AHFS Final Determination of Medical Acceptance: Off-label Use of Bevacizumab in Combination with Chemotherapy for the Treatment of Metastatic Breast Cancer Previously Treated with Cytotoxic Chemotherapy

Drug/Drug Combination: Bevacizumab in combination with chemotherapy

Off-label Use: Treatment of metastatic breast cancer previously treated with 1 or 2 cytotoxic chemotherapy regimen(s) for metastatic disease

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 in Metastatic Breast Cancer Previously Treated with Cytotoxic Chemotherapy:

The efficacy and safety of bevacizumab for the treatment of metastatic breast cancer† previously treated with cytotoxic chemotherapy has been studied in several randomized studies.[14, 74]

The first study (AVF2119g) was an open-label, randomized study in which 462 patients received either bevacizumab and capecitabine or capecitabine alone.[14,64] Patients with metastatic breast cancer who had received prior therapy with both an anthracycline (or anthracenedione) and a taxane and had received 1 or 2 prior chemotherapy regimens for metastatic disease were eligible to enroll in the study; patients who relapsed within 12 months of completing adjuvant anthracycline (or anthracenedione) and taxane therapy also were eligible to enroll in the study without having received additional chemotherapy.[14,75] Patients with HER2-overexpressing breast cancer were not eligible for the study unless their disease had progressed following treatment with trastuzumab.[14,75] Patients with CNS disease and those who had received prior therapy with

bevacizumab or capecitabine were excluded from the study.[14,75] The mean age of patients was about 51 years (range: 29–78 years), about 81% were white, 47% had estrogen receptor-positive disease, and 37% had progesterone receptor-positive disease.[14] Treatment consisted of capecitabine (1.25 g/m^2 orally twice daily on days 1–14 of each 3-week cycle) given alone or in combination with bevacizumab (15 mg/kg by IV infusion on day 1 of each 3-week cycle) for a maximum of 35 cycles or until disease progression or unacceptable toxicity occurred.[14] Patients without disease progression following 35 cycles of therapy could continue to receive their assigned treatment in an extension study.[14] Patients randomized to receive bevacizumab and capecitabine could continue to receive bevacizumab either alone or in combination with other therapies following initial disease progression.[14]

Patients receiving bevacizumab and capecitabine had higher response rates (19.8 versus 9.1%)[14] but similar median progression-free survival (4.9 versus 4.2 months) and overall survival (15.1 months versus 14.5 months) compared with those receiving capecitabine alone.[14,64] Hypertension (23.6 versus 2.3%, frequently grade 3), proteinuria (22.3 versus 7.4%, mostly grade 1 or 2), and hemorrhage (28.8 versus 11.2%, mostly grade 1) occurred more frequently in patients receiving bevacizumab and capecitabine than in those receiving capecitabine alone.[14]

The second study (AVF3693g, RIBBON2) was a double-blind, placebo-controlled trial evaluating safety and efficacy of bevacizumab in combination with taxanes (paclitaxel, albumin-bound paclitaxel, or docetaxel), capecitabine, gemcitabine, or vinorelbine as second-line therapy for locally recurrent or metastatic breast cancer in 684 patients who had received one prior cytotoxic chemotherapy regimen for metastatic disease.[65,74] Patients with HER2-overexpressing breast cancer, those with untreated CNS metastases, and those who had received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors were not eligible to enroll in the study.[74] The median age of patients was 55 years (range: 23–90 years) and about 72% had hormone receptor-positive disease.[74] Patients were randomized in a 2:1 ratio to receive either bevacizumab (15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks depending on the chemotherapy regimen) or placebo in combination with the investigator-selected chemotherapy regimen.[74] Most patients received a taxane (44.4%), gemcitabine (23.4%), or capecitabine (21.1%).[74] Bevacizumab could be continued until disease progression or unacceptable toxicity occurred, up to a maximum of 36 months of therapy; the chemotherapy regimen could be continued until disease progression or unacceptable toxicity occurred.[74] If chemotherapy was discontinued before disease progression occurred, patients could continue receiving bevacizumab (or placebo, as assigned) as monotherapy.[74]

At a median follow-up of 15 months, combined therapy with bevacizumab and chemotherapy prolonged median progression-free survival (7.2 versus 5.1 months) but was not associated with an overall survival benefit compared with chemotherapy alone;[65,74] in patients receiving bevacizumab and chemotherapy, median overall survival was 18 months and the one-year survival rate was 69.5%, compared with 16.4 months and 66.2%, respectively, for those receiving chemotherapy alone.[74] No significant difference in objective response rate was observed between patients receiving bevacizumab in combination with chemotherapy and those receiving chemotherapy alone (39.5 and 29.6%, respectively).[74] Subgroup analysis showed that the progression-free survival benefit observed when bevacizumab and chemotherapy were given in combination was not uniform across all 4 chemotherapy regimens.[74] When bevacizumab was

used in combination with capecitabine, gemcitabine, or a taxane, median progression-free survival was prolonged by 0.5–2.8 months (depending on the regimen) compared with the chemotherapy regimen alone; however, when bevacizumab was used in combination with vinorelbine, median progression-free survival was 1.3 months shorter than when vinorelbine was used alone.[74] Grade 3 or greater hypertension (9 versus 0.5%), neutropenia (17.7 versus 14.5%), proteinuria (3.1 versus 0.5%), and hemorrhage (1.7 versus 0%) occurred more frequently in patients receiving bevacizumab in combination with chemotherapy than in those receiving chemotherapy alone.[74] In each chemotherapy subgroup, the incidence of adverse effects requiring study drug discontinuance was higher when the chemotherapy regimen was given in combination with bevacizumab.[74]

Although combined therapy with bevacizumab and chemotherapy prolonged progression-free survival in the RIBBON2 study, the same benefit was not observed in the AVF2119g study;[14,74] in addition, combined therapy did not prolong overall survival in either study.[14,74] Therefore, usefulness of the drug in combination with chemotherapy for the treatment of metastatic breast cancer previously treated with cytotoxic chemotherapy is unclear. Use of bevacizumab in combination with chemotherapy for the treatment of metastatic breast cancer previously treated with cytotoxic chemotherapy currently is not fully established because of equivocal evidence.

References:

14. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol.* 2005; 23:792-9.

64. Genentech. Avastin® (bevacizumab) prescribing information. South San Francisco, CA; 2011 Sep.

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).

74. Brufsky AM, Hurvitz S, Perez E, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2011; 29:4286-93.

75. A study of rhuMAb VEGF (bevacizumab) in combination with chemotherapy in patients with previously treated breast cancer. From ClinicalTrials.gov registry. Accessed 2012 Feb 15.

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 #1: There is a modest effect on PFS but no effect on OS or QOL. The potential toxicity and cost of this treatment is not evidence for risk/benefit analysis.

Reviewer #2: The lack of survival benefit despite clear effects on prolonging progression-free survival makes the usefulness of this agent (bevacizumab) for this patient population not established. Disease manifested in a site where progression might result in significant impairment were it to progress might benefit from such therapy.

Reviewer #3: Reasonable therapy in second-line in patients with good performance status (ECOG 0 or 1). Would not recommend bevacizumab in patients with untreated brain mets, unstable angina; CHF; HX of MI, stroke or TIA in last 6 months.

Reviewer #5: I do not believe that the data from AVF2119g and Ribbon-2 are strong enough to support the use of bevacizumab in the 2nd line metastatic setting. AVF2119g failed to meet its primary endpoint of progression-free survival. It did not show an overall survival benefit or improvement in QOL for patients receiving bevacizumab. Although, ribbon-2 did show statistically significant improvement in progression-free survival, overall survival has not been improved and adverse effects were higher for patients receiving bevacizumab. Also, improvement in progression-free survival was not observed across all patient subgroups, particularly patients receiving vinorelbine. I do not think that the 2 month progression-free survival is clinically significant enough to support the use of bevacizumab.

Comments on Draft Narrative Summary:

Reviewer#1: I have reviewed the ODAC/FDA report and the articles provided. The PFS benefits are modest at best. There are numerous options in breast cancer. The Genentech studies did not meet the critical results of E2100. Risks and costs outweigh this benefit.

Reviewer #5: The progression-free survival benefit was not observed for patients receiving vinorelbine, gemcitabine, or capecitabine in combination with bevacizumab.

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:

Although combined therapy with bevacizumab and chemotherapy prolonged progression-free survival in the RIBBON2 study, the same benefit was not observed in the AVF2119g study;[14,74] in addition, combined therapy did not prolong overall survival in either study.[14,74] Therefore, usefulness of the drug in combination with chemotherapy for the treatment of metastatic breast cancer previously treated with cytotoxic chemotherapy is unclear. Use of bevacizumab in combination with chemotherapy for the treatment of metastatic breast cancer previously treated with cytotoxic chemotherapy currently is not fully established because of equivocal evidence.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

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.

Publication Date: August 23, 2012