Aetna considers cetuximab (Erbitux) medically necessary for the treatment of members with the following diseases:

- Advanced or metastatic colorectal adenocarcinoma expressing the wild type KRAS and NRAS gene (i.e., negative for the KRAS and NRAS mutations)
- Advanced or metastatic anal adenocarcinoma expressing the wild type KRAS and NRAS genes
- Advanced or metastatic adenocarcinoma of the small bowel or appendiceal cancer expressing the wild type KRAS and NRAS genes
- Menetrier’s disease
- Metastatic or recurrent non-small cell lung cancer
- Metastatic penile cancer
- Squamous cell carcinoma of the head and neck
- Occult primary head and neck cancers
- Squamous cell skin cancer for regional recurrence or distant metastases

Continued use of cetuximab is considered not medically necessary for persons whose disease has progressed with cetuximab or who have developed intolerance to this drug.

Aetna considers cetuximab experimental and investigational when used in combination with other monoclonal antibodies, and for use in persons who have previously been treated with panitumumab (Vectibix) because its effectiveness for these indications has not been established.

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.
Anal squamous cell carcinoma
Bile duct cancer (cholangiocarcinoma)
Bladder cancer/urachal carcinoma
Breast cancer
Carcinoid tumor
Cholangiocarcinoma
Chordoma
Dendritic cell neoplasms
Esophageal adenocarcinoma
Gallbladder cancer
Gastric cancer
Glioma
Hepatic spindle cell sarcoma
Hepatocellular carcinoma
Pancreatic cancer
Pheochromocytoma
Prostate cancer
Thyroid cancer
Vaginal cancer.

Aetna considers K-ras (KRAS) and N-ras (NRAS) gene (or genetics) analysis medically necessary for predicting non-response to cetuximab in the treatment of metastatic colorectal cancer, anal cancer, and small bowel adenocarcinoma (see CPB 0352 - Tumor Markers).

See also CPB 0371 - Brachytherapy, CPB 0375 - Photodynamic Therapy, CPB 0516 - Colorectal Cancer Screening, CPB 0535 - Virtual Gastrointestinal Endoscopy, and CPB 0683 - Oxaliplatin (Eloxatin).

Background

Colorectal cancer is the second-leading cause of cancer death in the United States. It is the nation’s third most common cancer accounting for approximately 15 % of all new cancer cases. Metastatic disease is present at diagnosis in 30 % of the patients, and about 50 % of early-stage patients will eventually present with metastatic disease. For many years, standard treatment of colorectal cancer was 5-fluorouracil (5-FU)-based therapy. Recent availability of newer agents, including capecitabine, irinotecan and oxaliplatin, has significantly expanded the options available for the management of patients with advanced colorectal cancer, with consequent improvements in survival.

The expression of various growth factors, growth inhibitors, and their receptors contributes to the development of colorectal cancer as well as to the proliferation and survival of cancerous cells. About 65 to 70 % of human colon carcinomas have been demonstrated to express the epidermal growth factor receptor (EGFR). It has been reported that expression of EGFR correlates with tumor progression, resistance to chemotherapy and a poorer prognosis. Epidermal growth factor receptor plays an important role in initiating signal transduction, and therapeutic approaches directed towards interrupting this pathway have been shown to impair tumor cell proliferation. These strategies include anti-EGFR monoclonal antibodies, immunotoxin conjugates, and EGFR tyrosine kinase inhibitors. Cetuximab is a genetically engineered mouse monoclonal antibody that works by inhibiting the EGFR. Additionally, cetuximab has the potential to partially reverse resistance to a chemotherapy drug.
On February 12, 2004, the Food and Drug Administration (FDA) approved cetuximab (Erbitux) under its accelerated approval program as a combination treatment with irinotecan for the treatment of patients with metastatic colorectal cancer; or alone if patients cannot tolerate irinotecan. The approval of cetuximab by the FDA was largely based on the findings of a randomized, controlled study with 329 patients -- 218 for cetuximab plus irinotecan combination therapy and 111 for cetuximab monotherapy. Furthermore, cetuximab was examined as a single agent in a third clinical study with 57 patients. Safety data from the 111 patients treated only with cetuximab was also assessed. All of the studies included patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving irinotecan. Results of these trials showed that the combination treatment of cetuximab and irinotecan shrunk tumors in 22.9 % of patients and delayed tumor growth by 4.1 months. For patients who received cetuximab alone, the tumor response rate was 10.8 % and tumor growth was delayed by 1.5 months. However, it should be noted that although cetuximab has been reported to shrink tumors in some patients and delay tumor growth, especially when used as a combination treatment, it has not been shown to increase survival. According to guidelines from the National Comprehensive Cancer Network (NCCN, 2009), cetuximab is not recommended for use as first-line therapy as a single agent unless the patient is unable to tolerate irinotecan. NCCN guidelines and the FDA-approved labeling of Erbitux also state that cetuximab should not be used in combination with other monoclonal antibodies.

Adverse effects associated with the use of cetuximab include difficulty in breathing and low blood pressure that usually occurs during the administration of the first treatment. Infrequent interstitial lung disease has also been reported. Other more common side effects of cetuximab treatment include acne-like rash, dry skin, tiredness or weakness, fever, constipation, and abdominal pain.

Cetuximab has also been shown to improve outcomes when used as first line therapy in combination with irinotecan-based regimens in patients with metastatic colorectal cancer. Van Cutsem et al (2007) investigated the effectiveness of cetuximab in combination with standard folic acid (leucovorin), 5-fluorouracil and irinotecan (FOLFIRI) compared with FOLFIRI alone in the first-line treatment of patients with metastatic colorectal cancer. Patients were randomized to receive either cetuximab plus FOLFIRI (n = 608) or FOLFIRI alone (n = 609). Median progression free survival (the primary study endpoint) was significantly longer for the cetuximab plus FOLFIRI arm (8.9 months) compared to the FOLFIRI alone arm (8 months) (p = 0.036). Response rate was also significantly increased by cetuximab (46.9 % versus 38.7 %, p = 0.005). The investigators reported that treatment was generally well-tolerated with neutropenia (26.7 % in cetuximab plus FOLFIRI versus 23.3 % in FOLFIRI alone), diarrhea (15.2 % and 10.5 %, respectively) and skin reactions (18.7 % and 0.2 %, respectively) being the most common grade 3/4 adverse events. The investigators concluded that cetuximab in combination with FOLFIRI significantly increases response rate and significantly prolongs progression-free survival in the first-line treatment of patients with metastatic colorectal cancer, reducing the relative risk of progression by approximately 15 %. Treatment-related side effects of cetuximab in combination with FOLFIRI were as expected, with diarrhea being moderately and skin reactions significantly more frequent as compared to FOLFIRI alone.

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.

There are no data to support the use of cetuximab or panitumumab (Vectibix) after failure
of the other drug. Colorectal cancer guidelines from the NCCN (2009) state: "If cetuximab
is used as initial therapy, then neither the 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." NCCN colorectal cancer
guidelines (2009) also state that routine use of bevacizumab (Avastin) and cetuximab is
not recommended in patients with prior disease progression on bevacizumab.

Guidelines on colorectal cancer from the NCCN (2009) cite evidence that the
effectiveness of cetuximab cannot be predicted on the base of the presence or absence of
EGFR receptors (see Cunningham et al, 2004; Hecht et al. 2006). The NCCN guidelines
recommend use of cetuximab for colorectal cancer without regard to EGFR receptor
status.

A provisional clinical opinion by the American Society for Clinical Oncology (ASCO, 2009)
recommends that patients with metastatic colorectal cancer receive testing for mutations
in the KRAS gene to predict whether patients will benefit from treatment with cetuximab
and other EGFR inhibitors. Colorectal cancer guidelines from the NCCN (2009) state that
the EGFR inhibitors cetuximab and panitumumab are now recommended only for patients
with tumors characterized by the wild-type KRAS gene.

The majority of head and neck cancers over-express the epidermal growth factor receptor
(EGFR), which is associated with aggressive tumor behavior and poor clinical outcome.
In a recent review, Caponigro et al (2004) noted that 3 phase II studies have evaluated the
combination of cetuximab with platinum-based chemotherapy in pre-treated patients with
recurrent/metastatic head and neck cancer, with a control rate ranging from 29 to 66 %.
However, the authors noted that a phase III placebo-controlled trial has shown that the
addition of cetuximab to cisplatin does not significantly improve median progression-free
survival, despite a difference in the response rate between the two arms.

Bonner et al (2004, 2006) reported on the results of a phase III trial to examine the impact
of combining cetuximab with high dose radiation on locoregional disease control and
survival in patients with locally advanced squamous cell carcinoma of the head and neck.
The investigators randomized 424 patients with locoregionally advanced squamous cell
carcinoma of the oropharynx, hypopharynx or larynx to either radiation alone for 6-7
weeks, or radiation plus weekly cetuximab. Following completion of treatment, patients
were followed by physical examination and radiographic imaging every 4 months for 2 years, and then every 6 months up to 5 years. Median survival was 54 months in subjects receiving cetuximab plus radiation therapy compared to 28 months in subjects receiving radiation therapy alone. The investigators noted that the overall toxicity profile was dominated by classic known effects of high dose head and neck radiation, although some additional toxicity was attributed to cetuximab. Significantly more subjects receiving combination therapy had grade 3/4 skin reactions (34 %) than subjects receiving radiation therapy alone (18 %). Grade 3/4 infusion reactions were seen in 3 % of subjects receiving cetuximab. The investigators concluded that the addition of cetuximab to high dose radiation in patients with locoregionally advanced squamous cell carcinoma of the head and neck demonstrated a statistically significant prolongation in overall survival. This clinical benefit was achieved with minimal enhancement in the overall toxicity profile associated with curative-intent radiation therapy. In an editorial that accompanied the 2006 article by Bonner et al, Posner and Wirth (2006) stated that "[a]t present, for patients who can tolerate it, chemoradiotherapy with cisplatin remains the standard of care. Patients who cannot tolerate platinum-based chemotherapy for any of a variety of reasons should be expected to benefit from the addition of cetuximab to radiotherapy".

Cetuximab has also been shown to be effective when combined with standard chemotherapy for locally advanced squamous cell carcinoma of the head and neck. Vermorken et al (2007) reported on the results of a multi-center phase III study to assess the efficacy and safety of cetuximab in combination with standard chemotherapy for persons with stage II/IV recurrent and/or metastatic squamous cell carcinoma of the head and neck, not suitable for local therapy. Patients from 35 European sites were randomized either to 2 groups. The chemotherapy plus cetuximab arm (n = 222) received cetuximab plus cisplatin or carboplatin and 5-fluorouracil (FU). The chemotherapy arm (n = 220) received cisplatin or carboplatin with 5-FU. Median survival (the primary study endpoint) was 7.4 months in the chemotherapy alone arm compared to 10.1 months for chemotherapy plus cetuximab arm (p = 0.036). The investigators concluded that the addition of cetuximab to standard chemotherapy resulted in a clinically meaningful survival benefit. The investigators noted that the observed median survival time of 10.1 months is among the longest ever reported in a phase III trial for these patients.

Guidelines from the NCCN (2009) indicate cetuximab as first-line therapy for recurrence or metastasis of non-small cell lung cancer (NSCLC).

Ciardiello et al (2004) stated that 3 drugs are currently in phase II and phase III development as single agents or in combination with other anti-cancer therapies in non-small cell lung cancer (NSCLC) patients: cetuximab (Erbitux), a chimeric human-mouse monoclonal IgG1 antibody that blocks ligand binding and functional EGFR activation; and erlotinib (Tarceva) and gefitinib (Iressa), 2 orally bioavailable, small-molecule EGFR inhibitors of tyrosine kinase enzymatic activity that prevent EGFR autophosphorylation and activation. The authors concluded that anti-EGFR has shown promising anti-tumor activity in NSCLC patients with a mild toxicity profile. However, a series of important clinical issues such as selection of potentially responsive patients and optimal combination with conventional anti-cancer treatments needs to be addressed to use these drugs better in lung cancer. This is in agreement with the observation by Langer (2004) who noted that EGFR inhibitors currently under investigation for the treatment of NSCLC include gefitinib and erlotinib, as well as cetuximab. Pre-clinical models have demonstrated synergy for all these agents in combination with either chemotherapy or radiotherapy, leading to great enthusiasm regarding their ultimate contribution to lung cancer therapy. However, serious
clinical challenges persist. These include the identification of the optimal dose(s); the proper integration of these agents into popular, established cytotoxic regimens; and the selection of the optimal setting(s) in which to test these compounds.

Hanna et al (2006) examined the effectiveness of cetuximab in patients with recurrent or progressive NSCLC after receiving at least one prior chemotherapy regimen. This was an open-label, phase II study of patients with EGFR-positive and EGFR-negative advanced NSCLC with Eastern Cooperative Oncology Group performance status 0 to 1. Patients received cetuximab 400 mg/m^2 intravenously (IV) during 120 mins on week 1 followed by weekly doses of cetuximab 250 mg/m^2 IV during 60 mins. A cycle was considered as 4 weeks of treatment and therapy was continued until disease progression or intolerable toxicities. The primary end point was to evaluate response rate. Secondary end points included an estimation of time to progression and survival. Patient and disease characteristics (n = 66) included EGFR-positive status (n = 60); EGFR-negative status (n = 6); number of prior regimens (one, n = 28; two, n = 27; greater than or equal to three, n = 11); male (n = 41); female (n = 25); adenocarcinoma (n = 36); and smoking status (never, n = 13; former, n = 45; current, n = 8). Grade 3/4 toxicities included acne-like rash (6.1 %), anaphylactic reactions (1.5 %), and diarrhea (1.5 %). The response rate for all patients (n = 66) was 4.5 % (95 % confidence interval [CI]: 0.9 % to 12.7 %) and the stable disease rate was 30.3 % (95 % CI: 19.6 % to 42.9 %). The response rate for patients with EGFR-positive tumors (n = 60) was 5 % (95 % CI: 1.0 % to 13.9 %). The median time to progression for all patients was 2.3 months (95 % CI: 2.1 to 2.6 months) and median survival time was 8.9 months (95 % CI: 6.2 to 12.6 months). The authors concluded that although the response rate with single-agent cetuximab in this heavily pretreated patient population with advanced NSCLC was only 4.5 %, the disease control rates and overall survival seem comparable to that of pemetrexed, docetaxel, and erlotinib in similar groups of patients.

Azim and Ganti (2006) stated that cytotoxic chemotherapy has helped improve the outcomes in patients with advanced NSCLC but seemed to have reached a plateau with respect to the benefit obtained. Also, a large subset of elderly patients and those with a poor performance status cannot tolerate these drugs at recommended doses. There is a growing need to incorporate newer drugs with different mechanisms of action and better safety profile. The EGFR and vascular endothelial growth factor (VEGF) have been identified as potential targets and agents acting specifically against these targets have been developed with the hope of improving outcomes. Although recent data with the small molecule EGFR tyrosine kinase inhibitors have been disappointing, there have been instances of dramatic responses, thus raising questions regarding the ideal patient to whom these drugs should be administered. Cetuximab, the anti-EGFR antibody has shown promising results. Bevacizumab, the anti-VEGF antibody was the first drug to demonstrate a survival benefit in first line treatment when added to chemotherapy.

Butts et al (2007) reported on a randomized phase II study to evaluate the efficacy of cetuximab added to first-line gemcitabine/platinum in chemotherapy-naive patients with advanced NSCLC. Chemotherapy-naive patients with recurrent/metastatic NSCLC (stage IV or stage IIIIB with malignant pleural effusion) received cisplatin or carboplatin, and gemcitabine plus cetuximab in arm A, or chemotherapy alone, in arm B. A total of 65 patients were randomly assigned to arm A and 66 to arm B. The investigators observed partial responses in 18 patients (27.7 %) in arm A and 12 (18.2 %) in arm B. Median progression-free survival was 5.09 months for arm A and 4.21 months in arm B. Median overall survival was 11.99 months and 9.26 months in arms A and B, respectively. The
investigators noted that overall toxicity was acceptable and consistent with the profiles of the individual agents. The investigators concluded that first-line treatment with cetuximab plus gemcitabine/platinum is well-tolerated and can be administered safely in patients with advanced NSCLC. The investigators stated that differences in response rate, progression-free survival, and overall survival suggest that the addition of cetuximab to platinum/gemcitabine may improve clinical outcomes. Per NCCN’s Drugs & Biologics Compendium (2013), cetuximab is indicated for various malignancies/cancers when prior platinum-based therapy has failed.

Rosell et al (2008) reported on the Lung Cancer Cetuximab Study, an open-label, randomized phase II pilot study of cisplatin and vinorelbine combined with cetuximab versus cisplatin and vinorelbine alone, in 83 patients with advanced EGFR-positive NSCLC. Following randomization, for a maximum of eight cycles, patients received 3-weekly cycles of cisplatin and vinorelbine alone or following cetuximab treatment. The investigators reported that response rates were 28 % in the cisplatin/vinorelbine arm (A) and 35 % in the cetuximab plus cisplatin/vinorelbine arm (B). Median progression-free survival (PFS) was 4.6 months in arm A and 5.0 months in arm B, with PFS rates at 12 months of 0 % and 15 %, respectively. Median survival was 7.3 months in arm A and 8.3 months in arm B. The 24-month survival rates were 0 % and 16 %, respectively. The investigators reported that the cetuximab combination was well-tolerated. The investigators concluded that, in the first-line treatment of advanced NSCLC, the combination of cetuximab plus cisplatin/vinorelbine demonstrated an acceptable safety profile and the potential to improve activity over cisplatin/vinorelbine alone.

NCCN guidelines (2010) recommend use of cetuximab in non-small cell lung cancer without regard to EGFR status. However, the American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer (Azzoli et al, 2009) stated that cetuximab is recommended with cisplatin-vinorelbine for patients with epidermal growth factor receptor (EGFR)-positive tumors by immunohistochemistry.

In a single-arm phase II trial in NSCLC combining cetuximab with carboplatin and paclitaxel, 31 patients had EGFR IHC performed; 4 patients who tested negative for EGFR IHC had a worse survival than those who tested positive for EGFR IHC (median overall survival [OS] 6 versus 14 months) (Borghaei et al, 2008). Also, in the pivotal phase III FLEX trial (Pirker et al, 2009; O’Byrne et al, 2009), patients were required to express EGFR IHC in at least 1 tumor cell, whereas in another pivotal phase III trial (BMS-099) (Lynch et al, 2008), there was no biomarker requirement for enrollment. This is one suggested theory as to why the FLEX trial was statistically significant for a survival benefit and the BMS-099 trial was negative. However, a retrospective analysis of the BMS-099 trial found that neither KRAS or EGFR mutations were predictive of response to treatment with cetuximab.

EGFR FISH analysis was evaluated in the SWOG 0342 trial, a phase II trial comparing concurrent cetuximab with chemotherapy versus sequential treatment (Hirsch et al, 2008). Although there was no difference in clinical efficacy between the SWOG 0342 concurrent and sequential arms, the biomarker analyses suggested that EGFR FISH positive or gene amplification may have predictive value for cetuximab treatment, as patients with higher gene copy numbers had better survival outcomes. Patients scored as 1 to 4 or low FISH (n = 18) had a median PFS of 3 months, whereas those patients with a score of 5 to 6 or high FISH (n = 26) had a median PFS of 6 months.
Cetuximab has been shown in a phase III study to lack efficacy in the treatment of pancreatic adenocarcinoma. Philip et al (2007) tested the efficacy of cetuximab and gemcitabine combination in the phase III setting in 735 patients with locally advanced unresectable or metastatic pancreatic cancer. Patients were stratified by performance status, stage and prior pancreatectomy, and randomized to either gemcitabine alone or gemcitabine plus cetuximab. The median survival was 6 months in the gemcitabine arm and 6.5 months in the gemcitabine plus cetuximab arm for an overall hazard ratio of 1.09 (95% CI: 0.93 to 1.27, p = 0.14). The corresponding progression free survival (the primary study endpoint) was 3 months and 3.5 months, for gemcitabine and gemcitabine plus cetuximab arms, respectively (hazard ratio = 1.13, 95% CI: 0.97 to 1.3, p = 0.058). The confirmed response probabilities were 7% in each arm, and inclusion of unconfirmed responses yielded 14% in the gemcitabine arm and 12% in the gemcitabine plus cetuximab arm. The investigators reported that 90 patients experienced at least one grade 4 toxicity; 14% on the gemcitabine plus cetuximab, 11% on gemcitabine alone. The investigators concluded that the study failed to demonstrate a clinically significant advantage of the addition of cetuximab to gemcitabine for overall survival, progression free survival and response in advanced pancreas cancer.

Wiseman et al (2007) noted that anaplastic thyroid cancer is an endocrine malignancy. Its rare and rapidly lethal disease course has made it challenging to study. Little is known regarding the expression by anaplastic tumors of molecular targets for new human anti-cancer agents that have been studied in the pre-clinical or clinical setting. These investigators evaluated the expression profile of anaplastic thyroid tumors for molecular targets for treatment. Of the 94 cases of anaplastic thyroid cancers diagnosed and treated in British Columbia, Canada over a 20-year period (1984 to 2004), 32 cases (34%) had adequate archival tissue available for evaluation. A tissue microarray was constructed from these anaplastic thyroid tumors and immuno-histochemistry was utilized to evaluate expression of 31 molecular markers. The markers evaluated were: EGFR, HER2, HER3, HER4, ER, PR, uPA-R, clusterin, E-cadherin, beta-catenin, AMF-R, c-kit, VEGF, ILK, aurora A, aurora B, aurora C, RET, CA-IX, IGF1-R, p53, MDM2, p21, Bcl-2, cyclin D1, cyclin E, p27, calcitonin, MIB-1, TTF-1, and thyroglobulin. A single tumor with strong calcitonin expression was identified as a poorly differentiated medullary carcinoma and excluded from the study cohort. The mean age of the anaplastic cohort was 66 years; 16 patients (51%) were females, and the median patient survival was 23 weeks. A wide range in molecular marker expression was observed by the anaplastic thyroid cancer tumors (0 to 100%). The therapeutic targets most frequently and most strongly over-expressed by the anaplastic tumors were: beta-catenin (41%), aurora A (41%), cyclin E (67%), cyclin D1 (77%), and EGFR (84%). The authors concluded that anaplastic thyroid tumors exhibit considerable derangement of their cell cycle and multiple signal transduction pathways that leads to uncontrolled cellular proliferation and the development of genomic instability. This report was the first to comprehensively evaluate a panel of molecular targets for therapy of anaplastic thyroid cancer and supported the development of clinical trials with agents such as cetuximab, small-molecule tyrosine kinase inhibitors, and aurora kinase inhibitors, which may offer new hope for individuals diagnosed with this fatal thyroid malignancy.

Zhu et al (2007) performed a phase 2 study with cetuximab in patients with advanced hepato-cellular carcinoma (HCC). Eligibility criteria included unresectable or metastatic measurable HCC, an Eastern Cooperative Oncology Group performance status less than or equal to 2, Cancer of the Liver Italian Program (CLIP) score less than or equal to 3, and
adequate organ functions. The initial dose of cetuximab was 400 mg/m(2) given intravenously followed by weekly intravenous infusions at 250 mg/m(2). Each cycle was defined as 6 consecutive weekly treatments. Expression of EGFR was assayed by immuno-histochemistry and trough serum concentrations of cetuximab were determined during the first cycle. A total of 30 patients were enrolled and assessable for efficacy and toxicity. No responses were seen; 5 patients had stable disease (median time of 4.2 months; range of 2.8 to 4.2 months). The median overall survival (OS) was 9.6 months (95 % CI: 4.3 to 12.1 months) and the median PFS was 1.4 months (95 % CI: 1.2 to 2.6 months). The treatment was generally well-tolerated. No treatment-related grade 4 to 5 toxicities occurred. Grade 3 (according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [version 3.0]) aspartate aminotransferase, hypomagnesemia, and fever without neutropenia were noted in 1 patient (3.3 %) each. On week 6 of cycle 1, arithmetic mean serum cetuximab concentrations for patients with Child-Turcotte-Pugh (CTP) A and CTP B disease were 47.6 mcg/ml and 66.9 mcg/ml, respectively. The authors concluded that although cetuximab could be safely administered with tolerable toxicity profiles, it demonstrated no anti-tumor activity in HCC in this phase 2 study. Cetuximab trough concentrations were not notably altered in patients with mild-to-moderate hepatic dysfunction.

Asnacios and associates (2008) conducted a phase 2 trial of cetuximab in combination with the gemcitabine plus oxaliplatin (GEMOX) regimen in patients with documented progressive HCC. A total of 45 untreated patients with advanced-stage progressive HCC were prospectively enrolled. Treatment consisted of cetuximab at a dose of 400 mg/m2 initially then 250 mg/m2 weekly, plus gemcitabine at a dose of 1000 mg/m2 on day 1 and oxaliplatin at a dose of 100 mg/m2 on day 2, every 2 weeks. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal. Overall, 306 cycles were administered. Grade 3 to 4 hematologic toxicity consisted of thrombocytopenia (24 %), neutropenia (20 %), and anemia (4 %). Grade 3 oxaliplatin-induced neurotoxicity occurred in 5 patients (11 %) and grade 3 cutaneous toxicity in 7 patients (16 %). There were no treatment-related deaths. The confirmed response rate was 20 % and disease stabilization was obtained in 40 % of patients. The median PFS and OS times were 4.7 months and 9.5 months, respectively. The 1-year survival rate was 40 %. The authors concluded that in poor-prognosis patients with progressive advanced-stage HCC, the GEMOX-cetuximab combination appears to be active and to have manageable toxicity. A comparative randomized trial is now being planned.

Neyns et al (2008) noted that both hepatic arterial infusion (HAI) of chemotherapy and cetuximab (CET) have interesting activity for the treatment of colorectal cancer liver metastases (CRC-LM). Intravenous CET with HAI oxaliplatin (OXA) or intravenous irinotecan (IRI) followed by HAI of infusion of folic acid modulated 5-fluorouracil 5-FU/I-FA was administered to patients with CRC-LM who had failed at least 1 line of prior chemotherapy. A total of 8 patients received intravenous CET with HAI-OXA (5 patients) and intravenous IRI (3 patients) and HAI-5-FU/I-FA. Adverse events included repeated grade 3 skin toxicity (1 patient), abdominal pain with elevated liver enzymes and asthenia (2 patients), duodenal ulcer (2 patients) with catheter migration and intestinal bleeding (1 patient), reversible interstitial pneumonitis (1 patient), and cystic bile duct dilatation (2 patients) with arterio-biliary fistulization (1 patient). A partial response was documented in 5 patients (62 %). The median time to progression was 8.7 months (95 % CI: 8 to 14 months). The authors concluded that intravenous administration of CET with HAI of chemotherapy is feasible and has promising activity but is associated with specific toxicity.
Czito and Willett (2009) stated that squamous cell carcinoma of the anal canal has been treated with abdomino-perineal resection, resulting in high rates of morbidity and local recurrence. Pioneering work led to the finding that radiation therapy (RT) combined with 5-FU and mitomycin results in high rates of local control as well as disease-free and colostomy-free survival without surgery. Prospective, randomized trials from Europe and the United States have shown the superiority of RT, 5-FU, and mitomycin over (i) RT alone, (ii) RT with 5-FU, and (iii) neoadjuvant cisplatin/5-FU with concurrent radiation, cisplatin, and 5-FU. At present, RT with 5-FU and mitomycin is the standard of care for anal cancer patients. Recent advances include the integration of positron emission tomography into staging, radiation treatment planning and monitoring, and the use of intensity modulated RT. European randomized trials are further evaluating the role of cisplatin in the neoadjuvant, concurrent, and adjuvant settings, as well as radiation dose escalation. Other studies are evaluating the use of capecitabine, oxaliplatin, and cetuximab with RT in this malignancy.

Agarwal and Hussain (2009) stated that cancer of the urinary bladder is the 5th most prevalent solid tumor in the United States. Urothelial carcinoma is the most common form of bladder cancer, accounting for about 90% of cases. About 25% of patients with bladder cancer have advanced disease (muscle-invasive or metastatic disease) at presentation and are candidates for systemic chemotherapy. Urothelial carcinoma is a chemo-sensitive disease, with a high overall and complete response rate to combinational chemotherapy. In the setting of muscle-invasive urothelial carcinoma, use of neoadjuvant chemotherapy is associated with overall survival benefit. The role of adjuvant chemotherapy in this setting is yet to be validated. In the setting of metastatic disease, use of cisplatin-based regimens improves survival. However, despite initial high response rates, the responses are typically not durable leading to recurrence and death in the vast majority of these patients. Currently, there is no standard second-line therapy for patients in whom first-line chemotherapy for metastatic disease has failed. Many newer chemotherapeutic agents have shown modest activity in urothelial carcinoma. Improved understanding of molecular biology and pathogenesis of urothelial carcinoma has opened avenues for the use of molecularly targeted therapies, several of which are being tested in clinical trials. Currently, several novel drugs seem particularly promising including inhibitors of the EGFR pathway, such as cetuximab, and inhibitors of tumor angiogenesis, such as bevacizumab and sunitinib. Development of reliable molecular predictive markers is expected to improve treatment decisions, therapy development and outcomes in urothelial carcinoma. Funding of and participation in clinical trials are key to advancing the care of urothelial cancer patients.

Guidelines on bone cancer from the NCCN (2012) no longer indicate the use of cetuximab for the treatment of chordoma. Previously, cetuximab in combination with erlotinib for chordoma received an NCCN Category 2B recommendation ("based on lower level evidence and there is nonuniform NCCN consensus (but no major disagreement)").

Fiske et al (2009) stated that Menetrier's disease is a rare pre-malignant disorder of the stomach with no proven effective medical therapy. Increased EGFR signaling has been implicated in the pathogenesis of Menetrier's disease. These investigators conducted a single-arm clinical trial with cetuximab in 9 patients (aged 29 to 79 years) with clinically and histologically documented severe Menetrier's disease that impaired quality of life to the extent that gastrectomy was being considered. Patients were treated with a loading dose of intravenous cetuximab (400 mg/m2 of body surface area), followed by 3
weekly intravenous infusions of 250 mg/m². Of the 7 patients who completed the 1-month course of treatment, all showed statistically significant improvement both clinically (quality-of-life indices) and biochemically (increased parietal cell mass and gastric acidity). Furthermore, all 7 patients who completed the 1-month trial elected to continue treatment (follow-up of 8 to 40 months), and 4 subsequently showed near-complete histological remission. The authors concluded that cetuximab should be considered as first-line therapy for Menetrier's disease.

In a phase II study, Neyns et al (2009) evaluated the anti-tumor activity and toxicity of single-agent cetuximab in patients with recurrent high-grade glioma (HGG) after failure of surgery, radiation therapy, and chemotherapy. In this 2-arm, open-label study patients were stratified according to their EGFR gene amplification status. Cetuximab was administered intravenously at a dose of 400 mg/m²(2) on week 1 followed by weekly dose of 250 mg/m(2). The primary end point for this study was the response rate in both study arms separately. A total of 55 eligible patients (28 with and 27 without EGFR amplification) tolerated cetuximab well. Three patients (5.5 %) had a partial response and 16 patients (29.6 %) had stable disease. The median time to progression was 1.9 months [95 % CI: 1.6 to 2.2 months]. Whereas the PFS was less than 6 months in the majority (n = 50/55) of patients, 5 patients (9.2 %) had a PFS on cetuximab of greater than 9 months. Median OS was 5.0 months (95 % CI: 4.2 to 5.9 months). No significant correlation was found between response, survival and EGFR amplification. The authors concluded that cetuximab was well-tolerated but had limited activity in this patient population with progressive HGG. A minority of patients may derive a more durable benefit but were not prospectively identified by EGFR gene copy number.

Loew et al (2009) stated that the EGFR is dysregulated in various tumor types such as glioblastoma multiforme (GBM), breast cancer, ovarian carcinoma, non-small cell lung cancer and other cancers. As the intracellular tyrosine kinase of the EGFR activates signaling cascades leading to cell proliferation, angiogenesis and inhibition of apoptosis, the EGFR represents an attractive target in cancer therapy. In GBM which is the most common primary central nervous system tumor in adults, the EGFR is over-expressed in about 40 to 50 % of cases, and almost half of these co-express the mutant receptor subtype EGFRvIII. This EGFR variant is constitutively activated, and thereby may contribute to the aggressive and refractory course of GBM which is associated with a median survival of only 40 to 60 weeks from diagnosis. Various trials are ongoing focusing on EGFR and EGFRvIII as new therapeutic targets in GBM. Anti-EGFR monoclonal antibodies (MAbs), e.g., cetuximab, and tyrosine kinase inhibitors (TKIs), e.g., erlotinib and gefitinib, are the most advanced in clinical development. Several trials are investigating MAbs or TKIs in combination with other agents such as inhibitors of the mammalian target of rapamycin. Other still preliminary approaches targeting the EGFR are small interfering RNA, antisense RNA and ribozymes, which lead to degradation of EGFR mRNA. The authors concluded that further studies are needed to define their clinical potential, to identify biological predictors of response and thus to characterize subgroups of patients who will benefit from treatment with these new agents.

In a phase II study, Hasselbalch et al (2010) examined the safety and effectiveness when combining cetuximab with bevacizumab and irinotecan in patients with recurrent primary GBM. Patients were included with recurrent primary GBM and progression within 6 months of ending standard treatment (radiotherapy and temozolomide). Bevacizumab and irinotecan were administered IV every 2 weeks. The first 10 patients received bevacizumab 5 mg/kg, but this was increased to 10 mg/kg after interim safety analysis.
Irinotecan dose was based on whether patients were taking enzyme-inducing anti-epileptic drugs or not: 340 and 125 mg/m(2), respectively. Cetuximab 400 mg/m(2) as loading dose followed by 250 mg/m(2) weekly was administered IV. Forty-three patients were enrolled in the trial, of which 32 were available for response. Radiographical responses were noted in 34 %, of which 2 patients had complete responses and 9 patients had partial responses. The 6-month PFS probability was 30 % and median OS was 29 weeks (95 % CI: 23 to 37 weeks). One patient had lacunar infarction, 1 patient had multiple pulmonary embolisms, and 3 patients had grade 3 skin toxicity, for which 1 patient needed plastic surgery. One patient was excluded due to suspicion of interstitial lung disease. Three patients had deep-vein thrombosis; all continued on study after adequate treatment. Cetuximab in combination with bevacizumab and irinotecan in recurrent GBM is well-tolerated except for skin toxicity, with an encouraging response rate. However, the efficacy data do not seem to be superior compared with results with bevacizumab and irinotecan alone.

In an Eastern Cooperative Oncology Group (ECOG) phase II study, Ramalingam et al (2011) evaluated cetuximab for the treatment of advanced bronchiolo-alveolar carcinoma (BAC). Patients with advanced-stage pure BAC or adenocarcinoma with BAC features, fewer than 2 prior chemotherapy regimens, and ECOG performance status of 0 to 2 were eligible. Those with prior EGFR inhibitor therapy were excluded. Cetuximab was given as a weekly intravenous infusion at 250 mg/m(2) after an initial loading dose of 400 mg/m(2) in week 1. The primary end point was determination of response rate. EGFR and KRAS mutations were evaluated by pyro-sequencing. A total of 72 patients were enrolled and 68 met eligibility requirements. Characteristics of patients included median age, 71 years; sex, 57 % females; PS 0 or 1, 88 % of patients; and smoking status, 19 % never-smokers. Central pathology review confirmed the diagnosis in 45 of 49 available specimens. Approximately 50 % of patients received more than 2 cycles of therapy (greater than 8 weeks). Skin rash was the most common toxicity (grade 3, 15 %). The confirmed response rate was 7 %, and stable disease was observed in 35 %. The median survival and PFS were 13 and 3.3 months, respectively. Only 1 of the 6 patients with an EGFR mutation and 1 of the 7 patients with a KRAS mutation had a partial response. The authors concluded that cetuximab was associated with modest effectiveness in patients with advanced BAC, despite a low response rate. They noted that EGFR and KRAS mutations were not predictive of response to cetuximab.

The NCCN guidelines on colon cancer (2011) stated that "[i]nterestingly, a recent publication from de Roock et al raises the possibility that codon 13 mutations may not be absolutely predictive of non-response. However, as stated in that manuscript, these findings are hypothesis-generating only, and prospective studies will be needed to determine if patients with codon 13 mutations can, in fact, benefit from anti-EGFR therapy. At present, use of anti-EGFR agents in patients whose tumors have codon 13 mutations remains investigational, and is not endorsed by the panel for routine practice".

The NCCN's Drugs and Biologics Compendium (2011) lists treatment of squamous cell skin cancer with regional recurrence or distant metastases as one of the indications of cetuximab.

Jalili and colleagues (2008) stated that cutaneous squamous cell carcinoma (SCC) is one of the most common cancers worldwide. Epidermal growth factor receptor is expressed at the cell surface by more than 90 % of SCCs and its activation is responsible for cell cycle progression, proliferation, survival, angiogenesis and metastasis.
(COX-2) is an enzyme up-regulated through EGFR signaling and responsible for some of the EGFR-dependent biological effects. These researchers presented the case of an 88-year-old man with a recurrent, locoregionally metastatic SCC of the right parietal region, which was resistant to radiotherapy. With a combination therapy of cetuximab and celecoxib, the tumor regressed partially and the patient's Karnofsky index improved. These investigators speculated that the combined use of cetuximab and COX-2 inhibitors can be a new and effective therapy for advanced and recurrent cutaneous SCCs.

Maubec et al (2011) evaluated the safety and effectiveness of cetuximab as a first-line monotherapy in patients with unresectable squamous cell carcinoma of the skin (SCCS). A total of 36 patients received cetuximab (initial dose of 400 mg/m(2) followed by subsequent weekly doses of 250 mg/m(2)) for at least 6 weeks with a 48-week follow-up. The primary end point was the disease control rate (DCR) at 6 weeks (according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria). Secondary end points included best response rate, OS, PFS, and toxicity assessment. Association of treatment efficacy with RAS mutations or FcγR genotypes was investigated. Median age of the study population was 79 years. Disease control rate at 6 weeks was obtained in 25 of 36 patients (69%; 95% CI: 52% to 84%) of the intention-to-treat population. The best responses were 8 partial responses and 2 complete responses. There were no cetuximab-related deaths. There were 3 related serious adverse events: 2 grade 4 infusion reactions and 1 grade 3 interstitial pneumopathy. Grade 1 to 2 acne-like rash occurred in 78% of patients and was associated with prolonged PFS. One HRAS mutation was identified. Combined FcγRIIa-131H/H and/or FcγRIIa-158V/V polymorphisms were not associated with the clinical outcomes. The authors concluded that as a first-line treatment in patients with unresectable SCCS, cetuximab achieved 69% DCR.

UpToDate reviews on "Treatment of advanced, unresectable gallbladder cancer" (Mehrotra, 2014a) and "Adjuvant treatment for localized, potentially resectable gallbladder cancer" (Mehrotra, 2014b) do not mention the use of cetuximab. Also, the 2014 NCCN Drugs and Biologics Compendium does not list gall bladder cancer as an indication of cetuximab.

UpToDate reviews on "Treatment of localized cholangiocarcinoma: Surgical management and adjuvant therapy" (Anderson and Stuart, 2014a), and "Treatment options for locally advanced cholangiocarcinoma" (Anderson and Stuart, 2014b) do not mention the use of cetuximab as a therapeutic option.

An UpToDate review on "Systemic therapy for advanced cholangiocarcinoma" (Stuart, 2014) states that "GEMOX plus cetuximab -- Two phase II trials have addressed the efficacy of combined therapy with GEMOX plus cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor: In an initial phase II study of 30 patients with previously untreated locally advanced or unresectable biliary tract cancer (27 cholangiocarcinoma, 3 gallbladder), 19 had objective responses (63%), 3 complete. Nine patients with locally advanced previously unresectable disease had sufficient tumor shrinkage to permit a later potentially curative resection, although long-term outcomes were not reported. Unfortunately, benefit for the addition of cetuximab to GEMOX could not be confirmed in a randomized phase II trial in which 150 patients with advanced cholangiocarcinoma (82%), gallbladder, or ampullary cancer were randomly assigned to GEMOX with or without cetuximab (500 mg/m2 every 2 weeks). Median PFS was modestly but not significantly higher with cetuximab (6.1 versus 5.5 months), but median overall survival was shorter (11 versus 12.4 months). Serious adverse events were
reported in 51 % of the cetuximab-treated patients compared to 35 % of the control group”. Furthermore, according to 2014 NCCN’s Drugs and Biologics Compendium, bile duct cancer/cholangiocarcinoma is not a listed indication of cetuximab (Erbitux).

Cathomas et al (2012) stated that the EGFR is over-expressed in the majority of metastatic castration-resistant prostate cancers (mCRPC) and might represent a valid therapeutic target. The combination of docetaxel and cetuximab, the monoclonal antibody against EGFR, has not been tested in patients with prostate cancer. Patients with mCRPC progressing during or within 90 days after at least 12 weeks of docetaxel were included in this phase II clinical trial. Treatment consisted of docetaxel (75 mg/m(2) every 3 weeks or 35 mg/m(2) on days 1, 8, 15 every 4 weeks) in combination with cetuximab (400 mg/m(2) on day 1 and then 250 mg/m(2) weekly). The primary endpoint was PFS at 12 weeks defined as the absence of prostate-specific antigen (PSA), radiographic, or clinical progression. Evaluation of known biomarkers of response and resistance to cetuximab (EGFR, PTEN, amphiregulin, epiregulin) was conducted. A total of 38 patients were enrolled at 15 Swiss centers. Median age was 68 years and median PSA was 212 ng/ml. Progression-free survival at 12 weeks was 34 % [95 % CI: 19 % to 52 %], PFS at 24 weeks was 20 %, and median OS was 13.3 months (95 % CI: 7.3 to 15.4). Seven patients (20 %) had a confirmed greater than or equal to 50 % and 11 patients (31%) a confirmed greater than or equal to 30 % PSA decline. About 47 % of enrolled patients experienced grade 3 and 8 % grade 4 toxicities. A significantly improved PFS was found in patients with over-expression of EGFR and persistent activity of PTEN. The authors concluded that EGFR inhibition with cetuximab might improve the outcome of patients with mCRPC. They stated that a potential correlation between EGFR over-expression, persistent expression of PTEN, and EGFR inhibition should be investigated further.

UpToDate reviews on “Overview of the treatment of disseminated prostate cancer” (Dawson, 2014) and “Treatment protocols for castration-resistant prostate cancer” (Brenner et al, 2014) do not mention the use of cetuximab as a therapeutic option. Also, the 2014 NCCN’s Drugs and biologics Compendium does not list prostate cancer as a recommended indication of cetuximab.


Rescigno et al (2012) stated that guidelines on the treatment of metastatic squamous cell carcinoma of the penis are limited to a few prospective trials. Cisplatin-based regimens represent the standard of treatment with promising activity of taxanes. Recently, EGFR over-expression has been shown in these patients. These researchers treated an elderly man with a docetaxel-cetuximab combination after failure of the cisplatin regimen. They observed a necrosis of the inguinal lymph nodes and a reduction of (18)F-fluorodeoxyglucose uptake at PET/CT scan. Only mild mucositis and skin toxicity had been detected. The authors concluded that this case report, the first in the literature, showed that this combination is active and well-tolerated in penile squamous cell carcinoma. These preliminary findings need to be validated by well-designed studies.

Brown et al (2014) described 3 cases of advanced refractory penile cancer treated with targeted therapy against the EGFR. These researchers identified 3 patients with advanced penile cancer who had disease progression after platinum chemotherapy refractory and who subsequently received EGFR-targeted therapy. Their tumor tissue was evaluated for expression of EGFR by immunohistochemistry and messenger RNA
quantitation and was also tested for the presence of human papillomavirus DNA by line hybridization. K-ras mutation was evaluated by polymerase chain reaction for 6 mutations in codon 12 and 1 mutation in codon 13. One patient responded to cetuximab and remained disease-free 42 months after presentation. One patient responded to panitumumab, then suffered relapse. One other progressed through EGFR-targeted therapy; EGFR expression by immunohistochemistry was 1-2+ in all cases, and messenger RNA expression ranged from 4.08 to 7.33. No K-ras mutations or human papillomavirus DNA was detected. The authors reported 3 cases in which EGFR-targeted therapy was used to treat platinum-refractory penile cancer patients. The authors concluded that because 2 of the 3 had clinical benefit, future prospective trials of EGFR-targeted therapy in penile cancer are warranted.

Carthon et al (2014) evaluated the safety and effectiveness of EGFR-targeted therapy in patients with advanced penile or scrotal cancer. These investigators retrospectively reviewed the charts of patients with penile or scrotal squamous cell carcinoma who had visited their tertiary cancer center between 2002 and 2009, including their subsequent treatment and follow-up. These researchers collected details of EGFR-targeted therapy and clinical outcomes. Treatment-associated time-to-disease-progression (TTP), OS, responses to therapy and toxicity were evaluated. A total of 24 patients had received EGFR-targeted therapies, including cetuximab, erlotinib and gefitinib. The most common treatment given (to 67% of patients) was cetuximab combined with 1 or more cytotoxic drugs. The most common adverse effect was skin rash (71%). The median (range) TTP and OS were 11.3 (1 to 40) and 29.6 (2 to 205) weeks, respectively. The OS time for patients with visceral or bone metastases was significantly shorter than it was for those without (24.7 versus 49.9 weeks, p = 0.013). Among 17 patients treated with cetuximab alone or in combination with cisplatin, there were 4 partial responses (23.5%) including 2 patients with apparently chemotherapy-resistant tumors. The authors concluded the findings of this study suggested that cetuximab has anti-tumor activity in metastatic penile cancer, and may enhance the effect of cisplatin-based chemotherapy. Moreover, they stated that prospective studies of EGFR-targeted therapies in men with these tumors are needed.

CPT Codes / HCPCS Codes / ICD-9 Codes

**CPT codes covered if selection criteria are met:**

81275  KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13

**Other CPT codes related to the CPB:**

88363  Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)

96401 - 96450  Chemotherapy administration
HCPCS codes covered if selection criteria are met:

J9055  Injection, cetuximab, 10 mg [not covered when used in combination with other monoclonal antibodies, and for use in persons who have previously been treated with panitumumab (Vectibix)]

Other HCPCS codes related to the CPB: J9206

Injection, irinotecan, 20 mg

J9303 Injection, panitumumab, 10 mg

Q0083 - Q0085 Chemotherapy administration

ICD-9 codes covered if selection criteria are met:

140.0 - 150.9  Malignant neoplasm of lip, tongue, salivary glands, gum, floor of mouth, other and unspecified parts of mouth, oropharynx, nasopharynx, hypopharynx, and esophagus [covered for squamous cell carcinoma of the head and neck only]

152.0 - 154.8  Malignant neoplasm of small intestine, including duodenum, colon, rectum, rectosigmoid junction and anus [covered for advanced or metastatic adenocarcinoma of the small bowel expressing the wild type KRAS and NRAS mutation only]

162.2 - 162.9  Malignant neoplasm of bronchus and lung [covered for metastatic or recurrent epidermal growth factor receptor (EGFR) positive non-small cell lung cancer only]

173.02, 173.12, 173.22, 173.32, 173.42  Squamous cell carcinoma of skin of lip, eyelid including canthus, ear and external auditory canal, other and unspecified parts of face, or scalp and skin of neck

195.0  Malignant neoplasm of head, face, and neck

231.2  Carcinoma in situ of bronchus and lung [covered for metastatic or recurrent non-small cell lung cancer only]

535.20  Gastric mucosal hypertrophy (without mention of hemorrhage) [Menetrier's disease]

535.21  Gastric mucosal hypertrophy with hemorrhage [Menetrier's disease]

V10.05 - V10.06  Personal history of malignant neoplasm of large intestine, rectum, rectosigmoid junction, and anus [covered for advanced or metastatic adenocarcinoma of the small bowel expressing the wild type KRAS mutation only]

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

155.0 - 162.0, 163.0 - 165.9, 170.0, 170.2, 170.3 Malignant neoplasm [other than squamous cell carcinoma of the head and neck, advanced or metastatic adenocarcinoma of the small bowel expressing the wild type KRAS and NRAS mutation,
Cetuximab (Erbitux)

170.6, 173.00 - metastatic colorectal cancer expressing the wild type KRAS and 173.01, 173.20 NRAS mutation, or metastatic or recurrent non-small cell lung - 173.21, cancer] 173.30 - 173.31, 173.40 - 173.41, 173.5 - 173.5 - 189.9, 191.0, 192.2, 209.00 - 209.29, 231.1, 231.8 - 234.9

Other ICD-9 codes related to the CPB:

V58.0 Encounter for radiotherapy
V58.11 - V58.12 Encounter for antineoplastic chemotherapy and immunotherapy
V58.12

K-ras (KRAS) and N-ras (NRAS) gene (or genetics) analysis:

CPT codes covered if selection criteria are met:

81275 KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13

ICD-9 codes covered if selection criteria are met:

153.0 - 154.8 Malignant neoplasm of colon, rectum, rectosigmoid junction, and anus

The above policy is based on the following references:


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87. Mehrotra B. Treatment of advanced, unresectable gallbladder cancer. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2014a.

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89. Anderson CD, Stuart KE. Treatment of localized cholangiocarcinoma: Surgical management and adjuvant therapy. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2013a.
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93. Brenner T, Duggal S, Natale J, Wirth SM. Treatment protocols for castration-resistant prostate cancer. UpToDate [serial online]. Waltham, MA; UpToDate; reviewed June 2014.


95. Carthon BC, Ng CS, Pettaway CA, Pagliaro LC. Epidermal growth factor receptor-targeted therapy in locally advanced or metastatic squamous cell carcinoma of the penis. BJU Int. 2014;113(6):871-877.


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