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Patient Health Protection

Assessment report for AVASTIN

International Non-proprietary Name: bevacizumab

Procedure No. EMEA/H/C/582/A-20/038

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

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1. Background information on the procedure

Avastin (bevacizumab) was first approved in 2005 for first line treatment of metastatic colon or rectum cancer in combination with fluoropyrimidine-based chemotherapy. Following the approval of two type II variations, the therapeutic indication for Avastin has been extended to include first-line treatment of metastatic breast cancer in combination with paclitaxel or docetaxel (II/08 and II/24, respectively).

The MAH submitted a request for a further variation (EMEA/H/C/582/II/0033) to extend the breast cancer indication with inclusion of treatment in combination with anthracycline-based or capecitabine cytotoxic chemotherapy. This request is based, *inter alia*, on the pivotal study AVF3694g (Ribbon-1).

This study included a cohort of patients who received a choice of taxane combination (either protein-bound paclitaxel [nab-paclitaxel] or docetaxel) and four different anthracycline regimens. While the study was not powered to demonstrate the efficacy of bevacizumab for each one of the combinations, a negative trend for overall survival (OS) was observed in the subgroup of patients receiving the combination bevacizumab + taxane, in addition to a benefit in terms of progression free survival (PFS) smaller than anticipated in previous studies. Furthermore, the addition of bevacizumab to the base treatment resulted in a higher incidence of some grade $\geq$ 3 adverse events including febrile neutropenia, diarrhoea, sepsis, dehydration, GI perforation and cellulites.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 23 September 2010 to assess the above concerns and its impact on the benefit/risk for Avastin, and to give its opinion on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

Metastatic breast cancer (mBC) is a complex disease that is essentially incurable. There is no single standard of care for mBC and treatment requires an individualised approach based on multiple factors. In determining the best choice of treatment, physicians consider the disease characteristics, prior breast cancer treatment, therapeutic goals, patient's characteristics and preferences. Taxane-based chemotherapy (paclitaxel or docetaxel), either alone or in combination with other agents, is recognised as a worldwide standard of care for the treatment of breast cancer. It is important to note that these agents are not interchangeable because of their differential efficacy and safety profiles.

Reducing the burden of disease (measured in clinical trials as response rate) and delaying the burden of disease (measured as PFS) are important patient and physician goals in the treatment of mBC. Both measures represent an important and meaningful clinical benefit that can be attributed directly to a specific treatment and are not confounded by subsequent lines of therapy. Increasing the time that a patient lives without the cancer growing or spreading represents a benefit in terms of maintaining symptom-free living, quality of life (QoL) and delaying the onset of clinical sequelae associated with worsening metastatic disease or additional chemotherapies.

PFS is a composite measure of time to disease progression or death. Because in mBC the extent of disease can be reliably measured on radiographs, PFS is an accepted measure of clinical efficacy that can be directly attributed to a regimen and an appropriate endpoint in clinical trials in oncology.

Ultimately, improving OS is a major goal of treatment. However, demonstrating an improvement in OS in first-line mBC clinical trials is difficult to achieve because OS is often confounded by subsequent lines of therapy for recurrent disease.

While it is accepted that in clinical trials an increase in PFS may not be accompanied by increased OS, it is important to ensure that OS is not ultimately compromised. A negative effect on OS observed in the presence of increased PFS and response rate could be indicative of a long-term negative effect of treatment.

In order for the CHMP to reconsider the benefit-risk balance of Avastin in the mBC indication, the MAH submitted a summary of all clinical trial data available on the combination of bevacizumab + taxanes (paclitaxel and docetaxel). It is important to note that as the two taxanes are not interchangeable the evaluation of benefit-risk balance for the combination of bevacizumab with paclitaxel and docetaxel must be done separately.

2.1. Clinical aspects

2.1.1. Clinical efficacy

The clinical benefit of bevacizumab combined with either paclitaxel or docetaxel was demonstrated in two large positive phase III randomised studies, E2100 and BO17708, respectively, which were the basis for the approval of the indication in the European Union. Additional supportive trials include the phase III AVF3694g study, phase II studies (which incorporated paclitaxel + bevacizumab as a control or experimental arm) and a large safety study (MO19391) conducted in the postmarketing setting (which included bevacizumab in combination with either paclitaxel or docetaxel).

Table 1 - Comparison of Studies E2100, BO17708 and AVF3694g

	E2100 (N = 722)	**BO17708 (N = 736)**	**AVF3694g (N = 1237)**
Study design	Phase III controlled trial, 1:1 randomisation to paclitaxel + bevacizumab (10 mg/kg every 2 weeks) or to paclitaxel alone	Phase III controlled, three-arm trial, randomised 1:1:1 to docetaxel + placebo, docetaxel + bevacizumab 7.5 mg/kg every 3 weeks (q3wk) or docetaxel + bevacizumab 15 mg/kg q3wk	Phase III controlled trial of bevacizumab plus either taxane-based, anthracycline-based, or capecitabine chemotherapy versus chemotherapy alone. 2:1 randomisation to chemotherapy + bevacizumab 15 mg/kg q3wk or to chemotherapy + placebo. The taxane/anthracycline cohort (622 patients) in this study was independently powered for efficacy; 307 patients were randomised to receive docetaxel or protein-bound paclitaxel
Minimization of bias	Independent radiological review of PFS	Double-blinded, placebo-controlled study	Double-blinded, placebo-controlled study; IRC of PFS (sensitivity analysis)
Chemotherapy	Paclitaxel 90 mg/m2 IV qwk for 3 weeks followed by 1 week of rest, until PD, death, unacceptable toxicity, or patient withdrawal. Each cycle was 4 weeks.	Docetaxel 100 mg/m2 IV q3wk for a maximum of 9 cycles or until PD, death, unacceptable toxicity, or patient withdrawal. Each cycle was 3 weeks.	Investigator's choice of chemotherapy (declared prior to randomisation). Chemotherapy given until PD, death, unacceptable toxicity, or patient withdrawal. Each cycle was 3 weeks. Taxane: Docetaxel 75–100 mg/m2 IV q3wk Protein-bound paclitaxel 260 mg/m2 IV q3wk Anthracycline-based FEC/FAC/AC/EC q3wk, with minimum 6 cycles and maximum 8 cycles of anthracycline (if maximum cumulative dose of anthracycline was reached, other components of chemotherapy could continue) Capecitabine: 1000 mg/m2 oral twice daily on Days 1–14 of every 3-week cycle
Primary endpoint	PFS by investigator	PFS by investigator	PFS by investigator
Secondary endpoints	PFS by IRC, ORR, OS, safety, QoL	ORR, OS, 1-year survival rate, safety, QoL	ORR, OS 1-year survival rate, duration of objective response,

	E2100 (N = 722)	BO17708 (N = 736)	AVF3694g (N = 1237)
			and PFS (IRC)
AE collection	Grade 3–5 non-haematologic and Grade 4 and 5 haematologic AEs	All AEs	Selected AEs; serious AEs, and AEs resulting in discontinuation of study drug.
Sample size (intent-to-treat)	Total n = 722 Pac alone: n = 354 Pac + bevacizumab: n = 368	Total n = 736 Doc + placebo: n = 241 Doc + bevacizumab 7.5: n = 248 Doc + bevacizumab 15: n = 247	Total n = 1237 T/Anth: n = 622 T/Anth + placebo: n = 207 (T: n = 104, Anth: n = 103) T/Anth + bevacizumab: n = 415 (T: n = 203, Anth: n = 212) Cap: n = 615 Cap + placebo: n = 206 Cap + bevacizumab: n = 409
Enrolment period	FPI: 21 December 2001 LPI: 26 May 2004 ~29 months	FPI: 20 March 2006 LPI: 12 April 2007 ~13 months	FPI: 15 December 2005 LPI: August 2007 ~21 months
Regions of study conduct	Primarily USA (plus Canada, South Africa, and Peru)	Western Europe, Eastern Europe, Australia, Canada, East Asia, Central and South America	USA, Western Europe, Eastern Europe, Australia, Canada, East Asia, Central and South America
Follow-up at data cut-off	PFS data cut-off: 9 February 2005 (~38 months from FPI; ~8.1 months from LPI). Extended survival data cut-off at 481 deaths: 21 October 2006.	PFS data cut-off (original analysis) and OS data cut-off (interim analysis): 31 October 2007 (~19.5 months from FPI; 6.5 months from LPI). PFS data cut-off (updated analysis) and OS data cut-off (final analysis): 30 April 2009 (25 months after LPI). OS data cut-off (follow-up analysis): 28 February 2010 (35 months after LPI)	PFS data cut-off: 31 July 2008 (~31.5 months from FPI; 11.5 months from LPI). Extended survival data cut-off: 23 February 2009 (18 months after LPI).
Tumour assessment schedule	Every 12 weeks while on protocol therapy until PD. For patients who had discontinued protocol therapy, every 3 months for up to 2 years from randomisation and every 6 months from 2 to 5 years from randomisation, until PD. Tumour response and disease progression were evaluated using RECIST.	Every 9 weeks until Week 36; every 12 weeks thereafter until PD. For patients who discontinued protocol therapy, every 3 months after discontinuation of therapy until PD. Tumour response and disease progression were evaluated using RECIST.	Every 9 weeks until PD, regardless whether patients had discontinued from study treatment. Tumour response and disease progression were evaluated using RECIST.
Post-PD bevacizumab use	Information not available.	Patients in either treatment arm could receive bevacizumab post-PD in the post-study phase.	Patients in either treatment arm could receive bevacizumab in the post-PD post-study phase.

E2100 (N = 722)	BO17708 (N = 736)	AVF3694g (N = 1237)

AC = doxorubicin and cyclophosphamide; AEs = adverse events; Cap = capecitabine; Doc = docetaxel; EC = epirubicin and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin, and cyclophosphamide; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; FPI = first patient in; IRC = independent review committee; LPI = last patient in; ORR = objective response rate; OS = overall survival; Pac = paclitaxel; PD = progressive disease; T/Anth = taxane/anthracycline.

Study AVF3694g

AVF3694g is the pivotal study submitted in the application for the approval of the combination bevacizumab+capecitabine (variation II/33). It was a phase III multicenter, double-blind, placebo-controlled randomised trial that investigated the combination of bevacizumab and standard chemotherapy in patients who had not received chemotherapy for their HER2-negative mBC. In order to reflect the oncology community standard practices and approach to treatment decisions, the class of chemotherapy (taxane/anthracycline-based chemotherapy or capecitabine) was chosen by the investigators prior to randomisation from a set of commonly used regimens specified in the study protocol. Patients were assigned in a 2:1 ratio to chemotherapy+bevacizumab or chemotherapy+placebo.

The primary objective was to compare PFS (as assessed by the investigator) in patients randomised to bevacizumab+chemotherapy versus placebo+chemotherapy. Statistical analyses were performed independently for 1) patients who received either taxane-based or anthracycline-based chemotherapy in combination with bevacizumab/placebo; and 2) patients who received capecitabine in combination with bevacizumab/placebo. The secondary objectives included ORR, OS, 1-year survival rate, duration of objective response, PFS by independent review committee and safety.

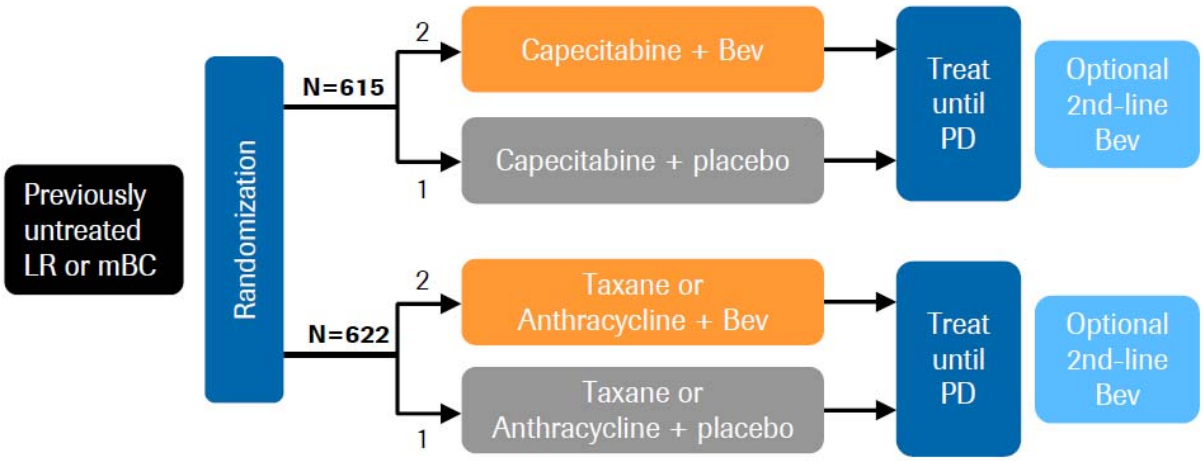


Figure 1 - AVF3694g study design.
Taxane = docetaxel or protein-bound paclitaxel.
Anthracycline = doxorubicin or epirubicin with cyclophosphamide or cyclophosphamide/5-fluorouracil.
Bevacizumab 15mg/kg q3w.

Both cohorts were independently powered for efficacy, but the individual combinations within the taxane/anthracycline cohort were not.

Study MO19391
Study MO19391, a Phase IV open-label, non-comparative, international, multicentre trial, was conducted in patients with first-line locally recurrent or mBC receiving bevacizumab in combination with a taxane or other chemotherapies. All patients received treatment with bevacizumab (weekly equivalent of 5 mg/kg/wk) plus taxane monotherapy or in combination with other chemotherapies. The primary objective was to assess the safety profile of bevacizumab when combined with taxane monotherapy or in combination with other chemotherapy. The most common treatment regimens during this study were paclitaxel + bevacizumab (779 [34.4%] patients) and docetaxel + bevacizumab (741 [32.7%] patients).

Additionally, four studies (Phase II and III) conducted by other sponsors and which incorporated bevacizumab + paclitaxel were identified:

- Randomised Phase II study of weekly versus every 3 week ixabepilone plus bevacizumab versus paclitaxel plus bevacizumab as first-line therapy for mBC.
  (Rugo H, Campone M, Amadori D, et al. Randomized phase II study of weekly versus every 3 week ixabepilone plus bevacizumab (ixa/bev) versus paclitaxel plus bev (pac/bev) as first-line therapy for metastatic breast cancer (MBC): final results. J Clin Oncol. 2010;28:15s (Supplement): Abstract No. 1040.)
- CIRG-TORI-010: Randomized Phase II trial of motenaxib plus weekly paclitaxel as first-line therapy in HER2-negative mBC.
  (Mackey J, et al. 10-Month analysis of a randomized phase II trial of motesanib plus weekly paclitaxel as first line therapy in HER2-negative metastatic breast cancer (MBC). SABCS 2009: Abstract No. 47.)
- JO19901: Phase II study of bevacizumab combined with weekly paclitaxel as first-line therapy for Japanese patients with HER2-negative mBC.
  (Masuda N et al. Phase II study of bevacizumab (Bev) combined with weekly paclitaxel (wPac) as first-line therapy for Japanese patients (pts) with HER2-negative metastatic breast cancer (mBC). J Clin Oncol. 2010; 28:15s(Supplement): Abstract No. 1121.)
- SUN 1094: A Phase III study of sunitinib in combination with paclitaxel versus bevacizumab with paclitaxel in the first-line advanced disease setting in patients having breast cancer.

2.1.1.1. Bevacizumab in combination with paclitaxel

Clinical studies

The benefit-risk assessment of bevacizumab in combination with paclitaxel as first-line treatment of patients with mBC is based on the primary data from study E2100.

Study AVF3694g included nab-paclitaxel as a choice within the taxane/anthracycline cohort. Albumin-bound paclitaxel is distinct from paclitaxel in its efficacy and safety profile despite sharing the same active moiety, as they differ in formulation. Nab-paclitaxel is a biologically interactive, nanometer-sized albumin-bound paclitaxel particle that was initially developed to increase efficacy and minimize the toxicities associated with standard paclitaxel therapy. Despite these differences, the data from the AVF3694g subset of the taxane/anthracycline cohort are relevant and are discussed in the benefit-risk assessment for paclitaxel + bevacizumab.

As such, the benefit-risk assessment for paclitaxel + bevacizumab is supported by relevant data from study AVF3694g, study MO19391, and other published phase II and phase III trials and is discussed in the following sections. The number of patients treated with paclitaxel or nab-paclitaxel is shown for each study in table 2.

Table 2 - Number of patients randomised in studies of bevacizumab + paclitaxel and/or nab-paclitaxel

	E2100 (N = 722)		AVF3694g (T/Anth Cohort) (N = 622)		MO19391 (N = 2264)
Randomisation (control: Bv-containing arm)	1:1		1:2		Open-Label
Arm	Pac	Pac + Bv	n-pac + Pl	n-pac +Bv	Pac + Bv
Patients randomised	354	368	46	78	779

n-pac= nab-paclitaxel; Bv = bevacizumab; Pac = paclitaxel; Pl = placebo; T/Anth = taxane/ anthracycline.

Progression-Free Survival

Study E2100

E2100 was designed as an open-label study in which the primary endpoint was PFS as assessed by the treating investigator. This section presents the analyses from both the investigator and the independent review assessments, with focus on the blinded independent review of PFS.

The results from the analysis of PFS by the investigator and independent review are shown in table 3. Disease progression and tumour response were assessed by the investigator and confirmed by ECOG (based on an unblinded review of data submitted by the investigator), according to RECIST (response evaluation criteria in solid tumours).

The stratified analysis of the primary endpoint of PFS based on investigator assessment for all randomised patients demonstrated a clinically and statistically significant increase in PFS among patients in the paclitaxel + bevacizumab arm compared with those in the paclitaxel alone arm ($p< 0.0001$), with an associated increase in median PFS from 5.8 to 11.4 months. The stratified hazard ratio (HR) for the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm was 0.42 (95% CI: 0.34, 0.52). These findings were corroborated by the blinded IRC assessment. Figure 2 presents the Kaplan–Meier plot for investigator-assessed PFS, and figure 3 presents the plot for PFS as assessed by the IRC review. Both curves are very similar and show an early and consistent separation between the two treatment groups, favouring the bevacizumab+paclitaxel arm.

Table 3 - Progression-Free Survival based on investigator and IRC assessments in study E2100 (randomised patients)

Parameter	Investigator Assessment		IRC Assessment	
	Pac (N = 354)	Pac + Bv (N = 368)	Pac (N = 354)	Pac + Bv (N = 368)
Patients with an event	244 (68.9%)	201 (54.6%)	184 (52.0%)	173 (47.0%)
Progression-free survival				
Median (months)	5.8	11.4	5.8	11.3
Unstratified analysis				
HR (relative to Pac)	0.48		0.54	
95% CI	(0.400, 0.585)		(0.439, 0.672)	
p-value (log-rank)	<0.0001		< 0.0001	
Stratified analysis				
HR (relative to Pac)	0.42		0.48	
95% CI	(0.343, 0.516)		(0.385, 0.607)	
p-value (log-rank)	<0.0001		< 0.0001	

Bv = bevacizumab; CI = confidence interval; HR = hazard ratio; IRC = independent review committee; Pac = paclitaxel.
Data cut-off: February 9, 2005.

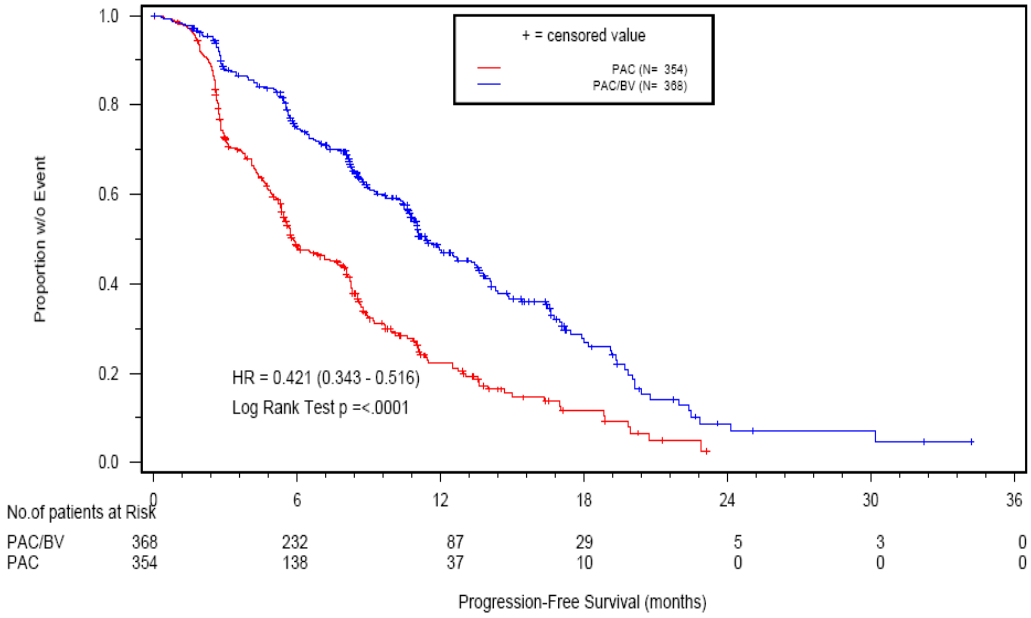


Figure 2 - Progression-Free Survival (tumour evaluation on or before February 9, 2005): Investigator-assessed results in study E2100 (randomised patients)

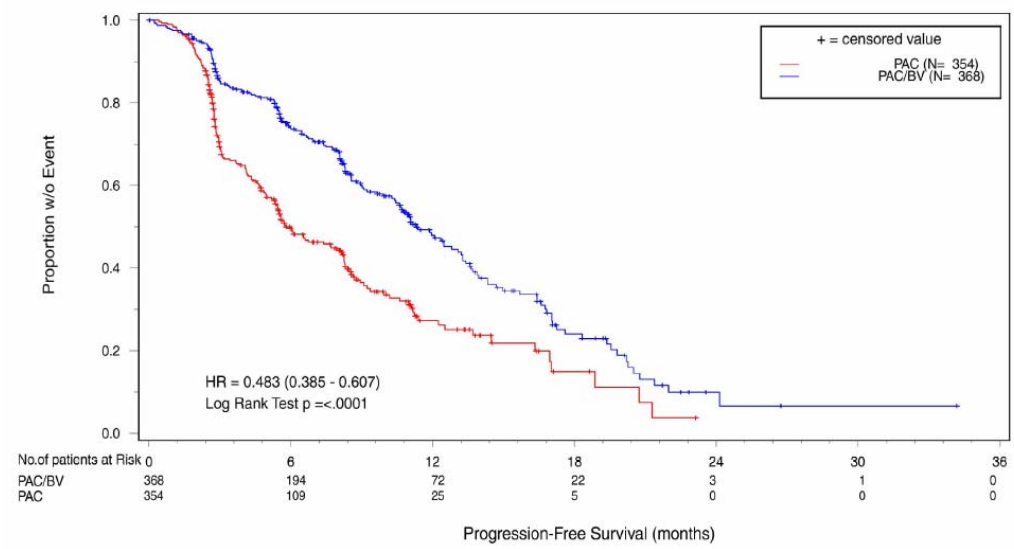


Figure 3 - Progression-Free Survival (tumour evaluation on or before February 9, 2005): IRC results in study E2100 (randomised patients)

BV = bevacizumab; HR = hazard ratio; IRC = independent review committee; PAC/BV = paclitaxel + bevacizumab.

Comparisons of results in subgroups based on the IRC assessment were performed. The reduction in the risk of progression or death in clinically important patient subgroups was generally consistent with the results seen in the overall analysis. There was a consistent increase in PFS observed across all subgroups of patients in the paclitaxel + bevacizumab arm, including those with a poor prognosis or response to treatment. The benefit of adding bevacizumab to paclitaxel was seen irrespective of age, prior therapy (anthracyclines or taxanes), disease-free interval, sites of disease or tumour burden quantified by size of target lesions in patients with measurable disease, or hormone receptor status, including patients with negative results for ER, progesterone receptor (PR), and HER2 (i.e., triple-negative patients).

As additional evidence to address potential biases and to assess the robustness of the primary results, a range of sensitivity analyses were conducted to evaluate the impact of tumour assessments as well

as missing IRC scans on the PFS results. The analyses also investigated the impact of not censoring for non-protocol therapy, including deaths that occurred at any time and patient discontinuation on PFS. In all cases, a statistically significant treatment effect was seen. The benefit in terms of a statistically significant HR in favour of paclitaxel+bevacizumab in E2100 was seen in all of the sensitivity analysis performed.

Published Phase II and III Studies and Study MO19391
Median PFS with the combination of bevacizumab+paclitaxel was reported in four recently published phase II and III clinical trials in patients with previously untreated (first-line) HER2-negative mBC.

Three of these four new studies reported a median PFS longer than 11 months, consistent with the result of 11.4 months from study E2100 for the paclitaxel + bevacizumab regimen.

Additionally, data from a large Phase IV study MO19391 in which 325 patients received weekly paclitaxel+bevacizumab, reported, after a median follow-up of 20.1 months, a Kaplan-Meier estimate for the median time to progression of 10.6 (95% CI 9.2, 11.8) months.

Study AVF3694g
The taxane/anthracycline comparison of study AVF3694g included a selection of either docetaxel or nab-paclitaxel. Exploratory analyses were conducted on the subset of patients treated with nab-paclitaxel+bevacizumab/placebo (table 4). In this small subgroup the hazard ratio of 0.64 for PFS with a $p<0.10$ is suggestive of a treatment benefit with a 2.9 month difference between median PFS of both treatment arms.

Table 4 - PFS in the nab-paclitaxel subset of patients in study AVF3694g

Parameter	n-pac + Pl (N = 46)	n-pac + Bv (N = 78)
Progression-free survival (investigator assessed: censored for NPT)		
Patients with an event	32 (69.6%)	46 (59.0%)
Median (months)	6.7	9.6
Stratified analysis		
Hazard ratio (95% CI) a	0.64 (0.39, 1.05)	
p-value (log–rank)	0.0779	
Unstratified analysis		
Hazard ratio (95% CI) a	0.66 (0.42; 1.03)	
p-value (log–rank)	0.0637	

n-pac = nab-paclitaxel, Bv = bevacizumab; CI = confidence interval; NPT = non-protocol-specified antineoplastic therapy; Pl = placebo.
a Relative to placebo.

The data from this subgroup analysis confirms the previously observed benefit in terms of PFS in E2100 from the combination of paclitaxel and bevacizumab compared with paclitaxel alone. Due to the small sample size (n=46 placebo and n=78 bevacizumab) the p-value was not significant, but the trend is clearly favorable for the combination therapy.

Overall Survival

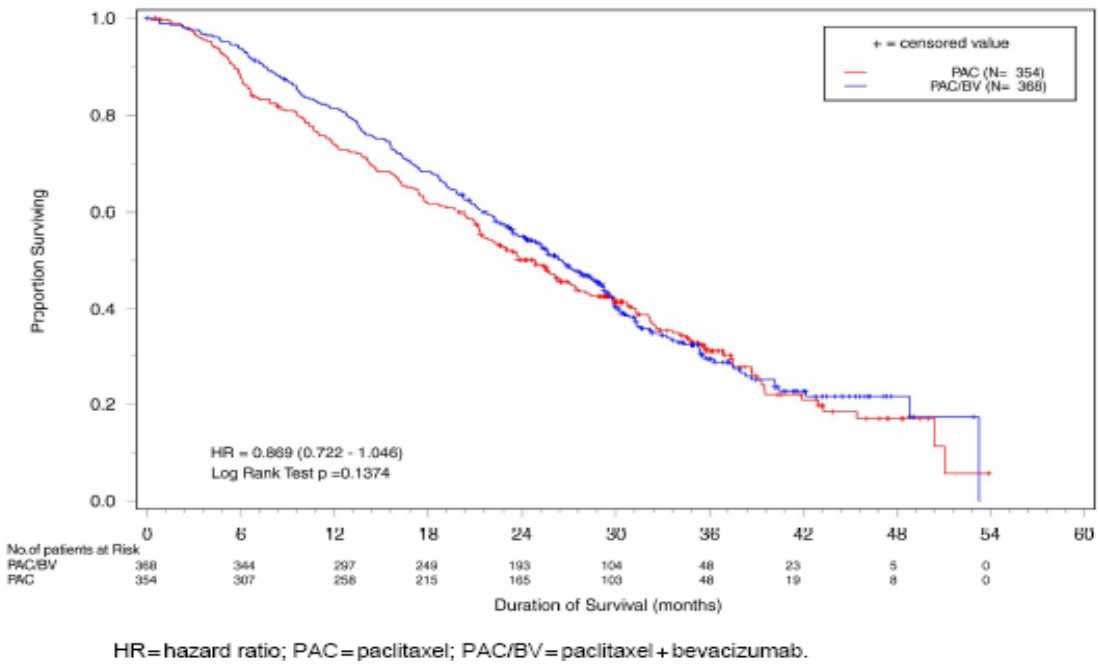
Study E2100
OS was included as a secondary outcome measure in study E2100. An updated and pre-specified analysis of OS at 481 deaths was performed with >60% of events included.
Median OS was 24.8 and 26.5 months for the paclitaxel alone and paclitaxel + bevacizumab arms, respectively (table 5), although the 1.7 month improvement was not statistically significant. As data for subsequent lines of therapy were not collected in this study it is not possible to interpret the potential impact of post-progression bevacizumab therapy on OS.

Table 5 - Overall Survival results in study E2100

Parameter	Pac (N = 354)	Pac + Bv (N = 368)
Overall survival a		
Patients who died	238 (67.2%)	243 (66.0%)
Median (months)	24.8	26.5
HR b (relative to placebo) (95% CI)	0.87 (0.72, 1.05)	
p-value (log-rank test)	0.14	

Bv = bevacizumab; CI = confidence interval; HR = hazard ratio; Pac = paclitaxel.
a Data cut-off: October 21, 2006.
b Stratified analysis.

The figure below shows an early separation of the OS curves in favour of the bevacizumab-containing arm. The separation is maintained for almost 30 months, after which the curves become overlapping with the rapidly decreasing number of patients at risk.



HR=hazard ratio; PAC=paclitaxel; PAC/BV=paclitaxel+bevacizumab.

Figure 4 - Kaplan-Meier estimates of overall survival in study E2100
Data cut-off: October 21, 2006.

Study AVF3694g

In Study AVF3694g, OS was also a secondary endpoint. For the taxane/anthracycline comparison of Study AVF3694g, the Kaplan–Meier curves showed no difference between treatment arms at any time point (HR=1.05; 95% 0.62-1.78).

Table 6 - Overall Survival in the nab-paclitaxel subset of study AVF3694g

Parameter	**n-pac + Pl (N = 46)**	**n-pac + Bv (N = 78)**
Overall survival [a]		
Patients who died	24 (52.2%)	40 (51.3%)
Median (months)	24.9	25.6
HR [b] (relative to placebo) (95% CI)	1.05 (0.62, 1.78)	

n-pac = nab-paclitaxel; Bv = bevacizumab; CI = confidence interval; HR = hazard ratio; Pl = placebo.
[a] Data cut-off: February 23, 2009.
[b] Stratified analysis.

Results of the exploratory analysis for the small number of patients in the nab-paclitaxel+bevacizumab (n = 78) and nab-paclitaxel+placebo (n = 46) subset, which was not stratified, should be interpreted with caution. Study AVF3694g included optional crossover to bevacizumab after disease progression.

Objective Response Rate

ORR, a direct measure of a product's activity, is particularly relevant for patients with rapidly progressive visceral metastatic disease.

Study E2100
ORR is commonly reported in patients with measurable disease. In study E2100, ORR was statistically significantly higher (p<0.0001) in the paclitaxel+bevacizumab arm (48.0%) compared with the paclitaxel alone arm (23.4%), an increase of 24.6%. The table below presents the overall response rate as determined by the investigator and the IRC.

Table 7 - ORR based on investigator and IRC assessments in study E2100 (randomised patients with measurable disease at baseline)

Parameter	Investigator Assessment		IRC Assessment	
	Pac (N = 273)	Pac + Bv (N = 252)	Pac (N = 243)	Pac + Bv (N = 229)
Patients with measurable disease	273	252	243	229
Patients with objective response	64 (23.4%)	121 (48.0%)	54 (22.2%)	114 (49.8%)
Best objective response				
Complete response	5 (1.8%)	20 (7.9%)	0 (0.0%)	0 (0.0%)
Partial response	59 (21.6%)	101 (40.1%)	54 (22.2%)	114 (49.8%)
Between-arm difference (95% CI)	24.6% (16.6%, 32.5%)		27.6% (19.2%, 35.9%)	
Stratified analysis				
p-value	< 0.0001		< 0.0001	

Bv = bevacizumab; CI = confidence interval; IRC = independent review committee; Pac = paclitaxel
Note: Objective response was defined as a complete or partial response (according to RECIST) determined by two consecutive investigator assessments ≥ 4 weeks apart. The 95% CI for response rate was computed using the normal approximation as described by Fleiss. The 95% CI for the difference in response rates was computed by using the standard normal approximation. The p-value is from the Pearson χ^2 test (unstratified analysis) or Cochran–Mantel–Haenszel test (stratified analysis). The strata were disease-free interval (≤ 24, > 24 months), number of metastatic sites (< 3, ≥ 3), adjuvant chemotherapy (yes, no), and ER status (positive, negative, or unknown).
Data cut-off: February 9, 2005.

The incidence of progressive disease (PD) as best overall response, i.e., PD at the first tumour assessment (an indication of no clinical benefit), was lower in the paclitaxel+bevacizumab arm of E2100 compared with the paclitaxel alone arm based on the IRC assessment (25.5% in paclitaxel alone arm vs. 11.8% in paclitaxel+bevacizumab arm).

Study AVF3694g
The response rate increase observed in the subset of nab-paclitaxel treated patients in study AVF3694g compared with control patients was similar to that observed in study E2100.

Table 8 - ORR in the nab-paclitaxel subset of study AVF3694g

Parameter	n-pac + Pl (N = 46)	n-pac + Bv (N = 78)
Patients with measurable disease	37	59
Patients with objective response	10 (27.0%)	30 (50.8%)
Best objective response		
Complete response	1 (2.7%)	1 (1.7%)
Partial response	9 (24.3%)	29 (49.2%)
Between-arm difference (95% CI)	23.8% (3.1%, 44.6%)	
Stratified analysis		
p–value (stratified analysis)	0.0212	

n-pac = nab-paclitaxel; Bv = bevacizumab; CI = confidence interval; Pl = placebo.

Quality of Life

Study E2100
In study E2100, QoL data were collected using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire and assessed as a secondary objective. The primary measure of QoL in study E2100 was measured by the treatment outcome index (TOI), which includes measurements of physical well-being, functional well-being, and breast cancer subscale. Using this QoL data, a number of analyses were performed, with different imputation rules for missing QoL values that correspond to various degrees of conservativeness. The analyses with and without imputation of missing values demonstrate a relative benefit of bevacizumab addition on QoL scores. The primary analysis, as specified in the statistical analysis plan, yields a statistically significant difference in favour of the bevacizumab-containing arm.

The QoL findings should be interpreted in the context of the main clinical efficacy results. The FACT-B is a validated questionnaire and a number of additional analyses with different imputations rules for missing data were performed to address a well known problem. This supports a relative benefit of bevacizumab addition on QoL scores. However the reliability of these data is questionable due to the open-label design of the study. QoL was not measured in the other supportive studies.

2.1.1.2. Bevacizumab in combination with docetaxel

Clinical studies

The benefit-risk assessment of bevacizumab in combination with docetaxel as first-line treatment of patients with mBC is based on the primary data from study BO17708.

The benefit-risk assessment for docetaxel+bevacizumab is supported by relevant data from study AVF3694g. The number of patients treated with docetaxel is shown for each study in table 9.

Table 9 - Number of patients randomised in studies of docetaxel + bevacizumab

Parameter	BO17708			AVF3694g (T/Anth Cohort)		MO19391
	(N=736)			(N = 622)		(N = 2264)
Randomisation (control: Bv-containing arm)	1:1:1			1:2		Open-Label
Arm	Pl + Doc	Bv7.5 + Doc	Bv15 + Doc	Pl + Doc	Bv + Doc	Bv + Doc
Patients randomised	241	248	247	58	123	741

Bv =bevacizumab; Bv7.5 = bevacizumab 7.5 mg/kg q3wk; Bv15 = bevacizumab 15 mg/kg q3wk; Doc = docetaxel; Pl = placebo; T/Anth = taxane/anthracycline
Note: All doses of bevacizumab are 15 mg/kg q3wk unless otherwise indicated.

The prespecified final analysis of PFS in study BO17708 was to occur when 430 events had been reached, corresponding to a data cut-off date of October 31, 2007. However, because of the rapid patient enrolment, the duration of follow-up at the time of the initial analysis was limited (median follow-up of approximately 10 months). Therefore, the dataset comprised predominantly patients who progressed early. Data from those patients still on treatment, which were censored in the analysis, limited the interpretation and hindered the reliable estimation of median PFS. The MAH performed a further PFS analysis at the time of the final OS analysis (data cut-off April 30, 2009), which provided sufficient follow-up.

Following the CHMP's request at the time of approval, further OS follow-up analysis was performed post authorisation (cut-off date of February 28, 2010).

For the primary efficacy and safety analysis, the April 30, 2009 cut-off will be the main focus of the discussion, with the exception of OS and mortality for which the February 28, 2010 cut-off will be discussed.

Progression-Free Survival

Study BO17708

In the updated analysis, the hazard ratio for PFS for bevacizumab-containing arms was similar to that reported for the original analysis. Median PFS for the bevacizumab-containing arm was 10.1 months and the difference between the both arms was 1.9 months.

Table 10 - Progression-Free Survival in study BO17708: Original and updated analysis

Parameter	Pl + Doc (N = 241)	Bv15 + Doc (N = 247)
PFS (unstratified) [a] (October 31, 2007)		
Patients with events	162	142
Median PFS (months)	8.0	8.8
Log-rank test p-value (unadjusted)	0.0099	
Hazard ratio (95% CI)	0.72 (0.57, 0.90)	
PFS (unstratified) [a] (April 30, 2009)		
Patients with events	219	220
Median PFS (months)	8.2	10.1
Log-rank test p-value (unadjusted)	0.0061	
Hazard ratio (95% CI)	0.77 (0.64, 0.93)	

Bv15 = bevacizumab 15 mg/kg q3wk; CI = confidence interval; Doc = docetaxel; PFS = progression-free survival; Pl = placebo. [a] Data were not censored at the use of non-protocol anti-cancer therapies.

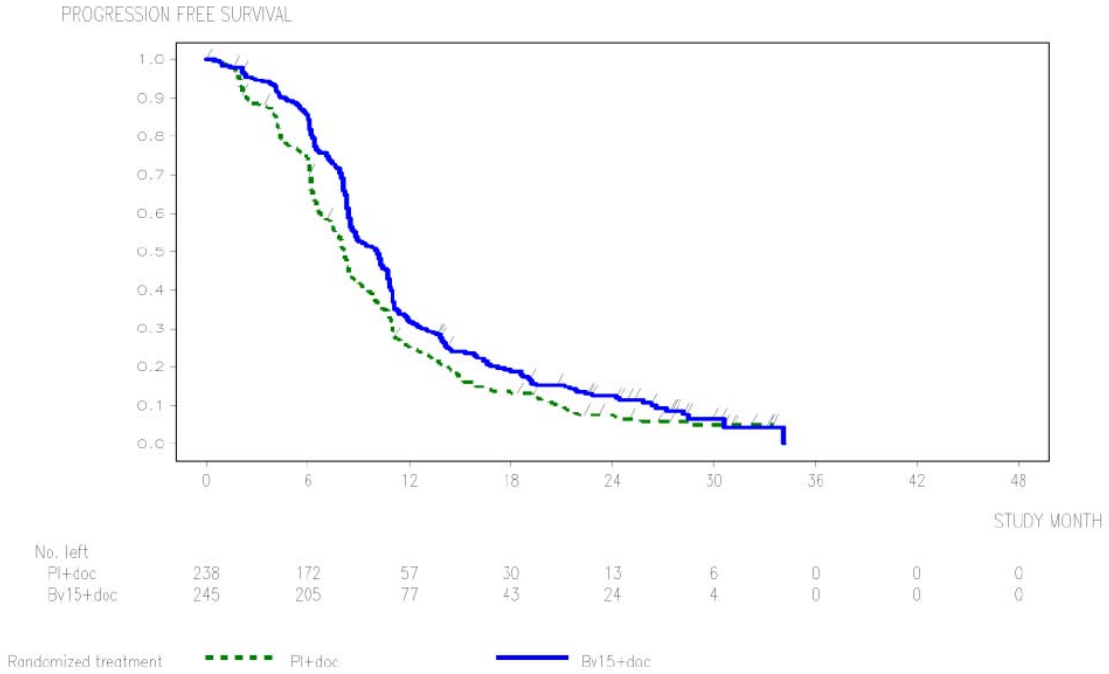


Figure 5 - Kaplan-Meier plot of Progression-Free Survival for the Pl + Doc arm versus the Bv15 + Doc arm: Updated analysis (Intent-to-Treat population)

Data cut-off: April 30, 2009.

Subgroup analyses were performed in order to assess the consistency of the PFS benefit in the Bv15 + Doc arm. The results of each of the subgroup analyses for PFS were consistent with those seen for all patients. It is noted that for women <50 years of age, the median PFS with addition of bevacizumab was 10.3 months and that in the placebo group it was 10.4 months. The HR was 0.96 (95% CI: 0.70 – 1.32). The number of patients in this subgroup was not inconsiderable (n=179) and there were approximately 80 events in both groups, but obviously the confidence intervals are wider compared to the ITT analysis. Likewise, for pre-menopausal women (n=115), the HR was 0.97. Thus, it seems that in younger pre-menopausal women, the effect of adding bevacizumab on PFS was even minor.

The robustness of the primary result was confirmed in an exploratory Cox regression analysis on PFS that took account of prognostic factors.

Study AVF3694g
Exploratory analyses were conducted on the subset of patients treated with docetaxel + bevacizumab/placebo. Table 11 summarizes the PFS results for the docetaxel subgroup in study AVF3694g. The hazard ratio of 0.78 indicates that the numeric improvement in PFS of 0.8 months observed was not statistically significant.

Table 11 - Progression-Free Survival for docetaxel-treated patients in study AVF3694g

Parameter	Doc + Pl (N = 58)	Doc + Bv (N = 123)
Patients with a PFS event	47 (81.0%)	78 (63.4%)
Progression-Free Survival		
Unstratified HR (95% CI)	0.78 (0.54, 1.12)	
p-value	0.17	
Median (months)	8.4	9.2

Bv = bevacizumab; CI = confidence interval; Doc = docetaxel; HR = hazard ratio; PFS = progression-free survival; Pl = placebo.

Overall survival

Study BO17708
For the primary analysis available at the time of approval of the combination between bevacizumab and docetaxel for first-line treatment of metastatic breast cancer, no statistically significant difference in OS was detected when comparing both arms. It was however noted that the curves cross over at 24 months and that the end of the curves is not reliable due to censoring.

For the follow-up analysis of OS (data cut-off February 28, 2010), survival information was collected up to 4 years after the first patient's initial dose of study treatment. No further information on treatment compliance, concurrent diseases, concomitant medications, or tumour progression was collected for this further OS follow-up analysis.

The results of the follow-up analysis, shown in the table below, are similar to the primary OS analysis. No impact on OS was observed. The hazard ratio for the stratified analysis for the bevacizumab arms compared with the placebo arm was 0.97 (95% CI: 0.76, 1.23). Median OS was 31.7 months in the docetaxel only arm and 28.1 months in the bevacizumab+docetaxel arm. The Kaplan–Meier curves are shown in figure 6.

Table 12 - Overall Survival and one-year survival results in study BO17708:

Parameter	Pl + Doc (N = 241)	Bv15 + Doc (N = 247)
Overall survival		
Patients with an event	144 (59.8%)	143 (57.9%)
Median survival time (months)	31.7	28.1
Unstratified HR (95% CI)	0.98 (0.78, 1.23)	
p-value (log-rank)	0.86	
Stratified HR (95% CI)	0.97 (0.76, 1.23)	
p-value (log-rank)	0.78	
One-year survival rate [a]	75.5%	84.3%
Difference (%) in rates from placebo (95% CI)	8.8 (1.7, 16.0)	
p-value	0.016	

Bv15 = bevacizumab 15 mg/kg; CI = confidence interval; Doc = docetaxel; HR = hazard ratio; Pl = placebo.
Data cut-off: February 28, 2010.
[a] Kaplan–Meier estimates.

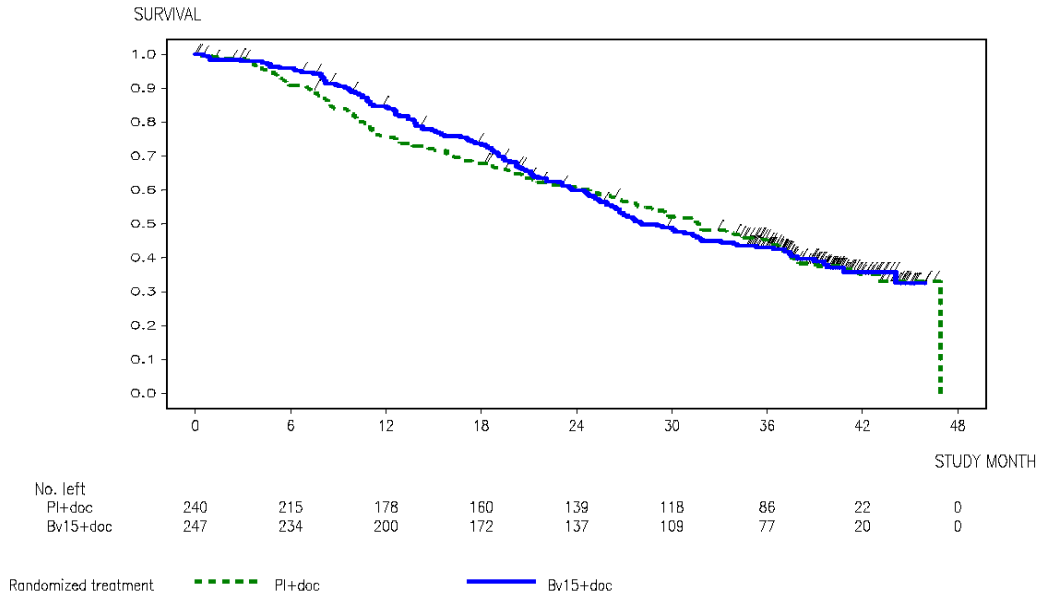


Figure 6 - Kaplan-Meier curves of Overall Survival in study BO17708: Follow-Up analysis
Data cut-off: February 28, 2010.

Study AVF3694g
Table 13 shows the OS results for the subgroup of docetaxel in study AVF3694g. While there was no statistically significant difference between treatment arms, a negative trend was observed (HR=1.45).

Table 13 - Overall Survival results for docetaxel-treated patients in study AVF3694g

Parameter	Doc + Pl (N = 58)	Doc + Bv (N = 123)
Overall survival		
Patients who died	21 (36.2%)	60 (48.8%)
Overall survival (months)		
Unstratified HR (95% CI)	1.45 (0.88, 2.39)	
p-value	0.14	
Median	NR	27.0

Bv = bevacizumab; CI = confidence interval; Doc = docetaxel; HR = hazard ratio; NR = not reached; Pl = placebo.
Data cut-off: February 23, 2009.

It is noted that there are imbalances between both treatment arms with respect to prognostic factors, although they were minor (up to 15% difference) and therefore do not explain the difference observed.

Within the subgroup of docetaxel treated patients, hazard ratios for OS for key clinical subgroups such as age, hormone receptor status and history of prior treatments did not reveal a specific subgroup that contributed significantly to the overall hazard ratio.

Objective response rate

Study BO17708
Consistent with the original analysis, the updated analysis, based on the cut-off date of April 30, 2009, showed that ORR was greater in the combination arm.

Table 14 - Objective response rates in study BO17708 (randomised patients)

Parameter	Doc + Pl (N = 241)	Doc + Bv15 (N = 247)
Objective response rate (October 31, 2007)		
Patients with measurable disease	207	206
Objective response rate	92 (44.4%)	130 (63.1%)
Between-arm difference	18.7%	
p-value (χ^2)	0.0001	
Objective response rate (April 30, 2009)		
Patients with measurable disease	207	206
Objective response rate	96 (46.4%)	132 (64.1%)
Between-arm difference	17.7%	
p-value (χ^2)	0.0003	

Bv15 = bevacizumab 15 mg/kg q3wk; CI = confidence interval; Doc = docetaxel; Pl = placebo.

The absolute difference in response rate between the two arms was 17.7%. The incidence of PD as best overall response, an indication of no clinical benefit, was lower in docetaxel + bevacizumab arm (3.4%) than in the docetaxel + placebo arm (11.1%) on the basis of both the original and the updated analyses.

Study AVF3694g

Table 15 shows ORR for the subgroup of docetaxel-treated patients in study AVF3694g. The bevacizumab-treated patients' ORR was 9.3% higher than the placebo-treated patients.

Table 15 - Objective response rates in docetaxel treated patients in study AVF3694g

Parameter	Doc + Pl (N = 58)	Doc + Bv (N = 123)
Patients with measurable disease	48	100
Objective response rate	20 (41.7%)	51 (51.0%)
Between-arm difference (95% CI)	9.3% (- 8.9%, 27.6%)	
p-value [a]	0.29	

Bv = bevacizumab; CI = confidence interval; Doc = docetaxel; Pl = placebo.
Data cut-off: July 31, 2008.
[a] Stratified analysis.

Quality of Life

Study BO17708

Patients' QoL was assessed using the self-reported FACT-B instrument as a secondary objective in study BO17708. In general, the results of the analyses utilizing different imputation rules to account for missing values consistently demonstrated relatively better QoL scores in those patients treated in the bevacizumab + docetaxel arm compared with the control arm.

QoL was not measured in the other supportive studies (AVF3694g and MO19391).

2.1.1.3. Discussion on efficacy

Bevacizumab in combination with paclitaxel

The pivotal study E2100 was an open-label, randomised, two armed, phase III study comparing bevacizumab+paclitaxel vs. paclitaxel alone in the first line treatment of patients with metastatic breast cancer. This study was the definite pivotal study in the evalution of the benefit-risk balance for the paclitaxel-bevacizumab combination.

In this study, the bevacizumab+paclitaxel arm exhibited an increase of 5.5 months in median progression-free survival compared to the paclitaxel alone arm (11.3 vs. 5.8 months, respectively; hazard ratio = 0.480, p<0.0001; based on IRC assessment).

Overall survival was not compromised (26.5 months for the combination vs. 24.8 months for paclitaxel alone, hazard ratio = 0.87 [95% CI 0.72, 1.05]; p=0.14).

Overall response rate was 22.2% and 49.8% in the paclitaxel alone and bevacizumab+paclitaxel arms, respectively (p<0.0001).

The data presented suggested an improvement in QoL for patients on the combination treatment, although the reliability of the scores can be questioned due to methodological limitations.

The analysis of PFS in the subgroup of patients receiving nab-paclitaxel in study AVF3694g is consistent with a beneficial effect on PFS by combining bevacizumab with paclitaxel as observed in E2100. Although the 2.9 month difference between treatment arms is smaller than previously observed and not statistically significant (a likely consequence of the study not being powered to allow for subgroup comparison), a trend favouring the combination therapy was observed.

In conclusion, the results of existing studies on the combination bevacizumab+paclitaxel are consistent and support a positive effect of therapy with a clear benefit to patients.

Bevacizumab in combination with docetaxel

The pivotal study BO17708 was a randomised, double-blind, placebo-controlled, multicentre, phase III trial to evaluate the efficacy and safety of bevacizumab+docetaxel vs. docetaxel alone, as first-line treatment for patients with HER2-negative metastatic or locally recurrent breast cancer.

In the updated analysis of this study, the bevacizumab+docetaxel arm exhibited an increase of 1.9 months in median progression-free survival compared to the docetaxel alone arm (10.1 vs. 8.2 months, respectively; hazard ratio = 0.77, p=0.0061). This improvement of PFS was considered by CHMP, at the time of approval of the combination, to be very modest but nevertheless acceptable given that no clearly detrimental effect was seen in overall survival (HR = 1.03; p=0.8524) and that benefits could be expected in terms of quality of life.

However there was a need to continue to follow-up the OS results to further reduce any uncertainties about a possible detrimental effect on OS, and therefore the CHMP requested for the full and final data to be submitted post authorisation. The updated results (cut-off date February 28, 2010) confirmed the primary analysis, in that no negative trend was seen in overall survival (31.7 months for the combination vs. 28.1 months for docetaxel alone, hazard ratio = 0.98 [95% CI 0.78, 1.23]; p=0.86), however there are uncertainties remaining in relation to this data due to the crossing of the curves at approximately 24 months and the fact that the end of the curves is unreliable due to heavy censoring.

Overall response rate (cut-off date April 30, 2009) was 64.1% and 46.4% in the combination and docetaxel alone arms, respectively (p=0.0003).

The data presented suggests an improvement in QoL for patients on the combination treatment, but the reliability of the scores is questionable due to methodological limitations. The only conclusion that can be drawn from the QoL data is that quality of life is not impaired by treatment.

The only supportive study for the efficacy of the combination is AVF3694g. In this study, an extremely modest improvement in PFS (median 0.8 months; HR=0.78, p=0.17) was seen in the small subgroup of patients to whom the combination bevacizumab+docetacel was offered (n=123) when compared to the docetaxel alone subgroup (n=58). No QoL data was collected.

Even less reassuring is the negative trend observed in the docetaxel+bevacizumab arm of AVF3694g for OS (HR=1.45, p=0.14). It is recognised that the results are not statistically significant, that the data concern a subgroup analysis in a small number of patients (n=181) and that patients in the control arm had better prognostic factors. However, the imbalances in prognostic factors between treatment arms were minor and are unlikely to be the explanation for the difference observed. It was argued by the MAH that the HR value may be the result of patients on the doxetaxel+placebo subgroup performing better than would be expected for the control group, particularly in comparison to study BO17708. However, when specifying key clinical subgroups within the docetaxel treated patients, no major contribution to the overall hazard ratio of 1.45 was identified.

In conclusion, the already very modest benefit observed in the pivotal trial BO17708 (median PFS improvement 1.9 months, no effect on OS) is further questioned by the results of the study AVF3694g. Although it is recognised that AVF3694g was not powered for subgroup comparison and that results of the bevacizumab+docetaxel combination should therefore be carefully considered, the extremely modest effect on PFS and the added uncertainty about OS in view of the negative trend observed cannot simply be ignored when such marginal benefit was shown in the pivotal study. These additional data raise the question as to whether this combination provides patients with any clinically significant benefit and whether the benefit outweighs the risks associated with the toxicity derived from the combination of bevacizumab+docetaxel.

The better outcome of the combination of paclitaxel with bevacizumab than docetaxel in the treatment of metastatic breast cancer is difficult to explain. However, although the two taxanes have similar chemical structures and similar mechanisms of action, they are not identical or interchangeable. In general, docetaxel is reported to have a higher activity than paclitaxel and that may help explain why the addition of bevacizumab to docetaxel does not produce an effect of the same magnitude as it does for paclitaxel.

2.1.2. Clinical safety

2.1.2.1. Bevacizumab in combination with paclitaxel

Adverse Events

Study E2100

Because the bevacizumab safety profile had been generated from prior large randomised clinical trials in solid tumours, only grade ≥3 non-haematologic and grade ≥4 haematologic AEs were collected in study E2100. Expedited reporting was not required for patients who received paclitaxel alone, thus introducing a bias in safety reporting favouring the control arm.

Table 16 shows the incidence of selected AEs (defined as commonly associated with bevacizumab or weekly paclitaxel) reported. The addition of bevacizumab to paclitaxel resulted in adverse events that were predictable, based on previous bevacizumab experience, and clinically manageable. AEs of particular interest in patients treated with paclitaxel include sensory neuropathy, and neutropenia, and febrile neutropenia. An increased incidence of grade ≥3 sensory neuropathy was observed in the paclitaxel + bevacizumab arm (24.8% vs. 18.1% in the control arm). The observed difference was due to the longer treatment duration in the paclitaxel + bevacizumab arm compared with the paclitaxel alone arm, and an analysis adjusting for the duration of study treatment showed that the incidence of sensory neuropathy was similar after the adjustment.

Table 16 - Incidence of grade ≥3 selected adverse events in study E2100

Selected Adverse Event Category	Pac (N = 348)	Pac + Bv (N = 363)
Any grade ≥ 3 selected adverse event	89 (25.6%)	180 (49.6%)
Sensory neuropathy	63 (18.1%)	90 (24.8%)
Hypertension	5 (1.4%)	58 (16.0%)
Infection	16 (4.6%)	33 (9.1%)
Neutropenia	14 (4.0%)	29 (8.0%)
Arterial thromboembolic event	0 (0.0%)	13 (3.6%)
Proteinuria	0 (0.0%)	11 (3.0%)
Venous thromboembolic event	15 (4.3%)	11 (3.0%)
Bleeding	1 (0.3%)	8 (2.2%)
LVSD	1 (0.3%)	8 (2.2%)
Febrile neutropenia	0 (0.0%)	6 (1.7%)
GI perforation	0 (0.0%)	2 (0.6%)

Bv = bevacizumab; GI = gastrointestinal; LVSD = left ventricular systolic dysfunction; Pac = paclitaxel.
Adverse events were reported using NCI-CTC v2.0

The incidence of grade 3 neutropenia and febrile neutropenia was increased in patients who received bevacizumab in combination with paclitaxel. However, these events occurred at a relatively low incidence (<10%) and were not associated with an increase in life-threatening events. Patients treated with paclitaxel + bevacizumab who developed neutropenia and those who developed infection received significantly more paclitaxel (median of 35 doses) than those who did not develop neutropenia or infection (median of 21 doses).

The incidences of adverse events that have previously been associated with bevacizumab, including grade ≥3 hypertension, left ventricular dysfunction, proteinuria, bleeding, GI perforation, and ATE events were increased in E2100 patients who received the combination of paclitaxel + bevacizumab, but were within the range of expected toxicity, both in terms of incidence and severity.

As expected, there was a higher incidence of grade 3 or 4 hypertension (16%) events among patients who received paclitaxel + bevacizumab than among those treated with paclitaxel alone (1.4%). Of the 58 patients with an event of grade 3 or above hypertension, only 2 experienced a grade 4 event. There were no grade 5 events reported. The risk of left ventricular dysfunction was not increased above that described in studies of patients with previously treated mBC.

Study AVF3694g

The incidence of selected grade ≥3 AEs in the subset of patients treated with nab-paclitaxel in study AVF3694g is shown in table 17. The incidence rates observed are consistent with those observed in study E2100 with the exception of sensory neuropathy. Placebo-treated patients had a higher incidence of sensory neuropathy relative to bevacizumab-treated patients, potentially explained by the small sample size of this subset. As in study E2100, the incidence of grade 3 neutropenia and febrile neutropenia in the AVF3694g patients receiving nab-paclitaxel+bevacizumab was increased.

Table 17 - Incidence of grade ≥3 selected adverse events in study AVF3694g (nab-paclitaxel subgroup)

Selected Adverse Event Category	n-pac + (N = 44)	Pl npac + Bv (N = 80)
Any Grade ≥ 3 selected adverse event	12 (27.3%)	36 (45.0%)
Hypertension	1 (2.3%)	12 (15.0%)
Sensory neuropathy	8 (18.2%)	9 (11.3%)
Neutropenia	2 (4.5%)	9 (11.3%)
Proteinuria	0 (0.0%)	6 (7.5%)
Bleeding	0 (0.0%)	5 (6.3%)
Febrile neutropenia	0 (0.0%)	3 (3.8%)
GI perforation	1 (2.3%)	1 (1.3%)
Venous thromboembolic event	2 (4.5%)	0 (0.0%)
LVSD	0 (0.0%)	0 (0.0%)
Arterial thromboembolic event	0 (0.0%)	0 (0.0%)

n-pac = nab-paclitaxel; Bv = bevacizumab; GI = gastrointestinal; LVSD = left ventricular systolic dysfunction; Pl = placebo

Study MO19391

The open-label, single-arm Phase IV study MO19391 also provides supportive evidence regarding the safety of bevacizumab and taxanes. In this study, 779 patients were treated with paclitaxel + bevacizumab, and the safety data demonstrated that the safety profile of this combination in the postmarketing setting was consistent with the experience in the E2100 pivotal trial and clinical study experience. The most common grade ≥3 adverse events were hypertension (5.1%), proteinuria (3.6%), and arterial/venous thromboembolism (3.6%).

Mortality

Study E2100

The majority of deaths in both treatment arms were due to the underlying mBC. A slightly increased number of deaths due to AE or protocol therapy (treatment-related mortality) were observed in the paclitaxel+bevacizumab arm compared with the paclitaxel alone arm (table 18). However the numbers were small and deaths with missing or unknown cause were more frequent in the paclitaxel only arm.

Table 18 - Cause of death in study E2100

Parameter	Pac (N = 348)	Pac + Bv (N = 363)
Deaths	257	256
mBC	241 (69.3%)	241 (66.4%)
AE or protocol therapy [a]	1 (0.3%)	6 (1.7%)
Other	7 (2.0%)	5 (1.4%)
Missing/ unknown cause	8 (2.3%)	4 (1.1%)

AE = adverse event; Bv = bevacizumab; mBC = metastatic breast cancer; Pac = paclitaxel.
[a] Paclitaxel alone arm: cardiac arrest (1); paclitaxel + bevacizumab arm: other (1), respiratory failure (1), myocardial infarction (2), sinus bradycardia (1), GI perforation (1).

Study AVF3694g
The combination of bevacizumab with nab-paclitaxel in study AVF3694g had similar mortality rates unrelated to disease progression relative to the control arm (table 19). Death due to other causes was more frequent in the nab-paclitaxel+bevacizumab arm than in the nab-paclitaxel only arm (5.0% vs. 2.3%).

Table 19 - Cause of death in nab-paclitaxel treated patients in study AVF3694g

Parameter	n-pac + Pl (N = 44)	n-pac + Bv (N = 80)
Deaths	23	41
mBC	20 (45.5%)	34 (42.5%)
AE or protocol therapy	2(4.5%)	3 (3.8%)
Other	1 (2.3%)	4 (5.0%)
Missing/unknown cause	0 (0.0%)	0 (0.0%)

n-pac = nab-paclitaxel; AE = adverse event; Bv = bevacizumab; mBC = metastatic breast cancer; Pl = placebo

Study MO19391
Of the 779 patients in the safety population in the open-label single-arm trial MO19391 who were treated with paclitaxel+bevacizumab, 416 (53.4%) died. Cause of death was attributed to: breast cancer (49.6%), other reason (2.3%), unknown (0.8%), concurrent illness (0.2%), toxicity of chemotherapy (0.2%), and bevacizumab toxicity (0.2%). This data confirms what was seen in previous studies.

2.1.2.2. Bevacizumab in combination with docetaxel

Adverse events

Study BO17708
In study BO17708, all adverse events of any severity were collected. For consistency in discussing the safety data from this study relative to the other trials, adverse events of grade ≥ 3 will be discussed.

Docetaxel's primary dose-limiting toxicities are neutropenia and febrile neutropenia. Common non-haematologic toxicities include alopecia, hypersensitivity, asthenia, fever without infection, infection, neuromotor and neurosensory toxicity, peripheral edema, pain, nail disorders, skin toxicity, and stomatitis.

As expected, the most frequent grade ≥ 3 adverse events in both treatment arms were neutropenia and febrile neutropenia, and were increased in the bevacizumab+docetaxel arm by 2.5% and 4.9%, respectively, compared with the placebo+docetaxel arm. The palmar-plantar erythrodysaesthesia syndrome (PPE) rate was also increased by 6% in the bevacizumab+docetaxel arm relative to control.

Increases were seen in other grade ≥3 non-haematologic toxicities associated with docetaxel: diarrhoea, fatigue, stomatitis, skin exfoliation, nail toxicity, and peripheral sensory neuropathy, all increased by less than 5% (table 20). The longer duration of treatment exposure in the Bv15 + Doc treatment arm compared with the control arm may have contributed to an increase in these events.

Table 20 - Selected docetaxel grade ≥3 adverse events in study BO17708 (safety population)

MedDRA (v.12.0) Adverse Event	Pl + Doc (N = 231)	Bv15 + Doc (N = 247)
Neutropenia	40 (17.3%)	49 (19.8%)
Febrile neutropenia	27 (11.7%)	41 (16.6%)
Asthenia	17 (7.3%)	16 (6.9%)
Diarrhea	9 (3.4%)	16 (6.9%)
Palmar-plantar erythrodysaesthesia syndrome	2 (0.9%)	16 (6.9%)
Fatigue	12 (5.2%)	15 (6.5%)
Nail Disorder	8 (3.4%)	11 (4.5%)
Peripheral Sensory Neuropathy	10 (4.3%)	19 (7.7%)
Alopecia	9 (3.9%)	9 (3.6%)
Stomatitis	1 (0.4%)	8 (3.2%)
Skin Exfoliation	0 (0%)	3 (1.2%)
Fever	1 (0.4%)	2 (0.8%)
Peripheral Edema	5 (2.1%)	1 (0.4%)
Infection	1 (2%)	0 (0%)

Bv15 = bevacizumab 15 mg/kg q3wk; Doc = docetaxel; MedDRA = Medical Dictionary for Regulatory Activities; Pl = placebo.
Data cut-off April 30, 2009.; excludes the open label phase of the study
[a]. Selected adverse event category.

The rates of peripheral edema and infection were higher in the placebo+docetaxel arm than in the bevacizumab+docetaxel arm.

Adverse events that were previously seen to have a higher incidence on bevacizumab treatment were reviewed (table 21). The following grade ≥3 bevacizumab-associated adverse events were similar (<2% difference or more frequent in the control arm) between both arms: thromboembolic events including venous and arterial events, bleeding including mucocutaneous and pulmonary events, GI perforation; abscess and fistula; wound-healing complication, proteinuria and LVSD. As expected, the rate of grade ≥3 hypertension was higher in the combination treatment arm than in the docetaxel only arm. There were no grade 5 hypertension events.

Table 21 - Grade ≥3 adverse events associated with bevacizumab treatment in study BO17708 (safety population)

Selected Adverse Event Category	Pl + Doc (N = 231)	Bv15 + Doc (N = 247)
Any adverse event of special interest	87 (37.7%)	112 (45.3%)
Hypertension	3 (1.3%)	11 (4.5%)
Proteinuria	0 (0.0%)	5 (2.0%)
Bleeding	2 (0.9%)	3 (1.2%)
Venous thromboembolic event	8 (3.5%)	3 (1.2%)
Arterial thromboembolic event	1 (0.4%)	2 (0.8%)
Fistula	1 (0.4%)	2 (0.8%)
GI perforation	2 (0.9%)	1 (0.4%)
Wound healing complication	2 (0.9%)	1 (0.4%)
LVSD	0 (0.0%)	0 (0.0%)

Bv15 = bevacizumab 15 mg/kg q3wk; Doc = docetaxel; LVSD = left ventricular systolic dysfunction; MedDRA = Medical Dictionary for Regulatory Activities; Pl = placebo.
Note: Multiple occurrences of a specific adverse event for any 1 patient were counted once at the most extreme intensity.
Data cut-off April 30, 2009.

The overall incidence of adverse events that led to the discontinuation of any treatment component was comparable among the treatment arms. With the exception of nail disorder, which occurred at a higher incidence in the combination arm, no marked difference between the treatment arms was observed with respect to the type and frequency of adverse events leading to discontinuation of any component of the study treatment.

Table 22 - Adverse events ≥2% in any treatment arm and leading to discontinuation of any component of study treatment in study BO17708 (safety population)

MedDRA (v10.1) Adverse Event Preferred Term	Pl + Doc (N = 231)	Bv15 + Doc (N = 247)
Any adverse event	63 (27.3%)	71 (28.7%)
Nail disorder	1 (0.4%)	6 (2.4%)
Asthenia	4 (1.7%)	5 (2.0%)
Oedema peripheral	5 (2.2%)	1 (0.4%)

Bv15 = bevacizumab 15 mg/kg q3wk; Doc = docetaxel; MedDRA = Medical Dictionary for Regulatory Activities; Pl = placebo.
Note: Multiple occurrences of a specific adverse event for any 1 patient were counted once at the most extreme intensity.
Data cut-off April 30, 2009.

Study AVF3694g

The safety results from the docetaxel subset of study AVF3694g are generally consistent with the safety data from Study BO17708 in terms of the type of adverse events reported. The more frequent adverse events include febrile neutropenia, neutropenia, hypertension, and sensory neuropathy. However a relevant difference in rate of reporting of adverse events is noted (43.1% for the combination vs. 19% for the docetaxel only subgroup).

Table 23 - Grade ≥3 selected adverse events among docetaxel treated patients in study AVF3694g

Selected Adverse Event Category	Doc + Pl (N = 58)	Doc + Bv (N = 123)
Any adverse event	11 (19.0%)	53 (43.1%)
Febrile neutropenia	2 (3.4%)	13 (10.6%)
Neutropenia	3 (5.2%)	10 (8.1%)
Sensory neuropathy	1 (1.7%)	8 (6.5%)
Hypertension	1 (1.7%)	7 (5.7%)
Bleeding	0 (0.0%)	6 (4.9%)
LVSD	0 (0.0%)	4 (3.3%)
Venous thromboembolic event	3 (5.2%)	4 (3.3%)
GI perforation	0 (0.0%)	3 (2.4%)
Wound dehiscence	1 (1.7%)	3 (2.4%)
Proteinuria	0 (0.0%)	2 (1.6%)
Arterial thromboembolic event	0 (0.0%)	1 (0.8%)

Bv = bevacizumab; Doc = docetaxel; GI = gastrointestinal; LVSD = left ventricular systolic dysfunction.

Study MO19391

This open-label, single-arm, phase IV study also provides supportive evidence regarding safety of bevacizumab and taxanes. In this study, 741 patients were treated with docetaxel+bevacizumab. Overall, the safety data demonstrated that the safety profile of this combination in the postmarketing setting was consistent with the experience in the BO17708 pivotal study. The most common grade 3 or higher adverse events included haemorrhage: 2.3%, hypertension 5.1%, and thromboembolic events (both arterial and venous thromboembolic), 2.8%.

Mortality

Study BO17708

The incidence of treatment-related deaths as assessed by the investigators, any death during study treatment and deaths due to adverse events did not differ between the arms in study BO17708.

Table 24 - Cause of death in study BO17708

Cause of Death	Pl + Doc (N = 241)	Bv15 + Doc (N = 247)
Deaths	144 (59.8%)	143 (57.9%)
mBC	135 (56.0%)	134 (54.3%)
AE or protocol therapy	6 (2.5%)	8 (3.2%)
Other	3 (1.2%)	1 (0.4%)
Missing/ unknown cause	0 (0.0%)	0 (0.0%)

AE = adverse event; Bv15 = bevacizumab 15 mg/kg q3wk;
Doc = docetaxel; Pl = placebo.
Data cut-off: February 2010.

Study AVF3694g

The cause of death for the docetaxel subset of Study AVF3694g is summarized in table 25. There were more deaths by metastatic breast cancer in the subgroup bevacizumab+docetaxel.

Table 25 - Cause of death in study AVF3694g

Cause of Death	Doc + Pl (N = 58)	Doc + Bv (N = 123)
Deaths	21 (36.2%)	60 (48.8%)
mBC	18 (31.0%)	56 (45.5%)
AE or protocol therapy	1 (1.7%)	2 (1.6%)
Other	2 (3.4%)	2(1.6%)
Missing/ unknown cause	0 (0.0%)	0 (0.0%)

AE = adverse event; Bv = bevacizumab; Doc = docetaxel;
mBC = metastatic breast cancer; Pl = placebo.
Data cut-off February 23, 2009.

Study MO19391

Of the 741 patients in the safety population who received docetaxel + bevacizumab in the open-label single-arm trial MO19391, 378 (51.0%) died and the cause of death was: breast cancer (47.5%); other reason (2.4%); unknown (0.1%); concurrent illness (0.4%); toxicity of chemotherapy (0.4%), and bevacizumab toxicity (0.1%).

2.1.2.3. Discussion on safety

Bevacizumab in combination with paclitaxel

In study E2100, only grades 3-5 haematological and grades 4-5 non-haematological adverse events were reported. The AEs observed with the combination arm are as would be expected from the knowledge of the safety profile of the two drugs. The most common, selected SAEs with a ≥ 2% difference in incidence between treatment arms, were sensory neuropathy (18.1% vs. 24.8%), hypertension (1.4% vs. 16%), infection (4.6% vs. 9.1%), neutropenia (4.0% vs. 8.0%) and arterial thromboembolic events (0% vs. 3.6%) for paclitaxel alone and for the bevacizumab combination, respectively.

The majority of deaths in both treatment arms were due to mBC. There was a greater incidence of deaths due to AEs or protocol therapy in the paclitaxel + bevacizumab treatment arm (1.7%) compared to the paclitaxel alone arm (0.3%), but deaths with missing or unknown cause was more frequent in the paclitaxel arm.

The safety data for the nab-paclitaxel subgroup of study AVF3694g revealed a pattern very similar to what was seen in study E2100. As expected, more common and severe AEs were observed in the combination arm, however there were no new or unexpected findings. Most AEs are manageable, although life-threatening and even fatal complications occur in a small number of patients.

In the phase IV study (MO19391) 779 patients were treated with paclitaxel+bevacizumab and showed similar safety results with the most common grade ≥ 3 AEs being hypertension (5.1%), proteinuria (3.6%) and arterial/venous thromboembolisms (3.6%).

Bevacizumab in combination with docetaxel

Added toxicity was observed in BO17708 for patients treated with the combination regimen but in general, the increase in individual incidence rates for selected, severe complications was relatively small. The largest differences between treatment arms were observed for febrile neutropenia (11.7% vs. 16.6%), diarrhea (3.4% vs. 6.9%), palmar-plantar erythrodysaestesia syndrome (0.9% vs. 6.9%), hypertension (1.3% vs. 4.5%) and peripheral sensory neuropathy (4.3% vs. 7.7%) for docetaxel and docetal-bevacizumab treated patients, respectively. Overall, the data did not reveal any unexpected bevacizumab-related toxicities. No difference between treatment arms was observed in treatment related mortality.

Data from studies AVF3694g and MO19391 are consistent with study BO17708 with regard to treatment related mortality. However, a relevant difference in rate of reporting of adverse events is noted (43.1% for the combination vs. 19% for the docetaxel only subgroup) and, in the docetaxel subgroup of study AVF3694g, there were more deaths due to mBC in the bevacizumab+docetaxel subgroup than in the docetaxel only treated patients.

Selected adverse events, adverse events leading to study discontinuation and serious adverse events were more frequent in the bevacizumab subgroup but did not result in more treatment related deaths. No single toxicity in a system organ class appeared to contribute significantly to a greater morbidity.

2.2. Risk minimisation activities

The Committee did not ask the MAH to submit an updated risk management plan as part of this review.

2.3. Product information

The CHMP recommended the amendments to be introduced in sections 4.1 and 5.1 of the summary of product characteristics (SPC), in the *conditions of the marketing authorisation* section of the Annex II, and section 1 of the package leaflet.

3. Overall discussion and benefit/risk assessment

In view of the uncertainty around the existing data, the CHMP convened a meeting of the SAG oncology to address the question below:

Based on the results of E2100, BO17708 (AVADO) and cohort 1 of AVF3694g (Ribbon-1), the SAG-O should discuss the clinical relevance and the Benefit/Risk balance for the following combinations in the 1st line treatment of patients with mBC:

- *Bevacizumab + paclitaxel*
- *Bevacizumab + docetaxel*

Concerning the combination of bevacizumab + paclitaxel, the SAG agreed that there are no new data to change the benefit-risk balance. The clinical relevance of the observed effect in terms of progression-free survival is not questioned, even in the absence of a clear effect on overall survival. Although the magnitude of the effect observed in the bevacizumab+abraxane subgroup of AVF3694g was smaller than that observed in E2100, this combination is of limited relevance due to the different types of agents. In conclusion, based on the additional data from AVF3694g, the benefit-risk balance of bevacizumab + paclitaxel is unchanged.

Concerning the combination of bevacizumab + docetaxel, the SAG agreed that based on the additional data from AVF3694g, there are no new data to change the benefit-risk balance. The SAG agreed that in principle the effect observed in terms of PFS for bevacizumab + docetaxel was very modest but still clinically relevant. Although this is largely based on expert clinical judgement, the effect in terms of PFS and ORR is expected to be associated with benefits in terms of symptom control.

The SAG, however, continues to have different views on the need for further data to rule out a possible adverse effect in terms of OS (as already expressed in the previous advice on this combination).

According to some experts, the available data in terms of PFS objective response and OS were sufficient. According to other experts further data on OS are needed to rule out a detrimental effect conclusively. This was considered particularly important because it is possible that anti-angiogenesis agents combinations with chemotherapy may alter the mechanisms and patterns of recurrence. The SAG agreed that the apparent negative trend in OS observed in the bevacizumab + docetaxel subgroup in the AVF3694g trial does not raise particular concerns because the statistical evidence for this effect is small and this is probably a chance finding.

All SAG members agreed that the best way to provide convincing additional efficacy data in the approved indications in first-line breast cancer should be to conduct trials based on biomarker data to select populations most likely to respond to bevacizumab. Although interesting exploratory findings are available, confirmatory studies with biomarkers are lacking. Results from such studies are urgently needed. The company should be asked to commit to conduct such studies.

Bevacizumab in combination with paclitaxel

In the pivotal study E2100, the bevacizumab+paclitaxel arm exhibited an increase of 5.5 months in median progression-free survival compared to the paclitaxel alone arm (11.3 vs. 5.8 months, respectively; hazard ratio = 0.480, p<0.0001; based on IRC assessment). Overall survival was not compromised (26.5 months for the combination vs. 24.8 months for paclitaxel alone, hazard ratio = 0.87 [95% CI 0.72, 1.05]; p=0.14). Overall response rate was 22.2% and 49.8% in the paclitaxel alone and bevacizumab+paclitaxel arms, respectively (p<0.0001). The data presented suggested an improvement in QoL for patients on the combination treatment, although the reliability of the scores can be questioned.

The analysis of PFS in the subgroup of patients receiving nab-paclitaxel in study AVF3694g is consistent with a beneficial effect on PFS by combining bevacizumab with paclitaxel as observed in E2100. Although the 2.9 month difference between treatment arms is smaller than previously observed and not statistically significant (a likely consequence of the study not being powered to allow for subgroup comparison), a trend favouring the combination therapy was observed.

The safety data for the nab-paclitaxel subgroup of study AVF3694g revealed a pattern very similar to what was seen in study E2100. As expected more common and severe AEs were observed in the combination arm, however there were no new or unexpected findings. Most AEs are manageable, although life-threatening and even fatal complications occur in a small number of patients.

In conclusion, the results of existing studies on the combination bevacizumab+paclitaxel are consistent and support a positive effect of therapy with a clear benefit to patients.

Benefit/risk balance

Taken this into account, the benefit/risk balance of bevacizumab in combination with paclitaxel for first-line treatment of patients with metastatic breast cancer is considered to be positive.

Bevacizumab in combination with docetaxel

In the pivotal study BO17708, the bevacizumab+docetaxel arm exhibited an increase of 1.9 months in median progression-free survival compared to the docetaxel alone arm (10.1 vs. 8.2 months, respectively; hazard ratio = 0.77, p=0.0061). This improvement of PFS was considered by CHMP, at the time of approval of the combination, to be very modest but nevertheless acceptable given that no clearly detrimental effect was seen in overall survival and that benefits could be expected in terms of quality of life.

However there was a need to continue to follow-up the OS results to further reduce any uncertainties about a possible detrimental effect on OS, and therefore the CHMP requested for the full and final data to be submitted post authorisation. The updated results (cut-off date February 28, 2010) confirmed the primary analysis, in that no negative trend was seen in overall survival (31.7 months for the combination vs. 28.1 months for docetaxel alone, hazard ratio = 0.98 [95% CI 0.78, 1.23]; p=0.86), however there are uncertainties remaining in relation to this data due to the crossing of the curves at approximately 24 months and the fact that the end of the curves is unreliable due to heavy censoring.

The only supportive study for the efficacy of the combination is AVF3694g. In this study, an extremely modest improvement in PFS (median 0.8 months; HR=0.78, p=0.17) was seen in the small subgroup of patients to whom the combination bevacizumab+docetacel was offered when compared to the docetaxel alone subgroup.

Even less reassuring is the negative trend observed in the docetaxel+bevacizumab arm of AVF3694g for OS (HR=1.45, p=0.14). It is recognised that the results are not statistically significant, that the data concern a subgroup analysis in a small number of patients (n=181) and that patients in the control arm had better prognostic factors. However, the imbalances in prognostic factors between treatment arms were minor and are unlikely to be the explanation for the difference observed. It was argued by the MAH that the HR value may be the result of patients on the doxetaxel+placebo subgroup performing better than would be expected for the control group, particularly in comparison to study BO17708. However, when specifying key clinical subgroups within the docetaxel treated patients, no major contribution to the overall hazard ratio of 1.45 was identified.

In conclusion, the already very modest benefit observed in the pivotal trial BO17708 (median PFS improvement 1.9 months, no effect on overall survival) is further questioned by the results of the study AVF3694g. Although it is recognised that AVF3694g was not powered for subgroup comparison and that results of the bevacizumab+docetaxel combination should therefore be carefully considered, the extremely modest effect on PFS and the added uncertainty about OS in view of the negative trend observed cannot simply be ignored when such marginal benefit was shown in the pivotal study. These additional data raise the question as to whether this combination provides patients with any clinically significant benefit and whether the benefit outweighs the risks associated with the toxicity derived from the combination of bevacizumab+docetaxel.

Added toxicity was observed in BO17708 for patients treated with the combination regimen but in general, the increase in individual incidence rates for selected, severe complications was relatively small. Overall, the data did not reveal any unexpected bevacizumab-related toxicities. No difference between treatment arms was observed in treatment related mortality.

However, in study AVF3694g a relevant difference in rate of reporting of adverse events is noted (43.1% for the combination vs. 19% for the docetaxel only subgroup) and, in the docetaxel subset, there were more deaths due to mBC in the bevacizumab+docetaxel subgroup than in the docetaxel only treated patients.

Benefit/risk balance

In view of the available data, the Committee concluded that the insufficient effect shown in terms of improvement in progression-free survival associated to the fact that a potential detrimental effect on overall survival can not be ruled out, no longer outweigh the risk of increased toxicity of the combination of docetaxel and bevacizumab.

Taken the above into account, the benefit/risk balance of bevacizumab in combination with docetaxel for first-line treatment of patients with metastatic breast cancer is considered to be negative.

During the Oral Explanation, the MAH presented information on an ongoing programme for the development of biomarkers that is expected to help identify the population most likely to benefit from treatment with Avastin for metastatic breast cancer. The MAH is therefore requested to commit to investigate suitable biomarkers (including VEGF-A) to allow identification and selection of a more targeted population of patients most likely to benefit from the combination of Avastin and paclitaxel in the treatment of first-line metastatic breast cancer.
A report on the research programme should be submitted within 3 months of the Commission Decision. Progress reports should be submitted on a yearly basis.

4. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanation, the CHMP concluded that:

- The benefit/risk balance of Avastin in combination with paclitaxel in the treatment of first-line metastatic breast cancer is positive.

- The benefit/risk balance of Avastin in combination with docetaxel in the treatment of first-line metastatic breast cancer is not positive.

Therefore, the CHMP recommended the amendment to the terms of the marketing authorisation for Avastin, for which the revised summary of product characteristics, conditions of the marketing authorisation and package leaflet are set out respectively in annexes I, II and IIIB of the opinion.

5. Conclusion and grounds for the recommendation

- The Committee reviewed all available data on the combination of either paclitaxel or docetaxel with bevacizumab in the first-line treatment of metastatic breast cancer.

- The Committee considered that the combination of paclitaxel with bevacizumab results in an improvement in terms of median progression-free survival which is considered clinically relevant. The Committee also considered that the results from the AVF3694g study support this conclusion.

- The Committee is of the opinion that for the combination of docetaxel and bevacizumab compared to docetaxel alone only a very modest improvement in progression-free survival was seen, which at the time of the initial approval was considered acceptable given that the data did not indicate a detrimental effect on overall survival.

- However, the Committee reviewed the new data from the AVF3694g study on the combination docetaxel and bevacizumab, and found that the improvement in PFS was considerably lower than seen at the time of approval of the combination, and below the limit of clinical significance. In addition, the Committee concluded that there is added uncertainty on the effect of the combination on overall survival, therefore a potential detrimental effect can no longer be ruled out.

- Therefore, in view of the available data, the Committee concluded that the insufficient effect shown in terms of improvement in progression-free survival associated to the fact that a potential detrimental effect on overall survival can not be ruled out, no longer outweigh the risk of increased toxicity of the combination of docetaxel and bevacizumab.

The Committee, as a consequence, concluded that the benefit/risk balance of bevacizumab in combination with docetaxel for the treatment of first-line metastatic breast cancer is not positive under normal conditions of use. Therefore, the CHMP is of the opinion that the related indication should be deleted.

The Committee also concluded that the benefit/risk balance of bevacizumab in combination with paclitaxel for the treatment of first-line metastatic breast cancer remains positive under normal conditions of use.

The CHMP has therefore recommended the variation of the marketing authorisation for Avastin and the amendment of the Product Information as set out in an annex I, II and IIIB to this opinion.