I. Description

Cetuximab (Erbitux) is a recombinant monoclonal IgG1 antibody that binds to and inhibits the biologic activity of the human epidermal growth factor receptor (EGFR). It is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma used in combination with irinotecan, in patients who are refractory to irinotecan-based chemotherapy; as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy; in combination with radiation therapy, for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck and as a single agent for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed.

Recent studies have identified a gene KRAS that when mutated, is resistant to EGFR-inhibitors. It is estimated that KRAS is mutated in 20 to 50% of colon tumors. The studies analyzed the efficacy of EGFR- inhibitors in patients with wild type versus mutated KRAS in metastatic colorectal cancer. The results have consistently shown a lack of clinical response to cetuximab and panitumumab in patients with mutated KRAS, with tumor response and prolongation of progression free and overall survival observed only in wild-type KRAS patients. Identifying patients whose tumors express mutated KRAS will avoid exposing patients to ineffective drugs, avoid exposure to unnecessary drug toxicities and expedite the use of the best available alternative therapy. Therefore, cetuximab for the treatment of metastatic colorectal cancer is only recommended for patients with tumors that express the wild-type KRAS gene.

The 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.
II. Criteria/Guidelines

A. Cetuximab is covered (subject to Limitations and Administrative Guidelines) when recommended by an oncologist for the following conditions:

1. Metastatic colorectal tumors expressing the wild type KRAS and NRAS gene (i.e., negative for KRAS and NRAS mutations):
   a. In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy.
   b. As a single-agent after failure of both irinotecan and oxaliplatin-based regimens.
   c. As a single-agent for patients who are intolerant to irinotecan-based regimens.
   d. Initial therapy in combination with fluorouracil, leucovorin and irinotecan (FOLFIRI) regimen for patients who can tolerate intensive therapy.
   e. For patients with unresectable metachronous metastases and previous adjuvant fluorouracil, leucovorin and oxaliplatin (FOLFOX) within the past 12 months in combination with irinotecan.
   f. In combination with FOLFIRI regimen as:
      i. Perioperative therapy for patients with synchronous liver and/or lung metastases or for patients with resectable metachronous metastases who received previous chemotherapy.
      ii. Therapy for patients with unresectable synchronous liver and/or lung metastases, with synchronous abdominal/peritoneal metastases, or with unresectable metachronous metastases.
      iii. For rectal cancer only, neoadjuvant therapy for patients with synchronous metastases.
      iv. For rectal cancer only, primary therapy for patients with unresectable synchronous metastases who are medically inoperable.
   g. For patients with unresectable advanced or metastatic disease who have not previously received cetuximab or panitumumab when used:
      i. As a single-agent or in combination with irinotecan after first progression, in patients previously receiving irinotecan based regimens.
      ii. In combination with FOLFIRI after first progression in patients who previously received oxaliplatin based regimens with or without bevacizumab.
      iii. As a single-agent or in combination with irinotecan after second progression.

2. Squamous cell carcinoma of the head and neck cancer (advanced, recurrent, persistent):
   a. In combination with radiation therapy for the initial treatment of locally or regionally advanced disease.
   b. As a single-agent for patients with recurrent or metastatic disease for whom prior platinum-based therapy has failed.
   c. Primary concurrent chemoradiation for non-nasopharyngeal cancer as single agent for patients with:
      i. Performance status (PS) 0-2 who have newly diagnosed T4b, any N. unresectable nodal disease with no metastases, or who are unfit for surgery.
      ii. Locoregional recurrence in PS 0-2 patients who have not received prior radiation therapy
d. Sequential chemoradiation following induction chemotherapy in PS 0-1 patients with non-nasopharyngeal cancer for:
   i. Newly diagnosed T4b, any N or unresectable nodal disease with no metastases, or patients unfit for surgery.
   ii. Unresectable locoregional recurrence in patients who have not received prior radiation therapy (RT).

e. Therapy as:
   i. Single agent for patients with non-nasopharyngeal cancer with a PS 3 with newly diagnosed T4b, any N, unresectable nodal disease with no metastases, or with unresectable locoregional recurrence and no prior RT or for patients unfit for surgery.
   ii. Single agent (with non-nasopharyngeal cancer) in PS 0-2 patients or in combination (PS 0-1) with carboplatin with (with non-nasopharyngeal cancer) or without (nasopharyngeal cancer) fluorouracil, in combination with cisplatin with or without fluorouracil, docetaxel, or paclitaxel (non-nasopharyngeal cancer), for unresectable locoregional recurrence or second primary in patients who have received RT or for distant metastases.

3. Squamous cell carcinoma of the head and neck: Cancer of the Glottic Larynx:
   Primary concurrent chemoradiation as a single agent for:
   a. For T3, N0-3 disease requiring (amendable to) total laryngectomy.
   b. T4a patients who decline surgery.

4. Squamous cell carcinoma of the head and neck: Cancer of the Hypopharynx:
   a. Primary concurrent chemoradiation as a single agent for:
      i. T1,N+
      ii. T2-3 any N disease (amendable to) pharyngectomy with total laryngectomy.
   b. Sequential chemoradiation for T4a, any N disease with partial response at the primary site and stable or improved disease in the neck following induction chemotherapy.

5. Squamous cell carcinoma of the head and neck: Cancer of the Lip:
   Primary concurrent chemoradiation as single agent:
   a. For patients with T3-4a, N0; OR
   b. For patients with any T, N1-3 disease who are candidates for surgery but do not receive surgery.

6. Squamous cell carcinoma of the head and neck: Cancer of the Nasopharynx:
   Primary therapy in combination with carboplatin with any T, and N, M1 disease.

7. Squamous cell carcinoma of the head and neck: Cancer of the Oropharynx:
   a. Primary concurrent chemoradiation as a single agent for:
      i. T3-4a, N0-1 disease
      ii. any T, N2-3 disease
   b. Sequential chemoradiation following induction chemotherapy for:
      i. T3-4a, N0-1 disease
      ii. Any T, N2-3 disease

8. Squamous cell carcinoma of the head and neck: Cancer of the Supraglottic Larynx:
   Primary concurrent chemoradiation as a single agent for:
   a. T3, N0 and most T3, N2-3 disease requiring (amendable to) total laryngectomy.
b. T1-2, N+ and selected T3, N1 disease amendable to larynx-preserving (conservation) surgery.

c. Consider for T4a, N0-3 patients who decline surgery.

9. Squamous cell carcinoma of the head and neck- Ethmold sinus tumors:
Primary concurrent chemoradiation as single agent for:

a. Newly diagnosed T3-Tb disease.
b. Patients who decline surgery.
c. Cancer diagnosed after incomplete excision with gross residual disease.

10. Squamous cell carcinoma of the head and neck-Maxillary sinus tumors:
Primary concurrent chemoradiation as single agent for T4b, any N.

11. Squamous cell carcinoma of the head and neck- Occult primary:
Initial definitive treatment as concurrent chemoradiation for \( > N2 \) disease.

12. Squamous cell skin cancer for regional recurrence or distant metastases.

13. Non-small cell lung cancer (NSCLC) when used:

a. As first-line therapy for recurrence or metastasis in combination with vinorelbine and cisplatin in patients with performance status 0-1.
b. As a single-agent for continuation maintenance therapy if given first line with chemotherapy for recurrence or metastasis in patients with performance status 0-2 who achieve tumor response or stable disease following first-line chemotherapy.

B. For all indications, HMSA follows NCCN level 1 or 2A and/or DrugDex level I or IIa recommendations.

C. Continuation of therapy is covered (subject to Limitations/Exclusions and Administrative Guidelines) when the initial therapy has been approved and the patient shows no progression of disease.

III. Limitations

A. Cetuximab is not covered if the patient has had progression of disease while on cetuximab.

B. Cetuximab is not covered if the patient has had progression of disease while being treated with panitumumab.

C. Cetuximab for the treatment of colorectal cancer is not covered in patients with tumors expressing the KRAS and/or NRAS mutation.

IV. Administrative Guidelines

A. Precertification is required for the initial three months of therapy. To precertify, please complete HMSA's Drug Review Request and mail or fax the form as indicated. Include the following documentation:

1. Clinical notes that include the history of previous treatment
2. Current oncology notes
3. Pathology reports
4. Imaging studies
5. CEA for colorectal cancer
6. Results from the KRAS and NRAS gene test for colorectal cancer
B. Precertification is required for continuation of therapy for up to an additional three months. The following documentation must be submitted:

1. Current oncology notes documenting the patient's response to treatment showing no disease progression.
2. Objective findings demonstrating no progression of disease (i.e., CEA and/or imaging).

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<th>HCPCS</th>
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V. Scientific Background

The efficacy and safety of cetuximab was evaluated in two clinical trials. Investigators in one randomized, controlled trial with 329 patients looked at cetuximab alone or in combination with irinotecan. A second study looked at cetuximab in combination with irinotecan in 138 patients in which all patients received both drugs. Cetuximab was further evaluated as a single agent in a third clinical trial with 57 patients. Safety data from an additional 111 patients treated only with cetuximab was also reviewed. All of the trials included patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving irinotecan.

For patients with tumors that express EGFR and who no longer responded to treatment with irinotecan alone or in combination with other chemotherapy drugs, the combination treatment of cetuximab and irinotecan shrank tumors in 22.9 percent of patients and delayed tumor growth by approximately 4.1 months. For patients who received cetuximab alone, the tumor response rate was 10.8 percent and tumor growth was delayed by 1.5 months.

Bonner et. al. (2006) lead a multi-national clinical trial to evaluate the addition of cetuximab to radiation therapy in the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (stage III/IV) (spread of cancer from site of origin but not to distant sites in the body) in 424 patients. Approximately half the patients were treated with cetuximab and high-dose radiation, the other half received high-dose radiation only.

- With an average follow-up of 54 months, patients treated with the addition of cetuximab to radiation therapy had improved outcomes compared to those treated with radiation therapy alone.
- The median duration of time that no cancer recurrences occurred in or near the site of original cancer was 24.4 months for patients treated with cetuximab/radiation therapy, compared to only 14.9 months for those treated with radiation therapy alone.
- The median duration of overall survival was 49 months for those treated with cetuximab/radiation therapy, compared to only 29.3 months for those treated with radiation therapy alone.
- Progression-free survival was significantly improved for patients treated with cetuximab/radiation therapy.
- Rash and reactions at the site of infusion were the most common side effects experienced by patients treated with cetuximab.
NCCN recommends that use of cetuximab not be dependent on EGFR expression of the tumor. This HMSA policy has taken the stance of the NCCN recommendation in spite of the FDA approval labeling for EGFR expressing colorectal tumors. Testing for EGFR expression has not been perfected at this time and patients who may benefit from cetuximab may not be eligible based on this test.

Results from phase II and III clinical trials of the anti-EGFR cetuximab and panitumumab when used either as monotherapy or in combination with chemotherapy have shown that patients with metastatic colorectal carcinoma may benefit from these therapies, and both agents are approved by the US Food and Drug Administration (FDA) for treatment of metastatic colorectal cancer. Stratified analyses of data from these trials by KRAS mutational status not detected (wild type) or abnormal (mutated) indicated that patients with KRAS mutation in codon 12 or 13 did not benefit from treatment with cetuximab or panitumumab.

The American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend that all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR monoclonal antibody therapy should have their tumors tested for KRAS and NRAS mutations in a CLIA-accredited laboratory. If KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR monoclonal antibody therapy as part of their treatment.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References

2. Erbitux (cetuximab) full prescribing information. ImClone Systems, Inc., Rev. March 2013
Cetuximab (Erbitux)

16. NCCN Drugs and Biologics Compendium-Cetuximab-2014