Report according to § 42b (2) German Drug Law

Protocol-No.:	**BO17708 (AVADO)**
Study Title:	A randomised, double blind, placebo-controlled, multi-centre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel compared with docetaxel plus placebo, as first line treatment for patients with HER2 negative metastatic and locally recurrent breast cancer
Date of Report:	**Final report 1058831 (April 2014)** **Roche Research Report 1023027 (Feb 2010),** report of overall survival (OS) analysis **Roche Research Report (April 2009),** Response to questions submitted to the CHMP **Roche Research Report 1021786 (Sep 2008),** updated exploratory analysis of efficacy and safety data **Research Report 1025622 (May 2008)** with Erratum (report 1031926; update of the full adverse event listing)
Study Sponsor(s)	F. Hoffmann-La Roche Ltd.
Study Date:	15 March 2006 to 24 October 2013 (first patient screened to last patient last visit).
Trial Phase:	III
Indication:	Metastatic breast cancer
Name of Finished Product:	Avastin®
Name of Active Substance:	Bevacizumab
Number of Patients:	Planned: 705 Analysed: Placebo + Docetaxel 241 Bevacizumab 7.5 mg/kg q3w + Docetaxel 248 Bevacizumab 15 mg/kg q3w + Docetaxel 247 Total 736
Study Interruptions/ Premature end:	N/A

Synopsis of final report 1058831 (April 2014)

Study BO17708

Data cut-off: 24 October 2013

Period covered by this report: 15 September 2008 to 24 October 2013 (Update analysis CSR to last patient last visit)

TITLE PAGE

RESEARCH REPORT NO. 1058831

Final Clinical Study Report – BO17708 - A randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel in comparison with docetaxel plus placebo as first line treatment for patients with HER2-negative metastatic and locally recurrent breast cancer. Research Report No. 1058831. April 2014.

Study Sponsor(s)	F. Hoffmann-La Roche Ltd.
Study Dates:	15 March 2006 to 24 October 2013 (first patient screened to last patient last visit). Period covered by this report: 15 September 2008 to 24 October 2013 (Update analysis CSR to last patient last visit).
Trial Phase:	III
Indication:	HER2-negative metastatic breast cancer
Name of Principal Investigator:	**Affiliation:**
Dr D.W. Miles	Mount Vernon Hospital, Middlesex, United Kingdom
Sponsor's Signatory:	Cornelia Irl

Personnel Responsible for Clinical and Statistical Analyses:

Clinical Scientist	Maria Milian
Statistician	Nicola Moore

GCP Compliance: This study was conducted in accordance with the principles of GCP.

SYNOPSIS OF RESEARCH REPORT 1058831 (PROTOCOL BO17708)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	**Final Clinical Study Report** - BO17708 - A randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel in comparison with docetaxel plus placebo as first line treatment for patients with HER2-negative metastatic and locally recurrent breast cancer. Research Report No. 1058831. April 2014. Prepared as a Synopsis Report due to limited additional data collected since the clinical cut-off for the update analysis (15 September 2008).
INVESTIGATORS / CENTERS AND COUNTRIES	106 centers in 24 countries (Western Europe/Australia/ Canada/Eastern Europe/East Asia/Central and South America). Principal investigator: Dr. David Miles, Mount Vernon Hospital, Middlesex, UK.
PUBLICATION (REFERENCE)	Miles D, et al. Phase III Study of Bevacizumab Plus Docetaxel Compared With Placebo Plus Docetaxel for the First-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer. J Clin Oncol. 2010;28(20):3239-3247.
PERIOD OF TRIAL	15 March 2006 to 24 October 2013 (first patient screened to last patient last visit). Period covered by this report: 15 September 2008 to 24 October 2013 (Update analysis CSR to last patient last visit).
CLINICAL PHASE	III
OBJECTIVES	Primary objective: • To compare Progression Free Survival (PFS) in patients randomized to bevacizumab plus docetaxel versus patients randomized to docetaxel plus placebo. Secondary objectives: • To compare best overall response (OR), duration of response (DR), time to treatment failure (TTF) and overall survival (OS) in patients randomized to bevacizumab plus docetaxel versus patients randomized to docetaxel plus placebo. • To determine the safety and tolerability of combining bevacizumab with docetaxel. • To assess change in quality of life in the bevacizumab-containing and control arms.

STUDY DESIGN	Multicenter, three-arm, randomized, double-blind, placebo controlled Phase III study.
NUMBER OF SUBJECTS	Placebo + Docetaxel 241 Bevacizumab 7.5 mg/kg q3w + Docetaxel 248 Bevacizumab 15 mg/kg q3w + Docetaxel 247 Total 736
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Metastatic or locally recurring breast cancer. • Pre- and post-menopausal female patients. • Age ≥ 18 years. • Histologically or cytologically confirmed HER2-negative adenocarcinoma of the breast. • Measurable or non-measurable disease. • Candidates for chemotherapy. • ECOG PS of 0 or 1. • Documented ER/PR status. • No previous chemotherapy or radiotherapy for metastatic or locally recurrent breast cancer. • Adequate liver, renal, cardiovascular, CNS and bone marrow function.
TRIAL DRUG / STROKE (BATCH) No.	Bevacizumab / B1887, B1947, B1948, B1953, B3068, B3071, B3219, B3124, B3138, B3227, B3335, B3351, B3377, B3360, B5021, B2016, B2020, B5020, B5022, B5025, B5027, B6005, B6014, B6017, B6038, B9000, B9001, B9002
DOSE / ROUTE / REGIMEN / DURATION	Main study phase: Bevacizumab 7.5 mg/kg or 15 mg/kg / IV / q3w until disease progression, unacceptable toxicity or patient withdrawal. Optional post-study phase: Bevacizumab 15 mg/kg / IV / q3w, irrespective of their main study treatment, until disease progression, unacceptable toxicity or patient withdrawal.
REFERENCE DRUG / STROKE (BATCH) No.	Docetaxel / D5G548/D5G141, D5G271/D5G140, D6A071/D5H525, D6C248/D6A437, D6A820/D6A438, D6D613/D6D764, D6D612/D6D528 , D6C248/D6A437, D6A071, D6C248, Placebo (for bevacizumab)
DOSE / ROUTE / REGIMEN / DURATION	Docetaxel 100 mg/m^2 / IV / q3w / max. 9 cycles Placebo / IV / q3w / until disease progression, unacceptable toxicity or patient withdrawal.
CRITERIA FOR EVALUATION	
EFFICACY:	Tumor assessments using RECIST criteria using CT/MRI/bone scans and/or X-rays at baseline and every 9 weeks until week 36 and then every 12 weeks until disease progression. Date of death for OS. Quality of Life (QoL): FACT-B and FACT-G version 4.
SAFETY:	Adverse events, laboratory tests, physical exam, vital signs, ECG, LVEF, brain CT scan/MRI

STATISTICAL METHODS	For the primary endpoint of PFS, the log-rank test (unstratified) was used to compare each of the two bevacizumab arms with the placebo arm. Kaplan-Meier curves and estimates of event rates over time were provided. Hazard ratios and corresponding 95% confidence intervals (CI) were calculated to assess the magnitude of the treatment benefit. Proportion of responders and non-responders in each of the three treatment arms was summarized for the OR, together with the two-sided 95% Person-Clopper CIs for response rates. For the TTF, DR and OS, Kaplan Meier curves and estimates were provided together with the log-rank test.

METHODOLOGY

Patients were randomized to one of three treatment arms: docetaxel 100 mg/m^2 q3w plus bevacizumab 7.5 mg/kg q3w, docetaxel 100 mg/m^2 q3w plus bevacizumab 15 mg/kg q3w or docetaxel 100 mg/m^2 q3w plus placebo q3w. Docetaxel was administered for a maximum of 9 cycles (27 weeks) and bevacizumab/placebo administered until confirmed disease progression, unacceptable toxicity (requiring discontinuation of study treatment) or withdrawal at patient request. In case of permanent discontinuation of one of the two treatment components (docetaxel or bevacizumab/placebo) for safety reasons, the other treatment component could be continued.

Upon evidence of disease progression, all study treatments were to be discontinued permanently. After documented disease progression, investigators had the option to enter patients into a post-study treatment phase, during which they could receive bevacizumab 15 mg/kg q3w in the second-line setting irrespective of the treatment they received in the main study phase. Patients could receive bevacizumab alone in the post-study treatment phase. However, the following antineoplastic therapies were allowed to be used concurrently with bevacizumab: capecitabine, taxol, gemcitabine, vinorelbine, hormones.

For those patients who continued with bevacizumab following database lock for the final OS analysis (30 April 2009), serious adverse event (SAE) data collection was continued. For patients continuing in the optional post-study phase, only SAEs that were considered to be related to study treatment by the investigator were to be reported.

EFFICACY RESULTS

The results of the protocol-defined primary efficacy (PFS) and secondary endpoints, including an interim OS analysis, with a data cut-off of 31 October 2007, were reported in a previous CSR (Roche Research Report 1025622) and erratum (Roche Research Report 1031926).

Subsequently, an update to the initial efficacy (and safety) data with a cut-off of 15 September 2008 was performed and reported (Roche Research Report 1021786), and a report of the final OS analysis, including an updated PFS analysis, with a data cut-off of 30 April 2009, was prepared as part of the Response to Questions submitted to the CHMP (see page 65). In addition, an exploratory follow-up OS analysis with a data cut-off of 28 February 2010 was performed and reported (Roche Research Report 1023027).

No further efficacy analyses were performed for this final CSR.

SAFETY RESULTS

The safety results from the time of the protocol-defined primary analysis (data cut-off 31 October, 2007) and update analysis (data cutoff 15 September. 2008) were fully reported in the two previous CSRs from this study (Roche Research Reports 1025622 (with erratum 1031926) and 1021786, respectively).

This final CSR includes additional safety data reported since the clinical cut-off for the update analysis (15 September 2008) until the date of the Last Patient Last Visit (LPLV: 24 October, 2013). During this period, 13 patients were ongoing in the Bv7.5+doc arm and 36 patients in the Bv15+doc arm. Note that after the final OS analysis (30 April, 2009), only SAEs were collected (and entered in the Roche Drug Safety database) up until the LPLV on 24 October 2013. Safety data from patients in the post-study treatment phase is not presented in this report.

Common Adverse Events

During the reporting period, 6/252 patients (2.4%) in the Bv7.5+doc arm and 31/261 patients (11.9%) in the Bv15+doc arm experienced one or more adverse events (AEs). The most commonly affected body systems in both bevacizumab treatment arms were infections and infestations (Bv7.5+doc; 0.4%: Bv15+doc; 6.1%), gastrointestinal disorders (Bv7.5+doc; 1.6%: Bv15+doc; 3.8%) and musculoskeletal and connective tissue disorders (Bv7.5+doc; 1.2%: Bv15+doc; 3.1%). A summary of all AEs by body system and trial treatment is shown on page 52 , and a listing of AEs by trial treatment and patient number is shown on page 78 .

A summary of AEs that occurred in 1% or more of patients in any treatment arm in the safety analysis population (SAP) is shown in Table 1. Proteinuria, diarrhoea, upper respiratory tract infection and headache were the most common AEs, all of which occurred more frequently in the Bv15+doc arm compared to the Bv7.5+doc arm.

Table 1 Summary of Adverse Events Occurring in ≥1% of Patients in Any Treatment Arm (SAP).

Body System/ Adverse Event	Pl+doc N = 217 No. (%)	Bv7.5+doc N = 252 No. (%)	Bv15+doc N = 261 No. (%)
PROTEINURIA	-	-	6 (2.3)
DIARRHOEA	-	1 (0.4)	5 (1.9)
UPPER RESPIRATORY TRACT INFECTION	-	-	4 (1.5)
HEADACHE	-	2 (0.8)	4 (1.5)
COUGH	-	1 (0.4)	3 (1.1)
EPISTAXIS	-	1 (0.4)	3 (1.1)
RHINORRHOEA	-	-	3 (1.1)
FATIGUE	-	1 (0.4)	3 (1.1)
HYPERTENSION	-	-	3 (1.1)

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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Grade ≥3 Adverse Events

A summary of Grade ≥3 AEs by body system and trial treatment is shown in Table 2.

Overall, 7 patients (2.7%) in the Bv15+doc arm and 2 patients (0.8%) in the Bv7.5+doc arm experienced 7 and 2 Grade ≥3 AEs, respectively.

The most common Grade ≥3 AEs were proteinuria in 3 patients (1.1%) and cerebral ischemia in 2 patients (0.8%) both of which occurred in the Bv15+doc arm.

Table 2 Summary of Grade ≥3 Adverse Events (SAP)

Body System/ Adverse Event	Pl+doc N = 217 No. (%)	Bv7.5+doc N = 252 No. (%)	Bv15+doc N = 261 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	-	2 (0.8)	7 (2.7)
Total Number of AEs	-	2	7
RENAL AND URINARY DISORDERS			
Total Pts With at Least one AE	-	-	3 (1.1)
PROTEINURIA	-	-	3 (1.1)
Total Number of AEs	-	-	3
NERVOUS SYSTEM DISORDERS			
Total Pts With at Least one AE	-	-	2 (0.8)
CEREBRAL ISCHAEMIA	-	-	2 (0.8)
Total Number of AEs	-	-	2

Table 2 Summary of Grade ≥ 3 Adverse Events (SAP) (cont.)

Body System/ Adverse Event	Pl+doc N = 217 No. (%)	Bv7.5+doc N = 252 No. (%)	Bv15+doc N = 261 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total Pts With at Least one AE	-	-	1 (0.4)
ANAEMIA	-	-	1 (0.4)
Total Number of AEs	-	-	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total Pts With at Least one AE	-	1 (0.4)	-
CHEST PAIN	-	1 (0.4)	-
Total Number of AEs	-	1	-
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total Pts With at Least one AE	-	1 (0.4)	-
ARTHRALGIA	-	1 (0.4)	-
Total Number of AEs	-	1	-
VASCULAR DISORDERS			
Total Pts With at Least one AE	-	-	1 (0.4)
HYPERTENSION	-	-	1 (0.4)
Total Number of AEs	-	-	1

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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Deaths

As shown in Table 3, the most common cause of death during the reporting period in each treatment arm was progressive disease (metastatic breast cancer); 22% of patients in the Pl+doc arm, 21% of patients in the Bv7.5+doc arm and 22% of patients in the Bv15+doc arm.

Three patients in the Bv15+doc arm, 2 patients in the Bv7.5+doc arm and 1 patient in the Pl+doc arm died from other causes (Table 3). These deaths occurred more than 28 days after the last dose of trial treatment. In addition, 1 patient who died from a pulmonary haemorrhage within 28 days of stopping bevacizumab treatment was not included in the Roche clinical database. Narratives for the patient with a pulmonary haemorrhage and for the patient with necrotizing pancreatitis can be found on page 13 .

A listing of deaths by trial treatment and patient number is shown on page 116.

Table 3 Summary of Deaths by Cause of Death (ITT)

Cause of Death	Pl+doc N = 241 No. (%)	Bv7.5+doc N = 248 No. (%)	Bv15+doc N = 247 No. (%)
Total No. of Deaths	54 (22)	53 (21)	55 (22)
DEATH FROM DISEASE PROGRESSION			
Total No. of Deaths	53 (22)	51 (21)	52 (21)
BREAST CANCER METASTATIC	53 (22)	51 (21)	52 (21)
DEATH FROM OTHER CAUSES			
Total No. of Deaths	1 (<1)	2 (<1)	3 (1)
CEREBROVASCULAR ACCIDENT	-	-	1 (<1)
LYMPHOCYTIC LEUKAEMIA	-	-	1 (<1)
NEUTROPENIC SEPSIS	-	-	1 (<1)
PANCREATITIS NECROTISING	-	1 (<1)	-
PNEUMONIA	1 (<1)	-	-
SEPSIS	-	1 (<1)	-

Investigator text for Cause of Death encoded using MedDRA version 16.1.
Percentages are based on N.
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Serious Adverse Events

Two SAEs of cerebral ischemia were reported in 2 patients (0.8%) in the Bv15+doc arm (Table 4). Neither SAE was considered to be related to bevacizumab treatment. None of the patients in the Bv7.5+doc arm experienced a SAE during the reporting period.

Updates to narratives previously reported for patients with SAEs related to bevacizumab or placebo treatment are shown on page 13 .

Table 4 Summary of Serious Adverse Events (SAP)

Body System/ Adverse Event	Pl+doc N = 217 No. (%)	Bv7.5+doc N = 252 No. (%)	Bv15+doc N = 261 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	-	-	2 (0.8)
Total Number of AEs	-	-	2
NERVOUS SYSTEM DISORDERS			
Total Pts With at Least one AE	-	-	2 (0.8)
CEREBRAL ISCHAEMIA	-	-	2 (0.8)
Total Number of AEs	-	-	2

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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Adverse Events Leading to Discontinuation of Trial Treatment

In the Bv15+doc arm, 3 patients (1.1%) discontinued any component of trial treatment, 2 patients due to cerebral ischemia and 1 patient because of proteinuria (Table 5). None of the patients in the Bv7.5+doc arm discontinued treatment during the reporting period.

Table 5 Summary of Adverse Events Leading to Discontinuation of Any Component of Study Treatment (SAP)

Body System/ Adverse Event	Pl+doc N = 217 No. (%)	Bv7.5+doc N = 252 No. (%)	Bv15+doc N = 261 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	-	-	3 (1.1)
Total Number of AEs	-	-	3
NERVOUS SYSTEM DISORDERS			
Total Pts With at Least one AE	-	-	2 (0.8)
CEREBRAL ISCHAEMIA	-	-	2 (0.8)
Total Number of AEs	-	-	2
RENAL AND URINARY DISORDERS			
Total Pts With at Least one AE	-	-	1 (0.4)
PROTEINURIA	-	-	1 (0.4)
Total Number of AEs	-	-	1

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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Adverse Events of Special Interest

Adverse events of special interest (AESI) were reported in 14 patients (5.4%) in the Bv15+doc arm and in 2 patients (0.8%) in the Bv7.5+doc arm. The most common AESIs in the Bv15+doc arm were proteinuria in 6 patients (2.3%), epistaxis in 3 patients (1.1%), hypertension in 3 patients (1.1%) and cerebral ischemia in 2 patients (0.8%) (Table 6).

Table 6 Summary of Adverse Events of Special Interest (SAP)

Body System/ Adverse Event	Pl+doc N = 217 No. (%)	Bv7.5+doc N = 252 No. (%)	Bv15+doc N = 261 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	-	2 (0.8)	14 (5.4)
Total Number of AEs	-	2	20
ALL BLEEDING			
Total Pts With at Least one AE	-	2 (0.8)	5 (1.9)
EPISTAXIS	-	1 (0.4)	3 (1.1)
GINGIVAL BLEEDING	-	-	1 (0.4)
HAEMATOMA	-	1 (0.4)	-
HAEMOPTYSIS	-	-	1 (0.4)
HAEMORRHOIDAL HAEMORRHAGE	-	-	1 (0.4)
METRORRHAGIA	-	-	1 (0.4)
RECTAL HAEMORRHAGE	-	-	1 (0.4)
Total Number of AEs	-	2	8
PROTEINURIA			
Total Pts With at Least one AE	-	-	7 (2.7)
PROTEINURIA	-	-	6 (2.3)
ALBUMINURIA	-	-	1 (0.4)
Total Number of AEs	-	-	7
HYPERTENSION			
Total Pts With at Least one AE	-	-	3 (1.1)
HYPERTENSION	-	-	3 (1.1)
Total Number of AEs	-	-	3
THROMBOEMBOLIC EVENTS			
Total Pts With at Least one AE	-	-	2 (0.8)
CEREBRAL ISCHAEMIA	-	-	2 (0.8)
Total Number of AEs	-	-	2
THROMBOEMBOLIC EVENTS - ARTERIAL			
Total Pts With at Least one AE	-	-	2 (0.8)
CEREBRAL ISCHAEMIA	-	-	2 (0.8)
Total Number of AEs	-	-	2

Investigator text for Adverse Events encoded using MedDRA version 16.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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CONCLUSIONS

During the period covered by this report, no new or unexpected safety findings were seen compared to those reported in the previous clinical study reports for this study.

Summary of Report 1023027 (Feb 2010),
Results of the Overall Survival Follow-up Analysis for Study BO17708

Data cut-off: 28 Feb 2010

Results of the Overall Survival Follow-up Analysis Data Cut-Off: February 28, 2010

A randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel in comparison with docetaxel plus placebo as first line treatment for patients with HER2-negative metastatic and locally recurrent breast cancer.

Original Clinical Data Cut-off: October 31, 2007
Updated Clinical Data Cut-off: February 28, 2010

Study BO17708 was a randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel, in comparison with docetaxel plus placebo, as first-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer (mBC). The primary endpoint was progression-free-survival (PFS); secondary endpoints included overall survival (OS). The study was designed with 80% power to detect an improvement in PFS with the hazard ratio (HR) of 0.70. The pre-specified interim OS analysis was performed at the time of the final PFS analysis (clinical cut-off date of October 31, 2007), and the main and final OS analysis (referred to also as 'updated analysis') took place with a clinical cut-off date of April 30, 2009. Subsequently, an amendment to the protocol (Amendment G) was issued so that an exploratory further OS follow-up analysis could be performed when the database would be more mature, (less than 50% of the patients had an OS event at time of the pre-specified final OS analysis). The further OS follow-up analysis was performed when 59% of OS events were observed (clinical cut-off date of February 28, 2010) and the results are presented in this report.
This report focuses mainly on a comparison of the bevacizumab 15 mg/kg every 3 weeks (q3wk) + docetaxel (Bv15 + Doc) arm with the placebo + docetaxel (Pl + Doc) arm, as this dose of bevacizumab is the approved dose in the EU for the treatment of mBC. Data from the Bv7.5 + Doc arm are included for completeness only.

Conclusion:
The results of this further OS follow-up analysis with a clinical cut-off date of February 28, 2010 are consistent with the final OS analysis dated April 30, 2009. The proportion of PD-related and non–PD-related deaths was similarly distributed in all arms. There was no difference in OS between the Bv15 + Doc arm and the Pl + Doc arm (unstratified HR = 0.98; 95% CI [0.78; 1.23]). Median OS was 28.1 months (95% CI [25.9; 34.1]) in the Bv15 + Doc arm and 31.7 months (95% CI [27.4; 36.7]) in the Pl + Doc arm. The added follow-up time with 63 more events results in tighter confidence intervals and provides greater certainty that there is no impairment in survival with bevacizumab. The results of this further OS follow-up analysis based on more mature data, including approximately 60% of death events, again show that the combination of bevacizumab and docetaxel compared with docetaxel alone did not have a detrimental effect on OS.

In conclusion, the further OS follow-up analysis, based on a mature database, showed no evidence of a long-term detrimental effect on OS for the patient population enrolled in Study BO17708 treated with bevacizumab and docetaxel.

Response to CHMP Questions (April 2009):
Results of the final OS analysis for study BO17708

Data cut-off: 30 April 2009

GLOSSARY OF ABBREVIATIONS

Bv	Bevacizumab
CI	Confidence interval
Doc	Docetaxel
ITT	Intent-to-treat
mBC	Metastatic breast cancer
Pl	Placebo
q3w	Every three weeks

1. SUMMARY OF OVERALL SURVIVAL RESULTS

This preliminary report of final analysis of the overall survival data from study BO17708 showed that:

- There was no difference in overall survival between the Bv 15 + Doc arm and the Pl + Doc arm in both the unstratified (hazard ratio 1.03 [95% CI: 0.79; 1.33]) and stratified (hazard ratio 1.00 [95% CI 0.76; 1.32]) analyses.
- A visual inspection of the Kaplan-Meier curves for overall survival shows an early benefit (including a superior 1-year survival) for the Bv 15 + doc arm, for the time period where there is minimal censoring, which is maintained for ~20 months, after which there is substantial censoring and the curves converge.
- The duration of overall survival (with an estimated median of more than 30 months) appears more favourable than that typically reported in the literature for first-line chemotherapy trials (22 - 24 months). Whether the extensive use of bevacizumab, first-line and post-progression, is contributing to the long duration of overall survival cannot be retrieved from the data due to the protocol design.
- The outcome of the overall survival analysis is confounded by patients receiving bevacizumab in the second-line setting, by placebo patients crossing over to bevacizumab before disease progression, and by the use of subsequent lines of therapy at the investigators discretion. Notably, in the first-line mBC setting, the time spent by patients post-first progression is double (2/3) that spent during first-line therapy (1/3), as also observed in study BO17708.
- The sample size (~240 patients per treatment arm) allows to reliably assess meaningful differences in PFS, but not similar differences in overall survival.
- In summary, the data show that treatment with bevacizumab plus docetaxel does not compromise patients' survival.

The considerations outlined above validate the choice of PFS as the primary endpoint in this study.

2. INTRODUCTION

This report has been prepared in response to the following question raised in the updated Assessment Report dated May 29, 2009:

'The MAH should submit updated survival analysis results since the latest cut-off (September - April 2009) in tabular format and the relevant Kaplan-Meier curves (without censoring for crossover) for the review of the CHMP'.

This report therefore presents the preliminary results of the protocol specified final analysis of the overall survival data from study BO17708.

As specified in the protocol, the final analysis of overall survival was planned to be performed when all patients had completed 24 months of follow-up, which resulted in a data cut-off of April 30, 2009. This analysis includes an additional 18 months of data compared to the initial analysis.

For completeness, an updated summary of the unstratified and stratified analysis of progression free survival and the response rate is included in the appendix (Appendix 2, Appendix 3, Appendix 4).

Full details of the study can be found in the Clinical Study Report for study BO17708 (Roche Research Report No. 1025622, May 2008 [11]).

3. STUDY TREATMENT

Patients were randomized in a ratio of 1:1:1 through a central randomization process using stratification factors to one of three treatment arms:

- Placebo plus docetaxel 100 mg/m^2 q3w (Pl + Doc; N = 241)
- Bevacizumab 7.5 mg/kg plus docetaxel 100 mg/m^2 q3w (Bv 7.5 + Doc; N = 248)
- Bevacizumab 15 mg/kg plus docetaxel 100 mg/m^2 q3w (Bv 15 + Doc; N = 247)

Patients could receive docetaxel for a maximum of 9 cycles, and bevacizumab or bevacizumab placebo was to be given until confirmed disease progression, unacceptable toxicity (requiring discontinuation of study treatment) or withdrawal at patient request.

Following documented disease progression, patients could enter into a post-study phase during which they received open-label bevacizumab (initially at the dose they were randomized to in the main study and then with 15 mg/kg q3w following initiation of protocol amendment D) as second-line treatment in combination with other chemotherapies (capecitabine, taxol, gemcitabine, vinorelbine, hormonal therapy) or as a monotherapy. After the study was unblinded, patients treated with placebo could receive open-label bevacizumab (15 mg/kg q3w) prior to disease progression.

4. STATISTICAL ANALYSIS

The analysis of overall survival was performed on the intent-to-treat (ITT) population which comprised all 736 patients randomized to treatment (241 in the Pl + Doc arm, 248 in the Bv 7.5 + Doc arm and 247 in the Bv 15 + Doc arm).

An unstratified analysis and a stratified analysis (stratified by region, prior adjuvant/neo-adjuvant taxane/time to relapse since last dose of adjuvant/ neo-adjuvant chemotherapy, measurable disease, hormone receptor status) of overall survival was performed.

Kaplan-Meier curves and estimates are provided and the log-rank test (stratified and unstratified) was used in an exploratory manner to assess differences between the bevacizumab arms and the placebo arm.

The p-values included in the tables in this report are considered exploratory in nature only, and no further statistical conclusions are drawn in addition to those from the original analysis.

5. RESULTS OF THE OVERALL SURVIVAL ANALYSIS

At the time of the data cut-off for the analysis of overall survival, 342 (46.5%) patients had died; 108 (44.8%) in the Pl + Doc arm, 118 (47.6%) in the Bv 7.5 + Doc arm and 116 (47.0%) in the Bv 15 + Doc arm (Table 1). Overall, the death rate in all three study arms are similar.

The hazard ratio for the unstratified analysis was 1.03 (95% CI: 0.79; 1.33) in the Bv 15 + Doc arm compared to Pl + Doc arm (Table 1), and for the stratified analysis of overall survival was 1.00 (95% CI: 0.76; 1.32) (Table 2).

The overall survival analysis is confounded by 102 patients in the placebo arm who received bevacizumab post progression compared to 63 patients in the Bv 15 + doc arm, corresponding to 42% and 26% of patients in the ITT population, respectively.

Due to the presence of substantial censoring after month 24, the medians can still not be reliably estimated. In all three treatment arms, the median duration of overall survival is currently greater than 30 months.

The Kaplan Meier curve of overall survival for the Bv 15 + Doc arm and the Pl + Doc arm is shown in Figure 1, and for the Bv 7.5 + Doc and the Pl + Doc arm in Appendix 1. The drop to the x-axis currently seen in the Bv 15 + doc arm is due to a single patient with the longest observation time having died.

In summary, the data show that treatment with bevacizumab plus docetaxel does not compromise patients' survival,

Table 1 Summary of Duration of Overall Survival (Study BO17708: ITT Population – Unstratified Analysis)

	Pl+doc (N=241)	Bv7.5+doc (N=248)	Bv15+doc (N=247)
Patients with event	108 (44.8 %)	118 (47.6 %)	116 (47.0 %)
Patients without events*	133 (55.2 %)	130 (52.4 %)	131 (53.0 %)
Time to event (months)			
Median#	31.9	30.8	30.2
95% CI for Median#	[26.9;.]	[25.4;35.8]	[25.9;36.4]
25% and 75%-ile	12.6;.	15.0;.	17.2;36.4
Range##	0.0 to 36.9	0.0 to 36.8	0.5 to 36.4
p-Value (Log-Rank Test)		0.7198	0.8528
Hazard Ratio		1.05	1.03
95% CI		[0.81;1.36]	[0.79;1.33]

Time to CSDIED [months] (TTMDIED) - Censoring: Overall Survival (CSDIED)

* censored
# Kaplan-Meier estimate
including censored observations

Program : $PROD/cdp10044/bo17708/ettd0_10.sas / Output : $PROD/cd10044y/r17708e/reports/ettd0_10_I001.lst
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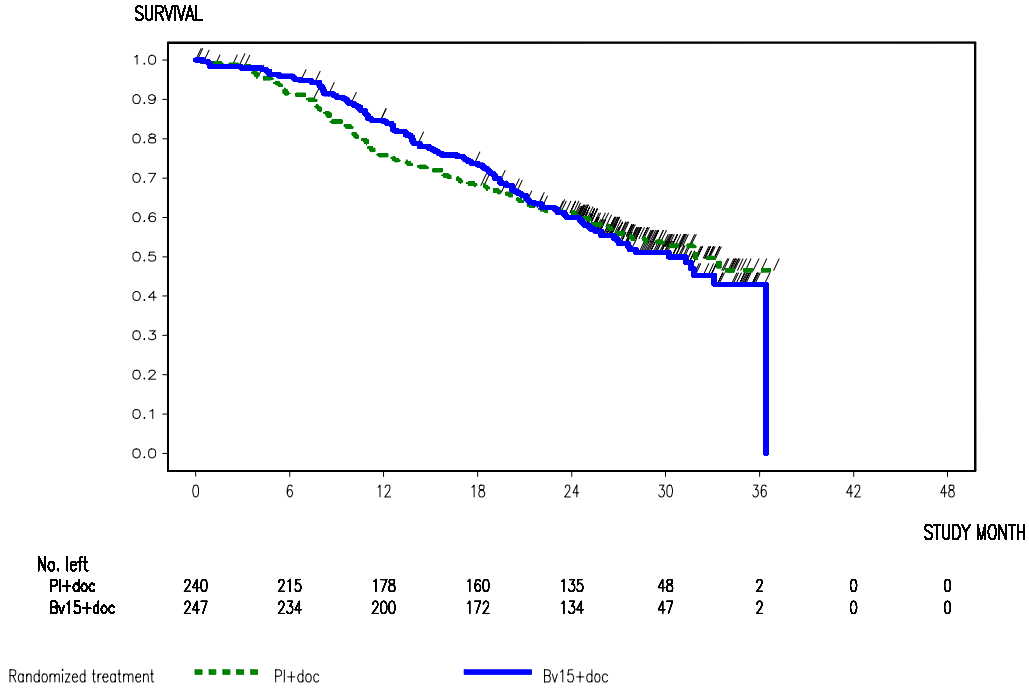
Figure 1 Kaplan Meier Curve of Duration of Overall Survival in the Bv 15 + Doc and Pl + Doc Arms (Study BO17708: ITT Population)

erated1_20_l001_PH Kaplan Meier Curve of Overall Surviva

Protocol(s): r17708e (bo17708)
Analysis: INTENT TO TREAT POPULATION
Filter Applied: WHERE S_ALLRND = 'YES'



Number of patients at risk includes patients who are at risk at end of time point.

Program : $PROD/cdp10044/bo17708/erated1_20.sas / Output : $PROD/cd10044y/r17708e/reports/erated1_20_l001_PH.cgm
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Table 2 Summary of Duration of Overall Survival (Study BO17708: ITT Population - Stratified Analysis)

	Pl+doc (N=241)	Bv7.5+doc (N=248)	Bv15+doc (N=247)
Patients with event	108 (44.8 %)	118 (47.6 %)	116 (47.0 %)
Patients without events*	133 (55.2 %)	130 (52.4 %)	131 (53.0 %)
Time to event (months)			
Median#	31.9	30.8	30.2
95% CI for Median#	[26.9;.]	[25.4;35.8]	[25.9;36.4]
25% and 75%-ile	12.6;.	15.0;.	17.2;36.4
Range##	0.0 to 36.9	0.0 to 36.8	0.5 to 36.4
p-Value (Log-Rank Test)		0.4833	0.9830
Hazard Ratio		1.10	1.00
95% CI		[0.84;1.45]	[0.76;1.32]

Time to CSDIED [months] (TTMDIED) - Censoring: Overall Survival (CSDIED)

* censored
\# Kaplan-Meier estimate
\## including censored observations

Program : $PROD/cdp10044/bo17708/ettds0_10.sas / Output :
$PROD/cd10044y/r17708e/reports/ettds0_10_I001.lst
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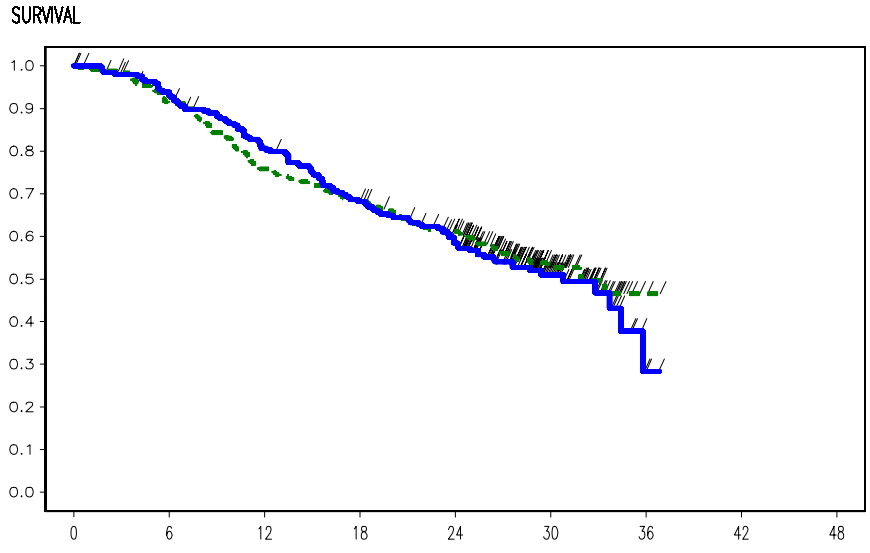
6. REFERENCES

1. A randomised, double-blind, placebo controlled, multicentre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel in comparison with docetaxel plus placebo as first line treatment for patients with HER2 negative metastatic and locally recurrent breast cancer. Roche Research Report No. 1025622. May 2008.

Appendix 1 Kaplan Meier Curve of Duration of Overall Survival in the Bv 7.5 + Doc and Pl + Doc Arms (Study BO17708: ITT Population)

erated1_20_l001_PL Kaplan Meier Curve of Overall Surviv

Protocol(s): r17708e (bo17708)
Analysis: INTENT TO TREAT POPULATION
Filter Applied: WHERE S_ALLRND = 'YES'



No. left									
Pl+doc	240	215	178	160	135	48	2	0	0
Bv7.5+doc	247	227	195	163	136	40	1	0	0

Randomized treatment Pl+doc Bv7.5+doc

Number of patients at risk includes patients who are at risk at end of time point.

Program : $PROD/cdp10044/bo17708/erated1_20.sas / Output : $PROD/cd10044y/r17708e/reports/erated1_20_l001_PL.cgm
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Appendix 2 Summary of Progression Free Survival (Study BO17708: ITT Population - Unstratified Analysis)

ettpfs0_10_I001 Summary of Progression Free Survival

Protocol(s): r17708e (bo17708)
Analysis: INTENT TO TREAT POPULATION
Filter Applied: WHERE S_ALLRND = 'YES'

	Pl+doc (N=241)	Bv7.5+doc (N=248)	Bv15+doc (N=247)
Patients with event	219 (90.9 %)	226 (91.1 %)	220 (89.1 %)
Patients without events*	22 (9.1 %)	22 (8.9 %)	27 (10.9 %)
Time to event (months)			
Median#	8.2	9.0	10.1
95% CI for Median#	[7.4;8.5]	[8.3;10.5]	[8.6;10.7]
25% and 75%-ile	5.9;12.0	6.2;13.8	7.1;14.2
Range##	0.0 to 33.5	0.0 to 32.7	0.0 to 34.1
p-Value (Log-Rank Test)		0.1163	0.0061
Hazard Ratio		0.86	0.77
95% CI		[0.72;1.04]	[0.64;0.93]

Time to CSPFS [months] (TTMPFS) - Censoring: First Inv PD or Death (CSPFS)

* censored
# Kaplan-Meier estimate
including censored observations
P-Values for PFS Analysis are Exploratory and not Adjusted for Multiplicity

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$PROD/cd10044y/r17708e/reports/ettpfs0_10_I001.lst
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Appendix 3 Summary of Progression Free Survival (Study BO17708: ITT Population - Stratified Analysis)

etttapfss0_10_I001 Summary of Progression Free Survival Before Start of Subsequent Antineoplastic Therapy (Stratified)

Protocol(s): r17708e (bo17708)
Analysis: INTENT TO TREAT POPULATION
Filter Applied: WHERE S_ALLRND = 'YES'

	Pl+doc (N=241)	Bv7.5+doc (N=248)	Bv15+doc (N=247)
Patients with event	201 (83.4 %)	196 (79.0 %)	199 (80.6 %)
Patients without events*	40 (16.6 %)	52 (21.0 %)	48 (19.4 %)
Time to event (months)			
Median#	8.1	9.0	10.0
95% CI for Median#	[7.3;8.4]	[8.3;10.6]	[8.5;10.7]
25% and 75%-ile	5.6;11.3	6.2;13.8	7.2;14.1
Range##	0.0 to 33.3	0.0 to 30.4	0.0 to 34.1
p-Value (Log-Rank Test)		0.0450	0.0002
Hazard Ratio		0.80	0.67
95% CI		[0.65;1.00]	[0.54;0.83]

Time to CSTAPFS [months] (TTMTAPFS) - Censoring: First Inv PFS before non-study Trt (CSTAPFS)

* censored
# Kaplan-Meier estimate
including censored observations
P-Values for PFS Analysis are Exploratory and not Adjusted for Multiplicity

Appendix 4 Summary of Best Overall Response (Study BO17708: Patients with Measurable disease at Baseline)

ebor0_md_a_10_I001 Summary of Best Overall Response (Patients with Measurable disease at Baseline only) by Trial Treatment
During Main Study Phase

Protocol(s): r17708e (bo17708)
Analysis: INTENT TO TREAT POPULATION
Filter Applied: WHERE S_ALLRND = 'YES'

	Pl+doc (N=241)	Bv7.5+doc (N=248)	Bv15+doc (N=247)
Patients included in analysis	207 (100.0 %)	201 (100.0 %)	206 (100.0 %)
Responders$	96 (46.4 %)	111 (55.2 %)	132 (64.1 %)
Non-Responders	111 (53.6 %)	90 (44.8 %)	74 (35.9 %)
95% CI for Response Rates*	[39.4; 53.4]	[48.1; 62.2]	[57.1; 70.6]
Difference in Response Rates		8.85	17.70
95% CI for Difference in Response Rates#		[-1.1; 18.8]	[8.0; 27.4]
p-Value (Chi-squared Test)		0.0739	0.0003
Complete Response (CR)	2 (1.0 %)	9 (4.5 %)	6 (2.9 %)
95% CI for CR Rates*	[0.1; 3.4]	[2.1; 8.3]	[1.1; 6.2]
Partial Response (PR)	94 (45.4 %)	102 (50.7 %)	126 (61.2 %)
95% CI for PR Rates*	[38.5; 52.5]	[43.6; 57.9]	[54.1; 67.9]
Stable Disease (SD)	77 (37.2 %)	69 (34.3 %)	50 (24.3 %)
95% CI for SD Rates*	[30.6; 44.2]	[27.8; 41.3]	[18.6; 30.7]
Progressive Disease (PD)	23 (11.1 %)	7 (3.5 %)	7 (3.4 %)
95% CI for PD Rates*	[7.2; 16.2]	[1.4; 7.0]	[1.4; 6.9]
Missing (No Response Assessment)	11 (5.3 %)	14 (7.0 %)	17 (8.3 %)

Best Overall Response (BORESP)
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method

$ Patients with best overall response of confirmed CR or PR
Missing category includes patients with no post baseline tumor assessment, patients who received Antineoplastic therapy not defined in the protocol before first tumor assessment, and patients whose first tumor assessment occurred more than 56 days after date of last dose of last component of study medication

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Summary of Report 1021786 (Sep 2008),
Report of the Updated Exploratory Analysis of Efficacy and Safety Data for Study BO17708

Data cut-off: 15 Sep 2008

Report of the Updated Exploratory Analysis of Efficacy and Safety Data for Study BO17708

A randomised, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel in comparison with docetaxel plus placebo as first line treatment for patients with HER2-negative metastatic and locally recurrent breast cancer.

Original Clinical Data Cut-off: October 31, 2007
Updated Clinical Data Cut-off: September 15, 2008

The unstratified updated exploratory analysis showed a reduction in the risk of progression or death by 25% in the Bv 15 + Doc arm and by 15% in the Bv 7.5 + Doc arm compared to the control arm. The median time to progression or death was longer in the Bv 15 + Doc (10.1 months) and Bv 7.5 + Doc (9.0 months) arms compared to the Pl + Doc arm (8.2 months).

The stratified analysis of PFS censored for NPT prior to disease progression showed a more pronounced reduction in the risk of progression or death by 33% in the Bv 15 + Doc arm and by 23% in the Bv 7.5 + Doc arm compared to the Pl + Doc arm. Median time to progression or death was longer in the Bv 15 + Doc arm (10.0) months) and Bv 7.5 + Doc arm (9.0 months) compared to the Pl + Doc arm (8.0 months).

A visual inspection of the Kaplan-Meier curves for PFS show an early benefit for the two bevacizumab containing arms at around 3 months which was maintained over time. For the Bv 15 + Doc arm, the separation of the curve compared to that for the Pl + Doc arm was approximately two months at the median and at most other time points.

These findings were supported by a superior result for the bevacizumab-containing arms (compared to the placebo arm) for the secondary endpoints of overall response rate, duration of response and time to treatment failure. No difference was seen in overall survival, however, at this point in time only a limited number of death events had occurred.

Within the limits of an expected safety profile of docetaxel at a dose of 100 mg/m2, the combination of docetaxel with both doses of bevacizumab was well tolerated from a bevacizumab point of view, and did not reveal any safety issues other than those known for the two drugs separately. The addition of bevacizumab had a limited impact on the known safety profile of docetaxel.

The Bv 15 + Doc arm showed a numerical advantage compared to the Bv 7.5 + Doc arm in the estimates for all of the primary and secondary efficacy measures, and this advantage was seen without a major impact on the safety profile.

These data further confirm the efficacy and safety of bevacizumab in combination with docetaxel in patients with metastatic breast cancer.

Synopsis of report 1025622 (May 2008)

Study BO17708

Data cut-off:	31 October 2007
Period covered by this report:	March 15, 2006 – October 31, 2007 (first patient screened to data cut-off)

TITLE PAGE

RESEARCH REPORT No. 1025622

Clinical Study Report – A randomised, double-blind, placebo controlled, multicentre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel in comparison with docetaxel plus placebo as first line treatment for patients with HER2 negative metastatic and locally recurrent breast cancer.

Date of Report:	May 2008
Study Sponsor(s)	F. Hoffmann-La Roche Ltd
Study Dates:	March 15, 2006 – October 31, 2007 (first patient screened to data cut-off)
Trial Phase:	III
Indication:	Breast cancer

Name of Principal Investigator:	**Affiliation:**
Dr D.W. Miles	Mount Vernon Hospital, Middlesex, United Kingdom

Personnel Responsible for Clinical and Statistical Analyses:

Dr Peter Cheverton – Clinical Science Leader	Roche Products Ltd, Welwyn Garden City, Herts, United Kingdom
Dr Cornelia Irl – Project Statistician	F. Hoffman La-Roche Ltd., Basel, Switzerland

GCP Compliance: This study was conducted in accordance with GCP guidelines.

SYNOPSIS OF RESEARCH REPORT 1025622 (PROTOCOL BO17708)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomised, double-blind, placebo controlled, multicentre study to evaluate the efficacy and safety of bevacizumab in combination with docetaxel in comparison with docetaxel plus placebo as first line treatment for patients with HER2 negative metastatic and locally recurrent breast cancer. Report No. 1025622. May 2008		
INVESTIGATORS / CENTERS AND COUNTRIES	106 centers in 24 countries (Western Europe/Australia/Canada; Eastern Europe; East Asia; Central and South America Principal investigator: Dr. David Miles, Mount Vernon Hospital, Middlesex, UK, CRTN 74796		
PUBLICATION (REFERENCE)	Miles DW, Chan A, Romieu G, et al. Randomised, double-blind, placebo controlled, phase III study of bevacizumab (BV) with docetaxel (D) or D with placebo (PL) as 1st line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. ASCO 2008 submitted.		
PERIOD OF TRIAL	March 15, 2006 to October 31, 2007 (first patient screened to data cut-off)	CLINICAL PHASE	III
OBJECTIVES	Primary objective: • To compare Progression Free Survival (PFS) in patients randomized to bevacizumab 7.5 mg/kg plus docetaxel 100 mg/m^2 q3w (Bv 7.5 + Doc) versus docetaxel 100 mg/m^2 plus bevacizumab placebo q3w (Pl + Doc), **OR** bevacizumab 15 mg/kg plus docetaxel 100 mg/m^2 q3w (Bv 15 + Doc) versus docetaxel 100 mg/m^2 plus bevacizumab placebo q3w (Pl + Doc). Secondary objectives: • To compare best overall response (OR), duration of response (DR), time to treatment failure (TTF) in patients randomized to bevacizumab 7.5 mg/kg plus docetaxel 100 mg/m^2 q3w versus docetaxel 100 mg/m^2 plus bevacizumab placebo q3w, **OR** bevacizumab 15 mg/kg plus docetaxel 100 mg/m^2 q3w versus docetaxel 100 mg/m^2 plus bevacizumab placebo q3w. • To compare overall survival (OS) in patients randomized to bevacizumab plus docetaxel versus patients randomized to docetaxel plus placebo. • To determine the safety and tolerability of combining bevacizumab 7.5 mg/kg q3w or bevacizumab 15 mg/kg q3w with docetaxel 100 mg/m^2. • To assess change in quality of life in the bevacizumab-containing and control arms.		
STUDY DESIGN	Multicenter three-arm, randomized, double-blind, placebo controlled Phase III study. Patients were randomly assigned to treatment groups on a 1:1:1 basis through a central randomization process using the following stratification factors: - Prior adjuvant/neo-adjuvant taxane/ time to relapse since last		

SYNOPSIS OF RESEARCH REPORT 1025622 (PROTOCOL BO17708)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	

	dose of adjuvant/neo-adjuvant chemotherapy. Patients were initially stratified for treatment with prior taxanes (Yes vs No). If 'no prior taxanes' a second stratification was performed ie, never received adjuvant/neoadjuvant chemotherapy or relapse ≥ 12 months since last dose of chemotherapy vs < 12 months since last dose of chemotherapy - Region - Measurable disease (Yes vs No) - Hormone receptor (HR) status (ER negative and PR vs ER and/or PR positive).
NUMBER OF SUBJECTS	Treatment / ITT / PP / Safety Pl + Doc: 241 / 215 / 238 Bv 7.5 + Doc: 248 / 225 / 247 Bv 15 + Doc: 247 / 218 / 245 Total: 736 / 658 / 730
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Metastatic or locally recurring breast cancer. – Pre- and post menopausal female patients. – Age ≥ 18 years. – Histologically or cytologically confirmed HER2-negative adenocarcinoma of the breast. – Measurable or non-measurable disease. – Candidates for chemotherapy. – ECOG PS of 0 or 1. – Documented ER/PR status. – No previous chemotherapy or radiotherapy for metastatic or locally recurrent breast cancer. – Adequate liver, renal, cardiovascular, CNS and bone marrow function.
TRIAL DRUG / STROKE (BATCH) No.	Bevacizumab / B1947, B1887, B1948, B3068, B3071, B3124, B3138, B9001, B9002, B3219, B3227, B9000, B3335
DOSE / ROUTE / REGIMEN / DURATION	7.5 mg/kg or 15 mg/kg / i.v / q3w / until disease progression, unacceptable toxicity or patient withdrawal
REFERENCE DRUG / STROKE (BATCH) No.	Docetaxel / D5G548/D5G141, D5G271/D5G140, D6A071/D5H525, D6C248/D6A437, D6A820/D6A438, D6D613/D6D764, D6D612/D6D528 Placebo (for bevacizumab)
DOSE / ROUTE / REGIMEN / DURATION	Docetaxel 100 mg/m^2 / i.v. / q3w / max. 9 cycles Placebo i.v. / q3w / until disease progression, unacceptable toxicity or patient withdrawal
CRITERIA FOR EVALUATION	
EFFICACY:	Tumor assessments using RECIST criteria using CT/MRI/bone scans and/or X-rays at baseline and every 9 weeks until week 36 and then every 12 weeks until disease progression.

SYNOPSIS OF RESEARCH REPORT 1025622 (PROTOCOL BO17708)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	

	Date of death for OS. QOL: FACT-B and FACT-G version 4.
PHARMACODYNAMICS:	N/A
PHARMACOKINETICS:	N/A
SAFETY:	Adverse events, laboratory tests, physical exam, vital signs, ECG, LVEF, brain CT scan/MRI
STATISTICAL METHODS	For the primary endpoint PFS, the log-rank test (unstratified) was used to compare each of the two bevacizumab arms with the placebo arm. To adjust for multiplicity, a closed test procedure was applied at an overall alpha level of 5%. Also a stratified version of the log-rank test was performed with the stratification factors used for randomization. Kaplan-Meier curves and estimates of event rates over time were provided. Hazard ratios and corresponding 95% confidence intervals were calculated to assess the magnitude of the treatment benefit. Proportion of responders and non-responders in each of the three treatment groups was summarized for the best overall response, together with the two-sided 95% Person-Clopper confidence intervals for response rates. Also 95% corresponding confidence intervals for treatment difference between the low dose of bevacizumab and placebo as well as the high dose of bevacizumab and placebo are provided. For the time to treatment failure, duration of response and overall survival, Kaplan Meier curves and estimates were provided together with the log-rank test results (stratified and unstratified). All tests for the secondary endpoints were performed at a two-sided 5% alpha level. No adjustment for the multiplicity of testing was applied for secondary endpoints.

METHODOLOGY:

After undergoing screening assessments and providing their informed consent, patients were randomized to one of three treatment arms: docetaxel 100 mg/m^2 q3w plus bevacizumab 7.5 mg/kg q3w, docetaxel 100 mg/m^2 q3w plus bevacizumab 15 mg/kg q3w or docetaxel 100 mg/m^2 q3w plus placebo q3w. Docetaxel was administered for a maximum of 9 cycles (27 weeks) and bevacizumab/placebo administered until confirmed disease progression, unacceptable toxicity (requiring discontinuation of study treatment) or withdrawal at patient request. In case of permanent discontinuation of one of the two treatment components (docetaxel or bevacizumab/placebo) for safety reasons, the other treatment component could be continued. Upon evidence of disease progression, all study treatments were to be discontinued permanently. After documented disease progression, investigators had the option to enter patients into a post-study treatment phase, during which they could receive bevacizumab in the second-line setting.

A maximum of five target lesions per organ and 10 lesions in total were to be identified, recorded, and measured at screening. All other lesions were to be recorded as non-measurable disease. Tumor measurements/assessments were made using modified RECIST criteria based on CT scans, MRI scans, X-ray, bone scan, and/or clinical examination until (confirmed) evidence of disease progression. Post screening assessments were to be done every nine weeks up to week 36 and every 12 weeks thereafter until

SYNOPSIS OF RESEARCH REPORT 1025622 (PROTOCOL BO17708)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	

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, hematology, 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. ECG was to be performed at baseline and thereafter as clinically indicated and LVEF measurement was performed at baseline and in the event of symptomatic cardiac failure. Blood biomarker assessment was performed at baseline and at disease progression.
In all patients, the following assessments were to be made 28 days after end of treatment: physical measurements including body weight, body temperature, pulse, hematology, blood chemistry, urinalysis, and blood pressure, concomitant treatments, and adverse events.
Survival follow-up for all patients (either on completion of treatment or at discontinuation after 28 days safety follow-up) is to continue until study closure ie, at least 24 months after the last patient had been enrolled. Visits were scheduled every three months.
The following assessments were requested:

- Patients not treated as part of the post-study treatment phase were followed for survival and safety.
- Patients without documented disease progression were to be followed for progression.
- Patients with documented disease progression were to be followed for survival only.
- Subsequent anti-cancer therapy
- Follow-up and reporting of specific adverse events of interest to bevacizumab for 6 months after last bevacizumab treatment
- Study drug related serious adverse events until the event had resolved

EFFICACY RESULTS:

This report presents the results of the final protocol-defined analysis of PFS and best overall response. The study was continuing for survival follow-up after closure of the database on January 18, 2008. The addition of bevacizumab to docetaxel as first-line therapy for patients with metastatic breast cancer resulted in the following:

- A clinically meaningful and statistically significant reduction in the risk of progression or death (PFS) in both the Bv 7.5 + Doc (hazard ratio 0.79, 95% CI [0.63, 0.98], log-rank p-value = 0.0318) and Bv 15 + Doc (hazard ratio 0.72, 95% CI [0.57, 0.90], log-rank p-value = 0.0099) treatment arms versus placebo based on the primary unstratified analysis.
- Based on the stratified analysis, a slightly more pronounced reduction in the risk of progression or death was seen in both the Bv 7.5 + Doc (hazard ratio 0.75, 95% CI [0.59, 0.95], log-rank p-value = 0.0156) and Bv 15 + Doc (hazard ratio 0.67, 95% CI [0.53, 0.85], log-rank p-value = 0.0009) treatment arms versus placebo
- In the population of patients with measurable disease at baseline, a statistically significant increase in the percentage of responders (CR + PR) in the Bv 7.5 + Doc (55.2%) and Bv 15 + Doc (63.1%) arms compared with the Pl + Doc arm (44.4%); difference in response rates, Bv 7.5 + Doc vs Pl + Doc: 10.8%, 95% CI [0.9, 20.7], p = 0.0295; Bv 15 + Doc vs Pl + Doc: 18.7%, 95% CI [9.0, 28.4], p = 0.0001.
- At the time of data cut-off, a higher percentage of patients in the Pl + Doc arm (57.6%) compared with the Bv 7.5 + Doc (52.3%) and Bv 15 + Doc (52.3%) arms among the patients analyzed had had an event that contributed to the analysis of duration of response. The median time to event from the

SYNOPSIS OF RESEARCH REPORT 1025622 (PROTOCOL BO17708)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	

Kaplan-Meier analysis was 6.4 months in the Pl + Doc arm, 7.2 months in the Bv 7.5 + Doc arm and 7.0 months in the Bv 15 + Doc arm.

- Median time to treatment failure was longer in the Bv 7.5 + Doc (7.0 months) and Bv 15 + Doc (7.7 months) compared with the Pl + Doc arm (6.1 months). The hazard ratio indicated a 21% reduction in the risk of treatment failure in the Bv 15 + Doc arm compared with the Pl + Doc arm (HR = 0.79, 95% CI 0.65; 0.97, log-rank p-value = 0.0241) and a 15% lower risk of treatment failure in the Bv 7.5 + Doc arm (HR 0.85, 95% CI 0.69; 1.04, log-rank p-value = 0.1105).
- At the time of data cut-off only a limited amount of OS events had occurred (18.5% of patients had died). For both the Bv 7.5 + Doc arm [hazard ratio 0.92, 95% CI 0.62; 1.37] and the Bv 15 + Doc arm [hazard ratio 0.68, 95% CI [0.45, 1.04], the hazard ratios pointed in favor of Bv with a trend for the Bv 15 + Doc arm versus placebo. A final analysis for OS will be performed with a data cut-off 24 months after the last patient was enrolled.
- An increase in PFS in most of the subgroups analyzed, which was generally consistent with the overall treatment effect. Of note are the subgroups with more intensive pretreatment such as adjuvant chemotherapy and adjuvant taxane pretreatment.
- Quality of Life as measured by the FACT-B questionnaire showed small decreases in mean FACT-B scores at each assessment in the Pl + Doc arm while both Bv + Doc arms showed slight improvements in the mean changes from screening.

SAFETY RESULTS:

Bevacizumab did not have a major impact on the safety profile of 100 mg/m^2 docetaxel. Overall, the safety data for bevacizumab were in line with observations in previous studies of bevacizumab in cancer patients. The most common adverse events in the Pl + Doc, Bv 7.5 + Doc and Bv 15 + Doc arms were alopecia (71.7% vs 71.6% vs 69.2%, respectively), diarrhea (46.4% vs 54.8% vs 50.6%, respectively), nausea (48.5% vs 39.2% vs 46.6%, respectively), nail disorder (39.9% vs 46.8% vs 43.7%, respectively), fatigue (41.6% vs 41.2% vs 38.9%, respectively), and stomatitis (27.0% vs 48.8% vs 44.1%, respectively). All 6 are established docetaxel-associated toxicities.

Compared with the Pl + Doc arm, the overall incidence of patients with grade 3-5 adverse events or serious adverse events was increased in the Bv + Doc arms. This was due in part to the adverse events known to occur with bevacizumab therapy, including patients with bleeding events (28.3% vs. 52.4% vs. 54.7%), hypertension (9.0% vs. 13.6% vs. 17.8%) and febrile neutropenia (12.0% vs. 15.6% vs. 18.2%). AEs leading to withdrawal from any part of the treatment regimen were not markedly different between the treatment arms.

There were six patients in the Pl + Doc arm, four patients in the Bv 7.5 + Doc arm and four patients in the Bv 15 + Doc arm who experienced an adverse event leading to death (other than disease progression) during the time from first drug administration until 21 days after last study drug administration. No particular pattern was seen in the reasons for death.

Laboratory tests did not show new clinically relevant safety signals. The incidence of patients with shifts from baseline was generally comparable between the study arms. No notable mean changes from baseline in vital signs, ECG parameters, and ECOG performance status were observed during the study.

SYNOPSIS OF RESEARCH REPORT 1025622 (PROTOCOL BO17708)

COMPANY: F. Hoffmann-La Roche Ltd NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	

Safety Parameter – Safety Population	Pl + Doc	Bv 7.5 + Doc	Bv 15 + Doc
Number (%) of patients with:			
at least one adverse event	232 (99.6%)	250 (100.0%)	246 (99.6%)
at least one NCI-CTC grade 3-5 adverse event	156 (67.0%)	187 (74.8%)	183 (74.1%)
at least one serious adverse event	76 (32.6%)	92 (36.8%)	104 (42.1%)
at least one AE leading to discontinuation of Bv	26 (11.2%)	20 (8.0%)	29 (11.7%)
at least one adverse event of special interest	140 (60.1%)	188 (75.2%)	193 (78.1%)
at least one NCI-CTCAE grade 3-5 AE of special interest	73 (31.3%)	88 (35.2%)	90 (36.4%)
Deaths	49 (21%)	50 (20%)	35 (14%)
Deaths not due to disease progression	6 (3%)	9 (4%)	5 (2%)
Deaths up to 21 days after last dose not due to disease progression	6 (2%)	4 (1%)	4 (2%)
Number (%) of patients with:			
Bleeding events (all events)	66 (28.3%)	131 (52.4%)	135 (54.7%)
Mucocutaneous bleeding	51 (21.9%)	118 (47.2%)	123 (49.8%)
Pulmonary hemorrhage	2 (0.9%)	3 (1.2%)	5 (2.0%)
Neutropenia	45 (19.3%)	54 (21.6%)	53 (21.5%)
Febrile neutropenia	28 (12.0%)	39 (15.6%)	45 (18.2%)
Hypertension	21 (9.0%)	34 (13.6%)	44 (17.8%)
Venous thromboembolic events	18 (7.7%)	15 (6.0%)	18 (7.3%)
Wound healing complications	3 (1.3%)	8 (3.2%)	12 (4.9%)
Proteinuria	4 (1.7%)	3 (1.2%)	8 (3.2%)
Abscesses and fistulae	1 (0.4%)	6 (2.4%)	6 (2.4%)
Congestive heart failure	1 (0.4%)	3 (1.2%)	2 (0.8%)
Gastrointestinal perforation	2 (0.9%)	1 (0.4%)	1 (0.4%)
Arterial thromboembolic events	2 (0.9%)	0	1 (0.4%)
RPLS	0	0	0

CONCLUSIONS:

Study BO17708 met its primary endpoint with both bevacizumab containing arms showing a clinically meaningful and statistically significant reduction in the risk of progression or death compared to the control arm. This finding was supported by a superior result for the bevacizumab-containing arms (compared with the placebo arm) for all secondary efficacy endpoints (overall response rate, time to progression, duration of response, time to treatment failure, and, despite immature follow-up, overall survival). The quality of life assessment revealed a small improvement in mean QoL scores with the addition of bevacizumab at either dose to docetaxel compared to a slight decline in the control arm.

Within the limits of an expected safety profile of docetaxel at a dose of 100 mg/m^2, the combination of docetaxel with bevacizumab was well tolerated from a bevacizumab point of view and did not reveal any safety issues other than those known for the two drugs separately nor any excess in dose modifications or delays.

There was a numerical advantage for the Bv 15 + Doc arm compared to the Bv 7.5 + Doc arm in estimates for all of the primary and secondary efficacy measures and this advantage was seen without a major impact on the safety profile of the Bv-containing arms.

Protocol Amendments

Study BO17708

Protocol Amendments

The protocol was amended four times after 15 March, 2006 when the first patients were screened. A summary of the major changes is given below. Full details can be found in the respective protocol amendment history documents

First Version A: 25 October 2005

Amendment B: 10 May 2006

The following changes were made to the protocol at the request of the Paul Ehrlich Institute, Germany:

– Investigators were provided with a retrospective analysis of the bleeding risk of full dose (therapeutic) anti-coagulated patients receiving bevacizumab.

– Investigators were provided with a clear definition of full dose (therapeutic) anticoagulation.

– It was ensured that full dose anti-coagulated patients were within the therapeutic ranges (based on INR and aPTT measurements) and data was collected on the stability of full dose anti-coagulation therapy at baseline or once initiated during study treatment.

– Guidance was provided to the investigators on treatment of patients receiving full dose anti-coagulation who suffered from a bleeding event whilst on study medication.

– The 20 patients receiving full dose anti-coagulation to be followed by DSMB were better defined.

– Specifically for Germany, it was required that patients must have received prior treatment with anthracyclines or alkylating agents in the neo/adjuvant setting.

· Text was added that appropriate diagnostic and therapeutic medical treatment including accurate antihypertensive treatment was mandatory for patients developing signs and symptoms of Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

· The study title was changed to reflect the study patient population since not only metastatic breast cancer patients were allowed but also locally recurrent breast cancer patients.

· The schedule of assessments was changed to accommodate the changes requested by the Paul Ehrlich Institute, and a clarification on the timing and procedures was made.

· The footnotes to Table 2 - Schedule of Assessments and Procedures were updated

· Protocol text was changed to include patients who had received prior neo-adjuvant chemotherapy and radiotherapy as this was allowed in addition to patients who had received prior adjuvant chemotherapy and radiotherapy.

· Text on study drug management was modified to allow the site to destroy the trial drugs after being used.

· Several typographical errors were corrected.

· The informed consent was updated to reflect the RPLS, the potential risk of the use of aspirin at dosages of at least 325 mg/day in bevacizumab studies, and that upon request of the Paul Ehrlich Institute, biomarker samples would be collected from all patients receiving full dose anticoagulation at study entry

Amendment C: 19 September 2006

· A washout period for hormone therapy was included in order to reflect the situation of a patient on endocrine treatment as part of an adjuvant treatment. The washout period was

reduced from three weeks to two weeks in order to appreciate the fact that such a long treatment interruption may be inappropriate for patients.

· Upon the recommendation of DSMB, text on the use of prophylactic antibiotics during Cycle 1 of docetaxel administration for febrile neutropenia prevention was added, and text was added in case of specific chemotherapy adverse event occurrences.

· Typographical errors were corrected.

· Missing sample procedures following protocol amendment B for patient management of patients on full-dose anticoagulant treatment at study entry was added, and tumor tissue handling and storage was clarified.

Amendment D: 24 November 2006

· The protocol was updated to be in line with the latest version of the docetaxel SmPC.

· In order to avoid bias at the time of the study's primary endpoint analysis due to a substantial amount of unblinding requests being made, patients considered for treatment with bevacizumab in the open-label phase of the study were allowed to enter into the post-study phase without unblinding, regardless of the first-line treatment (placebo or bevacizumab).

· Clarification was given for the assessment of the lesions situated in a previously irradiated area.

· Typographical errors were corrected.

Amendment E: 10 January 2008

· The text was changed to allow bevacizumab to be given for longer than 32 cycles (96 weeks) until confirmed disease progression, unacceptable toxicity (requiring discontinuation of study treatment) or withdrawal at patient request.

· If the analysis of this study (BO17708) showed significant improvements in efficacy, patients randomized to placebo that met specific eligibility criteria were allowed to receive bevacizumab.

· Information on how post-study safety data would be analyzed was added.

· The procedure for enrollment in the post-study phase was clarified

Amendment F: 9 March 2009

· The Protocol for this study has been updated to allow patients who continue to benefit from bevacizumab in the first or second line setting to continue to receive treatment after database closure for overall survival.

· Accordingly, end of study definition was clarified to allow these patients to continue to receive study drug from F. Hoffmann-La Roche and to allow for the collection of SAE data on such patients.

· As suggested by the Drug Safety Monitoring Board (DSMB), the dose of bevacizumab to be given to patients who are eligible for further treatment is defined as 15mg/kg.

· In addition the protocol has been updated in line with the latest Roche protocol template, and includes correction of typographical, formatting and spelling errors.

Amendment G: 16 July 2009

· The main reason for this protocol amendment was to extend the collection of survival data due to the insufficient number of events.

· This extension is reflected in all relevant sections of the protocol. To ensure compliance with the updated Roche policy on SUSAR distribution for long term follow up the SUSAR reporting section of the protocol has also been amended.

Amendment H: 18 July 2013

· The proposed amendment updates the clinical study protocol BO17708 version G to version H in order to change the End of Study definition. After thorough consideration to balance the need for long-term treatment of patients still enrolled, with the Sponsor's goal to reduce drug development costs, the Sponsor proposes to close the study as soon as this amendment is approved by this regulatory authority and the pertinent ethics committees, and therefore accurately defines the procedures for patients still receiving study treatment at the time of study closure.

· Other changes have been made to provide adverse event reporting instructions and contact information for patients continuing in the optional post-study phase. Overall, additional minor administrative changes have also been made to improve clarity and consistency.

Study sites
Study BO17708

Listing of Investigators by Site

Protocol : BO17708

Sites: All sites that have enrolled a patient

Investigator	Center	No of Patients Enrolled
	Olsztyński Ośrodek Onkologiczny Kopernik sp. z o.o., UL. KOPERNIKA 30, 10-513, OLSZTYN, POLAND	1
	Robert-Bosch-Krankenhaus; Interdisziplinäres Zentrum; Tumorzentrum, Auerbachstr. 110, 70376, Stuttgart, GERMANY	1
	Universitätsklinikum Ulm Am Michelsberg; Frauenklinik, Prittwitzstr. 43, 89075, Ulm, GERMANY	1
	Kantonsspital Graubünden;Onkologie und Hämatologie, Loestrasse 170, 7000, Chur, SWITZERLAND	3
	DIAKONESSENHUIS; KLINISCHE ONCOLOGIE, BOSBOOMSTRAAT 1, 3582 KE, UTRECHT, NETHERLANDS	9
	MEDISCH INSTITUUT ST. AUGUSTINUS; ONCOLOGY, OOSTERVELDLAAN 24, CTO departement, 2610, WILRIJK, BELGIUM	31
	BORDET INSTITUUT; ONCOLOGY, RUE HEGER BORDET, 1, 1000, BRUXELLES, BELGIUM	11
	HOSPITAL PRIVADO SAN JOSE; ONCOLOGIA, COAHUILA # 263 SUR, COLONIA CENTRO, 85000, OBREGON, MEXICO	4
	HOSPITAL REGIONAL ISSSTE MERIDA; ONCOLOGY, CALLE 7 S/N POR 36, COLONIA PENSIONES, 97500, MERIDA, MEXICO	4
	ISSSTEP PUEBLA, ; ONCOLOGY, AV. VENUSTIANO CARRANZA # 810, 72530, PUEBLA, MEXICO	5
	HOSPITAL REGIONAL ISSSTE; ONCOLOGIA, AV. ADOLFO LOPEZ MATEOS # 122, 64380, MONTERREY, MEXICO	1
	HOSPITAL ANGELES METROPOLITANO; ROOM 220, TLACOTALPAN NO 59, Col. Roma Sur Consultorio 220; Torre Diamante, 06760, MEXICO CITY, MEXICO	4
	Cetro Oncológico Hospital Punta Pacífica, Boulevard Pacífica y Vía Durán, 83-0669, PANAMA CITY, PANAMA	3
	WESTMEAD HOSPITAL; MEDICAL ONCOLOGY AND PALLATIVE CARE, CNR. HAWKESBURY & DARCY ROAD, 2145, WESTMEAD, AUSTRALIA	7

Site No = Clinical Research Task Number (center no.)

* = Current Investigator

Listing of Investigators by Site

Protocol : BO17708

Sites: All sites that have enrolled a patient

Investigator	Center	No of Patients Enrolled
	QUEEN ELIZABETH HOSPITAL; MEDICAL ONCOLOGY, 28 WOODVILLE ROAD, 5011, ADELAIDE, New South Wales, AUSTRALIA	3
	ROYAL PRINCE ALFRED HOSPITAL; MEDICAL ONCOLOGY, GLOUCESTER HOUSE, MISSENDEN ROAD, 2050, CAMPERDOWN, New South Wales, AUSTRALIA	9
	ST VINCENT'S HOSPITAL; MEDICAL ONCOLOGY, 41 VICTORIA PARADE, 3065, FITZROY, Victoria, AUSTRALIA	2
	FACULTY OF MED. SIRIRAJ HOSP.; MED.-DIV. OF MED. ONCOLOGY, 2 PRANNOK ROAD, 13 FL. CHALERMPRAKIAT BUILDING, 10700, BANGKOK, THAILAND	7
	SANDTON ONCOLOGY CENTRE, 159 Rivonia Road, MORNINGSIDE, 2196, Sandton, SOUTH AFRICA	2
	NATIONAL TAIWAN UNI HOSPITAL; DEPT OF ONCOLOGY, 7, Chung-Shan South Road, 100, Taipei, TAIWAN	4
	TRI-SERVICE GENERAL HOSPITAL; HEMATOLOGY AND ONCOLOGY, NO.325, SEC.2, CHENGGONG RD., NEIHU DISTRICT, 114, TAIPEI, TAIWAN	3
	VETERANS GENERAL HOSPITAL; SURGERY, No.386, Dajhong 1st Rd., Zuoying District, Kaohsiung City 813, Taiwan (R.O.C.), 813, Kaohsiung, TAIWAN	3
	Centre Georges Francois Leclerc; Oncologie 3, 1 Rue Professeur Marion, 21079, Dijon, FRANCE	10
	INSTITUT GUSTAVE ROUSSY; PATHOLOGIE MAMMAIRE, 114 Rue Edouard Vaillant 6Eme Etage, 94805, Villejuif, FRANCE	13
	CENTRE FRANCOIS BACLESSE; COMITE SEIN, Avenue General Harris Rez Chaussee Secteur Bleu Bp 5026, BP 5026, 14076, Caen, FRANCE	15
	Centre Oscar Lambret; Hopital De Jour, 3 Rue Frederic Combemale, BP 307, 59020, Lille, FRANCE	10
	Centre Jean Perrin; Hopital De Jour, 58 Rue Montalembert Rez De Chaussee Bp 392, 63011, Clermont Ferrand, FRANCE	5
	Institut Bergonie; Gastro Enterologie Oncologie, 229 COURS DE L 'ARGONNE, 33076, BORDEAUX, FRANCE	9
	HOPITAL JEAN MINJOZ; Oncologie, 3 Boulevard Alexander Fleming Niveau 1, 25030, Besancon, FRANCE	19

Site No = Clinical Research Task Number (center no.)

* = Current Investigator

Listing of Investigators by Site

Protocol : BO17708

Sites: All sites that have enrolled a patient

Investigator	Center	No of Patients Enrolled
	Institut régional du Cancer Montpellier, Centre val d'Aurelle, 326 rue des Apothicaires, 34298, Montpellier, FRANCE	35
	UNIVERSITETSSJUKHUSET; ONKOLOGKLINIKEN, LINKOPING, 58185, LINKOEPING, SWEDEN	6
	UNIVERSITÄTSKLINIK FÜR INNERE MEDIZIN I; KLINISCHE ABT. FÜR ONKOLOGIE, WÄHRINGER GÜRTEL 18-20, 1090, WIEN, AUSTRIA	8
	LKH SALZBURG - UNIV. KLINIKUM SALZBURG; III. MEDIZINISCHE ABT., Müllner Hauptstrasse 48, 5020, Salzburg, AUSTRIA	11
	LKH-UNIV. KLINIKUM GRAZ, Auenbruggerplatz 15, 8036, Graz, AUSTRIA	7
	LHK VÖCKLABRUCK; II. INTERNE ABT., Dr. Wilhelm-Bock-Strasse 1, 4840, Vöcklabruck, AUSTRIA	5
	Lithuanian University of Health. Sciences Kauno klinikos, Eiveniu 2, 50009, Kaunas, LITHUANIA	5
	INSTITUT OF ONCOLOGY AL. TRESTIOREANU BUCHAREST; ONCOLOGY, Sos. Fundeni nr. 252, 022328, Bucuresti, ROMANIA	14
	Cent.Onkologii-Instytut im. M. S-Curie, Klinika Now. Piesi i Chirurgii Rekon., ROENTGENA 5, 02-781, WARSZAWA, POLAND	12
	IPO de Lisboa; Servico de Oncologia Medica, RUA PROF. LIMA BASTOS, 1099-023, LISBOA, PORTUGAL	3
	IPO de Coimbra; Servico de Oncologia Medica, Av. Dr. Bissaya Barreto, 3000-075, Coimbra, PORTUGAL	3
	Oddzial Chemioterapii Szpitala Klinicznego Nr 1 w Poznaniu, 82/84 Szamarzewskiego str., 60-569, Poznan, POLAND	17
	CHULALONGKORN HOSPITAL; MEDICAL ONCOLOGY, RAMA IV ROAD, PATUMWAN, 10400, BANGKOK, THAILAND	10
	Steve Biko Academic Hospital; Oncology, 2nd Floor Radiotherapy, Prinshof Campus, 0002, Pretoria, SOUTH AFRICA	6
	ASAN MEDICAL CENTER, UNI ULSAN COLLEGEMEDICINE; DEPT.INTERNAL MEDICINE / DIVISIONHEMATOLOGY/ONCOLOGY, 88, Olympic-ro 43-gil, Songpa-gu, SONGPA-GU, 138-736, Seoul, KOREA, REPUBLIC OF	11

Site No = Clinical Research Task Number (center no.)

* = Current Investigator

Listing of Investigators by Site

Protocol : BO17708

Sites: All sites that have enrolled a patient

Investigator	Center	No of Patients Enrolled
*Schneeweiss, Andreas	Nationales Centrum für Tumorerkrankungen (NCT), Im Neuenheimer Feld 460, 69120, Heidelberg, GERMANY	12
*Clemens, Michael	Klinikum Mutterhaus der Borromaeerinnen gGmbH; Haematologie/Onkologie, Feldstrasse 16, 54290, Trier, GERMANY	6
*Dorn, Julia	Klinikum rechts der Isar der TU München; Frauenklinik & Poliklinik, Ismaninger Str. 22, 81675, München, GERMANY	4
Harbeck, Nadia		
*Mueller, Volkmar	Universitätsklinikum Hamburg-Eppendorf; Frauenklinik, Martinistr. 52, 20246, Hamburg, GERMANY	5
	Klinikum der Johann Wolfgang von Goethe Universität, Frauenklinik, Theodor-Stern-Kai 7, 60596, Frankfurt, GERMANY	2
*Tesch, Hans	Praxis Hr. Prof. Dr. med. H.-C. Tesch, Frankfurt; Onkologische Gemeinschaftspraxis, Im Pruefling 17-19, 60389, Frankfurt am Main, GERMANY	1
	CHINESE ACADEMY OF MEDICAL SCIENCE; CANCER INST. & HOSPITAL, 17 PAN JIA GARDEN, CHAOYANG DISTRICT, 100021, BEIJING, CHINA	6
	WESLEY MEDICAL CENTRE; CLINIC FOR HAEMATOLOGY AND ONCOLOGY, 40 CHASELY STREET, 4066, AUCHENFLOWER, Queensland, AUSTRALIA	8
	ONKOLOGISCHE SCHWERPUNKTPRAXIS (EPS-GMBH), Ernst-Abbe-Str. 15, 07743, Jena, GERMANY	3
*Grischke, Eva-Maria	Uniklinik Tübingen; Frauenklinik, Calwerstraße 7, 72076, Tübingen, GERMANY	7
	Hospital Duran i Reynals; Oncologia, Gran Via s/n Km 2,7, Gran Via s/n Km 2,7, 08907, Barcelona, BARCELONA, SPAIN	8
	Hospital Univ Vall d'Hebron; Servicio de Oncologia, Passeig De La Vall D'hebron 119-129, 08035, Barcelona, BARCELONA, SPAIN	23

Site No = Clinical Research Task Number (center no.)
* = Current Investigator

Listing of Investigators by Site

Protocol : BO17708

Sites: All sites that have enrolled a patient

Investigator	Center	No of Patients Enrolled
	Hospital Universitario 12 de Octubre; Servicio de Oncologia, Avenida Cordoba Km 5.4, 28041, Madrid, MADRID, SPAIN	11
	Hospital Clinico Universitario Virgen de la Victoria; Servicio de Oncologia, CAMPUS UNIVERSITARIO DE TEATINOS S/ N., 29010, Malaga, MALAGA, SPAIN	6
	Hospital Clínic i Provincial; Servicio de Hematología y Oncología, Villarroel 170, 08036, Barcelona, BARCELONA, SPAIN	5
	Complejo Hospitalario de Jaen-Hospital Universitario Medico Quirurgico; Servicio de Oncologia, AVDA. DEL EJERCITO ESPANOL S/N, 23007, JAEN, JAEN, SPAIN	2
	Hospital Sao Lucas - PUCRS, Av. Ipiranga, 6690, 4° Floor, 90610-000, Porto Alegre, RS, BRAZIL	2
	Hospital A. C. Camargo; Oncologia, RUA PROFESSOR ANTONIO PRUDENTE 211, 01509-010, Sao Paulo, SP, BRAZIL	4
	Hospital de Cancer de Barretos, Rua Antenor Duarte Vilela 1331, 14784-400, Barretos, SP, BRAZIL	9
	HOSPITAL ARAUJO JORGE; DEPARTAMENTO DE GINECOLOGIA E MAMA, Rua 239, nº 206, Quadra 89, lote 41/47 - Setor Universitário, SETOR UNIVERSITARIO, 74605-070, Goiania, GO, BRAZIL	11
	Centro de Pesquisas Oncologicas - CEPON, Rodovia Admar Gonzaga, SC 655, km 0,5, Itacorubi, 88034-000, Florianopolis, SC, BRAZIL	4
	Hospital Luxemburgo; Oncologia, Rua Gentios 1350, 31190-131, Belo Horizonte, MG, BRAZIL	3
	SAMSUNG MEDICAL CENTRE; DIVISION OF HEMATOLOGY/ONCOLOGY, 81, Irwon-ro, Gangnam-gu, 135-710, Seoul, KOREA, REPUBLIC OF	13
	NATIONAL CANCER INST., 268/1 RAMA VI ROAD, RAJATHEVEE, 10400, BANGKOK, THAILAND	2
	YONSEI UNI COLLEGE OF MEDICINE, SEVERANCE HOSPITAL; INTERNAL MEDICINE DEPT., 134 Shinchon-Dong, CPO BOX 8044, 120-752, Seoul, KOREA, REPUBLIC OF	15
	UNI ONCOLOGY INST. ; CHEMO - RADIATION DEPT, SANTARISKIU 1, 08660, VILNIUS, LITHUANIA	3
	BRITISH COLUMBIA CANCER AGENCY (BCCA) - VANCOUVER CANCER CENTRE, 600 WEST 10TH AVENUE, V5Z 4E6, VANCOUVER, British Columbia, CANADA	6

Site No = Clinical Research Task Number (center no.)

* = Current Investigator

Listing of Investigators by Site

Protocol : BO17708

Sites: All sites that have enrolled a patient

Investigator	Center	No of Patients Enrolled
	CROSS CANCER INSTITUTE ; DEPT OF MEDICAL ONCOLOGY, 11560 UNIVERSITY AVENUE, T6G 1Z2, EDMONTON, Alberta, CANADA	5
	TOM BAKER CANCER CENTRE; DEPT OF MEDICINE, 1331 29TH STREET NORTHWEST, T2N 4N2, Calgary, Alberta, CANADA	9
	CHU de Québec – Hôpital du Saint-Sacrement / ONCOLOGY, 1050 Chemin Sainte-Foy, G1S 4L8, Quebec, Quebec, CANADA	14
	Capital Health; QEII HSC; Oncology, 1276 South Park Street, B3H 2Y9, Halifax, Nova Scotia, CANADA	5
	HOPITAL DU SACRE COEUR DE MONTREAL; ONCOLOGY, 5400 BOUL. GOUIN OUEST, H4J 1C5, MONTREAL, Quebec, CANADA	2
	SUNNYBROOK ODETTE CANCER CENTRE, 2075 Bayview Avenue, Room T1-271, T1-155, M4N 3M5, Toronto, Ontario, CANADA	12
	The Ottawa Hospital; Division of Infectious Diseases, 501 Smyth Road, K1H 8L6, Ottawa, Ontario, CANADA	11
	NORTHEASTERN ONTARIO; REGIONAL CANCER CENTRE, 41 RAMSEY LAKE ROAD, P3E 5J1, SUDBURY, Ontario, CANADA	6
	Christie Hospital; Breast Cancer Research Office, 1st Floor, Manchester, M20 4BX, UNITED KINGDOM	12
	MOUNT VERNON HOSPITAL, RICKMANSWORTH ROAD, NORTHWOOD, MIDDLESEX, HA6 2RN, UNITED KINGDOM	6
	WESTERN GENERAL HOSPITAL; CLINICAL ONCOLOGY, CREWE ROAD SOUTH, EDINBURGH, EH4 2XU, UNITED KINGDOM	2
	ST THOMAS HOSPITAL; MEDICINE DIV., LAMBETH PALACE ROAD, LONDON, SE1 7EH, UNITED KINGDOM	5
	ADDENBROOKES NHS TRUST; ONCOLOGY CLINICAL TRIALS UNIT, ADDENBROOKE'S HOSPITAL CAMBRIDGE, HILLS ROAD, CAMBRIDGE, CB2 2QQ, UNITED KINGDOM	5
	ROYAL BOURNEMOUTH GENERAL HOSPITAL; ONCOLOGY, NHS Foundation Trust Castle Lane East, Bournemouth, BH7 7DW, UNITED KINGDOM	1
	ROYAL CORNWALL HOSPITAL; DEPT OF CLINICAL ONCOLOGY, CHY HOWLEK (SUNRISE BUILDING), TRURO, TR1 3LJ, UNITED KINGDOM	3

Site No = Clinical Research Task Number (center no.)

* = Current Investigator

Listing of Investigators by Site

Protocol : BO17708

Sites: All sites that have enrolled a patient

Investigator	Center	No of Patients Enrolled
	ST JAMES UNI HOSPITAL; ICRF CANCER MEDICINE RESEARCH UNIT, BECKETT STREET, LEEDS, LS9 7TF, UNITED KINGDOM	1
	Mount Medical Center, 146 MOUNTS BAY ROAD, 1ST FLOOR, 6000, PERTH, Western Australia, AUSTRALIA	34
	AZIENDA OSPEDALIERO-UNIVERSITARIA DIPARTIMENTO INTERAZIENDALE DI ONCOLOGIA, PIAZZALE S. M. DELLA MISERICORDIA 15, 33100, UDINE, Friuli-Venezia Giulia, ITALY	13
	OSPEDALE REGIONALE DI PARMA; DIVISIONE DI ONCOLOGIA MEDICA, Via Gramsci, 14, 43100, PARMA, Emilia-Romagna, ITALY	4
	OSPEDALE TREVIGLIO-CARAVAGGIO; UNITA OPERATIVA DI ONCOLOGIA MEDICA, PIAZZA OSPEDALE 1, 24047, TREVIGLIO, Lombardia, ITALY	5
	Ospedale Di Macerata; Oncologia, VIA SANTA LUCIA 2, 62100, MACERATA, Marche, ITALY	4
	AZ. OSP. TRIESTINA; CENTRO ONCOLOGICO, VIA DELLA PIETA 19, 34100, TRIESTE, Friuli-Venezia Giulia, ITALY	1
	AZ. OSP. S. ORSOLA MALPIGHI; ISTITUTO DI ONCOLOGIA SERAGNOLI, 15 VIA ALBERTONI, 40138, BOLOGNA, Emilia-Romagna, ITALY	5
	OSPEDALE DEGLI INFERMI DI BIELLA; REPARTO ONCOLOGIA MEDICA, VIA CARACCIO 5, 13900, BIELLA, Piemonte, ITALY	1
	OSPEDALE S. VINCENZO; ONCOLOGIA MEDICA, Contrada Sirina, 98030, Taormina, Sicilia, ITALY	2
	A.O. Universitaria Policlinico Di Modena; Oncologia, VIA DEL POZZO 71, 41100, MODENA, Emilia-Romagna, ITALY	8
	Skånes University Hospital, Skånes Department of Onclology, Getingevagen 4, 22185, Lund, SWEDEN	2
*Beckmann, Matthias W.	Universitätsklinikum Erlangen; Frauenklinik, Universitätsstraße 21-23, 91054, Erlangen, GERMANY	1
*HARTMANN, FRANK	Klinik Lippe Lemgo; Medizinische Klinik II/Haematoonkologie, RINTELNER STRAßE 85, 32657, LEMGO, GERMANY	2
*Thomssen, Christoph	Universitätsklinikum Halle (Saale); Universitätsklinik Und Poliklinik Für Gynäkologie, Ernst-Grube-Str. 40, 06120, Halle, GERMANY	1

Site No = Clinical Research Task Number (center no.)

* = Current Investigator

Listing of Investigators by Site

Protocol : BO17708

Sites: All sites that have enrolled a patient

Investigator	Center	No of Patients Enrolled
*KIRSCH, ANDREAS	Onkologischer Schwerpunkt am Oskar-Helene-Heim; Dres. Herrenberger, Keitel-Wittig u. Kirsch, Clayallee 225a, 14195, Berlin, GERMANY	8
	Hospital del Mar; Servicio de Oncologia, Paseo Maritimo 25-29, 08003, Barcelona, BARCELONA, SPAIN	5
	RYDYGIERA HOSPITAL; CHEMOTHERAPY, OSIEDLE ZLOTEJ JESLENL 1, 31-826, KRAKOW, POLAND	4
	BOX HILL HOSPITAL; ONCOLOGY, Suite 8, 28-32 Arnold Street, 3128, Box Hill, Victoria, AUSTRALIA	1
	MAROONDAH HOSPITAL; BREAST CLINIC, 20 Grey Street, 3135, Ringwood East, Victoria, AUSTRALIA	2