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# Bevacizumab in the first-line treatment of metastatic breast cancer

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ABSTRACT

Bevacizumab plus paclitaxel has proven efficacy as first-line therapy for metastatic breast cancer based on the results of a randomised, phase III study (E2100). It has been recently reported that the addition of bevacizumab to paclitaxel doubled the median progression-free survival from 5.9 to 11.8 months (hazard ratio [HR] = 0.60, $p < 0.0001$). This benefit was corroborated in an analysis submitted to health authorities globally, using the intent-to-treat population; median progression-free survival of 5.8 increased to 11.4 months (HR = 0.42, $p < 0.001$), and confirmed by an independent review facility (5.8 vs. 11.3 months, HR = 0.48). This significant progression-free survival benefit was maintained across a number of patient subgroups, including those who had received prior adjuvant taxane chemotherapy. While there was no significant difference in overall survival, the addition of bevacizumab to paclitaxel increased the 1-year survival rate (81.2% vs. 73.4%, $p = 0.01$). As compared with bevacizumab use in other indications, no new safety signals were evident with the combination therapy, which was generally well tolerated. The only grade 3 and 4 toxicities that were increased by $\geqslant$5% with the addition of bevacizumab to paclitaxel were hypertension, sensory neuropathy, fatigue and neutropenia, the latter ones likely to be caused by the increased duration of paclitaxel treatment.



## 1. Introduction

It has long been recognised that for cancers to survive and grow beyond around 2 mm in size, the production of new blood vessels (angiogenesis) is essential.[1] At early stages of tumour development, the predominant pro-angiogenic growth factor secreted is vascular endothelial growth factor (VEGF), while additional factors, including basic fibroblast growth factor (bFGF), transforming growth factor-β-1 (TGFβ-1) and placental growth factor (PlGF), are increasingly expressed as the tumour develops.[2] Thus, the efficacy of anti-VEGF agents such as bevacizumab may depend upon the relative importance of VEGF in the angiogenic process in the specific patient and tumour. One might anticipate therefore that bevacizumab may be more beneficial in patients at earlier stages of disease, for example as first-line therapy for the treatment of metastatic breast cancer, and perhaps as an adjuvant in resected tumours. Although there are no data comparing angiogenic factor expression in tumour biopsies from metastatic breast lesions as compared with their primary, reductions in VEGF expression have been found in liver metastases compared with the primary tumour in patients with colorectal cancer.[3] It has not been established whether such differences occur within the metastatic setting, for example whether tumours that have received several

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**Table 1 – E2100 data sets: investigator assessments**

| Data cut-off<br>Efficacy population | FDA submission [5]<br>February 9, 2005<br>All randomised patients (n = 722) | | | | EMEA submission [6]<br>April 14, 2005<br>All randomised patients (n = 722) | | ECOG analysis [4]<br>June 7, 2007<br>Patients who met the eligibility criteria (n = 673) | |
|---|---|---|---|---|---|---|---|---|
| | Investigator assessment | | Independent review facility assessment | | | | | |
| | Pac (*n* = 354) | Bev + Pac (*n* = 368) | Pac (*n* = 354) | Bev + Pac (*n* = 368) | Pac (*n* = 354) | Bev + Pac (*n* = 368) | Pac (*n* = 326) | Bev + Pac (*n* = 347) |
| Patients with PFS event, n | 244 | 201 | 184 | 173 | 207 | 188 | 308 | 316 |
| Median PFS, months | 5.8 | 11.4 | 5.8 | 11.3 | 6.7 | 13.3 | 5.9 | 11.8 |
| HR; *p*-value | HR = 0.42; $p < 0.0001$ | | HR = 0.48; $p < 0.0001$ | | HR = 0.48; $p < 0.0001$ | | HR = 0.60; $p < 0.001$ | |

Pac = paclitaxel; Bev = bevacizumab; HR = hazard ratio; PFS = progression-free survival; FDA = Food and Drug Administration; EMEA = European Medicine Evaluation Agency; ECOG = Eastern Cooperative Oncology Group.

lines of therapy express different angiogenic growth factors to those that are untreated in this setting.

To further investigate this hypothesis, a multicentre, randomised, phase III study compared the combination of bevacizumab with and without paclitaxel as first-line therapy in patients with advanced breast cancer not previously treated with chemotherapy. E2100 was designed to detect a significant improvement in progression-free survival (PFS) for patients in the bevacizumab plus paclitaxel arm. The trial was stopped after the first scheduled interim analysis on the recommendation of the independent Data Monitoring Committee, who concluded that the primary efficacy objective had already been met. Data from this study resulted in the EU approval of this combination therapy for first-line treatment of patients with metastatic breast cancer in March 2007.

This article describes efficacy results from the E2100 trial, including the results of an independent review.

## 2. Bevacizumab in first-line metastatic breast cancer: efficacy results from study E2100

Since the interim data from study E2100 were first released, a number of data sets have been presented; these vary as a result of different data cut-off dates, different statistical calculations and different study population definitions. Table 1 shows the data sets published by the Eastern Cooperative Oncology Group (ECOG),[4] who conducted the trial and those analysed for the Food and Drug Administration (FDA)[5] and European Medicine Evaluation Agency (EMEA)[6] regulatory submissions. While all the analyses confirm clinically significant improvements in time to progression and response rate, the existence of these multiple analyses may be confusing; this paper will discuss the reasons for the analyses and the differences between them.

Firstly, there are different populations of patients used for analyses of efficacy for regulatory purposes and those performed by ECOG for presentation and publication. ECOG analyses were based only on the population of patients meeting full eligibility criteria, while the regulatory analyses used the intent-to-treat (ITT) population, which included all randomised patients. Thus, 49 patients who were included in the regulatory analyses were excluded from the ECOG analysis as they did not meet all the pre-specified eligibility criteria.[4]

Secondly, all analyses used stratified log-rank tests, but whereas analyses for regulatory purposes utilised the four stratification factors used at patient randomisation (number of metastatic sites [<3 vs. ⩾3], oestrogen receptor [ER] status [positive vs. negative vs. unknown], prior adjuvant chemotherapy [yes vs. no] and disease-free interval [⩽24 vs. >24 months]), only the latter two were used by ECOG in its per-protocol population.[4]

Thirdly, different timings were used for 'data locks'. The published ECOG analysis was performed using a cut-off date of June 7, 2007, while the initial European submission was based on an earlier data cut-off date of April 14, 2005 (Table 1). Here we also present data used to support the FDA regulatory submission, using a cut-off date for efficacy analyses of February 9, 2005 (this analysis has recently been incorporated into the European label). This is consistent with the data cut-off for the first interim analysis, conducted by the study's independent Data Monitoring Committee, who concluded that the primary endpoint was met.[7] Since the FDA analysis was conducted later, there was a more complete dataset available on events in patients up to and including the cut-off date of February 9, 2005.[7] As this was an open-label study, an additional analysis was available based on the assessments performed by an independent review facility (IRF), who reviewed radiology and pertinent medical data blinded to treatment allocation and investigator efficacy assessments. Although these regulatory analyses have not been published, they are accepted by regulatory authorities as they are based on the ITT population.

**Table 2 – E2100: patient demographic and baseline characteristics (FDA analysis)** [7]

| | Paclitaxel ($n = 354$) | Bevacizumab + paclitaxel ($n = 368$) |
|---|---|---|
| Median age, years (range) | 55 (27–85) | 56 (29–84) |
| ER+, n (%) | 223 (63.0) | 223 (60.6) |
| PR+, n (%) | 158 (44.6) | 165 (45.1) |
| HER2+, n (%) | 6 (1.7) | 9 (2.4) |
| Disease-free interval, n (%) | | |
| ⩽24 months | 146 (41.2) | 150 (40.8) |
| >24 months | 208 (58.8) | 218 (59.2) |
| Number of metastatic sites, n (%) | | |
| <3 | 252 (71.2) | 262 (71.2) |
| ⩾3 | 102 (28.8) | 106 (28.8) |
| Prior taxane therapy, n (%) | 68 (19.2) | 74 (20.1) |
| Prior anthracycline therapy, n (%) | 180 (50.8) | 184 (50.0) |

ER+ = oestrogen receptor positive; PR+ = progesterone receptor positive; HER2+ = human epidermal growth factor receptor 2 positive

## 3. Patient population

Eligibility criteria have been previously published in detail. [4] Patients received paclitaxel 90 mg/m$^2$ alone every week for 3 out of 4 weeks or the same dose and schedule of paclitaxel plus bevacizumab 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity.

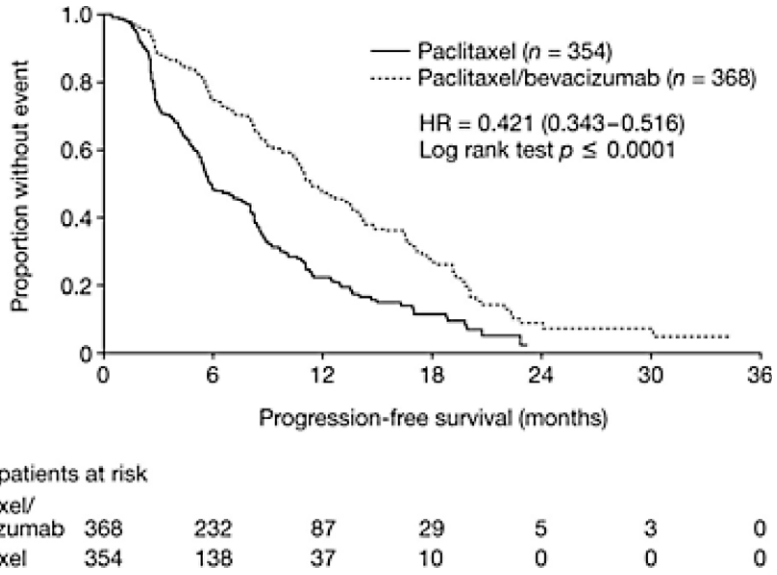
A total of 722 patients were randomised to study E2100, 354 to receive paclitaxel alone and 368 to receive paclitaxel plus bevacizumab. Efficacy analysis was performed on 673 patients by ECOG, 326 who received paclitaxel alone and 347 who received paclitaxel plus bevacizumab (Table 1); overall, 711 patients were treated and evaluated for safety. [4] The two patient groups were similar with respect to demographics and disease characteristics at baseline, except that more patients randomised to paclitaxel alone had either measurable disease or visceral involvement. [4] In the regulatory analyses, the entire ITT population of 722 patients was analysed for efficacy (Table 1). Eleven patients were excluded from the safety analysis: 10 patients never initiated protocol therapy, and the reason for exclusion was unknown for one patient. Of the 711 patients treated, 664 patients (92.0%) discontinued protocol therapy, 95.5% in the paclitaxel arm and 88.6% in the bevacizumab-containing arm (based on a safety cut-off date of August 9, 2005, as requested by the FDA in order to include as many patients as possible). Demographic and baseline characteristics were similar across the two treatment arms (Table 2).

## 4. Efficacy evaluations

The published ECOG data, using a data cut-off date of June 7, 2007, reported 624 events and a doubling of median PFS, the primary endpoint of the study, from 5.9 to 11.8 months (hazard ratio [HR] = 0.60, $p < 0.001$) with the addition of bevacizumab to paclitaxel (Table 1). [4]

As standard for regulatory purposes, any primary analysis for superiority must be based on the ITT population. Such analyses were conducted, and with a data entry cut-off of February 9, 2005, investigators had reported 445 events, with a significant increase in median PFS observed in patients receiving bevacizumab plus paclitaxel compared with paclitaxel alone (11.4 months vs. 5.8 months, respectively; HR = 0.42, log-rank test $p < 0.0001$) (Figure 1, Table 1). As agreed with the FDA, an independent review of efficacy was provided in June 2007, blinded to treatment allocation and using all available data up to February 9, 2005. Due to the fact that this review was conducted 2 years after the censoring date, more data were actually available, so only events occurring prior to February 9, 2005 were considered. The IRF analysis reported 357 PFS events. This independent analysis confirmed the significant increase in median PFS in patients receiving combination therapy versus paclitaxel alone (median PFS of 11.3 months vs. 5.8 months, respectively; HR = 0.48, $p < 0.0001$) (Table 1).

This significant PFS benefit was maintained across a number of patient subgroups in all of the analyses reported. ECOG reported that hazard ratios favoured combination therapy in all subgroups but did not reach statistical significance in some of the smaller subgroups. [4] Similar findings were reported by the regulatory analyses; a reduction in the risk of progression, as assessed by the IRF, was observed in all pre-specified patient subgroups, including age, hormone receptor status, disease-free interval, number of metastatic sites, measurable disease at baseline and prior adjuvant chemotherapy (Figure 2). [7] Similar findings were observed with pre-defined, IRF-assessed, subgroup analyses for prior taxane or anthracycline therapy. The exceptions to this were the smaller subsets of patients with HER2-




No. of patients at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Paclitaxel/ bevacizumab | 368 | 232 | 87 | 29 | 5 | 3 | 0 |
| Paclitaxel | 354 | 138 | 37 | 10 | 0 | 0 | 0 |

**Fig. 1 – E2100: PFS analysis by investigator assessment (FDA analysis).** [7]

positive and ER status unknown disease, which each contained fewer than 20 patients. Patient subgroups that traditionally have a poor prognosis and/or poor response to therapy were among those that benefited, including those with ER-negative (HR = 0.44) or triple-negative (HR = 0.49) disease and those with a disease-free interval of ⩽24 months (HR = 0.58). [7] One of the largest improvements in PFS was seen in the group of patients who had received prior taxane therapy in the adjuvant setting (HR = 0.33). [7] These patients are likely to have disease that is at least partially resistant to taxanes, so this finding would appear to be consistent with preclinical data suggesting that concomitant use of anti-VEGF therapy restores the sensitivity of cancer cells to taxanes. [8,9]

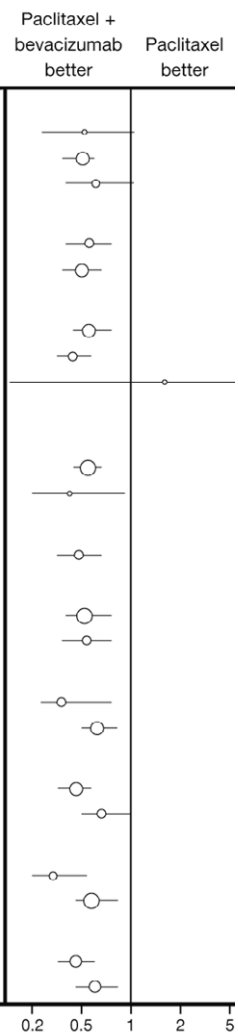
According to ECOG, at data cut-off (June 7, 2007) 483 patients had died, the majority (88%) from progressive disease. [4] Median overall survival was similar in the combination therapy group and in the group of patients receiving paclitaxel alone (26.7 vs. 25.2 months, HR = 0.88, $p = 0.16$). However, 1-year survival was statistically significantly better in the bevacizumab plus paclitaxel group than in the paclitaxel alone group (81.2% vs. 73.4%, $p = 0.01$). [4] Final analysis of overall survival for regulatory purposes was planned to be conducted after a total of 481 patients had died, resulting in a data cut-off date of October 21, 2006. [7] Investigator-assessed 1-year survival was statistically significantly better in the bevacizumab plus paclitaxel arm than in the paclitaxel alone arm (81.4% vs. 74.0%; $p = 0.017$). [7] Median overall survivals were not statistically significantly different (26.5 vs. 24.8 months, HR = 0.87, $p = 0.14$). [5]

The study protocol specified that after disease progression no cross-over to bevacizumab was permitted in patients receiving paclitaxel alone, and patients receiving combination therapy were not allowed to receive further bevacizumab. However, bevacizumab had been commercially available in the US at the time of first presentation of the E2100 results at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2005. Unfortunately, data on subsequent therapies after first progression were not collected, so that any possible effect of post-progression therapy on overall survival, particularly for patients in the paclitaxel arm, cannot be determined.

ECOG published response rates, in the subset of patients with measurable disease at baseline, of 49.2% and 25.2%, respectively, in patients receiving bevacizumab and paclitaxel versus paclitaxel alone ($p < 0.001$). [4] These response rates are different from those presented by ECOG at the ASCO meeting in 2005. The reason for this is that at the first public dissemination of the results from this trial, only those patients with a response confirmed by ECOG reviewers were included as responders, and over time more data were centrally reviewed by ECOG, thus increasing the confirmed response rate. According to analyses for regulatory purposes, the investigator-assessed objective response rate was significantly higher in those patients receiving bevacizumab plus paclitaxel, at 48.0% compared with 23.4% in patients receiving paclitaxel alone ($p < 0.0001$). [5] The IRF analysis confirmed this significant improvement, finding response rates respectively of 49.8% ($n = 229$) and 22.2% ($n = 243$); $p < 0.0001$. [5]

These different analyses all confirm the clinical benefit of the addition of bevacizumab to paclitaxel, with remarkably similar hazard ratios for PFS, and statistically significant benefits in PFS and objective response rate noted in all of the data sets analysed. [4–6] Similarly, all analyses revealed a trend towards an improvement in overall survival with the addition of bevacizumab to paclitaxel in previously untreated metastatic breast cancer patients. Note that the FDA has recently approved

| Subgroup + bevacizumab (*n* = 368) | *n* | Median PFS (months) Paclitaxel (*n* = 354) | Paclitaxel + bevacizumab (*n* = 368) | HR (95% CI) |
|---|---|---|---|---|
| *Age (years)* | | | | |
| <40 | 59 | 4.8 | 8.3 | 0.54 (0.26–1.09) |
| 40–64 | 496 | 6.1 | 12.1 | 0.51 (0.39–0.66) |
| ≥65 | 167 | 6.1 | 10.4 | 0.67 (0.42–1.05) |
| *Disease-free interval* | | | | |
| ≤24 months | 296 | 4.9 | 10.6 | 0.58 (0.42–0.79) |
| >24 months | 426 | 8.3 | 12.1 | 0.50 (0.38–0.67) |
| *ER status* | | | | |
| positive | 446 | 7.7 | 11.9 | 0.59 (0.44–0.78) |
| negative | 265 | 4.9 | 11.1 | 0.44 (0.31–0.61) |
| unknown | 11 | 21.3 | – | 1.70 (0.15–19.07) |
| *HER2 status* | | | | |
| positive | 15 | 2.4 | 11.3 | 0.00 (0.00– –) |
| negative | 650 | 6.1 | 11.1 | 0.57 (0.45–0.71) |
| unknown | 57 | 7.7 | 12.5 | 0.42 (0.19–0.93) |
| *ER/PR/HER2 combined* | | | | |
| negative | 232 | 5.3 | 10.6 | 0.49 (0.34–0.70) |
| *Metastatic sites* | | | | |
| <3 | 514 | 6.6 | 13.3 | 0.53 (0.41–0.69) |
| ≥3 | 208 | 4.8 | 8.3 | 0.56 (0.38–0.81) |
| *Measurable disease at baseline* | | | | |
| no | 250 | 4.1 | 16.6 | 0.37 (0.25–0.54) |
| yes | 472 | 6.7 | 10.7 | 0.66 (0.51–0.85) |
| *Prior adjuvant chemotherapy* | | | | |
| yes | 475 | 5.8 | 12.4 | 0.47 (0.36–0.61) |
| no | 247 | 6.1 | 11.2 | 0.70 (0.49–1.01) |
| *Prior taxane therapy* | | | | |
| yes | 142 | 5.8 | 13.1 | 0.33 (0.20–0.54) |
| no | 580 | 6.0 | 11.0 | 0.60 (0.47–0.76) |
| *Prior anthracycline therapy* | | | | |
| yes | 364 | 6.0 | 12.8 | 0.46 (0.34–0.62) |
| no | 358 | 5.7 | 10.6 | 0.64 (0.47–0.86) |




PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor.

**Fig. 2 – E2100: PFS subgroup analysis by IRF assessment (FDA analysis).** [7]

bevacizumab in combination with paclitaxel for first-line treatment of metastatic breast cancer, based on these data.

## 5. Safety

Treatment was discontinued as a result of toxicity for 142 patients (19.7%): 68 (19.2%) patients receiving paclitaxel alone and 74 (20.1%) patients receiving bevacizumab plus paclitaxel. [7] The median duration of therapy was 5.9 months in the paclitaxel arm and 9.7 months in the combined bevacizumab plus paclitaxel arm. [7] No new safety signals were identified with the addition of bevacizumab to paclitaxel compared with previous phase III experience. The increased incidence of grade 3–5 hypertension, proteinuria, arterial thromboembolic events, bleeding, congestive heart failure and gastrointestinal perforations seen in the bevacizumab arm relative to the paclitaxel alone arm was within the range previously reported in other bevacizumab studies (Table 3). No increase was seen in the incidence of grade 3–5 vascular thromboembolic events. The next article in this supplement discusses these adverse events in more detail and provides recommendations for their management in patients receiving bevacizumab.

Grade 3 and 4 adverse events that were increased by ⩾5% in patients receiving paclitaxel plus bevacizumab compared with those receiving paclitaxel alone were sensory neuropathy (24.2% vs. 17.5%), hypertension (16.0% vs. 1.4%), fatigue (10.7% vs. 5.2%) and neutropenia with or without infection (17.4% vs. 8.0%). [7] The increased incidence of neuropathy, fatigue and neutropenia (typically chemotherapy-related toxicities) in patients who received bevacizumab may be accounted for by the fact that these patients received more doses of paclitaxel than those treated with paclitaxel alone (median 24 vs. 17).

**Table 3 – E2100: incidence of grade 3–5 adverse events (FDA analysis)** [7]

| Adverse event | Incidence, n (%) | |
|---|---|---|
| | Paclitaxel ($n = 348$) | Bevacizumab + paclitaxel ($n = 363$) [a] |
| Hypertension | 5 (1.4) | 58 (16.0) |
| Proteinuria | 0 (0) | 11 (3.0) |
| Arterial thromboembolic events | 0 (0) | 13 (3.6) |
| Vascular thromboembolic events | 15 (4.3) | 11 (3.0) |
| Bleeding | 1 (0.3) | 8 (2.2) |
| Congestive heart failure | 1 (0.3) | 8 (2.2) |
| Gastrointestinal perforations | 0 (0) | 2 (0.6) |

[a] Includes NCI AdEERS mandatory collection in the paclitaxel plus bevacizumab arm only, which does not allow valid comparison between the two arms.

## 6. Dosing and administration information for bevacizumab

Bevacizumab in combination with paclitaxel has been approved in the European Union since March 2007, and in the US since February 2008, and is also approved in many other countries for first-line treatment of patients with metastatic breast cancer. The recommended dose is 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks as an intravenous infusion. This dose was selected based on the findings of a phase I/II trial, which examined three doses of bevacizumab (3, 10, and 20 mg/kg every 2 weeks) in patients who had received prior therapy for metastatic breast cancer. [10] While the sample size was too small to draw definite conclusions on the efficacy of the different doses, the dose-limiting toxicity of headache with nausea and vomiting at the 20 mg/kg dose led to the recommendation of 10 mg/kg every 2 weeks as the dose for further investigation in this indication. The licensed dose of bevacizumab for use in patients with colorectal cancer (5 mg/kg every 2 weeks) was determined independently from the breast cancer studies. Additional information on the optimal dose of bevacizumab in metastatic breast cancer will be provided in 2008 by the AVADO study, a randomised, double-blind, placebo-controlled, multicentre phase III trial investigating the safety and efficacy of bevacizumab (7.5 mg/kg or 15 mg/kg) in combination with docetaxel versus docetaxel alone.

The initial dose of bevacizumab should be delivered over 90 minutes. If well tolerated, the second infusion may be administered over 60 minutes, and again if well tolerated, subsequent infusions can be delivered over 30 minutes. [5] Research suggests that a 10 minute infusion is also feasible, [11] but this is not currently licensed. Bevacizumab must not be administered as an intravenous push or bolus. The initial dose should be administered following chemotherapy, with all subsequent doses administered before or after chemotherapy, according to local practice. It is recommended that treatment be continued until progression of the underlying disease as was the practice in the E2100 trial [10] and is supported by preclinical evidence. [12,13]

## 7. Discussion

Although bevacizumab functions by inhibiting a specific molecular target, currently there are no data to support a test to determine which subsets of breast cancers are sensitive to bevacizumab therapy. Several ongoing trials incorporate molecular studies in an attempt to identify predictive markers for benefit from this agent. To date, however, attempts to correlate potential markers with benefit from bevacizumab in large clinical trials in several tumour types have proved unsuccessful. Markers investigated include VEGF and other members of the same receptor family (VEGF-B, VEGF-C, VEGF-D, PIGF), VEGF receptors-1, -2 and -3, anti-angiogenic proteins (thrombospondin-2) and oncogenes (p53, HER2, k-Ras, b-Raf). [14–16] Further evaluation of some of these, particularly the VEGF family and their receptors, and other markers is planned and such analyses will be performed once efficacy data from currently ongoing bevacizumab studies are mature. Caution should be exercised, however, as samples from primary tumours and sera/plasma may not mimic the situation within the metastatic lesions.

Despite the significant improvement in PFS reported in the E2100 study, there was no significant difference in overall survival, though there were more patients alive one year after starting bevacizumab and paclitaxel than amongst those randomised to paclitaxel alone. [4,7] Overall survival was not the primary endpoint of the study, which had only 10–15% power to detect a 3-month improvement in this endpoint (80% power to detect a 7-month improvement). It is interesting to compare this to the studies of trastuzumab plus chemotherapy in metastatic breast cancer, where an agent that directly targets a defined subset of breast cancers significantly prolonged overall survival, despite the fact that patients were allowed to cross-over to trastuzumab therapy in later lines of treatment. [17,18] Unfortunately, data on later

lines of treatment were not collected for patients in the E2100 study, so it is impossible to investigate how subsequent lines of therapy or cross-over to bevacizumab in control arm patients could have affected overall survival in each arm. It is interesting, however, that the bevacizumab Kaplan-Meier curves are superior to the control arm curves for the first 30 months of observation.

## 8. Conclusions

The addition of bevacizumab to paclitaxel produced clinically meaningful and statistically significant improvements in both response rate and PFS in a phase III trial in previously untreated metastatic breast cancer patients. These findings were corroborated by more complete analyses for regulatory purposes, which were based on the ITT population and confirmed by an IRF. The subgroup of patients with triple-negative disease derived the same level of PFS benefit from bevacizumab treatment, with a HR of 0.49. A planned large phase III trial, BEATRICE, opened recruitment in November 2007 to investigate the addition of bevacizumab to defined standard adjuvant chemotherapy regimens in patients with triple-negative early breast cancer. The combination of bevacizumab and paclitaxel was generally well tolerated in trial E2100, with no new safety signals observed. These encouraging results have led to the development of multiple phase III trials of bevacizumab in combination with chemotherapy agents in first-line metastatic breast cancer. These, along with trials investigating the addition of bevacizumab to other anticancer therapies such as trastuzumab and endocrine agents, are discussed in the final paper of this supplement.

Several ongoing trials incorporate molecular studies in an attempt to identify predictive markers for benefit from bevacizumab. To date, however, no such biomarkers have been identified. Further evaluation of these markers is planned, with the aim of targeting the correct patient population for bevacizumab therapy.

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## Conflict of interest statement

Professor Cameron has received honoraria and advisory board fees from F. Hoffmann-La Roche and Pfizer and research funding from F. Hoffmann-La Roche Ltd.

## References

1. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971;**285**(21):1182–6.
2. Folkman J. Antiangiogenesis agents. In DeVita VT, Hellman S, Rosenberg SA, editors. *Cancer: principles and practice of oncology,* 7th edition. Philadelphia: Lippincott Williams & Wilkins; 2006.
3. Berney CR, Yang JL, Fisher RJ, et al. Vascular endothelial growth factor expression is reduced in liver metastasis from colon cancer and correlates with urokinase-type plasminogen activator. *Clin Exp Metastasis* 2000;**18**(8): 651–5.
4. Miller KD, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007;**357**(26):2666–76.
5. Avastin Summary of Product Characteristics. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/avastin/H-582-PI-en.pdf. Accessed 5 March 2008.
6. EMEA. Avastin European Public Assessment Report 2007. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/avastin/Avastin-AR-H-582-II-08.pdf. Accessed 5 September 2007.
7. F. Hoffmann-La Roche Ltd. Data on file.
8. Sweeney CJ, Miller KD, Sissons SE, et al. The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. *Cancer Res* 2001;**61**(8):3369–72.
9. Busby JE, Kim SJ, Yazici S, et al. Therapy of multidrug resistant human prostate tumors in the prostate of nude mice by simultaneous targeting of the epidermal growth factor receptor and vascular endothelial growth factor receptor on tumor-associated endothelial cells. *Prostate* 2006;**66**(16):1788–98.
10. Cobleigh MA, Langmuir VK, Sledge GW, et al. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. *Semin Oncol* 2003;**30**(Suppl 16):117–24.
11. Reidy DL, Chung KY, Timoney JP, et al. Bevacizumab 5 mg/kg can be infused safely over 10 minutes. *J Clin Oncol* 2007;**25**(19):2691–5.
12. Vosseler S, Mirancea N, Bohlen P, et al. Angiogenesis inhibition by vascular endothelial growth factor receptor-2 blockade reduces stromal matrix metalloproteinase expression, normalizes stromal tissue, and reverts epithelial tumor phenotype in surface heterotransplants. *Cancer Res* 2005;**65**(4):1294–305.
13. Mancuso MR, Davis R, Norberg SM, et al. Rapid vascular regrowth in tumors after reversal of VEGF inhibition. *J Clin Invest* 2006;**116**(10):2610–21.
14. Hillan KJ, Koeppen HKW, Tobin P, et al. The role of VEGF expression in response to bevacizumab plus capecitabine in metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 2003;**22**:191 [Abstract 766].
15. Jubb AM, Hurwitz HI, Bai W, et al. Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. *J Clin Oncol* 2006;**24**(2):217–27.
16. Ince WL, Jubb AM, Holden SN, et al. Association of k-ras, b-raf and p53 status with the treatment effect of bevacizumab. *J Natl Cancer Inst* 2005;**97**(13):981–9.

17. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;**344**(11):783–92.
18. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;**23**(19):4265–74.