TRUVEN HEALTH ANALYTICS

## COMPENDIA TRANSPARENCY TRACKING FORM

**DRUG:** Cetuximab

**INDICATION:** Gastric or gastroesophageal junction cancer, advanced, as first-line therapy in combination with fluoropyrimidine-based chemotherapy

| 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, L, R**
*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 |
|---|---|---|
| Lorenzen,S., et al: Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Annals of Oncology Oct 2009; Vol 20, Issue 10; pp. 1667-1673. | Study methodology comments:<br>This was an open-label, randomized, noncomparative phase II trial. The between-group analyses should be interpreted with much caution since they were not powered. Additional weaknesses included 1) open-label design without the use of independent reviewers; 2) partial explanation of method of randomization; and 3) possible selection bias since the patients were not recruited randomly or in a consecutive manner. Strengths were 1) confirmed diagnosis; 2) had inclusion and exclusion criteria; 3) defined primary and secondary outcomes; 4) defined response; 5) responses were confirmed at 4 weeks; 6) provided 95% confidence intervals; 7) conducted a power analysis; 8) examined the effect of potential confounding factors; 9) randomized centrally; and 10) compared baseline characteristics of groups. | 1 |
| Han,S.W., et al: Phase II study and biomarker analysis of cetuximab combined with modified FOLFOX6 in advanced gastric cancer. Br J Cancer Jan 27, 2009; Vol 100, Issue 2; pp. 298-304. | Study methodology comments:<br>This was an open-label, single-arm phase II trial conducted with a two-stage design that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of many potential confounds. Additional weaknesses included 1) open-label design without the use of independent reviewers; and 2) possible selection bias since the patients were not recruited randomly or in a consecutive manner. Strengths were 1) had inclusion and exclusion criteria; 2) defined primary and secondary outcomes; 3) defined response; 4) responses were confirmed at 4 weeks; 5) provided 95% confidence intervals; 6) examined the effect of potential confounding factors; 7) analyzed the intent-to-treat population; and 8) the use of a within-subject design to control for confounding effects of patient characteristics. | 3 |
| Lordick,F., et al: Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Br J Cancer Feb 02, 2010; Vol 102, Issue 3; pp. 500-505. | Study methodology comments:<br>This was an open-label, single-arm phase II trial conducted with a two-stage design that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of many potential confounds. Additional weaknesses included 1) open-label design without the use of independent reviewers; and 2) possible selection bias since the patients were not recruited randomly or in a consecutive manner. Strengths were 1) confirmed diagnosis; 2) presented eligibility criteria; 3) defined primary and secondary outcomes; 4) defined response; 5) responses were confirmed at 4 weeks; 6) provided 95% confidence intervals; 7) examined the effect of potential confounding factors; and 8) the use of a within-subject design to control for confounding effects of patient characteristics. | S |

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| Moehler,M., et al: Cetuximab with irinotecan, folinic acid and 5-fluorouracil as first-line treatment in advanced gastroesophageal cancer: a prospective multi-center biomarker-oriented phase II study. Annals of Oncology Jun 2011; Vol 22, Issue 6; pp. 1358-1366. | Study methodology comments:<br>This was an open-label, single-arm phase II trial conducted with a two-stage design that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of many potential confounds. Additional weaknesses included 1) open-label design without the use of independent reviewers; and 2) possible selection bias since the patients were not recruited randomly or in a consecutive manner. Strengths were 1) confirmed diagnosis; 2) had inclusion and exclusion criteria; 3) defined primary and secondary outcomes; 4) defined response; 5) responses were confirmed at 4 weeks; 6) defined exploratory analyses; 7) provided 95% confidence intervals; 8) examined the effect of potential confounding factors; and 9) the use of a within-subject design to control for confounding effects of patient characteristics. | S |
| Kim,C., et al: A prospective phase II study of cetuximab in combination with XELOX (capecitabine and oxaliplatin) in patients with metastatic and/or recurrent advanced gastric cancer. Invest New Drugs Apr 2011; Vol 29, Issue 2; pp. 366-373. | Study methodology comments:<br>This was an open-label, single-arm phase II trial conducted with a two-stage design that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of many potential confounds. Additional weaknesses included 1) open-label design without the use of independent reviewers; and 2) possible selection bias since the patients were not recruited randomly or in a consecutive manner. Strengths were 1) confirmed diagnosis; 2) had inclusion and exclusion criteria; 3) defined primary and secondary outcomes; 4) defined response; 5) responses were confirmed at 4 weeks; 6) provided 95% confidence intervals; 7) examined the effect of potential confounding factors; and 8) the use of a within-subject design to control for confounding effects of patient characteristics. | S |
| De Vita,F., et al: A multicenter phase II study of induction chemotherapy with FOLFOX-4 and cetuximab followed by radiation and cetuximab in locally advanced oesophageal cancer. Br J Cancer Feb 01, 2011; Vol 104, Issue 3; pp. 427-432.<br><br>De,Vita F., et al: A multicenter phase II study of induction CT with FOLFOX-4 and Cetuximab followed by RT and Cetuximab in locally advanced esophageal cancer (LLAEC): Final results. Annals of Oncology Jul 2010; Vol 21 SUPPL. 6, p. vi27. | Study methodology comments:<br>This was an open-label, single-arm phase II trial conducted with a two-stage design that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of many potential confounds. Additional weaknesses included 1) open-label design without the use of independent reviewers; and 2) possible selection bias since the patients were not recruited randomly or in a consecutive manner. Strengths were 1) confirmed diagnosis; 2) presented eligibility criteria; 3) defined primary and secondary outcomes; 4) defined response; 5) provided 95% confidence intervals; 6) examined the effect of potential confounding factors; 7) made statistical adjustments to preserve the type 1 error rate when analyzing cytokines; and 8) the use of a within-subject design to control for confounding effects of patient characteristics. | 1 |

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| Pinto,C., et al: Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). Annals of Oncology Mar 2007; Vol 18, Issue 3; pp. 510-517. | Study methodology comments:<br>This was an open-label, single-arm phase II trial conducted with a two-stage design that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of many potential confounds. Additional weaknesses included 1) open-label design without the use of independent reviewers; and 2) possible selection bias since the patients were not recruited randomly or in a consecutive manner. Strengths were 1) confirmed diagnosis; 2) presented inclusion and exclusion criteria; 3) defined primary and secondary outcomes; 4) defined response; 5) provided 95% confidence intervals; 6) examined the effect of potential confounding factors; 7) centrally assessed EGFR expression; and 8) the use of a within-subject design to control for confounding effects of patient characteristics. | 2 |
| Gold,P.J., et al: Cetuximab as second-line therapy in patients with metastatic esophageal adenocarcinoma: a phase II Southwest Oncology Group Study (S0415). Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer Sep 2010; Vol 5, Issue 9; pp. 1472-1476. | | 1 |
| Chan,J.A., et al: A multicenter phase II trial of single-agent cetuximab in advanced esophageal and gastric adenocarcinoma. Annals of Oncology Jun 2011; Vol 22, Issue 6; pp. 1367-1373. | | 1 |
| Yu,j., et al: An open label, multicenter clinical study of cetuximab combined with concurrent chemo-radiotherapy for locally advanced esophageal Squamous Cell Carcinoma: Preliminary Results of a Phase II Trial. International Journal of Radiation Oncology Biology Physics 2010; Vol 78, Issue 3; p. 1. | | 1 |

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| Pinto,C., et al: Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study). Br J Cancer Oct 20, 2009; Vol 101, Issue 8; pp. 1261-1268. | | 1 |
| Schoennemann,K.R.., et al: Biweekly cetuximab and irinotecan as second-line therapy in patients with gastro-esophageal cancer previously treated with platinum. Gastric Cancer Aug 2011; Vol 14, Issue 3; pp. 219-225. | | 1 |
| Ruhstaller,T., et al: Cetuximab in combination with chemoradiotherapy prior to surgery in patients with resectable, locally advanced esophageal carcinoma: A prospective, multicenter phase Ib-II trial of the Swiss Group for Clinical Cancer Research (SAKK 75/06). Journal of Clinical Oncology 2009; Vol 27, Issue 15 SUPPL. 1; p. 4570. | | 1 |
| Munoz Martin,A.J., et al: First-line treatment of advanced gastric cancer and hepatic dysfunction with oxaliplatin, 5-fluorouracil and cetuximab. Clin Transl Oncol Mar 2008; Vol 10, Issue 3; pp. 182-184. | | 3 |
| Cerea,G., et al: EGFR gene copy number and clinical outcome to cetuximab plus FOLFIRI regimen (folcetux) in first-line treatment of metastatic and locally advanced gastric cancer. Annals of Oncology 2006; Vol 17, pp. 250-250. | Abstract | 3 |

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| Enzinger,P.C., et al: CALGB 80403/ECOG 1206: A randomized phase II study of three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer. Journal of Clinical Oncology 2010; Vol 28, Issue 15 SUPPL. 1. | Abstract | 3 |
| Enzinger,P.C., et al: Phase II cisplatin, irinotecan, cetuximab and concurrent radiation therapy followed by surgery for locally advanced esophageal cancer. Journal of Clinical Oncology Jun 20, 2006; Vol 24, Issue 18; pp. 194S-194S. | Abstract | 3 |
| Fahlke,J., et al: Cetuximab Plus Docetaxel/Cisplatin (Dc) As First-Line Treatment for Locally Advanced Or Metastatic Gastric Cancer: Preliminary Results of A Phase Ii Study. Annals of Oncology 2009; Vol 20, pp. 47-47. | Abstract | 3 |
| Gibson,M.K., et al: E2205: A phase II study to measure response rate and toxicity of neoadjuvant chemoradiotherapy (CRT) with oxaliplatin (OX) and infusional 5-fluorouracil (5-FU) plus cetuximab (C) followed by postoperative docetaxel (DT) and C in patients with operable adenocarcinoma of the esophagus. Journal of Clinical Oncology 2010; Vol 28, Issue 15 SUPPL. 1. | Abstract | 3 |
| Han,S., et al: Phase II study and biomarker analysis of cetuximab in combination with oxaliplatin, 5-fluorouracil, leucovorin as first-line treatment in patients with recurrent or metastatic gastric cancer. Annals of Oncology 2008; Vol 19, pp. 46-46. | Abstract | 3 |

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| Hsu,C., et al: Concurrent chemoradiotherapy with cetuximab plus twice weekly paclitaxel and cisplatin followed by esophagectomy for locally advanced esophageal squamous cell carcinoma. Journal of Clinical Oncology 2010; Vol 28, Issue 15 SUPPL. 1. | Abstract | 3 |
| Kanzler,S., et al: Cetuximab with irinotecan/folinic acid/5-FU as first-line treatment in advanced gastric cancer: A nonrandomized multicenter AIO phase II study. Journal of Clinical Oncology May 20, 2009; Vol 27, Issue 15; p. 1. | Abstract | 3 |
| Li,J., et al: Phase II study of cetuximab in combination with modified FOLFIRI in patients with advanced gastric cancer who failed first-line chemotherapy (EFFI study). Journal of Clinical Oncology 2010; Vol 28, Issue 15 SUPPL. 1. | Abstract | 3 |
| Ma,H.Y., et al: Neoadjuvant therapy of gastric cancer with cetuximab added to both irinotecan and cisplatin, followed by surgical resection and adjuvant chemoradiation. Journal of Clinical Oncology May 20, 2009; Vol 27, Issue 15; p. 1. | Abstract | 3 |
| Moehler,M., et al: Cetuximab with Irinotecan/Folinic Acid/5-Fu As First-Line Treatment in Advanced Gastric Cancer: A Non-Randomised Multi-Center Aid Phase Ii Study. Annals of Oncology 2009; Vol 20, pp. 25-25. | Abstract | 3 |

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| Mueller,A., et al: Cetuximab with irinotecan/folinic acid/5-FU as first-line treatment inadvanced gastric cancer: A prospective multi-center phase II study and its molecular markers of the Arbeitsgemeinschaft Internistische Onkologie. EJC Supplements Oct 2009; Vol 7, Issue 4; pp. 25-25. | Abstract | 3 |
| Stein,A., et al: Targeting epithelial growth factor receptor (EGFR) with cetuximab in combination with irinotecan as salvage treatment in refractory gastric cancer patients: A retrospective analysis and review of the literature. European Journal of Clinical and Medical Oncology 2011; Vol 3, Issue 1. Date of Publication; p. 1. | Abstract | 3 |
| Suntharalingam,M., et al: A phase II trial evaluating the efficacy of weekly Cetuximab, paclitaxel, carboplatin and daily RT in esophageal cancer. International Journal of Radiation Oncology Biology Physics 2006; Vol 66, Issue 3; pp. S22-S23 | Abstract | 3 |
| Suntharalingam,M., et al: Cetuximab, paclitaxel, carboplatin and radiation for esophageal and gastric cancer. Journal of Clinical Oncology Jun 20, 2006; Vol 24, Issue 18; pp. 185S-185S. | Abstract | 3 |

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| Thomas,C.R., et al: Cetuximab (C225) Plus Cisplatin (CDDP) Irinotecan (CPT11) and Thoracic Radiotherapy (TRT) Definitive Treatment for Locally-advanced, Clinically Unresectable Esophageal Cancer: A Southwest Oncology Group (SWOG) Phase II Trial with Molecular Correlates (S0414). International Journal of Radiation Oncology Biology Physics 2009; Vol 75, Issue 3; pp. S168-S168. | Abstract | 3 |
| Wahab,M.A., Ezzelarab,L., and El Bendary,S.: Cetuximab Plus Capecitabine and Oxaloplatin for Chemonaive Patients with Advanced Gastric Cancer. Annals of Oncology Jun 2011; Vol 22, pp. v50-v50. | Abstract | 3 |
| Woell,E., et al: Oxaliplatin, irinotecan, and cetuximab in advanced gastric cancer. First efficacy results of a multicenter phase II trial (AGMT Gastric-2) of the Arbeitsgemeinschaft Medikamentoese Tumortherapie (AGMT). Journal of Clinical Oncology May 20, 2009; Vol 27, Issue 15; p. 1. | Abstract | 3 |
| Yeh,K.H., et al: Phase II Study of Cetuximab Plus Weekly Cisplatin and 24-Hour Infusion of High-Dose 5-Fluorouracil and Leucovorin for the First-Line Treatment of Advanced Gastric Cancer. Annals of Oncology Sep 2008; Vol 19, pp. 174-174. | Abstract | 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 | Jeffrey A. Bubis, DO | Other payments: Dendreon |
| Stacy LaClaire, PharmD | None | Edward P. Balaban, DO | None |
| Felicia Gelsey, MS | None | Thomas McNeil Beck, MD | None |
| | | Keith A. Thompson, MD | None |
| | | James E. Liebmann, MD | None |

## ASSIGNMENT OF RATINGS:

*to meet requirement 4

| | EFFICACY | STRENGTH OF RECOMMENDATION | COMMENTS | STRENGTH OF EVIDENCE |
|---|---|---|---|---|
| **MICROMEDEX** | --- | --- | | B |
| Jeffrey A. Bubis, DO | Evidence is inconclusive | Class III - Not Recommended | No randomized data. Seems difficult to justify in light of 2 small Phase ll trials. | N/A |
| Edward P. Balaban, DO | Evidence favors efficacy | Class IIb - Recommended, In Some Cases | Could be a lla – however lack of control group and subsequent phase lll trials limit interpretation. It is intriguing. | N/A |
| Thomas McNeil Beck, MD | Evidence favors efficacy | Class IIb - Recommended, In Some Cases | Evidence supportive – trials lacked controls. | N/A |
| Keith A. Thompson, MD | Evidence favors efficacy | Class IIb - Recommended, In Some Cases | None | N/A |

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| James E. Liebmann, MD | Evidence is inconclusive | Class IIb - Recommended, In Some Cases | The only reason I did not give a Class lll (Not Recommended) rating is because the definition of that rating is so restrictive. The current phase ll trials can be interpreted as no better than chemotherapy without Cetuximab. Only a positive phase lll trial showing benefit from Cetuximab would convince me to change this rating. | N/A |