Clinical Policy Bulletin:
Panitumumab (Vectibix)

Number: 0748

Policy

Aetna considers panitumumab (Vectibix) medically necessary for the following indications:

I. Advanced or metastatic colorectal cancer in tumors expressing the wild-type KRAS and NRAS genes (i.e., negative for the KRAS and NRAS mutations); or
II. Advanced or metastatic anal adenocarcinoma expressing the wild-type KRAS and NRAS genes; or
III. Advanced or metastatic adenocarcinomas of the appendix or small bowel expressing the wild-type KRAS and NRAS genes;
Continued use of panitumumab is considered not medically necessary for persons whose disease has progressed with panitumumab or who have developed intolerance to this drug.

Aetna considers panitumumab experimental and investigational for persons who have had clinical failure (disease progression) on cetuximab (Erbitux) because there is insufficient evidence to support the use of panitumumab after clinical failure on cetuximab.

These products are NOT covered for members with the following criteria:

Use not approved by the FDA; AND

The use is unapproved and not supported by the literature or evidence as an accepted off-label use.

Aetna considers the use of K-ras and N-ras mutation analysis medically necessary to predict non-response to panitumumab in persons with advanced or metastatic adenocarcinoma of the colon, rectum, anus, small bowel or appendix. See CPB 0352 - Tumor Markers.

See also CPB 0516 - Colorectal Cancer Screening, and CPB 0684 - Cetuximab (Erbitux).

Background

Colorectal cancer is the third most common cancer and the third most common cause of cancer mortality in the United States (ACS, 2007). The National Cancer Institute (2007) estimated that there will be 112,340 (colon cancer) and 41,420 (rectal cancer) new cases; and over 52,000 deaths (combined colon and rectal cancer) in 2007. About 70 to 80% of all colorectal carcinomas exhibited over-expression of the epidermal growth factor receptor (EGFR), which is known to be involved in carcinogenic processes, such as cell proliferation, apoptosis, angiogenesis and metastasis (Zhang et al, 2006).

Monoclonal antibodies targeting EGFR have been demonstrated to exhibit anti-tumor activity and improved the effectiveness of chemotherapy. Panitumumab (Vectibix) is a human monoclonal antibody that blocks the extra-cellular domain of the EGFR, and has not been associated with the formation of antibodies directed against it (Saadeh and Lee, 2007). In a phase II clinical trial, Berlin et al (2007) evaluated the safety and effectiveness of panitumumab administered with first-line irinotecan-containing regimens in patients with metastatic colorectal cancer. This was a 2-part multi-center study of panitumumab 2.5 mg/kg of body weight weekly with irinotecan, 5-fluorouracil (5-FU), and leucovorin. Part 1 used bolus 5-FU (IFL), and part 2 used infusional 5-FU (FOLFIRI). Tolerability (measured by grade 3/4 diarrhea) was the primary endpoint. Objective response, progression-free survival (PFS), overall survival (OS), and safety were also examined. Nineteen patients in part 1 and 24 patients in part 2 received panitumumab plus chemotherapy. Grade 3/4 diarrhea occurred in 11 patients (58%) in part 1 and 6 patients (25%) in part 2. All patients had a skin-related toxicity (no grade 4 events). Objective response rates were 46% in part 1 and 42% in part 2. Disease control rates were 74% in part 1 and 79% in part 2. Median PFS (95% confidence interval [CI]) was 5.6 months (4.4 to 8.3 months) for part 1 and 10.9 months (7.7 to 22.5 months) for part 2. Median OS (95% CI) was 17 months (13.7 months to not estimable) for part 1 and 22.5 months (14.4 months to not estimable) for part 2. The authors concluded that in patients with metastatic colorectal cancer, panitumumab/IFL was not well-tolerated. In contrast, panitumumab/FOLFIRI was well-tolerated and showed promising activity.

In another phase II multi-center study, Hecht and colleagues (2007) examined the safety and effectiveness of panitumumab in patients with metastatic colorectal cancer refractory to available therapies. Subjects had progressed on chemotherapy that included fluoropyrimidine and irinotecan or oxaliplatin, or both. All subjects had tumors with
greater than or equal to 10% 1+ EGFR staining by immunohistochemistry. They were stratified into 2 strata (high or low staining intensity) and received intravenous
Panitumumab 2.5 mg/kg of body weight weekly 8 of every 9 weeks until disease progression or unacceptable toxicity. In all, 148 patients received panitumumab (105 in the high EGFR stratum, and 43 in the low EGFR stratum). Overall response by central review was 9% (95% CI: 5 to 15%) and was similar between strata. An additional 29% of patients had stable disease. Median PFS was 14 weeks (95% CI: 8 to 16 weeks) and median OS was 9 months (95% CI: 6 to 10 months). Toxicities were manageable, with skin toxicity reported in 95% of patients (5% grade 3 or 4). Four patients discontinued therapy because of toxicity. No anti-panitumumab antibodies were detected. One patient had an infusion reaction but was able to continue therapy. The authors concluded that panitumumab given weekly was well-tolerated and had single-agent activity in previously treated patients with colorectal cancer. Dermatological toxicity was common but rarely severe.

On September 27, 2006, panitumumab (Vectibix) received an accelerated approval from the Food and Drug Administration (FDA) for use as a single agent for the treatment of patients with EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens (Giusti et al, 2007). There are no data to support the combination of panitumumab with chemotherapy in the treatment of colorectal cancer (National Comprehensive Cancer Network [NCCN], 2009). In addition, according to the FDA-approved labeling of Vectibix, panitumumab should not be used in combination with other monoclonal antibodies.

The FDA's approval of Vectibix was based on the findings of a phase III, randomized, controlled, clinical trial of 463 patients with metastatic colorectal cancer (Van Cutsem et al, 2007). Subjects with 1% or more EGFR tumor cell membrane staining, measurable disease, and radiological documentation of disease progression during or within 6 months of most recent chemotherapy were randomly assigned to one of the 2 groups: (i) panitumumab 6 mg/kg of body weight every 2 weeks plus best supportive care (BSC; n = 231); or (ii) BSC alone (n = 232). Tumor assessments by blinded central review were scheduled from week 8 until disease progression. The primary end point was PFS. Secondary end points included objective response, OS, and safety. Patients in the second group (BSC alone) who progressed could receive panitumumab in a cross-over study. Panitumumab significantly prolonged PFS (hazard ratio [HR], 0.54; 95% CI: 0.44 to 0.66, [p < 0.0001]). Median PFS time was 8 weeks (95% CI: 7.9 to 8.4 weeks) for panitumumab and 7.3 weeks (95% CI: 7.1 to 7.7 weeks) for BSC. Mean PFS time was 13.8 (0.8) weeks for panitumumab and 8.5 (0.5) weeks for BSC. Objective response rates also favored panitumumab over BSC; after a 12-month minimum follow-up, response rates were 10% for panitumumab and 0% for BSC (p < 0.0001). No difference was observed in OS (HR, 1.00; 95% CI: 0.82 to 1.22), which was confounded by similar activity of panitumumab after 76% of BSC patients entered the cross-over study. Panitumumab was well-tolerated. Skin toxicities, hypomagnesemia, and diarrhea were the most common adverse events observed. No patients had grade 3/4 infusion reactions. The authors concluded that panitumumab significantly improved PFS with manageable toxicity in patients with chemo-refractory colorectal cancer.

Grothey (2007) stated that in the past 20 years adjuvant chemotherapy has been the standard of care in patients with early-stage colon cancer at high risk of recurrence. Until now, treatment entails the use of cytotoxic drugs that have well-demonstrated effectiveness in advanced colorectal cancer. Most recently, targeted biological agents (i.e., antibodies against the EGFR and vascular endothelial growth factor [VEGF]) have
become essential components of the palliative medical treatment of colorectal cancer. Proof of effectiveness of these agents in advanced disease has led to the initiation of several trials testing EGFR and VEGF antibodies in the adjuvant setting. Although definitive results of ongoing adjuvant studies will not be available for several years, some oncologists might already inappropriately consider the use of these targeted agents as a component of adjuvant therapy in selected patients. Whether the results obtained in advanced colorectal cancer can be readily translated into a projected effectiveness in early-stage colon cancer, however, is unclear. Furthermore, the long-term safety of biological agents in potentially surgically cured patients has yet to be established.

According to guidelines from the NCCN (2009), EGFR testing of colorectal tumor cells has no demonstrated predictive value in determining likelihood of response to panitumumab or cetuximab. Therefore, NCCN colorectal cancer guidelines do not recommend routine EGFR testing, and states that no patient should be either considered or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results. The guidelines stated: "In contrast to the results for KRAS genetic testing, the testing of colon cancer tissue for EGFR has demonstrated no predictive value in determining the likelihood of response with cetuximab and panitumumab. Hence, routine EGFR testing is not recommended, and no patients should be excluded from therapy with either of these drugs on the basis of such testing."

There are no data or compelling rationale to show that panitumumab would be effective after disease progression with cetuximab (Erbitux). NCCN guidelines on colorectal cancer (2009; updated 2012) state: "If cetuximab is used as initial therapy, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy. There are no data, nor is there compelling rationale, to support the use of panitumumab after clinical failure on cetuximab, or cetuximab after clinical failure on panitumumab. As such, the use of one of these agents after therapeutic failure on the other is not recommended."

Saif and colleagues (2009a) reported successful re-challenge with panitumumab in 3 patients with gastrointestinal cancers who developed hyper-sensitivity reactions (HSR) to cetuximab. These patients were challenged with standard dose of panitumumab (6 mg/kg) after experiencing grade 3 HSR to standard dose of cetuximab under strict observation and no pre-medication. First patient, a 58-year old male with metastatic colorectal cancer (mCRC) developed grade 3 HSR during 8th dose of cetuximab. Second patient was a 58-year old female with mCRC developed grade 3 HSR during 12th dose of cetuximab. Third patient was a 61-year old male with pancreatic cancer who reported grade 3 HSR during loading dose of cetuximab. Charts were reviewed to find history of prior allergy, including H1 blocker use, drug allergy, bee sting allergy, eczema, allergic reactive airways disease, or food allergy. All patients were Caucasians with an average age of 59 years with no history of prior allergy. No patient received any pre-medication. First patient received panitumumab for 2 months, 2nd patient was treated for 6 months, and 3rd patient who was re-challenged 1 week after HSR to cetuximab had a partial response following 6 months of therapy. The authors concluded that HSR are serious complications associated with monoclonal antibodies (MAbs). Thanks to hybridoma technology that newer generations of MAbs contain less or no mouse-specific protein sequences, hence reducing the risk of HSR. Identification of individuals likely to develop severe and sometimes life-threatening HSR is challenging. They stated that this report of 3 patients successfully treated with panitumumab after they had severe HSR to cetuximab warrant further investigation.
Langerak et al (2009) presented 4 cases from a U.S. panitumumab compassionate-use program in which patients with mCRC who were intolerant to cetuximab received panitumumab. Eligible patients had failed previous fluoropyrimidine therapy with oxaliplatin- and irinotecan-containing chemotherapy, had cetuximab intolerance (i.e., experienced an infusion reaction), and were unable to participate in a panitumumab clinical trial. For each patient, individual FDA-approved single-patient treatment use. Investigational New Drug- and Institutional Review Board-approved protocols were used, informed consent was obtained, and data were collected independently by the investigator. All 4 patients (2 men, 2 women) had received previous bevacizumab and pre-medications before cetuximab administration. In response to cetuximab, all 4 patients experienced Common Terminology Criteria for Adverse Events grade 3 or grade 4 infusion-reaction symptoms, which required acute therapy. Time from cetuximab discontinuation to panitumumab administration ranged from 8 days to 5 months. Panitumumab monotherapy was given at approximately 6 mg/kg every 2 weeks. Two patients received pre-medications before panitumumab use. No physician reported any infusion reaction to panitumumab; 1 patient had stable disease, and 3 patients had disease progression. The authors concluded that although this small case series provided evidence that patients with mCRC intolerant to cetuximab can receive subsequent panitumumab monotherapy without experiencing infusion reactions, additional clinical testing is needed to definitively examine this finding.

Saif et al (2009b) reported successful de-sensitization with cetuximab after an infusion reaction to panitumumab in 2 patients with mCRC. The first case was a 42-year old female who received panitumumab as a third-line agent. She developed severe chest tightness, pain, and shortness of breath (SOB) 5 mins after first panitumumab infusion. The second case was a 70-year old male who developed severe facial flushing, back pain, SOB, tachycardia and hypotension 5 mins after second dose of panitumumab plus irinotecan as a second-line therapy. These 2 patients received de-sensitization protocol for cetuximab after a test dose of 20 mg IV over 10 mins followed by a slow infusion 10 % of original rate in 0 to 2 hrs, 25 % of original rate in 2 to 2.5 hrs, 50 % reduced rate in 2.5 to 3 hrs, and then 100 % infusion rate after 3 hrs. Patients were observed 4 hrs after completion of infusion. First patient received a total of 12 cycles of cetuximab with stable disease, no recurrence of IR, and grade 1 to 2 acniform rash that first developed after third cycle. Second patient received a total of 8 cycles uneventfully without IR. The authors concluded that to their knowledge, this is the first report of 2 patients with documented IR with panitumumab being de-sensitized successfully with cetuximab. Although anecdotal reports suggest safety of panitumumab in patients following IR with cetuximab, panitumumab can also cause severe IR. The authors’ experience suggested that in case of limited options, such patients can be successfully challenged with cetuximab in a hospital after appropriate de-sensitization and pre-medication. They stated that further studies focusing on de-sensitization and identifying hyper-sensitivity profile of different anti-EGFR antibodies are warranted.

Panitumumab is also being evaluated in the treatment of other types of solid tumors (Chua and Cunningham, 2006; Cohenuram and Saif, 2007; Moehler et al, 2007; Harari, 2007). Socinski (2007) noted that a large dose/schedule trial of panitumumab enrolled 96 patients with EGFR-positive solid tumors. No responses were seen in patients with lung cancer (n = 14). A randomized phase II trial of carboplatin/paclitaxel with or without panitumumab in patients with previously untreated advanced stage IIIB/IV non-small cell lung cancer (NSCLC; n = 166) did not find any benefit for the panitumumab arm.
compared with the chemotherapy alone arm with regard to response rates, time to
disease progression, or median survival time. The author stated that the lack of a
biomarker to identify a subset of NSCLC patients who may derive benefit from this
agent curtails any potential enthusiasm for further trials of panitumumab in the treatment
of NSCLC at the present time.

K-ras is the human homolog of the Kirsten rat sarcoma-2 virus oncogene. It can harbor
oncogenic mutations that yield a constitutively active protein. Such mutations are found
in about 30 % to 50 % of CRC. Several studies have suggested that the presence of
mutant K-ras in lung cancer as well as CRC correlates with poor prognosis, and is
associated with lack of response to EGFR inhibitors.

NCCN guidelines (2014) state that all patients with metastatic colorectal cancer should
have tumor tissue genotyped for RAS mutations (KRAS and NRAS). The guidelines state
that, at the very least, exon 2 KRAS mutation status should be determined. Whenever
possible, non-exon 2 KRAS mutation status and NRAS mutation status should also be
determined. Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS
mutation should not be treated with either cetuximab or panitumumab. Mutations in
codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of
response to therapy with antibodies targeted to the EGFR. The guidelines state that
testing for KRAS and NRAS mutations in codons 12 and 13 should be performed only in
laboratories that are certified under the clinical laboratory improvement amendments of
1988 (CLIA-88) as qualified to perform high complexity clinical laboratory (molecular
pathology) testing. No specific methodology is recommended (eg, sequencing,
hybridization). The guidelines note that testing can be performed on formalin-fixed
paraffin-embedded tissue. The testing can be performed on the primary colorectal
cancers and/or the metastasis, as literature has shown that the KRAS and NRAS
mutations are similar in both specimen types.

Freeman et al (2008) assessed the association of K-ras, BRAF, and PIK3CA gene
mutations with tumor resistance to panitumumab alone. From 3 phase II panitumumab
mCRC studies, 62 of 533 patient samples were available. Mutations were identified from
genomic DNA by sequencing. Of the 62 samples, 24 (38.7 %) harbored a K-ras
mutation, and 38 (61.3 %) were wild-type. In the wild-type K-ras group, 11 % of patients
had a partial response (PR), 53 % had stable disease (SD), and 37 % had progressive
disease (PD). In the mutant K-ras group, 21 % of patients had SD, and 79 % of patients
had PD; there were no responses. The absence of a K-ras mutation was associated with
response to panitumumab (PR versus SD versus PD; p = 0.0028). The HR for wild-type
versus mutant K-ras was 0.4 (95 % CI: 0.2 to 0.7) for PFS and 0.5 (95 % CI: 0.3 to 0.9)
for OS. Four patients had a V600E BRAF mutation, and 2 patients had a PIK3CA
mutation. The authors concluded that these data suggest that patients with mCRC with
activating K-ras mutations are less likely to respond to panitumumab alone. The small
sample size limited the authors from defining a predictive role of PIK3CA and BRAF
mutations for panitumumab treatment.

The findings of Freeman et al (2008) are in agreement with those of Amado et al (2008)
who reported that wild-type K-ras is needed for panitumumab efficacy in patients with
mCRC. In the study by Amado et al (2008), K-ras mutations were detected using
polymerase chain reaction on DNA from tumor sections collected in a phase III mCRC
trial comparing panitumumab monotherapy to BSC. These researchers tested if the
effect of panitumumab on PFS differed by K-ras status. K-ras status was ascertained in
427 (92%) of 463 patients (208 panitumumab, 219 BSC). K-ras mutations were found in 43% of patients. The treatment effect on PFS in the wild-type K-ras group (HR, 0.45; 95% CI: 0.34 to 0.59) was significantly greater (p < 0.0001) than in the mutant group (HR, 0.99; 95% CI: 0.73 to 1.36). Median PFS in the wild-type K-ras group was 12.3 weeks for panitumumab and 7.3 weeks for BSC. Response rates to panitumumab were 17% and 0% for the wild-type and mutant groups, respectively. Wild-type K-ras patients had longer OS (HR, 0.67; 95% CI: 0.55 to 0.82; treatment arms combined). Consistent with longer exposure, more grade III treatment-related toxicities occurred in the wild-type K-ras group. No significant differences in toxicity were observed between the wild-type K-ras group and the overall population. The authors concluded that panitumumab monotherapy efficacy in mCRC is confined to patients with wild-type K-ras tumors. K-ras status should be considered in selecting patients with mCRC as candidates for panitumumab monotherapy.

In an editorial that accompanied the study of Amado et al (2008), Baselga and Rosen (2008) stated that "by enriching our therapy population by excluding those patients with tumors bearing KRAS mutations, we are likely to improve the ability to identify the efficacy of cetuximab- or panitumumab-containing combinations in early stages colon cancer with WT RAS". Furthermore, the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) Medical Advisory Panel (BCBSA, 2008) concluded that the use of K-ras mutation analysis meets TEC criteria for predicting non-response to anti-EGFR monoclonal antibodies cetuximab (Erbitux) and panitumumab (Vectibix) in the treatment of mCRC.

The National Comprehensive Cancer Network's clinical practice guideline on "Colon cancer" (NCCN, 2011) states that "small bowel and appendiceal adenocarcinoma may be treated with systemic chemotherapy according to the NCCN Colon Cancer Guidelines; and panitumumab is one of the options (for patients with KRAS wild type gene only).

Okines and colleagues (2011) reported that cetuximab and panitumumab, 2 MAbs against EGFR, and the dual EGFR and HER2 tyrosine kinase inhibitor (TKI) lapatinib are currently undergoing phase III evaluation in esophagogastric cancer. In a review on targeting ErbB receptors in high-grade glioma, Berezowska and Schlegel (2011) noted that the ErbB receptor family of tyrosine kinases comprises 4 members: (i) EGFR (ErbB1/HER1), (ii) ErbB2 (HER2/neu), (iii) ErbB3 (HER3) and (iv) ErbB4 (HER4). Physiologically, signaling is induced by ligand initiated receptor homo- or heterodimerization, activating intra-cellular downstream signaling pathways and leading to increased cell proliferation, anti-apoptosis and migration. A truncated, constitutively activated mutant EGFR (EGFRvIII) is associated with poor survival in glioblastoma multiforme. Thus, to-date anti-ErbB approaches are mainly focused on EGFR. The 2 major classes of anti-ErbB therapeutics are monoclonal antibodies (e.g., cetuximab, panitumumab) and small molecule tyrosine kinase inhibitors (e.g., erlotinib, gefitinib, lapatinib). Some compounds entered clinical trials already, but clinical efficacy needs to be enhanced.

In a phase II clinical trial, Jensen et al (2012) reported the effect of chemotherapy with panitumumab as first-line therapy for KRAS wild-type irresectable biliary tract cancer. Patients were treated with gemcitabine 1,000 mg/m(2), oxaliplatin 60 mg/m(2), and panitumumab 6 mg/kg i.v. every 2 weeks followed by 2 daily administrations of capecitabine 1,000 mg/m(2) in 7 days. During 22 months, 46 patients were included in a
single institution. The primary end point, fraction of PFS at 6 months, was 31/42 [74%; 95% CI: 58% to 84%]. A total of 42 patients had measurable disease. Response rate was 33% and disease control rate was 86%. Median PFS was 8.3 months (95% CI: 6.7 to 8.7 months) and median OS was 10.0 months (95% CI: 7.4 to 12.7 months). Toxicity was manageable including 8 cases of EGFR-related skin adverse events of grade 2 or more. The authors concluded that Marker-driven patient selection is feasible in the systemic treatment of biliary tract cancer. They stated that combination chemotherapy with panitumumab in patients with KRAS wild-type tumors met the efficacy criteria for future testing in a randomized trial.

Gui and Shen (2012) stated that a majority of patients with ovarian carcinoma who receive conventional treatment of surgical staging and platinum-based chemotherapy recur and ultimately succumb to their diseases. Novel therapies that target specific pathways involved in ovarian tumorigenesis are rapidly emerging. The EGFR is over-expressed in 30 to 98% of epithelial ovarian carcinoma (EOC), and the signaling cascades activated are related with cell proliferation, migration and invasion, and angiogenesis, as well as resistance to cell apoptosis. Various trials are ongoing focusing on EGFR as an attractive target in treatment of EOC. Anti-EGFR Mabs, cetuximab and panitumumab, and TKIs, erlotinib and gefitinib, are the most advanced in clinical development. The available data suggested that MAbs and TKIs only show marginal activity when they are used alone, but combination with platinum-based chemotherapy can induce elevated overall response rate in recurrent EOC patients. Consequently, mechanisms for intrinsic and extrinsic resistance have been explored due to the poor clinical response to EGFR-targeted therapy. Careful consideration of these clinical studies and the possible mechanisms involved in resistance can provide evidence for improvements in subsequent research. Identification of responder profiles and development of rational regimen of combination therapy of EGFR-targeted therapy with other effective treatment modalities may eventually bring about substantial progress in the treatment of epithelial ovarian cancers.

In a randomized, open-label, phase III clinical trial, Waddell and colleagues (2013) examined the addition of the anti-EGFR antibody panitumumab to epirubicin, oxaliplatin, and capecitabine (EOC) in patients with advanced esophago-gastric adenocarcinoma. In this randomized, open-label phase III trial (REAL3), these investigators enrolled patients with untreated, metastatic, or locally advanced esophago-gastric adenocarcinoma at 63 centers (tertiary referral centers, teaching hospitals, and district general hospitals) in the United Kingdom. Eligible patients were randomly allocated (1:1) to receive up to 8 21-day cycles of open-label EOC (epirubicin 50 mg/m(2) and oxaliplatin 130 mg/m(2) on day 1 and capecitabine 1,250 mg/m(2) per day on days 1 to 21) or modified-dose EOC plus panitumumab (mEOC+P; epirubicin 50 mg/m(2) and oxaliplatin 100 mg/m(2) on day 1, capecitabine 1,000 mg/m(2) per day on days 1 to 21, and panitumumab 9 mg/kg on day 1). Randomization was blocked and stratified for center region, extent of disease, and performance status. The primary end-point was OS in the intention-to-treat population. These researchers assessed safety in all patients who received at least 1 dose of study drug. After a pre-planned independent data monitoring committee review in October, 2011, trial recruitment was halted and panitumumab withdrawn. Data for patients on treatment were censored at this time-point. Between June 2, 2008, and Oct 17, 2011, these researchers enrolled 553 eligible patients. Median OS in 275 patients allocated EOC was 11.3 months (95% CI: 9.6 to 13.0) compared with 8.8 months (7.7 to 9.8) in 278 patients allocated mEOC+P (HR 1.37, 95% CI: 1.07 to 1.76; p = 0.013). mEOC+P was associated with increased
incidence of grade 3-4 diarrhea (48 [17 %] of 276 patients allocated mEOC+P versus 29 [11 %] of 266 patients allocated EOC), rash (29 [11 %] versus 2 [1 %]), mucositis (14 [5 %] versus none), and hypomagnesaemia (13 [5 %] versus none) but reduced incidence of hematological toxicity (grade greater than or equal to 3 neutropenia 35 [13 %] versus 74 [28 %]). The authors concluded that addition of panitumumab to EOC chemotherapy does not increase OS and cannot be recommended for use in an unselected population with advanced esophago-gastric adenocarcinoma.

Nabholtz et al (2014) noted that triple-negative breast cancer (TNBC) is a heterogeneous group of tumors for some of which the EGFR pathway may play an important role. In a phase II study, these researchers investigated the efficacy and toxicity of panitumumab combined with a standard neoadjuvant anthracycline-taxane-based chemotherapy in patients with operable, stage II-III, TNBC. Treatment in this multi-centric neoadjuvant pilot study consisted of panitumumab (9 mg/kg) for 8 cycles q.3 weeks combined with 4 cycles of 5-fluorouracil, epixorubicin and cyclophosphamide (FEC100: 500/100/500 mg/m(2)) q.3 weeks, followed by 4 cycles of docetaxel (T: 100 mg/m(2)) q.3 weeks. Following therapy, all patients underwent surgical resection. Pathologic complete response (pCR) in assessable patients was the main end-point while clinical response, toxicity and ancillary studies were secondary end-points. Paraffin-embedded and frozen tumor samples were systematically collected with the aim to identify predictive biomarkers of efficacy and resistance in order to select biologically defined subpopulations for potential further clinical development of the anti-EGFR antibody. A total of 60 patients were included with 47 assessable for pathologic response. The pCR rates were 46.8 % [95 % CI: 32.5 % to 61.1 %] and 55.3 % [95 % CI: 41.1 % to 69.5 %] according, respectively, to Chevallier and Sataloff classifications. The complete clinical response (cCR) rate was 37.5 %. Conservative surgery was carried out in 87 % of cases. Toxicity was manageable. The association of high EGFR and low cytokeratin 8/18 expression in tumor cells on one hand and high density of CD8+ tumor-infiltrating lymphocytes on the other hand were significantly predictive of pCR. The authors concluded that panitumumab in combination with FEC100 followed by docetaxel appears efficacious, with acceptable toxicity, as neoadjuvant therapy of operable TNBC. Several biomarkers could help define large subsets of patients with a high probability of pCR, suggesting a potential interest to further develop this combination in biologically defined subgroups of patients with TNBC.

In a phase II clinical trial, Hezel et al (2014) reported the combination of panitumumab with gemcitabine (GEM) and oxaliplatin (OX) as first-line therapy for KRAS wild-type biliary tract cancer. Patients with histologically confirmed, previously untreated, unresectable or metastatic KRAS wild-type biliary tract or gallbladder adenocarcinoma with ECOG performance status 0 to 2 were treated with panitumumab 6 mg kg(-1), GEM 1,000 mg m(-2) (10 mg m(-2) min(-1)) and OX 85 mg m(-2) on days 1 and 15 of each 28-day cycle. The primary objective was to determine the overall response rate (ORR) by RECIST criteria v.1.1. Secondary objectives were to evaluate toxicity, PFS, and OS. A total of 31 patients received at least 1 cycle of treatment across 3 institutions, 28 had measurable disease. Response rate was 45 % and disease control rate was 90 %. Median PFS was 10.6 months (95 % CI: 5 to 24 months) and median OS was 20.3 months (95 % CI: 9 to 25 months). The most common grade 3/4 adverse events were anemia 26 %, leukopenia 23 %, fatigue 23 %, neuropathy 16 % and rash 10 %. The authors concluded that the combination of gemcitabine, oxaliplatin and panitumumab in KRAS wild type metastatic biliary tract cancer showed encouraging efficacy, additional efforts of genetic stratification and targeted therapy is warranted in biliary tract cancer.
In a phase II clinical trial, Foote and colleagues (2014) evaluated the safety and effectiveness of single agent panitumumab in the treatment of patients with cutaneous squamous cell carcinoma (CSCC) not suitable for local therapy. A total of 16 patients received single agent panitumumab at a dose of 6 mg/kg repeated every 2 weeks for a minimum of 3 cycles and continued until progression, a maximum of 9 cycles or dose limiting toxicity. The primary end-point was the best ORR as assessed by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) criteria. Secondary end-points included evaluation of safety, toxicity and PFS. Between May 2010 and May 2012, 16 patients were recruited; 14 were males and the median age was 68 years. Fifteen patients had loco-regionally advanced or recurrent disease with 14 patients receiving previous radiotherapy and 7 patients receiving previous cytotoxic chemotherapy. The best ORR (PR or CR) was 31 % (3/16 PR, 2/16 CR) with a further 6 of 16 patients achieving SD. The median PFS and OS were 8 and 11 months, respectively. Grade 3 or 4 events were observed in 5 patients (4 being skin toxicity) with 1 patient ceasing due to skin toxicity. With a median follow-up of 24 months, 10 patients died due to progressive disease, 6 are alive, 1 patient with no evidence of disease at the time of analysis. The authors concluded that single agent panitumumab is safe and effective in the management of patients with advanced CSCC even in a previously extensively pre-treated cohort. These early results need to be validated by phase III studies.

The NCCN Drugs & Biologics Compendium (2014) does not list breast cancer, cutaneous squamous cell carcinoma and gallbladder cancer as recommended indications of panitumumab.

NCCN guidelines previously recommended panitumum as single-agent therapy for second-line treatment of metastatic penile cancer; NCCN no longer recommends this use of panitumumab (NCCN, 2014).

CPT Codes / HCPCS Codes / ICD-9 codes

CPT codes covered if selection criteria are met:

81275
81404

Other CPT codes related to the CPB:

88363
96365 - 96368
96372
96379
96413 - 96417

HCPCS codes covered if selection criteria are met:

J9303 Injection, panitumumab, 10 mg
Other HCPCS codes related to the CPB:

J9055  Injection, cetuximab, 10 mg
J9190  Injection, fluorouracil, 500 mg
J9206  Injection, irinotecan, 20 mg
J9263  Injection, oxaliplatin, 0.5 mg

ICD-9 codes covered if selection criteria are met:

152.0 - 152.9  Malignant neoplasm of small intestine, including duodenum [covered for advanced or metastatic adenocarcinomas of the intestines expressing the wild-type KRAS and NRAS genes]
153.0 - 153.9  Malignant neoplasm of colon [covered for advanced or metastatic colorectal cancer in tumors and metastatic adenocarcinomas of the appendix that express the wild-type KRAS and NRAS genes]
154.0 - 154.8  Malignant neoplasm of rectum and rectosigmoid junction, and anus [covered for advanced or metastatic colorectal cancer in tumors that express the wild-type KRAS and NRAS genes]
187.1 - 187.4, 187.9  Malignant neoplasm of penis

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

150.0 - 150.9  Malignant neoplasm of esophagus
151.0 - 151.9  Malignant neoplasm of stomach
155.1  Malignant neoplasm of intrahepatic bile ducts
156.0 - 156.9  Malignant neoplasm of gallbladder and extrahepatic bile ducts
162.2 - 162.9  Malignant neoplasm of bronchus and lung
171.0  Malignant neoplasm of connective tissue and other soft tissue of the head, face, and neck
183.0  Malignant neoplasm of ovary
191.0 - 192.9  Malignant neoplasm of the brain [glioma]
195.0  Malignant neoplasm of other and ill-defined sites of head, face, and neck

The above policy is based on the following references:
