Safety of bevacizumab in metastatic breast cancer patients undergoing surgery

Javier Cortés a,*, Mireia Caralt b, Suzette Delalogue c, Hernan Cortes-Funes d, Jean-Yves Pierga e, Kathleen I. Pritchard f, David T. Bollag g, David W. Miles h

a Department of Oncology, Vall d’Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain
b Department of Hepatobiliopancreatic Surgery and Transplants, Vall d’Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain
c Breast Oncology Department, Institut Gustave Roussy, Villejuif Cedex, France
d Medical Oncology Division, ’12 de Octubre’ University Hospital, Madrid, Spain
e Department of Medical Oncology, Institut Curie, Université Paris Descartes, Paris, France
f Sunnybrook Odette Cancer Centre and the University of Toronto, Toronto, Canada
g Department of Clinical Research, Division of Oncology & Hematology, F. Hoffmann-La Roche Ltd., Basel, Switzerland
h Breast Unit, Mount Vernon Cancer Centre, Middlesex, United Kingdom

ABSTRACT

Background: Evaluate the safety of surgery in relation to bevacizumab in the first-line treatment of metastatic breast cancer (mBC) in two international trials.

Patients and methods: The incidence, type and timing of post-surgical bleeding events and wound-healing complications were assessed in surgical patients in the AVastin And DOce-taxel (AVADO) (NCT00333775) and Avastin THErapy for advaNced breAst cancer (ATHENA) (NCT00448591) trials. Both study protocols followed recommendations to withhold bevacizumab for at least 6 weeks before elective surgery and to wait 28 days (or until the wound was fully healed) after major surgery before recommencing bevacizumab therapy.

Results: In AVADO, 221 surgical procedures (55 major, 166 minor) were performed in 155 patients. In ATHENA, 1190 surgical procedures (435 major, 755 minor) were performed in 672 patients. One bevacizumab-treated AVADO patient (0.9%) who underwent surgery experienced a grade 3 bleeding event. In ATHENA, six patients (0.9%) who underwent surgery experienced grade 3 bleeding events and one patient (0.1%) experienced a grade 4 bleeding event. No grade 5 bleeding events in patients undergoing surgery were reported in either study. One grade 3 wound-healing complication was reported in each of the AVADO arms: placebo (n = 46, 2.2%), bevacizumab 7.5 mg/kg (n = 57, 1.8%) and bevacizumab 15 mg/kg (n = 52, 1.9%). Incidence of grade 3–4 wound-healing complications in ATHENA was 2.2% and 1.3% in patients undergoing minor or major surgery, respectively.

Conclusions: Surgery can be performed on patients with mBC undergoing bevacizumab therapy with a low risk of severe bleeding or wound-healing complications post surgery, if current labelling recommendations are adhered to.

© 2011 Elsevier Ltd. All rights reserved.

* Corresponding author: Tel.: +34 948 296696; fax: +34 948 255500.
E-mail address: jacortes@vhebron.net (J. Cortés).
0959-8049/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2011.11.021
1. Introduction

Bevacizumab (Avastin\textsuperscript{\textregistered}; F. Hoffmann-La Roche Ltd.), a recombinant humanised monoclonal antibody that blocks the activity of vascular endothelial growth factor (VEGF),\textsuperscript{1} has demonstrated significant clinical benefit in several solid tumours.\textsuperscript{2–4} In combination with other agents as a first-line therapy, bevacizumab has prolonged progression-free survival (PFS) and increased response rates in patients with locally recurrent (LR) or metastatic breast cancer (mBC).\textsuperscript{5–9} In the Eastern Cooperative Oncology Group 2100 (E2100) trial, bevacizumab plus weekly paclitaxel increased the median PFS from 5.8 to 11.4 months (hazard ratio [HR] 0.42, \(p < 0.0001\)) in patients who had received no previous chemotherapy for LR or mBC\textsuperscript{5,6}, which was confirmed by an independent review (5.8 versus 11.3 months, HR 0.48, \(p = 0.0001\)).\textsuperscript{6} In the placebo-controlled AVastin And DOcetaxel (AVADO) trial (BO17708), bevacizumab 15 mg/kg plus docetaxel significantly increased PFS versus placebo plus docetaxel (10.0 versus 8.1 months, respectively, stratified analysis: HR 0.67, \(p = 0.0002\)) and overall response rates (46% [placebo] versus 64%; \(p = 0.0003\)).\textsuperscript{4,5} The phase III, Regimens In Bevacizumab for Breast Oncology (RIBBON-1) study of bevacizumab combined with taxanes, anthracyclines or capecitabine, also met its primary end-point of improved PFS with combination therapy versus chemotherapy plus placebo.\textsuperscript{9}

Soft-tissue and vascular toxicities have been observed in patients undergoing major surgery while receiving bevacizumab.\textsuperscript{10,11} VEGF is a key mediator of angiogenesis and tumour progression,\textsuperscript{12,13} and likely plays multiple roles in normal wound-healing, inducing angiogenesis and stimulating epithelialisation and collagen deposition.\textsuperscript{14} VEGF inhibition may therefore impair or delay wound-healing, or result in bleeding; a consideration when performing routine and emergency surgery in patients with mBC. Given bevacizumab’s long elimination half-life (18–20 days)\textsuperscript{15} effects may persist despite treatment discontinuation during the pre-operative period. Current labelling recommends that bevacizumab is withheld for elective surgery, and that treatment is delayed for at least 28 days after major surgery or until the wound has fully healed.

Results from large, international trials including the phase III AVADO and phase IIB Avastin THERapy for advaNced breast cancer (ATHENA) studies have confirmed the general safety of bevacizumab as a first-line treatment option for mBC.\textsuperscript{3–5,9,16} As a proportion of patients in these trials underwent major or minor surgery as part of their ongoing cancer care, we report safety data for patients with mBC receiving bevacizumab in the surgical setting in AVADO and ATHENA.

2. Methods

Two large, international, multicentre studies, AVADO and ATHENA, were included in this analysis. The study methods, including patient eligibility criteria, study design, treatment and assessments, have been reported previously.\textsuperscript{5,16}

AVADO was a randomised, double-blind, placebo-controlled, phase III trial that investigated bevacizumab in combination with first-line docetaxel chemotherapy in patients with LR or mBC.\textsuperscript{4} From March 2006 to April 2007, 736 patients in 24 countries received docetaxel 100 mg/m\textsuperscript{2} every 3 weeks (q3w; maximum nine cycles) plus either placebo or bevacizumab (7.5 or 15 mg/kg q3w). The primary end-point was PFS, and secondary end-points included safety.

ATHENA was a single-arm trial that evaluated the safety of bevacizumab combined with first-line taxane-based (or other non-anthracycline) chemotherapy for LR or mBC.\textsuperscript{15} Between September 2006 and June 2008, 2251 patients were recruited from 37 countries. Patients received bevacizumab 10 mg/kg every 2 weeks or 15 mg/kg q3w plus a taxane (either alone or with other chemotherapy) or other non-anthracycline chemotherapy. The primary study end-point was safety, with particular emphasis on the incidence of serious adverse events (SAEs) and adverse events (AEs) of special interest with bevacizumab.

Minor surgery included any surgical procedure not involving general anaesthesia (local or regional anaesthesia permitted) or respiratory assistance. Major surgery included any surgical procedure involving anaesthesia or respiratory assistance; all operations involving opening body cavities or in which severe haemorrhage was possible; all potentially life-threatening conditions; and any procedure with the potential to induce permanent anatomic (physical) or physiological impairment and/or associated with orthopaedics or extensive tissue dissection.

Both studies excluded patients who had undergone major surgery, including open biopsy, within 28 days, or minor surgery within the previous 24 h at the time of randomisation. During the study, bevacizumab (or placebo in the blinded AVADO study) was withheld for at least 6 weeks (two half lives) before elective surgery. Both study protocols recommended waiting 28 days (or until wound fully healed) from major surgery to recommencement of therapy; no guidance was given for minor surgery. If necessary, it was recommended that emergency surgery be performed without delay after a careful risk–benefit assessment.

The incidence, type and timing of post-surgical bleeding events and wound-healing complications (WHC) were assessed in all patients who underwent surgery in ATHENA and AVADO. AEs were categorised by MedDRA (version 10.1) and AE severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.\textsuperscript{17} In general, the NCI-CTCAE grades are: Grade 1 Mild AE, Grade 2 Moderate AE, Grade 3 Severe AE, Grade 4 Life-threatening or disabling AE, Grade 5 Death related to AE. Specific details associated with grading of WHC and bleeding events are in the NCI-CTCAE guidelines.\textsuperscript{17}

3. Results

3.1. Types and number of procedures performed

A total of 221 major or minor surgical procedures were performed on 155 patients in AVADO, including those in the control group (87 procedures in the bevacizumab 7.5 mg/kg arm, 74 in the bevacizumab 15 mg/kg arm) (Table 1). In ATHENA, 1190 surgical procedures (435 major, 755 minor) were performed in 672 patients. Table 2 summarises the most common procedures in this study.
3.2. Time between dosing and surgery

In both AVADO and ATHENA, the median time from last bevacizumab dose to surgery was longer for major than for minor surgery (Fig. 1). Elective and emergency surgeries were common in both studies. However, in each trial, some major procedures took place within fewer than the 6 weeks post-bevacizumab time period recommended for elective surgery (time [range] between dosing and any surgery: ATHENA 0–933 days [Fig. 2]; AVADO: 0–126 days), suggesting that they were performed as emergency surgeries.

In AVADO, 79 of 109 bevacizumab-treated (72%) and 31 of 46 control (67%) patients who underwent surgery restarted bevacizumab or placebo. In ATHENA, 369 of 672 patients (55%) who underwent any type of surgery restarted bevacizumab afterwards. In both studies, patients who underwent major surgery were less likely to restart bevacizumab than those who underwent minor procedures (31–35% versus 70–84%, respectively). Median time from surgery to restarting bevacizumab was longer for major versus minor surgery (Fig. 3).

3.3. Bleeding events and WHC

In AVADO, grade 1–2 bleeding events were reported in one of the 46 patients (2.2%) undergoing surgery in the placebo arm (bevacizumab 7.5 mg/kg: 18 of 57 [31.6%]; bevacizumab 15 mg/kg: nine of 52 [17.3%]) (Table 3). There was only 1 grade ≥3 bleeding event: grade 3 epistaxis after minor surgery (a tooth extraction) in the bevacizumab 15 mg/kg arm. There was no evidence for a direct relationship between the

---

**Table 1 – Number and type of on-study surgical procedures.**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Placebo + docetaxel</th>
<th>Bevacizumab 7.5 mg/kg + docetaxel</th>
<th>Bevacizumab 15 mg/kg + docetaxel</th>
<th>Bevacizumab + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor surgery</td>
<td>40</td>
<td>67</td>
<td>59</td>
<td>755</td>
</tr>
<tr>
<td>Major surgery</td>
<td>20</td>
<td>20</td>
<td>15</td>
<td>435</td>
</tr>
<tr>
<td>Surgeries, n</td>
<td>60</td>
<td>87</td>
<td>74</td>
<td>1190</td>
</tr>
<tr>
<td>Patients, n</td>
<td>46</td>
<td>57</td>
<td>52</td>
<td>672</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>34</td>
<td>45</td>
<td>45</td>
<td>358</td>
</tr>
<tr>
<td>Major surgery</td>
<td>18</td>
<td>17</td>
<td>11</td>
<td>314</td>
</tr>
</tbody>
</table>

**Table 2 – The most frequently performed types of major and minor surgery in the Avastin THERapy for advaNced brAst cancer (ATHENA) study.**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Minor (%)</th>
<th>Major (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous catheterisation/catheter removal/catheter placement</td>
<td>194 (8.6)</td>
<td>Mastectomy/radical mastectomy 73 (3.2)</td>
</tr>
<tr>
<td>Aspiration pleural cavity/pleural effusion/thoracic cavity drainage/pneumothorax drainage</td>
<td>106 (4.7)</td>
<td>Osteosynthesis/humerus fracture/hip arthroplasty/bone operation (other) 40 (1.8)</td>
</tr>
<tr>
<td>Tooth extraction/tooth abscess/dental operation</td>
<td>72 (3.2)</td>
<td>Lymphadenectomy 32 (1.4)</td>
</tr>
<tr>
<td>Biopsy b</td>
<td>54 (2.4)</td>
<td>Malignant tumour excision – other 11 (0.5)</td>
</tr>
<tr>
<td>Abscess drainage</td>
<td>13 (0.6)</td>
<td>Hepatectomy 10 (0.4)</td>
</tr>
<tr>
<td>Osteonecrosis surgery</td>
<td>12 (0.5)</td>
<td>Paracentesis abdomen 10 (0.4)</td>
</tr>
</tbody>
</table>

---

Fig. 1 – Median time between last bevacizumab/placebo dose and surgery (n indicates number of patients).
procedures performed and the sites or types of events. For example, 11 of 18 patients (61%) receiving bevacizumab 7.5 mg/kg and four of 10 patients (40%) receiving bevacizumab 15 mg/kg who reported post-surgery bleeding events experienced epistaxis alone. In ATHENA, bleeding events occurred in 91 of 672 patients (13.5%) undergoing surgery (8.3% of major surgery patients, n = 314; 18.2% of minor surgery patients, n = 358). Only 19 (6.1%) and 56 patients (15.6%) undergoing major and minor surgery, respectively, experienced grade 1 bleeding events. Grade 3 bleeding occurred in six patients (0.9%), three of whom (0.4%) had undergone major surgery (sigmoidectomy, mastectomy and muscle operation). Four of these bleeding events (post-procedural haemorrhage, post-procedural haematoma, subcutaneous haematoma and gastrointestinal haemorrhage) may have been related to the procedure performed. One grade 4 bleeding event was

<table>
<thead>
<tr>
<th>Procedure</th>
<th>AVADO Placebo + docetaxel (n = 46)</th>
<th>Bevacizumab 7.5 mg/kg + docetaxel (n = 57)</th>
<th>Bevacizumab 15 mg/kg + docetaxel (n = 52)</th>
<th>Bevacizumab + chemotherapy (n = 672)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>(n = 28)</td>
<td>(n = 40)</td>
<td>(n = 41)</td>
<td>(n = 358)</td>
</tr>
<tr>
<td>Major</td>
<td>(n = 18)</td>
<td>(n = 17)</td>
<td>(n = 11)</td>
<td>(n = 314)</td>
</tr>
<tr>
<td>Grade 1–2, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding events</td>
<td>0 (0)</td>
<td>1 (5.5)</td>
<td>15 (37.5)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Grade 3–4, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding events</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 1–2, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHC</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 3–4, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHC</td>
<td>1 (3.6)</td>
<td>0 (0)</td>
<td>1 (5.9)</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

n indicates patients with at least one event.

Adverse events are not necessarily related to the surgical procedure and/or bevacizumab treatment but occurred after either intervention. For patients with major and minor surgeries, only events with onset after major surgeries are considered.

'Bleeding events' includes: epistaxis, gingival bleeding, haemorrhage, haemorrhage (rectal, vaginal, mouth, anal, haemorrhoidal, catheter site, conjunctival, gastric, gastrointestinal, intra-abdominal, post-procedural, upper gastrointestinal, uterine), haematuria, haemoptysis, haematomata, haematoma (post-procedural, periabdominal, subcutaneous, catheter site), cystitis haemorrhagic, diarrhoea haemorrhagic, haematochezia, haemorrhax, haematemesis, menorrhagia, metrorrhagia, melaena, central nervous system (CNS) bleeding (CNS haemorrhage). WHC includes: impaired healing, wound dehiscence, post-operative wound infection, wound abscess, wound infection, wound complication, wound haemorrhage.
reported, which was a haemothorax in a patient undergoing major surgery. No grade 5 bleeding was reported in patients who underwent surgery.

In AVADO, post-surgical WHC and infections occurred in one patient each in the placebo arm (2.2%) and the two bevacizumab arms (1.8% and 1.9%) (Table 3). All events were grade 3 and one occurred after major surgery. There was no suggestion that WHC were more severe or frequent with bevacizumab versus placebo. In ATHENA, grade 1–2 WHC occurred in 17 of 358 patients (4.7%) undergoing minor surgery and 10 of 314 patients (3.2%) undergoing major surgery. Grade 3–4 WHC were reported in 12 of 672 patients (1.8%) undergoing surgery (four cases after major surgery [impaired healing n = 3, wound dehiscence n = 1] and eight after minor surgery [impaired healing n = 6, post-operative wound infection n = 1, wound abscess n = 1]). Only two of the four patients with grade 3–4 events after major surgery restarted bevacizumab. No grade 5 WHC was noted following major or minor surgery. Across the two studies, in bevacizumab-treated patients undergoing major surgery who experienced grade 3–4 WHC, median duration of these complications was 23 days (range 6–204), suggesting that resolution was mostly relatively rapid. Of the five bevacizumab-treated patients in both studies who experienced grade 3–4 WHC after major surgery, three patients underwent surgery before the recommended 6 weeks after stopping bevacizumab (one patient each: pleural operation after 23 days and grade 4 wound dehiscence; modified radical mastectomy and lymphadenectomy after 21 days and grade 4 wound dehiscence; modified radical mastectomy after 28 days and grade 3 impaired wound-healing).

4. Discussion

With a considerable number of cancer patients undergoing routine or emergency surgery for unforeseen events before or during treatment for metastatic disease, it is important to determine the effect of bevacizumab on bleeding and wound-healing in those receiving the drug as part of a treatment regimen for mBC. Surgery as part of palliative therapy and for disease-related complications such as bleeding, ulceration or infection may also be necessary in patients with mBC. Surgery for curative purposes or in an attempt to prolong survival is also a consideration in patients with oligometastases18 or an initial stage IV diagnosis,19,20 although more evidence is required to demonstrate a survival benefit.21–24 Overall, data from AVADO and ATHENA suggest that if recommendations are followed, mBC patients receiving bevacizumab can undergo surgery with minimal risk of severe post-procedural haemorrhage or WHC. In AVADO, which included a relatively small number of bevacizumab-treated patients undergoing surgery (n = 109), only one patient (0.9%) experienced a grade ≥3 bleeding event. In ATHENA (n = 672), grade 3/4 bleeding was reported in four patients (1.3%) who had major surgery (no grade 5 events reported) and in three patients (0.8%) who underwent minor surgery. In AVADO, two grade 3 WHC (1.8%) occurred with bevacizumab and only one (0.9%) was in a patient undergoing major surgery. In ATHENA, grade 3–4 WHC occurred in four (1.3%) major surgery patients (no grade 5 events reported), and minor surgery, including biopsies and catheter insertion/removal, was performed with a low risk of severe (grade ≥3) AEs.

In both studies, wound-healing AEs typically occurred within 4 weeks of surgery. The average length of bevacizumab interruption on either side of a surgical procedure was longer for major than minor surgeries, suggesting that, generally, physicians followed trial protocol recommendations. In AVADO, WHC did not appear more severe or frequent in patients receiving bevacizumab compared with placebo.

This is the first report of surgical safety data from a large study (ATHENA; n = 2251), representative of a population of bevacizumab-treated patients with mBC seen in the general clinical setting. As a single-arm study, ATHENA had no control group with which to compare bevacizumab-related toxicities. The smaller AVADO study (n = 736), however, provided information on the safety of surgery in bevacizumab-treated patients in a randomised, placebo-controlled setting. Minor bleeding events were considerably more common in bevacizumab-treated patients versus control, however, this is a known side-effect of bevacizumab and most events appeared unrelated to the surgical procedures performed. No evidence was seen of an increased frequency of grade 3–5 AEs with bevacizumab relative to placebo in patients undergoing surgery.

AE rates among bevacizumab-treated patients with mBC undergoing surgery are in keeping with those from large safety studies in other first-line indications. In BEAT (n = 1914), an international safety trial that investigated bevacizumab plus standard chemotherapy in metastatic colorectal cancer, the WHC rate was 5% (2% grade 3–4 or SAE) in 225 patients who underwent surgery with curative intent for hepatic lesions.13 All-grade bleeding events, including non-surgery-related bleedings, occurred in 71 patients (32%) who underwent surgery. Serious and/or grade 3–5 bleeding events occurred in six patients (2.7%).10 WHC and bleeding events were also infrequent in patients having vascular access devices inserted before starting bevacizumab, even when <7 days had elapsed from implantation.15 In the United States of America (USA)-based BRITE safety study (n = 1953) of bevacizumab plus standard chemotherapy in metastatic colorectal cancer, 22 of the 622 patients (3.5%) undergoing any surgery experienced serious WHC (as determined by the investigator, not according to NCI criteria).26 Among patients with untreated locally advanced, metastatic or recurrent non-squamous non-small-cell lung cancer receiving bevacizumab plus standard chemotherapy in the international, SAIL study (n = 1940), grade ≥3 bleeding events occurred in seven (5.9%) of 118 patients who underwent surgery during bevacizumab therapy.27 Five (1.6%) of 316 patients who had surgery before and/or during the study reported WHC (0.3% grade ≥3).

Current recommendations advise that bevacizumab is not initiated for ≥28 days following major surgery or until the surgical wound is fully healed.14 This was based on pooled data from two randomised trials of bevacizumab in colorectal cancer, where the WHC rate after unplanned major surgery during treatment was 13% for 5-FU plus bevacizumab-treated patients compared with 3.4% for patients receiving chemotherapy alone.11 However, in patients who had undergone major surgery 28–60 days before commencing bevacizumab,
no significant difference in WHC was noted. A risk–benefit analysis is recommended ahead of emergency surgery during bevacizumab therapy.28

These results from AVADO and ATHENA have important implications for the potential future use of bevacizumab in early breast cancer, both in the adjuvant and neo-adjuvant setting, in which current trial protocols specify that surgery should be performed 4 weeks after the last bevacizumab dose. Ongoing phase III trials such as BEATRICE (NCT00528567), a two-arm, open-label study evaluating bevacizumab plus standard adjuvant therapy (anthracycline ± taxane or taxane only) in triple-negative early breast cancer, will add to current safety data in the adjuvant setting. Initial data from the ongoing phase III trial GEPARQUINTO, indicate no improvement in pathological response and an increase in SAEs, including wound-healing, in patients receiving bevacizumab with chemotherapy (epirubicin-cyclophosphamide-docetaxel) versus chemotherapy alone.29 The NSABP B-40 study, however, recently showed that addition of bevacizumab to neoadjuvant taxane-based chemotherapy improved pathological and clinical response rates with wound-healing issues to be followed up.30 No firm conclusions can be drawn from these initial data, but the outcomes from all these ongoing studies will help define the role of bevacizumab in early breast cancer.

Bevacizumab is a treatment option for patients with mBC and although concerns have been raised regarding its use in patients undergoing surgery,31,32 the data from AVADO and ATHENA suggest that physicians should not be deterred from performing elective or emergency surgery in bevacizumab-treated patients with mBC, provided labelling recommendations for therapy interruption are followed. Although recommendations are not available for minor surgery, evidence suggests that routine minor procedures (e.g. biopsies, catheter insertion/removal) can be conducted in bevacizumab-treated patients with little added risk for severe AEs.

**Conflict of interest statement**

Javier Cortés: received honoraria from F. Hoffmann-La Roche. Mireia Caralt: no conflict of interest. Suzette Delaloge: consulting/expert for Abraxis, Bayer, GSK, Novartis, Pfizer, F. Hoffmann-La Roche Ltd.; conferences/formations for Amgen, AstraZeneca, GE, GSK, Novartis, Pierre Fabre, Pfizer, Pharmamar, F. Hoffmann-La Roche Ltd., Sanofi; research grants/clinical trials for Amgen, AstraZeneca, BMS, Exonhit, GE, GSK, Merck, Novartis, Pierre Fabre, Pfizer, Pharmamar, F. Hoffmann-La Roche Ltd., Sanofi; patent for Exonhit. Hernan Cortes-Funes: no conflict of interest. Jean-Yves Pierga: has been a consultant for F. Hoffmann-La Roche, received honoraria for F. Hoffmann-La Roche; research funding from F. Hoffmann-La Roche. Kathleen Pritchard: has been a consultant for Sanofi-Aventis, AstraZeneca, F. Hoffmann-La Roche, Pfizer, Ortho-Biotech, YM Biosciences, Novartis, Abraxis, Amgen and GlaxoSmithKline; received honoraria or participated in Speaker’s Bureaus for Sanofi-Aventis, AstraZeneca, F. Hoffmann-La Roche, Pfizer, Novartis and Amgen; research funding from Sanofi-Aventis, AstraZeneca, Pfizer, Ortho-Biotech, Bristol Myers Squibb, Novartis, Amgen and GlaxoSmithKline; advisory committees for Sanofi-Aventis, AstraZeneca, F. Hoffmann-La Roche, Pfizer, Ortho-Biotech, YM Biosciences, Novartis, Amgen and GlaxoSmithKline; paid expert testimony for Sanofi-Aventis, AstraZeneca and GlaxoSmithKline. Dr. Pritchard is Co-Associate Editor for the breast cancer section of the European Journal of Cancer. David Bollag: employee of F. Hoffmann-La Roche. David Miles: acted as consultant for and received honoraria from F. Hoffmann-La Roche.

**Acknowledgements**

This study was supported by F. Hoffmann-La Roche Ltd. and support for third-party writing assistance for this manuscript was provided by F. Hoffmann-La Roche Ltd.

**References**


5. Miles DW, Chan A, Romieu G, et al. Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC). *Cancer Res* 2009;69(Suppl. 3):495s [abstract 41].


