

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erbitux® (cetuximab injection for intravenous infusion – ImClone LLC/Eli Lilly and Company)

APPROVAL DATE: 07/24/2019

OVERVIEW

Erbitux is indicated for the treatment of *KRAS* wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for the following uses: in combination with FOLFIRI (irinotecan, 5-fluorouracil [5-FU], leucovorin) for first-line treatment; in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy; and as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.¹ Limitation of use: Erbitux is not indicated for treatment of *RAS*-mutant colorectal cancer (CRC) or when the results of the *RAS* mutation tests are unknown. Erbitux is also indicated in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN); in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN; and as a single agent in patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.

Erbitux is a chimeric monoclonal antibody that binds specifically to the human EGFR.¹ Signal transduction through the EGFR can result in activation of wild-type *RAS* proteins. However, in cells with activating *RAS* somatic mutations, the resulting mutant *RAS* proteins are continuously active regardless of EGFR regulation. The EGFR plays a key role in activation of the signaling pathways involved in the pathogenesis of CRC and is often overexpressed in mCRC.^{2,3} Erbitux blocks EGFR action and is not effective if downstream signaling pathways are activated independent of EGFR. Detecting mutations that lead to activation of signaling pathways downstream from EGFR can predict resistance to therapy with Erbitux in CRC. Overexpression of EGFR and/or common ligands have been reported in > 90% of SCCHN.⁴

Guidelines

Colon Cancer:

The National Comprehensive Cancer Network (NCCN) colon cancer guidelines (version 2.2019 – May 15, 2019) recommend Erbitux as primary therapy for unresectable, advanced, or metastatic *KRAS/NRAS/BRAF* wild-type gene and left-sided tumors only, in combination with irinotecan, FOLFOX (5-FU, leucovorin, oxaliplatin), FOLFIRI, or FOLFOXIRI (5-FU, leucovorin, oxaliplatin, irinotecan) regimens in patients who can tolerate intensive therapy or as a single agent in patients who cannot tolerate intensive therapy.^{2,7} Reference to left-sided only disease refers to a primary tumor that originated in the left side of the colon and only refers to use of Erbitux as first-line therapy for metastatic disease. Therapies recommended after first progression vary depending on the initial treatment regimen (i.e., 5-FU/leucovorin-based or capecitabine-based therapy) that was used. The NCCN guidelines also recommend Erbitux, in combination with irinotecan and Zelboraf (vemurafenib tablets), Tafinlar (dabrafenib capsules) and Mekinist (trametinib tablets), or Braftovi (encorafenib capsules) and Mektovi (binimetinib tablets), for the subsequent treatment of *BRAF V600E* positive disease.

Rectal Cancer:

The NCCN rectal cancer guidelines (version 2.2019 – May 15, 2019) recommend Erbitux as primary therapy for unresectable, advanced, or metastatic *KRAS/NRAS/BRAF* wild-type tumors in combination

with irinotecan, FOLFOX, FOLFIRI, or FOLFOXIRI regimens in patients who can tolerate intensive therapy or as a single agent in patients who cannot tolerate intensive therapy.^{3,7} Therapies recommended after first progression vary depending on the initial treatment regimen (i.e., 5-FU/leucovorin-based or capecitabine-based therapy) that was used. The NCCN guidelines also recommend Erbitux, in combination with irinotecan and Zelboraf, Tafinlar and Mekinist, or Braftovi and Mektovi, for the subsequent treatment of *BRAF V600E* positive disease.

Head and Neck Cancer:

The NCCN head and neck cancers guidelines (version 2.2019 – June 28, 2019) recommend Erbitux in combination with radiation therapy, with a platinum agent (cisplatin or carboplatin) with or without 5-FU, with a platinum agent plus either docetaxel or paclitaxel, or as a single agent.^{4,7}

Non-Small Cell Lung Cancer (NSCLC):

The NCCN guidelines on NSCLC (version 5.2019 – June 7, 2019) recommend Erbitux in combination with Gilotrif (afatinib tablets) as subsequent therapy for recurrent, advanced, or metastatic disease in patients with a known sensitizing *EGFR* mutation who are *EGFR T790M* negative, have progressed on *EGFR* tyrosine kinase inhibitor therapy, and have multiple symptomatic systemic lesions.^{5,7}

In one multicenter, Phase 1b trial conducted in the US and the Netherlands, patients (n = 126) with *EGFR*-mutant lung cancer with acquired resistance to Tarceva or Iressa received oral Gilotrif 40 mg daily plus Erbitux 500 mg/m² intravenously every 2 weeks.⁶ Patients were heavily pretreated with 52% (n = 65/126) having received ≥ 2 lines of therapy; 79% of patients had received cytotoxic chemotherapy in addition to Tarceva or Iressa. At baseline, the *EGFR* mutation status was as follows: Deletion 19 positive (n = 78), L858R positive (n = 41); and other (n = 4). *T790M* mutation status was available in 124 patients with 71 patients being *T790M* positive and 53 patients being *T790M* negative. The rate of confirmed overall response was 29% (n = 37/126) with all being partial responses; 18% of patient had ≥ 50% tumor shrinkage from baseline. There was no significant difference in overall response rate between patients harboring *T790M*-positive and *T790M*-negative tumors (32% vs. 25%, respectively; P = 0.341). Median duration of response was 5.7 months.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Erbitux. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Erbitux as well as the monitoring required for adverse events and long-term efficacy, approval requires Erbitux to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erbitux is recommended in those who meet the following criteria:

FDA-Approved Indications

- 1. Colon and Rectal Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E): _

- A) Erbitux is prescribed by or in consultation with an oncologist; AND
 - B) Patient has advanced or metastatic disease; AND
 - C) The patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and/or *NRAS* wild-type) [that is, the tumor or metastases are *KRAS* and/or *NRAS* mutation negative]; AND
 - D) If Erbitux is being used for first-line treatment, the primary tumor originated on the left side of the colon (from splenic flexure to rectum); AND
 - E) Patient meets ONE of the following criteria (i or ii):
 - i. The patient's tumor or metastases are wild-type *BRAF* (that is, the tumor or metastases are *BRAF V600E* mutation-negative); OR
 - ii. The patient's tumor or metastases are *BRAF V600E* mutation-positive and the patient meets the following (a and b):
 - a) The patient has previously received a chemotherapy regimen for colon or rectal cancer. NOTE: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine, oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin); AND
 - b) Erbitux is prescribed as part of a combination regimen for colon or rectal cancer. NOTE: Examples of combination regimens include: Erbitux/irinotecan/Zelboraf (vemurafenib tablets), or Erbitux/Tafinlar (dabrafenib capsules)/Mekinist (trametinib tablets), or Erbitux/Braftovi (encorafenib capsules)/Mektovi (binimetinib tablets).^{2,3}
2. **Head and Neck Squamous Cell Carcinoma (HNSCC):** Approve for 1 year if the patient meets the following criteria (A and B):
- A) Erbitux is prescribed by or in consultation with an oncologist; AND
 - B) Patient meets ONE of the following criteria (i, ii, or iii):
 - i. Erbitux will be used in combination with radiation therapy; OR
 - ii. Erbitux will be used in combination with platinum-based therapy. NOTE: Examples of platinum chemotherapy include cisplatin and carboplatin; OR
 - iii. Erbitux will be used as a single agent in patients who have failed prior platinum-based therapy. NOTE: Examples of platinum chemotherapy include cisplatin and carboplatin.

Other Uses with Supportive Evidence

3. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, and F):
- A) Erbitux is prescribed by or in consultation with an oncologist; AND
 - B) The patient has advanced, or metastatic non-small cell lung cancer; AND
 - C) The patient has a known sensitizing epidermal growth factor receptor (*EGFR*) mutation; AND
 - D) The patient has received at least ONE tyrosine kinase inhibitor. NOTE: Examples of tyrosine kinase inhibitors include Tarceva[®] (erlotinib tablets), Iressa[®] (gefitinib tablets), or Gilotrif[®] (afatinib tablets); AND
 - E) Testing is negative for epidermal growth factor receptor (*EGFR*) *T790M* mutation; AND
 - F) Erbitux will be used in combination with Gilotrif (afatinib tablets).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Erbitux has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Erbitux® injection for intravenous infusion [prescribing information]. Indianapolis, IN: Eli Lilly and Company/ImClone LLC; April, 2019.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed July 3, 2019.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – May 15, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed July 5, 2019.
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6. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov.* 2014;4:1036-1045.
7. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on July 3, 2019. Search term: cetuximab.

OTHER REFERENCES UTILIZED

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- Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15:1065-1075.
- De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol.* 2010;11:753-762.
- Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. *J Clin Oncol.* 2016;34:179-185.