TRUVEN HEALTH ANALYTICS
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COMPENDIA TRANSPARENCY TRACKING FORM

DATE: 5/3/2018

PACKET: 1661

DRUG: Capecitabine

USE: Metastatic colorectal cancer, maintenance therapy following oxaliplatin-based induction chemotherapy in previously untreated patients

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
Goey,K.K.H., et al: Maintenance treatment with capecitabine and bevacizumab versus observation in metastatic colorectal cancer: Updated results and molecular subgroup analyses of the phase 3 CAIRO3 study. Ann Oncol 2017; Vol 28, Issue 9; pp. 2128-2134.		3
Simkens,L.H., van,Tinteren H., May,A., et al: Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet May 09, 2015; Vol 385, Issue 9980; pp. 1843-1852.	Comments: The CAIRO3 study was an open-label, multicenter, phase 3 randomized trial that recruited patients from 64 hospitals in the Netherlands. 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. An independent radiologist reviewed masked CT scans of a random selection of patients. The study was powered and controlled for the effect of potential confounding factors.	S
Hegewisch-Becker,S., et al: Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, open-label, phase 3 trial. Lancet Oncol Oct 2015; Vol 16, Issue 13; pp. 1355-1369.	Comments: This was an open-label, non-inferiority, randomized phase 3 trial that recruited patients from 106 German institutions. A major caveat of the study was that it ended early. As of Oct 12, 2014, it became evident that the expected number of time to failure of strategy events could not be reached within a reasonable timeframe because of losses to follow-up and an overall more favorable disease course than anticipated. Therefore, the steering committee decided to close the database for the final analysis (except overall survival) on Dec 20, 2014. 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. Additionally, the study controlled for the effect of potential confounding factors. For subjective outcomes, there was potentially high risk of bias for performance bias and detection bias due to the open-label design that did not use independent reviewers or assessors.	3

Luo,H.Y., et al: Single-agent capecitabine as maintenance therapy afterinduction of XELOX (or. Ann Oncol 2016; Vol 27, Issue 6; pp. 1074-1081.	Comments: This was an open-label, multicenter, phase 3 randomized trial that recruited patients from 11 sites in China. Overall, this study was at low risk of biases associated with lack of allocation concealment and blinding (for objective outcomes only), incomplete accounting of patients and outcome events, and selective outcome reporting. The risk of bias associated with poor random sequence generation was unclear and not discussed in the paper. For subjective outcomes, there was potentially high risk of bias for performance bias and detection bias due to the open-label design that did not use independent reviewers or assessors. The study was powered and controlled for the effect of potential confounding factors.	S
Hagman,H., et al: A randomized study of KRAS-guided maintenance therapy with bevacizumab, erlotinib or metronomic capecitabine after first-line induction treatment of metastatic colorectal cancer: The Nordic ACT2 trial. Annals of Oncology Jan 01, 2016; Vol 27, Issue 1; pp. 140-147.	Comments: The ACT2 study was an open-label, multicenter, phase 3 randomized trial that recruited patients from 11 sites in Sweden and one in Denmark. Overall, this study was at low risk of biases associated with lack of blinding (for objective outcomes only), incomplete accounting of patients and outcome events, and selective outcome reporting. The risk of bias associated with poor random sequence generation and allocation concealment was unclear and not discussed in the paper. For subjective outcomes, there was potentially high risk of bias for performance bias and detection bias due to the open-label design that did not use independent reviewers or assessors. The study was powered.	3
Yalcin,S., et al: Bevacizumab + capecitabine as maintenance therapy after initial bevacizumab + XELOX treatment in previously untreated patients with metastatic colorectal cancer: Phase III 'stop and go' study results-A Turkish oncology group trial. ONCOLOGY 2013; Vol 85, Issue 6; pp. 328-335.	Comments: This was an open-label, multicenter, phase 3 randomized trial. Overall, this study was at low risk of biases associated with lack of blinding (for objective outcomes only), incomplete accounting of patients and outcome events, and selective outcome reporting. The risk of bias associated with poor random sequence generation and allocation concealment was unclear and not discussed in the paper. For subjective outcomes, there was potentially high risk of bias for performance bias and detection bias due to the open-label design that did not use independent reviewers or assessors.	S
Yi,Y., Dai,D.-J., and Meng,H.: Efficacy and safety of capecitabine as maintenance treatment after primary chemotherapy using oxaliplatin and capecitabine in stage III colorectal cancer. J Pract Oncol Jun 2014; Vol 29, Issue 3; pp. 255-258.		4

Li,Y., Li,J., Lu,M., et al: Capecitabine maintenance therapy after first-line chemotherapy in patients with metastatic colorectal cancer. Chin J Cancer Res 2010; Vol 22, Issue 3; pp. 181-185		3
Van Cutsem,E., Cervantes,A., Adam,R., et al: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annals of Oncology Aug 01, 2016; Vol 27, Issue 8; pp. 1386-1422		S

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.

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ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases		B
John D Roberts	Evidence is Inconclusive	Class IIb: Recommended, in Some Cases	Two prospective trials of maintenance therapy with capecitabine with or without bevacizumab showed modest increases in progression free survival (without significant increases in overall survival) with moderate toxicity. Almost all patients in these studies were performance status 0 or 1. In the larger and better performed trial, all patients on active treatment received capecitabine plus bevacizumab; in the other trial patients received capecitabine alone. Patients and clinicians must decide whether the risk, toxicity, inconvenience, and cost of maintenance therapy merit the modest benefits. Delivery of either treatment to patients with performance status 2 or greater would be expected to produce more toxicity, further decreasing any risk-toxicity: benefit ratio. (A third trial compared two capecitabine-containing arms and therefore did not address the value of capecitabine maintenance as compared with no therapy.)	N/A
Jeffrey Klein	Evidence Favors Efficacy	Class III: Not recommended	The small gains in efficacy do not substitute for the types of and severity of adverse reactions seen with capecitabine. One also has to wonder if the benefits in therapy are the result of the bevacizumab component only.	N/A
Richard LoCicero	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	A randomized clinical trial demonstrated improved progression free survival (PFS) with maintenance capecitabine following oxliplatin based induction therapy. Overall survival benefit was not observed. Two additional trials demonstrated improved PFS with capecitabine (in addition to bevacizumab) maintenance therapy without excess toxicity. The toxicity observed compared to observation is typical of the maintenance therapy used.	N/A