AHFS Final Determination of Medical Acceptance: Off-label Use of Bevacizumab in Combination with Paclitaxel for the First-line Treatment of Metastatic Breast Cancer

Drug/Drug Combination: Bevacizumab and paclitaxel

Off-label Use: First-line treatment of metastatic breast cancer

Criteria Used in Selection of Off-label Use for Review:

- Clinical results from a trial demonstrating a difference (improvement) in outcomes (progression-free survival) compared with a reasonable standard of care

Strength of Evidence: Level 2 (Moderate strength/quality)

Strength of Study End Point(s): Progression-free survival

Grade of Recommendation: Not fully established (Equivocal)

Narrative Summary:

Use as First-line Treatment for Metastatic Breast Cancer:

Although bevacizumab in combination with paclitaxel previously was labeled for use as first-line treatment of metastatic HER2-negative breast cancer†,[44] FDA concluded that such use has not been shown in postmarketing studies to prolong overall survival or provide sufficient clinical benefit (e.g., prolongation of progression-free survival, amelioration of disease-related symptoms, improvement in quality of life) to outweigh the risk of severe, potentially fatal, adverse effects (e.g., myocardial infarction [MI], heart failure, severe hypertension, bleeding or hemorrhage, perforation and fistula/abscess formation, [44] wound healing complications).[65,66,68] On November 18, 2011, the agency rescinded approval of bevacizumab for use (in combination with paclitaxel) as first-line treatment of metastatic HER2-negative breast cancer;[68] as a result, this indication no longer appears in bevacizumab's current approved labeling.[1] (See FDA Decisions Regarding Breast Cancer Indication.) Following FDA's decision, Health Canada, but not the European Medicines Agency (EMA), took similar action.[65,69] The United Kingdom's National Institute for Health and Clinical Excellence (NICE) reached similar conclusions about the lack of evidence of clinical benefit and has not supported this use.[65,70] The AHFS Oncology

Expert Committee concluded that use of bevacizumab in combination with paclitaxel for the first-line treatment of metastatic breast cancer currently is not fully established because of equivocal evidence; additional studies are needed to identify subgroups of patients who might derive clinical benefit from bevacizumab treatment. (See AHFS Oncology Expert Committee Decision Regarding Use as First-line Therapy.)

Patients currently receiving bevacizumab for breast cancer should consult their clinician about whether to continue bevacizumab therapy or consider other treatment options.[67] Clinicians should use clinical judgment in deciding whether patients should continue receiving bevacizumab in combination with paclitaxel, receive paclitaxel monotherapy, or consider other treatment options.[67]

FDA Decisions Regarding Breast Cancer Indication.

Bevacizumab (in combination with paclitaxel) received approval for use as first-line treatment of metastatic HER2-negative breast cancer in February 2008 under the principles and procedures of FDA's accelerated review process that allows approval based on analysis of surrogate markers of response (i.e., prolongation of progression-free survival) rather than clinical endpoints (e.g., prolongation of overall survival, amelioration of disease-related symptoms).[54,55,65] Approval for this indication was based principally on the results of a single multicenter, open-label, randomized study (E2100) in which 722 patients received bevacizumab and paclitaxel or paclitaxel alone as first-line therapy for locally recurrent or metastatic breast cancer.[15,44,54,55] Patients with HER2-overexpressing breast cancer were not eligible for the study unless they had received previous therapy with trastuzumab.[15,44] Patients who had received hormonal therapy for metastatic disease or adjuvant therapy (chemotherapy or hormonal therapy) for breast cancer were eligible for the study.[15,44] Patients who had received adjuvant taxane therapy were eligible for the study if they had completed treatment at least 12 months prior to entry to the study.[15,44] Patients with CNS metastasis were excluded from the study.[15,44] The median age of the patients was 55 years (range: 27–85 years), 76% were white, about 55% were postmenopausal, and 64% had estrogen receptor-positive and/or progesterone receptor-positive disease; 36% had received hormonal therapy for advanced disease and 66% had received adjuvant therapy for breast cancer, including 20% with previous taxane use and 50% with previous anthracycline use.[44] Treatment consisted of paclitaxel 90 mg/m^2 IV once weekly for 3 out of 4 weeks, with or without bevacizumab 10 mg/kg by IV infusion every 2 weeks, until disease progression or unacceptable toxicity occurred.[15,44] Among patients randomized to receive the combination regimen in whom paclitaxel was withheld or discontinued, bevacizumab monotherapy was allowed to continue until disease progression or unacceptable toxicity occurred.[15,44]

Because study E2100 was open-label and included patients without measurable disease, efficacy data from a planned interim analysis were subjected to independent, retrospective, blinded review.[76] Although some data points were missing, this analysis of interim data confirmed a higher response rate (48.9 versus 22.2%, partial responses only[44]) and a progression-free survival benefit (11.3 versus 5.8 months) for combined therapy with bevacizumab and paclitaxel compared with paclitaxel alone, and achieved 76–80% concordance with investigator assessments of individual patient results.[76] Final analyses performed by the investigators indicated that patients receiving bevacizumab and paclitaxel had longer progression-free survival

(11.8 versus 5.9 months), similar overall survival (26.7 versus 25.2 months), and a higher response rate (36.9 versus 21.2%) compared with those receiving paclitaxel alone as first-line therapy for metastatic breast cancer.[15] Grade 3–4 adverse effects, including sensory neuropathy (24 versus 18%), hypertension (15 versus 0%), fatigue (9 versus 5%), infection (9 versus 3%), proteinuria (4 versus 0%), nausea (3 versus 1%), arthralgia (3 versus 1%), headache (2 versus 0%), and cerebrovascular ischemia (2 versus 0%) occurred more frequently in patients receiving bevacizumab and paclitaxel than in those receiving paclitaxel alone.[15]

As a condition of the accelerated approval process, the manufacturer of bevacizumab was required to submit data from 2 controlled clinical studies (AVADO and RIBBON1) to confirm the progression-free survival benefit that was observed with use of bevacizumab in study E2100 and to provide additional information regarding effects of the drug on overall survival of patients with metastatic HER2-negative breast cancer.[54] In the AVADO study, 736 patients were randomized to receive bevacizumab (7.5 or 15 mg/kg) plus docetaxel (100 mg/m^2) or docetaxel (100 mg/m^2) plus placebo every 3 weeks as first-line therapy for metastatic or locally recurrent HER2-negative breast cancer; bevacizumab or placebo was continued until disease progression or unacceptable toxicity occurred, while docetaxel was administered for up to 9 cycles.[39] In the RIBBON1 study, 1237 patients were randomized to receive either bevacizumab (15 mg/kg every 3 weeks) or placebo in conjunction with a taxane- or anthracycline-based regimen or in conjunction with capecitabine as first-line therapy for metastatic or locally recurrent HER2-negative breast cancer; treatment was continued until disease progression or unacceptable toxicity occurred.[73]

In the AVADO study, objective response rates were higher for patients receiving bevacizumab 7.5 or 15 mg/kg plus docetaxel (55.2 or 64.1%, respectively) compared with those receiving docetaxel alone (46.4%).[39] Inclusion of bevacizumab in the treatment regimen prolonged median progression-free survival by 0.8–1.9 months but did not prolong overall survival.[39] Among patients receiving bevacizumab 7.5 mg/kg plus docetaxel, bevacizumab 15 mg/kg plus docetaxel, or docetaxel alone, median progression-free survival was 9, 10.1, or 8.2 months, respectively, and median overall survival was 30.8, 30.2, or 31.9 months, respectively.[39]

In the RIBBON1 study, patients receiving bevacizumab in conjunction with capecitabine or in conjunction with a taxane- or anthracycline-based regimen had higher objective response rates and longer progression-free survival than did those receiving either capecitabine or a taxane- or anthracycline-based regimen alone; inclusion of bevacizumab in the treatment regimen did not significantly prolong overall survival.[65,73] Patients receiving bevacizumab and capecitabine had a higher objective response rate (35.4 versus 23.6%) and longer median progression-free survival (8.6 versus 5.7 months), but not a significantly longer median overall survival (25.7 versus 22.8 months), compared with patients receiving capecitabine alone.[65,73] Similarly, patients receiving bevacizumab in conjunction with a taxane- or anthracycline-based regimen had a higher objective response rate (51.3 versus 37.9%) and longer median progression-free survival (9.2 versus 8 months) compared with patients receiving a taxane- or anthracycline-based regimen alone; inclusion of bevacizumab in these regimens did not provide an overall survival benefit (hazard ratio of 1.11 favoring the use of a taxane- or anthracycline-based regimen).[65,73]

In both the AVADO and RIBBON1 studies, adverse effects described as grade 3–5 in severity and serious adverse effects (i.e., those requiring medical intervention or hospitalization or resulting in death) were more common in patients receiving bevacizumab-containing regimens

compared with those receiving comparator regimens.[39,54,55,73] In the AVADO study, patients were more likely to experience adverse effects requiring docetaxel modification (discontinuance, interruption, dosage reduction) if they received concomitant therapy with bevacizumab.[54,55]

The FDA Oncologic Drugs Advisory Committee (ODAC) reviewed data from the AVADO and RIBBON1 studies in July 2010 and concluded that these studies did not provide evidence of an overall survival benefit for bevacizumab in patients with metastatic HER2-negative breast cancer; the committee also concluded that the increases in progression-free survival observed in the confirmatory studies were marginal compared with that observed in study E2100 and not clinically meaningful.[55] The committee recommended that the current indication for use of bevacizumab in combination with paclitaxel in the first-line treatment of metastatic HER2-negative breast cancer be removed from the drug's approved labeling.[55]

In December 2010, after reviewing the committee's recommendation and data from 4 clinical studies (i.e., E2100, AVADO, RIBBON1, AVF2119g), FDA's Center for Drug Evaluation and Research (CDER) concurred with the committee, stating that bevacizumab does not prolong overall survival in patients with metastatic HER2-negative breast cancer or provide a sufficient benefit in slowing disease progression to outweigh the substantial risk of serious adverse effects (e.g., hypertension, bleeding or hemorrhage, wound healing complications or wound dehiscence, perforation and fistula/abscess formation, MI, heart failure).[58,59,65] Because bevacizumab (in combination with paclitaxel) has not been shown to be safe and effective for first-line treatment of metastatic HER2-negative breast cancer, CDER recommended that this indication be removed from the drug's approved labeling.[58,60] A public hearing on this recommendation was held on June 28–29, 2011.[61]

On November 18, 2011, after reviewing submissions from the manufacturer and CDER, recommendations from ODAC, and public comments, the FDA Commissioner issued a final decision to rescind approval of bevacizumab for use in combination with paclitaxel as first-line treatment of metastatic HER2-negative breast cancer, citing 3 main reasons for the decision: lack of clinical benefit, unfavorable benefit-to-risk ratio, and lack of other compelling reasons (i.e., special circumstances) to support continued accelerated approval.[65] In evaluating clinical benefit, the commissioner noted that confirmatory studies (AVADO and RIBBON1) failed to verify the magnitude of effect on progression-free survival observed in study E2100, and that none of the 5 studies submitted by the manufacturer (E2100, AVADO, RIBBON1, AVF2119g, RIBBON2) demonstrated an overall survival benefit or an improvement in quality of life.[65] In evaluating the regimen's safety profile, it was noted that the addition of bevacizumab to chemotherapy resulted in an increased risk of severe (grade 3 or greater) adverse effects (e.g., neutropenia, sensory neuropathy, hypertension, febrile neutropenia, proteinuria, arterial thromboembolic events, left ventricular systolic dysfunction, hemorrhage, wound healing complications, fistula formation, GI perforation) that was considered unacceptable for a regimen that has not demonstrated clinical benefit.[65] In evaluating special circumstances that may justify continuing accelerated approval (e.g., until clinical benefit is fully established or until a subset of patients likely to benefit from therapy is identified), the commissioner concluded that continuing an approval that is no longer supported by current data and allowing a substantial length of time for additional studies to be completed would be inconsistent with the protection of public health.[65] The commissioner noted that because FDA does not regulate the practice of medicine, clinicians may continue to prescribe bevacizumab for the treatment of metastatic breast cancer (i.e., unlabeled [off-label] use) despite withdrawal of approval for this use.[65]

AHFS Oncology Expert Committee Decision Regarding Use as First-line Therapy.

The AHFS Oncology Expert Committee was concerned that the E2100 study failed to demonstrate an overall survival benefit despite showing prolonged disease-free survival in patients receiving combined therapy with bevacizumab and paclitaxel, and also was concerned by the failure of the confirmatory studies (AVADO and RIBBON1) to verify the same magnitude of effect on progression-free survival as observed in the E2100 study. These studies provide a basis for assessing tolerability of bevacizumab in patients with previously untreated metastatic breast cancer, but the results provide equivocal evidence of the drug's efficacy for this use. In the absence of additional data, attempts to identify subgroups of patients in whom bevacizumab might provide clinical benefit (e.g., prolonged progression-free survival, prolonged overall survival, improved quality of life) and achieve a favorable benefit-to-risk ratio are speculative; additional studies are needed to identify subgroups of patients with previously untreated metastatic breast cancer who might derive clinical benefit from bevacizumab treatment. Therefore, the committee concluded that use of bevacizumab in combination with paclitaxel for the first-line treatment of metastatic breast cancer currently is not fully established because of equivocal evidence.

Dosage in First-line Treatment for Metastatic Breast Cancer:

For the first-line treatment of metastatic breast cancer, a bevacizumab dosage of 10 mg/kg, administered by IV infusion every 2 weeks, has been used in combination with IV paclitaxel.[64] However, this combination regimen has not been shown to prolong overall survival or provide sufficient clinical benefit to outweigh the risk of severe, potentially fatal, adverse effects.[65]

References:

15. Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007; 357:2666-76.

39. Miles DW, Chan A, Dirix LY et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol.* 2010; 28:3239-47.

44. Genentech. Avastin® (bevacizumab) prescribing information. South San Francisco, CA; 2008 Feb.

54. US Food and Drug Administration. FDA briefing document from the oncology drugs advisory committee, July 20, 2010. From FDA website (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeeting

Materials/Drugs/OncologicDrugsAdvisoryCommittee/UCM219224.pdf).

55. Summary minutes of the oncologic drugs advisory committee, July 20, 2010. From FDA website (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeeting Materials/Drugs/OncologicDrugsAdvisoryCommittee/UCM224753.pdf).

58. Food and Drug Administration. FDA drug safety communication: Avastin (bevacizumab): Process for removal of breast cancer indication begun. Rockville, MD; 2010 Dec 16. From FDA website (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm237280.htm)..

59. Food and Drug Administration. Memorandum to the file BLA 125085 Avastin (bevacizumab): Regulatory decision to withdraw Avastin (bevacizumab) first-line metastatic breast cancer indication. Rockville, MD; 2010 Dec 15. From FDA website (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237171.pdf).

60. Woodcock J. Dear breast cancer community letter. Silver Spring, MD: Food and Drug Administration; 2010 Dec 16. From FDA website (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237286.pdf).

61. Food and Drug Administration. Avastin (bevacizumab) information. Rockville, MD; 2011 Jun 29. From FDA website (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm193900.htm).

65. Food and Drug Administration. Proposal to withdraw approval for the breast cancer indication for Avastin: Decision of the Commissioner. Rockville, MD; 2011 Nov 18. From FDA website (http://www.fda.gov/downloads/NewsEvents/Newsroom/UCM280546.pdf).

66. Food and Drug Administration. Commissioner's opening statement from media call. Rockville, MD; accessed 2011 Nov 18. From FDA website (http://www.fda.gov/NewsEvents/Newsroom/ucm280585.htm).

67. Food and Drug Administration. Questions and answers: Removing metastatic breast cancer as an indication from Avastin's product labeling. Rockville, MD; accessed 2011 Nov 18. From FDA website (http://www.fda.gov/NewsEvents/Newsroom/ucm280533.htm).

68. Food and Drug Administration. FDA news release: FDA Commissioner announces Avastin decision. Rockville, MD; 2011 Nov 18. From FDA

website (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280536.htm).

69. Health Canada. Health Canada directs Hoffmann-La Roche to remove use of Avastin (bevacizumab) for the treatment of metastatic breast cancer from the product label. Ottawa, Canada; 2011 Nov 28. From Health Canada website (http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_159-eng.php).

70. National Institute for Health and Clinical Excellence. Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer. NICE technology appraisal guidance 214. London, England. 2011 Feb. From NICE website (http://www.nice.org.uk/nicemedia/live/13342/53167/53167.pdf).

73. Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol.* 2011; 29:1252-60.

76. Gray R, Bhattacharya S, Bowden C, et al. Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. *J Clin Oncol.* 2009; 27:4966-72.

Oncology Expert Committee Voting Results and Comments:

First-Round Vote:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); progression-free survival

Concur with rating: 4 votes

Do not concur with rating: 1 vote (Level 3)

Grade of Recommendation:

Recommended use (Accepted): 0 votes

Reasonable choice (Accepted, treatment option): 1 vote

Not fully established (Equivocal): 2 votes

Not recommended (Unaccepted): 2 votes

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

Reviewer #2: The lack of survival benefit despite clear prolongation of progression-free survival is troubling and would suggest that the usefulness of this agent would be most appropriate for patients whose disease is in a critical area that progression would result in severe debilitation or decrease in quality of life. Unfortunately this is speculation.

Reviewer #3: Reasonable choice as first-line therapy in combination with weekly paclitaxel in patients with MBC. Patients must have good performance status (ECOG 0 or 1) adequate renal, hepatic, and hematologic function.

Reviewer #5: I do not think that paclitaxel and bevacizumab should be recommended in the first-line treatment of metastatic breast cancer. Although E2100 did show an impressive progression-free survival benefit for the combination, it failed to show an overall survival benefit and was associated with higher rates of grade 3-4 toxicities. The follow-up trials, AVADO, and RIBBON1, also failed to show an overall survival benefit and had higher rates of hemorrhage, hypertension, and proteinuria in the bevacizumab containing arm. The progression-free survival benefit in these studies, although statistical significant, was not nearly as clinically significant as E2100. I feel that the risk-benefit profile and lack of overall survival benefit outweigh the progression-free survival benefit.

Consensus Vote:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); progression-free survival

Proposed Grade of Recommendation: Not fully established (Equivocal)

Proposed Consensus Recommendation:

The AHFS Oncology Expert Committee was concerned that the E2100 study failed to demonstrate an overall survival benefit despite showing prolonged disease-free survival in patients receiving combined therapy with bevacizumab and paclitaxel, and also was concerned by the failure of the confirmatory studies (AVADO and RIBBON1) to verify the same magnitude of effect on progression-free survival as observed in the E2100 study. These studies provide a basis for assessing tolerability of bevacizumab in patients with previously untreated metastatic breast cancer, but the results provide equivocal evidence of the drug's efficacy for this use. In the absence of additional data, attempts to identify subgroups of patients in whom bevacizumab might provide clinical benefit (e.g., prolonged progression-free survival, prolonged overall survival, improved quality of life) and achieve a favorable benefit-to-risk ratio are speculative; additional studies are needed to identify subgroups of patients with previously untreated metastatic breast cancer who might derive clinical benefit from bevacizumab treatment. Therefore, the committee concluded that use of bevacizumab in combination with paclitaxel for the first-line treatment of metastatic breast cancer currently is not fully established because of equivocal evidence.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Comments on Proposed Narrative Summary:

Reviewer #1: Docetaxel dosage should be per m^2, not per kg.

Comments on Proposed Consensus Recommendation:

None submitted.

Participants:

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP; Jane Miller, Pharm.D.

AHFS Oncology Expert Committee Members (reviewing and voting): Peter Rosen, M.D.; Raymond Hohl, M.D., Ph.D.; James Trovato, Pharm.D., M.B.A., BCOP, FASHP; Danielle Roman, Pharm.D., BCOP; LeAnne Kennedy, Pharm.D., BCOP

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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