Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 05/01/2020**
Policy Number: PA.CP.PHAR.322	**Effective Date: 01/2018** **Revision Date: 04/15/2020**
Policy Name: Pembrolizumab (Keytruda)	

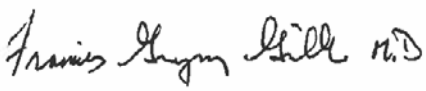
Type of Submission – Check all that apply:

- ☐ **New Policy**
- ✓ **Revised Policy***
- ☐ **Annual Review - No Revisions**
- ☐ **Statewide PDL -** *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

- FDA Approved Indication(s) section updated;
- Cervical Cancer Criteria changes:
  - Added reference to Appendix B for examples of systemic therapy
  - Added treatment duration limitation of 24 months
- Melanoma criteria changes:
  - Removed off-label designation for uveal melanoma
  - Added age restriction to 18 yr and older
  - Added lymph node positive disease for coverage
  - Added treatment duration limitation of 12 months for adjuvant treatment
- NSCLC criteria changes:
  - Added age restriction to 18 yr and older
  - Added advanced disease for coverage
  - Added single-agent therapy for brain metastasis per NCCN
  - Removed histology requirements
  - Mutational status requirements are limited to EGFR and ALK per the FDA label for primary therapy and to the additional NCCN directed requirement of prior ROS1 targeted therapy
  - Subsequent therapy requirement for platinum-based chemotherapy when TPS ≥ 1% is removed since Keytruda is now FDA-approved as first-line therapy when TPS ≥ 1%
- Criteria added for Small Cell Lung Cancer
- HNSCC criteria changes:
  - Clarified subtypes by location
  - Added oncologist prescriber limitation
  - Added age restriction to 18 yr and older
  - Revised to include first-line combination therapy and first-line single-agent therapy, the latter if PD-L1 ≥ 1.
  - Disease characteristics for HNSCC are updated from recurrent or metastatic, to unresectable, recurrent or metastatic
  - Added treatment duration limitation of 24 months
- cHL criteria changes:
  - Added oncologist, hematologist prescriber limitation

- Lowered age restriction to ≥ 2 years
- Added reference to Appendix B for examples of systemic therapy
- Revised dosing regimens to adult and pediatric dosing

- Urothelial Carcinoma criteria changes:
  - Added urologist to allowed prescribers
  - Added age restriction to 18 yr and older
  - Progression as a response to platinum therapy is removed as response may include persistence or partial response
  - Added criterion for BCG-unresponsive, high-risk, NMIBC with CIS
  - Added treatment duration limitation of 24 months
- MSI-H or dMMR criteria changes:
  - Added reference to Appendix D for examples of solid tumors listed in the NCCN compendium and FDA label
  - Added age restriction to ≥ 2 years
  - Subsequent therapy requirement is removed where recommended per NCCN
  - Disease characteristics (e.g., metastatic) are removed to encompass NCCN recommended uses
- Gastric, EGJ, or esophageal adenocarcinoma criteria changes:
  - Added age restriction to 18 yr and older
  - Clarified to include unresectable disease
  - Added reference to Appendix B for examples of systemic therapy
  - Added treatment duration limitation of 24 months
- Added criteria set for Esophageal Squamous Cell Carcinoma
- PMBCL criteria changes:
  - Added reference to Appendix B for examples of systemic therapy
  - Revised dosing regimens to adult and pediatric dosing
- HCC criteria changes:
  - Add treatment duration limitation of 24 months
- MCC criteria changes:
  - Removed Off-label designation
  - Lowered age restriction to ≥ 2 years
  - Added criterion to indicate use in recurrent, locally advanced, or metastatic disease
  - Revised dosing regimens to adult and pediatric dosing
- Added criteria set for Renal Cell Carcinoma
- Add criteria set for Endometrial Carcinoma
- Add criteria set for NCCN recommended Uses (off-label)
- Revised dosing regimens under continued approval to align with individual indications
- Appendices updated
- Section IV. Dosage and Administration updated
- Product Availability section updated
- References reviewed and updated

Name of Authorized Individual (Please type or print):	**Signature of Authorized Individual:**
Francis G. Grillo, MD	

Clinical Policy: Pembrolizumab (Keytruda)

Reference Number: PA.CP.PHAR.322
Effective Date: 01/18
Last Review Date: 04/2020

Coding Implications
Revision Log

Description
Pembrolizumab (Keytruda®) is a programmed cell death receptor-1 (PD-1)-blocking antibody.

FDA Approved Indication(s)
Keytruda is indicated for the treatment of:

- **Melanoma**
  - For the treatment of patients with unresectable or metastatic melanoma.
  - For the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- **Non-Small Cell Lung Cancer (NSCLC)**
  - In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations
  - In combination with carboplatin and either paclitaxel or nab-paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC
  - As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥ 1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
    - Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
    - Metastatic.
  - As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda
- **Small cell lung cancer (SCLC)**
  - For the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.*
- **Head and Neck Squamous Cell Cancer (HNSCC)**
  - In combination with platinum and fluorouracil (FU) for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
  - As a single agent for the first line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test.
  - As a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum containing chemotherapy.
- **Classical Hodgkin Lymphoma (cHL)**
  - For the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy*
- **Primary Mediastinal Large B-Cell Lymphoma (PMBCL)**

- For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy*
- Limitation(s) of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy

- **Urothelial Carcinoma**
  - For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status*
  - For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
  - For the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
- **Microsatellite Instability-High Cancer**
  - For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)*
    - Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
    - Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
  - Limitation(s) of use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established
- **Gastric Cancer**
  - For the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy.*
- **Esophageal cancer**
  - For the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.
- **Cervical Cancer**
  - For the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test*
- **Hepatocellular Carcinoma (HCC)**
  - For the treatment of patients with HCC who have been previously treated with sorafenib*
- **Merkel cell carcinoma (MCC)**

- For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic MCC.*

- **Renal cell carcinoma (RCC)**
  - For use in combination with axitinib for the first-line treatment of patients with advanced RCC.
- **Endometrial carcinoma (EC)**
  - In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.*

* This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Pennsylvania Health and Wellness ® that Keytruda is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cervical Cancer (must meet all)**:**

1. Diagnosis of cervical cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is recurrent or metastatic;
5. Tumors express PD-L1 [CPS ≥ 1];
6. Disease has progressed on or after ≥ 1 line of systemic therapy *(see Appendix B for examples*);
7. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

B. Melanoma (must meet all):

1. Diagnosis of melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is lymph node positive, recurrent, unresectable, or metastatic;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks (for a maximum of 12 months if adjuvant treatment);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

C. Non-Small Cell Lung Cancer (must meet all):
1. Diagnosis of non-small cell lung cancer (NSCLC);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is recurrent, advanced, or metastatic;
5. If disease is positive for an EGFR, ALK, or ROS1 mutation, disease has progressed on or after targeted therapy *(see Appendix B for examples of targeted therapy);*
6. Request is for one of the following (a, b, or c):
   a. Tumor expresses PD-L1 (TPS ≥ 1%);
   b. Keytruda is prescribed as first-line therapy in combination with a chemotherapy regimen *(see Appendix B for examples of combination therapy)*;
   c. Keytruda is prescribed as single-agent therapy for brain metastasis;
7. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks for maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

D. Small Cell Lung Cancer (must meet all)**:**
1. Diagnosis of SCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is unresectable or metastatic;
5. Disease has progressed on or after platinum-based chemotherapy (e.g., cisplatin, carboplatin);
6. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

E. Head and Neck Squamous Cell Carcinoma (must meet all):
1. Diagnosis of HNSCC (*locations include paranasal sinuses, larynx, pharynx, lip, oral cavity, salivary glands; may be occult primary - i.e., primary source unknown*);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is unresectable, recurrent, or metastatic;
5. Meets one of the following (a, b, or c):
   a. Keytruda is requested as first-line therapy in combination with platinum-containing chemotherapy and FU;
   b. Keytruda is requested as a first-line single agent and the tumor expresses PD-L1 with a CPS of ≥ 1;
   c. Keytruda is requested as a single agent for disease that has progressed on or after platinum-containing chemotherapy (e.g., cisplatin, carboplatin);
6. Request meets one of the following (a or b):

a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
b. Requested dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

F. Classical Hodgkin Lymphoma (must meet all):
1. Diagnosis of classical Hodgkin lymphoma (cHL);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 2 years;
4. Disease is refractory to ≥ 1 line of therapy or has relapsed after ≥ 3 lines of therapy *(a line of therapy may include systemic therapy or transplantation; see Appendix B for examples of systemic therapy)*;
1. Request meets one of the following (a, b, or c):
   a. Adults: Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Pediatrics: Dose does not exceed 2 mg/kg (up to 200 mg) every 3 weeks for a maximum of 24 months;
   a. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration: 6 months

G. Urothelial Carcinoma (must meet all):
1. Diagnosis of urothelial carcinoma;
2. Prescribed by or in consultation with an oncologist or urologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. For locally advanced or metastatic disease, member is ineligible for or has previously received platinum-containing chemotherapy (e.g., cisplatin, carboplatin);
   b. For BCG-unresponsive, high-risk, NMIBC with CIS, member is ineligible for or has elected not to undergo cystectomy;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

H. Microsatellite Instability-High/Mismatch Repair Deficient Cancer (must meet all):
1. Diagnosis of a solid tumor classified as MSI-H or dMMR (indicative of MMR gene mutation or loss of expression) *(see Appendix D for examples of solid tumors)*;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 2 years;
4. Keytruda is prescribed as subsequent therapy for solid tumors other than colorectal cancer, gallbladder cancer, or intrahepatic/extrahepatic cholangiocarcinoma;
5. Request meets one of the following (a or b):*

a. Adults: Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
b. Pediatrics: Dose does not exceed 2 mg/kg (up to 200 mg) every 3 weeks for a maximum of 24 months;
c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*)

Approval duration: 6 months

I. Gastric, EGJ, and Esophageal Adenocarcinoma Cancer (must meet all):
1. Diagnosis of gastric, EGJ, or esophageal adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is unresectable, locally advanced, recurrent, or metastatic;
5. Tumor expresses PD-L1 (CPS ≥ 1);
6. Disease has progressed on or after ≥ 2 lines of systemic therapy *(see Appendix B for examples)*;
7. Request meets any of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

J. Esophageal Squamous Cell Carcinoma (must meet all)**:**
1. Diagnosis of esophageal squamous cell carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is locally advanced, recurrent, or metastatic;
5. Tumor expresses PD-L1 (CPS ≥ 10);
6. Disease has progressed on or after one or more lines of systemic therapy *(see Appendix B for examples)*;
7. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

K. Primary Mediastinal Large B-Cell Lymphoma (must meet all)**:**
1. Diagnosis of PMBCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 2 years;
4. Disease is refractory to or has relapsed after ≥ 1 line of therapy *(a line of therapy may include systemic therapy or transplantation; see Appendix B for examples of systemic therapy)*;
6. Request meets one of the following (a, b, or c):
   a. Adults: Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;

b. Pediatrics: Dose does not exceed 2 mg/kg (up to 200 mg) every 3 weeks for a maximum of 24 months;
c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration: 6 months

L. Hepatocellular Carcinoma (must meet all):
1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease has progressed on or after therapy with Nexavar®;
   **Prior authorization is required for Nexavar*
5. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeksfor a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration: 6 months

M. Merkel Cell Carcinoma (must meet all)**:**
1. Diagnosis of Merkel cell carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 2 years;
4. Disease is recurrent, locally advanced, or metastatic;
5. Request meets one of the following (a, b, or c):
   a. Adults: Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Pediatrics: Dose does not exceed 2 mg/kg (up to 200 mg) every 3 weeks for a maximum of 24 months;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

N. Renal Cell Carcinoma (must meet all)**:**
1. Diagnosis of advanced RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with Inlyta®;
   **Prior authorization may be required for Inlyta.*
5. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

O. Endometrial Carcinoma (must meet all)**:**
1. Diagnosis of EC;
2. Prescribed by or in consultation with an oncologist;

3. Age ≥ 18 years;
4. Request meets one of the following (a or b):
   a. Prescribed in combination with Lenvima® and disease is not MSI-H or dMMR (i.e., disease is not indicative of MMR gene mutation or loss of expression);
   **Prior authorization may be required for Lenvima*
   b. Disease is MSI-H or dMMR (i.e., disease is indicative of MMR gene mutation or loss of expression);
5. Disease has progressed following prior systemic therapy (e.g., carboplatin/paclitaxel);
6. Member is not a candidate for curative surgery or radiation;
7. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

P. NCCN Recommended Uses (off-label) (must meet all)**:**

1. One of the following diagnoses:
   a. Keytruda is prescribed as primary or subsequent therapy:
      i. Stage III mycosis fungoides;
      ii. Stage IV Sezary syndrome;
   b. Keytruda is prescribed as subsequent therapy:
      i. Metastatic anal carcinoma;
      ii. Gestational trophoblastic neoplasia;
      iii. Malignant pleural mesothelioma;
      iv. Extranodal NK/T-cell lymphoma, nasal type;
      v. Metastatic or unresectable thymic carcinoma;
      vi. Advanced, recurrent, or metastatic PD-L1-positive (CPS ≥ 1) vulvar carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

Q. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PA.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, c, or d):
   a. Melanoma: New dose does not exceed 200 mg every 3 weeks (for a maximum of 12 months if adjuvant treatment);
   b. EC: New dose does not exceed 200 mg every 3 weeks;

c. All other FDA-approved indications: New dose does not exceed 200 mg every 3 weeks for a maximum of 24 months;
d. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PA.01) applies; or
2. Refer to PA.CP.PMN.53

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase
BCG: Bacillus Calmette-Guerin
cHL: classical Hodgkin lymphoma
CIS: carcinoma in situ
CPS: combined positive score
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
EC: endometrial carcinoma
FDA: Food and Drug Administration
HCC: hepatocellular carcinoma
HER2: human epidermal growth factor receptor 2
HNSCC: head and neck squamous cell carcinoma
MCC: Merkel cell carcinoma
MSI-H: microsatellite instability-high
NCCN: National Comprehensive Cancer Network
NMIBC: non-muscle invasive bladder cancer
NSCLC: non-small cell lung cancer
PD-1: programmed death protein 1
PD-L1: programmed death-ligand 1
RCC: renal cell carcinoma
ROS1: ROS proto-oncogene 1
SCLC: small cell lung cancer
TPS: tumor proportion score

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Section I.B: Non-Small Cell Lung Cancer Examples of drugs used in combination with Keytruda: • Carboplatin, cisplatin, pemetrexed, paclitaxel Examples of targeted therapies: • Sensitizing EGFR mutation: erlotinib, afatinib, gefitinib, osimertinib, dacomitinib • ALK mutation: crizotinib, ceritinib, alectinib, brigatinib • ROS1 mutation: crizotinib, ceritinib	Varies	Varies
Section I.E: Classical Hodgkin Lymphoma Examples of chemotherapy regimens:	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
• ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) • Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone) • BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, probarbazine, prednisone) • AVD (doxorubicin, vinblastine, dacarbazine) • BV (brentuximab vedotin)		
Section I.F: Primary Mediastinal Large B-Cell Lymphoma Examples of drugs used in single- or multi-drug chemotherapy regimens: • Bendamustine, brentuximab vedotin, carboplatin, cisplatin, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, gemcitabine, ibrutinib, ifosfamide, lenalidomide, mesna, mitoxantrone, methylprednisolone, oxaliplatin, prednisone, procarbazine, rituximab, vincristine, vinorelbine* **Various combinations of the listed drugs are components of the following chemotherapy regimens: CEOP, CEPP, DHAP, DHAX, EPOCH-R, ESHAP, GDP, GemOx, ICE, MINE, RCDOP, RCEOP, RCEPP, RCHOP, RGCVP*	Varies	Varies
Section I.G: Urothelial Carcinoma TICE® BCG (attenuated, live culture preparation of the Bacillus of Calmette and Guerin strain of *Mycobacterium bovis* for ***intravesical*** use). References for BCG dosing, dosing in the setting of a BCG shortage, and BCG shortage status are listed below: 1. TICE BCG package insert: https://www.fda.gov/vaccines-blood-biologics/vaccines/tice-bcg 2. American Urological Association: Important message about the BCG shortage: https://www.auanet.org/about-us/bcg-shortage-info 3. Centers for Disease Control's current shortages page: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages	Varies	Varies
Section I.I and I.J: Gastric, EGJ, and Esophageal Cancer Examples of drugs used in single- or multi-drug chemotherapy regimens:* • Cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel, fluorouracil, capecitabine, irinotecan, leucovorin, epirubicin, ramucirumab (for EGJ adenocarcinoma or esophageal adenocarcinoma only) **Trastuzumab may be added to some chemotherapy regimens for HER2 overexpression.*	Varies	Varies
Section I.K: Cervical Cancer	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of drugs used in single- or multi-drug chemotherapy regimens: • Cisplatin, carboplatin, paclitaxel, docetaxel, bevacizumab, topotecan, fluorouracil, gemcitabine, ifosfamide, irinotecan, topotecan, mitomycin, pemetrexed, vinorelbine		
Section I.L: Hepatocellular Carcinoma Nexavar (sorafenib)	400 mg PO BID	800 mg/day
Section I.O: Endometrial Carcinoma Examples of chemotherapy regimens:* • Carboplatin/paclitaxel, cisplatin/docetaxel, cisplatin/doxorubicin, carboplatin/paclitaxel/bevacizumab, carboplatin/paclitaxel/trastuzumab, ifosfamide/paclitaxel, cisplatin/ifosfamide, everolimus/letrozole, temsirolimus, Keytruda (pembrolizumab) _____ **Individual drugs used in combination regimens may also be used as monotherapy (refer to NCCN Uterine Neoplasms Guidelines)*	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

*Appendix D: Examples of Solid Tumors**
- Adrenal gland tumor
- Bladder or renal cell cancer
- Breast cancer
- Cervical, endometrial, vulvar, ovarian, fallopian tube, or primary peritoneal cancer
- Colorectal cancer
- Gallbladder cancer or intrahepatic/extrahepatic cholangiocarcinoma
- Gastric, EGJ, esophageal, or small intestinal cancer
- Pancreatic or thyroid cancer
- Penile, prostate, or testicular cancer
- Retroperitoneal adenocarcinoma
- Sarcoma (bone cancer - e.g., Ewing sarcoma; osteosarcoma; chondrosarcoma)
- Small cell lung cancer

_____
**Examples are drawn from Keytruda pivotal trials and the NCCN compendium.*

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Melanoma	Adults: 200 mg IV every 3 weeks If adjuvant therapy, up to 12 months	200 mg every 3 weeks

Indication	Dosing Regimen	Maximum Dose
NSCLC, SCLC, HNSCC, cHL, PMBCL, urothelial carcinoma, MSI-H cancer, gastric cancer, esophageal squamous cell carcinoma, cervical cancer, HCC, MCC	Adults: 200 mg IV every 3 weeks up to 24 months	200 mg every 3 weeks
cHL, PMBCL, MSI-H cancer, MCC	Pediatrics: 2 mg/kg IV every 3 weeks up to 24 months	200 mg every 3 weeks
RCC	Adults: 200 mg IV every 3 weeks in combination with axitinib up to 24 months	200 mg every 3 weeks
EC	Adults: 200 mg IV every 3 weeks in combination with lenvatinib	200 mg every 3 weeks

V. Product Availability

Solution, single-dose vial: 100 mg/4 mL

VI. References

1. Keytruda Prescribing Information. Whitehouse Station, NJ: Merck and Co.; January 2020. Available at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed January 13, 2020
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed January 29, 2020.
3. National Comprehensive Cancer Network Guidelines. Cutaneous Melanoma Version 1.2019. Available at www.nccn.org. Accessed February 26, 2019.
4. National Comprehensive Cancer Network Guidelines. Uveal Melanoma Version 1.2018. Available at www.nccn.org. Accessed February 26, 2019.
5. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer Version 3.2019. Available at www.nccn.org. Accessed April 17, 2019.
6. National Comprehensive Cancer Network Guidelines. Small Cell Lung Cancer Version 1.2019. Available at www.nccn.org. Accessed June 25, 2019.
7. National Comprehensive Cancer Network Guidelines. Head and Neck Cancers Version 1.2019. Available at www.nccn.org. Accessed June 25, 2019.
8. National Comprehensive Cancer Network Guidelines. Hodgkin Lymphoma Version 3.2018. Available at www.nccn.org. Accessed February 26, 2019.
9. National Comprehensive Cancer Network. B-Cell Lymphomas Version 1.2019. Available at: www.nccn.org. Accessed February 26, 2019.
10. National Comprehensive Cancer Network Guidelines. Bladder Cancer Version 3.2020. Available at www.nccn.org. Accessed January 29, 2020.
11. National Comprehensive Cancer Network. Hepatobiliary Cancers Version 2.2019. Available at www.nccn.org. Accessed March 11, 2019.
12. National Comprehensive Cancer Network Guidelines. Gastric Cancer Version 2.2018. Available at www.nccn.org. Accessed February 27, 2019.
13. National Comprehensive Cancer Network Guidelines. Merkel Cell Carcinoma Version 2.2019. Available at www.nccn.org. Accessed February 27, 2019.

14. National Comprehensive Cancer Network. Cervical Cancer Version 3.2019. Available at www.nccn.org. Accessed February 27, 2019.
15. National Comprehensive Cancer Network. Kidney Cancer Version 3.2019. Available at www.nccn.org. Accessed April 20, 2019.
16. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers Version 2.2019. Available at www.nccn.org. Accessed August 19, 2019.
17. National Comprehensive Cancer Network. Uterine Neoplasms Version 4.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed September 23, 2019.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9271	Injection, Pembrolizumab, 1mg

Reviews, Revisions, and Approvals	Date	Approval Date
Added max dose requirement to both initial and re-auth criteria. Increased all approval durations from 3/6 months to 6/12 months. Removed reasons to discontinue. Added requirement for documentation of positive response to therapy. References reviewed and updated.	02/18	
1Q 2019 Criteria added for new FDA indications HCC and as first-line therapy for metastatic squamous NSCLC in combination with chemotherapy; re-added criteria for PMBCL as previously approved; referenced reviewed and updated.	01/19	
4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	10/30/19	
• FDA Approved Indication(s) section updated; • Cervical Cancer Criteria changes: o Added reference to Appendix B for examples of systemic therapy o Added treatment duration limitation of 24 months • Melanoma criteria changes: o Removed off-label designation for uveal melanoma o Added age restriction to 18 yr and older o Added lymph node positive disease for coverage o Added treatment duration limitation of 12 months for adjuvant treatment • NSCLC criteria changes:	04/2020	

Reviews, Revisions, and Approvals	Date	Approval Date
o Added age restriction to 18 yr and older o Added advanced disease for coverage o Added single-agent therapy for brain metastasis per NCCN o Removed histology requirements o Mutational status requirements are limited to EGFR and ALK per the FDA label for primary therapy and to the additional NCCN directed requirement of prior ROS1 targeted therapy o Subsequent therapy requirement for platinum-based chemotherapy when TPS ≥ 1% is removed since Keytruda is now FDA-approved as first-line therapy when TPS ≥ 1% • Criteria added for Small Cell Lung Cancer • HNSCC criteria changes: o Clarified subtypes by location o Added oncologist prescriber limitation o Added age restriction to 18 yr and older o Revised to include first-line combination therapy and first-line single-agent therapy, the latter if PD-L1 ≥ 1. o Disease characteristics for HNSCC are updated from recurrent or metastatic, to unresectable, recurrent or metastatic o Added treatment duration limitation of 24 months • cHL criteria changes: o Added oncologist, hematologist prescriber limitation o Lowered age restriction to ≥ 2 years o Added reference to Appendix B for examples of systemic therapy o Revised dosing regimens to adult and pediatric dosing • Urothelial Carcinoma criteria changes: o Added urologist to allowed prescribers o Added age restriction to 18 yr and older o Progression as a response to platinum therapy is removed as response may include persistence or partial response o Added criterion for BCG-unresponsive, high-risk, NMIBC with CIS o Added treatment duration limitation of 24 months • MSI-H or dMMR criteria changes: o Added reference to Appendix D for examples of solid tumors listed in the NCCN compendium and FDA label o Added age restriction to ≥ 2 years o Subsequent therapy requirement is removed where recommended per NCCN		

Reviews, Revisions, and Approvals	Date	Approval Date
○ Disease characteristics (e.g., metastatic) are removed to encompass NCCN recommended uses • Gastric, EGJ, or esophageal adenocarcinoma criteria changes: ○ Added age restriction to 18 yr and older ○ Clarified to include unresectable disease ○ Added reference to Appendix B for examples of systemic therapy ○ Added treatment duration limitation of 24 months • Added criteria set for Esophageal Squamous Cell Carcinoma • PMBCL criteria changes: ○ Added reference to Appendix B for examples of systemic therapy ○ Revised dosing regimens to adult and pediatric dosing • HCC criteria changes: ○ Add treatment duration limitation of 24 months • MCC criteria changes: ○ Removed Off-label designation ○ Lowered age restriction to ≥ 2 years ○ Added criterion to indicate use in recurrent, locally advanced, or metastatic disease ○ Revised dosing regimens to adult and pediatric dosing • Added criteria set for Renal Cell Carcinoma • Add criteria set for Endometrial Carcinoma • Add criteria set for NCCN recommended Uses (off-label) • Revised dosing regimens under continued approval to align with individual indications • Appendices updated • Section IV. Dosage and Administration updated • Product Availability section updated • References reviewed and updated		