



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 May 2011
EMA/CHMP/443982/2011
Human Medicines Development and Evaluation

Assessment Report
For
Avastin
(bevacizumab)

Procedure No.: EMEA/H/C/000582/II/0033

**Variation Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted**



CHMP variation assessment report

Type II variation EMEA/H/C/000582/II/0033

| | |
|---|--|
| Invented name/name: | Avastin |
| International non-proprietary name/common name: | bevacizumab |
| Indication summary (as last approved): | treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer, non-small cell lung cancer and renal cell cancer |
| Marketing authorisation holder: | Roche Registration Ltd. |

1. Scope of the variation and changes to the dossier

| | |
|-------------------------------|---|
| Scope of the variation: | <p>To extend the indication to the use of Avastin in combination with capecitabine for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate.</p> <p>Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine. For further information about HER2 status, refer to section 5.1.</p> <p>Consequently, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated to reflect the change in the indication accordingly. Finally Annex II has been updated in order to take into account the latest version of the RMP.</p> |
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| Co-Rapporteur: | Eva Skovlund |
| <i>For the re-examination</i> | |
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|------------------------------------|--|
| Co-Rapporteur: | Daniela Melchiorri |
| Product presentations affected: | See Annex A to the Opinion |
| Dossier modules/sections affected: | Modules 1, 2 and 5 |
| Product Information affected: | Summary of Product Characteristics and Annex II (Attachment 1 - changes highlighted) |

2. Steps taken for the assessment

| Step | Step date |
|---|------------------|
| Submission date: | 9 November 2009 |
| Start of procedure: | 22 November 2009 |
| Rapporteur's preliminary assessment report circulated on: | 19 January 2010 |
| Rapporteur's assessment report circulated on: | 15 January 2010 |
| Request for supplementary information and extension of timetable adopted by the CHMP on : | 18 February 2010 |
| MAH's responses submitted to the CHMP on : | 22 April 2010 |
| Rapporteur's and Co-Rapporteur's joint preliminary assessment report on the MAH's responses circulated on: | 01 June 2010 |
| Rapporteur's and Co-Rapporteur's updated joint assessment report circulated on: | 18 June 2010 |
| 2 nd Request for supplementary information and extension of timetable adopted by the CHMP on : | 24 June 2010 |
| Revised 2 nd Request for supplementary information and extension of timetable adopted by the CHMP on : | 22 July 2010 |
| MAH's responses submitted to the CHMP on : | 18 August 2010 |
| Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses circulated on: | 01 October 2010 |
| 3 rd Request for supplementary information and extension of timetable adopted by the CHMP on: | 21 October 2010 |
| MAH's responses submitted to the CHMP on : | 16 November 2010 |
| Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses circulated on: | 29 November 2010 |
| Rapporteur's and Co-Rapporteur's updated joint assessment report circulated on: | 9 December 2010 |

3. Scientific discussion

3.1. Introduction

Breast cancer is the most common cancer in women worldwide and the highest rate of occurrence is in Western Europe and North America. In 2002, an estimated 1.15 million new cases of breast cancer occurred globally, of which approximately 350,000 occurred in Europe and 230,000 in the US. Breast cancer is the leading cause of cancer mortality in women with approximately 400,000 deaths annually (Parkin et al, *CA Cancer J Clin* (2005), 55:74-108). For women who are not candidates for hormonal therapy and whose tumours are human epidermal growth factor receptor 2 (HER2)-negative, cytotoxic chemotherapy is the treatment of choice for metastatic disease or locally recurrent disease requiring systemic therapy (Kataja et al, *Ann Oncol* (2008), 19, Suppl 2:ii1-ii13). A large number of cytotoxic agents have demonstrated activity in the treatment of metastatic breast cancer (mBC), including anthracyclines, taxanes, alkylating agents, vinca alkaloids, and antimetabolites, such as 5-fluorouracil, capecitabine, or methotrexate. In the metastatic setting despite the variety of chemotherapy agents available, patients are typically treated with palliative intent.

No single regimen has emerged as a sole standard of care that can be applied to all patients. Compared with single agent regimens, combinations of cytotoxic agents may provide a greater objective response rate and longer progression-free intervals in the first-line setting. However, those gains come at the expense of more side effects and overlapping toxicity. As a result, the use of sequential single agent cytotoxic therapy remains a frequent approach.

The introduction of taxanes (paclitaxel and docetaxel) in the 1990s has led to significant improvements in the management of mBC. A Cochrane meta-analysis of randomized trials comparing taxane-containing with non-taxane-containing chemotherapy regimens in women with mBC showed that regimens containing taxanes improved overall survival (OS), time to progression (TTP), and objective response rates (ORR) (Ghersi et al, *Cochrane Database Syst Review* (2005), 18(2):CD003366). Paclitaxel and docetaxel share similar chemical structures and anti-tumour activities but differ in haematological toxicity profiles (Verweij et al, *Ann Oncol* (1994), 5:495-505).

Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody. It inhibits angiogenesis by neutralizing all isoforms of human vascular endothelial growth factor (VEGF)-A and by blocking their binding to VEGF receptors. Bevacizumab was initially approved in the European Union (EU) on January 12, 2005 for the first-line treatment of patients with metastatic cancer of the colon or rectum (mCRC) in combination with intravenous 5-fluorouracil / folinic acid or intravenous 5-fluorouracil / folinic acid / irinotecan.

The following type II variations were subsequently approved in the EU to extend the use of bevacizumab: (1) in combination with paclitaxel for first-line treatment of mBC (March 27, 2007), (2) in combination with platinum based chemotherapy for first-line treatment of unresectable advanced metastatic or recurrent non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology (August 21, 2007), (3) in combination with interferon alfa-2a for first line treatment of advanced and/or metastatic renal cell cancer (December 14, 2007), (4) in combination with fluoropyrimidine-based chemotherapy for treatment of mCRC (January 25, 2008) and (5) in combination with docetaxel for first-line treatment of mBC (July 23, 2009).

This variation concerned an application for extension of the approved indications for Avastin to include:

“Avastin (bevacizumab) with standard cytotoxic chemotherapy is indicated for first-line treatment of patients with metastatic breast cancer. For further information as to HER2 status, please refer to Section 5.1”.

A revised proposed wording for the requested indication has been presented by the MAH at the Oral Explanation as follows:

“Avastin in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom other chemotherapy options are not preferred. Patients who have received taxane and anthracycline-containing regimen in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine.

For further information as to the observed differential efficacy depending on the choice of chemotherapy regimen and as to HER2 status, please refer to section 5.1”.

3.1.1 GCP aspects /Scientific Advice

According to the MAH, the primary study in this application, AVF3694g was conducted in accordance with current United States Food and Drug Administration (FDA) Good Clinical Practices (GCPs), the International Conference on Harmonization (ICH) E6 Guideline for GCP and national and local ethical and legal requirements.

3.2 Clinical aspects

3.2.1 Clinical pharmacology

No new PK/PD or interaction studies have been submitted with the current application.

3.2.2 Clinical efficacy

The data in the current application are mainly from a multicentre, randomized, double-blind, placebo-controlled phase III trial (AVF3694g) comparing bevacizumab in combination with chemotherapy to placebo and chemotherapy in patients with previously untreated mBC. It is supported by data from previously submitted phase III studies E2100 and BO17708 of bevacizumab in combination with paclitaxel and docetaxel, respectively, as first-line treatment for patients with mBC. An earlier phase III study of bevacizumab in combination with capecitabine in patients with mBC who had previously failed therapy with anthracycline and a taxane (AVF2119g) was also submitted. All studies are presented in Table 1.

Table 1: Overview of phase III studies of bevacizumab in patients with mBC (AVF3694g, BO17708, E2100, AVF2119g)

| Study No | Treatment | Patients Randomized/Treated | Region | Primary Endpoint |
|-------------------------------|---|---|--|------------------|
| AVF3694g Pivotal | First-line taxane (docetaxel or paclitaxel [protein-bound particles]) or anthracycline-based or capecitabine + bevacizumab or placebo | Taxane group: 307/305 Anthracycline group: 315/310 Capecitabine cohort: 615/605 | USA, Western Europe, Eastern Europe, Australia, Canada, East Asia, Central and South America | PFS |
| BO17708 Supportive | First-line docetaxel + bevacizumab or placebo | 736/730 | Western Europe, Eastern Europe, Australia, Canada, East Asia, Central and South America | PFS |
| E2100 Supportive | First-line paclitaxel alone or in combination with open-label bevacizumab | 722/711 | Primarily USA (plus Canada, South Africa, and Peru) | PFS |
| AVF2119g Supportive | Capecitabine alone or in combination with open-label bevacizumab (following previous treatment with anthracycline and a taxane) | 462/444 | USA | PFS |

- **Main study**

AVF3694g (Ribbon-1) Study

AVF3694g is a phase III, multicentre, randomised, placebo-controlled study, designed to evaluate the efficacy and safety of bevacizumab combined with any of several standard cytotoxic chemotherapies (two taxanes, four anthracycline-based therapies, or capecitabine).

METHODS

Study Participants

The inclusion criteria were the following:

- Histologically or cytologically confirmed adenocarcinoma of the breast, with measurable or non-measurable locally recurrent or metastatic disease. Locally recurrent disease must not have been amenable to resection with curative intent.
- ≥18 years of age.
- Patients in the anthracycline-based chemotherapy cohort had to have adequate left ventricular function at study entry, which was defined as a left ventricular ejection function (LVEF) ≥ 50% by either multiple-gated acquisition (MUGA) scan or echocardiogram (ECHO).
- Patients, who had received recent radiation therapy, had to have recovered from any significant (Grade ≥3) acute toxicity prior to day 0 of the study.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- For women of childbearing potential, use of accepted and effective method of non-hormonal contraception.

Key exclusion criteria were as follows:

- HER-2 positive patients not previously treated with trastuzumab were excluded from the study as were patients.
- Prior chemotherapy for locally recurrent or mBC.
- Prior hormonal therapy <1 week prior to Day 0 (baseline).
- Prior adjuvant or neoadjuvant chemotherapy within 12 months prior to Day 0, prior anthracycline treatment as part of neoadjuvant or adjuvant therapy for localized breast cancer (anthracycline-based chemotherapy cohort only).
- Investigational therapy within 28 days of Day 0.
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 0, or anticipation of need for major surgical procedure during the course of the study.
- Minor surgical procedures, such as fine needle aspirations or core biopsies, within 7 days prior to Day 0.
- Prior therapy with bevasizumab, sorafenib, sunitimib, or other vascular endothelial growth factor (VEGF) pathway-targeted therapy.

Treatments

Eligible patients with locally recurrent or metastatic adenocarcinoma of the breast were randomized in a 2:1 ratio to receive chemotherapy plus bevacizumab [15 mg/kg every 3 weeks (q3w)] or chemotherapy plus placebo in a double-blind fashion. The protocol specified three chemotherapy options, from which the investigator chose one prior to randomization of each individual patient:

1. Taxane: Either of the following taxanes administered intravenously every 3 weeks:

Docetaxel 75-100 mg/m²

Paclitaxel protein-bound particles (Abraxane) 260 mg/m²

2. Anthracycline-based (for patients not previously treated with anthracyclines): Any of the following combinations, administered intravenously q3w for a maximum of 8 cycles:

FEC:5-fluorouracil 500 mg/m², epirubicin 90-100 mg/m², and cyclophosphamide 500 mg/m² on day 1

FAC:5-fluorouracil 500 mg/m², doxorubicin 50 mg/m², and cyclophosphamide 500 mg/m²

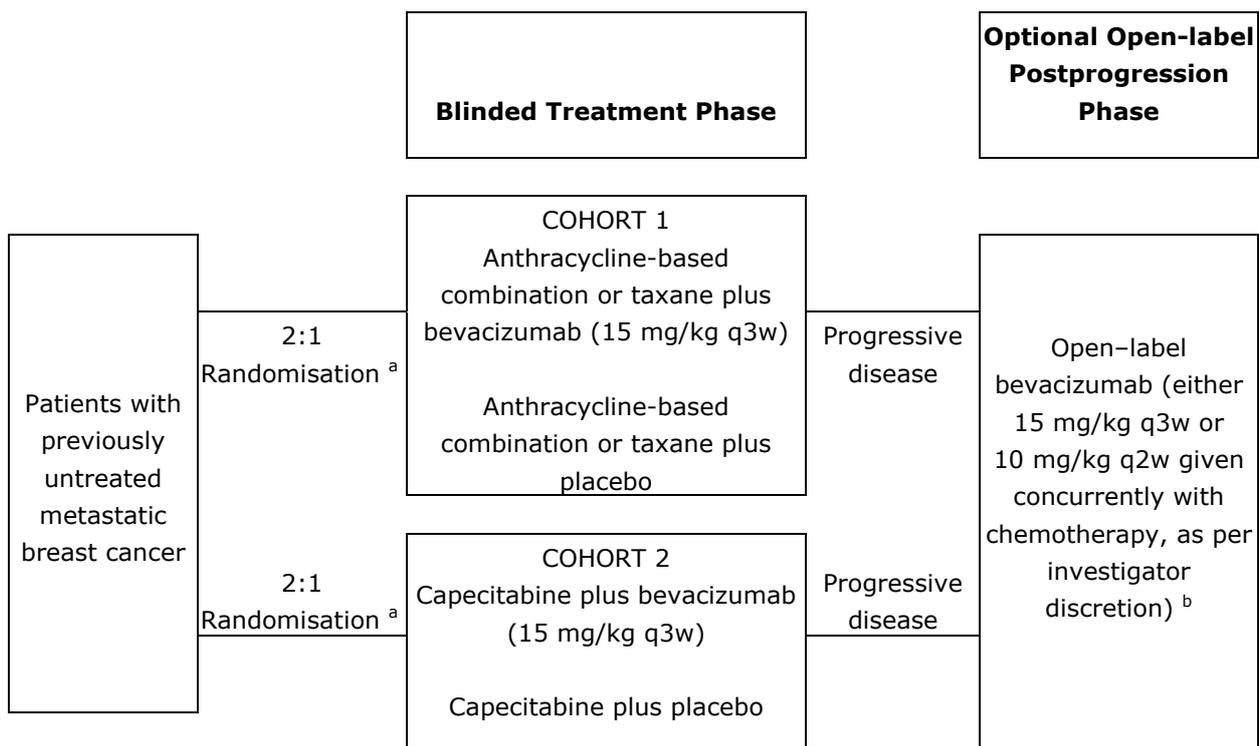
AC:Doxorubicin 50-60 mg/m² and cyclophosphamide 500-600 mg/m²

EC:Epirubicin 90-100 mg/m² and cyclophosphamide 500-600 mg/m²

3. Capecitabine: 1000 mg/m² orally twice daily on days 1-14 of each 3-week cycle.

The design of the study is presented in figure 1.

Figure 1: Overview of the design of study AVF3694g



^a The chemotherapy regimen was chosen by the investigator prior to randomization.

^b Determined by the investigator depending on the concurrent chemotherapy schedule.

Objectives

The primary objective of the study was to determine the clinical benefit of the addition of bevacizumab to standard chemotherapy regimens for previously untreated mBC.

Secondary objectives were to evaluate the efficacy and safety of bevacizumab combined with any of several standard cytotoxic chemotherapies (two taxanes, four anthracycline-based therapies, or capecitabine).

Outcomes/endpoints

The primary efficacy endpoint was Progression Free Survival (PFS) based on investigator assessment for 1) patients receiving either taxane therapy or anthracycline-based therapy and 2) patients receiving capecitabine therapy.

PFS was defined as the time from randomization to time of first documented disease progression or death, whichever occurred first. Patients without an event were censored at the last tumour assessment or last follow-up for disease progression at which they were known to be progression free. Patients without any post-baseline tumour assessment were censored at randomization.

The secondary efficacy endpoints included

- Objective response rate (ORR): complete response (CR) or partial response (PR) as assessed by response evaluation criteria in solid tumours (RECIST) determined on two consecutive investigator assessments ≥ 4 weeks apart during first-line therapy. The primary analysis of OR was based on patients in the Intent-to treat (ITT) population with measurable disease at baseline.

- Duration of objective response (DR): the time from date of objective response to disease progression or death due to any cause, whichever occurred first. Only patients who were responders were included in the analysis of duration of response.
- Overall Survival: the time from randomization until death from any cause. For patients who had not died at the time of analysis or were lost to follow-up, data were censored at the date the patient was last known to be alive. This was the randomization date plus 1 day for patients who were randomized, not treated, and immediately lost to follow-up.
- One-Year Survival Rate: the percentage of patients who were alive at 1 year after the randomization.
- Progression Free Survival Independent Review Committee (IRC) assessed.

Sample size

Cohort 1 (Taxane or Anthracycline-Based Chemotherapy)

The sample size for this cohort was based on the assumption of a projected enrolment rate of approximately 38 patients per month, a two-sided log-rank test and a 5% significance level. Based on these assumptions, a total of 600 patients (300 taxane treated patients and 300 treated anthracycline patients) would result in approximately 405 events during a total trial period of approximately 28 months. This allowed for approximately 90% power to detect an improvement in median time to disease progression or death from 7 months in the chemotherapy + placebo arm to 10 months in the chemotherapy + bevacizumab arm [Hazard Ratio (HR) = 0.70].

Cohort 2 (Capecitabine)

Based on an accrual assumption of 29 patients recruited per month, a total of 600 patients would result in approximately 415 events during a total trial period of approximately 28 months. This allowed for approximately 80% power to detect an improvement in median time to disease progression or death from 6 months in the placebo-containing arm to 8 months in the bevacizumab-containing arm (HR = 0.75) at the 5% level of significance.

Randomisation

Patients were randomized in a 2:1 ratio to the bevacizumab-containing arm or the placebo-containing arm using the hierarchical dynamic randomization schema with the following stratification factors:

- choice of chemotherapy (taxane, anthracycline-based, capecitabine),
- disease-free interval (≤ 12 months, > 12 months since completion of adjuvant chemotherapy, or definitive surgery if no adjuvant chemotherapy),
- prior adjuvant chemotherapy (yes, no),
- number of metastatic sites (< 3 , ≥ 3).

Patients were to start their first dose of study treatment on the day of randomization but not later than 5 working days after randomization.

Blinding (masking)

The study included a double-blinded treatment phase and an optional open-label post-progression phase during which patients were followed-up for survival. During the blinded treatment phase, patients received chemotherapy and bevacizumab or placebo every 3 weeks until disease progression, treatment limiting toxicity, or death due to any cause.

Statistical methods

Primary Efficacy Endpoint

Both analysis cohorts were independently powered to detect a statistically significant increase in PFS at a type I error rate of 0.05 for each cohort.

The analysis of PFS was formally tested using a stratified log-rank test at the two-sided $\alpha = 0.05$ level. The stratification factors in the stratified analyses were those used for randomization: disease-free interval (≤ 12 months, > 12 months), prior adjuvant chemotherapy (yes, no), number of metastatic sites (< 3 , ≥ 3), and choice of chemotherapy (taxane, anthracycline-based; Cohort 1 only). The HR was estimated using a stratified Cox regression model with the same stratification variables as used in the stratified log-rank test.

In both the investigator and IRC-based analysis, for those patients who received non-protocol-specified antineoplastic therapy (NPT) ≥ 30 days prior to investigator or IRC-determined disease progression, PFS data were censored at the time of the last tumour assessment prior to the initiation of NPT. For patients who started open-label bevacizumab prior to documented disease progression based on investigator or IRC review, data were censored at the last tumour assessment prior to initiation of open-label bevacizumab.

Secondary Efficacy Endpoints

For the key secondary endpoints of ORR, OS, and 1-year survival rate, the following test procedures were used to maintain an overall type I error rate of $\alpha = 0.05$ (two-sided):

- Step 1: The secondary endpoint of ORR was tested at the type I error rate of 0.01.
- Step 2a: If a statistically significant result was observed for ORR, OS was tested at the type I error rate of 0.05.
- Step 2b: Otherwise, OS was tested at the type I error rate of 0.04.
- Step 3: One-year survival rate was compared only when a statistically significant result was observed in OS between the two treatment arms. The type I error rate for 1-year survival rate was the same as that used for OS.

No adjustments for multiplicity (of endpoints or treatment comparisons) were incorporated into the analyses of duration of objective response and PFS based on IRC-reviewed data.

ORR was formally compared between the two treatment arms using the Cochran-Mantel-Haenszel test, stratified by the randomization stratification factors.

OS was formally tested at the time of the final PFS analyses. This was considered as the final analysis of OS. A stratified log-rank test was used to compare the OS between treatment arms. The HR was estimated using the stratified Cox proportional hazards regression model.

One-year survival rate for each treatment arm was estimated using the Kaplan-Meier method and the 95% confidence intervals using Greenwood's formula. The difference in 1-year survival rate between treatment arms was assessed using the normal approximation method.

PFS Based on IRC-Reviewed Data was analyzed as for the primary analysis of PFS.

Three types of analysis populations were defined as follows:

- The ITT population, defined as all patients who were randomized, regardless of whether they received any study drug or completed the full course of treatment.

- The safety evaluable population (SAP) was defined as all patients who received at least one dose of study treatment.
- The post-progression SAP was all patients who received bevacizumab in the optional open-label post-progression phase.

PFS Sensitivity Analyses

The following sensitivity analyses were conducted for PFS:

- Without censoring NPT: For patients who started NPT prior to progressive disease, any progression or death occurring after initiation of NPT was considered a PFS event. Otherwise, PFS was censored at the last tumour assessments.
- Early discontinuation: Initiation of NPT prior to progressive disease or death or discontinuation of first-line therapy for a reason other than progressive disease or death was treated as an event. The time of event was the last tumour assessment prior to NPT or treatment discontinuation plus 1 day.
- Missing tumour assessments: For patients with a PFS event who missed scheduled assessments or had assessments that were deemed “unable to assess” immediately prior to progressive disease, the date of progression was replaced by the date of the first missing assessment.
- PFS on treatment: For patients who died or had disease progression >63 days after the last dose of blinded study drug, PFS was censored at the last tumour assessment within 63 days (one tumour assessment cycle) after the last dose of blinded study drug. Data were censored at the last tumour assessment for patients who did not have disease progression or die.
- Worst-case analysis: For patients who were lost to follow-up, i.e., alive without any tumour assessments >126 days (two tumour assessment cycles) prior to the clinical data cut-off, patients in the bevacizumab-containing arm were considered to have disease progression at the first missing tumour assessment. For patients in the placebo-arm who were lost to follow-up, PFS was censored at the last available tumour assessment.

The following post-hoc sensitivity analyses were performed on the updated OS data to assess how the use of bevacizumab in the open-label phase may have affected OS.

- *Discounting OS for patients who received bevacizumab in the open-label phase*

Assuming that the use of bevacizumab in the open-label phase prolonged OS, the survival time after the initiation of bevacizumab in the open-label phase was discounted by 25% and 50% for both treatment arms.

- *Censoring OS at the initiation of bevacizumab use in the open-label phase*

This sensitivity analysis was performed to assess the treatment effect of bevacizumab on OS, assuming that bevacizumab in the open-label phase was not available.

- *OS in patients who did or did not receive bevacizumab in the open label phase.*

OS was compared between treatment arms in patients who did or did not receive bevacizumab in the open-label phase.

RESULTS

Participant flow

A total of 1237 patients (1232 female and 5 male) with locally recurrent or mBC were randomized to treatment with either Taxane/Anthracycline (T/Anth) + Bevacizumab (Bv) (N = 415), T/Anth + Placebo

(PI) (N = 207), Capecitabine (Cap) + Bv (N = 409) or Cap + PI (N = 206). In the taxane subgroup, 203 patients were enrolled in the T + Bv arm and 104 patients in the T + PI arm. In the anthracycline-based chemotherapy subgroup, 212 patients were enrolled in the Anth + Bv arm and 103 patients in the Anth + PI arm.

In Cohort 1, 36 patients (8.7%) in the T/Anth + Bv arm and 7 patients (3.4%) in the T/Anth + PI arm remained on blinded study drug at the time of the clinical data cut-off for the final analyses (July 31, 2008). In Cohort 2, 55 patients (13.4%) in the Cap + Bv arm and 22 patients (10.7%) in the Cap + PI arm remained on blinded study drug at the time of the clinical data cut-off. The patient disposition is presented in Table 2.

Table 2: Patient Disposition (ITT Population)

| Parameter | Cohort 1 | | Cohort 2 | |
|---|-------------|-------------|-------------|-------------|
| | T/Anth + PI | T/Anth + Bv | Cap + PI | Cap + Bv |
| Randomized | 207 | 415 | 206 | 409 |
| Treated | 206 (99.5%) | 409 (98.6%) | 201 (97.6%) | 404 (98.8%) |
| Discontinued blinded phase | 199 (96.1%) | 373 (89.9%) | 179 (86.9%) | 349 (85.3%) |
| Withdrawn due to: | | | | |
| Progressive disease | 146 (70.5%) | 187 (45.1%) | 145 (70.4%) | 245 (59.9%) |
| Patient/physician decision | 26 (12.6%) | 91 (21.9%) | 11 (5.3%) | 42 (10.3%) |
| Adverse event | 10 (4.8%) | 63 (15.2%) | 11 (5.3%) | 37 (9.0%) |
| Death | 7 (3.4%) | 14 (3.4%) | 6 (2.9%) | 11 (2.7%) |
| Lost to follow-up | 3 (1.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Other ^a | 7 (3.4%) | 18 (4.3%) | 6 (2.9%) | 14 (3.4%) |
| Treated with bevacizumab in the optional open-label phase | 89 (43.0%) | 123 (29.6%) | 107 (51.9%) | 142 (34.7%) |
| Discontinued the optional open-label phase | 63 (30.4%) | 100 (24.1%) | 84 (40.8%) | 100 (24.4%) |
| Patients in the survival follow-up phase ^b | 93 (44.9%) | 193 (46.5%) | 75 (36.4%) | 168 (41.1%) |

^a > 60 days since last administration of study drug, treatment completed, or other; ^b Includes all patients who discontinued from either the blinded treatment phase or the optional open-label post-progression phase.

Recruitment

The study period was from 15 December 2005 to 31 July 2008. A total of 1237 patients were enrolled at 232 centres in the United States, Europe, and the rest of the world.

Conduct of the study

The protocol was finalized on 4 October 2005 and amended five times as follows:

- The first amendment to Study AVF3694g (effective on 1 February 2006) revised the protocol to provide more clarity and rigorous guidelines for study therapy in both the blinded treatment and optional open-label post-progression phases. Safety information was updated to be consistent with current standard bevacizumab dose modification guidelines. Protocol-specified selected adverse events and special reporting for non-serious cardiac adverse events were further defined. All intracranial haemorrhages were to be reported as serious and were therefore subject to serious adverse event reporting requirements. Safety monitoring of left ventricular function during initial screening was added for patients with prior exposure to

anthracycline-based therapy, rather than only for patients entering the anthracycline-based chemotherapy subgroup. All Grade \geq 2 left ventricular systolic dysfunction (LVSD) events were to be reported immediately to the sponsor to allow for a timely and thorough review of cardiotoxicity events by the Data Monitoring Committee (DMC).

- The second amendment to the protocol was effective on 22 November 2006. Secondary objectives and outcome measures were amended to include 1-year survival rate. Additional changes were made to provide more clarity and rigorous guidelines for study therapy during both the blinded treatment and optional open-label post-progression phases. A provision allowing optional unblinding was added for patients with documented progressive disease if such information was believed to be instrumental in determining the next course of treatment.
- The third amendment to the protocol was effective on 20 February 2007. The amendment was triggered by the FDA's comments on the study design. Key changes to the protocol included the following: The sample size of the capecitabine cohort was increased to fully power the capecitabine cohort in order to ascertain the clinical benefit of the addition of bevacizumab to capecitabine therapy. The second primary objective of this trial was amended in order to ascertain the clinical benefit, as measured by PFS, of the addition of bevacizumab to capecitabine therapy compared with capecitabine alone.
- In response to the FDA's comments on Amendment 3, the protocol was amended a fourth time on 24 July 2007 to provide more information in support of the primary endpoint of PFS and the secondary endpoint of overall survival. An IRC assessment of PFS was added as a sensitivity analysis to provide support for the primary endpoint of investigator-assessed PFS. Additional capture of subsequent anti-cancer therapy during the survival follow-up phase for all patients was designed to provide information on therapies that may have contributed to the OS of patients after they had discontinued from the blinded treatment phase of the study. The definition of PFS was also revised to allow better characterization and to be more consistent with the definitions accepted by the regulatory communities.
- The protocol was amended a fifth time on 27 March 2008. The optional open-label post-progression phase was extended to all patients receiving study treatment when the study analysis was complete if the primary efficacy analysis showed significant improvement with bevacizumab without a detrimental effect on patient safety. The maximum duration of treatment with bevacizumab was increased to 48 months.

Baseline data

Baseline demographic characteristics of the patients in the pivotal study are presented in the Table 3.

Table 3: Demographic data (ITT population)

| Parameter | Cohort 1 | | Cohort 2 | |
|--------------------|--------------------------|--------------------------|-----------------------|--------------------------|
| | T/Anth + PI (N = 207) | T/Anth + Bv (N = 415) | Cap + PI (N = 206) | Cap + Bv (N = 409) |
| Age (years) | | | | |
| Mean (SD) | 54.3 (10.4) | 55.7 (11.0) | 57.1 (12.1) | 56.6 (11.5) |
| Median (range) | 55 (29–85) | 55 (28–88) | 57 (23–88) | 56 (28–91) |
| <40 | 14 (6.8%) | 29 (7.0%) | 15 (7.3%) | 21 (5.1%) |
| 40–64 | 160 (77.3%) | 295 (71.1%) | 137 (66.5%) | 289 (70.7%) |
| > 65 | 33 (15.9%) | 91 (21.9%) | 54 (26.2%) | 99 (24.2%) |
| Race/ethnicity | | | | |
| White | 175 (84.5%) | 341 (82.2%) | 157 (76.2%) | 308 (75.3%) |
| Black | 10 (4.8%) | 22 (5.3%) | 10 (4.9%) | 21 (5.1%) |
| Other ^a | 22 (10.6%) | 52 (12.5%) | 39 (19.0%) | 80 (19.5%) |
| Geographic region | | | | |
| North America | 110 (53.1%) | 198 (47.7%) | 104 (50.5%) | 226 (55.3%) |
| Western Europe | 39 (18.8%) | 92 (22.2%) | 28 (13.6%) | 57 (13.9%) |
| Eastern Europe | 40 (19.3%) | 83 (20.0%) | 32 (15.5%) | 53 (13.0%) |
| Asia | 17 (8.2%) | 28 (6.7%) | 18 (8.7%) | 31 (7.6%) |
| Latin America | 1 (0.5%) | 14 (3.4%) | 24 (11.7%) | 42 (10.3%) |
| ECOG PS | | | | |
| 0 | 110 (53.1%) | 216 (52.0%) | 110 (53.4%) | 214 (52.7%) ^b |
| 1 | 96 (46.4%) | 195 (47.0%) | 96 (46.6%) | 192 (47.3%) ^b |

Anth = anthracycline-based chemotherapy; Bv = bevacizumab; Cap = capecitabine; ECOG PS = Eastern Cooperative Oncology Group Performance Score; PI = placebo; SD = standard deviation; T = taxane.

^a Asian and Hispanic; ^b Cap + Bv arm; N = 406

The disease characteristics at baseline were:

Table 4: Baseline Disease Characteristics (ITT Population)

| Parameter | Cohort 1 | | Cohort 2 | |
|-----------------------------------|--------------------------|--------------------------|-----------------------|-----------------------|
| | T/Anth + PI (N = 207) | T/Anth + Bv (N = 415) | Cap + PI (N = 206) | Cap + Bv (N = 409) |
| Sites of involvement | | | | |
| Bone | 123 (59.4%) | 255 (61.4%) | 130 (63.4%) | 281 (68.7%) |
| Local-regional | 104 (50.2%) | 211 (50.8%) | 107 (52.2%) | 177 (43.3%) |
| Lung | 106 (51.2%) | 197 (47.5%) | 87 (42.4%) | 163 (39.9%) |
| Liver | 93 (44.9%) | 177 (42.7%) | 76 (37.0%) | 168 (41.1%) |
| Distant nodes | 91 (44.0%) | 162 (39.0%) | 83 (40.5%) | 156 (38.1%) |
| Effusion/ascites | 33 (15.9%) | 74 (17.8%) | 39 (19.0%) | 78 (19.1%) |
| Ipsilateral supraclavicular nodes | 19 (9.2%) | 37 (8.9%) | 26 (12.7%) | 38 (9.3%) |
| Distant skin/subcutaneous | 12 (5.8%) | 23 (5.5%) | 13 (6.3%) | 26 (6.4%) |
| Opposite breast | 4 (1.9%) | 21 (5.1%) | 6 (2.9%) | 18 (4.4%) |
| Adrenal | 9 (4.3%) | 16 (3.9%) | 7 (3.4%) | 13 (3.2%) |
| Bone marrow | 2 (1.0%) | 3 (0.7%) | 3 (1.5%) | 5 (1.2%) |

| Parameter | Cohort 1 | | Cohort 2 | |
|--------------------------------|--------------------------|--------------------------|-----------------------|-----------------------|
| | T/Anth + PI (N = 207) | T/Anth + Bv (N = 415) | Cap + PI (N = 206) | Cap + Bv (N = 409) |
| Other | 19 (9.2%) | 37 (8.9%) | 21 (10.2%) | 36 (8.8%) |
| Number of metastatic sites | | | | |
| <3 | 114 (55.1%) | 227 (54.7%) | 113 (54.9%) | 232 (56.7%) |
| ≥3 | 93 (44.9%) | 188 (45.3%) | 93 (45.1%) | 177 (43.3%) |
| Bone lesion only | | | | |
| Yes | 8 (3.9%) | 26 (6.3%) | 21 (10.2%) | 36 (8.8%) |
| No | 199 (96.1%) | 389 (93.7%) | 185 (89.8%) | 373 (91.2%) |
| Hormone receptor status | | | | |
| Positive (ER + and/or PgR +) | 153 (76.9%) | 306 (76.1%) | 146 (73.7%) | 312 (77.4%) |
| Negative (ER – and PgR –) | 46 (23.1%) | 96 (23.9%) | 52 (26.3%) | 91 (22.6%) |
| HER2 status by FISH/IHC | | | | |
| Positive | 0 (0.0%) | 1 (0.2%) | 6 (2.9%) | 8 (2.0%) |
| ER/PgR/HER2–negative combined | | | | |
| Yes | 46 (23.1%) | 96 (23.9%) | 50 (25.3%) | 87 (21.7%) |
| Disease–free interval – months | | | | |
| ≤12 | 84 (40.6%) | 155 (37.3%) | 45 (21.8%) | 109 (26.7%) |
| >12 | 123 (59.4%) | 260 (62.7%) | 161 (78.2%) | 300 (73.3%) |
| Measurable disease at baseline | | | | |
| Yes | 177 (85.5%) | 345 (83.1%) | 161 (78.5%) | 325 (79.5%) |
| No | 30 (14.5%) | 70 (16.9%) | 44 (21.5%) | 84 (20.5%) |

Anth = anthracycline–based chemotherapy; Bv = bevacizumab; Cap = capecitabine; PI = placebo;
PS = performance status; SD = standard deviation; T = taxane.

Concomitant Treatments

The selected concomitant treatments are presented in the table 5:

Table 5: Selected Concomitant Treatments (Safety Population)

| Parameter | Cohort 1 | | Cohort 2 | |
|--|--------------------------|--------------------------|-----------------------|-----------------------|
| | T/Anth + PI (N = 207) | T/Anth + Bv (N = 415) | Cap + PI (N = 206) | Cap + Bv (N = 409) |
| No. (%) patients taking any medication | 66 (32.7%) | 135 (32.7%) | 47 (23.4%) | 105 (26.0%) |
| Bisphosphonate | 34 (16.8%) | 88 (21.3%) | 26 (12.9%) | 56 (13.9%) |
| Use in patients with bone disease ^a | 33 (27.7%) | 85 (33.3%) | 22 (17.6%) | 50 (18.1%) |
| Warfarin | 9 (4.5%) | 13 (3.1%) | 5 (2.5%) | 14 (3.5%) |
| Heparin, low molecular weight | 7 (3.5%) | 10 (2.4%) | 3 (1.5%) | 9 (2.2%) |
| Megace (mesgestrol acetate) | 4 (2.0%) | 9 (2.2%) | 1 (0.5%) | 8 (2.0%) |
| Heparin, unfractionated | 5 (2.5%) | 2 (0.5%) | 5 (2.5%) | 12 (3.0%) |
| Other | 18 (8.9%) | 38 (9.2%) | 16 (8.0%) | 26 (6.4%) |

Anth = anthracycline-based chemotherapy; Bv = bevacizumab; Cap = capecitabine; PI = placebo; T = taxane.

^a The denominator is the number of patients with bone disease.

Prior cancer therapy

The proportion of patients receiving prior cancer therapies was generally similar across treatment arms within each cohort (table 6). The most common prior cancer therapies were surgery and chemotherapy in the neo-adjuvant and/or adjuvant setting.

Table 6: Prior Cancer Therapy (ITT Population)

| Parameter | Cohort 1 | | Cohort 2 | |
|--|--------------------------|--------------------------|-----------------------|-----------------------|
| | T/Anth + PI (N = 207) | T/Anth + Bv (N = 415) | Cap + PI (N = 206) | Cap + Bv (N = 409) |
| No. (%) patients with prior therapy for primary breast cancer | 157 (75.8%) | 326 (78.6%) | 190 (92.2%) | 374 (91.4%) |
| Surgery | 157 (75.8%) | 321 (77.3%) | 188 (91.3%) | 365 (89.2%) |
| Chemotherapy | 97 (46.9%) | 186 (44.8%) | 156 (75.7%) | 288 (70.4%) |
| Taxane | 31 (15.0%) | 63 (15.2%) | 84 (40.8%) | 161 (39.4%) |
| Anthracycline-based agent | 63 (30.4%) | 123 (29.6%) | 143 (69.4%) | 247 (60.4%) |
| Radiotherapy | 82 (39.6%) | 172 (41.4%) | 140 (68.0%) | 254 (62.1%) |
| Hormonal therapy | 79 (38.2%) | 158 (38.1%) | 109 (52.9%) | 203 (49.6%) |
| Prior treatment for locally recurrent metastatic breast cancer | 69 (33.3%) | 133 (32.0%) | 98 (47.6%) | 207 (50.6%) |
| Hormonal therapy | 54 (26.1%) | 109 (26.3%) | 89 (43.2%) | 188 (46.0%) |
| Radiotherapy | 39 (18.8%) | 70 (16.9%) | 49 (23.8%) | 113 (27.6%) |

Anth = anthracycline-based chemotherapy; Bv = bevacizumab; Cap = capecitabine; PI = placebo; T = taxane.

The number of patients included in each analysis population is summarised in Table 7.

Table 7: Analysis population

| | Bv15+T/Anth | T/Anth + PI | Bv15+Cap | Cap + PI |
|-----------------------------|-------------|-------------|------------|------------|
| ITT population | 415 | 207 | 409 | 206 |
| SAP | 413 | 202 | 404 | 201 |
| Post-progression SAP | 123 | 89 | 142 | 107 |

Outcomes and estimation

• Cohort 1: Taxane or Anthracycline-Based Chemotherapy

An overview of the results of the efficacy parameters analyzed in study AVF3694g, Cohort 1, is shown in table 8.

Table 8: Overview of Efficacy Results Cohort 1: T/Anth+Bv/PI (ITT Population)

| Efficacy Parameter | T/Anth + PI (N = 207) | T/Anth + Bv (N = 415) |
|---|-------------------------------|--------------------------|
| Primary Efficacy Parameter | | |
| PFS (Investigator-assessed, censored for non-protocol therapy) | | |
| Number of patients (%) with an event | 160 (77.3%) | 249 (60.0%) |
| Median / months [95% CI] | 8.0 [6.7;8.4] | 9.2 [8.6;10.1] |
| Stratified analysis, censored for non-protocol therapy | | |
| Hazard ratio [95% CI] ^a , p-value (log-rank) | 0.64 [0.52;0.80], p < 0.0001 | |
| Unstratified analysis, censored for non-protocol therapy | | |
| Hazard ratio [95% CI] ^a , p-value (log-rank) | 0.66 [0.54;0.81], p < 0.0001 | |
| Key sensitivity analysis: | | |
| Stratified, not censored for non-protocol therapy | | |
| Number of patients (%) with an event | 178 (86.0%) | 288 (69.4%) |
| Median / months [95% CI] | 8.2 [6.9;8.5] | 9.3 [8.6;10.3] |
| Hazard ratio [95% CI] ^a , p-value (log-rank) | 0.66 [0.54;0.80], p < 0.0001 | |
| Secondary Efficacy Parameters | | |
| Number of patients with measurable disease | 177 | 345 |
| Objective response: No of patients (%) ^b | 67 (37.9%) | 177 (51.3%) |
| p-value (stratified analysis) | 0.0054 | |
| Between-arm difference / % [95% CI] | 13.5% [4.6%;22.3%] | |
| Complete response: No of patients (%) | 5 (2.8%) | 7 (2.0%) |
| Partial response: No of patients (%) | 62 (35.0%) | 170 (49.3%) |
| Duration of objective response | | |
| Median / months [95% CI] | 7.1 [6.2;8.8] | 8.3 [7.2;10.7] |
| Number of patients (%) who died (original analysis) ^c | | |
| Overall survival (stratified analysis) | 73 (35.3%) | 141 (34.0%) |
| Median / months [95% CI] | 23.8 [21.0; -] | 25.2 [23.3; -] |
| Hazard ratio [95% CI] ^a , p-value (log-rank) | 1.03 [0.77;1.38], p = 0.83 | |
| Number of patients (%) who died (updated analysis) ^c | | |
| Overall survival (stratified analysis) | 89 (43.0%) | 189 (45.5%) |
| Median / months [95% CI] | - [23.6; -] | 27.5 [25.6;31.4] |
| Hazard ratio [95% CI] ^a , p-value (log-rank) | 1.11 [0.86;1.43], p = 0.44 | |
| One-year survival rate (original analysis) | | |
| Survival rate / % | 83.2% | 80.7% |
| Difference in 1-year survival rate [95% CI] ^d , p-value (log-rank) | -2.6% [-9.0%;3.9%], p = 0.435 | |
| PFS (IRC assessed - stratified analysis) | | |
| Number of patients (%) with an event | 106 (51.2%) | 198 (47.7%) |
| Median / months [95% CI] | 8.3 [8.0;9.9] | 10.7 [9.9;12.1] |
| Hazard ratio [95% CI] ^a , p-value (log-rank) | 0.77 [0.60;0.99], p = 0.040 | |

^a Relative to placebo; ^b Complete or partial response; ^c Clinical data cut-off original analysis: July 31, 2008; updated analysis: February 23, 2009; ^d T/Anth+Bv – T/Anth+PI.

Table 9: Overview of efficacy results in the Anthracycline-Based Chemotherapy Subgroup (ITT Population)

| Efficacy Parameter | Anth + PI (N = 103) | Anth + Bv (N = 212) |
|--|--------------------------------|--------------------------------|
| Progression-free survival (Investigator assessed) | | |
| Number of patients with an event | 81 (78.6%) | 124 (58.5%) |
| Median - months | 7.9 | 9.2 |
| Stratified analysis | | |
| Hazard ratio (95% CI) ^a | 0.55 (0.40; 0.74) | |
| p-value (log-rank) | <0.0001 | |
| Unstratified | | |
| Hazard ratio (95% CI) ^a | 0.60 (0.45; 0.79) | |
| p-value (log-rank) | 0.0003 | |
| Number of patients with measurable disease | 92 | 184 |
| Objective response ^b | 37 (40.2%) | 96 (52.2%) |
| p-value (stratified analysis) | 0.0988 | |
| Between-arm difference (95% CI) | 12.0% (-0.4%; 24.3%) | |
| Complete response | 2 (2.2%) | 3 (1.6%) |
| Partial response | 35 (38.0%) | 95 (50.5%) |
| Duration of objective response | | |
| Median - months | 6.0 | 8.1 |
| 95% CI | (4.4; 8.4) | (6.9; 12.5) |
| Number of patients who died (updated analysis) | 44 (42.7%) | 88 (41.5%) |
| Overall survival (stratified analysis) | | |
| Median - months | - | 28.7 |
| Hazard ratio (95% CI) ^a | 0.97 (0.67; 1.41) | |
| p-value (log-rank) | 0.8903 | |
| One-year survival rate | | |
| Survival rate | 81.8% | 82.3% |
| Difference in one-year survival rate (95% CI) ^c | 0.5% (-8.8%; 9.7%) | |
| p-value | 0.923 | |
| Progression-free survival (IRC assessed - stratified analysis) | | |
| Number of patients with an event | 53 (51.5%) | 98 (46.2%) |
| Median - months | 8.6 | 10.9 |
| Hazard ratio (95% CI) ^a | 0.73 (0.51; 1.04) | |
| p-value (log-rank) | 0.0828 | |

Anth = anthracycline-based chemotherapy; Bv = bevacizumab; CI = confidence interval; IRC = Independent Review Committee; PI = placebo; T = taxane. ^a Relative to placebo; ^b Complete or partial response; ^c Anth + Bv - Anth + PI

- Cohort 2: Capecitabine therapy

An overview of the results of the efficacy parameters analyzed in study AVF3694g, Cohort 2, is shown in table 10.

Table 10: Overview of Efficacy Results Cohort 2: Cap + Bv/PI (ITT Population)

| Efficacy Parameter | Cap + PI (N = 206) | Cap + Bv (N = 409) |
|---|-------------------------------|-------------------------------|
| Primary Efficacy Parameter | | |
| Progression-free survival (Investigator assessed) | | |
| Number (%) of patients with an event | 162 (78.6%) | 291 (71.1%) |
| Median - months | 5.7 | 8.6 |
| Stratified analysis | | |
| Hazard ratio (95% CI) ^a | 0.69 (0.564; 0.840) | |
| p-value (log-rank) | 0.0002 | |
| Unstratified analysis | | |
| Hazard ratio (95% CI) ^a | 0.67 (0.554; 0.816) | |
| p-value (log-rank) | <0.0001 | |
| Secondary Efficacy Parameters | | |
| Number of patients with measurable disease | 161 | 325 |
| Objective response ^b | 38 (23.6%) | 115 (35.4%) |
| p-value (stratified analysis) | 0.0097 | |
| Between-arm difference (95% CI) | 11.8% (3.4%; 20.2%) | |
| Complete response | 1 (0.6%) | 7 (2.2%) |
| Partial response | 37 (23.0%) | 108 (33.2%) |
| Duration of objective response | | |
| Median - months (95% CI) | 7.2 (5.1; 9.3) | 9.2 (8.5; 10.4) |
| Number of patients who died (updated analysis) | 99 (48.1%) | 186 (45.4%) |
| Overall survival (stratified analysis) | | |
| Median - months | 22.8 | 25.7 |
| Hazard ratio (95% CI) ^a | 0.88 (0.69; 1.13) | |
| p-value (log-rank) | 0.33 | |
| One-year survival rate (updated analysis) | | |
| Survival rate | 74.8% | 81.0% |
| Difference in one-year survival rate (95% CI) ^c | 6.2% (-1.0%; 13.4%) | |
| p-value | 0.092 | |
| Progression-free survival (IRC assessed – stratified analysis) | | |
| Number (%) of patients with an event | 119 (57.8%) | 219 (53.5%) |
| Median -months | 6.2 | 9.8 |
| Hazard ratio (95% CI) ^a | 0.68 (0.54; 0.86) | |
| p-value (log-rank) | 0.0011 | |
| Key Sensitivity Analysis | | |
| Progression-free survival (Investigator assessed, not censored for NPT - stratified analysis) | | |
| Number (%) of patients with an event | 168 (81.6%) | 309 (75.6%) |
| Median -months) | 5.5 | 8.8 |
| Hazard ratio (95% CI) ^a | 0.66 (0.55; 0.81) | |
| p-value (log-rank) | < 0.0001 | |

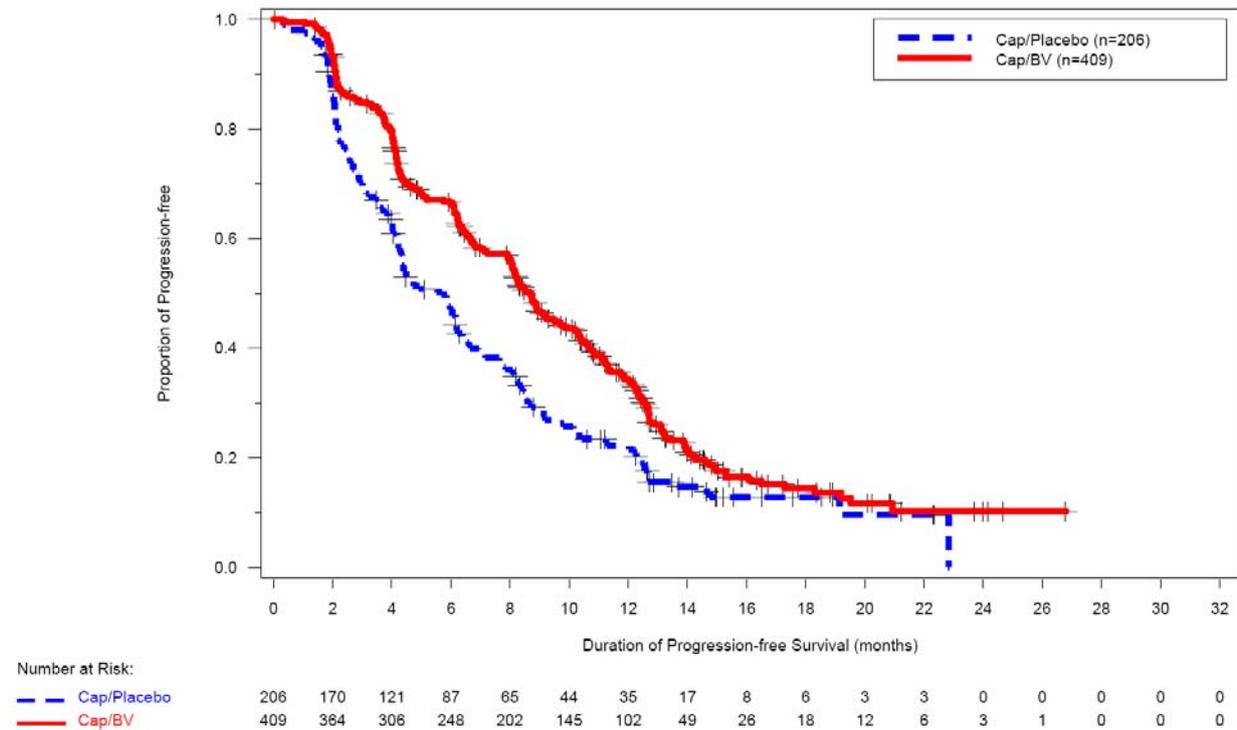
Bv = bevacizumab; Cap = capecitabine; CI = confidence interval; IRC = Independent Review Committee; NPT = non-protocol specified antineoplastic therapy; PI = placebo; Clinical data cut-off original analysis: July 31, 2008; updated analysis: February 23, 2009; ^a Relative to placebo

Primary Efficacy Endpoint

Progression Free Survival

The Kaplan Meier plot of PFS is presented in figure 2:

Figure 2: Kaplan Meier Plot of PFS (Investigator Assessed) Cohort 2: Cap + Bv/PI (ITT Population – Censored for NPT)



BV = bevacizumab, Cap = capecitabine

Sensitivity analyses for PFS

The results from the sensitivity analyses for PFS are presented in Table 11.

Table 11: Sensitivity Analyses of PFS (investigator assessed) Cohort 2: Cap + Bv/PI (ITT population)

| PFS Analysis | Median PFS – months | | Hazard Ratio (95% CI) ^a |
|---------------------------|---------------------|----------|------------------------------------|
| | Cap + PI | Cap + Bv | |
| Primary efficacy analysis | 5.7 | 8.6 | 0.69 (0.56, 0.84) |
| Early discontinuation | 4.2 | 6.4 | 0.77 (0.64, 0.92) |
| Without censoring NPT | 5.5 | 8.8 | 0.66 (0.55, 0.81) |
| Missing tumour assessment | 4.9 | 8.3 | 0.69 (0.57, 0.84) |
| PFS on treatment | 5.7 | 8.7 | 0.65 (0.53, 0.80) |
| Worst-case analysis | 5.7 | 8.3 | 0.75 (0.62, 0.92) |
| IRC-based analysis | 6.2 | 9.8 | 0.68 (0.52, 0.84) |
| IRC sensitivity analysis | 6.2 | 10.1 | 0.66 (0.52, 0.84) |

Bv = bevacizumab; Cap = capecitabine; CI = confidence interval; NPT = non-protocol specified antineoplastic therapy; PFS = progression-free survival; PI = placebo;^a Estimated from stratified Cox regression models; The stratification factors are the same as those for the analysis of the primary endpoint, PFS.

Secondary Efficacy endpoints

Objective Response Rate

The ORR was 35.4% in the Cap+Bv arm vs. 23.6% in the Cap+PI arm (stratified p = 0.0097, see table 12).

Table 12: ORR: Cohort 2 : Cap + Bv/PI - ITT Population With Measurable Disease at

Baseline)

| Parameter | Cap + PI (N = 206) | Cap + Bv (N =409) |
|----------------------------------|-----------------------|----------------------|
| Patients with measurable disease | 161 | 325 |
| Objective response a | 38 (23.6%) | 115 (35.4%) |
| 95% CI b | (17.6%; 30.7%) | (30.2%; 40.6%) |
| p-value (stratified analysis) | 0.0097 | |
| Between-arm difference | 11.8% | |
| 95% CI c | (3.4%; 20.2%) | |
| Best objective response d | | |
| Complete response | 1 (0.6%) | 7 (2.2%) |
| Partial response | 37 (23.0%) | 108 (33.2%) |

Bv = bevacizumab; Cap = capecitabine; CI = confidence interval; PI = placebo.

a Complete or partial response confirmed \square 28 days after initial documentation of response.

b Based on Blyth–Still–Casella method.

c Based on normal approximation to the binomial distribution.

d Best objective response was a complete response if a complete response was confirmed with another complete response. Otherwise, best objective response was a partial response.

Duration of Objective Response

The median duration of objective response was 9.2 months in the Cap+Bv arm (9.2 months) vs. 7.2 months in the Cap+PI arm (Table 13).

Table 13: Duration of Objective Response: Cohort 2: Cap + Bv/PI – (ITT Population With Measurable Disease at Baseline and an Objective Response)

| Parameter | Cap + PI (N = 206) | Cap + Bv (N =409) |
|--|-----------------------|----------------------|
| Patients with an objective response | 38 | 115 |
| No. (%) patients with an event ^a | 26 (68.4%) | 70 (60.9%) |
| Duration of objective response ^b - months | | |
| Median | 7.2 | 9.2 |
| 95% CI | (5.1; 9.3) | (8.5; 10.4) |

Bv = bevacizumab; Cap = capecitabine; CI = confidence interval; PI = placebo.

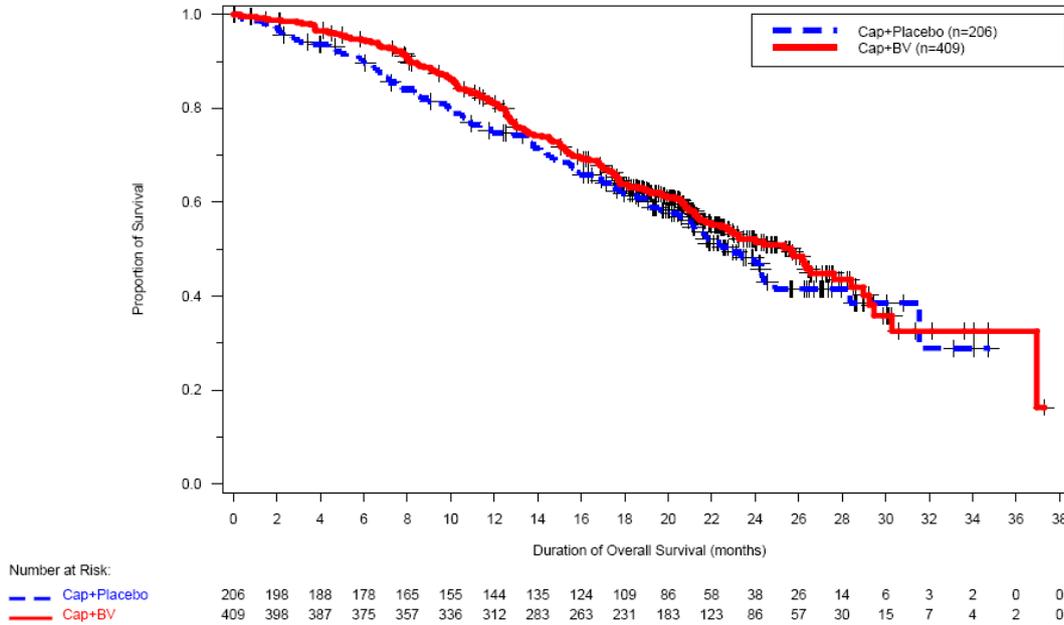
^a Disease progression or death.

^b Summary statistics are from Kaplan–Meier analysis; 95% CI was computed using the Brookmeyer–Crowley method.

Overall Survival:

The Kaplan Meier plot of OS is presented in figure 3:

Figure 3: Kaplan Meier Plot of OS (Investigator Assessed) Cohort 2 –Cap + Bv/PI (ITT Population – Updated Analysis)



Progression-free Survival (IRC-assessed)

Median PFS based on the IRC assessment was 9.8 months in the capecitabine+bevacizumab arm vs. 6.2 months the capecitabine+placebo arm (Table 14).

Table 14: PFS (IRC Assessed): Cohort 2: Cap + Bv/ PI (ITT Population)

| Parameter | Cap + PI (N = 206) | Cap + Bv (N = 409) |
|---|-----------------------|-----------------------|
| No. (%) patients with an event | 119 (57.8%) | 219 (53.5%) |
| Earliest contributing event | | |
| Disease progression | 106 (51.5%) | 191 (46.7%) |
| Death | 13 (6.3%) | 28 (6.8%) |
| Progression-free survival - months ^a | | |
| Median (95% CI) | 6.2 (4.7; 7.8) | 9.8 (8.4; 10.4) |
| Stratified analysis ^b | | |
| Hazard ratio - relative to placebo ^c | | 0.68 |
| (95% CI) | | (0.54; 0.86) |
| p-value (log-rank) | | 0.0011 |
| Unstratified analysis | | |
| Hazard ratio - relative to placebo | | 0.70 |
| (95% CI) | | (0.56; 0.87) |
| p-value (log-rank) | | 0.0016 |

Bv = bevacizumab; Cap = capecitabine; CI = confidence interval; PI = placebo.

^a Summary statistics are from Kaplan–Meier analysis; 95% CI was computed using the Brookmeyer–Crowley method.

^b Stratification factors: disease-free interval (≤ 12 months, > 12 months), prior adjuvant chemotherapy (yes, no), and number of metastatic sites (< 3 , ≥ 3).

^c Estimated by Cox regression.

Supportive studies

Studies E2100, BO17708 and AVF2119G are supportive studies. Studies E2100 and BO17708 (Avado study) formed the basis for the approval of bevacizumab in mBC in combination with paclitaxel (EMA/582/II/08) and docetaxel (EMA/582/II/24), respectively. In the 3rd RSI, the MAH was specifically asked by the CHMP to present supportive data on the bevacizumab-capecitabine combination based on study AVF3693g (Ribbon-2).

Final analysis of OS in BO17708 has been submitted as part of the responses to the 2nd RfSI. However, the assessment of these data was deferred to the Article 20 procedure that was initiated on 23 September 2010.

- **AVF2119G**

This was a randomised, open-label Phase III trial designed to compare the efficacy and safety of capecitabine with or without bevacizumab, in women with mainly refractory/resistant mBC (previously exposed to anthracyclines and taxanes or with relapses < 12 months after adjuvant therapy).

Patients were randomly assigned to receive capecitabine (2,500 mg/m²/d) twice daily on day 1 through 14 every 3 weeks, alone or in combination with bevacizumab (15 mg/kg) on day 1.

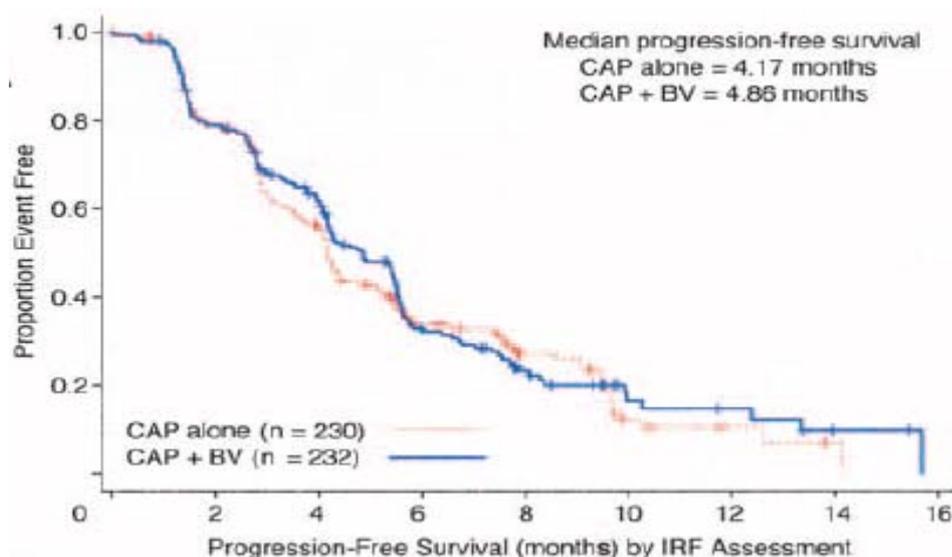
The primary end point was PFS, as determined by an independent review facility (IRF). From November 2000 to March 2002, 462 patients were enrolled (230 patients in the capecitabine arm and 232 in the capecitabine + bevacizumab arm).

Results in Study AVF2119G

The combination of capecitabine+bevacizumab did not increase PFS as determined by the IRF. The median PFS was 4.86 months for the capecitabine+bevacizumab arm v.s. 4.17 for the bevacizumab arm (HR=0.98 [95% CI, 0.77 to 1.25]; P =0.857).

The Kaplan-Meier curve for PFS is shown in figure 4.

Figure 4: Kaplan-Meier Curve of Progression-Free Survival: AVF2119G study



The response rates results were 19.8% [95% CI, 14.7 to 25.0] for the capecitabine/bevacizumab arm v.s. 9.1% [95% CI, 5.4 to 12.9] for the bevacizumab arm (p = 0.001) as determined by the IRF review.

In Study AVF2119g, QoL data was collected using the Functional Assessment of Cancer Therapy-Breast (FACT-B) instrument, which consists of 36 items from 5 subscales (physical well-being, functional well-being, emotional well-being, social well-being, breast cancer subscale). FACT-B was administered to patients every 6 weeks for the first 24 weeks then every 9 weeks thereafter. The Trial Outcome Index-Breast (TOI-B), which includes the physical well-being, functional well-being, and breast cancer subscales of the FACT-B instrument, was pre-specified as the primary measure of QoL. The primary analysis of QoL was based on the time to deterioration in QoL (TDQ). TDQ is defined as the time from randomization to the earliest time-point of clinically meaningful decline in QoL or disease progression/death.

No significant difference was observed between treatment arms in TDQ, based on the other six summary scores of the FACT-B instrument (FACT-B total, physical well-being, functional well-being, emotional well-being, social well-being, breast cancer subscale).

- ***AVF3693g (Ribbon-2)***

Study AVF3693g was a Phase III, multicenter, randomized, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of bevacizumab when combined with standard chemotherapy compared with chemotherapy plus placebo in patients with previously treated HER2-negative mBC. All patients in this study had received only one prior line of therapy for metastatic disease. The study was designed to demonstrate prolongation of PFS by addition of bevacizumab to any of four commonly used second-line mBC cytotoxic chemotherapy treatment options in recurrent/metastatic breast cancer, namely taxanes, gemcitabine, capecitabine, or vinorelbine. The dose and schedule of capecitabine used in this trial was the generally used starting dose of 1000 mg/m² orally twice daily on Days 1–14 of each 3 week cycle.

In Study AVF3693g, the choice of chemotherapy for an individual patient was determined at the discretion of the individual investigator prior to randomization. The primary efficacy endpoint of Study AVF3693g was PFS based on investigator assessments, pooled across chemotherapy cohorts. Although no chemotherapy subgroup was individually powered, a pre-specified secondary endpoint was PFS outcome by chemotherapy cohort.

Results in Study AVF3693g

The stratified HR for PFS for the chemotherapy + bevacizumab arm relative to the chemotherapy + placebo arm (pooled, ITT analysis) was 0.78 (p = 0.0072), representing a 22% risk reduction of disease progression or death with a delta at the median of 2.1 months (table 15).

Table 15: Overview of Efficacy Results: Pooled Chemotherapy Cohort - Study AVF3693g**(Randomized Patients)**

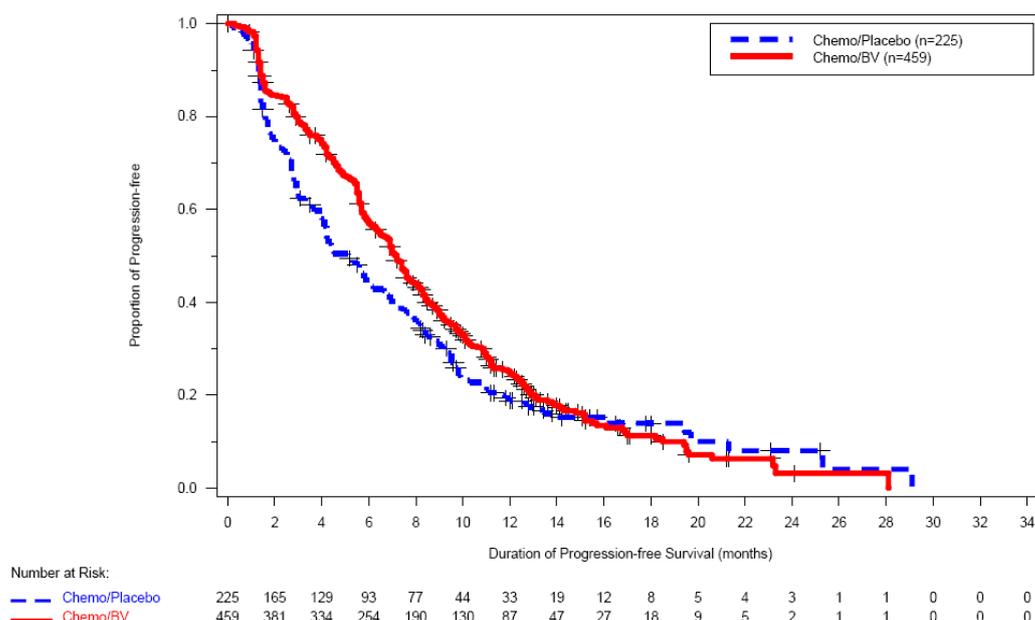
| Efficacy Parameter | Chemo + PI (N = 225) | Chemo + Bv (N = 459) |
|---|--------------------------------|-------------------------|
| Primary Efficacy Parameter | | |
| PFS (Investigator-assessed) | | |
| Number of patients (%) with an event | 184 (81.8%) | 372 (81.0%) |
| Median - months [95% CI] | 5.1 [4.1; 6.0] | 7.2 [6.5; 7.6] |
| Stratified analysis | | |
| Hazard ratio [95% CI] a, p-value (log-rank) | 0.78 [0.64; 0.93] p = 0.0072 | |
| Unstratified analysis | | |
| Hazard ratio [95% CI] a, p-value (log-rank) | 0.83 [0.69; 0.99] p = 0.0361 | |
| Secondary Efficacy Parameters | | |
| Objective response | | |
| Number of patients with measurable disease | 179 | 362 |
| No of patients (%) with objective response b | 53 (29.6%) | 143 (39.5%) |
| p-value (stratified analysis) | 0.0193 | |
| p-value (unstratified analysis) | 0.0287 | |
| Between-arm difference - % [95% CI] | 9.9% [1.5%; 18.3%] | |
| Complete response: No of patients (%) | 2 (1.1%) | 8 (2.2%) |
| Partial response: No of patients (%) | 51 (28.5%) | 135 (37.3%) |
| Overall survival (interim analysis) | | |
| Number (%) of patients who died | 109 (48.4%) | 206 (44.9%) |
| Median - months [95% CI] | 16.4 [14.6; 20.2] | 18.0 [17.1; 20.2] |
| Stratified analysis | | |
| Hazard ratio [95% CI] a, p-value (log-rank) | 0.90 [0.71; 1.14] p = 0.3741 | |
| Unstratified analysis | | |
| Hazard ratio [95% CI] a, p-value (log-rank) | 0.89 [0.71; 1.13] p = 0.3334 | |
| One-year survival rate (interim analysis) | | |
| Survival rate - % | 66.2% | 69.5% |
| Difference in 1-year survival rate [95% CI], p-value (log-rank) | 3.3% [-4.8%; 11.3%], p = 0.426 | |

a Relative to chemo + placebo.

b Complete or partial response.

The Kaplan-Meier plot for PFS is presented in figure 5.

Figure 5: Kaplan-Meier Curve of Progression-Free Survival: Pooled Chemotherapy Cohort - Study AVF3693g



Efficacy Results in the Capecitabine Cohort

One hundred and forty-four (21%) patients from Study AVF3693g received capecitabine. The results of this subgroup are presented in Table 16.

Table 16: Overview of Efficacy Results: Capecitabine-Cohort - Study AVF3693g (Randomized Patients)

| Efficacy Parameter | AVF3693g Capecitabine Cohort ^a | |
|---|---|----------------------|
| | Cap + PI (n = 47) | Cap + Bv (n = 97) |
| PFS | | |
| Patients with a PFS event, no. (%) | 39 (83.0%) | 87 (89.7%) |
| Earliest contributing event, no. (%) | | |
| Disease | 36 (76.6%) | 82 (84.5%) |
| Death | 3 (6.4%) | 5 (5.2%) |
| Median - months (95% CI) | 4.1 (2.8; 5.1) | 6.9 (5.5; 8.5) |
| Stratified analysis | | |
| HR (relative to control) (95% CI) | 0.73 (0.49; 1.48) | |
| p-value (log-rank) | 0.1271 | |
| Unstratified analysis | | |
| HR (relative to control) (95% CI) | 0.78 (0.53; 1.14) | |
| p-value (log-rank) | 0.2015 | |
| Objective response | | |
| Number of patients with measurable disease | 39 | 81 |
| No of patients (%) with objective response | 6 (15.4%) | 29 (35.8%) |
| p-value (stratified analysis) | 0.0225 | |
| p-value (unstratified analysis) | 0.0310 | |
| Between-arm difference - % [95% CI] | 20.4% (5.0%, 35.8%) | |
| Overall survival (interim analysis) | | |
| Number (%) of patients who died | 25 (53.2%) | 39 (40.2%) |
| Median - months (95% CI) | 16.2 (12.8, 30.4) | 20.9 (18.0, 24.2) |
| Stratified analysis | | |
| Hazard ratio [95% CI] ^a , p-value (log-rank) | 0.65 [0.39, 1.10] p = 0.1089 | |
| Unstratified analysis | | |
| Hazard ratio [95% CI] ^a , p-value (log-rank) | 0.63 [0.38, 1.05] p = 0.074 | |

Bv, bevacizumab; Cap, capecitabine; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Notes: Summaries of progression-free survival (medians) are estimated from Kaplan-Meier curves.

The 95% CI for median is computed using the method of Brookmeyer and Crowley.

The hazard ratio is estimated by Cox regression.

^aBased on investigator assessment.

The MAH performed analysis across the trials (pooled analysis and meta-analysis). The data is presented below:

- *Overview of Efficacy Across Studies – Bevacizumab in Combination with Capecitabine*

Table 17: Key Efficacy Results across Studies (AVF3694g, AVF2119g): Cap + Bv

| Parameter | AVF3694g | | AVF2119g | |
|---|-------------------------|-------------------|-------------------------|---------------------|
| | Cap + PI N=206 | Cap + Bv N=409 | Cap N = 230 | Cap + Bv N = 232 |
| PFS^a | | | | |
| Median / months [95% CI] | 5.7 [4.3;6.2] | 8.6 [8.1;9.5] | 4.17 [3.71;5.13] | 4.86 [4.17;5.52] |
| Stratified HR [95% CI] | 0.69 [0.56;0.84] | | 0.98 [0.77;1.25] | |
| Unstratified HR [95% CI] | 0.67 [0.55;0.82] | | 0.92 [0.73;1.17] | |
| Objective response^b | | | | |
| Number of patients | 161 | 325 | 230 | 232 |
| OR (n, %) | 38 (23.6%) | 115 (35.4%) | 21 (9.1%) | 46 (19.8%) |
| Duration of Response^b | | | | |
| Median / months [95% CI] | 7.2 [5.1;9.3] | 9.2 [8.5;10.4] | 7.56[6.24;12.68] | 4.96 [4.11;7.66] |
| OS^c | | | | |
| Median / months | 22.8 | 25.7 | 14.52 | 15.05 |
| Stratified HR [95% CI] | 0.88 [0.69;1.13] | | not available | |
| Unstratified HR [95% CI] | 0.88 [0.69;1.12] | | 1.08 [0.80;1.45] | |

AVF2119g: Cap = either 2500 mg/m² or 1875 mg/m² orally per day, split into two daily doses administered for 14 days of a 3-week cycle; Cap+Bv = Cap as above + Bv 15 mg/kg iv q3w. ^a primary analysis shown in bold; AVF3694g: investigator-assessed, censoring for NPT; AVF2119g: IRC-assessment (unless unavailable) ^b Patients with measurable disease at baseline; IRC assessments for AVF2119g ^b updated analysis for AVF3694g

- *Pooled Analysis of OS*

The OS results across the studies and the results from the pooled analysis are presented in table 18.

Table 18: OS Results across Studies (AVF3694g, BO17708, E2100) and Pooled Analysis (ITT Population)

| | AVF3694g: T/Anth | | AVF3694g: Cap | | BO17708 | | E2100 | | Pooled ^a | |
|---------------------------------------|----------------------|----------------------|---------------------|---------------------|-------------------|-----------------------|------------------|---------------------|---------------------|----------------|
| | T/Anth+PI N = 207 | T/Anth+Bv N = 415 | Cap + PI N = 206 | Cap + Bv N = 409 | PI+Doc N = 241 | Bv15 + Doc N = 247 | Pac N = 354 | Bv + Pac N = 368 | Non-Bv N = 1008 | Bv N = 1439 |
| Original Analysis ^b | | | | | | | | | | |
| Deaths / % | 35 | 34 | 35 | 30 | 21 | 15 | 67 | 66 | 43 | 38 |
| Median overall survival / months | 23.8 | 25.2 | 21.2 | 29 | - | - | 24.8 | 26.5 | 23.8 | 26.5 |
| Hazard ratio | 1.03 [0.77;1.38] | | 0.85 [0.63;1.14] | | 0.65 [0.42;1.02] | | 0.87 [0.72;1.05] | | 0.89 [0.78;1.01] | |
| | p = 0.83 | | p = 0.27 | | p = 0.057 | | p = 0.14 | | p = 0.074 | |
| Updated Analysis ^b | | | | | | | | | | |
| Deaths / % | 43 | 46 | 48 | 46 | 45 | 47 | | | 53 | 51 |
| Median overall survival / months | - | 27.5 | 22.8 | 25.7 | 31.9 | 30.2 | | | 26.4 | 26.7 |
| Hazard ratio | 1.11 [0.86;1.43] | | 0.88 [0.69;1.13] | | 1.00 [0.76;1.32] | | | | 0.97 [0.86;1.08] | |
| | p = 0.44 | | p = 0.33 | | p = 0.98 | | | | p = 0.56 | |
| One-year survival rate / % | 83.2 | 80.7 | 74.8 | 81.0 | 75.8 | 84.3 | | | 76.5 | 81.6 |
| | p = 0.44 | | p = 0.092 | | p = 0.020 | | | | p = 0.003 | |

^a The Kaplan-Meier method was used to estimate overall survival. The stratified log-rank test was used to assess the difference in overall survival between the bevacizumab-containing and non-bevacizumab-containing arms. Hazard ratios for pooled overall survival were obtained using a stratified Cox model. The stratification factor was each study (AVF3694g T/Anth, AVF3694g Cap, BO17708, E2100).

^b Overall survival data with the clinical data cut-off date of February 23, 2009, for AVF3694g, April 30, 2009, for BO17708, and October 21, 2006, for E2100 were used.

- *Biomarkers*

In reply to CHMP request, the MAH has performed an extensive review of the attempts to identify a valid biomarker predictive of benefit from VEGF-targeted therapy.

The introduction of a new assay to measure VEGF-A levels has produced highly interesting results compatible with relevant predictive value of VEGF-A and VEGFR2 as promising candidate markers with prognostic and predictive properties for bevacizumab. Further investigation of these markers and assay characterisation will be performed to further understand these data. The MAH has adequately described the steps taken in the development of the old and new ELISA assay, the availability of serum samples from all finalised and ongoing randomised studies for the reassessment VEGF-A levels at baseline and on treatment as well as the timelines for the submission of these data which at the earliest will be in Q1, 2011.

- Discussion on clinical efficacy

No new PK/PD or interaction studies have been submitted with the current application. This is acceptable as several former trials have investigated the interaction of bevacizumab with all the major groups of chemotherapies.

The protocol of AVF3694g (Ribbon-1) study specified three chemotherapy options, from which the investigator chose one prior to randomization of each individual patient. The selected chemotherapy regimens represent the current standard of care in the first-line treatment of locally recurrent/mBC in the EU.

The demographic data and disease characteristics were well balanced between treatment arms.

For the primary endpoint PFS (investigator-assessed) in the **taxane/anthracycline cohort**, HR was 0.64 [95% CI, 0.52 to 0.80]; $p < 0.0001$).

The CHMP concluded at an earlier stage of the procedure that the gain in terms of PFS in taxane/anthracycline + bevacizumab treated patients was overall considered of modest clinical significance. Furthermore, no adjustment for multiplicity was incorporated into the analysis of PFS based on IRC-reviewed data. Finally, no investigations of QoL had been included in the Ribbon-1 study submitted which was considered a shortcoming of the present application.

As a consequence to major objection raised by the CHMP, an indication including anthracycline or Abraxane (albumin-bound paclitaxel) was no longer requested.

The data from the **capecitabine cohort** of the AVF3694g study showed a statistically significant effect of bevacizumab on PFS (median PFS of 8.6 months in the capecitabine+bevacizumab arm versus 5.7 months in the capecitabine + placebo arm, respectively) with a stratified HR of 0.69 ([95% CI, 0.564 to 0.840]; $p = 0.0002$). The effect of adding bevacizumab to capecitabine on PFS over time is not supported by a sustained OS advantage.

No QoL data was collected in study AVF3694.

In study AVF2119g the addition of bevacizumab to capecitabine (as a 1st to 3rd line therapy following previous treatment with anthracycline and a taxane) resulted in a doubling of the ORR (19.8%) compared with patients treated with capecitabine alone (9.1%). However, the increased response rate was not associated with an improvement in PFS (HR=0.98 [95% CI, 0.77 to 1.25]) or in OS (HR=1.08 [95% CI, 0.80 to 1.45]). Study AVF2119g enrolled patients who were more heavily pretreated in a more advanced stage of the disease or patients with disease characteristics associated with a poor prognosis.

In the 3rd RSI, the MAH was specifically asked by the CHMP to present supportive data on the bevacizumab + capecitabine combination based on study AVF3693g (Ribbon-2). In the subgroup of 144 patients (21%) who received capecitabine in combination with either bevacizumab (n= 97) or placebo (n=47), the addition of bevacizumab to capecitabine lead to a median PFS of 6.9 months in the bevacizumab arm vs. 4.1 months in the placebo arm. However, no statistical significance was reached.

The SAG-O was consulted on the following question:

- The SAG-O should discuss the use, clinical relevance and benefit/risk balance of the bevacizumab + capecitabine combination as 1st line treatment in patients with mBC based on the results of cohort 2 of the AVF3694g (Ribbon-1) study and the supportive AVF2119g study (2nd line).

The SAG agreed that in principle the effect observed in terms of PFS for bevacizumab + capecitabine (median 5.7 and 8.6 months for placebo + capecitabine and bevacizumab + capecitabine, respectively)

based on the AVF3694g trial was modest but clinically relevant for the same reasons listed above, and that the benefit-risk balance was positive. However, the SAG had different views about the strength of evidence of efficacy of the bevacizumab + capecitabine combination due to inconsistencies with the results of study AVF2119g.

According to one view, the evidence of clinical efficacy is convincing in the population studied. It should be noted that selection criteria for the pivotal AVF3694g trial excluded patients with prior adjuvant or neoadjuvant chemotherapy within 12 months. This group of patients represents a population with better prognosis. Therefore, extrapolations to the general metastatic breast cancer population are difficult. In addition, this combination appears to be less active compared to a number of available options including taxanes and should therefore only be used in case of clear preference for decreased toxicity at the expense of decreased antitumor activity, or in case of failure to taxanes in the adjuvant setting. Prescribing information should give clear instructions about the risk of decreased efficacy with this combination. Concerning the apparently inconsistent results of supportive study AVF2119g, these were not considered of concern because the trial was conducted in a more advanced setting (second and third-line treatment).

Other SAG members questioned the consistency of the efficacy results of the bevacizumab + capecitabine combination. The effect on PFS associated with bevacizumab in combination with capecitabine was somewhere in between the effect associated with bevacizumab with paclitaxel and docetaxel and as such, the effect was convincing. However, the results of supportive study AVF2119g in second and third-line treatment strongly question the validity of this observation. Although in a different population (mainly refractory/resistant mBC previously exposed to anthracyclines and taxanes or with relapses < 12 months after adjuvant therapy), in this study the median PFS was 4.86 months for the capecitabine + bevacizumab arm v.s. 4.17 for the capecitabine arm (HR=0.98 [95% CI, 0.77 to 1.25]; P =0.857). According to this view, the conflicting results in terms of PFS in trials AVF3694g and AVF2119g have not been sufficiently explained. Rather, they may indicate that the efficacy has been overestimated in trial AVF3694g and that there is insufficient evidence of efficacy for bevacizumab + capecitabine combination. Further data to confirm the efficacy of this combination should be provided before a positive benefit-risk balance can be established in the light of the results observed in study AVF2119g. Confirmation of efficacy is particularly important since this combination already appears to be less active compared to a number of available options including taxanes.

A revised proposed wording for the requested indication has been presented by the MAH at the Oral Explanation as follows:

“Avastin in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom other chemotherapy options are not preferred. Patients who have received taxane and anthracycline-containing regimen in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine.

For further information as to the observed differential efficacy depending on the choice of chemotherapy regimen and as to HER2 status, please refer to section 5.1”.

3.2.3 Clinical safety

The safety data is based on the later clinical cut-off date of 23 February 2009 of study AVF3694g.

- Patient exposure

Overall, 817 patients were exposed to bevacizumab (15 mg/kg q3w). The mean number of bevacizumab doses per patient for all 3 types of chemotherapy regimens (during the blinded treatment phase) is presented in table 19.

Table 19: Exposure to Bv/PI (Safety Population)

| | T | | Anth | | Cap | |
|----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | PI (N = 102) | Bv (N = 203) | PI (N = 100) | Bv (N = 210) | PI (N = 201) | Bv (N = 404) |
| Doses received per patient | | | | | | |
| Mean (SD) | 10.7 (8.0) | 11.7 (9.0) | 10.5 (6.9) | 11.9 (7.9) | 9.6 (8.1) | 11.8 (8.6) |
| Median (range) | 9 (1–40) | 9 (1–49) | 9 (1–33) | 9 (1–38) | 6 (1–36) | 10 (1–44) |
| Overall dose intensity (%) | | | | | | |
| Mean (SD) | 96.8 (5.9) | 96.5 (6.3) | 95.9 (7.0) | 93.9 (7.8) | 97.0 (5.8) | 95.1 (7.8) |
| Median (range) | 100 (75–104) | 100 (60–102) | 100 (67–102) | 100 (67–100) | 100 (67–102) | 100 (55–102) |

Note: Dose intensity was defined as the actual amount of drug received divided by the amount of drug that would have been administered per the protocol-specified dose and schedule in the same time period.

A total of 543 patients were enrolled in the optional open-label post progression phase and received treatment with bevacizumab: 330 patients who had received chemotherapy + bevacizumab (T/Anth+Bv: 146; Cap+Bv: 184) and 213 patients who had received chemotherapy + placebo (T/Anth+PI: 93; Cap+PI: 120).

- Adverse events (AEs)

The types of AEs reported in study AVF3694g are summarised in table 20. The analyses of AEs include all events that occurred during the blinded treatment phase with a date of onset on or after the first dose of study drug or chemotherapy until 30 days after the last dose of study drug.

Table 20: Overview of Safety During the Blinded Treatment Phase (Safety Population)

| Parameter | T | | Anth | | Cap | |
|---|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| | PI (N = 102) | Bv (N = 203) | PI (N = 100) | Bv (N = 210) | PI (N = 201) | Bv (N = 404) |
| No. (%) patients with at least one: | | | | | | |
| Adverse event ^a | 42 (41.2%) | 128 (63.1%) | 21 (21.0%) | 82 (39.0%) | 54 (26.9%) | 162 (40.1%) |
| Grade 3–5 adverse event | 39 (38.2%) | 116 (57.1%) | 15 (15.0%) | 73 (34.8%) | 46 (22.9%) | 148 (36.6%) |
| Serious adverse event | 27 (26.5%) | 85 (41.9%) | 16 (16.0%) | 48 (22.9%) | 41 (20.4%) | 102 (25.2%) |
| Adverse event leading to bevacizumab or placebo discontinuation | 9 (8.8%) | 51 (25.1%) | 4 (4.0%) | 32 (15.2%) | 24 (11.9%) | 51 (12.6%) |
| Adverse event of special interest | 23 (22.5%) | 91 (44.8%) | 16 (16.0%) | 59 (28.1%) | 18 (9.0%) | 92 (22.8%) |
| All deaths (including disease progression) | 44 (43.1%) | 101 (49.8%) | 44 (44.0%) | 86 (41.0%) | 97 (48.3%) | 185 (45.8%) |
| Deaths unrelated to disease progression ^b | 3 (2.9%) | 5 (2.5%) | 3 (3.0%) | 2 (1.0%) | 5 (2.5%) | 6 (1.5%) |
| No. (%) patients with at least one ^c : | | | | | | |
| Arterial thromboembolic event | 0 (0.0%) | 1 (0.5%) | 1 (1.0%) | 3 (1.4%) | 3 (1.5%) | 8 (2.0%) |
| Bleeding | 0 (0.0%) | 11 (5.4%) | 0 (0.0%) | 2 (1.0%) | 1 (0.5%) | 1 (0.2%) |
| Febrile neutropenia | 2 (2.0%) | 17 (8.4%) | 5 (5.0%) | 8 (3.8%) | 0 (0.0%) | 0 (0.0%) |
| Fistula | 1 (1.0%) | 1 (0.5%) | 0 (0.0%) | 0 (0.0%) | 1 (0.5%) | 1 (0.2%) |
| Gastrointestinal perforation | 1 (1.0%) | 5 (2.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Hypertension | 2 (2.0%) | 19 (9.4%) | 0 (0.0%) | 22 (10.5%) | 2 (1.0%) | 43 (10.6%) |
| Left ventricular systolic dysfunction | 0 (0.0%) | 5 (2.5%) | 6 (6.0%) | 13 (6.2%) | 1 (0.5%) | 6 (1.5%) |

| Parameter | T | | Anth | | Cap | |
|-----------------------------|----------|-----------|----------|----------|----------|-----------|
| | | | | | | |
| Neutropenia | 5 (4.9%) | 19 (9.4%) | 4 (4.0%) | 9 (4.3%) | 2 (1.0%) | 5 (1.2%) |
| Proteinuria | 0 (0.0%) | 9 (4.4%) | 0 (0.0%) | 6 (2.9%) | 0 (0.0%) | 9 (2.2%) |
| RPLS | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Sensory neuropathy | 9 (8.8%) | 17 (8.4%) | 0 (0.0%) | 1 (0.5%) | 1 (0.5%) | 12 (3.0%) |
| Venous thromboembolic event | 5 (4.9%) | 4 (2.0%) | 1 (1.0%) | 6 (2.9%) | 7 (3.5%) | 20 (5.0%) |
| Wound dehiscence | 1 (1.0%) | 3 (1.5%) | 0 (0.0%) | 2 (1.0%) | 0 (0.0%) | 3 (0.7%) |

Anth = anthracycline-based chemotherapy; Bv = bevacizumab; Cap = capecitabine; PI = placebo; RPLS = reversible posterior leukoencephalopathy syndrome; T = taxane.

^a Adverse events collected as per study protocol (adverse events of special interest, adverse events resulting in treatment discontinuation, serious adverse events,)

^b Deaths occurring within 30 days of the last dose of study drug due to a reason other than disease progression

^c Adverse events of special interest identified through clinical review

Adverse events reported during the blinded treatment phase which occurred with a $\geq 2\%$ difference in incidence between treatment arms in any chemotherapy class are summarised in table 21.

Table 21: Summary of AEs Reported During the Blinded Treatment Phase by Chemotherapy Class ($\geq 2\%$ Difference in Incidence between Treatment Arms in Any Chemotherapy Class) (Safety Population)

| MedDRA System Organ Class/ Preferred Term | T | | Anth | | Cap | |
|---|--------------------|-----------------|--------------------|--------------------|--------------------|-----------------|
| | PI (N = 102) | Bv (N = 203) | PI (N = 100) | Bv (N = 210) | PI (N = 201) | Bv (N = 404) |
| No. (%) patients with at least one adverse event ^a | 42 (41.2%) | 128 (63.1%) | 21 (21.0%) | 82 (39.0%) | 54 (26.9%) | 162 (40.1%) |
| Blood and lymphatic system disorders | | | | | | |
| Neutropenia | 5 (4.9%) | 18 (8.9%) | 2 (2.0%) | 9 (4.3%) | 2 (1.0%) | 5 (1.2%) |
| Febrile neutropenia | 2 (2.0%) | 17 (8.4%) | 5 (5.0%) | 8 (3.8%) | 0 (0.0%) | 0 (0.0%) |
| Cardiac disorders | | | | | | |
| Left ventricular dysfunction | 0 (0.0%) | 5 (2.5%) | 5 (5.0%) | 12 (5.7%) | 1 (0.5%) | 4 (1.0%) |
| Gastrointestinal disorders | | | | | | |
| Diarrhoea | 0 (0.0%) | 6 (3.0%) | 0 (0.0%) | 3 (1.4%) | 2 (1.0%) | 7 (1.7%) |
| Gastrointestinal haemorrhage | 0 (0.0%) | 4 (2.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Gastrointestinal perforation | 0 (0.0%) | 5 (2.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Infections and infestations | | | | | | |
| Neutropenic sepsis | 0 (0.0%) | 1 (0.5%) | 2 (2.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Sepsis | 1 (1.0%) | 6 (3.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (0.7%) |
| Cellulitis | 0 (0.0%) | 5 (2.5%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) | 1 (0.2%) |
| Urinary tract infection | 2 (2.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Metabolism and nutrition disorders | | | | | | |
| Dehydration | 1 (1.0%) | 7 (3.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 7 (1.7%) |
| Nervous system disorders | | | | | | |
| Peripheral sensory neuropathy | 9 (8.8%) | 17 (8.4%) | 0 (0.0%) | 0 (0.0%) | 1 (0.5%) | 12 (3.0%) |
| Renal and urinary disorders | | | | | | |
| Proteinuria | 0 (0.0%) | 9 (4.4%) | 0 (0.0%) | 6 (2.9%) | 0 (0.0%) | 9 (2.2%) |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Epistaxis | 0 (0.0%) | 4 (2.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.2%) |
| Vascular disorders | | | | | | |
| Hypertension | 2 (2.0%) | 19 (9.4%) | 0 (0.0%) | 22 (10.5%) | 2 (1.0%) | 43 (10.6%) |

Anth = anthracycline-based chemotherapy; Bv = bevacizumab; Cap = capecitabine; MedDRA = Medical Dictionary for Regulatory Activities; PI = placebo; T = taxane.

^a Adverse events collected as per study protocol

- Adverse events of special interest

Arterial Thromboembolic Events

The incidences of ATEs were $\leq 2.0\%$ between treatment arms. One event in the Cap+PI arm led to the death of the patient.

Bleeding

Eleven patients (5.4%) in the T+Bv arm experienced 15 grade 3 or 4 bleeding events compared to none in the T+PI arm. Nine of the events were GI haemorrhages, 4 events were epistaxis, and there was one event each of post-procedural haemorrhage and haematoma. Bleeding events in the other two chemotherapy subgroups were uncommon (incidence $\leq 0.5\%$). The only grade 5 bleeding event (haemothorax) was reported in the Cap+PI arm.

Febrile Neutropenia

The incidence of febrile neutropenia observed in the T+Bv arm was 8.4% vs. 2.0% in the T+PI arm. Six of the 17 reported events in the T+Bv arm were grade 4, whereas both events in the T+PI arm were grade 3. The incidence of febrile neutropenia events was 3.8% in the Anth+Bv vs. 5.0% in the Anth+PI arm. There was one case of grade 5 febrile neutropenia in the Anth+PI arm. No febrile neutropenia events were reported in the capecitabine cohort.

Fistula

There were 4 reports of fistula during the trial, one in each of the taxane and capecitabine containing arms. The one case reported in the T+Bv arm was a grade 5 abdominal abscess. No fistula events were reported in the anthracycline-based chemotherapy subgroup.

Gastrointestinal (GI) Perforation

The incidence of GI perforations was 2.5% in the T+Bv arm vs. 1.0% in the T+PI arm (one of these events in the T+Bv arm was grade 4 and one grade 5). There were no GI perforation events in the anthracycline-based chemotherapy subgroup or in the capecitabine cohort.

Hypertension

The incidence of hypertension in the bevacizumab-containing arms compared with the placebo-containing arms across the three chemotherapy regimens was 1) taxane: 9.4% vs. 2.0%, 2) anthracycline: 10.5% vs. 0.0% and 3) capecitabine: 10.6% vs. 1.0%. Most AEs of hypertension were grade 3. In the Anth+Bv arm, the incidence of grade 3 or 4 hypertension was 16.2% in patients ≥ 65 years of age vs. 8.7% in those < 65 years of age.

Left Ventricular Systolic Dysfunction (LVSD)

Five patients (2.5%) experienced LVSD in the T+Bv arm (four grade 3 events and one grade 2) compared to none in the T+PI arm. According to the patient narratives, 4 of these 5 patients had received previous adjuvant therapy with an anthracycline of the clinical study report.

For patients who were treated with anthracycline-based chemotherapy, the cardiac adverse event rate was 6.2% in the Anth+Bv arm vs. 6.0% in the Anth+PI arm. For patients who received anthracyclines concomitantly with bevacizumab, the incidence of grade 3 or higher Congestive Heart Failure (CHF) was 6 of 210 patients (2.9%) in the Anth+Bv arm vs. none of 100 patients in the Anth+PI arm.

The incidence of LVSD was 1.5% in the Cap+Bv arm compared and 0.5% in the Cap+PI arm. Two grade 5 cardiac AEs (cardiogenic shock, cardiac failure/cardiorespiratory arrest) were reported in the Cap+Bv arm.

Neutropenia

The incidence of neutropenia in the bevacizumab-containing arms compared with the placebo-containing arms across the three chemotherapy regimens was 1) taxane: 9.4% vs. 4.9%, 2) anthracycline: 4.3% vs. 4.0% and 3) capecitabine: 1.2% vs. 1.0%. One grade 5 neutropenia event was reported in the Anth+PI arm.

Proteinuria

A higher incidence of proteinuria, especially grade 3 proteinuria, was observed in the bevacizumab-containing arms compared with the placebo-containing arms across the 3 classes of chemotherapy (T+Bv: 4.4%; Anth+Bv: 2.9%; Cap+Bv: 2.2%) compared to patients receiving placebo (0.0%).

Overall, a higher percentage of Abraxane-treated patients experienced proteinuria than docetaxel-treated patients. An increase in the incidence of proteinuria was observed in the bevacizumab-containing arm compared with the placebo-containing arm for both subgroups (Abraxane: 7.5% vs. 0.0%; docetaxel: 2.4% vs. 0.0%).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

One patient in the T+Bv arm (0.5%) had a grade 3 RPLS event. No RPLS events were reported in either the anthracycline-based chemotherapy subgroup or the capecitabine cohort.

Sensory Neuropathy

More patients in the taxane subgroup had sensory neuropathy reported than in the anthracycline subgroup, although the incidence and grade of sensory neuropathy were similar across treatment arms with each subgroup (Taxane 8%-9%: anthracycline 0%-0.5%). Most cases in the taxane subgroup were grade 3. There was a higher incidence of grade ≥ 3 sensory neuropathy events in the Cap+Bv arm relative to the Cap+PI arm (3.0% vs. 0.5%).

Venous Thromboembolic Events (VTE)

The incidence of VTE events in the bevacizumab-containing arms compared with the placebo-containing arms across the three chemotherapy regimens was 1) taxane : 4.9% vs. 2.0%, 2) anthracycline: 2.9% vs. 1.0% and 3) capecitabine 5.0% vs. 3.5% (most of the increase was in grade 3 events). Four grade 5 VTE events (all cases of pulmonary embolism) occurred in placebo treated patients; one each in the T+PI and Anth+PI arm, and two in the Cap+PI arm.

Wound Dehiscence

The incidence of wound dehiscence between the bevacizumab-containing and placebo-containing arms across the three chemotherapy regimens was: 1) taxane: 1.5% vs. 1.0%, 2) anthracycline: 1.0% vs. 0.0% and 3) capecitabine: 0.7% vs. 0.0%). Most of the events were grade 3.

- Serious adverse events and deaths

Serious adverse events (SAEs)

Serious adverse events reported during the blinded treatment phase which occurred with a $\geq 2\%$ difference in incidence between treatment arms in any chemotherapy class are summarized in table 22.

Table 22: SAEs Reported During the Blinded Treatment Phase ($\geq 2\%$ Difference in Incidence Between Treatment Arms in Any Chemotherapy Class): Safety Population

| MedDRA System Organ Class/ Preferred Term | T | | Anth | | Cap | |
|--|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | PI (N = 102) | Bv (N = 203) | PI (N = 100) | Bv (N = 210) | PI (N = 201) | Bv (N = 404) |
| No. (%) patients with at least one serious adverse event | 27 (26.5%) | 85 (41.9%) | 16 (16.0%) | 48 (22.9%) | 41 (20.4%) | 102 (25.2%) |
| Blood and lymphatic system disorders | | | | | | |
| Febrile neutropenia | 2 (2.0%) | 15 (7.4%) | 5 (5.0%) | 7 (3.3%) | 0 (0.0%) | 0 (0.0%) |
| Gastrointestinal disorders | | | | | | |
| Diarrhoea | 0 (0.0%) | 6 (3.0%) | 0 (0.0%) | 2 (1.0%) | 2 (1.0%) | 5 (1.2%) |
| Gastrointestinal perforation | 0 (0.0%) | 4 (2.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Infections and infestations | | | | | | |
| Sepsis | 1 (1.0%) | 6 (3.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 3 (0.7%) |
| Cellulitis | 0 (0.0%) | 5 (2.5%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) | 1 (0.2%) |
| Neutropenic sepsis | 0 (0.0%) | 1 (0.5%) | 2 (2.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Urinary tract infection | 2 (2.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Metabolism and nutrition disorders | | | | | | |
| Dehydration | 1 (1.0%) | 6 (3.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 5 (1.2%) |

Anth = anthracycline-based chemotherapy; Bv = bevacizumab; Cap = capecitabine; MedDRA = Medical Dictionary for Regulatory Activities; PI = placebo; T = taxane.

As expected, the incidence of reported SAEs was higher in the bevacizumab-containing arms compared to the placebo-containing arms: 1) taxane subgroup: 41.9% vs. 26.5%, 2) anthracycline-based subgroup: 22.9% vs. 16.0% and 3) capecitabine cohort: 25.2% vs. 20.4%. The only individual SAE occurring at a $>5\%$ higher incidence in patients treated with bevacizumab was febrile neutropenia (7.4% in the T+Bv arm and 2.0% in the placebo arm). SAEs with a $\geq 2\%$ but $<5\%$ higher incidence in T+Bv patients compared to T+PI were diarrhoea (3.0% vs. 0%), sepsis (3.0% vs. 1.0%), dehydration (3.0% vs. 1.0%), GI perforation (2.0% vs. 0%), and cellulitis (2.5% vs. 0%). In patients receiving anthracycline-based chemotherapy, febrile neutropenia was the only SAE which occurred with a $\geq 2\%$ incidence in Anth+Bv (3.3%) and Anth+PI patients (5.0%). In the capecitabine cohort, there were no SAEs with a $\geq 2\%$ higher incidence in patients receiving bevacizumab or placebo.

Deaths

Table 23 provides an overview of the incidence of deaths and the cause of death according to the trial treatment received.

Table 23: Overview Deaths and Cause of Death: Safety Population

| Cause of death | T | | Anth | | Cap | |
|-------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | PI (N = 102) | Bv (N = 203) | PI (N = 100) | Bv (N = 210) | PI (N = 201) | Bv (N = 404) |
| Total No. (%) of deaths | 44 (43.1%) | 101 (49.8%) | 44 (44.0%) | 86 (41.0%) | 97 (48.3%) | 185 (45.8%) |
| Disease progression | 38 (37.3%) | 90 (44.3%) | 40 (40.0%) | 82 (39.0%) | 89 (44.3%) | 166 (41.1%) |
| Other | 6 (5.9%) | 11 (5.4%) | 4 (4.0%) | 4 (1.9%) | 8 (4.0%) | 19 (4.7%) |

Anth = anthracycline-based chemotherapy; Bv = bevacizumab; Cap = capecitabine; PI = placebo; T = taxane

The most common cause of death in all treatments arms was disease progression which accounted for 91% of all deaths. Approximately 10% of deaths occurred within 30 days of the last dose of blinded study drug. Of these deaths, 60% were due to investigator-reported disease progression; the

remaining deaths were due to an adverse event. None of the deaths from causes other than disease progression were attributed to study drug by the investigators.

Deaths in Patients Receiving Capecitabine Therapy

Grade 5 Adverse Events

The overall incidence of adverse events during the blinded treatment phase that resulted in death is presented in table 24.

Table 24: Grade 5 Adverse Events Reported During the Blinded Treatment Phase in Patients Receiving Capecitabine Therapy (Safety Population)

| MedDRA Preferred Term | Cap + PI (N = 201) | Cap + Bv (N = 404) |
|---|-------------------------------|-------------------------------|
| No. (%) patients with Grade 5 adverse events ^a | 7 (3.5%) | 10 (2.5%) |
| Cardiac arrest ^b | 0 (0.0%) | 2 (0.5%) |
| Pulmonary embolism | 2 (1.0%) | 0 (0.0%) |
| Bronchopulmonary aspergillosis | 0 (0.0%) | 1 (0.2%) |
| Cardiac failure ^c | 0 (0.0%) | 1 (0.2%) |
| Cardiogenic shock | 0 (0.0%) | 1 (0.2%) |
| Cardiorespiratory arrest ^c | 0 (0.0%) | 1 (0.2%) |
| Hypotension ^d | 0 (0.0%) | 1 (0.2%) |
| Mucosal inflammation | 0 (0.0%) | 1 (0.2%) |
| Myocardial infarction ^b | 0 (0.0%) | 1 (0.2%) |
| Respiratory failure | 0 (0.0%) | 1 (0.2%) |
| Restrictive cardiomyopathy | 0 (0.0%) | 1 (0.2%) |
| Sepsis ^d | 0 (0.0%) | 1 (0.2%) |
| Sudden death | 0 (0.0%) | 1 (0.2%) |
| Cerebral ischemia | 1 (0.5%) | 0 (0.0%) |
| Decubitus ulcer | 1 (0.5%) | 0 (0.0%) |
| Gastrointestinal toxicity | 1 (0.5%) | 0 (0.0%) |
| Hemothorax | 1 (0.5%) | 0 (0.0%) |
| Pleural effusion | 1 (0.5%) | 0 (0.0%) |

Bv = bevacizumab; Cap = capecitabine; MedDRA = Medical Dictionary for Regulatory Activities; PI = placebo.

^a Some patients experienced more than 1 Grade 5 adverse event.

^b One patient had a Grade 5 myocardial infarction on the Selected AE CRF and a Grade 5 cardiac adverse event on the SAE CRF.

^c One patient had Grade 5 cardiorespiratory arrest on the Selected AE CRF and Grade 5 cardiac failure on the SAE CRF. Clinical review deemed these two adverse events to be the same event.

^d One patient had Grade 5 hypotension on the Selected AE CRF and Grade 5 sepsis on the SAE CRF. Clinical review deemed these two adverse events to be the same event.

- Laboratory findings and vital signs

Laboratory tests for safety were not performed in study AVF3694g with the exception of screening laboratory values and urine protein/creatinine ratio.

For patients who were treated with anthracycline-based chemotherapy, the mean left ventricular ejection fraction (LVEF) decreased slightly. The decline in LVEF in the two treatment arms was: 1) Anth+Bv arm baseline vs. highest postbaseline value: 65.7% vs. 59.6% and 2) Anth+PI arm baseline vs. highest postbaseline value: 64.7% vs. 60.8%. There were no other notable findings in the analyses of vital signs.

- Safety in special populations

Adverse events by age group

In general, elderly patients (≥ 65 years old) experienced a higher incidence of Grade ≥ 3 adverse events compared with younger patients, regardless of treatment arm. Consistent with what was reported in the overall study population, the incidence of adverse events in the bevacizumab-containing arm was higher than that in the placebo-containing arm for each subgroup across chemotherapy classes.

Adverse Events by Age Group in Patients Receiving Capecitabine Therapy

Adverse events with a $\geq 2\%$ difference in incidence between treatment arms and more than one occurrence in each subgroup are summarised for patients treated with capecitabine therapy in table 25.

Of the 605 patients who received capecitabine therapy, 150 (24.8%) were ≥ 65 years old. Hypertension was the only adverse event with a $>5\%$ incidence in either subgroup. Adverse events with a $\geq 2\%$ but $<5\%$ difference in incidence between treatment arms and more than one occurrence per subgroup, but not meeting these criteria in the overall population were diarrhoea, mucosal inflammation, pain, asthenia, sepsis, hip fracture, dehydration, mental status change, pleural effusion, pulmonary embolism and palmar-plantar erythrodysesthesia syndrome.

Table 25: AEs by Age Group in Patients Receiving Capecitabine ($\geq 2\%$ Difference in Incidence Between Treatment Arms and More Than One Occurrence in Any Subgroup):

Safety Population

| MedDRA System Organ Class/ Preferred Term | Age <65 years | | Age ≥ 65 years | |
|--|--------------------------------------|-------------------------------|---------------------------------------|------------------------------|
| | Cap + Pl (N = 148) | Cap + Bv (N = 307) | Cap + Pl (N = 53) | Cap + Bv (N = 97) |
| No. (%) patients with at least one adverse event | 38 (25.7%) | 111 (36.2%) | 16 (30.2%) | 51 (52.6%) |
| Gastrointestinal disorders | | | | |
| Diarrhoea | 2 (1.4%) | 3 (1.0%) | 0 (0.0%) | 4 (4.1%) |
| General disorders and administration site conditions | | | | |
| Mucosal inflammation | 0 (0.0%) | 1 (0.3%) | 1 (1.9%) | 4 (4.1%) |
| Asthenia | 0 (0.0%) | 0 (0.0%) | 2 (3.8%) | 0 (0.0%) |
| Infections and infestations | | | | |
| Sepsis | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) | 2 (2.1%) |
| Injury, poisoning and procedural complications | | | | |
| Hip fracture | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) | 2 (2.1%) |
| Metabolism and nutritional disorders | | | | |
| Dehydration | 0 (0.0%) | 6 (2.0%) | 0 (0.0%) | 1 (1.0%) |
| Nervous system disorders | | | | |
| Peripheral sensory neuropathy | 0 (0.0%) | 9 (2.9%) | 1 (1.9%) | 3 (3.1%) |
| Psychiatric disorders | | | | |
| Mental status changes | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) | 2 (2.1%) |
| Renal and urinary disorders | | | | |
| Proteinuria | 0 (0.0%) | 7 (2.3%) | 0 (0.0%) | 2 (2.1%) |
| Respiratory, thoracic, and mediastinal disorders | | | | |
| Pleural effusion | 3 (2.0%) | 3 (1.0%) | 2 (3.8%) | 0 (0.0%) |
| Pulmonary embolism | 4 (2.7%) | 4 (2.0%) | 0 (0.0%) | 1 (1.0%) |
| Skin and subcutaneous tissue disorders | | | | |
| Palmar-plantar erythrodysesthesia syndrome | 4 (2.7%) | 4 (1.3%) | 0 (0.0%) | 3 (3.1%) |
| Vascular disorders | | | | |
| Hypertension | 0 (0.0%) | 30 (9.8%) | 2 (3.8%) | 13 (13.4%) |

Bv = bevacizumab; Cap = capecitabine; MedDRA = Medical Dictionary for Regulatory Activities; Pl = placebo.

- Discontinuation due to AES

Table 26: AE leading to bevacizumab/placebo discontinuation reported during the blinded treatment phase ($\geq 2\%$ difference in incidence between treatment arms in any chemotherapy class): Safety population

| MedDRA System Organ Class/Preferred Term | T | | Anth | | Cap | |
|---|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | PI (N = 102) | Bv (N = 203) | PI (N = 100) | Bv (N = 210) | PI (N = 201) | Bv (N = 404) |
| No. (%) patients with at least one adverse event leading to Bv/PI discontinuation | 9 (8.8%) | 51 (25.1%) | 4 (4.0%) | 32 (15.2%) | 24 (11.9%) | 51 (12.6%) |
| Gastrointestinal disorders | | | | | | |
| Gastrointestinal perforation | 0 (0.0%) | 5 (2.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Renal and urinary disorders | | | | | | |
| Proteinuria | 0 (0.0%) | 4 (2.0%) | 0 (0.0%) | 2 (1.0%) | 0 (0.0%) | 2 (0.5%) |
| Vascular disorders | | | | | | |
| Hypertension | 0 (0.0%) | 5 (2.5%) | 0 (0.0%) | 6 (2.9%) | 0 (0.0%) | 3 (0.7%) |
| Deep vein thrombosis | 2 (2.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) | 3 (0.7%) |

Anth = anthracycline-based chemotherapy; Bv = bevacizumab; Cap = capecitabine; MedDRA = Medical Dictionary for Regulatory Activities; PI = placebo; T = taxane.

- Post marketing experience

No data was submitted.

- Discussion on clinical safety

The overall incidence of adverse events was higher in Bv-treated arms than in the placebo-containing arms across all 3 chemotherapy regimens.

In Cap-treated patients, hypertension was the only AE with $\geq 5\%$ increase in incidence in the Cap + Bv arm versus the Cap + PI arm. Adverse events with a $\geq 2\%$ but $< 5\%$ difference in incidence between treatment arms were peripheral sensory neuropathy, and proteinuria.

Among patients with AEs, patients with Grade 3-5 events were quite frequent, particularly in the T+Bv arm (57.1%).

The addition of Bv to the 3 different chemotherapy backbones resulted in a higher incidence of SAEs compared to the PI-containing arms: T: 41.9% (Bv) vs. 26.5% (PI), Anth: 22.9% (Bv) vs. 16.0% (PI), Cap: 25.2% (Bv) vs. 20.4% (PI).

A higher incidence of hypertension was observed in all the bevacizumab-containing arms compared to the placebo-containing arms across the 3 chemotherapy regimens (T: 9.4% vs. 2.0%; Anth: 10.5% vs. 0.0%; Cap: 10.6% vs. 1.0%). Most adverse events of hypertension were grade 3. Likewise, a higher incidence of proteinuria, especially grade 3 proteinuria, was observed in the bevacizumab-containing arms compared with the placebo-containing arms across the 3 classes of chemotherapy (T+Bv: 4.4% (highest in Abraxane-treated patients); Anth+Bv: 2.9%; Cap+Bv: 2.2%) compared to patients receiving placebo (0.0%). For patients who were treated with anthracycline-based chemotherapy, the cardiac adverse event rate was similar across treatment arms (Anth+Bv: 6.2% vs.; Anth+PI: 6.0%). However, more patients had a higher grade of LVSD in the Anth+Bv arm compared with the Anth+PI arm. In addition, an independent and blinded cardiologist has re-evaluated these events and concluded that only 2 patients had true evidence of severe treatment-related CHF.

A higher proportion of T/Bv and T/Anth-treated patients discontinued study treatment due to AEs compared to their respective PI-containing arms : T : 25.1% (Bv) vs. 8.8% (PI), Anth : 15.2% (Bv) vs. 4.0% (PI), Cap : 12.6% (Bev) vs. 11.9% (PI). The most common events leading to discontinuations were GI perforations, proteinuria and hypertension.

The most common AEs related to the treatment of bevacizumab are hypertension and proteinuria. Much attention is being put on severe, bevacizumab-associated events like high grade bleeding, arterial thromboembolic events, GI perforation and wound-healing complications. These events occur at low incidence. Overall, the safety profile of bevacizumab in mBC seems consistent with our previous experience in other indications. Finally, no difference in toxicity-related mortality has been observed between treatment arms.

Pharmacovigilance

Risk Management Plan

The MAH has provided an updated Risk Management Plan with the application for the extended indication for Avastin.

Table 27: Summary of the EU RMP

| <i>Safety Concern</i> | <i>Proposed PhV activities</i> | <i>Proposed risk minimization activities</i> |
|-----------------------------------|--|--|
| Important identified risks | | |
| Haemorrhage | <ul style="list-style-type: none"> - prospective data collection on the use of aspirin and other anti-platelet prophylactic antiaggregation therapy - evaluation of the effect of anticoagulation in several studies - yearly update report as requested by the CHMP - guided questionnaires - AVF3729g: retrospective case analysis of E4599 and BO17704 - AVASQ / BRIDGE: evaluation in patients with squamous NSCLC - In the light of the findings of the drug safety report (DSR Nr 1030386) the contraindication of untreated brain metastases has been removed from Section 2.3 Contraindications of the CDS. Information has been updated under Sections 2.4 Warnings and Precautions and 2.6 Undesirable Effects to reflect the removal of the contraindication. In particular, information relating to CNS bleeding has been added to these sections. A corresponding approval to remove this contraindication from the Avastin SPC was granted as per the Commission Decision of 25 March 2009 (Variation number: EMEA/H/C/582/II/025). | <p>Routine.</p> <p>EU SmPC section 4.4: Haemorrhage Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Avastin should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Avastin therapy. Patients with untreated CNS metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in case of intracranial bleeding. There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore,</p> |

| | | |
|---|--|--|
| | | <p>caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of grade 3 or above bleeding when treated with a full dose of warfarin and Avastin concomitantly.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| Pulmonary haemorrhage | <ul style="list-style-type: none"> - A Genentech-sponsored study (AVF3744g is examining the safety of patients with predominant squamous NSCLC in a defined patient population and with additional safety measures when treated with bevacizumab. - AVF3729g: retrospective case review of cases of pulmonary haemorrhage in studies E4599 and BO17704. - guided questionnaire. | <p>Routine.</p> <p>EU SmPC section 4.4: Pulmonary Haemorrhage/Haemoptysis Patients with non-small cell lung cancer treated with Avastin may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/ haemoptysis (> 2.5 ml of red blood) should not be treated with Avastin.</p> <p>Labelled in section 4.8 of the EU SmPC</p> |
| Arterial thromboembolic events (ATE) | <ul style="list-style-type: none"> - prospective data collection on the use of aspirin and other anti-platelets as well as history of arterial disease and risk factors for ATE - guided questionnaire | <p>Routine.</p> <p>EU SmPC section 4.4: In five randomised clinical trials, the incidence of arterial thromboembolic events including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone. Patients, receiving Avastin plus chemotherapy, with a history of arterial thromboembolism or age greater than 65 years have an increased risk of developing arterial thromboembolic events during therapy. Caution should be taken when treating these patients with Avastin. Therapy should be permanently discontinued in patients who develop arterial thromboembolic events.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| Hypertension | - prospective data collection for evaluation | Routine. |

| | | |
|--------------------|---|---|
| | of incidence and reversibility | <p>EU SmPC section 4.4: An increased incidence of hypertension was observed in Avastin-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre existing hypertension should be adequately controlled before starting Avastin treatment. There is no information on the effect of Avastin in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy. In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Avastin should be permanently discontinued, if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| Proteinuria | - prospective data collection for evaluation of incidence and reversibility | <p>Routine.</p> <p>EU SmPC section 4.4: Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that Grade 1 [US National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0] proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephritic syndrome).</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |

| | | |
|---|--|---|
| <p>Congestive heart failure</p> | <ul style="list-style-type: none"> - in defined studies <ul style="list-style-type: none"> - safety monitoring plan - sequential regular LVEF monitoring - cardiology expert advising DSMBs - cardiac advisory board - guided questionnaire | <p>Routine.</p> <p>EU SmPC section 4.4: Events consistent with CHF were reported in clinical trials. The symptoms ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF, such as pre-existing coronary heart disease or concomitant cardiotoxic therapy. Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure with Avastin.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| <p>Wound healing complications</p> | <ul style="list-style-type: none"> - prospective data collection to evaluate incidence and risk factors - evaluation of the safety of surgery in study MO18725 - monitoring by DSMB will be implemented in planned Roche-sponsored glioblastoma studies to assess safety on an ongoing basis. In addition, definition in the study protocols of in- and exclusion criteria (e.g. time between surgical procedures or traumatic injury and initiation of bevacizumab therapy), and not permitted concomitant treatment (e.g. craniotomy, intratumoral interstitial therapy, radiosurgery). | <p>Routine.</p> <p>EU SmPC section 4.4: Avastin may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| <p>Gastrointestinal perforations</p> | <ul style="list-style-type: none"> - AVF4095g in ovarian cancer patients - guided questionnaire | <p>Routine.</p> <p>EU SmPC section 4.4: Patients may be at an increased risk for the development of gastrointestinal perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently</p> |

| | | |
|--|----------------------|---|
| | | <p>discontinued in patients who develop gastrointestinal perforation.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| <p>Reversible posterior leukoencephalopathy syndrome (RPLS)</p> | <p>- routine PhV</p> | <p>Routine.</p> <p>EU SmPC section 4.4: There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing RPLS is not known.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| <p>Neutropenia</p> | <p>- routine PhV</p> | <p>Routine.</p> <p>EU SmPC section 4.4: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| <p>Venous thromboembolic events (VTE)</p> | <p>- routine PhV</p> | <p>Routine.</p> <p>EU SmPC section 4.4: Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under Avastin treatment. Avastin should be discontinued in patients with life-threatening (Grade 4) pulmonary embolism,</p> |

| | | |
|--|--|--|
| | | <p>patients with \leqGrade 3 need to be closely monitored.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| Fistula | - data collection in BO17920 | <p>Routine.</p> <p>EU SmPC section 4.4: Patients may be at increased risk for the development of fistulae when treated with Avastin. Permanently discontinue Avastin in patients with TE (tracheoesophageal) fistula or any grade 4 fistula. Limited information is available on the continued use of Avastin in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of Avastin should be considered.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| Thrombotic microangiopathy | - routine PhV | <p>Routine.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| Pulmonary hypertension | - routine PhV | <p>Routine.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| Important potential risks | | |
| Embryo-foetal development disturbance | - routine PV | <p>Routine.</p> <p>Labelled in section 5.3 of the EU SmPC.</p> |
| Physal dysplasia | - routine PhV | <p>Routine.</p> <p>Labelled in section 5.3 of the EU SmPC.</p> |
| Peripheral sensory neuropathy | - routine PhV | <p>Routine.</p> <p>Labelled in section 4.8 of the EU SmPC.</p> |
| Ovarian failure | - prospective data collection (NSABP C-08) | <p>Routine.</p> <p>Labelled in section 5.3 of the EU SmPC.</p> |
| Cardiac disorders (excl. CHF and ATE) | - cardiac monitoring in BO17920 - QTc study | <p>Routine.</p> <p>Supraventricular tachycardia is labelled in section 4.8 of the EU SmPC.</p> |
| Important missing information | | |

| | | |
|---|---|--|
| Safety profile of the different treatment combinations in patients with non-squamous NSCLC | - guided questionnaire | Routine. EU SmPC text not applicable. |
| Long-term use in paediatric patients | Patients participating in study BO20924 will be followed within the context of this trial for a minimum follow-up for overall survival and long-term safety of 5.5 years to observe long-term survivors for the long-term consequences of cancer treatment incorporating bevacizumab as part of the cancer treatment. | Routine. EU SmPC text not applicable. |
| Patients with renal impairment | - routine PhV | Routine. EU SmPC section 4.2: safety and efficacy have not been studied in patients with renal impairment. |
| Patients with hepatic impairment | - routine PhV | Routine EU SmPC section 4.2: safety and efficacy have not been studied in patients with hepatic impairment. |

The Annex II has been updated accordingly.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

The RMP was acceptable to the CHMP.

4. Benefit Risk Assessment

Benefits

The data from the capecitabine cohort of the AVF3694g (Ribbon-1) study resulted in 2.9 months gain in median PFS (8.6 months in the capecitabine + bevacizumab arm compared with 5.7 months in the capecitabine-placebo arm). The HR was 0.69 ([95% CI, 0.56 to 0.84]; log rank p=0.0002). In support of the primary analysis, the ORR was 35.4% in the capecitabine + bevacizumab arm vs. 23.6% in the capecitabine + placebo arm (p=0.0097).

Uncertainty in the knowledge about the beneficial effects

In the more heavily pretreated patient population in supportive study AVF2119g, the increased ORR was not associated with an improvement in PFS (HR=0.98 [95% CI, 0.77 to 1.25]) or OS (HR=1.08 [95% CI, 0.80 to 1.45]) which may reflect the increasing degree of tumour resistance that develops over time with the successive lines of therapy.

No statistical significance was reached in the PFS results of study AVF3693g (Ribbon-2). In addition, the ORR was 35.8% in the bevacizumab arm vs. 15.4% in the control arm (p=0.0225) but no statistically significant.

No formal comparison with other standard available first line therapeutic options are made neither the patient population which may eventually benefit from first line capecitabine has been clearly defined.

Risks

The safety profiles of both capecitabine as well as bevacizumab have been well-characterized. Common AEs associated with capecitabine include gastrointestinal disorders, hand-foot syndrome, fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction in patients with pre-existing renal insufficiency and thromboembolism. The addition of bevacizumab to capecitabine has not lead to new safety concerns.

The overall incidence of reported AEs was higher in the combination arm (40.1%) compared to the placebo arm (26.9%). Particularly, the incidences of hypertension, peripheral sensory neuropathy and proteinuria were increased. There were no SAEs with a $\geq 2\%$ difference in incidence between treatment arms. The percentage of deaths unrelated to disease progression was 2.5% in the placebo-containing arm vs. 1.5% in the bevacizumab-containing arm.

Concerning the bevacizumab + capecitabine combination, the proportion of patients experiencing grade 3-5 adverse events was 37% *versus* 23% associated with capecitabine + placebo.

Benefit-risk balance

The claimed improvement in PFS associated with the combination of bevacizumab+capecitabine compared to capecitabine alone based on the AVF3694g trial was modest and no important effects have been observed in terms of other clinically relevant endpoints such as OS or health-related quality of life. No important effects were observed in terms of clinical efficacy in study AVF2119g in a relevant patient population.

The bevacizumab + capecitabine combination was associated with significant toxicity. This is of particular relevance since the proposed indication is aimed at first-line treatment of patients with metastatic breast cancer for whom a more tolerable regimen is preferred compared to more active chemotherapy.

In the absence of an established clinical efficacy or other clinically relevant benefits, and considering the significant toxicity of the combination of bevacizumab+capecitabine, the benefit-risk cannot be considered positive in the proposed indication.

Recommendation

On 16 December the CHMP considered this Type II variation and agreed that the changes to the terms of the Marketing Authorisation should be refused on the following grounds:

- The claimed improvement in PFS associated with the combination of bevacizumab+capecitabine compared to capecitabine alone based on the AVF3694g trial was modest and no important effects have been observed in terms of other clinically relevant endpoints such as OS or health-related quality of life.
- No important effects were observed in terms of clinical efficacy in study AVF2119g in a relevant patient population.
- The bevacizumab + capecitabine combination was associated with significant toxicity. This is of particular relevance since the proposed indication is aimed at first-line treatment of patients with metastatic breast cancer for whom a more tolerable regimen is preferred compared to more active chemotherapy.

- In the absence of an established clinical efficacy or other clinically relevant benefits, and considering the significant toxicity of the combination of bevacizumab+capecitabine, the benefit-risk cannot be considered positive in the proposed indication.

5. Re-examination of the CHMP opinion of 16 December 2011

Following the CHMP conclusion that the benefit-risk for Avastin in combination with capecitabine for first-line treatment of patients with metastatic breast cancer in whom other chemotherapy options are not preferred, could not be considered positive, the MAH submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the MAH

The MAH presented in writing and at an oral explanation a number of arguments regarding the grounds for refusal:

Ground No 1

The MAH argued that in Study AVF3694g, bevacizumab in combination with capecitabine has demonstrated a statistically significant, clinically relevant, and robust improvement in PFS, which was supported by a superior ORR as well as by a numerical improvement in OS:

- Capecitabine in combination with bevacizumab was superior to capecitabine alone, with a clinically meaningful improvement in PFS (stratified HR 0.69, log-rank $p=0.0002$; median PFS 8.6 vs. 5.7 months, a 2.9 month improvement in the median PFS), corresponding to a reduction in the risk of progression or death by 31%. These data were corroborated by a blinded independent review committee (HR 0.68; median PFS 9.8 vs. 6.2 months, a 3.6 month improvement in the median PFS).
- Improvements in PFS were seen across all prognostic categories and patient subgroups, including patients who had received anthracyclines and/or taxanes for early breast cancer.
- Multiple sensitivity analyses confirmed the robustness of the primary PFS analysis.
- The clinical benefit was supported by a superior ORR for capecitabine + bevacizumab treated patients compared with those treated with capecitabine + placebo (35.4% vs. 23.6%). The incidence of PD as best OR, an indication of the ineffectiveness of treatment, was lower in the combination arm (14.8% vs. 27.3%).
- OS numerically favoured the bevacizumab-containing arm, as measured by both the hazard ratio (HR 0.88; 95% CI [0.69 to 1.13]) and the medians (capecitabine + placebo: 22.8 months, capecitabine + bevacizumab: 25.7 months).
 - Overall more patients who received bevacizumab were alive at 1 year (1-year survival: 81.0%) than with chemotherapy alone (1-year survival: 74.8%).
 - There was no increase in treatment-related deaths or deaths overall in women treated with capecitabine + bevacizumab versus capecitabine + placebo.
 - Sensitivity analyses have shown that the 62% crossover of control arm patients in this study could have had the effect of appreciably diluting the magnitude of the OS benefit that might have been observed in the absence of crossover.

Ground No 2

The MAH disagreed with the ground of refusal No 2 for the following reasons:

- In contrast to the capecitabine cohort in the first-line Study AVF3694g, Study AVF2119g enrolled a heterogeneous population of patients with more advanced chemotherapy-resistant or refractory disease in the first to third-line and later line setting.
- The refractory nature of the population of patients enrolled in Study AVF2119g was reflected in the inadequate response to capecitabine alone, as shown by the low objective response rate.
- Given the substantial differences in the patient populations enrolled in studies AVF2119g and AVF3694g, it is not considered appropriate to compare the efficacy results of the two trials.
- It is more appropriate to make a comparison to Study AVF3693g which indicated that the combination of bevacizumab and capecitabine is efficacious as second-line treatment of patients with mBC.

Ground No 3

The MAH stated that the safety profile of bevacizumab in combination with capecitabine in study AVF3694g was generally consistent with the well-established profile observed in the more than 90,000 women who have been treated with bevacizumab worldwide for mBC, and as described in the currently approved Avastin SmPC:

- The addition of bevacizumab to capecitabine does not add unexpected toxicities in patients with previously untreated mBC. The most common adverse events observed in the capecitabine + bevacizumab arm were hypertension, proteinuria, and sensory neuropathy. (Note: palmar-plantar erythrodysesthesia (PPE), a common side effect associated with the use of capecitabine, was most likely reported as sensory neuropathy in this study).
- The incidence of hypertension was, as expected, higher in the capecitabine + bevacizumab arm. The maximum grade of hypertension observed in this study was Grade 3 and characterized as asymptomatic, manageable with routine clinical intervention and allowed continuation of bevacizumab and capecitabine administration.
- Severe safety events known to be associated with bevacizumab were either not observed (gastrointestinal perforation), or occurred at a low incidence and at a rate similar to the capecitabine + placebo arm (arterial thromboembolic events (ATE): 2.0% vs. 1.5%, venous thromboembolic events (VTE): 5.0% vs. 3.5%) and similar to the known safety profile of bevacizumab.
- Adverse events that are common to cytotoxic chemotherapy, such as haematological toxicity or alopecia were infrequently or not observed in patients who were randomized to the capecitabine cohort of AVF3694g.
- The incidence of adverse events leading to study drug discontinuation was similar in both treatment arms, and the incidence of discontinuation due to hypertension or proteinuria was very low.
- The overall number of deaths was lower in the bevacizumab-containing arm and there was no increase in treatment-related deaths with bevacizumab treatment.

In conclusion, the combination of bevacizumab and capecitabine was generally well tolerated as first-line treatment for patients with mBC. The study population comprised approximately 40% of anthracycline and taxane adjuvant pre-treated patients; a patient population where treatment choice is driven primarily by efficacy considerations, which is in contrast to the assertion of the CHMP that capecitabine treatment is primarily for a patient population for whom a more tolerable regimen is preferred.

Ground No 4

The choice of chemotherapy to use in patients as first-line treatment for mBC is based upon multiple clinical, biologic, and patient-specific factors. These factors include disease, hormone and HER2 receptor status, the patient's disease-free interval from adjuvant treatment, type of prior treatment and presence of residual toxicity from previous therapy, sites of disease, pace of disease progression, presence or absence of symptoms, treatment priority, anticipated tolerance to treatment, and co-morbid conditions that would dictate choice of treatment and last but not least patient's preference.

Among the many chemotherapy agents available, capecitabine is an attractive option for patients given its ease of administration via the oral route, lack of alopecia, manageable and reversible toxicities, and infrequent myelosuppression. Because of its proven efficacy and safety profile, capecitabine is considered appropriate in particular for patients who have received both anthracycline and taxane based chemotherapy for early breast cancer, patients with slowly growing progressive disease, those who prefer oral chemotherapy treatment, patients who elect to avoid alopecia, those who cannot tolerate myelosuppressive treatment or are intolerant of cumulative toxicity and elderly patients or those who are less fit.

From clinical efficacy and safety data presented above, the MAH is of viewpoint that the clinically meaningful and statistically significant improvement in PFS supported by an improvement of basically all efficacy parameters together with a well-characterized and manageable safety profile supports the positive benefit-risk balance for the combination of bevacizumab with capecitabine as an important treatment option for patients in the first-line mBC setting.

Overall conclusion on grounds for re-examination

The CHMP opinion remained negative regarding the previous proposed indication for first-line treatment of patients with metastatic breast cancer in whom other chemotherapy options are "not preferred".

The CHMP considered that the indication should be more rigorously defined since preference alone is not informative in guiding patient selection and does not necessarily identify patients for whom other treatment options including taxanes and anthracyclines are not available. The CHMP maintained that in a population where patient characteristics allowed treatment options including taxanes and anthracyclines, the benefit-risk of bevacizumab plus capecitabine combination could not be considered positive.

However, the CHMP acknowledged that there is a population in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. The CHMP considered that capecitabine was an acceptable treatment choice and comparator in the subgroup of patients who are not candidates for more aggressive chemotherapy including taxanes or anthracyclines. Such patients include those who may have received anthracyclines and taxanes in the adjuvant treatment setting, who are unlikely to tolerate myelosuppressive treatment, or who are intolerant of cumulative toxicity, elderly patients, or patients with slow-growing disease. Based on this and the data provided, the CHMP agreed that it can be concluded that a clear effect in terms of PFS is seen with the addition of bevacizumab to capecitabine.

Therefore the indication was amended to exclude patients eligible for treatment including taxanes or anthracyclines, as follows: "*Avastin in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received*

taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine”.

The CHMP discussed the clinical relevance of the 2.9 months difference observed in median PFS in this population in AVF3694g (Ribbon-1) trial. The CHMP concluded that this difference was still modest but that the clinical relevance of this effect needs to be assessed in the context of the benefit-risk evaluation in this population for which there are limited alternative treatment options. In terms of other clinically relevant endpoints, the CHMP acknowledged that a detrimental effect in terms of overall survival was unlikely.

The single pivotal trial AVF3694g (Ribbon-1) conducted was sufficiently robust to allow drawing meaningful conclusions in the revised proposed indication. In particular, the effect observed for bevacizumab+capecitabine was considered to be consistent across subgroups and robust to different assumptions explored in sensitivity analyses. The CHMP agreed that the lack of supportive data from study AVF2119g due to the more advanced population included (second and third-line treatment) was no longer considered as a major pitfall in view of the robustness of the pivotal trial and the clear effect seen in terms of PFS.

The overall incidence of reported AEs was higher in the combination arm (40.1%) compared to the placebo arm (26.9%). Particularly, the incidences of hypertension, peripheral sensory neuropathy and proteinuria were increased. However, there were no major differences between treatment groups in terms of SAEs or deaths unrelated to disease progression. The CHMP concluded that despite the toxicity associated with bevacizumab in combination with capecitabine is significant, it is outweighed by a sufficient clinical relevance in terms of PFS for this restricted population and therefore its acceptability has to be assessed in the context of the benefit-risk balance for this restricted population.

Patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate have limited therapeutic options. In this population, the modest effect observed with bevacizumab in combination with capecitabine may be considered of sufficient clinical relevance as it is expected to be associated with benefits in terms of symptom control. Although the addition of bevacizumab resulted in increased toxicity, this was not considered a major concern in view of the clinically relevant effect in this population with limited alternative treatment options. Therefore, the CHMP concluded that in the indication of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate the grounds for negative opinion no longer hold. The CHMP concluded that the benefit-risk balance for bevacizumab in combination with capecitabine as first-line treatment of patients with metastatic breast cancer, in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate, is considered positive.

Product Information

The main changes agreed in the product information are summarised below (deletions in strikethrough; additions underlined).

- Section 4.1 of the SmPC

[...]

Avastin in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing

regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1.

[...]

- Section 4.4 of the SmPC

[...]

Congestive heart failure (CHF) (see section 4.8)

Events consistent with CHF were reported in clinical trials. The ~~symptoms~~ findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Avastin.

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF, ~~such as pre-existing coronary heart disease or concomitant cardiotoxic therapy were present.~~

In patients in AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. CHF grade 3 or higher events were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (see section 4.8).

~~Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure with Avastin.~~

[...]

- Section 4.8 of the SmPC

[...]

Congestive heart failure (CHF)

In clinical trials with Avastin, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In ~~two~~ four phase III trials (AVF2119g, ~~and~~ E2100, BO17708 and AVF3694g) in patients with metastatic breast cancer ~~an increase of CHF Grade 3 or more higher was reported in up to 3.5% of patients treated with Avastin was seen in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of grade 3 or higher CHF for the respective bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidences of all grade CHF were similar between the anthracycline + Avastin (6.2%) and the anthracycline + placebo arms (6.0%).~~

Most patients ~~of these~~ who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

[...]

- Section 5.1 of the SmPC

[...]

Metastatic breast cancer (mBC)

Two large Phase III trials were designed to investigate the treatment effect of Avastin in combination with two individual chemotherapy agents, as measured by the primary endpoint of PFS. A clinically meaningful and statistically significant improvement in PFS was observed in both trials.

Summarised below are PFS results for the individual chemotherapy agents included in the indication:

- Study E2100 (paclitaxel)
 - Median PFS increase 5.6 months, HR 0.421 (p = <0.0001, 95% CI 0.343 ; 0.516)
- Study AVF3694g (capecitabine)
 - Median PFS increase 2.9 months, HR 0.69 (p = 0.0002, 95% CI 0.56 ; 0.84)

Further details of each study and the results are provided below.

[...]

AVF3694g

Study AVF3694g was a Phase III, multicentre, randomised, placebo-controlled trial designed to evaluate the efficacy and safety of Avastin in combination with chemotherapy compared to chemotherapy plus placebo as first-line treatment for patients with HER2-negative metastatic or locally recurrent breast cancer.

Chemotherapy was chosen at the investigator's discretion prior to randomization in a 2:1 ratio to receive either chemotherapy plus □Avastin or chemotherapy plus□ placebo. The choices of chemotherapy included capecitabine, taxane (protein-bound paclitaxel, docetaxel), and anthracycline-based agents (doxorubicin/ cyclophosphamide, epirubicin/ cyclophosphamide, 5-fluorouracil/ doxorubicin/ cyclophosphamide, 5-fluorouracil/epirubicin/cyclophosphamide) given every three weeks (q3w). Avastin or placebo was administered at a dose of 15 mg/kg q3w.

This study included a blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and study drug (Avastin or placebo) every 3 weeks until disease progression, treatment-limiting toxicity, or death. On documented disease progression, patients who entered the optional open-label phase could receive open-label Avastin together with a wide-range of second line therapies.

Statistical analyses were performed independently for 1) patients who received capecitabine in combination with Avastin or placebo; 2) patients who received taxane-based or anthracycline-based chemotherapy in combination with Avastin or placebo. The primary endpoint of the study was PFS by investigator assessment. In addition, the primary endpoint was also assessed by an independent review committee (IRC).

The results of this study from the final protocol defined analyses for progression free survival and response rates for the independently powered capecitabine cohort of Study AVF3694g are presented in Table 9. Results from an exploratory overall survival analysis which include an additional 7 months of follow-up (approximately 46% of patients had died) are also presented. The percentage of patients who received Avastin in the open-label phase was 62.1% in the capecitabine + placebo arm and 49.9% in the capecitabine + Avastin arm.

Table 9 Efficacy results for study AVF3694g: – Capecitabine^a and Avastin/Placebo (Cap + Avastin/PI)

| Progression-free survival ^b | | | | |
|---|-------------------------|-----------------------|-----------------------|-----------------------|
| | Investigator Assessment | | IRC Assessment | |
| | Cap + PI (n=206) | Cap + Avastin (n=409) | Cap + PI (n=206) | Cap + Avastin (n=409) |
| Median PFS (months) | 5.7 | 8.6 | 6.2 | 9.8 |
| Hazard ratio vs. placebo arm (95% CI) | 0.69 (0.56; 0.84) | | 0.68 (0.54; 0.86) | |
| p-value | 0.0002 | | 0.0011 | |
| Response rate (for patients with measurable disease) ^b | | | | |
| | Cap + PI (n= 161) | | Cap + Avastin (n=325) | |
| % pts with objective response | 23.6 | | 35.4 | |
| p-value | 0.0097 | | | |
| Overall survival ^b | | | | |
| HR (95% CI) | 0.88 (0.69, 1.13) | | | |
| p-value (exploratory) | 0.33 | | | |

^a1000 mg/m² oral twice daily for 14 days administered every 3 weeks

^bStratified analysis included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression; data from those patients were censored at the last tumour assessment prior to starting NPT.

An unstratified analysis of PFS (investigator assessed) was performed that did not censor for non-protocol therapy prior to disease progression. The results of these analyses were very similar to the primary PFS results.

[...]

Finally Annex II has been updated in order to reflect the latest version of the RMP.

Recommendation following re-examination

On 14 April 2011 and subsequently 19 May 2011 the CHMP considered the re-examination of this Type II variation and in its final opinion concluded by majority that the risk-benefit balance of Avastin in the indication

“Avastin in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-

containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine. For further information about HER2 status, refer to section 5.1"

was positive.