TRUVEN HEALTH ANALYTICS

COMPENDIA TRANSPARENCY TRACKING FORM

DRUG: Bevacizumab

INDICATION: Metastatic breast cancer, HER2-negative, first-line therapy in combination with chemotherapy (except paclitaxel)

COMPENDIA TRANSPARENCY REQUIREMENTS	
1	Provide criteria used to evaluate/prioritize the request (therapy)
2	Disclose evidentiary materials reviewed or considered
3	Provide names of individuals who have substantively participated in the review or disposition of the request and disclose their potential direct or indirect conflicts of interest
4	Provide meeting minutes and records of votes for disposition of the request (therapy)

EVALUATION/PRIORITIZATION CRITERIA: **C, S**
*to meet requirement 1

CODE	EVALUATION/PRIORITIZATION CRITERIA
A	Treatment represents an established standard of care or significant **advance** over current therapies
C	**Cancer** or cancer-related condition
E	Quantity and robustness of **evidence** for use support consideration
L	**Limited** alternative therapies exist for condition of interest
P	**Pediatric** condition
R	**Rare** disease
S	**Serious**, life-threatening condition

Note: a combination of codes may be applied to fully reflect points of consideration [eg, therapy may represent an advance in the treatment of a life-threatening condition with limited treatment alternatives (ASL)]

TRUVEN HEALTH ANALYTICS

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Miles,David W., 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. Journal of clinical oncology - official journal of the American Society of Clinical Oncology Jul 10, 2010; Vol 28, Issue 20; pp. 3239-3247.	Study methodology comments: This was a double-blind, randomized, placebo-controlled, phase III trial. Many potential confounding factors were controlled through the study design, statistical analyses, and eligibility criteria. Additional strengths of the study included: 1) defined primary and secondary outcomes and clinical response; 2) conducted power analysis; 3) provided 95% confidence intervals; 4) conducted analyses on the intent-to-treat population; 5) confirmed diagnosis; 6) had inclusion and exclusion criteria; 7) confirmed response at 4 weeks; 8) explained method of randomization; 9) compared baseline characteristics of groups; and 10) made statistical adjustments to preserve the type 1 error rate. Selection bias may have been present since subjects were not recruited randomly or in a consecutive manner.	S
Robert,N.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. Journal of Clinical Oncology Apr 01, 2011; Vol 29, Issue 10; pp. 1252-1260.	Study methodology comments: This was a rigorously designed randomized, double-blind, placebo-controlled, phase III trial with many strengths. Additional strengths included 1) defined primary and secondary outcomes; 2) conducted a power analysis; 3) conducted analyses on the intent-to-treat population; 4) had inclusion and exclusion criteria; 5) compared baseline characteristics of treatment groups; 6) presented 95% confidence intervals; 7) defined tumor response; 8) tumor responses were confirmed at 4 weeks; 9) explained method of randomization; and 10) examined the effect of potential confounding factors on treatment outcome. Progression-free survival was also assessed by an independent review panel to confirm the results but their results were not presented. Selection bias may have been present since subjects were not recruited in a random or consecutive manner.	S
Smith,I.E., et al: First-line bevacizumab plus taxane-based chemotherapy for locally recurrent or metastatic breast cancer: safety and efficacy in an open-label study in 2,251 patients. Annals of Oncology Mar 2011; Vol 22, Issue 3; pp. 595-602.	Study methodology comments: This was an open-label, single-arm trial. A major weakness of the study was the absence of a control group which would have controlled for many potential confounds. Additional weaknesses included 1) open-label design without the use of independent reviewers; 2) possible selection bias since the patients were not recruited randomly or in a consecutive manner; 3) partial discussion on power; and 4) did not examine the effect of potential confounding factors on outcomes. Strengths included 1) the use of a within-subject design to control for confounding effects of patient characteristics; 2) defined primary and secondary outcomes and tumor response; 3) confirmed diagnosis; 4) had both inclusion and exclusion criteria; and 5) included 95% confidence intervals.	S

Pivot,X., et al: Efficacy and safety of bevacizumab in combination with docetaxel for the first-line treatment of elderly patients with locally recurrent or metastatic breast cancer: Results from AVADO. Eur J Cancer Jul 12, 2011; Vol Epub, p. Epub.		3
Hurvitz,Sara A., et al: A phase II trial of docetaxel with bevacizumab as first-line therapy for HER2-negative metastatic breast cancer (TORI B01). Clinical Breast Cancer Aug 01, 2010; Vol 10, Issue 4; pp. 307-312.		3
Choueiri,T.K., et al: Congestive Heart Failure Risk in Patients With Breast Cancer Treated With Bevacizumab. Journal of Clinical Oncology Feb 20, 2011; Vol 29, Issue 6; pp. 632-638.		3
Guarneri,Valentina, et al: Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. Breast cancer Research and Treatment Jul 2010; Vol 122, Issue 1; pp. 181-188.		3
Mailliez,A., et al: Nasal septum perforation: a side effect of bevacizumab chemotherapy in breast cancer patients. British Journal of Cancer Sep 07, 2010; Vol 103, Issue 6; pp. 772-775.		3
Perez,E.A., et al: North Central Cancer Treatment Group (NCCTG) N0432: phase II trial of docetaxel with capecitabine and bevacizumab as first-line chemotherapy for patients with metastatic breast cancer. Annals of Oncology Feb 2010; Vol 21, Issue 2; pp. 269-274.		1

Ramaswamy B., et al: Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients. Clinical cancer research - an official journal of the American Association for Cancer Research May 15, 2006; Vol 12, Issue 10; pp. 3124-3129.		1
Chan,A., et al: Efficacy of bevacizumab (BV) plus docetaxel (D) does not correlate with hypertension (HTN) or G-CSF use in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) in the AVAIDO phase III study. Cancer Research Jan 15, 2009; Vol 69, Issue 2; pp. 114S-114S	Abstract	3
Chan,A., et al: Evidence from the phase III AVADO study reveals no increase in tumour malignant potential following treatment of metastatic breast cancer (mBC) with bevacizumab (BV) and docetaxel (D). EJC Supplements Mar 2010; Vol 8, Issue 3; pp. 199-200.	Abstract	3
Dirix,L.Y., et al: Safety of bevacizumab (BV) plus docetaxel (D) in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) who developed brain metastases during the AVADO phase III study. Cancer Research Jan 15, 2009; Vol 69, Issue 2; pp. 285S-285S.	Abstract	3
Fumoleau,P., et al: Bevacizumab (BV) maintenance therapy significantly delays disease progression (PD) or death compared with placebo (PL) in the AVADO trial (BV plus docetaxel [D] vs D + PL in 1st-line HER2-negative locally recurrent [LR] or metastatic breast cancer [mBC]). Cancer research Jan 15, 2009; Vol 69, Issue N2,S; pp. 104S-104S.	Abstract	3

Greil,R., et al: Quality of Life (Qol) Among Patients (Pts) with Locally Recurrent (Lr) Or Metastatic Breast Cancer (Mbc): Results from the Phase III Avado Study of First-Line Bevacizumab (Bv) Plus Docetaxel (D) Versus D Plus Placebo (Pl). Annals of Oncology Sep 2008; Vol 19, Issue Suppl; pp. 67-67.	Abstract	3
Harbeck,N., et al: No Clinical Evidence for Increase in Tumour Malignant Potential in Patients (Pts) with Metastatic Breast Cancer (mBC) Treated with Bevacizumab (BV) and Docetaxel (D) in the Phase III AVADO Study. Cancer Research Dec 15, 2009; Vol 69, Issue 24; pp. 852S-852S.	Abstract	3
Lyons,J.A., et al: Toxicity results and early outcome data on a randomized phase II study of docetaxel +/- bevacizumab for locally advanced, unresectable breast cancer. Journal of Clinical Oncology Jun 20, 2006; Vol 24, Issue 18; pp. 133S-133S.	Abstract	3
Makhoul,I., et al: Primary systemic therapy using docetaxel/cyclophosphamide/bevacizumab (TCB) followed by doxorubicin (A) in operable or locally advanced breast cancer (BC). Breast cancer Research and Treatment Jun 2008; Vol 109, Issue N3; pp. 592-593.	Abstract	3

Miles,D.W., 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 Research Dec 15, 2009; Vol 69, Issue 24; pp. 495S-495S.	Abstract	3
Ramaswamy,B., et al: CTEP-sponsored phase II trial of bevacizumab (Avastin (TM)) in combination with docetaxel (Taxotere (R)) in metastatic breast cancer. Breast Cancer Research and Treatment 2003; Vol 82, Issue Suppl; pp. S50-S50.	Abstract	3
Amar,Surabhi, Roy,Vivek, and Perez,Edith A.: Treatment of metastatic breast cancer: looking towards the future. Breast cancer Research and Treatment Apr 2009; Vol 114, Issue 3; pp. 413-422.		4
Cameron,D.: Bevacizumab in the first-line treatment of metastatic breast cancer. EJC Supplements Mar 2008; Vol 6, Issue N6; pp. 21-28.		4
Chane, A, Miles, DW, and Pivot, X: Bevacizumab, in combination with taxanes, for the first-line treatment of metastatic breast cancer. Annals of Oncology 2010; Vol 21, Issue 12; p. 2305.		4
Goldfarb,Shari B., Traina,Tiffany A., and Dickler,Maura N.: Bevacizumab for advanced breast cancer. Women's health (London, England) Jan 2010; Vol 6, Issue 1; pp. 17-25.		4

Gradishar,W.J.: AVADO: Bevacizumab/docetaxel provides small benefit in PFS. Commentary. Oncology Report 2008; Vol 2008, Issue FALL; p. 23.		4
Hamilton, EP and Blackwell, KL: Safety of bevacizumab in patients with metastatic breast cancer. Oncology Jul 19, 2011; Vol 80, Issue 5-6; pp. 314-325.		4
Prat,A., et al: Acute lung injury associated with docetaxel and bevacizumab. Clinical Oncology (Royal College of Radiologists) Dec 2007; Vol 19, Issue 10; pp. 803-805.		4
Ramaswamy,B. and Shapiro,C.L.: Phase II trial of bevacizumab in combination with docetaxel in women with advanced breast cancer. Clinical Breast Cancer Oct 2003; Vol 4, Issue 4; pp. 292-294.		4
Traina,Tiffany A.: Bevacizumab in the treatment of metastatic breast cancer. Oncology (Williston Park, N Y) Apr 15, 2009; Vol 23, Issue 4; pp. 327-332.		4

Literature evaluation codes: S = Literature selected; 1 = Literature rejected = Topic not suitable for scope of content; 2 = Literature rejected = Does not add clinically significant new information; 3 = Literature rejected = Methodology flawed/Methodology limited and unacceptable; 4 = Other (review article, letter, commentary, or editorial)

CONTRIBUTORS:

*to meet requirement 3

PACKET PREPARATION	DISCLOSURES	EXPERT REVIEW	DISCLOSURES
Margi Schiefelbein, PA	None	Jeffrey A. Bubis, DO	Other payments: Dendreon
Stacy LaClaire, PharmD	None	Edward P. Balaban, DO	None
Felicia Gelsey, MS	None	James E. Liebmann, MD	None
		Jeffrey F. Patton, MD	None
		Gerald J. Robbins, MD	None

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	---			B
Jeffrey A. Bubis, DO	Ineffective	Class lll: Not Recommended	No OS benefit. No QQL benefit. PFS is not relevant in 1st line metastatic breast cancer.	N/A
Edward P. Balaban, DO	Evidence Favors Efficacy	Class llb: Recommended, In Some Cases	Bev and chemotx impact on progression free survival seems undisputable. No impact however on overall survival. Adverse effects will limit its use to only those with the best performance status at the onset of therapy.	N/A

James E. Liebmann, MD	Evidence is Inconclusive	Class lll: Not Recommended	A consistent theme has emerged from the Bevacizumab-chemotherapy studies (BV-CT) in metastatic breast cancer. All studies show that BV-CT, compared to CT alone, results in: i)improved response rate ii) increased progression free survival But, iii) no effect on overall survival iv) increased toxicity/side effects The question then becomes if the benefits of BV-CT (i and ii above) outweigh the negative aspects of BV-CT (iii and iv above). I do not believe they do. Adding an intervention to standard therapy must do better than this to be worthwhile.	N/A
Jeffrey F. Patton, MD	Evidence Favors Efficacy	Class llb: Recommended, In Some Cases	None	N/A
Gerald J. Robbins, MD	Evidence Favors Efficacy	Class llb: Recommended, In Some Cases	Studies met endpoints of PFS. Since crossover was allowed, OS cannot be fully assessed for efficacy. mPFS was improved by 1-3 months. Additional studies obtained similar stats. Toxicity not insignificant (therefore patients must be carefully selected).	N/A