Erbitux® (cetuximab)
(Intravenous)

-E-

Document Number: MODA-0494

Last Review Date: 04/06/2021
Date of Origin: 09/03/2019
Dates Reviewed: 09/2019, 01/2020, 04/2020, 07/2020, 10/2020, 01/2021, 04/2021

I. Length of Authorization [1]

Coverage will be provided for six months and may be renewed unless otherwise specified.

- SCCHN in combination with radiation therapy: Coverage will be provided for the duration of radiation therapy (6-7 weeks).

II. Dosing Limits

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

	Weekly	Every two weeks
Erbitux 100 mg/50 mL solution for injection	1 vial every 7 days	1 vial every 14 days
Erbitux 200 mg/100 mL solution for injection	3 vials every 7 days (5 vials for first dose only)	6 vials every 14 days

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

Weekly	Every two weeks
– Load: 100 billable units x 1 dose – Maintenance Dose: 60 billable units every 7 days	120 billable units every 14 days

III. Initial Approval Criteria [1,2,14-27]

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 first-line or primary therapy *(Note: Colon cancer patients must have left sided tumors)*; **AND**
      - Used in combination with FOLFIRI; **OR**
      - Used in combination with FOLFOX; **OR**
      - Used in combination with irinotecan after previous adjuvant FOLFOX or CapeOX within the past 12 months; **OR**
    - Used as subsequent therapy; **AND**
      - Used in one of the following:
        - Used in combination with irinotecan for oxaliplatin- and/or irinotecan-refractory disease; **OR**
        - Used in combination with FOLFIRI for oxaliplatin-refractory disease; **OR**
        - Used as a single agent for oxaliplatin- and irinotecan-refractory disease OR irinotecan-intolerant disease; **OR**
    - Used in combination with FOLFOX or FOLFIRI for one of the following *(Note: Colon cancer patients must have left sided tumors)*:
      - Disease that remains unresectable after primary systemic therapy; **OR**
      - Patients who have received adjuvant FOLFOX or CapeOX more than 12 months ago OR who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy; **OR**
      - Disease progression on non-intensive therapy with improvement in functional status *(excluding patients previously treated with fluoropyrimidine)*; **OR**
  - Patient has BRAF V600E mutation positive disease; **AND**
    - Used in combination with encorafenib; **AND**
      - Used as subsequent therapy for disease progression after at least one prior line of treatment in the advanced or metastatic disease setting; **OR**
      - Used as primary treatment for unresectable metastatic disease after previous adjuvant FOLFOX or CapeOX within the past 12 months

Squamous Cell Carcinoma of the Head and Neck (SCCHN) † Φ [2,14,16,25,17e-23e,25e-29e]

- Used in one of the following regimens: †
  - As a single agent in combination with radiation therapy for first-line treatment of regionally or locally advanced disease; **OR**
  - As a single agent in recurrent or metastatic disease after failure on platinum-based therapy; **OR**
  - In combination with platinum-based therapy for first-line treatment of recurrent, loco-regional, or metastatic disease; **AND**

        - Must be used in combination with fluorouracil (5-FU) unless there is a contraindication or intolerance; **AND**
- Patient has one of the following sub-types of SCCHN: ‡
    - Cancer of the Glottic Larynx
    - Cancer of the Hypopharynx
    - Cancer of the Lip (mucosa) *(excluding use in combination with radiation therapy)*
    - Cancer of the Oral Cavity *(excluding use in combination with radiation therapy)*
    - Cancer of the Oropharynx
    - Cancer of the Supraglottic Larynx
    - Ethmoid Sinus Tumors *(excluding use in combination with radiation therapy)*
    - Maxillary Sinus Tumors *(excluding use in combination with radiation therapy)*
    - Very Advanced Head and Neck Cancer (i.e., newly diagnosed locally advanced T4b (M0) disease, newly diagnosed unresectable nodal disease, metastatic disease at initial presentation (M1), recurrent or persistent disease, or patients unfit for surgery)
        - Cetuximab may also be used subsequent therapy in combination with platinum-based therapy *(except for locoregional recurrence without prior radiation therapy)*

Squamous Cell Skin Cancer ‡ [2,21,27]

- Used as a single agent; **AND**
    - Patient is ineligible for or progressed on immune checkpoint inhibitor therapy and clinical trials; **AND**
        - Patient has locally advanced, high-risk, or very high-risk disease; **AND**
            - Curative surgery and curative radiation therapy are not feasible; **AND**
                - Used as primary therapy for non-surgical candidates; **OR**
        - Used for unresectable regional recurrence

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); Φ Orphan Drug

IV. Renewal Criteria [1,2,14-27]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet 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: anaphylactic reactions, severe infusion reactions, cardiopulmonary arrest, pulmonary toxicity/interstitial lung disease, dermatologic toxicity, hypomagnesemia/electrolyte abnormalities, etc.

V. Dosage/Administration [1,3,4,6,20-23]

Indication	Dose
Colorectal Cancer	400 mg/m² loading dose intravenously, then 250 mg/m² intravenously every 7 days until disease progression or unacceptable toxicity; **OR** 500 mg/m² intravenously every 14 days until disease progression or unacceptable toxicity
SCCHN	In combination with radiation therapy: 400 mg/m² loading dose, then 250 mg/m² every 7 days for the duration of radiation therapy (6-7 weeks) Monotherapy or in combination with platinum-based therapy: 400 mg/m² loading dose, then 250 mg/m² every 7 days until disease progression or unacceptable toxicity
All other indications	400 mg/m² loading dose, then 250 mg/m² 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-use vial; solution for injection: 66733-0948-xx
- Erbitux 200 mg/100 mL single-use vial; solution for injection: 66733-0958-xx

VII. References (STANDARD)

1. Erbitux [package insert]. Branchburg, NJ; ImClone LLC; November 2020; Accessed March 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) cetuximab. National Comprehensive Cancer Network, 2021. 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 March 2021.
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 2.2021. National Comprehensive Cancer Network, 2021. 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 March 2021.
13. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Rectal Cancer, Version 1.2021. National Comprehensive Cancer Network, 2021. 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 March 2021.
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-Senyarich 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 4.2021. National Comprehensive Cancer Network, 2021. 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 March 2021.
25. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Head and Neck Cancers, Version 1.2021. National Comprehensive Cancer Network, 2021. 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 March 2021.

26. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Penile Cancer. Version 1.2021. National Comprehensive Cancer Network, 2021. 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 March 2021.
27. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Squamous Cell Skin Cancer. Version 1.2021. National Comprehensive Cancer Network, 2021. 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 March 2021.

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 (1º) 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 platin-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-Seguin 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. Magellan Health, Magellan Rx Management. Erbitux Clinical Literature Review Analysis. Last updated March 2021. Accessed March 2021.

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
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

ICD-10	ICD-10 Description
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
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
C17.0	Malignant neoplasm duodenum
C17.1	Malignant neoplasm jejunum
C17.2	Malignant neoplasm ileum
C17.8	Malignant neoplasm of overlapping sites of small intestines
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon

ICD-10	ICD-10 Description
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
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

ICD-10	ICD-10 Description
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
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
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.828	Personal history of other malignant neoplasm of skin

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: http://www.cms.gov/medicare-coverage-database/search/advanced-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)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; pCR = pathologic complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; DCR = disease control rate; FOLFOX = fluorouracil, leucovorin, and oxaliplatin; FOLFIRI = fluorouracil, leucovorin, and irinotecan

Colorectal Cancer (CRC)

First-line or primary therapy for metastatic CRC							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Cetuximab + FOLFIRI	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes (with FOLFIRI)	Phase 3 (CRYSTAL), randomized, open-label, multi-center Updated analysis	FOLFIRI	PFS	First-line	• First-line treatment with cetuximab plus FOLFIRI, as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer. The benefit of cetuximab was limited to patients with KRAS wild-type tumors.
Cetuximab + FOLFOX	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes (with FOLFIRI)	Phase 3 (TAILOR), open-label, randomized	FOLFOX	PFS	First-line	• Combination of FOLFOX with cetuximab is effective in first-line treatment of patients with RAS wild-type mCRC with a benefit in both PFS and OS.
Panitumumab + FOLFOX	2A (for KRAS/ NRAS WT and	Yes	Phase 3 (PRIME),	FOLFOX	PFS	First-line	• Additional RAS mutations predicted a lack of response in patients who received panitumumab-FOLFOX4. In patients who had metastatic colorectal cancer without RAS

	left-sided tumors only)		randomized, open-label Final results				mutations, improvements in overall survival were observed with panitumumab-FOLFOX4 therapy
Bevacizumab + FOLFIRI	2A	Yes	Phase 3 (FIRE-3), randomized, open-label Primary tumor location analysis	Cetuximab + FOLFIRI	ORR	First-line	• The proportion of patients who achieved an objective response did not significantly differ between the FOLFIRI plus cetuximab and FOLFIRI plus bevacizumab. A longer association in OS with FOLFIRI plus cetuximab was demonstrated for patients with KRAS exon 2 wild-type metastatic colorectal cancer. • More benefit was shown for cetuximab in left-sided tumors than bevacizumab.
Cetuximab + FOLFOX or FOLFIRI	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes (with FOLFIRI)	Phase 3 (CALGB/ SWOG 80405), randomized, open-label, multi-center	Bevacizumab (BV) + FOLFOX or FOLFIRI vs. Cetuximab + bevacizumab + FOLFOX or FOLFIRI	OS	First-line for advanced or metastatic disease	• OS and PFS were prolonged with cetuximab in left-sided tumors and with bevacizumab in right-sided tumors. OS and PFS were poorer with cetuximab in right-sided tumors.
Panitumumab + FOLFOX	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes	Phase 2 (PEAK), randomized, multi-center Final analysis	Bevacizumab + FOLFOX	PFS	First-line for advanced or metastatic disease	• First-line panitumumab + FOLFOX increases PFS versus bevacizumab + FOLFOX in patients with RAS wild-type mCRC.
Cetuximab + irinotecan	2A	No	No clinical evidence to support use				

Subsequent therapy for metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Cetuximab + irinotecan	2A	Yes	Randomized, multi-center trial (BOND)	Cetuximab	ORR	After prior irinotecan-based therapy	• The combination-therapy group had a significantly higher response rate and a significantly longer time to progression than the monotherapy group in patients with irinotecan-refractory colorectal cancer.
Cetuximab + irinotecan	2A	Yes	Phase 3 (EPIC), multi-center, open-label	Irinotecan	OS	After fluoropyrimidine and oxaliplatin	• Cetuximab and irinotecan improved PFS and ORR versus irinotecan alone. OS was similar between study groups
Cetuximab + FOLFIRI	2A	No	No clinical evidence specifically for FOLFIRI. See cetuximab + irinotecan subsequent therapy above.				
Cetuximab + FOLFOX	2A	No	No clinical evidence to support use				
Panitumumab	2A	No	Phase 3 (ASPECCT), randomized, multi-center, open-label, non-inferiority	Cetuximab	Non-inferiority OS	Chemo-refractory	• Panitumumab is non-inferior to cetuximab. These agents provide similar overall survival benefit in patients with KRAS wild type mCRC.
Cetuximab	2A	Yes	Phase 3 (Study CA225-025), randomized	Best supportive care (BSC)	OS	Failed prior regimen containing irinotecan and a prior regimen containing oxaliplatin for	• The benefit in OS and PFS of cetuximab versus best supportive care was shown to be enhanced in patients with KRAS wild-type tumors.

						metastatic disease or relapsed within 6 months after adjuvant therapy	
Bevacizumab + FOLFIRI	2A (preferred after previous oxaliplatin- or fluoropyrimidine-based therapy without irinotecan or oxaliplatin)	Yes	Phase 2 (SPIRITT), randomized, multi-center	Panitumumab + FOLFIRI	PFS	Second-line after oxaliplatin-based therapy plus bevacizumab	• Panitumumab or bevacizumab with FOLFIRI as second-line treatment had efficacy similar in patients whose disease progressed during oxaliplatin-based chemotherapy with bevacizumab
BRAF V600E mutation positive disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Cetuximab + vemurafenib + irinotecan	2A	No	Phase 2 (SWOG S1406)	Cetuximab + irinotecan	PFS	After 1 or 2 prior regimens	• Triplet therapy with cetuximab, vemurafenib, and irinotecan demonstrated a clinical benefit with an improved PFS and response rates compared to therapy without vemurafenib in patients with treatment-refractory BRAFV600E mutated mCRC.
Dabrafenib + trametinib + panitumumab	2A	No	Phase 1/2, open-label	Dabrafenib + trametinib	Safety	All lines of therapy	• Combined BRAF, MEK, and EGFR inhibition with D+T+P demonstrated increased efficacy, with a confirmed and unconfirmed response rate of 21%.

Encorafenib + binimetinib + cetuximab	2A (encorafenib + cetuximab)	No	Phase 3 (BEACON CRC), open-label, randomized	Encorafenib + cetuximab vs. control (irinotecan + cetuximab or FOLFIRI + cetuximab)	OS	After 1-2 previous regimens	• In the BEACON CRC study, the combination of ENCO+BINI+CETUX improved OS and ORR in patients with BRAF V600E-mutant mCRC when compared with current standard of care chemotherapy and had a safety profile consistent with the known safety profile of each agent.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Chemoradiation therapy for locally or regionally advanced disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Cetuximab + radiation	2B	Yes	Phase 3 (BONNER), randomized, multi-center, controlled	Radiation (RT)	Duration of loco-regional control	First line therapy	• Treatment of locoregionally advanced head and neck cancer with concomitant high-dose radiotherapy plus cetuximab improves locoregional control and reduces mortality without increasing the common toxic effects associated with radiotherapy to the head and neck.
Cisplatin + radiation	1 preferred	No	Phase 3, randomized	Radiation (RT) vs. Cisplatin + 5-FU + radiation	----	First line therapy	• The addition of concurrent high-dose, single-agent cisplatin to conventional single daily fractionated radiation significantly improves survival, although it also increases toxicity.
Cetuximab + radiation	2B	Yes	Phase 2, randomized	Cisplatin + radiation	Compliance to treatment	First line therapy	• Cetuximab concomitant to radiation lowered compliance and increased acute toxicity rates. Efficacy outcomes were similar in both arms.

Cetuximab + radiation	2B	Yes	Phase 3 (RTOG 1016), randomized, multi-center, non-inferiority	Cisplatin + radiation	OS	First line therapy	• For patients with HPV-positive oropharyngeal carcinoma, radiotherapy plus cetuximab showed inferior overall survival and progression-free survival compared with radiotherapy plus cisplatin.
Cetuximab + radiation	2B	Yes	Phase 3 (De-ESCALaTE HPV), open-label, randomized	Cisplatin + radiation	Grade 3-5 toxicity	First line therapy	• Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumor control.
Cetuximab + cisplatin + radiation	2B	No	Phase 3 (RTOG 0522)	Cisplatin + radiation	PFS	First line therapy	• Adding cetuximab to radiation-cisplatin did not offer any advantages in terms of OS or PFS.
Cetuximab + carboplatin + fluorouracil + radiation	2B	No	Phase 3 (GORTEC 2001-01), randomized	Cetuximab + radiation	PFS	First line therapy	• The addition of concurrent carboplatin and fluorouracil to cetux-RT improved PFS and locoregional control, with a nonsignificant gain in survival.
First-line therapy of recurrent, loco-regional, or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Cetuximab + cisplatin (or carboplatin) + fluorouracil, followed by	1 other	Yes	Phase 3 (EXTREME), randomized	Cisplatin (or carboplatin) + fluorouracil	OS	First-line therapy	• As compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum-fluorouracil chemotherapy improved overall survival when given as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck.

maintenance cetuximab							
Cetuximab + cisplatin	2A	Yes	Phase 3, randomized	Cisplatin + placebo	PFS	First-line therapy	• Addition of cetuximab to cisplatin significantly improves response rate however PFS and OS were not significantly improved by the addition of cetuximab in this study.
Cetuximab + cisplatin (CetCis)	2A	Yes	Phase 2b, randomized, non-inferiority study	Cetuximab + cisplatin + paclitaxel (CetCisPac)	PFS	First-line therapy	• The two-drug CetCis regimen proved to be non-inferior in PFS to a three-drug combination with CetCisPac. The median OS of both regimens is comparable with that observed in the EXTREME study.
Cisplatin + fluorouracil (CF)	2A	No	Phase 3 (E1395), randomized	Cisplatin + paclitaxel (CP)	OS	First-line therapy	• This phase III, randomized, multicenter trial showed no difference in survival between patients treated with CF or CP.
Pembrolizumab + cisplatin (or carboplatin) + 5-FU vs. Pembrolizumab	2A preferred Single-agent 1 preferred if CPS ≥20	Yes (monotherapy for PD-L1 [CPS ≥ 1])	Phase 3 (KEYNOTE-048), open-label, randomized	EXTREME regimen [cetuximab + carboplatin (or cisplatin) + 5-FU]	OS PFS	First-line	• The addition of pembrolizumab to a platinum and fluorouracil combination improved overall survival compared with cetuximab plus a platinum and fluorouracil combination. For those with high PD-L1 expression (CPS ≥1), single-agent pembrolizumab also improved overall survival compared with cetuximab plus a platinum and fluorouracil combination.
Cisplatin + gemcitabine	1 preferred	No	Phase 3, multi-center, randomized, open-label	Cisplatin + fluorouracil	PFS	First-line	• Gemcitabine plus cisplatin prolongs progression-free survival when used as first-line therapy in patients with recurrent or metastatic nasopharyngeal carcinoma.
Subsequent therapy							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Cetuximab	2A	Yes	Phase 2, open-label, multi-center	N/A	ORR	After platinum-based therapy	• Single-agent cetuximab demonstrated an ORR of 13% in the treatment of recurrent and/or metastatic SCCHN that progressed on platinum therapy. Response was comparable to that seen with cetuximab plus platinum combination regimens in the same setting.
Cetuximab + cisplatin	2A	No	Phase 2	N/A	-----	After platinum-based therapy	• Cetuximab and cisplatin is an active regimen in refractory SCCHN demonstrating an ORR 20% in patients with progressive disease and ORR 18% in patients with stable disease after platinum-based therapy.
Nivolumab	1 preferred	Yes	Phase 3 (CheckMate-141), randomized, open-label	Investigator's choice (methotrexate, docetaxel, cetuximab)	OS	After platinum-based chemo for recurrent or metastatic disease	• Among patients with platinum-refractory, recurrent squamous-cell carcinoma of the head and neck, treatment with nivolumab resulted in longer overall survival than treatment with standard, single-agent therapy. No OS advantage was demonstrated for the nivolumab-treated patients with PD-L1 expression less than 1%.
Pembrolizumab	1 preferred	Yes	Phase 3 (KEYNOTE-040), randomized, open-label	Investigator's choice (methotrexate, docetaxel, cetuximab)	OS	After platinum-based chemo for recurrent or metastatic disease	• Pembrolizumab improved OS compared to the standard of care arm. Results for OS was also statistically significant for patients with tumors with positive PD-L1 expression.
Capecitabine	2A	No	Phase 2	N/A	ORR	After platinum-based chemo	• Capecitabine demonstrated an ORR of 24.2% in patients previously treated with platinum-based therapy.

						for recurrent or metastatic disease	
Paclitaxel	2A	No	Prospective study	N/A	-----	Platinum-resistant disease	• Paclitaxel demonstrated a partial response rate of 43.3% in patients with platinum-resistant advanced head and neck cancer.
Cetuximab + carboplatin *(Nasopharyngeal)*	2A	Yes	Phase 2, multi-center, open-label	N/A	ORR	After platinum-based chemo for recurrent or metastatic disease	• Cetuximab in combination with carboplatin demonstrates an ORR of 11.7% in heavily pretreated patients with recurrent or metastatic NPC who had previously experienced treatment failure with platinum-based therapy.

Occult Primary Head and Neck Cancers – *see Squamous Cell Carcinoma of the Head and Neck (SCCHN)*

Squamous Cell Skin Cancer

Regional recurrence, inoperable positive regional lymph nodes, or distant metastases							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Cetuximab	2A	No	Phase 2	N/A	DCR	First-line	• As a first-line treatment in patients with unresectable SCCS, cetuximab achieved 69% DCR.
Cetuximab	2A	No	Retrospective study	Cetuximab + platinum + fluorouracil		Neoadjuvant setting	• Efficacy of cetuximab either alone or with platinum-based therapy was demonstrated with 92% of patients proceeding to surgery and 65% of patients achieving a complete response as neoadjuvant therapy for the treatment of unresectable advanced

							non-metastatic cutaneous squamous cell carcinomas.
Cisplatin + 5-FU + bleomycin	2A	No	Prospective study	N/A	-----	----------	• Cisplatin-based therapy demonstrated an overall response rate of 84%.
Cetuximab	2A	No	Retrospective study	Platinum- or taxane-based chemotherapy	-----	----------	• Use of platinum-based therapy significantly improved PFS and OS, whereas taxanes and cetuximab had no impact in this small cohort.
Cetuximab	2A	No	Retrospective study	Cisplatin	-----	----------	• This retrospective analysis demonstrated a higher complete response and overall response rate with cetuximab as well as a longer disease-free survival.
Cemiplimab	2A preferred	Yes (not candidates for surgery or radiation)	Phase 2 (EMPOWER), open-label, multi-center	N/A	ORR	Untreated and previously treated	• Cemiplimab induced a response in approximately half (47%) of the patients with metastatic disease.
Pembrolizumab	2A preferred	Yes (not candidates for surgery or radiation)	Phase 2 (KEYNOTE-629), open-label, multi-center	N/A	ORR	Any line of therapy	• Pembrolizumab demonstrated an ORR 34.3% and median duration of response was not reached in patients with recurrent or metastatic cSCC, most of whom were heavily pretreated.

Penile Cancer

Subsequent treatment							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Cetuximab ± platinum-based therapy	2A	No	Retrospective study	N/A	-----	After at least one prior line of systemic therapy	• Cetuximab alone or in combination with platinum-based therapy demonstrated antitumor activity in metastatic penile cancer with a median OS of 29.6 weeks.
Pembrolizumab	2A preferred (for MSI-H or dMMR)	Yes (for MSI-H or dMMR cancer)	Proof-of-concept study	N/A	-----	After at least one prior line of systemic therapy	• This study demonstrated an objective radiographic response rate of 53% in patients with mismatch repair-deficient cancers, regardless of the cancers' tissue of origin.
Paclitaxel	2A	No	Phase 2, multi-center	N/A	ORR	Previously treated disease	• Paclitaxel demonstrated a partial response rate of 20% in patients with pre-treated metastatic penile cancer.

Non-Small Cell Lung Cancer (NSCLC)

Subsequent therapy - recurrent, advanced, or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Cetuximab + afatinib	2A	No	Phase 1b	N/A	Toxicity	After prior erlotinib or gefitinib	• Cetuximab plus afatinib demonstrated clinical activity of a targeted treatment regimen in EGFR-mutant lung cancers with acquired resistance to erlotinib or gefitinib with a confirmed OR rate of 29%. Response rates and PFS were similar in patients with and without T790M mutations.