



Erbitux® (cetuximab) (Intravenous)

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I. Length of Authorization ^{1,30}

Coverage will be provided for 6 months and may be renewed (unless otherwise specified).

Head and Neck Cancer

- In combination with radiation therapy: Coverage will be provided starting one week prior and for the duration of radiation therapy (up to 8 total weeks).

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Erbitux 100 mg/50 mL solution for injection single-dose vial: 1 vial every 7 days
- Erbitux 200 mg/100 mL solution for injection single-dose vial: 5 vials x 1 dose, then 3 vials every 7 days

B. Max Units (per dose and over time) [HPCS Unit]:

Indication	Billable Units (BU)	Per unit time (days)
Colorectal Cancer, Head and Neck Cancer	100 BU	7 days
	130 BU	14 days
Squamous Cell Skin Cancer	100 BU	7 days

III. Initial Approval Criteria ¹

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Colorectal Cancer (CRC) † ‡ 1,2,12,13,17,19,2e,5e-8e,10e-12e,15e

- Patient is both KRAS and NRAS mutation negative (wild-type) as determined by FDA-approved or CLIA-compliant test ♦; **AND**
- Will not be used as part of an adjuvant treatment regimen; **AND**
- Patient has not been previously treated with cetuximab or panitumumab; **AND**
- Will not be used in combination with an anti-VEGF agent (e.g., bevacizumab, ramucirumab); **AND**
 - Patient has metastatic, unresectable (or medically inoperable), or advanced disease that is BRAF mutation negative (wild-type); **AND**
 - Used as primary treatment §; **AND**
 - Used in combination with FOLFIRI †; **OR**
 - Used in combination with CapeOx or FOLFOX; **AND**
 - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
 - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease **AND** is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **OR**
 - Used in combination with an irinotecan-based regimen after previous FOLFOX or CapeOX within the past 12 months; **AND**
 - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
 - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease **AND** is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **OR**
 - Used in combination with CapeOx, FOLFOX, or FOLFIRI for rectal cancer if resection is contraindicated following neoadjuvant therapy; **AND**
 - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
 - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease **AND** is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **OR**
 - Used as subsequent therapy; **AND**
 - Used as a single agent; **AND**
 - Patient has oxaliplatin- and irinotecan-refractory disease †; **OR**
 - Patient has irinotecan-intolerant disease †; **OR**
 - Used in combination with irinotecan for irinotecan-refractory disease †; **OR**
 - Used in combination with irinotecan for oxaliplatin-refractory disease or oxaliplatin- and irinotecan-refractory disease §; **AND**
 - Patient has one of the following:
 - ♦ Mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**

- ◆ Mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease AND is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **AND**

In combination with irinotecan for oxaliplatin-refractory disease ONLY:

- Patient must demonstrate an inadequate response to bevacizumab (*or a commercially available bevacizumab biosimilar agent*) in combination with irinotecan, unless there is a contraindication or intolerance, prior to approval of cetuximab; **OR**

- Used in combination with FOLFIRI for oxaliplatin-refractory disease §**;
AND

- Patient has one of the following:

- ◆ Mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
- ◆ Mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease AND is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **AND**

- Use of cetuximab will be restricted to patients with a contraindication or intolerance to bevacizumab (*or a commercially available bevacizumab biosimilar agent*) in combination with FOLFIRI; **OR**

- Used in combination with FOLFOX or CapeOx for irinotecan-refractory disease §**;
AND

- Patient has one of the following:

- ◆ Mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
- ◆ Mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease AND is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **AND**

- Use of cetuximab will be restricted to patients with a contraindication or intolerance to bevacizumab (*or a commercially available bevacizumab biosimilar agent*) in combination with either FOLFOX or CapeOx; **OR**

- Patient has BRAF V600E mutation positive disease as determined by an FDA-approved or CLIA-compliant test◆ †; **AND**
 - Used in combination with encorafenib; **AND**
 - Used as subsequent therapy for progression after at least one prior line of treatment in the advanced or metastatic disease setting; **OR**
 - Used as initial treatment for unresectable metastatic disease after previous adjuvant FOLFOX or CapeOX within the past 12 months; **AND**

- Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease

****May also be used for progression on non-intensive therapy, except if received previous fluoropyrimidine, with improvement in functional status (Note: Step therapy does not apply if patient had progression on non-intensive therapy).**

§ Colon cancer patients must have left-sided tumors only.

Head and Neck Cancer † ‡ Ⓢ 1,2,14,16,25,29,30,17e-23e,25e-29e

- Patient has squamous cell carcinoma; **AND**
 - Used in combination with radiation as a single agent †; **AND**

- Use of cetuximab in combination with radiation therapy for first-line treatment will be restricted to patients with a contraindication or intolerance to cisplatin- or carboplatin-based therapy; **OR**
 - Used as first-line therapy; **AND**
 - Used in combination with platinum-based therapy †; **AND**

- Use of cetuximab will be restricted to patients with a contraindication or intolerance to one of the following regimens:
 - Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU
 - Pembrolizumab monotherapy (*patients with CPS ≥1 only*)
 - Generically available agent/regimen (e.g., cisplatin/paclitaxel, etc. [see *NCCN Head and Neck Cancers guideline for complete list of alternatives*]); **OR**
 - Used in combination with nivolumab for very advanced head and neck cancer* (non-nasopharyngeal) and PS 0-1; **AND**

- Use of cetuximab will be restricted to patients with a contraindication or intolerance to one of the following:
 - Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU
 - Pembrolizumab monotherapy (*patients with CPS ≥1 only*)
 - Generically available agent/regimen (e.g., cisplatin/paclitaxel, etc. [see *NCCN Head and Neck Cancers guideline for complete list of alternatives*]); **OR**
 - Used as subsequent therapy; **AND**
 - Used as a single agent after failure on platinum-based therapy †; **AND**

- Use of cetuximab after failure on platinum-based therapy will be restricted to patients with a contraindication or intolerance to one of the following, if not previously used:
 - Pembrolizumab (*patients with CPS ≥1 only*)

– Nivolumab (*patients with PD-L1 ≥ 1 only*)

** Very Advanced Head and Neck Cancers include: newly diagnosed locally advanced T4b [M0] disease; newly diagnosed unresectable regional nodal disease, typically N3; metastatic disease at initial presentation [M1]; or recurrent or persistent disease.*

Squamous Cell Skin Cancer ‡^{2,21,27}

- Used as a single agent without radiation therapy; **AND**
- Patient is ineligible for or progressed on immune checkpoint inhibitor therapy and clinical trials; **AND**
- Patient is chemotherapy-naïve; **AND**
 - Patient has locally advanced disease and curative surgery and curative radiation therapy are not feasible; **OR**
 - Patient has unresectable disease AND curative radiation therapy is not feasible; **OR**
 - Patient has regional recurrence or distant metastatic disease

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

❖ *If confirmed using an FDA approved assay – <http://www.fda.gov/companiondiagnostics>*

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Ⓢ Orphan Drug

IV. Renewal Criteria^{1,30}

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion reactions/anaphylactic reactions, cardiopulmonary arrest, pulmonary toxicity/interstitial lung disease, dermatologic toxicity, hypomagnesemia/electrolyte abnormalities, etc.

Head and Neck Cancer (in combination with radiation therapy)

- Patient has not exceeded a maximum of 8 weeks of therapy

V. Dosage/Administration ^{1,12,13,20-23,29,30}

Indication	Dose
Colorectal Cancer	400 mg/m ² loading dose intravenously, then 250 mg/m ² intravenously every 7 days until disease progression or unacceptable toxicity OR 500 mg/m ² intravenously every 14 days until disease progression or unacceptable toxicity
Head and Neck Cancer	<u>In combination with radiation therapy:</u> 400 mg/m ² loading dose intravenously 1 week prior to radiation therapy, then 250 mg/m ² intravenously every 7 days for the duration of radiation therapy (up to 8 total weeks of therapy) <u>Monotherapy or in combination with platinum-based therapy:</u> 400 mg/m ² loading dose intravenously, then 250 mg/m ² intravenously every 7 days until disease progression or unacceptable toxicity OR 500 mg/m ² intravenously every 14 days until disease progression or unacceptable toxicity <u>In combination with nivolumab:</u> 500 mg/m ² intravenously every 14 days until disease progression or unacceptable toxicity
Squamous Cell Skin Cancer	400 mg/m ² loading dose intravenously, then 250 mg/m ² intravenously every 7 days until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J9055 – Injection, cetuximab, 10 mg; 1 billable unit = 10 mg

NDC(s):

- Erbitux 100 mg/50 mL single-dose vial; solution for injection: 66733-0948-xx
- Erbitux 200 mg/100 mL single-dose vial; solution for injection: 66733-0958-xx

VII. References (STANDARD)

1. Erbitux [package insert]. Branchburg, NJ; ImClone LLC; September 2021; Accessed September 2023.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) cetuximab. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2023.

3. Bouchahda M, Macarulla G, Lledo F, et al. Efficacy and safety of cetuximab (C) given with a simplified, every other week (q2w), schedule in patients (pts) with advanced colorectal cancer (aCRC): a multicenter, retrospective study. *J Clin Oncol*. 2008; 26(15S): Abstract 15118. Presented at: The 44th American Society of Clinical Oncology Annual Meeting (ASCO). May 30–June 3, 2008. Chicago, Illinois.
4. Mrabti H, La Fouchardiere C, Desseigne F, Dussart S, Negrier S, Errihani H. Irinotecan associated with cetuximab given every 2 weeks versus cetuximab weekly in metastatic colorectal cancer. *J Can Res Ther*. 2009; 5:272-6.
5. Shitara K, Yuki S, Yoshida M, et al. Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for wild-type KRAS metastatic colorectal cancer refractory to irinotecan, oxaliplatin, and fluoropyrimidines *World J Gastroenterol*, 2011, April 14; 17(14): 1879-1888
6. Pfeiffer P, Bjerregarrd JK, Qvortrup C, et al, “Simplification of Cetuximab (Cet) Administration: Double Dose Every Second Week as a 60 Minute Infusion,” *J Clin Oncol*, 2007, 25(18S):4133 [abstract 4133 from 2007 ASCO Annual Meeting Proceedings, Part I].
7. Pfeiffer P, Nielsen D, Bjerregaard J, et al, “Biweekly Cetuximab and Irinotecan as Third-Line Therapy in Patients with Advanced Colorectal Cancer after Failure to Irinotecan, Oxaliplatin and 5-Fluorouracil,” *Ann Oncol*, 2008, 19(6):1141-5.
8. Carneiro BA, Ramanathan RK, Fakih MG, et al. Phase II study of irinotecan and cetuximab given every 2 weeks as second-line therapy for advanced colorectal cancer. *Clin Colorectal Cancer*. 2012 Mar; 11(1):53-9.
9. Fahrenbruch R, Kintzel P, Bott AM, et al. Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association. *J Oncol Pract*. 2018 Mar;14(3):e130-e136.
10. Hematology/Oncology Pharmacy Association (2019). Intravenous Cancer Drug Waste Issue Brief. Retrieved from http://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/Drug_Waste_2019.pdf
11. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. *BMJ*. 2016 Feb 29;352:i788
12. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Colon Cancer, Version 2.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2023.
13. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Rectal Cancer, Version 4.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2023.

14. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006 Feb 9;354(6):567-78.
15. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008 Sep 11;359(11):1116-27. doi: 10.1056/NEJMoa0802656.
16. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol*. 2007 Jun 1;25(16):2171-7.
17. Van Cutsem E, Köhne CH, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009 Apr 2;360(14):1408-17. doi: 10.1056/NEJMoa0805019.
18. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. 2007 Nov 15;357(20):2040-8.
19. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004 Jul 22;351(4):337-45.
20. Samstein RM, Ho AL, Lee NY, et al. Locally advanced and unresectable cutaneous squamous cell carcinoma: outcomes of concurrent cetuximab and radiotherapy. *J Skin Cancer*. 2014;2014:284582. doi: 10.1155/2014/284582. Epub 2014 Jul 21.
21. Maubec E, Petrow P, Scheer-Senyearich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol*. 2011 Sep 1;29(25):3419-26. doi: 10.1200/JCO.2010.34.1735. Epub 2011 Aug 1.
22. Carthon BC, Ng CS, Pettaway CA, et al. Epidermal growth factor receptor-targeted therapy in locally advanced or metastatic squamous cell carcinoma of the penis. *BJU Int*. 2014 Jun;113(6):871-7. doi: 10.1111/bju.12450.
23. 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 Sep;4(9):1036-45. doi: 10.1158/2159-8290.CD-14-0326. Epub 2014 Jul 29.
24. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Non-Small Cell Lung Cancer, Version 3.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2023.
25. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Head and Neck Cancers, Version 2.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN

GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2023.

26. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Penile Cancer. Version 1.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2023.
27. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Squamous Cell Skin Cancer. Version 1.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2023.
28. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. *N Engl J Med*. 2019 Oct 24;381(17):1632-1643. doi: 10.1056/NEJMoa1908075. Epub 2019 Sep 30.
29. Chung C, Li J, Steuer C, et al. Phase II Multi-institutional Clinical Trial Result of Concurrent Cetuximab and Nivolumab in Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma. *Clin Cancer Res*. 2022 Jun 1;28(11):2329-2338. doi: 10.1158/1078-0432.CCR-21-3849.
30. Mesía R, Vázquez S, Grau JJ, et al; Spanish Head and Neck Cancer Cooperative Group (TTCC). A Phase 2 Open Label, Single-Arm Trial to Evaluate the Combination of Cetuximab Plus Taxotere, Cisplatin, and 5-Fluorouracil as an Induction Regimen in Patients With Unresectable Squamous Cell Carcinoma of the Head and Neck. *Int J Radiat Oncol Biol Phys*. 2016 Feb 1;94(2):289-96.

VIII. References (ENHANCED)

- 1e. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol*. 2011 May 20;29(15):2011-9.
- 2e. Qin S, Li J, Wang L, et al. Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in Patients With RAS Wild-Type Metastatic Colorectal Cancer: The Open-Label, Randomized, Phase III TAILOR Trial. *J Clin Oncol*. 2018;36(30):3031–3039. doi:10.1200/JCO.2018.78.3183
- 3e. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013 Sep 12;369(11):1023-34.

- 4e. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol*. 2014 Jul;25(7):1346-55.
- 5e. 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 Sep;15(10):1065-75.
- 6e. Heinemann V, Modest DP, von Weikersthal LF, et al. Gender and tumor location as predictors for efficacy: Influence on endpoints in first-line treatment with FOLFIRI in combination with cetuximab or bevacizumab in the AIO KRK 0306 (FIRE3) trial. *J Clin Oncol*. 2014;32:(15_suppl):3600.
- 7e. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *ASCO Meeting Abstracts* 2016; 34:3504.
- 8e. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. *J Clin Oncol*. 2014 Jul 20;32(21):2240-7.
- 9e. Rivera F, Karthaus M, Hecht JR, et al. Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma. *Int J Colorectal Dis*. 2017;32(8):1179–1190. doi:10.1007/s00384-017-2800-1.
- 10e. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008 May 10;26(14):2311-9.
- 11e. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014 May;15(6):569-79.
- 12e. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008 Oct 23;359(17):1757-65.
- 13e. Kopetz S, McDonogh SL, Lenz HJ, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406). *J Clin Oncol* 2017;35 (suppl):3505.
- 14e. Corcoran RB, André T, Atreya CE, et al. Combined BRAF, EGFR, and MEK Inhibition in Patients with BRAFV600E-Mutant Colorectal Cancer. *Cancer Discov*. 2018;8(4):428–443. doi:10.1158/2159-8290.CD-17-1226
- 15e. Kopetz S, Grothey A, Van Cutsem E, et al. Encorafenib plus cetuximab with or without binimetinib for BRAF V600E-mutant metastatic colorectal cancer: Quality-of-life results

- from a randomized, three-arm, phase III study versus the choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC) [abstract]. *J Clin Oncol* 2020;38,(suppl 4;abstr 8).
- 16e. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 2003 Jan 1;21(1):92-8.
- 17e. Magrini SM, Buglione M, Corvò R, et al. Cetuximab and Radiotherapy Versus Cisplatin and Radiotherapy for Locally Advanced Head and Neck Cancer: A Randomized Phase II Trial. *J Clin Oncol*. 2016 Feb 10;34(5):427-35.
- 18e. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet*. 2019 Jan 5;393(10166):40-50.
- 19e. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol*. 2014;32(27):2940–2950.
doi:10.1200/JCO.2013.53.5633.
- 20e. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet*. 2019;393(10166):51–60.
doi:10.1016/S0140-6736(18)32752-1.
- 21e. Tao Y, Auperin A, Sire C, et al. Improved Outcome by Adding Concurrent Chemotherapy to Cetuximab and Radiotherapy for Locally Advanced Head and Neck Carcinomas: Results of the GORTEC 2007-01 Phase III Randomized Trial. *J Clin Oncol*. 2018 Jun 7;JCO2017762518.
- 22e. Burtneß B, Goldwasser MA, Flood W, et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol*. 2005 Dec 1;23(34):8646-54.
- 23e. Bossi P, Miceli R, Locati LD, et al. A randomized, phase 2 study of cetuximab plus cisplatin with or without paclitaxel for the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Ann Oncol*. 2017 Nov 1;28(11):2820-2826.
- 24e. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2005 May 20;23(15):3562-7.
- 25e. Rischin D, Harrington KJ, Greil R, et al. Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab (pembro) as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). ASCO 2019.

- 26e. Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2016 Oct 15;388(10054):1883-1892.
- 27e. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 2016;375(19):1856–1867. doi:10.1056/NEJMoa1602252.
- 28e. Cohen EEW, Soulières D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet*. 2019 Jan 12;393(10167):156-167.
- 29e. Martinez-Trufero J, Isla D, Adansa JC, et al. Phase II study of capecitabine as palliative treatment for patients with recurrent and metastatic squamous head and neck cancer after previous platinum-based treatment. *Br J Cancer*. 2010;102(12):1687–1691. doi:10.1038/sj.bjc.6605697.
- 30e. Grau JJ, Caballero M, Verger E, Monzó M, Blanch JL. Weekly paclitaxel for platinum-resistant stage IV head and neck cancer patients. *Acta Otolaryngol*. 2009 Nov;129(11):1294-9.
- 31e. Chan AT, Hsu MM, Goh BC, et al. Multicenter, phase II study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. *J Clin Oncol*. 2005 May 20;23(15):3568-76.
- 32e. Reigneau M, Robert C, Routier E, et al. Efficacy of neoadjuvant cetuximab alone or with platinum salt for the treatment of unresectable advanced nonmetastatic cutaneous squamous cell carcinomas. *Br J Dermatol*. 2015 Aug;173(2):527-34.
- 33e. Sadek H, Azli N, Wendling JL, et al. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. *Cancer*. 1990 Oct 15;66(8):1692-6.
- 34e. Jarkowski A 3rd, Hare R, Loud P, et al. Systemic Therapy in Advanced Cutaneous Squamous Cell Carcinoma (CSCC): The Roswell Park Experience and a Review of the Literature. *Am J Clin Oncol*. 2016 Dec;39(6):545-548.
- 35e. Trodello C1, Pepper JP, Wong M, Wysong A. Cisplatin and Cetuximab Treatment for Metastatic Cutaneous Squamous Cell Carcinoma: A Systematic Review. *Dermatol Surg*. 2017 Jan;43(1):40-49.
- 36e. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357(6349):409–413. doi:10.1126/science.aan6733.
- 37e. Di Lorenzo G, Federico P, Buonerba C, et al. Paclitaxel in pretreated metastatic penile cancer: final results of a phase 2 study. *Eur Urol*. 2011 Dec;60(6):1280-4.
- 38e. Hecht JR, Cohn A, Dakhil S, et al. SPIRITT: A Randomized, Multicenter, Phase II Study of Panitumumab with FOLFIRI and Bevacizumab with FOLFIRI as Second-Line Treatment in Patients with Unresectable Wild Type KRAS Metastatic Colorectal Cancer. *Clin Colorectal Cancer*. 2015 Jun;14(2):72-80.

- 39e. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2005;23(24):5578-5587. doi:10.1200/JCO.2005.07.120.
- 40e. Burtneß B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study [published correction appears in *Lancet.* 2020 Jan 25;395(10220):272] [published correction appears in *Lancet.* 2020 Feb 22;395(10224):564]. *Lancet.* 2019;394(10212):1915-1928. doi:10.1016/S0140-6736(19)32591-7.
- 41e. Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. *N Engl J Med.* 2018 Jul 26;379(4):341-351. doi: 10.1056/NEJMoa1805131.
- 42e. Grob JJ, Gonzalez R, Basset-Seguín N, et al. Pembrolizumab Monotherapy for Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma: A Single-Arm Phase II Trial (KEYNOTE-629). *J Clin Oncol.* 2020 Sep 1;38(25):2916-2925. doi: 10.1200/JCO.19.03054.
- 43e. Hirt S, Borg C, Bertaut A, et al. Bevacizumab or cetuximab plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wtKRAS metastatic colorectal cancer: A randomized phase II study (Prodige 18 –UNICANCER GI). *Journal of Clinical Oncology* 2016 34:15_suppl, 3514-3514.
- 44e. Iwamoto S, Maeda H, Hazama S, et al. Efficacy of CapeOX plus Cetuximab Treatment as a First-Line Therapy for Patients with Extended RAS/BRAF/PIK3CA Wild-Type Advanced or Metastatic Colorectal Cancer. *J Cancer.* 2018 Oct 18;9(22):4092-4098. doi: 10.7150/jca.26840.
- 45e. Moretto R, Cremolini C, Rossini D, et al. Location of Primary Tumor and Benefit From Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies in Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer. *Oncologist.* 2016 Aug;21(8):988-94. doi: 10.1634/theoncologist.2016-0084. Epub 2016 Jul 5.
- 46e. Guigay J, Fayette J, Dillies AF, et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. *Ann Oncol.* 2015 Sep;26(9):1941-1947. doi: 10.1093/annonc/mdv268.
- 47e. Magellan Rx Management. Erbitux Clinical Literature Review Analysis. Last updated September 2023. Accessed September 2023.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C00.0	Malignant neoplasm of external upper lip
C00.1	Malignant neoplasm of external lower lip
C00.2	Malignant neoplasm of external lip, unspecified

ICD-10	ICD-10 Description
C00.3	Malignant neoplasm of upper lip, inner aspect
C00.4	Malignant neoplasm of lower lip, inner aspect
C00.5	Malignant neoplasm of lip, unspecified, inner aspect
C00.6	Malignant neoplasm of commissure of lip, unspecified
C00.8	Malignant neoplasm of overlapping sites of lip
C00.9	Malignant neoplasm of lip, unspecified
C01	Malignant neoplasm of base of tongue
C02.0	Malignant neoplasm of dorsal surface of tongue
C02.1	Malignant neoplasm of border of tongue
C02.2	Malignant neoplasm of ventral surface of tongue
C02.3	Malignant neoplasm of anterior two-thirds of tongue, part unspecified
C02.4	Malignant neoplasm of lingual tonsil
C02.8	Malignant neoplasm of overlapping sites of tongue
C02.9	Malignant neoplasm of tongue, unspecified
C03.0	Malignant neoplasm of upper gum
C03.1	Malignant neoplasm of lower gum
C03.9	Malignant neoplasm of gum, unspecified
C04.0	Malignant neoplasm of anterior floor of mouth
C04.1	Malignant neoplasm of lateral floor of mouth
C04.8	Malignant neoplasm of overlapping sites of floor of mouth
C04.9	Malignant neoplasm of floor of mouth, unspecified
C05.0	Malignant neoplasm of hard palate
C05.1	Malignant neoplasm of soft palate
C05.8	Malignant neoplasm of overlapping sites of palate
C05.9	Malignant neoplasm of palate, unspecified
C06.0	Malignant neoplasm of cheek mucosa
C06.2	Malignant neoplasm of retromolar area
C06.80	Malignant neoplasm of overlapping sites of unspecified parts of mouth
C06.89	Malignant neoplasm of overlapping sites of other parts of mouth
C06.9	Malignant neoplasm of mouth, unspecified
C09.0	Malignant neoplasm of tonsillar fossa
C09.1	Malignant neoplasm of tonsillar pillar (anterior) (posterior)
C09.8	Malignant neoplasm of overlapping sites of tonsil
C09.9	Malignant neoplasm of tonsil, unspecified
C10.0	Malignant neoplasm of vallecula
C10.1	Malignant neoplasm of anterior surface of epiglottis
C10.2	Malignant neoplasm of lateral wall of oropharynx
C10.3	Malignant neoplasm of posterior wall of oropharynx

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ICD-10	ICD-10 Description
C10.4	Malignant neoplasm of branchial cleft
C10.8	Malignant neoplasm of overlapping sites of oropharynx
C10.9	Malignant neoplasm of oropharynx, unspecified
C11.0	Malignant neoplasm of superior wall of nasopharynx
C11.1	Malignant neoplasm of posterior wall of nasopharynx
C11.2	Malignant neoplasm of lateral wall of nasopharynx
C11.3	Malignant neoplasm of anterior wall of nasopharynx
C11.8	Malignant neoplasm of overlapping sites of nasopharynx
C11.9	Malignant neoplasm of nasopharynx, unspecified
C12	Malignant neoplasm of pyriform sinus
C13.0	Malignant neoplasm of postcricoid region
C13.1	Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
C13.2	Malignant neoplasm of posterior wall of hypopharynx
C13.8	Malignant neoplasm of overlapping sites of hypopharynx
C13.9	Malignant neoplasm of hypopharynx, unspecified
C14.0	Malignant neoplasm of pharynx, unspecified
C14.2	Malignant neoplasm of Waldeyer's ring
C14.8	Malignant neoplasm of overlapping sites of lip, oral cavity and pharynx
C18.0	Malignant neoplasm of cecum
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of large intestines
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C30.0	Malignant neoplasm of nasal cavity
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C32.0	Malignant neoplasm of glottis
C32.1	Malignant neoplasm of supraglottis
C32.2	Malignant neoplasm of subglottis
C32.3	Malignant neoplasm of laryngeal cartilage
C32.8	Malignant neoplasm of overlapping sites of larynx

ICD-10	ICD-10 Description
C32.9	Malignant neoplasm of larynx, unspecified
C44.00	Unspecified malignant neoplasm of skin of lip
C44.02	Squamous cell carcinoma of skin of lip
C44.09	Other specified malignant neoplasm of skin of lip
C44.121	Squamous cell carcinoma of skin of unspecified eyelid, including canthus
C44.1221	Squamous cell carcinoma of skin of right upper eyelid, including canthus
C44.1222	Squamous cell carcinoma of skin of right lower eyelid, including canthus
C44.1291	Squamous cell carcinoma of skin of left upper eyelid, including canthus
C44.1292	Squamous cell carcinoma of skin of left lower eyelid, including canthus
C44.221	Squamous cell carcinoma of skin of unspecified ear and external auricular canal
C44.222	Squamous cell carcinoma of skin of right ear and external auricular canal
C44.229	Squamous cell carcinoma of skin of left ear and external auricular canal
C44.320	Squamous cell carcinoma of skin of unspecified parts of face
C44.321	Squamous cell carcinoma of skin of nose
C44.329	Squamous cell carcinoma of skin of other parts of face
C44.42	Squamous cell carcinoma of skin of scalp and neck
C44.520	Squamous cell carcinoma of anal skin
C44.521	Squamous cell carcinoma of skin of breast
C44.529	Squamous cell carcinoma of skin of other part of trunk
C44.621	Squamous cell carcinoma of skin of unspecified upper limb, including shoulder
C44.622	Squamous cell carcinoma of skin of right upper limb, including shoulder
C44.629	Squamous cell carcinoma of skin of left upper limb, including shoulder
C44.721	Squamous cell carcinoma of skin of unspecified lower limb, including hip
C44.722	Squamous cell carcinoma of skin of right lower limb, including hip
C44.729	Squamous cell carcinoma of skin of left lower limb, including hip
C44.82	Squamous cell carcinoma of overlapping sites of skin
C44.92	Squamous cell carcinoma of skin, unspecified
C76.0	Malignant neoplasm of head, face and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D37.01	Neoplasm of uncertain behavior of lip
D37.02	Neoplasm of uncertain behavior of tongue
D37.05	Neoplasm of uncertain behavior of pharynx
D37.09	Neoplasm of uncertain behavior of other specified sites of the oral cavity

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ICD-10	ICD-10 Description
D38.0	Neoplasm of uncertain behavior of larynx
D38.5	Neoplasm of uncertain behavior of other respiratory organs
D38.6	Neoplasm of uncertain behavior of respiratory organ, unspecified
Z85.038	Personal history of other malignant neoplasm of large intestine

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: <https://www.cms.gov/medicare-coverage-database/search.aspx>. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC