TRUVEN HEALTH ANALYTICS
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COMPENDIA TRANSPARENCY TRACKING FORM

DATE: 5/3/2018

PACKET: 1210

DRUG: Bevacizumab

USE: Nonsquamous nonsmall cell neoplasm of lung, stage IIIB/IV or recurrent disease with EGFR exon 19 deletion or exon 21 mutation, first-line therapy in combination with erlotinib

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, R, 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
Batson,S., et al: Tyrosine kinase inhibitor combination therapy in first-line treatment of non-small-cell lung cancer: systematic review and network meta-analysis. OncoTargets Ther May 2017; Vol 10, pp. 2473-2482.		3
Kato,T., et al: Erlotinib plus bevacizumab phase ll study in patients with advanced non-small-cell lung cancer (JO25567): updated safety results. Drug Saf Oct 17, 2017; Vol 41, Issue 2; pp. 229-237		2
Seto,T., Kato,T., Nishio,M., et al: Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncology Oct 2014; Vol 15, Issue 11; pp. 1236-1244.	Comments: This was a randomized, open-label, multicentre, phase 2 study in patients with stage IIIB/IV or recurrent NSCLC with activating EGFR mutations. An independent review committee of clinicians and radiologists masked to treatment assignment reviewed all tumour images and determined tumour response and progression status. The primary endpoint was progression-free survival, as determined by an independent review committee. The study met power requirements. Key bias criteria evaluated were (1) random sequence generation of randomization; (2) lack of allocation concealment, (3) lack of blinding, (4) incomplete accounting of patients and outcome events, and (5) selective outcome reporting bias. The study was at low risk of bias for these key criteria, and no additional biases were identified.	S

Ciuleanu,T., et al: A phase II study of erlotinib in combination with bevacizumab versus chemotherapy plus bevacizumab in the first-line treatment of advanced non-squamous non-small cell lung cancer. Lung Cancer Nov 2013; Vol 82, Issue 2; pp. 276-281.	Comments: TASK was a phase II, open-label, multicenter, randomized, first-line study in patients with advanced non-squamous NSCLC. A pre-planned interim analysis was undertaken on 17 September 2008. This analysis was to assess whether to stop or evaluate the study if efficacy in the BE arm was worse than the BC arm. If the HR was greater than 1.25, indicating BC treatment was better than BE, the study would be re-evaluated. An updated analysis was performed on 6 January 2009 in order to increase the follow-up period of the randomized patients. The final analysis was on 9 September 2011 showing an HR greater than 1.25 and stopping enrollment for the study. The open-label design was at high risk of bias for subjective outcomes and low for objective outcomes. Other key bias criteria evaluated were (1) random sequence generation of randomization; (2) lack of allocation concealment, (3) incomplete accounting of patients and outcome events, and (4) selective outcome reporting bias. The study was at low risk of bias for these key criteria.	3
Rosell,R., et al: Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial. Lancet Respir Med May 2017; Vol 5, Issue 5; pp. 435-444		3
Riggs,H., et al: Erlotinib and bevacizumab in newly diagnosed performance status 2 or elderly patients with nonsquamous non-small-cell lung cancer, a phase II study of the Hoosier Oncology Group: LUN04-77. Clin Lung Cancer May 2013; Vol 14, Issue 3; pp. 224-229.		3
Zhang,L.: First-line management of EGFR Mutant NSCLC. J Thorac Oncol 2017; Vol 12, Issue 11 Supplement 2; p. S1656.		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
Felicia Gelsey, MS	None		
Stacy LaClaire, PharmD	None		
Catherine Sabatos, PharmD	None		
		John D Roberts	None
		Jeffrey Klein	None
		Richard LoCicero	Incyte Corporation Local PI for REVEAL. Study is a multicenter, non-interventional, non-randomized, prospective, observational study in an adult population for patients who have been diagnosed with clinically overt PV and are being followed in either community or academic medical centers in the US who will be enrolled over a 12-month period and observed for 36 months.

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	Evidence is Inconclusive	Class III: Not Recommended		B
John D Roberts	Evidence is Inconclusive	Class III: Not Recommended	The single randomized trial for which data is available showed an impressive 6 month increase in disease free survival with the addition of bevacizumab to erlotinib. The trial was relatively small, involving a total of ~150 patients, and was labelled a phase II trial. At the time of publication in 2014, overall survival data were quite limited. The combination involved much more toxicity, albeit manageable, in terms of hypertension and proteinuria, and bevacizumab was discontinued in about 40% of patients, albeit generally after many months of treatment. Administration of bevacizumab significantly increased inconvenience due to every three week infusions. In a follow-up publication in October 2017 the authors update safety information, but they do not update overall survival data. This is disappointing and raises the concern that the combination may not confer a survival benefit.	N/A
Jeffrey Klein	Evidence Favors Efficacy	Class IIa: Recommended, in Most Cases	The use of Bevacizumab with erlotinib to treat first line NSCLC patients showed a significant benefit with regard to progression free survival. The patients in this study had to demonstrate a particular gene mutation. One wonders if all insurance companies will cover this particular gene mutation test? Adverse reactions such as proteinuria, skin rash, and hypertension were seen in moderate numbers in the testing group that received the combination therapy.	N/A
Richard LoCicero	Evidence is Inconclusive	Class III: Not Recommended	A single phase II open-label, randomized, multicenter study of 154 patients evaluated the efficacy of Erlotinib alone, or in combination with bevacizumab. While progression free survival was improved with the addition of bevacizumab, overall survival data is immature. Further data maturity and clinical trial study is warranted before this combination can be an established treatment.	N/A