

UTILIZATION REVIEW MEDICAL POLICY

- POLICY:** Oncology (Injectable) – Erbitux Utilization Review Medical Policy
- Erbitux® (cetuximab injection for intravenous infusion – ImClone LLC/Eli Lilly and Company)

REVIEW DATE: 07/22/2020

OVERVIEW

Erbitux, an epidermal growth factor receptor (EGFR) chimeric monoclonal antibody, is indicated for the treatment of the following conditions:

- **Colorectal cancer (CRC)**, *KRAS* wild-type, EGFR-expressing, metastatic CRC 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.

Limitation of use: Erbitux is not indicated for treatment of *RAS*-mutant CRC or when the results of the *RAS* mutation tests are unknown.

- **Squamous Cell Carcinoma of the Head and Neck:**
 - In combination with radiation therapy for the initial treatment of locally or regionally advanced disease;
 - In combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional or metastatic disease; and
 - As a single agent in patients with recurrent or metastatic disease for whom prior platinum-based therapy has failed.¹

Guidelines

Colon and Rectal Cancer

The National Comprehensive Cancer Network (NCCN) colon cancer guidelines (version 4.2020 – June 15, 2020) 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 recommend Erbitux, in combination with irinotecan, FOLFOX, or FOLFIRI for the subsequent treatment of *KRAS/NRAS/BRAF* wild-type tumors; or in combination with Braftovi (encorafenib capsules) for the subsequent treatment of *BRAF V600E* positive disease. The NCCN rectal cancer guidelines (version 6.2020 – June 25, 2020) make the same recommendations for Erbitux for the treatment of rectal cancer.^{3,7}

Head and Neck Cancer

The NCCN head and neck cancers guidelines (version 2.2020 – June 9, 2020) 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 6.2020 – June 15, 2020) 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 (TKI) therapy, and have multiple symptomatic systemic lesions; or with a known sensitizing *EGFR* mutation who have progressed on *EGFR* TKI therapy, and have asymptomatic disease, symptomatic brain lesions, or isolated symptomatic 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.

Penile Cancer

The NCCN guidelines on penile cancer (version 1.2020 – January 14, 2020) recommend Erbitux as a single agent for the subsequent treatment of patients with metastatic disease.^{7,8}

Squamous Cell Skin Cancer

The NCCN guidelines on squamous cell skin cancer (version 2.2020 – July 14, 2020) recommend Erbitux in combination with radiation therapy for inoperable or incompletely resected regional disease, or as systemic therapy alone in patients ineligible for checkpoint inhibitors with inoperable or incompletely resected regional disease, or regional recurrence or distant metastases.^{7,10}

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Erbitux. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

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.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erbitux is recommended in those who meet one of 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) Patient has advanced or metastatic disease; AND
- B) 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
- C) 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
- D) Patient meets ONE of the following criteria (i or ii):
 - i. Patient's tumor or metastases are wild-type *BRAF* (that is, the tumor or metastases are *BRAF V600E* mutation-negative); OR
 - ii. Patient's tumor or metastases are *BRAF V600E* mutation-positive and the patient meets the following (a and b):
 - a) Patient has previously received a chemotherapy regimen for colon or rectal cancer; AND
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).
 - b) Erbitux is prescribed in combination with Braftovi (encorafenib capsules); AND
- E) Erbitux is prescribed by or in consultation with an oncologist.

Dosing. Approve one of the following dosing regimens (A or B):

- A) Each individual dose must not exceed 400 mg/m² administered by intravenous infusion, given no more frequently than once weekly; OR
- B) Each individual dose must not exceed 500 mg/m² administered by intravenous infusion, given no more frequently than once every 2 weeks.

2. Head and Neck Squamous Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):

- A) 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; OR
Note: Examples of platinum chemotherapy include cisplatin and carboplatin.
 - iii. Erbitux will be used as a single agent; AND
- B) Erbitux is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimen: Each individual dose must not exceed 400 mg/m² administered by intravenous infusion given no more frequently than once weekly.

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, and E):

- A) Patient has advanced, or metastatic non-small cell lung cancer; AND

- B) Patient has a known sensitizing epidermal growth factor receptor (*EGFR*) mutation; AND
- C) Patient has received at least ONE tyrosine kinase inhibitor; AND
Note: Examples of tyrosine kinase inhibitors include Tarceva® (erlotinib tablets), Iressa® (gefitinib tablets), or Gilotrif® (afatinib tablets).
- D) Erbitux will be used in combination with Gilotrif (afatinib tablets).
- E) Erbitux is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimen: Each individual dose must not exceed 500 mg/m² administered by intravenous infusion no more frequently than once every 2 weeks.

4. Penile Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

- A) Patient has metastatic disease; AND
- B) Erbitux will be used as subsequent therapy; AND
- C) Erbitux will be used as a single agent; AND
- D) Erbitux is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimen: Each individual dose must not exceed 400 mg/m² administered by intravenous infusion given no more frequently than once weekly.

5. Squamous Cell Skin Cancer. Approve for 1 year if the patient meets the following criteria (A and B):

- A) Patient meets one of the following (i, ii, or iii):
 - i. Patient has inoperable or incompletely resected regional disease; OR
 - ii. Patient has regional recurrence; OR
 - iii. Patient has distant metastases; AND
- B) Erbitux is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimen: Each individual dose must not exceed 400 mg/m² administered by intravenous infusion given no more frequently than once weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Erbitux is not recommended in the following situations:

- 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 4.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed July 16, 2020.
- 3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 25, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed July 16, 2020.
- 4. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – June 9, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on July 17, 2020.

5. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – June 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on July 17, 2020.
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. © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on July 15, 2020. Search term: cetuximab.
8. The NCCN Penile Cancer Clinical Practice Guidelines in Oncology (Version 1.2020 – January 14, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on July 17, 2020.
9. 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;113:871-877.
10. The NCCN Squamous Cell Skin Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – July 14, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on July 17, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual	Colorectal cancer criteria updated to include: Erbitux in combination with irinotecan, or irinotecan plus vemurafenib (<i>BRAF V600E</i> mutation positive). Removed Patient has been Started on Erbitux criteria. Added pulmonary toxicity as another reason for dose modification.	08/08/2018
Annual	Removed Initial Approval/Extended Approval, Duration of Therapy and Labs/Diagnostics sections from each indication. Increased approval duration to 1 year for all indications. Revised Colon and Rectal cancer criteria E to include the management of patients with <i>BRAF V600E</i> mutation-positive and mutation-negative disease. Revised NSCLC by adding criteria that the patient has a known sensitizing EGFR mutation. Removed Other Cancer Indications. Removed Waste Management section. Revised Conditions not Recommended for Approval section.	07/24/2019
Annual revision	Colon and Rectal Cancer. Revised criteria for <i>BRAF V600E</i> criteria to allow Erbitux use in combination with Braftovi only. Head and Neck Squamous Cell Carcinoma. Revised criteria for single agent use of Erbitux by removing “in patients who have failed prior platinum-based therapy” and removed the Note. Non-Small Cell Lung Cancer. Removed criteria for testing to be negative for epidermal growth factor <i>T790M</i> mutation. Penile Cancer. Added criteria for penile cancer. Squamous Cell Skin Cancer. Added criteria for squamous cell skin cancer.	07/22/2020