Pembrolizumab (Keytruda®)

NDC CODE(S) 00006-3026-XX KEYTRUDA 100 MG/4ML Solution (MERCK SHARP & DOHME)

DESCRIPTION

Pembrolizumab is a human programmed death receptor (PD-1)-blocking humanized monoclonal antibody. It blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2 by binding to the PD-1 receptor which is found on T-cells. This releases PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response, which results in decreased tumor growth.

POLICY

- Pembrolizumab for the treatment of the following is considered ***medically necessary*** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Adrenal Gland Tumors
  - Anal Carcinoma
  - Central Nervous System Cancers
  - Cervical Cancer
  - Cutaneous Squamous Cell Carcinoma (cSCC)
  - Diffuse Large B-Cell Lymphoma (see Primary Mediastinal Large B-Cell Lymphoma [PMBCL])
  - Endometrial Carcinoma (Uterine Cancer)
  - Esophageal Cancer
  - Gastric or Gastroesophageal Junction Cancer
  - Gestational Trophoblastic Neoplasia
  - Head and Neck Cancers
  - Hepatocellular Carcinoma (HCC)
  - Hodgkin Lymphoma, Classical
  - Melanoma, Cutaneous
  - Melanoma, Uveal
  - Merkel Cell Carcinoma
  - Mesothelioma
  - Microsatellite Instability-High (MSI-H)/ Mismatch Repair Deficient (dMMR) Cancers
  - Mycosis Fungoides/Sézary Syndrome
  - Non-Small Cell Lung Cancer (NSCLC)
  - Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
  - Renal Cell Carcinoma (RCC) (Kidney Cancer)
  - Small Cell Lung Cancer (SCLC)
  - Soft Tissue Sarcoma
  - T-Cell Lymphoma/Extranodal NK, nasal type
  - Thymic Carcinoma
  - Triple Negative Breast Cancer (TNBC)
  - Tumor Mutational Burden-High (TMB-H) Cancer
  - Urothelial Carcinoma (Bladder Cancer)
  - Vulvar Cancer
- Pembrolizumab for the treatment of other conditions/diseases is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL CRITERIA

- Patient is at least 18 years of age (unless otherwise specified); **AND**

Universal Criteria

- Patient has not received previous therapy with a programmed death (PD-1/PD-L1)-directed therapy (e.g., cemiplimab, avelumab, nivolumab, atezolizumab, durvalumab, etc.) unless otherwise specified; AND

Cutaneous Melanoma

- Used as first-line therapy as a single agent for unresectable or metastatic disease; **OR**
- Used as subsequent therapy for unresectable or metastatic* disease after disease progression or maximum clinical benefit from BRAF targeted therapy; **AND**
  - Used as a single agent; AND
    - Anti-PD-1 immunotherapy was not previously used; **OR**
    - Used as re-induction therapy in patients who experienced disease control *(i.e., complete response, partial response, or stable disease with no residual toxicity*) from prior anti-PD-1 immunotherapy but subsequently have disease progression/relapse > 3 months after treatment discontinuation; **OR**
  - Used in combination with ipilimumab; **AND**
    - Used after progression on single-agent anti-PD-1 immunotherapy and combination ipilimumab/anti-PD-1 immunotherapy not previously used; **OR**
    - Used as re-induction therapy in patients who experienced disease control *(i.e., complete response, partial response, or stable disease with no residual toxicity)* from prior combination ipilimumab/anti-PD-1 immunotherapy, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; **OR**
- Used as a single agent for adjuvant treatment; **AND**
  - Patient has lymph node involvement and has undergone complete resection, complete lymph node dissection (CLND), therapeutic lymph node dissection (TLND), or nodal basin ultrasound surveillance; **OR**
  - Patient has satellite/in-transit metastases or recurrence and has no evidence of disease after complete excision; **OR**
  - Patient has undergone TLND and/or complete resection of nodal recurrence; **OR**
  - Patient has undergone complete resection of distant metastatic disease

**Metastatic disease includes stage III clinical satellite/in transit metastases or local satellite/in-transit recurrence in patients with limited resectable and unresectable disease, unresectable nodal recurrence, and disseminated (unresectable) distant metastatic disease*

Uveal Melanoma

- Used as a single agent; **AND**
- Patient has distant metastatic disease

Gastric or Gastroesophageal Junction Cancer

- Patient has recurrent, unresectable (or is not a candidate for surgery) locally advanced, or metastatic disease; **AND**
  - Used as a single agent: **AND**
    - Patient has adenocarcinoma histology; **AND**
    - Tumor expresses PD-L1 (Combined Positive Score [CPS] ≥1) as determined by an FDA-approved or CLIA compliant test**; **AND**
    - Patient progressed on or after at least two prior systemic treatments; **AND**

    - Patients with HER2 positive disease must have previously failed on HER2 directed therapy (e.g., trastuzumab, etc.); **OR**
  - Used in combination with oxaliplatin or cisplatin AND either fluorouracil or capecitabine *(Gastroesophageal Junction Cancer only)*; **AND**
    - Tumor expresses PD-L1 (CPS ≥ 10); **AND**
    - Used as palliative first-line therapy for HER2 negative disease

Esophageal Cancer

- Patient has recurrent, unresectable (or is not a candidate for surgery) locally advanced, or metastatic disease; **AND**
  - Used in combination with oxaliplatin or cisplatin AND either fluorouracil or capecitabine; **AND**
    - Tumor expresses PD-L1 (CPS ≥ 10); **AND**
    - Used as palliative first-line therapy for HER2 negative disease; **OR**
  - ~~o~~ Used as a single agent; **AND**
    - Patient has squamous cell histology; **AND**
      - Tumor expresses PD-L1 (CPS ≥ 10) as determined by an FDA-approved or CLIA compliant test**; **AND**
      - Patient progressed on or after at least one prior systemic treatment; **OR**
    - Patient has adenocarcinoma histology; **AND**
      - Tumor expresses PD-L1 (CPS ≥ 1); **AND**
      - Used as palliative third-line or subsequent therapy; **AND**
      - Patients with HER2 positive disease must have previously failed on HER2 directed therapy (e.g., trastuzumab, etc.)

Merkel Cell Carcinoma (MCC)

- Patient is at least 2 years of age; **AND**
- Used as a single agent; **AND**
  - Patient has recurrent disease AND both curative surgery and curative radiation therapy are not feasible; **OR**
  - Patient has recurrent locally advanced or metastatic disease

Non-Small Cell Lung Cancer (NSCLC)

- Used for stage III disease; **AND**
  - Used as first-line therapy as a single-agent in patients who are not candidates for surgical resection or definitive chemoradiation with tumors that are expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved or CLIA compliant test** and with no EGFR or ALK genomic tumor aberrations; **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:
      - PD-L1 expression-positive (TPS ≥1%) tumors, as detected by an FDA or CLIA compliant test**, that are EGFR, ALK, ROS1, BRAF, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, and RET rearrangement negative*
      - Patients with performance status (PS) 0-1 who have EGFR, ALK, ROS1, BRAF, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, and RET rearrangement negative* tumors and PD-L1 expression <1%
      - Patients with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E mutation, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, or RET rearrangements; **AND**

- Used in combination with pemetrexed AND either carboplatin or cisplatin for non-squamous cell histology; **OR**
- Used in combination with carboplatin AND either paclitaxel or albumin-bound paclitaxel for squamous cell histology; **OR**
- Used as single agent therapy *(for PD-L1 expression-positive tumors ONLY)*; **OR**

- Used as subsequent therapy; **AND**
  - Used in patients with tumors expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved or CLIA compliant test**; **AND**
  - Used as single agent therapy; **OR**
  - Used for one of the following:
    - Patients with PS 0-1 who have EGFR, ALK, or ROS1 positive tumors and prior targeted therapy**§**
    - Patients with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E mutations, NTRK1/2/3 gene fusions, MET exon 14 skipping mutation or RET rearrangements; **AND**
      - Used in combination with carboplatin AND either paclitaxel or albumin-bound paclitaxel for squamous cell histology; **OR**
      - Used in combination with pemetrexed AND either carboplatin or cisplatin for non-squamous cell histology; **OR**
- Used as continuation maintenance therapy in patients who have achieved tumor response or stable disease following initial therapy; **AND**
  - Used in combination with pemetrexed following a first-line pembrolizumab/pemetrexed/(carboplatin or cisplatin) regimen for disease of nonsquamous cell histology; **OR**
  - Used as a single agent following a first-line pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel) regimen for disease of squamous cell histology; **OR**
  - Used as a single agent following a first-line pembrolizumab monotherapy regimen

** Note: If there is insufficient issue to allow testing for all of EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET and RET, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.*

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- Patient has unresectable, recurrent/persistent, or metastatic disease; **AND**
  - Used as first-line therapy; **AND**
    - Used as a single-agent for tumors expressing PD-L1 (CPS ≥1) as determined by an FDA-approved or CLIA-compliant test**; **OR**
    - Used in combination with fluorouracil and a platinum chemotherapy agent; **OR**
  - Used as subsequent therapy; **AND**
    - Used as a single-agent therapy for disease that has progressed on or after platinum-containing chemotherapy; **OR**
    - Used in combination with fluorouracil and a platinum chemotherapy agent in patients with non-nasopharyngeal disease and performance status 0-1

Adult Classical Hodgkin Lymphoma (cHL)

- Used as a single agent for relapsed or refractory disease

Pediatric Classical Hodgkin Lymphoma

- Patient is at least 2 years of age*; **AND**
- Used as a single agent; **AND**

- Patient has refractory disease; **OR**
- Patient has relapsed disease after two or more prior lines of therapy; **OR**
- Used in patients heavily pretreated with platinum or anthracycline-based chemotherapy; **OR**
- Used as subsequent therapy in patients with an observed decrease in cardiac function

** Pediatric Classical Hodgkin Lymphoma may be applicable to adolescent and young adult (AYA) patients up to the age of 39 years.*

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- Patient is at least 2 years of age; **AND**
- Used as single agent; **AND**
- Patient has relapsed or refractory disease; **AND**
- Patient does not require urgent cytoreductive therapy

Urothelial Carcinoma (Bladder Cancer)

- Patient has Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) defined as one of the following:
  - Persistent disease despite adequate BCG therapy*; **OR**
  - Disease recurrence after an initial tumor free state following an adequate BCG course of therapy*; **OR**
  - T1 disease following a single induction course of BCG; **AND**
  - Patient has carcinoma in situ (CIS); **AND**
  - Patient is ineligible for or has elected not to undergo cystectomy; **AND**
  - Used as a single agent

** Adequate BCG therapy is defined as administration of at least five of six doses of an initial induction course AND at least two of three doses of maintenance therapy or at least two of six doses of a second induction course*

- OR -

- Used as a single agent; **AND**
- Patient has one of the following diagnoses:
  - Locally advanced or metastatic urothelial carcinoma; **OR**
  - Muscle invasive bladder cancer with local recurrence or persistent disease in a preserved bladder; **OR**
  - Metastatic or local bladder cancer recurrence post-cystectomy; **OR**
  - Primary carcinoma of the urethra; **AND**
    - Used for metastatic or recurrent disease *(excluding recurrence of stage T3-4 disease*
    - *or palpable inguinal lymph nodes)*; **OR**
    - Used for clinical stage T3-4, cN1-2 disease, or cN1-2 palpable inguinal lymph nodes *(first-line therapy only)*; **AND**
  - Metastatic upper genitourinary (GU) tract tumors; **OR**
  - Metastatic urothelial carcinoma of the prostate; **AND**
- Used as subsequent therapy after previous platinum treatment*; **OR**
- Used as first-line therapy in cisplatin-ineligible patients*; **AND**
  - Patient is carboplatin-ineligible*; **OR**
  - Tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved or CLIA-compliant test**

** Note:*

- *If platinum treatment occurred greater than 12 months ago, the patient should be re-treated with platinum-based therapy if the patient is still platinum eligible (see below for cisplatin- or carboplatin-ineligible comorbidities).*
  - *Cisplatin-ineligible comorbidities may include the following: GFR < 60 mL/min, PS ≥ 2, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, or grades ≥ 2 peripheral neuropathy. Carboplatin may be substituted for cisplatin particularly in those patients with a GFR <60 mL/min or a PS of 2.*
  - *Carboplatin-ineligible comorbidities may include the following: GFR < 30 mL/min, PS ≥ 3, grade ≥ 3 peripheral neuropathy, or NYHA class ≥ 3, etc.*

Cervical Cancer

- Used as a single agent: **AND**
- Patient has persistent, recurrent, or metastatic disease; **AND**
- Tumor expresses PD-L1 (e.g., CPS ≥1) as determined by an FDA-approved or CLIA-compliant test**; **AND**
- Disease has progressed on or after chemotherapy

Microsatellite Instability-High (MSI-H) Cancer

- Patient must be at least 2 years of age; **AND**
- Used as a single agent; **AND**
- Patient's disease must be microsatellite instability-high (MSI-H) or mismatch repair
- deficient (dMMR); **AND**
- Pediatric patients must not have a diagnosis of MSI-H central nervous system cancer; **AND**
- Patient has one of the following cancers:
  - Colorectal Cancer
    - Used as first-line therapy ~~in patients with~~ for unresectable (or medically inoperable) or metastatic disease; **OR**
    - Used as primary treatment for resectable liver and/or lung metastases (Rectal Cancer only); **OR**
    - Used as neoadjuvant therapy for resectable liver and/or lung metastases (Colon Cancer only); **OR**
    - Used for unresectable metastases that remain unresectable after primary systemic therapy; **OR**
    - Used for disease progression on non-intensive therapy with improvement in functional status (excluding patients previously treated with fluoropyrimidine); **OR**
    - Used for unresectable, advanced, or metastatic disease that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and/or irinotecan
  - Pancreatic Adenocarcinoma
    - Used as ~~second-line~~ subsequent therapy for locally advanced or metastatic disease after progression; **OR**
    - Used for recurrent or metastatic disease after resection; **OR**
    - Used as first-line therapy for metastatic disease ~~for~~ in patients with poor performance status (i.e., ECOG ≥2)
  - Bone Cancer (Ewing Sarcoma, Chondrosarcoma *[excluding dedifferentiated or mesenchymal subtypes], or Osteosarcoma [excluding high-grade undifferentiated pleomorphic sarcoma]*)
    - Used for unresectable or metastatic disease that has progressed following prior treatment; **AND**
    - Patient has no satisfactory alternative treatment options
  - Gastric Adenocarcinoma OR Esophageal/Gastroesophageal Junction Adenocarcinoma or Squamous Cell Carcinoma
    - Used as subsequent therapy for unresectable (or not a candidate for surgery) locally advanced, recurrent, or metastatic disease
  - Ovarian Cancer (epithelial ovarian, fallopian tube, and primary peritoneal cancers)

- Patient has carcinosarcoma, clear cell, endometrioid, mucinous, or serous histology; **AND**
- Used for patients with persistent or recurrent disease; **AND**
- Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 with no radiographic evidence of disease)

- Uterine Cancer (endometrial carcinoma)
  - Patient has recurrent, metastatic, or high-risk disease that has progressed following prior treatment
- Penile Cancer
  - Used as subsequent treatment of unresectable or metastatic disease that has progressed following prior treatment; **AND**
  - Patient has no satisfactory alternative treatment options
- Testicular Cancer
  - Used as third-line therapy
- Hepatobiliary Adenocarcinoma (gallbladder cancer, intra-/extra-hepatic cholangiocarcinoma)
  - Used as primary treatment for unresectable or metastatic disease; **OR**
  - Used for unresectable or metastatic disease that has progressed following prior treatment
- Vulvar Squamous Cell Carcinoma
  - Used for advanced, recurrent, or metastatic disease as second-line therapy
- Cervical Cancer
  - Used as second-line therapy for persistent, recurrent, or metastatic disease
- Small Bowel Adenocarcinoma or Advanced Ampullary Cancer
  - Used for advanced or metastatic disease
- Breast Cancer
  - Used for recurrent, metastatic, or unresectable disease that has progressed following prior treatment; **AND**
  - Patient has no satisfactory alternative treatment options
- Occult Primary/Cancer of Unknown Primary (CUP)
  - Used ~~for~~ in symptomatic patients with PS 1-2 OR asymptomatic patients with PS 0 and aggressive disease; **AND**
  - Patient has adenocarcinoma or carcinoma not otherwise specified; **AND**
  - Patient has one of the following:
    - Axillary involvement in men if clinically indicated
    - Lung nodules or breast marker-negative pleural effusion
    - Resectable liver disease
    - Peritoneal mass or ascites with non-ovarian histology
    - Retroperitoneal mass of non-germ cell histology in selected patients
    - Unresectable liver disease or disseminated metastases
- Very Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN)
  - Patient has non-nasopharyngeal cancer
- Prostate Cancer
  - Patient has castration-resistant metastatic disease; **AND**
  - Patient will continue androgen deprivation therapy (ADT); **AND**
  - Patient previously received docetaxel or novel hormone therapy; **OR**
  - Patient previously received docetaxel and novel hormone therapy; **AND**
    - Patient does not have visceral metastases
- Other Solid Tumor (e.g., adrenal gland tumors, poorly differentiated-high grade neuroendocrine tumors [NET], large or small cell carcinoma [other than lung], etc.)
  - Used for unresectable or metastatic disease that progressed following prior treatment; **AND**
  - Patient has no satisfactory alternative treatment options

Vulvar Squamous Cell Carcinoma

- Used as a single agent; **AND**
- Patient has advanced, recurrent, or metastatic disease; **AND**
- Tumor expresses PD-L1 (CPS ≥1) as determined by an FDA-approved or CLIA-compliant test**; **AND**
- Used as second-line therapy for disease progression on or after chemotherapy

Thymic Carcinoma

- Used as a single agent; **AND**
  - Used, as first line therapy or postoperative treatment, in patients who are unable to tolerate first-line combination regimens; **OR**
  - Used as second-line therapy for unresectable or metastatic disease

Malignant Pleural Mesothelioma

- Used as subsequent therapy as a single agent

Central Nervous System (CNS) Cancer

- Used as single agent therapy; **AND**
- Primary tumor is due to melanoma or PD-L1 positive non-small cell lung cancer (NSCLC); **AND**
  - Used as initial treatment in patients with small asymptomatic brain metastases; **OR**
  - Used for relapsed disease in patients with limited brain metastases and stable systemic disease or reasonable treatment options; **OR**
  - Patient has recurrent limited brain metastases; **OR**
  - Used for recurrent disease in patients with extensive brain metastases and stable systemic disease or reasonable systemic treatment options

T-Cell Lymphoma/Extranodal NK

- Patient has relapsed or refractory nasal type disease; **AND**
- Disease progressed following additional treatment with an alternative asparaginase-based chemotherapy regimen not previously used; **AND**
- Participation in a clinical trial is unavailable

Anal Carcinoma

- Patient has metastatic squamous cell disease; **AND**
- Used as a single agent for subsequent therapy

Gestational Trophoblastic Neoplasia

- Used as single-agent therapy for multiagent chemotherapy-resistant disease; AND
  - Patient has intermediate placental site trophoblastic (PSTT) or epithelioid trophoblastic tumor (ETT); **AND**
    - Patient has recurrent or progressive disease; **AND**
    - Patient was previously treated with a platinum/etoposide -containing regimen; **OR**
  - Patient has methotrexate-resistant high risk disease (i.e., FIGO stages II-III and ≥7 Prognostic score OR FIGO stage IV disease)

Small Cell Lung Cancer (SCLC)

- Used as a single agent for subsequent therapy; **AND**
  - Used for metastatic disease with progression on or after platinum-based treatment and at least one other line of therapy; **OR**
  - Patient relapsed within 6 months following a complete or partial response or after stable disease with initial treatment; **AND**
    - Patient did not relapse while on maintenance atezolizumab or durvalumab; **OR**
  - Patient has primary progressive disease

Hepatocellular Carcinoma (HCC)

- Used as a single agent; **AND**
- Patient progressed on or was intolerant to sorafenib; **AND**
- Patient has Child-Pugh Class A liver impairment (i.e., excluding Child-Pugh Class B and C)

Mycosis Fungoides/Sezary Syndrome

- Used as primary therapy OR for relapsed or persistent disease; **AND**
  - Patient has stage III Mycosis Fungoides; **OR**
  - Patient has stage IV Sezary Syndrome; **OR**
- Used for disease refractory to multiple previous therapies

Renal Cell Carcinoma (RCC)

- Patient has advanced, relapsed, or metastatic disease; **AND**
- Patient has clear cell histology; **AND**
- Used in combination with axitinib

Endometrial Carcinoma (Uterine Cancer)

- Patient has advanced or recurrent disease; **AND**
- Disease has progressed following prior systemic therapy; **AND**
- Patient is not a candidate for curative surgery or radiation; **AND**
- Used in combination with lenvatinib

Soft Tissue Sarcoma

- Used as a single agent; **AND**
  - Patient has alveolar soft part sarcoma (ASPS); **OR**
  - Patient has cutaneous angiosarcoma; **OR**
  - Patient has myxofibrosarcoma, undifferentiated pleomorphic sarcoma (UPS), or undifferentiated sarcoma (Retroperitoneal/Intra-Abdominal or Extremity/Body Wall, Head/Neck soft tissue sarcomas); **AND**
    - Used as subsequent therapy for advanced or metastatic disease

Tumor Mutational Burden-High (TMB-H) Cancer

- Patient must be at least 2 years old; **AND**
- Patient has solid tumors that are tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] as determined by an FDA-approved or CLIA-compliant test**; **AND**
- Used as a single agent; **AND**
- Pediatric patients must not have a diagnosis of TMB-H central nervous system cancer; **AND**

- Patient has one of the following cancers:
  - Bone Cancer (Ewing Sarcoma, Chordoma, Chondrosarcoma *[excluding dedifferentiated or mesenchymal subtypes]*, or Osteosarcoma *[excluding undifferentiated pleomorphic sarcoma]*)
    - Patient has unresectable or metastatic disease that progressed following prior treatment; **AND**
    - Patient has no satisfactory alternative treatment options
  - Breast Cancer
    - Patient has unresectable or metastatic disease that progressed following prior treatment; **AND**
    - Patient has no satisfactory alternative treatment options
  - Cervical Cancer
    - Used as second-line therapy for unresectable or metastatic disease; **AND**
    - Patient has no satisfactory alternative treatment options
  - Gastric Adenocarcinoma OR Esophageal/Gastroesophageal Junction Adenocarcinoma or Squamous Cell Carcinoma
    - Used as subsequent therapy for unresectable (or not a candidate for surgery) locally advanced, recurrent, or metastatic disease
  - Salivary Gland Tumors
    - Used for recurrent metastatic disease in patients with a PS 0-3; **OR**
    - Used for unresectable locoregional recurrence or second primary with prior radiation therapy
  - Thyroid Carcinoma
    - Anaplastic Carcinoma
      - Patient has metastatic disease
    - Follicular Carcinoma, Papillary Carcinoma, Hürthle Cell Carcinoma
      - Used for unresectable recurrent, persistent, or metastatic disease not amenable to radioactive iodine (RAI)
    - Medullary Carcinoma
      - Patient has unresectable, recurrent, or persistent metastatic disease
  - Uterine Cancer (uterine sarcoma *[excluding low-grade endometrial stromal sarcoma]*, endometrial carcinoma)
    - Patient has unresectable or metastatic disease that progressed following prior treatment; **AND**
    - Patient has no satisfactory alternative treatment options
  - Vulvar Squamous Cell Carcinoma
    - Used for ~~unresectable~~ advanced, recurrent, or metastatic disease as second-line therapy; **AND**
    - Patient has no satisfactory alternative treatment options
  - Testicular Cancer
    - Used as third-line therapy
  - Occult Primary/Cancer of Unknown Primary (CUP)
    - Used in symptomatic patients with PS 1-2 OR asymptomatic patients with PS 0 and aggressive disease; **AND**
      - Patient has squamous cell carcinoma; **AND**
        - Patient has multiple lung nodules, pleural effusion, or disseminated metastases; **OR**
      - Patient has adenocarcinoma or carcinoma not otherwise specified; **AND**
        - Patient has one of the following:
          - Axillary involvement in men if clinically indicated
          - Lung nodules or breast marker-negative pleural effusion
          - Resectable liver disease
          - Peritoneal mass or ascites with non-ovarian histology
          - Retroperitoneal mass of non-germ cell histology in selected patients
          - Unresectable liver disease or disseminated metastases
  - Other Solid Tumor (e.g., poorly differentiated-high grade-neuroendocrine tumors [NET], large or small cell carcinoma [other than lung], etc.)
    - Patient has unresectable or metastatic disease that progressed following prior treatment; **AND**

- Patient has no satisfactory alternative treatment options

Cutaneous Squamous Cell Carcinoma (cSCC)

- Used as a single agent; **AND**
- Patient has locally advanced, inoperable, or not fully resectable, recurrent, or metastatic disease that is not curable by surgery or radiation

Adrenal Gland Tumors

- Patient has metastatic adrenocortical carcinoma (ACC)

Triple Negative Breast Cancer (TNBC)

- Used in combination with chemotherapy; **AND**
- Patient has recurrent unresectable or metastatic disease; **AND**
- Tumor expresses PD-L1 (CPS ≥10) as determined by an FDA-approved or CLIA-compliant test**

***If confirmed using an immunotherapy assay-http://www.fda.gov/companiondiagnostics*

Genomic Aberration Targeted Therapies (***not all inclusive, refer to guidelines for appropriate use***)
Sensitizing *EGFR* mutation-positive tumors Afatinib Dacomitinib Erlotinib Gefitinib Osimertinib
ALK rearrangement-positive tumors Alectinib Brigatinib Ceritinib Crizotinib Lorlatinib
ROS1 rearrangement-positive tumors Ceritinib Crizotinib Entrectinib
BRAF V600E-mutation positive tumors Dabrafenib±Trametinib Vemurafenib
NTRK Gene Fusion positive tumors Entrectinib Larotrectinib
PD-L1 expression-positive tumors (≥1%)

Atezolizumab Entrectinib Pembrolizumab
MET Exon-14 skipping mutations Capmatinib Crizotinib
RET rearrangement-positive tumors Cabozantinib Selpercatinib Vandetanib

RENEWAL CRITERIA

- Patient continues to meet universal and other indication-specific relevant criteria identified in Initial Approval Criteria; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion reactions, severe immune-mediated adverse reactions (e.g., pneumonitis, hepatitis, colitis, endocrinopathies, nephritis and renal dysfunction, dermatologic adverse reactions/rashes, hypophysitis, thyroid disorders, etc.), hepatoxicity when used in combination with axitinib, etc.; AND
- For the follow indications, patient has not exceeded a maximum of twenty-four (24) months of therapy:
  - Squamous Cell Carcinoma of the Head and Neck (SCCHN)
  - Non-Small Cell Lung Cancer (NSCLC)
  - Classical Hodgkin Lymphoma (cHL)
  - Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
  - Bladder Cancer/Urothelial Carcinoma
  - MSI-H/dMMR Cancer (including the following cancers: colorectal, pancreatic, bone, gastric/gastroesophageal, ovarian, uterine, penile, testicular, hepatobiliary, occult primary, and other solid tumors)
  - Anal Carcinoma
  - Malignant Pleural Mesothelioma (MPM)
  - Gastric/GEJ Cancer
  - Esophageal Cancer
  - Cervical Cancer
  - Vulvar Squamous Cell Carcinoma
  - Merkel Cell Carcinoma (MCC)
  - Mycosis Fungoides/Sezary Syndrome
  - Renal Cell Carcinoma (RCC)
  - Small Cell Lung Cancer (SCLC)
  - Hepatocellular Carcinoma (HCC)
  - Endometrial Carcinoma
  - Thymic Carcinoma
  - Uveal Melanoma
  - Tumor Mutational Burden-High Cancer (including the following cancers: bone, cervical, salivary gland, thyroid, uterine, vulvar, testicular, occult primary, and other solid tumors)
  - Cutaneous Squamous Cell Carcinoma (cSCC)

- Triple Negative Breast Cancer (TNBC)

Cutaneous Melanoma (adjuvant treatment)

- Patient has not exceeded a maximum of twelve (12) months of therapy

Cutaneous Melanoma (subsequent treatment after prior anti-PD-1 immunotherapy)

- Refer to Initial Approval Criteria

Continuation Maintenance Therapy for NSCLC

- Refer to Initial Approval Criteria

DOSAGE/ADMINISTRATION

INDICATION	DOSE
NSCLC, SCLC, HCC, SCCHN, Gastric, GEJ, Esophageal, Cervical, Bladder Cancer/ Urothelial Carcinoma, RCC, Endometrial Carcinoma (that is NOT MSI-H/dMMR), cSCC, & TNBC	200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks up to a maximum of 24 months in patients without disease progression or unacceptable toxicity **NMIBC treatment may continue up to a maximum of 24 months in patients without persistent or recurrent disease, disease progression, or unacceptable toxicity.*
Thymic Carcinoma & Vulvar Carcinoma	200 mg intravenously every 3 weeks up to a maximum of 24 months in patients without disease progression or unacceptable toxicity
Cutaneous Melanoma	Single agent therapy (excluding adjuvant treatment): 200 mg intravenously every 3 weeks or 400 mg every 6 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: 200 mg intravenously every 3 weeks up to a maximum of 24 months in patients without disease progression or unacceptable toxicity Adjuvant treatment: 200 mg intravenously every 3 weeks or 400 mg every 6 weeks up to a maximum of 12 months in patients without disease recurrence or unacceptable toxicity
Uveal Melanoma	2 mg/kg intravenously every 3 weeks until up to a maximum of 24 months in patients without disease progression or unacceptable toxicity
CNS metastases	10 mg/kg intravenously every 2 weeks until progression or unacceptable toxicity
cHL, PMBCL, MCC, MSI-H/dMMR Cancer, TMB-H Cancer	Adults*: 200 mg intravenously every 3 weeks or 400 mg every 6 weeks Pediatrics*: 2 mg/kg (up to 200 mg) intravenously every 21 days **Up to a maximum of 24 months in patients without disease progression or unacceptable toxicity*
MPM	10 mg/kg intravenously every 2 weeks for up to 24 months or until confirmed progression or unacceptable toxicity
NK/T-Cell Lymphoma	2 mg/kg intravenously every 3 weeks
MF/SS	2 mg/kg intravenously every 3 weeks up to a maximum of 24 months in patients without disease progression or unacceptable toxicity

Gestational Trophoblastic Tumor	200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks
Soft Tissue Sarcoma & Adrenal Gland Tumors (NOT MSIH/dMMR)	200 mg intravenously every 3 weeks
Anal Carcinoma	200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks or 2 mg/kg intravenously every 3 weeks, up to a maximum of 24 months in patients without disease progression or unacceptable toxicity
Dosing should be calculated using actual body weight and not flat dosing (as applicable) based on the following: • Standard dose 200 mg IV every 3 weeks for patients > 50 kg • Use 100 mg IV every 3 weeks for patients ≤ 50 kg -OR- • Standard dose 400 mg IV every 6 weeks for patients weighing > 82.5 kg • Use 300 mg IV every 6 weeks for patients weighing between 56 to 82.5 kg • Use 200 mg IV every 6 weeks for patients weighing ≤ 55 kg *Note: This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide. Patient-specific variables should be taken into account.*	

LENGTH OF AUTHORIZATION

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

- SCCHN, cHL, NSCLC, SCLC, HCC, Bladder Cancer/Urothelial Carcinoma, MPM, MSIH/dMMR, PMBCL, Cervical, Anal, Vulvar, MCC, Mycosis Fungoides/Sezary Syndrome, RCC, Thymic, Esophageal, GEJ, Gastric, Uveal Melanoma, TMB-H Cancer, cSCC, Endometrial Carcinoma, TNBC and Cutaneous Melanoma (in combination with ipilimumab) can be authorized up to a maximum of twenty-four (24) months of therapy.
- Adjuvant therapy in cutaneous melanoma can be authorized up to a maximum of twelve (12) months of therapy.

DOSING LIMITS

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

Indication	Billable Units (BU)	Per unit time (days)
SCCHN, cHL, NSCLC, SCLC, Melanoma, Urothelial, Gastric, Esophageal, GEJ, PMBCL, Cervical, Vulvar, MSI- H/dMMR, MCC, RCC, Thymic, HCC, Gestational Trophoblastic Tumor, Soft Tissue Sarcoma, TMB-H Cancer, cSCC, Endometrial Carcinoma (that is not MSI-H/dMMR), Adrenal Gland Tumors (that are not MSI-H/dMMR), & TNBC	200 BU	21 days
MPM & CNS metastases	1150 BU	14 days
Anal Carcinoma, NK/T-Cell Lymphoma, MF/SS, & Uveal Melanoma	250 BU	21 days

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-

label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

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