Medical Policy:

Opdivo® (nivolumab) Intravenous

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.97	March 4, 2025	January 1, 2020

The treating physician or primary care provider must submit to EmblemHealth, or ConnectiCare, as applicable (hereinafter jointly referred to as "EmblemHealth"), the clinical evidence that the member meets the criteria for the treatment or surgical procedure. Without this documentation and information, EmblemHealth will not be able to properly review the request preauthorization or post-payment review. The clinical review criteria expressed below reflects how EmblemHealth determines whether certain services or supplies are medically necessary. This clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Health care providers are expected to exercise their medical judgment in rendering appropriate care.

EmblemHealth established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). EmblemHealth expressly reserves the right to revise these conclusions as clinical information changes and welcomes further relevant information. Each benefit program defines which services are covered. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered and/or paid for by EmblemHealth, as some programs exclude coverage for services or supplies that EmblemHealth considers medically necessary.

If there is a discrepancy between this guideline and a member's benefits program, the benefits program will govern. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test or procedure over another. In addition, coverage may be mandated by applicable legal requirements of a state, the Federal Government or the Centers for Medicare & Medicaid Services (CMS) for Medicare and Medicaid members. All coding and web site links are accurate at time of publication.

EmblemHealth may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. EmblemHealth Services Company, LLC, has adopted this policy in providing management, administrative and other services to EmblemHealth Plan, Inc., EmblemHealth Insurance Company, EmblemHealth Services Company, LLC, and Health Insurance Plan of Greater New York (HIP) related to health benefit plans offered by these entities. ConnectiCare, an EmblemHealth company, has also adopted this policy. All of the aforementioned entities are affiliated companies under common control of EmblemHealth Inc.

Length of Authorization

Coverage will be provided for six months and may be renewed.

- Adjuvant use in the treatment of melanoma patients can be authorized up to a maximum of 12 months of therapy.

Dosing Limits [Medical Benefit]

Max Units (per dose and over time):

Indication	Billable Units (BU)	Per unit time (days)
HCC, Cutaneous Melanoma, Uveal Melanoma	120 BU	21 days
Bladder/Urothelial Cancer, CRC, Esophageal Cancer, GEJ Cancer, Gastric, GTN, SCCHN, HCC, cHL, RCC, MPM, Cutaneous Melanoma, NSCLC	240 BU	14 days

CRC, Esophageal Cancer, MPM, , Uveal Melanoma, Cutaneous Melanoma,	240 BU	14 days
CRC, cHL, RCC,	340 BU	21 days
Esophageal Cancer, GEJ Cancer, Gastric Cancer, MPM, , & NSCLC	360 BU	21 days
Urothelial (Bladder) Cancer, CRC, Esophageal Cancer, GEJ Cancer, SCCHN, HCC, cHL, RCC, Cutaneous Melanoma, NSCLC,	480 BU	28 days
Uveal Melanoma	1140 BU	14 days

Guideline

I. INITIAL CRITERIA

Coverage is provided for the following conditions:

- Patient must be 18 years of age or older (unless otherwise specified); **AND**
- Patient has not received previous therapy with a programmed death (PD-1/PD-L1)-directed therapy (e.g., avelumab, pembrolizumab, atezolizumab, durvalumab, etc.) unless otherwise specified; **AND**

Melanoma †

1. Patient has unresectable or metastatic uveal melanoma; **AND**
   A. Used as a single agent or in combination with ipilimumab; **OR**
2. Used as first-line therapy for unresectable or metastatic* disease; **AND**
   A. Patient is at least 12 years of age; **AND**
   B. Used as a single agent or in combination with ipilimumab; **OR**
3. Used as initial therapy for limited resectable disease; **AND**
   A. Used as a single agent; **AND**
      i. Patient has stage III disease with clinical satellite/in-transit metastases; **OR**
      ii. Patient has local satellite/in-transit recurrence; **OR**
4. Used as subsequent therapy for unresectable or metastatic* disease; **AND**
   A. Patient is at least 12 years of age; **AND**
      i. Used as re-induction therapy in patients who experienced disease control (i.e., complete or partial response or stable disease) and no residual toxicity from prior anti-PD-1 immunotherapy, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; **AND**
         a. Used as a single agent or in combination with ipilimumab; **OR**
      ii. Used after disease progression, intolerance, and/or projected risk of progression with BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); **AND**
         a. Used as a single agent or in combination with ipilimumab if anti-PD-1 therapy was not previously used; **OR**
         b. Used in combination with ipilimumab for disease progression on single agent anti-PD-1 therapy; **OR**
5. Used as adjuvant treatment; **AND**
   A. Used as a single agent; **AND**
      i. Patient is at least 12 years of age; **AND**

a. Patient has stage IIB, stage IIC, or metastatic disease and has undergone complete resection †; **OR**

b. Patient has stage III disease; **AND**

1.) Patient has undergone complete resection †; **OR**

2.) Patient has sentinel node positive disease either during observation without additional nodal surgery and with mandatory radiographic nodal surveillance **OR** after complete lymph node dissection (CLND); **OR**

3.) Patient has clinically positive node(s) following wide excision of the primary tumor and therapeutic lymph node dissection (TLND) **OR** following neoadjuvant therapy; **OR**

4.) Patient has clinical satellite/in-transit metastases and has no evidence of disease (NED) after complete excision; **OR**

5.) Used following wide excision alone (stage IIIB/C/D disease only); **OR**

6.) Used following wide excision with negative sentinel lymph node biopsy; **OR**

7.) Used for disease that is sentinel lymph node negative or sentinel lymph node biopsy not performed (stage IIIB/C/D disease only); **OR**

c. Patient has local satellite/in-transit recurrence and has NED after complete excision; **OR**

d. Patient has resectable disease limited to nodal recurrence following excision and complete TLND OR following neoadjuvant therapy; **OR**

e. Patient has oligometastatic disease and NED following metastasis-directed therapy (i.e., stereotactic ablative therapy or complete resection) or systemic therapy followed by resection; **OR**

B. Used in combination with ipilimumab; **AND**

i. Patient has oligometastatic disease and no evidence of disease following metastasisdirected therapy (i.e., complete resection, stereotactic ablative therapy or TVEC/intralesional therapy) or systemic therapy followed by resection

6. Used as neoadjuvant therapy; **AND**

A. Used as a single agent or in combination with ipilimumab; **AND**

i. Patient has stage III disease; **AND**

a. Used as primary treatment for clinically positive, resectable nodal disease; **OR**

b. Used for limited resectable disease with clinical satellite/in-transit metastases; **OR**

ii. Patient has limited resectable local satellite/in-transit recurrence; **OR**

iii. Patient has resectable disease limited to nodal recurrence

**Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s)or clinical satellite/in-transit metastases, or as well as unresectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease*.

<u>Hepatocellular Carcinoma (HCC) †</u>

1. Used for **ONE** of the following:

A. Patient was previously treated with sorafenib (for use in combination with ipilimumab ONLY) †; **OR**

B. Patient has unresectable disease and is not a transplant candidate; **OR**

C. Patient has liver-confined disease that is inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic-disease; **OR**

D. Patient has metastatic disease or extensive liver tumor burden; **AND**

i. Used in combination with ipilimumab; **AND**

a. Patient has Child-Pugh Class A hepatic impairment; **AND**

b. Used as subsequent therapy for progressive disease; **OR**

ii. Used as a single agent; **AND**

a. Patient has Child-Pugh Class B hepatic impairment

Non-Small Cell Lung Cancer (NSCLC) †

1. Used as neoadjuvant therapy for resectable (tumors ≥ 4 cm or node positive) disease; **AND**

A. Used in combination with platinum-doublet chemotherapy (e.g., cisplatin/carboplatin in combination with paclitaxel, pemetrexed, or gemcitabine); **AND**

B. Patient is negative for EGFR or ALK rearrangements; **OR**

2. Used for recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**

A. Used as first-line therapy; **AND**

i. Used for **ONE** of the following:

a. Patients with a performance status (PS) 0-1 who have tumors that are negative for actionable molecular biomarkers** ¥; and PD-L1 expression <1%

b. Patients with a PS 0-1 who are positive for one of the following molecular biomarkers: EGFR exon 20, KRAS G12C, BRAF V600E, NTRK1/2/3 gene fusion, MET exon 14 skipping, RET rearrangement, or ERBB2 (HER2)

c. PD-L1 expression-positive (PD-L1 ≥1%) tumors, as detected by an FDA or CLIA compliant test, that are negative for actionable molecular biomarkers** ¥; **AND**

1.) Used in combination with ipilimumab; **OR**

2.) Used in combination with ipilimumab and platinum-doublet chemotherapy(e.g., pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology, or paclitaxel and carboplatin for squamous cell histology, etc.); **OR**

B. Used as subsequent therapy; **AND**

i. Used as a single agent; **OR**

ii. Used for **ONE** of the following:

a. Patients with a PS 0-1 who are positive for one of the following molecular biomarkers and have received prior targeted therapy§:EGFR exon 19 deletion or exon 21 L858R tumors, EGFR S768I, L861Q, and/or G719X, ALK rearrangement, or ROS1 rearrangement

b. Patients with a PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E, NTRK1/2/3 gene fusion, MET exon 14 skipping, or RET rearrangement; **AND**

1.) Used in combination with ipilimumab; **OR**

2.) Used in combination with ipilimumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology; **OR**

3.) Used in combination with ipilimumab, paclitaxel, and carboplatin for squamous cell histology; **OR**

C. Used as continuation maintenance therapy in combination with ipilimumab; **AND**

i. Patient has achieved a response or stable disease following first-line therapy with nivolumab and ipilimumab with or without chemotherapy

*** Note: Actionable molecular genomic biomarkers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2). Complete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2) via biopsy and/or plasma testing. If a clinically actionable marker is found, it is reasonable to start therapy based on the*

identified marker. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

¥ May also be used for patients with KRAS G12C mutation positive tumors.

Renal Cell Carcinoma (RCC) †

1. Used in combination with ipilimumab; **AND**
   A. Patient has clear cell histology; **AND**
      i. Used as first-line therapy in patients with poor or intermediate risk advanced, relapsed, or stage IV disease; **OR**
      ii. Used as first-line therapy in patients with favorable risk relapsed or stage IV disease; **OR**
      iii. Used as subsequent therapy in patients with relapsed or stage IV disease Δ; **OR**
2. Used as a single agent; **AND**
   A. Used as subsequent therapy in patients with advanced, relapsed, or stage IV disease and clear cell histology; **OR**
   B. Patient has relapsed or stage IV disease and non-clear cell histology; **OR**
3. Used in combination with cabozantinib (Cabometyx only); **AND**
   A. Patient has clear cell histology; **AND**
      i. Used as first-line therapy for advanced, relapsed, or stage IV disease; **OR**
      ii. Used as subsequent therapy in patients with relapsed or stage IV disease Δ; **OR**
   B. Patient has non-clear cell histology; **AND**
      i. Patient has relapsed or stage IV disease

Classical Hodgkin Lymphoma (cHL) †

1. Used as a single agent; **AND**
   A. Patient has relapsed or progressive disease after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin †; **OR**
   B. Used for disease that is refractory to at least 3 prior lines of therapy including autologous HSCT †; **OR**
   C. Used as palliative therapy in patients > 60 years of age or with poor performance status or with substantial comorbidities; **AND**
      i. Patient has relapsed or refractory disease; **OR**

2. Used in combination with brentuximab vedotin or ICE (ifosfamide, carboplatin, etoposide) in patients 18 to 60 years of age; **AND**
   A. Used as second-line therapy for relapsed or refractory disease; **OR**
   B. Used as subsequent therapy (if not previously used) for relapsed or refractory disease; **AND**
      i. Patient has a Deauville scale score of 4 or 5 following restaging with FDG-PET/CT

Squamous Cell Carcinoma of the Head and Neck (SCCHN) †

1. Patient has Cancer of the Nasopharynx; **AND**
   A. Used in combination with cisplatin and gemcitabine for oligometastatic or metastatic disease; **OR**
2. Patient has Very Advanced Head and Neck Cancer*; **AND**
   A. Patient has nasopharyngeal cancer; **AND**
      i. Used in combination with cisplatin and gemcitabine for patients with performance status (PS) 0-1; **AND**
      ii. Used for **ONE** of the following:
         a. Unresectable locoregional recurrence with prior radiation therapy (RT)
         b. Unresectable second primary with prior RT
         c. Unresectable persistent disease with prior RT
         d. Recurrent/persistent disease with distant metastases; **OR**

B. Patient has NON-nasopharyngeal cancer; **AND**
    i. Used as a single agent; **AND**
        a. Patient has unresectable, recurrent, persistent, or metastatic disease; **AND**
        b. Disease has progressed on or after platinum-containing chemotherapy; **OR**
    ii. Used in combination with cetuximab for patients with performance status (PS) 0-1; **AND**
        a. Used for **ONE** of the following:
            1.) Metastatic disease at initial presentation
            2.) Recurrent/persistent disease with distant metastases
            3.) Unresectable locoregional recurrence with prior RT
            4.) Unresectable second primary with prior RT
            5.) Unresectable persistent disease with prior RT

** Very Advanced Head and Neck Cancer includes: 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.*

Colorectal Cancer †

1. Adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease **OR** polymerase epsilon/delta (POLE/POLD1) mutation as determined by an FDA approved or CLIA-compliant test; **AND**
2. Used as a single agent or in combination with ipilimumab*; **AND**
    i. Used as subsequent therapy; **AND**
        a. Patient has metastatic, unresectable, or medically inoperable disease; **OR**
    ii. Used as primary or initial treatment; **AND**
        a. Used for isolated pelvic/anastomotic recurrence of rectal cancer; **OR**
        b. Patient has T3, N Any; T1-2, N1-2; T4, N Any rectal cancer; **OR**
        c. Patient has metastatic, unresectable, or medically inoperable disease; **OR**
3. Used as neoadjuvant therapy; **AND**
    i. Patient has clinical T4b colon cancer (for dMMR/MSI-H disease ONLY); **OR**
    ii. Patent has resectable liver and/or lung metastases; **OR**
    iii. Patient has T3, N Any; T1-2, N1-2; T4, N Any, locally unresectable, or medically inoperable rectal cancer (single agent therapy for dMMR/MSI-H disease ONLY)

** Single agent nivolumab should be used in patients who are not candidates for intensive therapy*

Urothelial Carcinoma †

1. Must be used as a single agent; **AND**
    A. Must be used as subsequent systemic therapy after previous platinum treatment* * **OR** as second-line treatment after chemotherapy other than a platinum; **AND**
        i. Patient has **ONE** of the following:
            a. Locally advanced or metastatic disease; **OR**
            b. Muscle invasive bladder cancer with local recurrence or persistent disease in a preserved bladder ‡; **OR**
            c. Disease recurrence post-cystectomy **‡**; **OR**
            d. Recurrent or metastatic Primary Carcinoma of the Urethra **‡; AND**
                1.) Patient does not have recurrent stage T3-4 disease or palpable inguinal lymph nodes; **OR**
            e. Metastatic Upper GU Tract Tumors **‡; OR**
            f. Metastatic Urothelial Carcinoma of the Prostate **‡; OR**
    B. Used as adjuvant therapy **†**; **AND**

i. Patient has urothelial carcinoma of the bladder, bulbar urethra, prostate with stromal invasion, ureter, or renal pelvis; **AND**

ii. Patient underwent radical surgical resection or partial cystectomy; **AND**

iii. Patient is at high risk of disease recurrence**

C. Used in combination with cisplatin and gemcitabine followed by nivolumab maintenance therapy; **AND**

i. Used as first-line systemic therapy in cisplatin eligible patients*; **AND**

a. Patient has **ONE** of the following diagnoses:

1.) Locally advanced, unresectable, or metastatic urothelial carcinoma †

2.) Muscle invasive bladder cancer with local recurrence or persistent disease in a preserved bladder

3.) Metastatic or local bladder cancer recurrence post-cystectomy

4.) Recurrent or metastatic primary carcinoma of the urethra; **AND**

- Patient does not have recurrence of stage T3-4 disease or palpable inguinal lymph nodes

5.) Metastatic upper genitourinary (GU) tract tumors

6.) Metastatic urothelial carcinoma of the prostate

** Note: – If patient was progression free for >12 months after platinum therapy, consider re-treatment with platinum-based therapy if the patient is still platinum eligible (see below for cisplatin- or platinumineligible comorbidities).*

- *Cisplatin-ineligible comorbidities may include the following: CrCl < 60 mL/min, ECOG PS ≥ 2 or KPS ≤ 70%, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, grade ≥ 2 peripheral neuropathy, or NYHA Heart Failure class ≥ 3. Carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients such as those with a GFR less than 60 mL/min.*
- *Platinum-ineligible comorbidities may include the following: CrCl < 30 mL/min, ECOG PS ≥ 3, grade ≥ 2 peripheral neuropathy, or NYHA Heart Failure class > 3, etc.*

*** High risk of disease recurrence is defined as:*
ypT2-ypT4a or ypN+ for patients who received neoadjuvant cisplatin; OR
pT3-pT4a or pN+ for patients who did not receive neoadjuvant cisplatin and are also ineligible for or refused adjuvant cisplatin therapy

<u>Esophageal Squamous Cell Carcinoma (ESCC)</u>†

1. Used as first-line therapy; **AND**

A. Patient has squamous cell carcinoma †; **AND**

i. Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**

a. Used in combination with ipilimumab*; **OR**

b. Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; **OR**

B. Patient has adenocarcinoma; **AND**

i. Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**

a. Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; **OR**

b. Used in combination with ipilimumab; **AND**

1.) Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA compliant test; **OR**

2. Used as subsequent therapy; **AND**

A. Patient has squamous cell carcinoma; **AND**

i. Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**

a. Used as a single agent; **OR**

b. Used in combination with ipilimumab; **AND**

1.) Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA compliant test; **OR**

B. Patient has adenocarcinoma; **AND**

i. Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease; **AND**

ii. Used in combination with ipilimumab; **AND**

iii. Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; **OR**

3. Used as adjuvant treatment of completely resected disease †; **AND**

A. Used as a single agent in patients with residual disease following neoadjuvant chemoradiotherapy (CRT); **OR**

4. Used as neoadjuvant or perioperative therapy; **AND**

A. Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; **AND**

B. Patient has adenocarcinoma; **AND**

i. Used in combination with ipilimumab; **AND**

a. Used as primary treatment for patients who are medically fit for surgery with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, Any N disease; **OR**

ii. Used as a single agent ; **AND**

a. Used as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab

**Note: Combination therapy with ipilimumab OR oxaliplatin and fluorouracil or capecitabine may also be used for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test*

Unresectable Malignant Pleural Mesothelioma (MPM) †

1. Used as a single agent or in combination with ipilimumab as subsequent therapy (if chemotherapy was administered first-line); **OR**
2. Used in combination with ipilimumab as first-line therapy; **AND**
   A. Patient has clinical stage IIIB or IV disease; **OR**
   B. Patient has sarcomatoid or biphasic histology; **OR**
   C. Disease is medically inoperable or unresectable; **OR**
   D. Patient has clinical stage I-IIIA disease with epithelioid histology and did not receive induction chemotherapy

**Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.*

Gastric Cancer†

1. Used as first-line therapy; **AND**

A. Patient is not a surgical candidate or has unresectable, advanced, recurrent, or metastatic disease; **AND**

i. Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; **OR**

ii. Used in combination with ipilimumab; **AND**

a. Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; **OR**

2. Used as subsequent therapy; **AND**

A. Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease; **AND**

B. Used in combination with ipilimumab; **AND**

C. Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; **OR**

3. Used as neoadjuvant or perioperative therapy; **AND**

A. Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; **AND**

i. Used in combination with ipilimumab; **AND**

a. Used as primary treatment prior to surgery for potentially resectable locoregional disease (cT2 or higher, any N) in patients who are medically fit for surgery; **OR**

ii. Used as a single agent; **AND**

b. Used as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab

**Note: Combination therapy with oxaliplatin and fluorouracil or capecitabine may also be used for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test*

<u>Esophageal Cancer and Esophagogastric/Gastroesophageal Junction Cancers † ‡ Φ</u>

1. Used as first-line therapy; **AND**

A. Patient has squamous cell carcinoma †; **AND**

i. Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**

a. Used in combination with ipilimumab*; **OR**

b. Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; **OR**

B. Patient has adenocarcinoma; **AND**

i. Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**

a. Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; **OR**

b. Used in combination with ipilimumab; **AND**

1.) Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA compliant test; **OR**

2. Used as subsequent therapy; **AND**

A. Patient has squamous cell carcinoma; **AND**

i. Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**

a. Used as a single agent; **OR**

b. Used in combination with ipilimumab; **AND**

1.) Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; **OR**

B. Patient has adenocarcinoma; **AND**

i. Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease; **AND**

ii. Used in combination with ipilimumab; **AND**

iii. Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; **OR**

3. Used as adjuvant treatment of completely resected disease †; **AND**

A. Used as a single agent in patients with residual disease following neoadjuvant chemoradiotherapy (CRT); **OR**

4. Used as neoadjuvant or perioperative therapy; **AND**

A. Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; **AND**

B. Patient has adenocarcinoma; **AND**

i. Used in combination with ipilimumab; **AND**

a. Used as primary treatment for patients who are medically fit for surgery with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, Any N disease; **OR**

ii. Used as a single agent ; **AND**

b. Used as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab

**Note: Combination therapy with ipilimumab OR oxaliplatin and fluorouracil or capecitabine may also be used for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test*

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

II. RENEWAL CRITERIA

Authorizations can be renewed based on the following criteria:

1. Patient continues to meet the criteria identified above; **AND**
2. Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe infusion reactions, complications of allogeneic HSCT, severe immune-mediated adverse reactions such as pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, rash, encephalitis, etc.; **AND**
3. Tumor response with stabilization of disease or decrease in size of tumor or tumor spread; **AND**
4. For the following indication, the patient has not exceeded a maximum of twelve (12) months of therapy:
    b. Adjuvant treatment of melanoma (as a single agent); **OR**
5. For the following indication, the patient has not exceeded a maximum of twenty four (24) months of therapy:
    a. Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (first-line therapy)
    b. MSI-H/dMMR Gastric, Esophageal, and Esophagogastric/Gastroesophageal Junction Cancer (first-line and subsequent therapy
    c. Gastric Cancer (in combination with fluoropyrimidine- and platinum-containing chemotherapy **OR** ipilimumab)
    d. Malignant Pleural Mesothelioma (initial therapy in combination with ipilimumab)
    e. Non-Small Cell Lung Cancer (in combination with ipilimumab with or without platinum-doublet chemotherapy)
    f. Renal Cell Carcinoma (in combination with cabozantinib)
    g. Urothelial Carcinoma (first line therapy in combination with gemcitabine and cisplatin, followed by single-agent maintenance therapy
6. **Non-Small Cell Lung Cancer (neoadjuvant therapy in combination with platinum-doublet chemotherapy)**

• Patient has not exceeded a maximum of three (3) cycles

7. **Urothelial Carcinoma (adjuvant therapy)**
   • Patient has not exceeded a maximum of one (1) year of therapy
8. **Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (adjuvant therapy)**
   • Patient has not exceeded a maximum of one (1) year of therapy
9. **Classical Hodgkin Lymphoma (in combination with brentuximab vedotin**)
   • Patient has not exceeded a maximum of twelve (12) weeks of therapy
10. **Classical Hodgkin Lymphoma (in combination with ICE)**
    • Patient has not exceeded a maximum of 12 weeks of therapy (6 doses)
11. **MSI-H/dMMR Gastric, Esophageal, and Esophagogastric/Gastroesophageal Junction Cancer** (neoadjuvant or perioperative therapy)
    • Patient has not exceeded a maximum of 12 weeks of pre-operative therapy (6 doses), followed by a maximum of 36 weeks (9 doses) of postoperative therapy after surgery
12. **Cutaneous Melanoma (adjuvant therapy in combination with ipilimumab)**
    • Patient has not exceeded a maximum of four (4) doses
13. **Cutaneous Melanoma (neoadjuvant therapy as a single agent)**
    • Patient has not exceeded a maximum of four (4) doses
14. **Cutaneous Melanoma (neoadjuvant therapy in combination with ipilimumab)**
    • Patient has not exceeded a maximum of three (3) doses
15. **Retreatment for Melanoma (metastatic or unresectable disease) ‡**
    A. Refer to Initial Criteria Section for criteria (see Cutaneous Melanoma – Used for retreatment of disease as re-induction)
16. **Non-Small Cell Lung Cancer (maintenance therapy)**
    • Refer to Initial Criteria section for criteria

Δ Notes:

- Patients responding to therapy who relapse ≥ 6 months after discontinuation due to duration (i.e., receipt of 24 months of therapy) are eligible to re-initiate PD-directed therapy
- Patients previously presenting with aggressive disease who are exhibiting stable disease on treatment as their best response (or if therapy improved performance status) may be eligible for continued therapy beyond the 24-month limit without interruption or discontinuation.
- Patients who complete adjuvant therapy and progress ≥ 6 months after discontinuation are eligible to re-initiate PD-directed therapy for metastatic disease.
- Patients whose tumors, upon re-biopsy, demonstrate a change in actionable mutation (e.g., MSS initial biopsy; MSI-H subsequent biopsy) may be eligible to re-initiate PDdirected therapy and will be evaluated on a case-by-case basis.
- Patients diagnosed with Renal Cell Carcinoma with clear cell histology who have received previous immuno-oncology therapy may be eligible for treatment with nivolumab as subsequent therapy and will be evaluated on a case-by-case basis.

Limitations/Exclusions

Opdivo is considered investigational when used for any indication not listed above.

Applicable Procedure Codes

Code	Description
J9299	Injection, nivolumab, 1 mg; 1 billable unit = 1 mg

Applicable NDCs

Code	Description
00003-3772-xx	Opdivo 40 mg/4 mL single-use vial
00003-3774-xx	Opdivo 100 mg/10 mL single-use vial
00003-3756-xx	Opdivo 120 mg/12 mL single-dose vial
00003-3734-xx	Opdivo 240 mg/24 mL single-use vial

ICD-10 Diagnoses

Code	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
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
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
C10.3	Malignant neoplasm of posterior wall of oropharynx
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 of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.8	Malignant neoplasm of overlapping sites of small intestine
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
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 colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
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
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C45.0	Mesothelioma of pleura
C38.4	Malignant neoplasm of pleura
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, 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
C4A.0	Merkel cell carcinoma of lip
C4A.10	Merkel cell carcinoma of eyelid, including canthus
C4A.111	Merkel cell carcinoma of right upper eyelid, including canthus
C4A.112	Merkel cell carcinoma of right lower eyelid, including canthus
C4A.121	Merkel cell carcinoma of left upper eyelid, including canthus
C4A.122	Merkel cell carcinoma of left lower eyelid, including canthus
C4A.20	Merkel cell carcinoma of unspecified ear and external auricular canal
C4A.21	Merkel cell carcinoma of right ear and external auricular canal
C4A.22	Merkel cell carcinoma of left ear and external auricular canal
C4A.30	Merkel cell carcinoma of unspecified part of face
C4A.31	Merkel cell carcinoma of nose
C4A.39	Merkel cell carcinoma of other parts of face
C4A.4	Merkel cell carcinoma of scalp and neck
C4A.51	Merkel cell carcinoma of anal skin
C4A.52	Merkel cell carcinoma of skin of breast
C4A.59	Merkel cell carcinoma of other part of trunk
C4A.60	Merkel cell carcinoma of unspecified upper limb, including shoulder
C4A.61	Merkel cell carcinoma of right upper limb, including shoulder
C4A.62	Merkel cell carcinoma of left upper limb, including shoulder
C4A.70	Merkel cell carcinoma of unspecified lower limb, including hip
C4A.71	Merkel cell carcinoma of right lower limb, including hip
C4A.72	Merkel cell carcinoma of left lower limb, including hip
C4A.8	Merkel cell carcinoma of overlapping sites
C4A.9	Merkel cell carcinoma, unspecified
C61	Malignant neoplasm of prostate
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C66.1	Malignant neoplasm of right ureter
C66.2	Malignant neoplasm of left ureter
C66.9	Malignant neoplasm of unspecified ureter
C67.0	Malignant neoplasm of trigone of bladder
C67.1	Malignant neoplasm of dome of bladder
C67.2	Malignant neoplasm of lateral wall of bladder
C67.3	Malignant neoplasm of anterior wall of bladder
C67.4	Malignant neoplasm of posterior wall of bladder
C67.5	Malignant neoplasm of bladder neck
C67.6	Malignant neoplasm of ureteric orifice
C67.7	Malignant neoplasm of urachus
C67.8	Malignant neoplasm of overlapping sites of bladder

C67.9	Malignant neoplasm of bladder, unspecified
C68.0	Malignant neoplasm of urethra
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C69.91	Malignant neoplasm of unspecified site of right eye
C69.92	Malignant neoplasm of unspecified site of left eye
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
C78.89	Secondary malignant neoplasm of other digestive organs
C79.31	Secondary malignant neoplasm of brain
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7B.1	Secondary Merkel cell carcinoma
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant (primary) neoplasm, unspecified
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C81.11	Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.12	Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes
C81.13	Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes
C81.14	Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.15	Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.16	Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes
C81.17	Nodular sclerosis Hodgkin lymphoma, spleen
C81.18	Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites
C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites
C81.20	Mixed cellularity Hodgkin lymphoma, unspecified site
C81.21	Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.22	Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes
C81.23	Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes
C81.24	Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.25	Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.26	Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes

C81.27	Mixed cellularity Hodgkin lymphoma, spleen
C81.28	Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.30	Lymphocyte depleted Hodgkin lymphoma, unspecified site
C81.31	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.32	Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes
C81.33	Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes
C81.34	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.35	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.36	Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes
C81.37	Lymphocyte depleted Hodgkin lymphoma, spleen
C81.38	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites
C81.40	Lymphocyte-rich Hodgkin lymphoma, unspecified site
C81.41	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.42	Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes
C81.43	Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes
C81.44	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.45	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.46	Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes
C81.47	Lymphocyte-rich Hodgkin lymphoma, spleen
C81.48	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.70	Other Hodgkin lymphoma unspecified site
C81.71	Other Hodgkin lymphoma lymph nodes of head, face, and neck
C81.72	Other Hodgkin lymphoma intrathoracic lymph nodes
C81.73	Other Hodgkin lymphoma intra-abdominal lymph nodes
C81.74	Other Hodgkin lymphoma lymph nodes of axilla and upper limb
C81.75	Other Hodgkin lymphoma lymph nodes of inguinal region and lower limb
C81.76	Other Hodgkin lymphoma intrapelvic lymph nodes
C81.77	Other Hodgkin lymphoma spleen
C81.78	Other Hodgkin lymphoma lymph nodes of multiple sites
C81.79	Other Hodgkin lymphoma extranodal and solid organ sites
C81.90	Hodgkin lymphoma, unspecified site
C81.91	Hodgkin lymphoma, unspecified lymph nodes of head, face, and neck
C81.92	Hodgkin lymphoma, unspecified intrathoracic lymph nodes
C81.93	Hodgkin lymphoma, unspecified intra-abdominal lymph nodes
C81.94	Hodgkin lymphoma, unspecified lymph nodes of axilla and upper limb
C81.95	Hodgkin lymphoma, unspecified lymph nodes of inguinal region and lower limb
C81.96	Hodgkin lymphoma, unspecified intrapelvic lymph nodes
C81.97	Hodgkin lymphoma, unspecified spleen
C81.98	Hodgkin lymphoma, unspecified lymph nodes of multiple sites
C81.99	Hodgkin lymphoma, unspecified extranodal and solid organ sites
D09.0	Carcinoma in situ of bladder
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
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.21	Personal history of malignant neoplasm of larynx
Z85.22	Personal history of malignant neoplasm of nasal cavities, middle ear, and accessory sinuses
Z85.51	Personal history of malignant neoplasm of bladder
Z85.528	Personal history of other malignant neoplasm of kidney
Z85.59	Personal history of malignant neoplasm of other urinary tract organ
Z85.71	Personal history of Hodgkin lymphoma
Z85.810	Personal history of malignant neoplasm of tongue
Z85.818	Personal history of malignant neoplasm of other sites of lip, oral cavity and pharynx
Z85.819	Personal history of malignant neoplasm of unspecified site of lip, oral cavity and pharynx
Z85.820	Personal history of malignant melanoma of skin
Z85.821	Personal history of Merkel cell carcinoma

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	3/4/2025	Annual Review: Updated dosing limits. Initial Criteria: Melanoma † Removed to reword: "Patient's disease is unresectable or metastatic; AND Used as a single agent or in combination with ipilimumab; OR Used as adjuvant treatment as a single agent; AND Patient has lymph node involvement or metastatic disease and has undergone complete resection; OR Used for retreatment of disease (*see Renewal Criteria)" Added: "*Used as first-line therapy for unresectable or metastatic* disease; AND Patient is at least 12 years of age; AND Used as a single agent or in combination with ipilimumab; OR Used as initial therapy for limited resectable disease; AND Used as a single agent; AND Patient has stage III disease with clinical satellite/in-transit metastases; OR Patient has local satellite/in-transit recurrence; OR Used as subsequent therapy for unresectable or metastatic* disease; AND Patient is at least 12 years of age; AND Used as re-induction therapy in patients who experienced disease control (i.e., complete or partial response or stable disease) and no residual toxicity from prior anti-PD-1 immunotherapy, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; AND Used as a single agent or in combination with ipilimumab; OR Used after disease progression, intolerance, and/or projected risk of progression with BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); AND Used as a single agent or in combination with ipilimumab if anti-PD-1 therapy was not previously used; OR Used in combination with ipilimumab for disease progression on single agent anti-PD-1 therapy; OR Used as adjuvant treatment; AND Used as a single agent; AND Patient is at least 12 years of age; AND Patient has stage IIB, stage IIC, or metastatic disease and has undergone complete resection †; OR Patient has stage III disease; AND Patient has undergone complete resection †; OR Patient has sentinel node positive disease either during observation without additional nodal surgery and with mandatory radiographic nodal surveillance OR after complete lymph node dissection

		(CLND); OR Patient has clinically positive node(s) following wide excision of the primary tumor and therapeutic lymph node dissection (TLND) OR following neoadjuvant therapy; OR Patient has clinical satellite/in-transit metastases and has no evidence of disease (NED) after complete excision; OR Used following wide excision alone (stage IIIB/C/D disease only); OR Used following wide excision with negative sentinel lymph node biopsy; OR Used for disease that is sentinel lymph node negative or sentinel lymph node biopsy not performed (stage IIIB/C/D disease only); OR Patient has local satellite/in-transit recurrence and has NED after complete excision; OR Patient has resectable disease limited to nodal recurrence following excision and complete TLND OR following neoadjuvant therapy; OR Patient has oligometastatic disease and NED following metastasis-directed therapy (i.e., stereotactic ablative therapy or complete resection) or systemic therapy followed by resection; OR Used in combination with ipilimumab; AND Patient has oligometastatic disease and no evidence of disease following metastasis directed therapy (i.e., complete resection, stereotactic ablative therapy or TVEC/intralesional therapy) or systemic therapy followed by resection Used as neoadjuvant therapy; AND Used as a single agent or in combination with ipilimumab; AND Patient has stage III disease; AND Used as primary treatment for clinically positive, resectable nodal disease; OR Used for limited resectable disease with clinical satellite/in-transit metastases; OR Patient has limited resectable local satellite/in-transit recurrence; OR Patient has resectable disease limited to nodal recurrence **Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s)or clinical satellite/in-transit metastases, or as well as unresectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease*." Hepatocellular Carcinoma (HCC) †: Removed and reworded: "Used in combination with ipilimumab; AND Patient progressed on or was intolerant to sorafenib; AND Patient has a laboratory confirmed diagnosis of hepatocellular carcinoma; AND Patient has Child-Pugh Class A : Updated with: "Used for one of the following:Patient was previously treated with sorafenib (for use in combination with ipilimumab ONLY) † Patient has unresectable disease and is not a transplant candidate Patient has liver-confined disease that is inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic-disease Patient has metastatic disease or extensive liver tumor burden; AND Used in combination with ipilimumab; AND Patient has Child-Pugh Class A hepatic impairment; AND Used as subsequent therapy for progressive disease; OR Used as a single agent; AND Patient has Child-Pugh Class B hepatic impairment" Non-Small Cell Lung Cancer (NSCLC) † Removed and reworded:" Indicated for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab; OR In combination with ipilimumab, it is indicated for the first line treatment of adult patients with metastatic non small cell lung cancer (NSCLC) whose tumors express PD L1 (≥1%) as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations; OR In combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, it is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations. For the Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer: In combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC)."Added: " Used as neoadjuvant therapy for resectable (tumors ≥ 4 cm or node positive) disease; AND Used in combination with platinum-doublet chemotherapy (e.g., cisplatin/carboplatin in combination with paclitaxel, pemetrexed, or gemcitabine); AND Patient is negative for EGFR or ALK rearrangements; OR

		Used for recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; AND Used as first-line therapy; AND Used for one of the following: Patients with a performance status (PS) 0-1 who have tumors that are negative for actionable molecular biomarkers** ¥; and PD-L1 expression <1% Patients with a PS 0-1 who are positive for one of the following molecular biomarkers: EGFR exon 20, KRAS G12C, BRAF V600E, NTRK1/2/3 gene fusion, MET exon 14 skipping, RET rearrangement, or ERBB2 (HER2)PD-L1 expression-positive (PD-L1 ≥1%) tumors, as detected by an FDA or CLIA compliant test, that are negative for actionable molecular biomarkers** ¥; AND Used in combination with ipilimumab; OR Used in combination with ipilimumab and platinum-doublet chemotherapy(e.g., pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology, or paclitaxel and carboplatin for squamous cell histology, etc.); OR Used as subsequent therapy; AND Used as a single agent; OR Used for one of the following: Patients with a PS 0-1 who are positive for one of the following molecular biomarkers and have received prior targeted therapy§:EGFR exon 19 deletion or exon 21 L858R tumors, EGFR S768I, L861Q, and/or G719X, ALK rearrangement, or ROS1 rearrangement Patients with a PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E, NTRK1/2/3 gene fusion, MET exon 14 skipping, or RET rearrangement; AND Used in combination with ipilimumab; OR Used in combination with ipilimumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology; OR Used in combination with ipilimumab, paclitaxel, and carboplatin for squamous cell histology; OR Used as continuation maintenance therapy in combination with ipilimumab; AND Patient has achieved a response or stable disease following first-line therapy with nivolumab and ipilimumab with or without chemotherapy *** Note: Actionable molecular genomic biomarkers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2). Complete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2) via biopsy and/or plasma testing. If a clinically actionable marker is found, it is reasonable to start therapy based on the identified marker. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.¥ May also be used for patients with KRAS G12C mutation positive tumors".* Renal Cell Carcinoma (RCC) † removed to reword: "Used in combination with ipilimumab; AND Used as initial therapy in patients with advanced or metastatic disease with intermediate or poor risk; OR Used as first-line therapy in patients with relapsed or stage IV disease with favorable risk; OR Used as subsequent therapy in patients with relapsed or stage IV disease OR Used as a single agent; AND Patient has advanced disease with intermediate or poor risk; OR Patient has relapsed, unresectable metastatic disease; AND Used as subsequent therapy for clear cell histology; OR Patient has non-clear cell histology Used in combination with cabozantinib, Used for the first-line treatment of patients with advanced disease; OR Used as subsequent therapy in patients with relapsed or stage IV disease" Added: "Used in combination with ipilimumab; AND Patient has clear cell histology; AND Used as first-line therapy in patients with poor or intermediate risk advanced, relapsed, or stage IV disease; OR Used as first-line therapy in patients with favorable risk relapsed or stage IV disease; OR Used as subsequent therapy in patients with relapsed or stage IV disease Δ; OR Used as a single agent; ANDUsed as subsequent therapy in patients with advanced, relapsed, or stage IV disease and clear cell histology; OR Patient has relapsed or stage IV disease and non-clear cell histology; OR Used in combination with cabozantinib (Cabometyx only); AND Patient has clear cell histology; AND Used as first-line therapy for advanced, relapsed, or stage IV disease; OR Used as subsequent therapy in patients with relapsed or stage IV

		disease Δ; OR Patient has non-clear cell histology; AND Patient has relapsed or stage IV disease" Classical Hodgkin Lymphoma (cHL) † Removed to reword: "Patient has relapsed or progressive disease; AND Patient had an autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin; OR Patient has received 3 or more lines of systemic therapy that includes autologous HSCT" Added: "Used as a single agent; AND Patient has relapsed or progressive disease after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin †; OR Used for disease that is refractory to at least 3 prior lines of therapy including autologous HSCT †; OR Used as palliative therapy in patients > 60 years of age or with poor performance status or with substantial comorbidities; AND Patient has relapsed or refractory disease; OR Used in combination with brentuximab vedotin or ICE (ifosfamide, carboplatin, etoposide) in patients 18 to 60 years of age; AND Used as second-line therapy for relapsed or refractory disease; OR Used as subsequent therapy (if not previously used) for relapsed or refractory disease; AND Patient has a Deauville scale score of 4 or 5 following restaging with FDG-PET/CT" Squamous Cell Carcinoma of the Head and Neck (SCCHN) † Removed to reword: "Patient has recurrent, or metastatic disease; AND Patient has progressed on or after platinum-based therapy; AND"Added: " Patient has Cancer of the Nasopharynx; AND Used in combination with cisplatin and gemcitabine for oligometastatic or metastatic disease; OR Patient has Very Advanced Head and Neck Cancer*; AND Patient has nasopharyngeal cancer; AND Used in combination with cisplatin and gemcitabine for patients with performance status (PS) 0-1; AND Used for one of the following: Unresectable locoregional recurrence with prior radiation therapy (RT) Unresectable second primary with prior RT Unresectable persistent disease with prior RT Recurrent/persistent disease with distant metastases; OR Patient has NON-nasopharyngeal cancer; AND Used as a single agent; AND Patient has unresectable, recurrent, persistent, or metastatic disease; AND Disease has progressed on or after platinum-containing chemotherapy; OR Used in combination with cetuximab for patients with performance status (PS) 0-1; AND Used for one of the following: Metastatic disease at initial presentation Recurrent/persistent disease with distant metastases Unresectable locoregional recurrence with prior RT Unresectable second primary with prior R Unresectable persistent disease with prior RT * *Very Advanced Head and Neck Cancer includes: 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."* Colorectal Cancer † Added:" OR polymerase epsilon/delta (POLE/POLD1) mutation as determined by an FDA approved or CLIA-compliant test" to the following statement: " Adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease OR polymerase epsilon/delta (POLE/POLD1) mutation as determined by an FDA approved or CLIA-compliant test; AND" Removed: "Disease progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab. " Added: "Used as a single agent or in combination with ipilimumab*; AND Used as subsequent therapy; AND Patient has metastatic, unresectable, or medically inoperable disease; OR Used as primary or initial treatment; AND Used for isolated pelvic/anastomotic recurrence of rectal cancer; OR Patient has T3, N Any; T1-2, N1-2; T4, N Any rectal cancer; OR Patient has metastatic, unresectable, or medically inoperable disease; OR Used as neoadjuvant therapy; AND Patient has clinical T4b colon cancer (for dMMR/MSI-H disease ONLY); OR Patent has resectable liver and/or lung metastases; OR Patient has T3, N Any; T1-2, N1-2; T4, N Any, locally unresectable, or medically inoperable rectal cancer (single agent therapy for

		dMMR/MSI-H disease ONLY)* *Single agent nivolumab should be used in patients who are not candidates for intensive therapy"* Urothelial Carcinoma † Added: "Used in combination with cisplatin and gemcitabine followed by nivolumab maintenance therapy; AND Used as first-line systemic therapy in cisplatin eligible patients*; AND Patient has one of the following diagnoses: Locally advanced, unresectable, or metastatic urothelial carcinoma †Muscle invasive bladder cancer with local recurrence or persistent disease in a preserved bladder Metastatic or local bladder cancer recurrence post-cystectomy Recurrent or metastatic primary carcinoma of the urethra; AND Patient does not have recurrence of stage T3-4 disease or palpable inguinal lymph nodes Metastatic upper genitourinary (GU) tract tumors Metastatic urothelial carcinoma of the prostate" Removed:**If platinum treatment occurred greater than 12 months ago, the patient should be re-treated with platinum-based therapy. Patients with comorbidities (e.g., hearing loss, neuropathy, poor PS, renal insufficiency, etc.) may not be eligible for cisplatin. Carboplatin may be substituted for cisplatin particularly in those patients with a GFR <60 mL/min or a PS of 2." Updated with: "* Note: – If patient was progression free for >12 months after platinum therapy, consider re-treatment with platinum-based therapy if the patient is still platinum eligible (see below for cisplatin- or platinumineligible comorbidities). Cisplatin-ineligible comorbidities may include the following: CrCl < 60 mL/min, ECOG PS ≥ 2 or KPS ≤ 70%, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, grade ≥ 2 peripheral neuropathy, or NYHA Heart Failure class ≥ 3. Carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients such as those with a GFR less than 60 mL/min. Platinum-ineligible comorbidities may include the following: CrCl < 30 mL/min, ECOG PS ≥ 3, grade ≥ 2 peripheral neuropathy, or NYHA Heart Failure class > 3, etc."* Esophageal Squamous Cell Carcinoma (ESCC)† Removed to reword: "Patient with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy. The medication is being used as adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT); OR The medication is being used in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC); OR The medication is being used in combination with ipilimumab, for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC); OR The medication is being used for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy." Updated with: " Used as first-line therapy; AND Patient has squamous cell carcinoma †; AND Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; AND Used in combination with ipilimumab*; OR Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; OR Patient has adenocarcinoma; AND Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; AND Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; OR Used in combination with ipilimumab; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA compliant test; OR Used as subsequent therapy; AND Patient has squamous cell carcinoma; AND Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; AND Used as a single agent; OR Used in combination with ipilimumab; AND Patient has microsatellite instability-high (MSI-H) or mismatch

		repair deficient (dMMR) disease as determined by an FDA-approved or CLIA compliant test; OR Patient has adenocarcinoma; AND Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease; AND Used in combination with ipilimumab; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; OR Used as adjuvant treatment of completely resected disease †; AND Used as a single agent in patients with residual disease following neoadjuvant chemoradiotherapy (CRT); OR Used as neoadjuvant or perioperative therapy; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; AND Patient has adenocarcinoma; AND Used in combination with ipilimumab; AND Used as primary treatment for patients who are medically fit for surgery with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, Any N disease; OR Used as a single agent ; AND Used as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab**Note: Combination therapy with ipilimumab OR oxaliplatin and fluorouracil or capecitabine may also be used for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test"* Unresectable Malignant Pleural Mesothelioma (MPM) † Removed to reword: "Used as a first-line therapy: Nivolumab is used in combination with ipilimumab; OR Used as a subsequent systemic therapy‡ As a single agent; OR Nivolumab is used in combination with ipilimumab (if not administered first-line)." Added: " Used as a single agent or in combination with ipilimumab as subsequent therapy (if chemotherapy was administered first-line); OR Used in combination with ipilimumab as first-line therapy; AND Patient has clinical stage IIIB or IV disease; OR Patient has sarcomatoid or biphasic histology; OR Disease is medically inoperable or unresectable; OR Patient has clinical stage I-IIIA disease with epithelioid histology and did not receive induction chemotherapy **Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma."* Gastric Cancer, Gastroesophageal Junction Cancer and Esophageal Adenocarcinoma† Removed "Gastroesophageal Junction Cancer and Esophageal Adenocarcinoma" from the title to separate out. Removed: "The patient has advanced or metastatic disease; AND Opdivo will be used in combination with fluoropyrimidine- and platinum-containing chemotherapy" Added: "Used as first-line therapy; AND Patient is not a surgical candidate or has unresectable, advanced, recurrent, or metastatic disease; AND Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; OR Used in combination with ipilimumab; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; OR Used as subsequent therapy; AND Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease; AND Used in combination with ipilimumab; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; OR Used as neoadjuvant or perioperative therapy; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; AND Used in combination with ipilimumab; AND Used as primary treatment prior to surgery for potentially resectable locoregional disease (cT2 or higher, any N) in patients who are medically fit for surgery; OR Used as a single agent; AND Used as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab **Note: Combination therapy with oxaliplatin and fluorouracil or capecitabine may also be used for*

		patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test" Esophageal Cancer and Esophagogastric/Gastroesophageal Junction Cancers † ‡ Φ Added: " Used as first-line therapy; AND Patient has squamous cell carcinoma †; AND Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; AND Used in combination with ipilimumab*; OR Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; OR Patient has adenocarcinoma; AND Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; AND Used in combination with fluoropyrimidine- and platinum-containing chemotherapy*; OR Used in combination with ipilimumab; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA compliant test; OR Used as subsequent therapy; AND Patient has squamous cell carcinoma; AND Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; AND Used as a single agent; OR Used in combination with ipilimumab; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA compliant test OR Patient has adenocarcinoma; AND Patient is not a surgical candidate or has unresectable locally advanced, recurrent, or metastatic disease; AND Used in combination with ipilimumab; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; OR Used as adjuvant treatment of completely resected disease †; AND Used as a single agent in patients with residual disease following neoadjuvant chemoradiotherapy (CRT); ORUsed as neoadjuvant or perioperative therapy; AND Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test; AND Patient has adenocarcinoma; AND Used in combination with ipilimumab; AND Used as primary treatment for patients who are medically fit for surgery with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, Any N disease; OR Used as a single agent ; AND Used as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab **Note: Combination therapy with ipilimumab OR oxaliplatin and fluorouracil or capecitabine may also be used for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test"* Renewal Criteria: For the following indication, the patient has not exceeded a maximum of twelve (12) months of therapy Added "as a single agent" to the following statement ":Adjuvant treatment of melanoma (as a single agent); OR "For the following indication, the patient has not exceeded a maximum of twenty four (24) months of therapy: Removed: "Esophageal Cancer (in combination with fluoropyrimidine- and platinum-containing chemotherapy OR ipilimumab)" Added: "Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (first-line therapy) MSI-H/dMMR Gastric, Esophageal, and Esophagogastric/Gastroesophageal Junction Cancer (first-line and subsequent therapy Gastric Cancer (in combination with fluoropyrimidine- and platinum-containing chemotherapy **OR** ipilimumab)" Removed: "Esophagogastric/Gastroesophageal Junction Cancer (in combination with fluoropyrimidine- and platinum-containing chemotherapy)" Added:" initial therapy in combination with ipilimumab)" to the following statement: Malignant Pleural Mesothelioma (initial therapy in combination with ipilimumab)" Added: "Urothelial Carcinoma (first line therapy in combination with gemcitabine and cisplatin, followed by single-agent maintenance therapy Classical Hodgkin Lymphoma (in combination with ICE) Patient has not exceeded a maximum of 12 weeks of therapy (6 doses) MSI-H/dMMR Gastric, Esophageal, and Esophagogastric/Gastroesophageal Junction Cancer

		(neoadjuvant or perioperative therapy) Patient has not exceeded a maximum of 12 weeks of pre-operative therapy (6 doses), followed by a maximum of 36 weeks (9 doses) of postoperative therapy after surgery Cutaneous Melanoma (adjuvant therapy in combination with ipilimumab) Patient has not exceeded a maximum of four (4) doses Cutaneous Melanoma (neoadjuvant therapy as a single agent) • Patient has not exceeded a maximum of four (4) doses Cutaneous Melanoma (neoadjuvant therapy in combination with ipilimumab) Patient has not exceeded a maximum of three (3) doses" Removed: "Used for re-treatment of patients who experienced disease control, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; OR Used as subsequent therapy in combination with ipilimumab, in patients who experienced disease relapse and/or progression within 3 months after initial monotherapy with an immune checkpoint-inhibitor; OR Used as a single agent or in combination with ipilimumab if anti-PD-1 was not previously used" Added: "Refer to Initial Criteria Section for criteria (see Cutaneous Melanoma – Used for retreatment of disease as re-induction) Non-Small Cell Lung Cancer (maintenance therapy) Refer to Initial Criteria section for criteria"
EmblemHealth & ConnectiCare	1/29/2024	Annual Review: Initial Criteria: Melanoma †: Added: "Patient is 12 years of age or older" Hepatocellular Carcinoma (HCC): removed "as a single agent" in the Statement: "Used as a single agent; *or* in combination with ipilimumab; AND" and removed Patient has Child-Pugh Class B7 disease Renal Cell Carcinoma (RCC) † Added: "Used as first-line therapy in patients with relapsed or stage IV disease with favorable risk; OR" Removed: "unresectable metastatic disease with clear cell histology; " from the statement: "Used as subsequent therapy in patients with relapsed, unresectable metastatic disease with clear cell histology; or stage IV disease" Added "Used as subsequent therapy in patients with relapsed or stage IV disease" under: Used in combination with cabozantinib, Classical Hodgkin Lymphoma (cHL) † Removed: Must be used as a single agent; Renewal Criteria: Retreatment for Melanoma (metastatic or unresectable disease) Added: "Used as a single agent or in combination with ipilimumab if anti-PD-1 was not previously used" Added NDC 00003-3756-xx
EmblemHealth & ConnectiCare	5/25/2023	Annual Review: <u>Urothelial Carcinoma</u>- Initial Criteria, Added "OR as second-line treatment after chemotherapy other than a platinum;" "Muscle invasive bladder cancer with local recurrence or persistent disease in a preserved bladder ‡;" and "Used as adjuvant therapy †; AND a. Patient has urothelial carcinoma of the bladder, bulbar urethra, prostate with stromal invasion, ureter, or renal pelvis; AND b .Patient underwent radical surgical resection or partial cystectomy; AND c. Patient is at high risk of disease recurrence**" AND "** High risk of disease recurrence is defined as: ypT2-ypT4a or ypN+ for patients who received neoadjuvant cisplatin; OR pT3-pT4a or pN+ for patients who did not receive neoadjuvant cisplatin and are also ineligible for or refused adjuvant cisplatin therapy" <u>Squamous Cell Carcinoma of the Head and Neck;</u> Initial Criteria: Removed "Patient has unresectable disease" and "Must be used as a single agent" Added "Gastric Cancer, Gastroesophageal Junction Cancer and Esophageal Adenocarcinoma" Indications and initial criteria. <u>Esophageal Squamous Cell Carcinoma</u> Initial Criteria: Removed "Patient with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy." Added "The medication is being used as

		adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT); OR B. The medication is being used in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC); OR C. The medication is being used in combination with ipilimumab, for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC); OR D. The medication is being used for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy." RCC: Initial Criteria: Added " Used in combination with cabozantinib, for the first-line treatment of patients with advanced disease." NSCLC: Initial Criteria: added "Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer: in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC)." Renewal Criteria: added "5. For the following indication, the patient has not exceeded a maximum of twenty four (24) months of therapy: b. Esophageal Cancer (in combination with fluoropyrimidine- and platinum-containing chemotherapy OR ipilimumab) c. Esophagogastric/Gastroesophageal Junction Cancer (in combination with fluoropyrimidine- and platinum-containing chemotherapy) e. Malignant Pleural Mesothelioma g.Non-Small Cell Lung Cancer (in combination with ipilimumab with or without platinum-doublet chemotherapy) h.Renal Cell Carcinoma (in combination with cabozantinib)" added "1 Non-Small Cell Lung Cancer (neoadjuvant therapy in combination with platinum-doublet chemotherapy) • Patient has not exceeded a maximum of three (3) cycles 2.Urothelial Carcinoma (adjuvant therapy) • Patient has not exceeded a maximum of one (1) year of therapy 3.Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (adjuvant therapy) • Patient has not exceeded a maximum of one (1) year of therapy 4.Classical Hodgkin Lymphoma (in combination with brentuximab vedotin) • Patient has not exceeded a maximum of twelve (12) weeks of therapy" Updated dosing limits chart
EmblemHealth & ConnectiCare	09/15/2022	Transferred policy to new template
EmblemHealth & ConnectiCare	2/25/2020	Removed small-cell lung cancer indication from policy as per updated FDA labeling and NCCN guideline recommendation
EmblemHealth & ConnectiCare	11/19/2020	Added newest NSCLC indication for patients with no EGFR or ALK genomic tumor aberrations in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy
EmblemHealth & ConnectiCare	10/16/2020	Added Malignant Pleural Mesothelioma indication per FDA label update and NCCN guidelines. Added ICD 10 codes

EmblemHealth & ConnectiCare	06/16/2020	Under Covered Indications (added indication and criteria): Esophageal Squamous Cell Carcinoma (ESCC) and dosing per FDA Label
EmblemHealth & ConnectiCare	06/15/2020	Added dosing limits per FDA label for NSCLC
EmblemHealth & ConnectiCare	06/01/2020	Added under Initial Approval Criteria (NSCLC): In combination with ipilimumab, it is indicated for the first line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD L1 (≥1%) as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations.
EmblemHealth & ConnectiCare	03/30/2020	Added max dosing limits when in combination with ipilimumab for Hepatocellular Carcinoma (HCC)
EmblemHealth & ConnectiCare	01/01/2020	-Under Guideline, added Small Cell Lung Cancer indication, platinum-based chemotherapy and at least one other line of therapy -Under Guideline, added Metastatic Colorectal Cancer indication per FDA label

References

1. Opdivo [package insert]. Princeton, NJ; Bristol-Myers Squibb Company; October 2020. AccessedOctober 2020.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) nivolumab. National Comprehensive Cancer Network, 2018. 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 2020.
3. Scherpereel A, Mazieres J, Greillier L, et al. Second- or third-line nivolumab (Nivo) versus nivo plus ipilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase II trial. [Abstract]. J Clin Oncol 2017;35: Abstract LBA 8507.
4. Walocko FM, Scheier BY, Harms PW, et al. Metastatic Merkel cell carcinoma response to nivolumab. J Immunother Cancer. 2016 Nov 15; 4:79.
5. Tawbi HA-H, Forsyth PAJ, Algazi AP, et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204. J Clin Oncol 2017;35(15_suppl): abstr 9507.
6. Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017 Apr;18(4):446-453. doi: 10.1016/S1470-2045(17)30104-3. Epub 2017 Feb 18.
7. Zhao X, Ivaturi V, Gopalakrishnan M, et al. Abstract CT 101: A model-based exposure-response (E-R) assessment of a nivolumab (NIVO) 4-weekly (Q4W) dosing schedule across multiple tumor types. Cancer Res July 1 2017 (77) (13 Supplement) CT101; **DOI:** 10.1158/1538-7445.AM2017-CT101
8. National Government Services, Inc. Local Coverage Article: Nivolumab (Opdivo®) – Related to LCD L33394 (A54862). Centers for Medicare & Medicaid Services, Inc. Updated on 8/3/2018 with effective date 7/10/2018. Accessed August 2018.