TRUVEN HEALTH ANALYTICS

COMPENDIA TRANSPARENCY TRACKING FORM

DRUG: Bevacizumab

INDICATION: Nonsquamous non-small cell lung cancer, advanced or recurrent, first-line therapy in combination with cisplatin and gemcitabine

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)]

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EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Reck,M., et al: Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. Journal of Clinical Oncology Mar 10, 2009; Vol 27, Issue 8; pp. 1227-1234.	Study methodology comments: This was a rigorously designed randomized, double-blind, placebo-controlled, multicenter trial with many strengths. 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) compared baseline characteristics of groups; 6) made statistical adjustments to preserve the type 1 error rate; 7) had both inclusion and exclusion criteria; 8) confirmed diagnosis; and 9) tumor response was confirmed at 4 weeks. Selection bias may have been present since subjects were not recruited in a random or consecutive manner.	S
Reck,M., et al: Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Annals of Oncology Sep 2010; Vol 21, Issue 9; pp. 1804-1809.	Study methodology comments: This paper presented the overall survival data from the AVAiL trial.	S
Leighl,N.B., et al: Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer in the phase III BO17704 study (AVAiL). Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer Dec 2010; Vol 5, Issue 12; pp. 1970-1976.	Study methodology comments: This paper presented the results of a preplanned subgroup analysis assessing efficacy among patients 65 years of age and older in the AVAiL trial.	S

Crinò L, et al. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study. Lancet Oncol. 2010 Aug;11(8):733-40. Epub 2010 Jul 23.	Study methodology comments: This was an open-label, single-arm, multicenter, phase 4 trial that should be interpreted with some caution. There were two major caveats of the study. First, the study did not include a control group which would have controlled for many potential confounds. Second, no specific evaluation method or frequency was mandated for tumor assessments. A centralized independent assessment was not conducted. Additional weaknesses included 1) open-label design without the use of independent reviewers; 2) possible selection bias since the patients were not recruited in a random or consecutive manner; and 3) did not examine the effect of potential confounding factors on outcomes. Strengths of the study included: 1) defined primary and secondary outcomes; 2) provided 95% confidence intervals; 3) conducted analyses on the intent-to-treat population; 4) had both inclusion and exclusion criteria; 5) confirmed diagnosis; 6) all gradable events were classified by standardized method; and 7) the use of a within-subject design to control for confounding effects of patient characteristics.	S
Azzoli CG, et al. American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2009;27(36):6251-6266.	Study methodology comments:	S
Clement-Duchene,C., et al: A phase II first-line study of gemcitabine, carboplatin, and bevacizumab in advanced stage nonsquamous non-small cell lung cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer Nov 2010; Vol 5, Issue 11; pp. 1821-1825.		3
Nuijten,M., Heigener,D.F., Bischoff,H.G., et al: Effectiveness of bevacizumab- and pemetrexed-cisplatin treatment for patients with advanced non-squamous non-small cell lung cancer. Lung Cancer Aug 2010; Vol 69 Suppl 1, pp. S4-10.		3

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)

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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	Cindy L. O'Bryant, PharmD	None
		James E. Liebmann, MD	None
		Keith A. Thompson, 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 III: Not Recommended	Lack of survival data: Carboplatin/Alimta superior. Carboplatin and Taxol and Avastin superior	N/A
Edward P. Balaban, DO	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	In Stage IIB-IV NSCLC (nonsquamous) appears to be efficacious. Enough data to support at least in some case if not in most cases. (Recommendation IIA)	N/A

Cindy L.O'Bryant,PharmD	Effective	Class IIa: Recommended, In Most Cases	PFS: In a large randomized Phase III trial (AVAiL) the combination of bevacizumab with gem/cis has been shown to demonstrate a durable and significant improvement in PFS (Reck et al, JCO 2009, Reck et al, Ann Oncol 2010) Overall survival was not found to be significantly improved, but did trend towards that, however, this is potentially confounded by a high percentage of patients who received post study treatment and the efficacy of those treatments. However, this trend to OS outcome is consistent with data presented at the 2011 ASCO Annual Meeting (Thomas, M; Abstract #7504) bevacizumab with gem/cis was compared with erlotinib bevacizumab in a Phase III trial. Again OS was not statistically significant, but trended towards improvement (HR 0.73 (95%CI 0.5-1.06), p=0.1. In the AVAiL trial no differences in efficacy outcomes were seen in the elderly population and the lower bevacizumab low does (7.5mg/kg) demonstrated slightly better outcomes as compared to the high dose (15 mg/kg). Safety: Results of the AVAiL trial and the SAiL trial (Crino et al ; Lancet 2010) report AEs with bevacizumab that are consistent with the type and incidence seen in other NSCLC trials. The AVAiL trial showed no increase risk of AEs in the elderly. Since this information was published after the release of the ASCO Clinical Practice Guideline Update on Chemo for Stage IV NSCLC the guideline has not been updated to reflect the data and outcomes presented in these studies.	N/A

James E. Liebmann, MD	Evidence is Inconclusive	Class lll: Not Recommended	The AVAiL trial shows little meaningful benefit from the addition of Avastin to Cisplatin and Gemcitabine. Improved PFS is obtained at the cost of significantly increased toxicity from Avastin and no improvement in overall survival. One can question the use of Gemcitabine in this patient population since that drug is inferior at least to pemetrexed in these patients. However, the reality is that simply improving PFS and RR does not justify the additional toxicity of Avastin.	N/A
Keith A. Thompson, MD	Evidence is Inconclusive	Class lll: Not Recommended	None	N/A