Policy Title:	Keytruda (pembrolizumab) (Intravenous)		
Policy Number:	000692	**Department:**	PHA
Effective Date:	09/01/2019		
Review Date:			
Revision Date:			

Purpose: To support safe, effective and appropriate use of Keytruda (pembrolizumab).

Scope: Medicaid, Exchange, Integrity

Policy Statement: Keytruda (pembrolizumab) is covered under the Medical Benefit when used within the following guidelines. Use outside of these guidelines may result in non-payment unless approved under an exception process.

Procedure: Coverage of Keytruda (pembrolizumab) will be reviewed prospectively via the prior authorization process based on criteria below.

Initial Criteria Coverage:

- 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., cemiplimab, avelumab, nivolumab, atezolizumab, durvalumab, etc.) unless otherwise specified; AND

Melanoma †

- Used as a single agent; AND
  - Patient has unresectable or metastatic disease; OR
  - Used as adjuvant treatment; OR
  - Patient has unresectable or metastatic Uveal Melanoma; OR
  - Used as re-induction therapy for Melanoma (metastatic or unresectable disease) in patients who experienced disease control, but subsequently have disease progression/relapse > 3 months after treatment discontinuation.

Gastric Cancer †

- Used as a single agent; AND
- Patient has gastric or gastro-esophageal junction adenocarcinoma; AND
- Patient has recurrent, unresectable (or is not a candidate) locally advanced, or metastatic disease; AND
- Tumor expresses PD-L1 (Combined Positive Score [CPS] ≥1%) as determined by an FDA-approved test; AND

- Patient progressed on or after at least two prior systemic treatments which must have included a fluoropyrimidine and platinum-containing regimen; AND
- Patients with HER2 positive disease must have previously failed on HER2 directed therapy.

Merkel Cell Carcinoma ‡

- Patients must be at least 2 years old; AND
- Used as a single agent; AND
- Patient has recurrent locally advanced or metastatic disease.

Non-Small Cell Lung Cancer (NSCLC) †

- Tumor has high PD-L1 expression (Tumor Proportion Score [TPS] ≥50%) as determined by an FDA-approved test; AND
    - Used as continuation maintenance therapy for recurrent (excluding locoregional recurrent without evidence of disseminated disease), advanced, or metastatic disease and performance status (PS) ≤ 2; AND
        - Patient tumors are EGFR, ALK negative or unknown and patient achieved tumor response or stable disease following initial therapy; AND
        - Used in combination with pemetrexed; AND
            - ❖ Pembrolizumab was given first-line in combination with pemetrexed and either carboplatin or cisplatin for disease of non-squamous cell histology; OR
        - Used as a single agent; AND
            - ❖ Pembrolizumab was given first-line or following systemic therapy in combination with carboplatin or cisplatin AND paclitaxel or nabpaclitaxel for disease of squamous cell histology; OR
            - ❖ Pembrolizumab was given first-line or following systemic therapy as a single agent for disease of squamous or non-squamous cell histology; OR
- Used for recurrent (excluding locoregional recurrent without evidence of disseminated disease), advanced, or metastatic disease that are EGFR, ALK negative or unknown; AND
    - Used as initial therapy and a PS ≤ 2:
        - In combination with pemetrexed AND either carboplatin or cisplatin for nonsquamous cell histology; OR
        - In combination with carboplatin or cisplatin AND either paclitaxel or albumin-bound paclitaxel for squamous cell histology; OR
        - As single agent therapy; OR
    - Used as subsequent therapy and a PS ≤ 1 with no prior platinum doublet therapy, in combination with:
        - Pemetrexed AND either carboplatin or cisplatin for nonsquamous cell histology; OR
        - Carboplatin or cisplatin AND either paclitaxel or albumin-bound paclitaxel for squamous cell histology.
- Tumor expresses PD-L1 (TPS ≥1%) as determined by an FDA-approved test; AND
    - Used as a single agent for recurrent (excluding locoregional recurrent without evidence of disseminated disease), advanced, or metastatic disease; AND
        - Disease must have progressed during or following cytotoxic therapy; AND

        - Patients with genomic tumor aberrations must have progressed following systemic therapy for those aberrations (e.g., EGFR, ALK, etc.). §See chart below
- Used for recurrent (excluding locoregional recurrent without evidence of disseminated disease), advanced, or metastatic disease with PS ≤ 1 in combination with:
    - Pemetrexed AND carboplatin or cisplatin for non-squamous cell histology; OR
    - Carboplatin or cisplatin AND paclitaxel or nab-paclitaxel for squamous cell histology; AND
        - Used as first-line therapy for genomic tumor aberration (e.g., EGFR, ALK, ROS1 and BRAF) negative or unknown**, and PD-L1 expression < 50% or unknown; OR
        - Used as first-line therapy for BRAF V600E-mutation positive tumors; OR
        - Used as subsequent therapy for genomic tumor aberration (e.g., EGFR, BRAF V600E, ALK, and ROS1) positive and prior targeted therapy§; OR
- Used for continuation maintenance therapy (excluding locoregional recurrent without evidence of disseminated disease); AND
    - Patient achieved tumor response or stable disease following initial systemic therapy; AND
    - Patient has PS 0-2; AND
    - Patient has recurrent, advanced, metastatic disease; AND
        - Given in combination with pemetrexed if given 1st line with carbo-/cis-plating and pemetrexed for nonsquamous cell histology; OR
        - Used as a single agent if given 1st line with carbo-/cis-platin and paclitaxel/nab-paclitaxel for squamous cell histology.

**Every effort needs to be made to establish the genetic alteration status. A blood assay may be used if a tissue assay is not feasible.

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

- Used as a single agent; AND
- Patient has unresectable, recurrent, persistent or metastatic disease; AND
- Patient has non-nasopharyngeal disease; AND
- Disease progressed on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma (cHL) †

- Used as a single agent; AND
- Patients must be at least 2 years old; AND
    - Patient relapsed after three or more prior lines of therapy; OR
    - Used for refractory disease.

Primary Mediastinal Large B-Cell Lymphoma (PMBCL) †

- Used as single agent; AND
- Patient has relapsed or refractory disease; AND
- Patient must be at least 2 years old; AND
- Used after two or more prior lines of therapy.

Bladder Cancer/Urothelial Carcinoma † ‡

- Must be used as a single agent; AND
- Patient has one of the following diagnoses:
    - Locally advanced or metastatic Urothelial Carcinoma; OR
    - Disease recurrence post-cystectomy; OR
    - Primary Carcinoma of the Urethra; AND
        - Used for recurrent or metastatic disease and the patient does not have recurrence of stage T3-4 disease or palpable inguinal lymph nodes; OR
        - Used as primary treatment for clinical stage T3-4, cN1-2 disease or cN1-2 palpable inguinal lymph nodes; OR
    - Metastatic Upper 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
- Patient has a PD-L1 expression of ≥10%**

*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 < 60mL/min or a PS of 2.

**As confirmed using an immunotherapy assay such as the PD-L1 IHC 22C3 pharmDx.

Cervical Cancer †

- Used as a single agent; AND
- Patient has recurrent or metastatic disease; AND
- Tumor expresses PD-L1 (combined positive score [CPS ≥1]) as determined by an FDA approved test; AND
- Disease progressed on or after chemotherapy.

Microsatellite Instability-High (MSI-H) Cancer †

- Patient must be at least 2 years old; 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 ‡
    - Initial therapy in patients with unresectable or metastatic disease who are not candidates for intensive therapy; OR
    - Used as primary treatment in patients with unresectable or metastatic disease who failed adjuvant treatment with FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine-oxaliplatin) in the previous 12 months; OR
    - Used for unresectable or metastatic disease that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan †
  - Pancreatic Adenocarcinoma ‡
    - Second-line therapy for locally advanced, recurrent, or metastatic disease after progression for patients with good (ECOG 0-1) performance status (PS).
  - Bone Cancer (Ewing Sarcoma, Mesenchymal Chondrosarcoma, Osteosarcoma, Dedifferentiated Chondrosarcoma, or High-Grade Undifferentiated Pleomorphic Sarcoma) ‡
    - Used for unresectable or metastatic disease after progression following prior treatment and patient has no satisfactory alternative treatment options.
  - Gastric adenocarcinoma OR esophageal/gastroesophageal junction adenocarcinoma or squamous cell carcinoma ‡
    - Subsequent therapy for unresectable (or not a candidate) locally advanced, recurrent, or metastatic disease; AND
    - Patient has a performance score of ECOG ≤ 2 or Karnofsky ≥ 60%.
  - Ovarian Cancer (epithelial ovarian, fallopian tube, and primary peritoneal cancers) ‡
    - Used for patients with persistent or recurrent disease; AND
    - Patient is not experiencing an immediate biochemical relapse.
  - Uterine Cancer (Endometrial Carcinoma) ‡
    - Used for patients with high risk tumors, or recurrent or metastatic disease, that have progressed following prior cytotoxic chemotherapy.
  - Penile Cancer ‡
    - Used as subsequent treatment of unresectable or metastatic disease that is progressive and there are no other satisfactory treatment options.
  - Testicular Cancer ‡
    - Used as single-agent third-line therapy.
  - Hepatobiliary Cancer (Gall bladder cancer; intra-/extra-hepatic cholangiocarcinoma) ‡
    - Used as initial therapy for unresectable or metastatic disease; OR
    - Used for resected gross residual disease (R2).
  - Vulvar Squamous Cell Carcinoma
    - Used for advanced, recurrent or metastatic disease as second-line therapy.
  - Cervical Cancer
    - Used second-line for recurrent or metastatic disease.
  - Other Solid Tumor (e.g., adrenal gland tumors, etc.) ‡
    - Used for unresectable or metastatic disease that progressed following prior treatment and there are no satisfactory alternative treatment options.

Vulvar Squamous Cell Carcinoma ‡

- Used as second-line therapy as a single agent; AND
- Patient has progressive advanced, recurrent or metastatic disease; AND
- Tumor expresses PD-L1 (CPS ≥1%) as determined by an FDA-approved test.

Malignant Pleural Mesothelioma ‡

- Used as subsequent therapy as a single agent.

Central Nervous System Cancer ‡

- Used for newly diagnosed or recurrent disease as a single agent for brain metastases; AND
- Primary tumor is melanoma or NSCLC.

T-Cell Lymphoma/Extranodal NK ‡

- Patient has relapsed or refractory nasal type disease; AND
- Disease progressed following additional treatment with asparaginase-based chemotherapy, clinical trials or other best supportive care.

Anal Carcinoma ‡

- Patient has metastatic squamous cell disease; AND
- Used as a single agent for second-line therapy.

Gestational Trophoblastic Neoplasia ‡

- Used as single-agent therapy; AND
- Patient has recurrent or progressive disease; AND
    - Patient has intermediate placental or epithelioid trophoblastic tumor; AND
    - Patient was previously treated with a platinum/etoposide containing regimen; OR
- Patient has methotrexate-resistant high risk disease.

Small Cell Lung Cancer (SCLC) ‡

- Used as subsequent single-agent therapy; AND
- Patient has a PS score of 0-2; AND
    - Patient has primary progressive disease; OR
    - Patient relapsed within 6 months following a complete or partial response or after stable disease after initial treatment.

Hepatocellular Carcinoma (HCC) †

- Used as a single agent; 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 (excluding Child-Pugh Class B and C) liver impairment.

Mycosis Fungoides/Sezary Syndrome ‡

- Patient has stage III Mycosis Fungoides; OR
- Patient has stage IV Sezary Syndrome and will be used as primary therapy or for relapsed or persistent disease.

† FDA Approved Indication(s); ‡ Compendia Approved Indication(s)

Genomic Aberration Targeted Therapies (not all inclusive) §
Sensitizing EGFR mutation-positive tumors • Erlotinib • Afatinib • Gefitinib • Osimertinib • Dacomitinib
ALK rearrangement-positive tumors: • Crizotinib • Ceritinib • Brigatinib • Alectinib • Lorlatinib
ROS1 rearrangement-positive tumors: • Crizotinib • Ceritinib
BRAF V600E-mutation positive tumors: • Dabrafenib/Trametinib
PD-L1 expression-positive tumors (≥50%): • Pembrolizumab • Atezolizumab

Renewal coverage:

- Patient continues to meet initial criteria; AND
- Tumor response with stabilization of disease or decrease in size of tumor or tumor spread; AND
- Patient is tolerating treatment with absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include severe infusion reactions, immune-mediated adverse reactions (e.g., pneumonitis, hepatitis, colitis, endocrinopathies, nephritis and renal dysfunction, rash, etc.).

- For the following 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)
    - Urothelial Carcinoma
    - MSI-H Cancer (including the following cancers: colorectal, pancreatic, bone, gastric/gastroesophageal, ovarian, uterine, penile, testicular, hepatobiliary and other solid tumors)
    - Anal Cancer
    - Malignant Pleural Mesothelioma
    - Gastric/GEJ Adenocarcinoma
    - Cervical Cancer
    - Vulvar Squamous Cell Carcinoma
    - Merkel Cell Carcinoma
- Mycosis Fungoides/Sezary Syndrome.

Dosage/Administration:

Indication	Dose (1 billable unit = 1 mg)
NSCLC, SCLC, HCC, SCCHN, Gastric/GEJ Carcinoma, Anal, Cervical, Vulvar and Urothelial Carcinoma	200 mg every 21 days up to a maximum of 24 months in patients without disease progression
Melanoma	200 mg every 21 days (adjuvant therapy for up to 1 year of treatment)
CNS metastases	200 mg every 21 days
cHL, PMBCL, MCC, & MSI-H/dMMR Cancer	Adults*: 200 mg every 21 days Pediatrics*: 2 mg/kg (up to 200 mg) every 21 days *Up to a maximum of 24 months in patients without disease progression or unacceptable toxicity
MPM & Uterine Cancer	10 mg/kg every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity
NK/T-Cell Lymphoma & MF/SS	2 mg/kg every 21 days
Gestational Trophoblastic Tumor	3 mg/kg every 21 days
Dosing should be calculated using actual body weight or flat dosing to minimize drug waste and consolidate the number of vials used. Flat dosing (as applicable) is based on weight and is indicated below: • Standard dose 200 mg IV every 3 weeks for patients > 50 kg • Use 100 mg IV every 3 weeks for patients ≤ 50 kg	

Dosing Limits:

Maximum units (per dose and over time):

Disease state	Maximum units
SCCHN, cHL, NSCLC, SCLC, Melanoma, Urothelial, Gastric, CNS metastases, PMBCL, Anal, Cervical, Vulvar, MSI-H/dMMR, MCC & HCC Cancer:	200 billable units every 21 days
MPM & Uterine Cancer	1150 billable units every 14 days
NK/T-Cell Lymphoma & MF/SS	250 billable units every 21 days
Gestational Trophoblastic Tumor	300 billable units every 21 days

Coverage durations:

- Initial & Renewal Coverage = 6 months
- SCCHN, cHL, NSCLC, SCLC, HCC, Urothelial Carcinoma, MPM, MSI-H/dMMR, PMBCL, Cervical, Anal, Vulvar, MCC, Mycosis Fungoides/Sezary Syndrome, & Gastric Cancers can be authorized up to a maximum of 24 months of therapy.
- Adjuvant therapy in melanoma can be authorized up to a maximum of 12 months of therapy.

Investigational Use: All therapies are considered investigational when used at a dose or for a condition other than those that are recognized as medically accepted indications as defined in any one of the following standard reference compendia: American Hospital Formulary Service Drug Information (AHFS-DI), Thomson Micromedex DrugDex, Clinical Pharmacology, Wolters Kluwer Lexi-Drugs, or Peer-reviewed published medical literature indicating that sufficient evidence exists to support use. Neighborhood does not provide coverage for drugs when used for investigational purposes.

Applicable Codes: Below is a list of billing codes applicable for covered treatment options. The below tables are provided for reference purposes and may not be all-inclusive. Requests received with codes from tables below do not guarantee coverage. Requests must meet all criteria provided in the procedure section.

The following HCPCS/CPT codes are:

HCPCS/CPT Code	Description
J9271	J9271 - Injection, pembrolizumab

References:

1. Keytruda [package insert]. Whitehouse Station, NJ; Merck & Co, Inc; February 2019. Accessed February 2019.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) pembrolizumab. National Comprehensive Cancer Network, 2019. 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 January 2019.
3. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncol. 2017 May;18(5):623-630.
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9. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Merkel Cell Carcinoma. Version 2.2019. National Comprehensive Cancer Network, 2019. 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 January 2019.
10. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Bladder Cancer. Version 1.2019. National Comprehensive Cancer Network, 2019. 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 January 2019.

11. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Non-Small Cell Lung Cancer. Version 3.2019. National Comprehensive Cancer Network, 2019. 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 January 2019
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