The US FDA's withdrawal of the breast cancer indication for Avastin (bevacizumab)

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Abstract On November 18, 2011, the US Food and Drug Administration (US FDA) announced that breast cancer indication for Avastin (bevacizumab) had been withdrawn after concluding that the drug has not been shown to be safe and effective for the treatment of breast cancer. The specific indication that was withdrawn was for the use of bevacizumab in metastatic breast cancer, with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

The US FDA's decision has been met with emotion and confusion among the public and health professionals. The purpose of this article is to review the regulatory history of bevacizumab for breast cancer and to examine the scientific evidence that led to the approval and subsequent withdrawal of this indication. Bevacizumab also provides the opportunity to illustrate the value of free publicly available US FDA reviews that may contain rigorously reviewed unpublished data and analyses and to contrast the decisions made in the US and Europe about bevacizumab and breast cancer.

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1. Introduction

On November 18, 2011, US FDA Commissioner Margaret Hamburg announced that her agency was revoking breast cancer indication for Avastin (bevacizumab) after concluding that the drug has not been shown to be safe and effective for the treatment of breast cancer. The specific indication that was revoked was for the use of bevacizumab in metastatic breast cancer, with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer (US Food and Drug, 2011).

The US FDA's final decision to remove bevacizumab breast cancer indication has been met with emotion and confusion among public and health professionals. The purpose of this article is to review the regulatory history of bevacizumab for...
breast cancer and to examine the scientific evidence that led to the approval and withdrawal of this indication. The bevacizumab case also provides the opportunity to illustrate the value of free publicly available US FDA reviews and to contrast different decisions made in the US and Europe about Avastin and breast cancer.

Bevacizumab is now indicated for metastatic colorectal cancer, with IV 5 fluorouracil based chemotherapy for first or second-line treatment; non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease; glioblastoma, as a single agent for adult patients with progressive disease following prior therapy (no data are available demonstrating improvement in disease-related symptoms or survival with Avastin); and metastatic renal cell carcinoma with interferon.

Bevacizumab was first approved in the US in February 2004 for the treatment of advanced colon cancer and has been approved since for advanced lung (2006), kidney and brain (glioblastoma) cancers (2009). Avastin was approved for metastatic breast cancer in 2008 under the US FDAs Accelerated Approval Program. In 2010 worldwide sales of bevacizumab were US$ 6.8 billion.

Under the Accelerated Approval Program regulations a drug may be approved based on its effect on a biomarker or surrogate endpoint such as tumor shrinkage that suggests the drug has an important clinical benefit for patients. However, the regulations require additional clinical trials that confirm that there is a meaningful clinical benefit to patients such as increased survival.

While reading this article two facts are to be kept in mind. First, bevacizumab is a drug with substantial toxicity. The US FDA requires that Avastin display a Black Box Warning in the drug’s professional product leaflet. A Black Box Warning is the strongest type of safety alert that the US FDA can require in a drug’s product leaflet (Genentech Inc., 2011).

The second is that Accelerated Approval may be granted to drugs to treat life-threatening conditions for which there is no effective therapy but there is preliminary evidence that the drug might be effective. Most often this involves drugs for cancer, HIV/AIDS, and inhalation anthrax. By regulation it is the responsibility of drug’s manufacturer to confirm that the drug actually provides a meaningful clinical benefit such as increased survival for patients.

Drugs such as bevacizumab that are granted Accelerated Approval are also subject to Accelerated Withdrawal if the required confirmatory studies fail to verify a clinical benefit or the drug is not shown to be safe and effective.

As noted above bevacizumab was first approved in the US in February 2004. The following are the major events involved in the Accelerated Approval and Withdrawal of breast cancer indication for Avastin.

2. Oncologic Drugs Advisory Committee – December 5, 2007

The US FDA convened a meeting of its outside Oncologic Drugs Advisory Committee (ODAC) to consider the Genentech, Inc. application to market bevacizumab for use in combination with paclitaxel, for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic, HER2-negative breast cancer (US Food and Drug, 2007a).

Study E2100 was presented to the Advisory Committee to support the new breast cancer indication for Avastin. This study was an open-label, randomized trial that enrolled 722 subjects who had not previously received chemotherapy for their locally recurrent or metastatic breast cancer. The subjects were randomized (1:1) to receive paclitaxel alone or paclitaxel plus bevacizumab. The primary efficacy endpoint used is progression-free survival (PFS). More discussion of PFS appears later in this article.

The secondary endpoints in study E2100 were overall survival, objective response rate, duration of objective response, and quality of life (QOL). The study was sponsored by the US National Cancer Institute (NCI) and conducted by the Eastern Cooperative Oncology Group (ECOG).

The addition of bevacizumab to paclitaxel resulted in a 5.5-month increase in median PFS with no statistically significant improvement in overall survival based on the analysis by independent reviewers. The tumor response rate was higher with bevacizumab plus paclitaxel as compared to paclitaxel alone, 48.9% versus 22.2%, respectively.

The results of study E2100 are summarized in Table 1.

The collection of adverse events was limited to US National Cancer Institute (NCI) Common Toxicity Criteria (CTC) grade 3-5 adverse events. There was a 20.2% increase in grade 3-5 toxicity in the bevacizumab plus paclitaxel arm over paclitaxel alone. Bevacizumab’s major safety concerns are hypertension, thromboembolic events, left ventricular dysfunction, myocardial infarction, gastrointestinal perforation and proteinuria. Death attributed to study drug by the FDA was 1.7% (6/363) in the Avastin plus paclitaxel arm when compared zero (0/348) with paclitaxel alone.

The E2100 trial results were published in the New England Journal of Medicine on December 27, 2007. The conclusion read: “Initial therapy of metastatic breast cancer with paclitaxel plus bevacizumab prolongs progression-free survival, but not overall survival, as compared with paclitaxel alone.” (Miller et al., 2007).

The Advisory Committee member voted 5 to 4 against recommending approval of Avastin for breast cancer (US Food and Drug, 2007b).


The US FDAs decision to allow accelerated bevacizumab in the treatment of breast cancer was not based on evidence showing the drug improved survival or QOL. Additionally, there was imbalance in the number of deaths in the bevacizumab paclitaxel and paclitaxel only arms of study E2100 (US Food and Drug, 2007a).

The approval of Avastin was based on the drug’s effect in study E2100 on PFS. PFS measures time between the time when a subject starts taking the drug or treatment of interest, in this case Avastin plus paclitaxel, or the control, paclitaxel alone and either death, or evidence, from radiological assessment the tumor size has increased. At the time of bevacizumab’s approval the evidence was a 5.5 month increase in median PFS that was statistically significant. Avastin’s effect on PFS was the basis for the drug’s approval.
The Oncologic Drugs Advisory Committee was asked in July 2010 to make a recommendation to the US FDA on whether or not the bevacizumab breast cancer indication should be withdrawn (US Food and Drug, 2010a).

As a condition for bevacizumab’s Accelerated Approval the drug’s manufacturer was required by regulation to submit data from two ongoing, placebo-controlled trials (AVADO and RIBBON 1) to provide verification of the Avastin’s treatment effect on PFS and to provide additional information on the effects of the drug on overall survival.

The first, the AVADO trial was a double blind, placebo-controlled, three-arm trial of docetaxel plus placebo, docetaxel plus bevacizumab 7.5 mg/kg, and docetaxel plus bevacizumab 15 mg/kg. A total of 736 subjects with HER2-neu negative tumors who had not received prior chemotherapy for metastatic breast cancer were enrolled. The addition of bevacizumab 7.5 mg/kg to docetaxel resulted in a 30% increase in PFS [HR 0.70 (95% CI 0.55, 0.90)] with an observed 0.8-month difference in median PFS while the addition of bevacizumab 15 mg/kg to docetaxel resulted in a 39% increase in PFS [HR 0.62 (95% CI 0.48, 0.79)] with an observed 0.88-month difference in median PFS. Objective responses were observed in 44% of patients in the placebo arm, 55% in the Avastin 7.5 mg/kg arm (p-value 0.0295) and 63% in the Avastin 15 mg/kg arm (p-value 0.0001). Mature survival data showed an HR of 1.103 (95% CI 0.84, 1.45) favoring the placebo arm over the 7.5 mg/kg Avastin arm. The HR for overall survival was 1.003 (95% CI 0.76, 1.32) for the 15 mg/kg bevacizumab arm compared to the placebo arm.

There was an absolute decrease in survival in both bevacizumab arms of AVADO trial though these differences were not statistically significant.

In the AVADO trial there was an increase of NCI CTC grade 3-5 adverse events, serious adverse events and study drug discontinuation with the addition of Avastin to docetaxel. More patients in the Avastin containing arms required interruption or dose reduction or discontinuation of docetaxel due to an adverse event.

The second trial, the RIBBON 1 study was a double blind, randomized, parallel group study conducted in women with metastatic or locally recurrent HER2-neu negative adenocarcinoma of the breast that had not received prior chemotherapy for their advanced or metastatic cancer. A total of 1237 subjects were randomized (2:1) to receive anthracycline- or taxane-based chemotherapy (n = 622) or capecitabine (n = 615) in combination with Avastin or placebo.

The addition of bevacizumab to taxane/anthracycline-based chemotherapy resulted in a 36% increase in PFS [HR 0.64 (95% CI 0.52, 0.80)], with an observed 1.2-month difference in median PFS. Objective response rate was higher in the bevacizumab containing arm, with an absolute increase of 13.5% (95% CI 4.6, 22.3%) with the addition of Avastin to docetaxel.

**Table 1** Results of study E2100.

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel + Avastin</td>
<td>11.3</td>
<td>26.5</td>
<td>48.9%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>5.8</td>
<td>24.8</td>
<td>22.2%</td>
</tr>
<tr>
<td>Between-arm difference</td>
<td>5.5</td>
<td>1.7</td>
<td>26.7%</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.48 (0.39-0.61) p &lt; 0.0001</td>
<td>0.87 (0.72-1.05) p = 0.137</td>
<td>(18.4%, 35%) p &lt; 0001</td>
</tr>
</tbody>
</table>

CI = confidence interval; ORR = objective response rate; OS = overall survival; PFS = progression free survival.

**Table 2** Summary of AVADO and RIBBON 1 results.

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AVADO</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel + Avastin 15 mg/kg</td>
<td>8.8</td>
<td>3.2</td>
<td>63.1%</td>
</tr>
<tr>
<td>Docetaxel + Placebo</td>
<td>7.9</td>
<td>31.9</td>
<td>44.4%</td>
</tr>
<tr>
<td>Between-arm difference</td>
<td>0.9</td>
<td>-1.7</td>
<td>18.7%</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.62 (0.48-0.79) p = 0.0003</td>
<td>1.00 (0.76-1.32) p = 0.98</td>
<td>(9.0%, 28.4%) p = 0.001</td>
</tr>
<tr>
<td>Docetaxel + Avastin 7.5 mg/kg</td>
<td>8.7</td>
<td>30.8</td>
<td>55.2%</td>
</tr>
<tr>
<td>Docetaxel + Placebo</td>
<td>7.9</td>
<td>31.9</td>
<td>44.4%</td>
</tr>
<tr>
<td>Between-arm difference</td>
<td>0.8</td>
<td>-1.1</td>
<td>10.8%</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.70 (0.55-0.90) p = 0.0054</td>
<td>1.10 (0.84-1.45) p = 0.48</td>
<td>(9.0%, 20.7%) p = 0.0295</td>
</tr>
<tr>
<td><strong>RIBBON 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxene/Anthracycline + Avastin</td>
<td>9.2</td>
<td>27.5</td>
<td>51.3%</td>
</tr>
<tr>
<td>Taxene/Anthracycline + Placebo</td>
<td>8.0</td>
<td>NR</td>
<td>37.9%</td>
</tr>
<tr>
<td>Between-arm difference</td>
<td>1.2</td>
<td>NR</td>
<td>13.5%</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.64 (0.52-0.80) p &lt; 0.0001</td>
<td>1.11 (0.86-1.43) p = 0.44</td>
<td>(4.6%, 22.3%) p = 0.0054</td>
</tr>
<tr>
<td>Capecitabine + Avastin</td>
<td>8.6</td>
<td>25.7</td>
<td>35.4%</td>
</tr>
<tr>
<td>Capecitabine + Placebo</td>
<td>5.7</td>
<td>22.8</td>
<td>23.6%</td>
</tr>
<tr>
<td>Between-arm difference</td>
<td>2.9</td>
<td>2.9</td>
<td>11.8%</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.69 (0.56-0.84) p = 0.0002</td>
<td>0.88 (0.69-1.13)</td>
<td>(3.4%, 26.2%) p = 0.0097</td>
</tr>
</tbody>
</table>

CI = confidence interval; NR = not reached; ORR = objective response rate.
anthracycline/taxane-based chemotherapy. Mature survival analysis yielded an HR of 1.11 (95% CI 0.86, 1.43) favoring the placebo arm.

The addition of bevacizumab to capecitabine resulted in a 31% increase in PFS [HR 0.69 (95% CI 0.56, 0.84)], with an observed difference of 2.9 months in median PFS. Objective response rate was higher in the Avastin containing arm, with an absolute increase of 11.8% (95% CI 3.4, 20.2%) observed with the addition of bevacizumab to capecitabine. A comparison of the mature survival analysis for the capecitabine cohort showed an HR of 0.88 (95% CI 0.69, 1.13) favoring the bevacizumab containing arm.

Overall, the incidence of NCI CTC grade 3-5 adverse events and serious adverse events were almost twice as high in the bevacizumab arms compared to placebo arms in both cohorts.

The size of the improvement in PFS observed in the AVADO and RIBBON 1 studies failed to confirm the magnitude of PFS improvement observed in the E2100 trial, the basis for bevacizumab’s Accelerated Approval. The size of the treatment effect is clinically important because it is a measure of delaying symptoms from tumor progression, which has to be weighed against the drug’s toxicity that is present for the duration of treatment. The addition of bevacizumab to chemotherapy resulted in an increased rate of serious adverse events, in NCI CTC grade 3-5 adverse events and of adverse events attributable to bevacizumab in both studies. Overall survival data showed hazard ratios favoring the placebo arms in both the AVADO study and the taxane/anthracycline cohort of the RIBBON 1 study.

Table 2 below summarizes the results of the AVADO and RIBBON 1 studies.

The Oncology Drugs Advisory Committee voted Yes = 12; No = 1; and Abstain = 0 to withdraw the metastatic breast cancer indication for Avastin (US Food and Drug, 2010b).

5. Submission of AVADO and RIBBON 1 trials to the US FDA and the US FDA briefing documents

The importance of the US FDA free publicly available briefing documents is highlighted by the bevacizumab AVADO and RIBBON 1 trials. US FDA briefing documents are safety and efficacy analyses prepared by the agency for discussion at public advisory committee meetings. The briefing documents may contain rigorously conducted analyses of data submitted by a manufacturer that are never published or not published in a timely manner.

The analyses of the AVADO and RIBBON 1 trials were first made available to the public before the July 10, 2010, Oncologic Drugs Advisory Committee (US Food and Drug, 2010a).

The AVADO results were published online from the European Journal of Cancer on July 15, 2011 (Pivot et al., 2011). This is one year after the analyses were available on the US FDA’s Web site and eight months after the agency announced that it was beginning procedures to withdraw bevacizumab’s breast cancer indication (US Food and Drug, 2010c). The authors of the European Journal of Cancer paper concluded:

In this exploratory sub-analysis in AVADO, bevacizumab plus docetaxel showed efficacy in elderly patients similar to the overall study population. There were no unexpected safety signals in patients aged 65 years or older.

This sub-analysis was not pre-specified and gives an impression of the safety and efficacy of Avastin that may be interpreted as quite different from the analyses presented in the US FDA briefing documents.

RIBBON 1 was published in the Journal of Clinical Oncology on April 1, 2010 (Robert et al., 2011). This was 10 months after the posting of the RIBBON 1 analyses on the US FDA’s Web site. And this was four months after the US FDA had begun the regulatory procedures to remove bevacizumab’s breast cancer indication (US Food and Drug, 2010c).

The authors of the published RIBBON 1 study concluded:

These data, together with those from E2100 and AVADO, provide a clear rationale for adding BC [bevacizumab] to first-line cytotoxic therapy for patients with HER2-negative MBC [metastatic breast cancer].

Accessing publicly available US FDA briefing documents provide analyses that may not be published that may lead to different conclusions of the therapeutic value of a drug than conclusions that rely only on the published medical literature.

6. European Medicines Agency (EMEA) and Avastin for breast cancer

The bevacizumab breast cancer indication remains in Europe. The EMEA issued the following statement in December 2010.

For Avastin in combination with paclitaxel, the Committee concluded that the benefits continue to outweigh the risks, because the available data have convincingly shown to prolong progression-free survival of breast cancer patients without a negative effect on the overall survival (European Medicines, 2011).

The US FDA and EMEA have reached different scientific conclusions on the efficacy and safety of drugs in the past. There is an agreement between bevacizumab’s manufacturer, the US FDA that there is no benefit in survival or QOL with the bevacizumab paclitaxel combination for breast cancer (US Food and Drug, 2011).

The reasons for different decisions are not readily apparent between the US FDA and EMEA. There is a lack of transparency in EMEA that must be contrasted with the US FDA’s publicly available reviews of bevacizumab.

Each country’s national drug regulatory authority must reach its own decisions based on its own regulations to approve or withdraw approval of a drug or a drug’s specific indications. In developing and emerging countries accessing free publicly available reviews may allow an independent analysis of the therapeutic value of the drug that is not possible by relying solely on the published medical literature including clinical practice guidelines, review articles, and electronic databases.

References


US Food and Drug Administration, 2010c. FDA news release: FDA begins process to remove breast cancer from Avastin label.