TRUVEN HEALTH ANALYTICS

COMPENDIA TRANSPARENCY TRACKING FORM

DRUG: Bevacizumab

INDICATION: Liver carcinoma, advanced

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)]

TRUVEN HEALTH ANALYTICS

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Kaseb,A.O., Garrett-Mayer,E., Morris,J.S., et al: Efficacy of bevacizumab plus erlotinib for advanced hepatocellular carcinoma and predictors of outcome: final results of a phase II trial. Oncology 2012; Vol 82, Issue 2; pp. 67-74.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. All subjects were included in the analyses. The results should be interpreted with caution since the study lacked a control group.	S
Siegel,A.B., Cohen,E.I., Ocean,A., et al: Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. Journal of Clinical Oncology Jun 20, 2008; Vol 26, Issue 18; pp. 2992-2998.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. All subjects were included in the analyses. The results should be interpreted with caution since the study lacked a control group.	S
Hsu CH,et al. Bevacizumab with Erlotinib as First-line Therapy in Asian Patients with Advanced Hepatocellular Carcinoma: A Multicenter Phase II Study. Oncology. 2013;85(1):44-52.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. Analyses were conducted with the intent-to-treat population. The results should be interpreted with caution since the study lacked a control group.	S
Hsu,C.H., Yang,T.S., Hsu,C., et al: Efficacy and tolerability of bevacizumab plus capecitabine as first-line therapy in patients with advanced hepatocellular carcinoma. British Journal of Cancer Mar 16, 2010; Vol 102, Issue 6; pp. 981-986.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. Only one subject was lost to follow-up. The results should be interpreted with caution since the study lacked a control group.	S

Boige,V., Malka,D., Bourredjem,A., et al: Efficacy, safety, and biomarkers of single-agent bevacizumab therapy in patients with advanced hepatocellular carcinoma. Oncologist 2012; Vol 17, Issue 8; pp. 1063-1072.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. A small number of patients were lost to follow-up. The results should be interpreted with caution since the study lacked a control group.	S
Thomas,M.B., Morris,J.S., Chadha,R., et al: Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. Journal of Clinical Oncology Feb 20, 2009; Vol 27, Issue 6; pp. 843-850.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. Analyses were based on the intent-to-treat population. The results should be interpreted with caution since the study lacked a control group.	4
Sun,W., Sohal,D., Haller,D.G., et al: Phase 2 trial of bevacizumab, capecitabine, and oxaliplatin in treatment of advanced hepatocellular carcinoma. Cancer Jul 15, 2011; Vol 117, Issue 14; pp. 3187-3192.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. Analyses were based on the intent-to-treat population. The results should be interpreted with caution since the study lacked a control group.	S
Zhu,A.X., Blaszkowsky,L.S., Ryan,D.P., et al: Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. Journal of Clinical Oncology Apr 20, 2006; Vol 24, Issue 12; pp. 1898-1903.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. Analyses were based on the intent-to-treat population. The results should be interpreted with caution since the study lacked a control group.	S
Govindarajan,R., et al: Bevacizumab and erlotinib in previously untreated inoperable and metastatic hepatocellular carcinoma. American Journal of Clinical Oncology Jun 2012; Vol 36, Issue 3; pp. 254-257.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. A small number of subjects were lost to follow-up. The results should be interpreted with caution since the study lacked a control group.	S
Philip,P.A., Mahoney,M.R., Holen,K.D., et al: Phase 2 study of bevacizumab plus erlotinib in patients with advanced hepatocellular cancer. Cancer May 01, 2012; Vol 118, Issue 9; pp. 2424-2430.	Study methodology comments: This was an open-label, single-arm phase II clinical trial. There was low risk of bias associated with selection of cohorts and assessment of outcomes. Data was gathered prospectively for objective outcomes. Four subjects were lost to follow-up. The results should be interpreted with caution since the study lacked a control group.	S

Yau,T., Wong,H., Chan,P., et al: Phase II study of bevacizumab and erlotinib in the treatment of advanced hepatocellular carcinoma patients with sorafenib-refractory disease. Investigational New Drugs Dec 2012; Vol 30, Issue 6; pp. 2384-2390.		3
Fang,P., Hu,J., Cheng,Z., et al: Efficacy and Safety of Bevacizumab for the Treatment of Advanced Hepatocellular Carcinoma: A Systematic Review of Phase II Trials. 2012		3
Jelic,S. and Sotiropoulos,G.C.: Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol May 2010; Vol 21 Suppl 5, pp. v59-v64.		4
Treiber, G, Wex, T, Schneider, G, et al: Treatment of advanced or metastatic hepatocellular cancer (HCC): Final clinical results of a single-arm phase II study of bevacizumab and everolimus.. J Clin Oncol 2012; Vol 30, Issue Suppl; p. 4107.	Abstract only	3
Chelis,L., Deftereos,S., Xenidis,N., et al: Bevacizumab plus temsirolimus as second-line treatment for advanced hepatocellular carcinoma (HCC). Journal of Clinical Oncology 2012; Vol 30, Issue 15 Suppl 1; p. e14567	Abstract only	3

Yau,T., Wong,H., Chan,P., et al: Combination of bevacizumab and erlotinib in the treatment of patients with advanced hepatocellular carcinoma with sorafenib refractory disease: Results of a pilot phase II study. European Journal of Cancer Apr 2012; Vol 48 SUPPL. 4, pp. S1-S2.	Abstract only	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)

CONTRIBUTORS:

*to meet requirement 3

PACKET PREPARATION	DISCLOSURES	EXPERT REVIEW	DISCLOSURES
Margi Schiefelbein, PA	None	James E. Liebmann, MD	None
Stacy LaClaire, PharmD	None	Edward P. Balaban, DO	None
Felicia Gelsey, MS	None	Jeffrey A. Bubis, DO	Other payments: Dendreon
		Keith A. Thompson, MD	None
		John M. Valgus, PharmD	None

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	---	---		**B**

James E. Liebmann, MD	Evidence is inconclusive	Class III - Not Recommended	There is no rationale for treating with bevacizumab and another drug – it is not clear from the various studies that outcomes are better with bevacizumab combinations than bevacizumab alone. The study with single agent bevacizumab resulted in mediocre response rates and an unimpressive overall survival rate. Most importantly, however, it is not clear how many patients enrolled in these studies had received sorafenib. There is no information how patients treated with sorafenib responded to bevacizumab. Since the current standard of care for unresectable hepatocellular carcinoma is sorafenib, the real question is how effective bevacizumab is in patients treated first with sorafenib. There is no way to determine this from these papers. However, the low response rates and overall survival outcomes cannot justify the use of bevacizumab in this setting.	N/A
Edward P. Balaban, DO	Evidence is inconclusive	Class IIb - Recommended, In Some Cases	The studies thus far predictably involve small numbers. The impact of adding Bev to the treatment seems to be possibly effective, but the collective results along with the biologic variability of the disease makes for the need to study Bev further in the disease, but far from recommending its use.	N/A
Jeffrey A. Bubis, DO	Evidence is inconclusive	Class III - Not Recommended	There is a lack of convincing data that demonstrates an outcomes benefit for Avastin in HCC.	N/A
Keith A. Thompson, MD	Evidence is inconclusive	Class IIb - Recommended, In Some Cases	None	N/A

John M. Valgus, PharmD	Evidence is inconclusive	Class IIb - Recommended, In Some Cases	Although there are several clinical trials which demonstrate some activity and promising RRs with bevacizumab – containing regimens, none of these are randomized to compare without bev. Some studies with conflicting results (ie bev-erlotinib). Future studies need to be performed to demonstrate efficacy.	N/A