objectives of the study were:

- To assess overall survival in patients with previous untreated locally advanced or metastatic (stage IIIb with malignant pleural effusion or stage IV or recurrent) NSCLC (excluding NSCLC categorised as squamous cell treated with carboplatin/paclitaxel ± bevacizumab)
- To assess objective response rate, PFS, and toxicity in patients with previous untreated locally advanced or metastatic (stage IIIb with malignant pleural effusion or stage IV or recurrent) NSCLC (excluding NSCLC categorised as squamous cell treated with carboplatin/paclitaxel ± bevacizumab)

Overall the E4599 Study Protocol was amended nine times. None of the amendments were made at the request of Genentech; they were initiated by ECOG. Timing of tumour assessments performed after completion of six cycles of chemotherapy was changed from 6 weeks to 3 months in Arm A (carboplatin/paclitaxel) until progression.

Main inclusion criteria were:

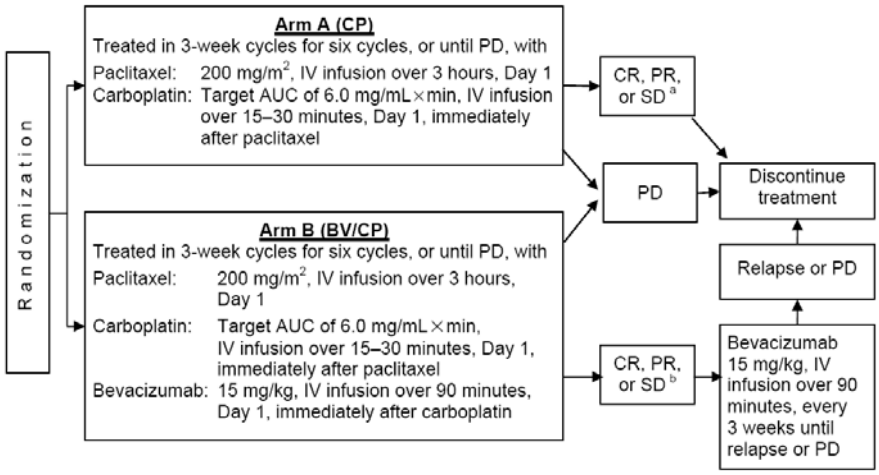
- Histologically or cytologically confirmed NSCLC except squamous-cell carcinoma. Mixed tumours were categorized by the predominant cell type; however, if small-cell elements were present, the patient was ineligible. Cytologic or histologic confirmation was based on metastatic tumour aspirates or biopsy.
- Advanced NSCLC, defined as Stage IIIb with malignant pleural effusion, Stage IV, or recurrent disease
- Measurable or non-measurable disease
- ECOG performance status of 0 or 1

Main exclusion criteria were:

- Central nervous system (CNS) metastases
- Prior or current use of systemic chemotherapy
- Immunotherapy, hormonal therapy, or radiotherapy within 3 weeks prior to randomization
  Patients who had not recovered from adverse events due to agents that were administered ≥3 weeks prior to randomization were also ineligible
- Several safety concerns (see study report)

Treatments

Figure 1. Study schema



AUC =area under the curve; CR =complete response; IV =intravenous; PD =progressive disease; PR =partial response; SD =stable disease. Notes: Dose calculations were based on actual body weight. Carboplatin dosing was based on the Calvert formula: Total dose (mg) = (Target AUC) × (GFR +25), where GFR was the glomerular filtration rate in ml per minute, and the target AUC was 6.0 mg/mL × min. For males, GFR was calculated using the Cockcroft–Gault formula (Cockcroft and Gault 1976): GFR =(140 −age) × weight/72 × serum creatinine, where age was in years, weight was in kilograms, and serum creatinine was in mg/dL. Actual, not ideal weight was used. For females, GFR was calculated by multiplying the result of the above formula by 0.85. a/b different tumour assessments; see under section outcomes/endpoints. Module 5(2)

Patients who experienced protocol-defined toxicity to paclitaxel, carboplatin, or bevacizumab were required to discontinue treatment with the corresponding agent. The bevacizumab dose was never reduced below 15 mg/kg.

Supportive Studies

Overall, the primary and secondary efficacy endpoints are shown for each study in Table 2. Differences between studies in definitions, censoring rules, and handling of missing data are outlined below.

Table 2 Primary and Secondary Endpoints

Endpoint	E4599 Phase II/III	AVF0757g Phase II	BO17704 Phase III
Primary	- Duration of survival	- Time to progression - Best (confirmed) tumor response ([CR or PR] rates [a]	- Progression free survival [d]
Secondary	- Objective response rate [b] - Progression free survival - Duration of response [b]	- Duration of survival - Duration of response [c]	- Duration of survival - Time to Treatment Failure - Objective Response Rate - Duration of response

CR, complete response; PR, partial response. a Based on the investigator assessment. The IRF (cavitation) assessment was exploratory) b The formal analysis only included patients who had measurable disease at baseline. c Not determined for non-squamous population. d Changed to PFS from overall survival in protocol amendment C.

AVF0757g: Objectives:

- To evaluate the efficacy of multiple administrations of bevacizumab when combined with chemotherapy for the treatment of advanced NSCLC, as measured by time to disease progression, response rate, duration of response, and survival for all subjects.
- To evaluate the safety of multiple administrations of bevacizumab when combined with chemotherapy for the treatment of advanced NSCLC
- To evaluate the serum pharmacokinetics and pharmacodynamics of bevacizumab in subjects with advanced NSCLC receiving concomitant chemotherapy.

BO17704: Primary objective:

- To demonstrate superiority in progression-free survival (PFS) when bevacizumab is added to cisplatin and gemcitabine

Secondary objectives:

- To compare overall survival
- To compare time to treatment failure (TTF)
- To compare response rate and assess duration of response
- To evaluate and compare the safety profile of patients treated with two different doses of bevacizumab + cisplatin/gemcitabine versus cisplatin/gemcitabine.
- To study coagulation parameters
- To characterise the pharmacokinetics of the combination of bevacizumab, cisplatin and gemcitabine
- To evaluate the relationship between baseline VEGF and clinical outcome parameters.
- To assess Quality of Life
- To analyse pharmacoecomics in all treatment arms
- To analyse pharmacogenomics in all treatment arms.

RESULTS Study E4599:

In the pivotal E4599 study, compared to the use of CP alone, the use of bevacizumab in addition to CP resulted in a statistically significant and clinically relevant efficacy benefit. In the final stratified analysis for all randomized patients, a statistically significant increase in the duration of overall survival was observed in the Bv15+CP arm compared to the control CP arm ($p=0.003$). This was reflected in a clinically meaningful increase in median survival (12.3 months vs. 10.3 months), and a 20% decrease in the risk of death (HR 0.8, 95% CI [0.69, 0.93]). The statistical significance of study E4599, which was originally established by the crossing of the pre-specified efficacy boundary for overall survival at the second interim analysis, was therefore confirmed by this final analysis. Patients in the Bv15+CP arm also had a significantly prolonged duration of PFS ($p<0.0001$; Kaplan-Meier estimated median 4.8 months vs. 6.4 months; HR 0.65 [95% CI: 0.561, 0.764]) and, among patients with measurable disease at baseline, a significantly higher objective response rate (29% vs. 13%; $p<0.0001$).

Duration of overall survival was the primary endpoint in study E4599. This is the most comprehensive source of survival information related to the use of bevacizumab in NSCLC available to date

Based on the final ECOG dataset transfer to Genentech on 30 December 2005, 698 deaths had occurred in the all randomized population; 363/444 (81.8%) in the control CP arm and 335/434 (77.2%) in the Bv15+CP arm. Data reported in E4599 Treatment and Long-term Follow-up forms showed that the vast majority of deaths in both treatment arms (approximately 70%) were considered by the investigators to be associated with disease progression, indicating that overall survival reflects efficacy rather than toxicity.

The Kaplan Meier plot for duration of survival shows that the benefit of bevacizumab was apparent from approximately 3 months and was maintained for at least 2.5 years after randomization ( ). The 12-month survival rates (based on Kaplan Meier analysis) were 44% in the control CP arm and 51% in the Bv15+CP arm. At 24 months, survival rates were 15.4% and 22.0%, respectively.

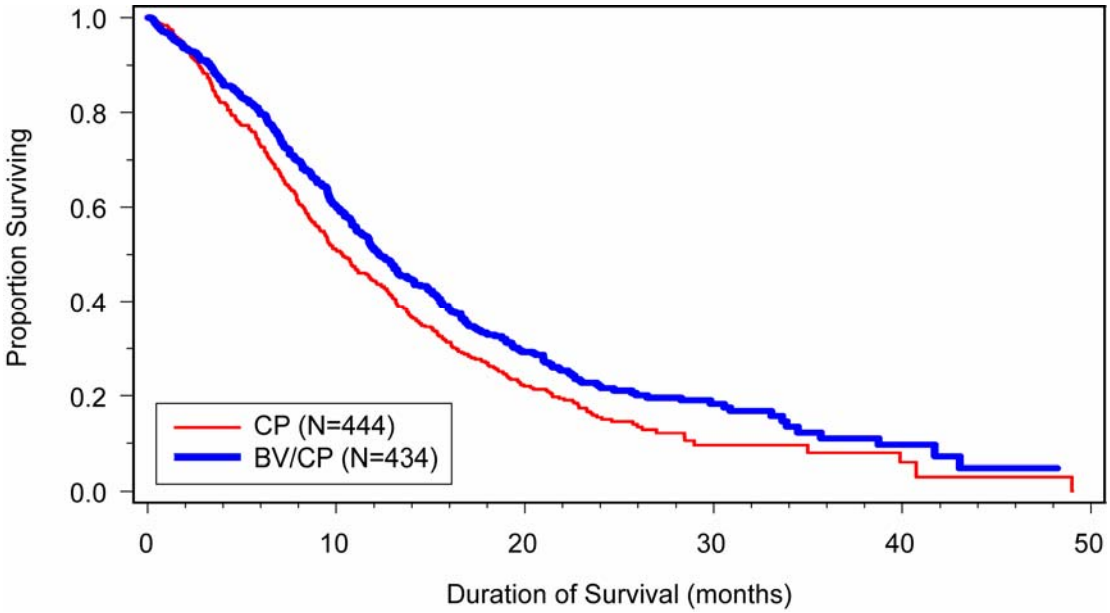
Table 3: E4599 Final Analysis: Duration of Overall Survival (All Randomized Patients)

	CP N = 444	Bv15+CP N = 434
Patients who died (No. [%])	363 (81.8)	335 (77.2)
Patients alive (No. [%])	81 (18.2)	99 (22.8)
Duration of survival (months) [a]		
Median	10.3	12.3
95% CI	[9.36, 11.73]	[11.30, 13.73]
25th–75th Percentile	5.7–18.8	7.0–22.3
Minimum–maximum	0.0+–49.0	0.0+–48.2+
Stratified analysis [b]		
Hazard ratio (relative to CP)		0.80
95% CI		[0.69, 0.93]
p-value (Log-rank)		0.0030

CI, confidence interval; +, censored value. [a] Summaries of duration of survival (median, percentiles) were estimated from Kaplan-Meier curves. 95% CI for median was computed using the method of Brookmeyer and Crowley.
[b] Unstratified analysis provided in E4599 CSR Table 14.2/1. Hazard ratios were estimated by Cox regression. The strata are tumor measurability (yes vs. no), prior radiotherapy (yes vs. no), weight loss (< 5% vs. ≥ 5%), and stage (IIIB vs. IV or recurrent).

The objective response was higher in the BV/CP arm than in the control arm (CP), 29% vs. 12.9%, respectively.

Figure 2 Plot of Kaplan-Meier Estimates for Overall Survival in Study E4599 (ITT population)



BV/CP = bevacizumab + carboplatin/paclitaxel; CP = carboplatin/paclitaxel.

In pre-specified exploratory subgroup analyses, consistent benefits of bevacizumab treatment were observed across all subgroups in terms of PFS and objective response rates. Both endpoints are considered to be direct measures of the drug-induced treatment effect. The survival benefit associated with bevacizumab use was also seen in all patient subgroups defined by race, ECOG PS, prior radiotherapy, measurable disease, and tumor burden. Four subgroups did not show a clear bevacizumab-related improvement in duration of survival: females, patients aged ≥ 65 years of age, patients with weight loss ≥ 5% at baseline, and patients with 'not otherwise specified' (NOS) NSCLC histology.

RESULTS – Study AVF0757g

In the AVF0757g study, among all randomized patients (ie, including those with squamous cell histology), the addition of 15 mg/kg/q3w bevacizumab to carboplatin/paclitaxel chemotherapy was associated with a significant improvement in investigator-assessed TTP (Table 4). The objective response rate and duration of overall survival were also numerically higher in the Bv15+CP arm compared to the control CP arm. Median survival time was unexpectedly high in the control CP arm; this may be explained, at least in part, by an effect of bevacizumab on survival time in the 19/32 (59%) control CP patients who crossed over to receive single agent bevacizumab after disease progression.

Table 4: Study AVF0757g: Summary of Efficacy Results (All Randomized Patients)

	CP N = 32	Bv7.5+CP N = 32	Bv15+CP N = 35
Objective response rate (no. [%)] [a]	6 (18.8)	9 (28.1)	11 (31.4)
Median time to progression (months) [a]	4.2	4.3	7.4 * [b]
Median overall survival (months)	13.2	11.6	14.3 [b]

a Based on investigator assessment. b n = 34. * p = 0.0234 (difference from control CP arm).

Improvements in the Bv7.5+CP arm were numerically lower than in the Bv15+CP arm. However, significant imbalances in prognostic disease characteristics at baseline (especially the high number of patients with squamous histology in the Bv7.5+CP arm), did not allow a definitive conclusion regarding a possible relationship between dose and treatment effect to be reached.

RESULTS – Study BO17704

The addition of bevacizumab (at both 7.5 and 15 mg/kg/q3w doses) to CG chemotherapy resulted in clinically meaningful and statistically significant improvements in both PFS (the primary efficacy parameter) and objective response rate. The duration of response was also improved in both bevacizumab arms compared to the Pl+CG arm. No statistical difference in PFS was demonstrated between the Bv7.5+CG and Bv15+CG arms in an exploratory analysis. (Table 5).

Table 5: BO17704: Summary of Efficacy Results (ITT Population)

	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
Objectivel response rate			
n a	324	323	332
Overall response	65 (20%)	110 (34%)	101 (30%)
Complete response	0	3 (1%)	4 (1%)
Partial response	65 (20%)	107 (33%)	97 (29%)
Duration of response KM estimate	4.7 months	6.1 months	6.1 months
Overall survival b HR (95% CI)		0.88 (0.68; 1.14)	1.02 (0.79; 1.31)

a Analysis based on randomized patients with measurable disease.

b Exploratory analysis based on approximately 50% of the 709 deaths required for the protocol-specified final analysis of overall survival.

2.2 Clinical safety

Safety data on bevacizumab are available for a total of 1134 patients with non-squamous NSCLC. Of these, 475 received bevacizumab in addition to carboplatin / paclitaxel (CP) (in studies E4599 and AVF0757g) and the remaining 659 patients received bevacizumab in addition to cisplatin/gemcitabine (GC) (study BO17704).

The E4599 study was not set up to collect complete safety data. In particular, no Grade 1/2 adverse events (AEs) or laboratory data (other than protein dipstick and those reported as Grade 3/4 AEs) were collected, and no AEs were classified as Serious Adverse Events (SAE), since no definition was specified in the protocol. However, events qualifying for expedited reporting via the NCI Adverse Event Expedited Reporting System (AdEERS), occurring in the bevacizumab arm, were reported and made available to Genentech and subsequently to Roche. These expedited reports as well as the AEs collected on the study's CRF overlap considerably with SAEs, making it likely that any AEs qualifying as "serious" (by ICH definition) would have been recorded.

To facilitate cross-study comparison and to conform to Regulatory guidelines, AE terms from all three studies were re-coded using the Medical Dictionary for Regulatory Activities (MedDRA version 9.1).

The most common AEs were as expected of a platinum-based regimen in patients with NSCLC. Proportionally more patients in the bevacizumab-containing arms (77% to 82%) compared with the control arms (65% to 76%) experienced at least one grade ≥ 3 adverse event.

The most common SOC in which grade ≥ 3 adverse events were reported was 'blood and lymphatic' (50% to 55% in BO17704; 20% to 48% in AVF0757g). It should be noted that, for coding reasons, very few patients in study E4599 appear to have reported adverse events in this SOC.

Neutropenia (including neutrophil count) was the single most common type of severe hematologic toxicity reported in all studies. The overall incidence of grade ≥ 3 febrile neutropenia was low in all studies but occurred at a slightly higher incidence in the bevacizumab-containing arms (1% to 2%

control vs. 2% to 4% bevacizumab). The higher incidence of grade ≥ 4 neutrophil count (17% CP vs. 26% Bv15+CP) as well as grade ≥ 3 febrile neutropenia (2% CP vs. 4% Bv15+CP) seen in E4599 was associated with a higher incidence of grade ≥ 3 infections (5% CP vs 10% Bv15+CP). However, due to limitations associated with data collection on the CRF, it was not possible to establish whether there was a temporal association between neutropenia and infections. In BO17704, the higher incidence of grade ≥ 3 neutropenia seen in the Bv7.5+CG arm was associated with a slightly higher incidence of grade ≥ 3 infections (5% Pl+CG vs 8% Bv7.5+CG, 5% Bv15+CG).

Severe (grade ≥ 3) bleeding is a rare complication of bevacizumab therapy and was reported at an incidence of 4% in the bevacizumab-containing arms compared with 2% in the control arm of study BO17704).

Other common grade ≥ 3 adverse events reported in all studies included fatigue/asthenia, vomiting, nausea and hypertension. Specifically with the CP regimen, grade ≥ 3 dyspnoea and peripheral sensory neuropathy were commonly reported adverse events.

With both the CP and CG chemotherapy regimens (E4599 and BO17704, respectively), the addition of bevacizumab increased the incidence (≥ 2%) of grade 4 neutrophil count as well as ≥ 3 neutropenia, hypertension, and fatigue/asthenia relative to control. Grade ≥ 3 AEs which occurred at a higher incidence with the addition of bevacizumab (≥ 2%) specifically with the CP regimen included hyponatraemia, infections, febrile neutropenia and proteinuria whilst those seen specifically in combination with the CG regimen included thrombocytopenia, vomiting and epistaxis. Other grade ≥ 3 adverse events which occurred at a higher incidence in the bevacizumab containing arms of both studies (eg, hypertension, proteinuria) have already been identified as belonging to the safety profile of bevacizumab.

Table 6 Comparison of Common (≥ 5%) Grade ≥ 3 Adverse Events

Body System/ Adverse Event	E4599 CP N = 441 No. (%)	E4599 Bv15+CP N = 427 No. (%)	BO17704 Pl+CG N = 327 No. (%)	BO17704 Bv7.5+CG N = 330 No. (%)	BO17704 Bv15+CG N = 329 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS					
NEUTROPENIA	-	-	104 (32)	132 (40)	117 (36)
THROMBOCYTOPENIA	-	-	76 (23)	89 (27)	77 (23)
ANAEMIA	-	-	45 (14)	35 (11)	34 (10)
LEUKOPENIA	-	-	24 (7)	22 (7)	23 (7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
FATIGUE	57 (13)	67 (16)	19 (6)	23 (7)	22 (7)
ASTHENIA	-	-	9 (3)	18 (5)	15 (5)
GASTROINTESTINAL DISORDERS					
VOMITING	20 (5)	24 (6)	12 (4)	24 (7)	31 (9)
NAUSEA	25 (6)	26 (6)	16 (5)	16 (5)	20 (6)
INVESTIGATIONS					
NEUTROPHIL COUNT	76 (17)	112 (26)	-	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
DYSPNOEA	66 (15)	55 (13)	11 (3)	9 (3)	9 (3)
METABOLISM AND NUTRITION DISORDERS					
ANOREXIA	17 (4)	22 (5)	5 (2)	6 (2)	9 (3)
DEHYDRATION	18 (4)	22 (5)	3 (<1)	1 (<1)	5 (2)
HYPERGLYCAEMIA	17 (4)	17 (4)	3 (<1)	3 (<1)	2 (<1)
NERVOUS SYSTEM DISORDERS					
PERIPHERAL SENSORY NEUROPATHY	48 (11)	39 (9)	-	-	-
HEADACHE	2 (<1)	13 (3)	-	6 (2)	4 (1)
CEREBROVASCULAR ACCIDENT	-	-	1 (<1)	2 (<1)	1 (<1)
NEUROPATHY PERIPHERAL	-	-	-	-	-
VASCULAR DISORDERS					
HYPERTENSION	3 (<1)	32 (7)	5 (2)	21 (6)	28 (9)
DEEP VEIN THROMBOSIS		-	5 (2)	4 (1)	9 (3)
THROMBOSIS		-	-	5 (2)	2 (<1)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS					
ARTHRALGIA	16 (4)	17 (4)	3 (<1)	3 (<1)	2 (<1)
MYALGIA	21 (5)	16 (4)	-	3 (<1)	-
MUSCULOSKELETAL CHEST PAIN	-	-	2 (<1)	1 (<1)	2 (<1)
INFECTIONS AND INFESTATIONS					
INFECTION	15 (3)	28 (7)	-	1 (<1)	-

Investigator text for Adverse Events encoded using MedDRA version 9.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
In study E4599 Grade 3 haematological AEs were not collected on the CRF

Body System/ Adverse Event	AVF0757g CP N = 25 No. (%)	AVF0757g Bv7.5+CP N = 22 No. (%)	AVF0757g Bv15+CP N = 31 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
NEUTROPENIA	5 (20)	8 (36)	12 (39)
THROMBOCYTOPENIA	-	-	-
ANAEMIA	-	-	1 (3)
LEUKOPENIA	-	1 (5)	3 (10)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
FATIGUE	-	-	1 (3)
ASTHENIA	-	1 (5)	3 (10)
GASTROINTESTINAL DISORDERS			
VOMITING	1 (4)	2 (9)	1 (3)
NAUSEA	1 (4)	-	2 (6)
INVESTIGATIONS			
NEUTROPHIL COUNT	-	-	-
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
DYSPNOEA	3 (12)	3 (14)	2 (6)
METABOLISM AND NUTRITION DISORDERS			
ANOREXIA	-	-	-
DEHYDRATION	1 (4)	-	1 (3)
HYPERGLYCAEMIA	-	1 (5)	2 (6)
NERVOUS SYSTEM DISORDERS			
PERIPHERAL SENSORY NEUROPATHY	-	-	-
HEADACHE	-	1 (5)	2 (6)
CEREBROVASCULAR ACCIDENT	-	-	2 (6)
NEUROPATHY PERIPHERAL	-	-	2 (6)
VASCULAR DISORDERS			
HYPERTENSION	-	-	2 (6)
DEEP VEIN THROMBOSIS	-	-	2 (6)
THROMBOSIS	-	-	2 (6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
ARTHRALGIA	-	1 (5)	2 (6)
MYALGIA	2 (8)	-	1 (3)
MUSCULOSKELETAL CHEST PAIN	2 (8)	-	-
INFECTIONS AND INFESTATIONS			
INFECTION	1 (4)	-	1 (3)

Investigator text for Adverse Events encoded using MedDRA version 9.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Table 7. **Summary of Deaths**

Study	E4599		BO17704			AVF0757g		
	CP N = 437 No. (%)	Bv15+CP N = 422 No. (%)	Pl+CG N = 327 No. (%)	Bv7.5+CG N = 330 No. (%)	Bv15+CG N = 329 No. (%)	CP N = 25 No.(%)	Bv7.5+CP N = 22 No. (%)	Bv15+CP N = 31 No. (%)
All cause deaths	361 (82)	329 (77)	113 (35)	107 (32)	109 (33)	13 (52)	11 (50)	13 (42)
Deaths within 60 days of randomisation***	29/438 (7)	25/426 (6)	14/319 (4)	10/322 (3)	14/318 (4)	4/25 (16)	-	1/31 (3)
AEs leading to death	9 (2)	23 (5)**	17 (5)	17 (5)	20 (6)	1 (4)	1 (5)	3 (10)

***In E4599 and BO17704, the denominator is the number of pts who died in the first 60 days, plus those known to be alive on or after day 60 whereas in AVF0757g, the denominator is the number of patients who died in the first 60 days, plus those who received drug on day 60 or beyond.

Based on data collected on the CRF, more patients in the Bv15+CP arm (23/427 patients or 5%) compared to the CP arm (9/441 patients or 2%) had AEs which led to a fatal outcome. The most common AEs leading to death were bleeding events: a total of 11 patients (3 CP, 8 Bv15+CP) died as a result of a hemorrhagic AE (haemoptysis, haemorrhage, gastrointestinal haemorrhage, hematemesis) with the most common being haemoptysis (1 CP vs 5 Bv15+CP).

Other Serious Adverse Events

- **Thromboembolic Events**

In E4599, the incidence of grade ≥ 3 arterial thromboembolic events (ATEs) was higher in the bevacizumab 15 mg/kg arm compared with the control arm, whereas in study BO17704, the incidence was higher in the placebo-containing arm. Very few grade ≥ 3 ATE events were reported in AVF0757g.

In AVF0757g and BO17704, the majority of ATEs were of grades 1 or 2 severity whereas VTE were generally of grade ≥ 3 severity.

The overall rate of fatal thromboembolic events was low across the studies. Based on the E4599 CSR, the rate of fatal ATEs was 1/441 in the CP arm compared with 5/427 in the Bv15+CP arm. There were no fatal VTEs in the CP arm compared with 1/427 events in the Bv15+CP arm.

- **Hypertension**

Hypertension, which is known to be associated was bevacizumab therapy, was reported at a higher incidence in the bevacizumab containing arms in all three studies.
Hypertensive events were manageable and no events resulted in a fatal outcome.

- **Proteinuria**

In study E4599, the incidence of grade ≥ 3 proteinuria was 3% in the Bv15+CP arm compared with no events in the control arm.

The incidence of proteinuria in study AVF0757g was low with no noteworthy differences between the study arms.

In BO17704, more patients in the bevacizumab-containing arms compared with the placebo-containing arms had proteinuria reported as an adverse event (2 Pl+CG vs. 9 Bv7.5+CG, 12 Bv15+CG). The majority of cases were of grade 1 or 2 severity, although five patients (1 Bv7.5+CG, 4 Bv15+CG) discontinued bevacizumab for this reason. Most cases of proteinuria resolved without sequelae.

- **Congestive Heart Failure**

The incidence of congestive heart failure across all studies was low with no noteworthy differences between the study arms.

- **Clinical Laboratory Evaluations**

Study E4599: There was a higher incidence of grade ≥ 1 proteinuria in the Bv15+CP arm compared with the CP arm.

Study AVF0757g: With the exception of hyperglycaemia, which was more common in the control arm, there were no noteworthy differences in the incidence and type of other grade 3/4 laboratory abnormalities. Grade 1 or 2 proteinuria was more common in the bevacizumab containing arms compared with the control arm

Study BO17704: There were no noteworthy differences between the study arms with respect to the incidence of grade 3 or 4 laboratory abnormalities with the following exceptions:
The incidence of grade 3 or 4 neutropenia was slightly higher in the bevacizumab containing arms compared with the control arm. Grade 3 or 4 laboratory abnormalities for thrombocytopenia were more common in the Bv7.5+CG arm (43%) compared with the other study arms (37% Pl+CG and 35% Bv15+CG). More patients in the Bv7.5+CG arm (9 cases) compared with the other study arms 1 Pl+CG, 4 Bv15+CG) experienced grade 3 or 4 abnormalities for ALT. The incidence of grade 3 or 4 laboratory abnormalities for hypokalaemia (<1%, 3%, 4%) and hyponatraemia (3%, 6%, 7%) was slightly higher in the bevacizumab containing arms compared with the control arm. More patients in the Bv7.5+CG arm had grade 3 or 4 laboratory abnormalities for hypocalcaemia compared with the other study arms (7 Pl+CG vs. 11 Bv7.5+CG, 7 Bv15+CG).

Overall, due to differences in trial design (including differences in comparator regimen) and ways of collecting safety information across studies, it is not considered clinically benefitful to provide pooled integrated displays of safety data for studies AVF0757g and BO17704. Many of the adverse events are typically described in patients who receive chemotherapy e.g. constipation, diarrhoea, arthralgia, alopecia, rash, fatigue/ asthenia, nausea and vomiting. Similar to other bevacizumab studies, the high incidence of headache, hypertension and epistaxis is related to bevacizumab treatment.

- **Adverse Events by Age (Study E4599)**

There was no evidence of a clinically relevant difference in the safety profile of bevacizumab in young (< 65 yrs) compared with elderly patients (≥ 65 yrs).

- **Adverse Events by Gender (Study E4599)**

Overall, there was no evidence of a significant difference in the AE profile of bevacizumab between males and females.

- **Adverse Events by Histologic Type (Study E4599)**

There was no evidence that NSCLC patients with unspecified histologic subtype were at increased risk of grade severe (≥ grade 3) haemoptysis.

Post marketing experience/Risk management

The post-marketing experience with bevacizumab is based on the safety data contained in two previously submitted Periodic Safety Update Reports (PSUR) covering the period from February 26 2004 to 25 February 2006. During this 2 year period, an estimated 93,000 patients were treated with bevacizumab in the post-marketing setting or in company sponsored clinical trials.
A total of 5.115 AEs of which 4.373 were serious, were reported in 2.857 patients across several indications. In total 318 treatment-related deaths were reported.

The most frequently reported AEs in cancer patients treated with bevacizumab were gastrointestinal disorders (23%) such as diarrhea, vomiting, nausea and intestinal perforation; vascular disorders (12%) such as deep vein thrombosis, hypertension and vasculitis; and respiratory, thoracic and mediastinal disorders (10%) such as pulmonary embolism and dyspnea (Table 6).

Table 6 Summary of Adverse Events by System Organ Class

System Organ Class	No. Patients with at least one AE/SOC[1]	Serious Adverse Events		Total Adverse Events	
		N	%	N	%
Infections and Infestations	243	266	6.1	279	5.5
Neoplasms Benign, Malignant And Unspecified (Including Cysts And Polyps)	52	50	1.1	54	1.1
Blood And Lymphatic System Disorders	179	174	4.0	207	4.1
Immune System Disorders	19	18	0.4	19	0.4
Endocrine Disorders	9	7	0.2	9	0.2
Metabolism And Nutrition Disorders	201	256	5.9	271	5.3
Psychiatric Disorders	48	46	1.1	52	1.0
Nervous System Disorders	325	332	7.6	370	7.2
Eye Disorders	36	26	0.6	38	0.7
Ear And Labyrinth Disorders	4	3	0.1	6	0.1
Cardiac Disorders	209	247	5.6	250	4.9
Vascular Disorders	559	510	11.7	596	11.6
Respiratory, Thoracic And Mediastinal Disorders	440	458	10.5	505	9.9
Gastrointestinal Disorders	861	1071	24.5	1176	23.0
Hepatobiliary Disorders	30	33	0.7	37	0.7
Skin And Subcutaneous Tissue Disorders	93	34	0.8	100	1.9
Musculoskeletal And Connective Tissue Disorders	81	68	1.6	89	1.7
Renal And Urinary Disorders	183	112	2.6	200	3.9
Pregnancy, Puerperium And Perinatal Conditions	0	0	0.0	0	0.0
Reproductive System And Breast Disorders	31	24	0.5	32	0.6
Congenital, Familial And Genetic Disorders	0	0	0.0	0	0.0
General Disorders And Administration Site Conditions	405	347	7.9	444	8.6
Investigations	200	211	4.8	281	5.5
Injury, Poisoning And Procedural Complications	94	77	1.8	97	1.9
Surgical And Medical Procedures	3	3	0.1	3	0.1
Social Circumstances	0	0	0.0	0	0.0
Total	**N/A**	**4373**	**100.0**	**5115**	**100.0**

[1] All case reports from spontaneous sources, clinical trials, literature, regulatory authority, contractual partners, special registries, poison control centers, epidemiological investigations.
Source: Cumulative data from PSURs Nos. 1019578 and 1020721 covering the period from February 26, 2004 to 25 February 2006.

3. BENEFIT RISK ASSESSMENT

The pivotal E4599 study is a large randomized study carried out according to accepted principles. It showed a significant and clinically meaningful improvement in overall survival by the addition of bevacizumab to a two-drug regimen containing platinum. The pivotal study also showed a highly significant improvement in response rate and progression-free survival. These findings are considered as supported by the two studies, AVF9757g and BO17704, of which the BO17704 study at present is lacking mature overall survival data, but acceptable PFS data has been shown. The BO17704 OS data is expected for 1Q 2008, and will be forwarded as commitment.

The dose of bevacizumab was 15 mg/kg/q3w in the pivotal study. Data from the supportive studies are not conclusive with regard to the effect of the 7.5 mg/kg/q3w tested in those studies and the choice of dose was extensively discussed. The CHMP agreed to recommend both doses and requested a commitment to investigate the lower dose and if appropriate change the dose recommendations according to the result. The MAH therefore committed to conducting a clinical study investigating the correlation of potential predictive biomarkers to clinical outcome in patients receiving either

7.5 mg/kg/q3w or 15 mg/kg/q3w bevacizumab in combination with carboplatin chemotherapy regimens. The study will also include exploratory analyses of efficacy and safety.

The duration of treatment with bevacizumab is in accordance with the available data "until progression of the underlying disease". This concept of treatment although could be justified by the mechanism of action, the type of the compound and the stage of the disease, the issue of duration of treatment should be reviewed in the future in the light of the experience gained with the product.

Generally, there were no unexpected toxicities with the use of bevacizumab in addition to platinum-based chemotherapy in studies E4955, AVF0757g, BO17704. The principal significant risk shown to be associated with bevacizumab in this population was an increase in Grade ≥ 3 hemorrhage. Grade ≥ 3 non-hematological AEs with higher incidence in the bevacizumab treatment arms included those already recognized as belonging to the safety profile of bevacizumab (arterial and venous thromboembolic events, hypertension and proteinuria). Other Grade ≥ 3 non-hematologic AEs that had an apparent increased incidence rate in bevacizumab arms compared to control arm in each study are as follows; Study E4599: hyponatraemia, infection, headache and fatigue; Study AVF0757g: asthenia; Study BO17704: anorexia, vomiting and hypertension.

Although bevacizumab has side effects, the significant, albeit modest, improvement in overall survival with the addition of the drug to standard platinum-based chemotherapy represents an important benefit for patients with locally advanced, metastatic or recurrent NSCLC other than predominant squamous cell, a disease which is invariably fatal with a short expected survival.

The benefit of adding bevacizumab as seen from the data of study BO17704 can be extrapolated to other platinum regimens and consequently a broad indication can be justified. This assumption is supported by the findings of a publication in *N Engl J Med 346:92;2002 (Schiller et al.):* where a a randomized study in 1207 patients with advanced non-small-cell lung cancer compared four chemotherapy regimens, (Cis + pacli;Cis+gem; Cis+docetax, Carbo+pacli) and none of four chemotherapy regimens offered a significant advantage over the others in the treatment of advanced non–small-cell lung cancer. Therefore, the benefit-risk for the indication:

> Avastin, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

is positive. The recommended dose of Avastin is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion for up to 6 cycles of treatment, followed by Avastin as a single agent until disease progression.

4. CONCLUSION

- On 19 July 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area[1]	Description	Due date[2]
Clinical	**Clinical study to investigate the lower dose of Avastin** The MAH commits to conducting a clinical study investigating investigating the correlation of potential predictive biomarkers to clinical outcome in patients receiving either 7.5 mg/kg/q3w or 15 mg/kg/q3w bevacizumab in combination with carboplatin chemotherapy regimens. The study will also include exploratory analyses of efficacy and safety	31/10/2010
Clinical	**Provision of overall Survival data for Study BO17704** The MAH commits to provide a survival update report for study BO17704, and if appropriate, submit a Type II variation to update the SmPC to reflect the overall survival analysis.	15/11/2008
Pharmacovigilance	**RMP Measures regarding use of Avastin with various chemotherapy regimens** The MAH commits to collect detailed information regarding the chemotherapy regimens administered to patients who report an adverse event from either spontaneous reports or investigator sponsored studies for at least 1 year post-approval of the indication extension. These measures will be included in the next version of the Risk Management Plan, and the analyses will be presented in the annual PSURs which will be submitted by 25 April 2008 and 25 April 2009.	Annual PSURs: 25/04/2008 25/04/2009

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.