Clinical Policy Title:	pembrolizumab
Policy Number:	RxA.192
Drug(s) Applied:	Keytruda®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Pembrolizumab is a programmed death receptor-1 (PD-1)-blocking antibody and 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 non squamous 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) of 1% or greater] 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 of 1% or greater) 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 pembrolizumab.

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) of 1 or higher] 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,
- For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more 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: Pembrolizumab 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 (CPS of 10 or higher) 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 or Mismatch Repair Deficient 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.*
  - 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.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

- For the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

Gastric Cancer

- For the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (esophagogastric junction; EGJ) adenocarcinoma whose tumors express PD-L1 (CPS of 1 or higher) 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 locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

- in combination with platinum- and fluoropyrimidine-based chemotherapy, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS of 10 or higher) as determined by an FDA-approved test

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 of 1 or higher) 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)
- 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.*

Cutaneous squamous cell carcinoma (cSCC)
- For the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.

Tumor Mutational Burden-High (TMB-H) cancer
- For the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [10 or more mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.*
- Limitations of Use: The safety and effectiveness of pembrolizumab in pediatric patients with TMB-H central nervous system cancers have not been established.

Triple-Negative Breast Cancer (TNBC)
- In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS of 10 or higher) as determined by an FDA approved test.

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
pembrolizumab (Keytruda®)	Melanoma, NSCLC, HNSCC, Urothelial Carcinoma, MSI-H or dMMR CRC, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, cSCC, TNBC	200 mg every 3 weeks or 400 mg every 6 weeks.	200 mg IV every 3 weeks OR 400 mg IV every 6 weeks
	cHL or PMBCL,	200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics.	200 mg IV every 3 weeks OR 400 mg IV every 6 weeks
	MSI-H or dMMR Cancer, TMB-H Cancer, MCC	200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics.	200 mg IV every 3 weeks OR 400 mg IV every 6 weeks

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
	RCC	200 mg every 3 weeks or 400 mg every 6 weeks with axitinib 5 mg orally twice daily.	200 mg IV every 3 weeks OR 400 mg IV every 6 weeks
	EC	200 mg every 3 weeks or 400 mg every 6 weeks with lenvatinib 20 mg orally once daily for tumors that are not MSI-H or dMMR.	200 mg IV every 3 weeks OR 400 mg IV every 6 weeks

Pembrolizumab is indicated for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.

** When axitinib is used in combination with* pembrolizumab*, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.*

Dosage Forms

- Injection, single-dose vial: 100 mg/4 mL solution (25 mg/mL)

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

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

1. Diagnosis of locally recurrent, unresectable or metastatic triple negative breast cancer that (a or b):
   a. Has PD-L1 (CPS of 10 or greater) expression as determined by an FDA approved test;
   b. Is microsatellite instability-high or mismatch repair deficient;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Prescribed as monotherapy or in combination with paclitaxel, albumin-bound paclitaxel, or gemcitabine with carboplatin;
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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration

Commercial: 6 months

Medicaid: 6 months

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

1. Diagnosis of recurrent or metastatic cervical cancer that (a or b):
   a. Expresses PD-L1 (CPS of 1 or higher) as determined by an FDA-approved test; or
   b. Is MSHI-H or dMMR;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Disease has progressed on or after one (1) or more lines of systemic chemotherapy (*see Appendix B for examples*);
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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

C. Classical Hodgkin Lymphoma (must meet all)**:**

1. Diagnosis of relapsed or refractory cHL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 2 years of age or older;
4. Disease is refractory to one (1) or more lines of chemotherapy or has relapsed after two (2) or more lines of chemotherapy *(a line of therapy may include systemic therapy or transplantation; see Appendix B for examples of systemic therapy)*;
5. Prescribed as monotherapy;
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)*.
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

D. Cutaneous Squamous Cell Carcinoma (must meet all)**:**

1. Diagnosis of recurrent or metastatic cutaneous squamous cell carcinoma**;**
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Disease has progressed on or not curable by surgery or radiation;
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).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration

Commercial: 6 months
Medicaid: 6 months

E. Endometrial Carcinoma (must meet all)**:**

1. Diagnosis of recurrent, metastatic, or unresectable EC;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years or older;
4. Request meets one of the following (a or b):
   a. Prescribed in combination with lenvatinib (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 lenv*atinib (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).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

F. Esophageal Squamous Cell Carcinoma (must meet all)**:**

1. Diagnosis of locally advanced, recurrent, or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimetres above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either**;**
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Tumor expresses PD-L1 (CPS of 10 or higher);
5. Pembrolizumab is prescribed in combination with platinum- and fluoropyrimidine-based chemotherapy;
6. Disease has progressed on or after one (1) 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).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN*.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

G. Gastric, Esophagogastric Junction, and Esophageal Adenocarcinoma (must meet all)**:**

1. Diagnosis of unresectable, locally advanced, recurrent, or metastatic gastric, EGJ, or esophageal adenocarcinoma and member is not a surgical candidate;
2. Prescribed by or in consultation with an oncologist;

3. Member is 18 years of age or older;
4. Tumor expresses PD-L1 (CPS of 1 or higher);
5. Disease has progressed on or after two (2) or more lines of systemic therapy *(see Appendix B for examples)*;
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).*

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

H. Head and Neck Squamous Cell Carcinoma (must meet all)**:**
1. Diagnosis of unresectable, recurrent, or metastatic 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. Member is 18 years of age or older;
4. Request meets one of the following (a, b, or c):
   a. Pembrolizumab is requested as first-line therapy in combination with platinum-containing chemotherapy and FU;
   b. Pembrolizumab is requested as a first-line single agent and the tumor expresses PD-L1 with a CPS of 1 or higher;
   c. Pembrolizumab is requested as a single agent for disease that has progressed on or after platinum-containing chemotherapy (e.g., cisplatin, carboplatin);
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)*.

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

I. Hepatocellular Carcinoma (must meet all):
1. Diagnosis of unresectable or metastatic HCC;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Disease has progressed on or after therapy with sorafenib (Nexavar®)
   **Prior authorization may be required for sorafenib (Nexavar®)*
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).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*.

Approval Duration
Commercial: 6 months

Medicaid: 6 months

J. Melanoma (must meet all)**:**

1. Diagnosis of lymph node positive, recurrent, unresectable, or metastatic melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. 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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

K. Merkel Cell Carcinoma (must meet all)**:**

1. Diagnosis of recurrent, locally advanced, or metastatic MCC;
2. Prescribed by or in consultation with an oncologist;
3. Member is 2 years of age or older;
4. 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).*

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

L. 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. Member is 2 years of age or older;
4. Used as first-line treatment for patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer;
5. Pembrolizumab is prescribed as subsequent therapy for solid tumors other than colorectal cancer, gallbladder cancer, or intrahepatic/extrahepatic cholangiocarcinoma;
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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*.

Approval Duration

Commercial: 6 months
Medicaid: 6 months

M. Non-Small Cell Lung Cancer (must meet all)**:**

1. Diagnosis of recurrent, advanced, or metastatic NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. 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*);
5. Request is for one of the following (a, b, or c):
   a. Tumor expresses PD-L1 (TPS of 1 or higher);
   b. Pembrolizumab is prescribed as first-line therapy in combination with a chemotherapy regimen (*see Appendix B for examples of combination therapy*);
   c. Pembrolizumab is prescribed as single-agent therapy for brain metastases;
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).

**Prescribed regimen must be FDA-approved or recommended by NCCN*.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

N. Primary Mediastinal Large B-Cell Lymphoma (must meet all)**:**

1. Diagnosis of relapsed or refractory PMBCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 2 years of age or older;
4. Disease is refractory to or has relapsed after one (1) or more lines of chemotherapy *(a line of therapy may include systemic therapy or transplantation; see Appendix B for examples of systemic therapy)*;
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)*.

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

O. Renal Cell Carcinoma (must meet all)**:**

1. Diagnosis of relapsed or stage IV RCC;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Prescribed in combination with axitinib (Inlyta®)* or lenvatinib (Lenvima®)*;
   **Prior authorization may be required.*

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).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

P. Tumor Mutational Burden-High Cancer (must meet all)**:**
1. Diagnosis of unresectable or metastatic tumor mutational burden-high (TMB-H) solid tumors;
2. Prescribed by or in consultation with an oncologist;
3. Member is 2 years of age or older;
4. Disease has progressed following prior treatment and no satisfactory alternative treatment options are available;
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
Commercial: 6 months
Medicaid: 6 months

Q. Urothelial Carcinoma (must meet all)**:**
1. Diagnosis of one of the following (a, b, or c):
   a. For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors expresses PD-L1 (CPS of 10 or higher), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status and pembrolizumab is used as monotherapy;
   b. For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or an immune checkpoint inhibitor or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy and pembrolizumab is used as monotherapy;
   c. For the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. 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*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months

Medicaid: 6 months

R. Gestational Trophoblastic Neoplasia (off-label) (must meet all):
1. Diagnosis of recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epitheliod trophoblastic tumor) following treatment with a platinum/etoposide-containing chemotherapy regimen;
2. Prescribed by or in consultation with an oncologist;
3. Request meets one of the following (a or b):*
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

S. Malignant Pleural Mesothelioma (off-label) (must meet all):
1. Diagnosis of malignant pleural mesothelioma;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Prescribed as subsequent systemic therapy as monotherapy;
5. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

T. Soft Tissue Sarcoma (off-label) (must meet all):
1. Request meets one of the following (a or b):
   a. Diagnosis of advanced, metastatic, recurrent, or unresectable soft tissue sarcoma (e.g., myxofibrosarcoma, undifferentiated pleomorphic sarcoma, cutaneous angiosarcoma, or undifferentiated sarcoma) with disseminated metastases as subsequent systemic therapy as monotherapy;
   b. Alveolar soft part sarcoma as monotherapy;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

U. T-Cell Lymphomas (off-label) (must meet all):
1. Diagnosis of relapsed or refractory extranodal NK/T-Cell lymphoma (nasal type);
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;

4. Prescribed as subsequent therapy following an asparaginase-based chemotherapy regimen and a clinical trial is not available;
5. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

V. Thymic Carcinoma (off-label) (must meet all):

1. Diagnosis of locally advanced or metastatic thymic carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Prescribed as monotherapy following first-line chemotherapy or in members who cannot tolerate first-line chemotherapy regimens;
4. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy.
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).*

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

ALK: Anaplastic lymphoma kinase
cHL: Classical Hodgkin lymphoma
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
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
TPS: Tumor proportion score
BCG: Bacillus Calmette Guerin
NMIBC: Non-muscle invasive bladder cancer
CIS: Carcinoma in situ
cSCC: Cutaneous squamous cell carcinoma
CPC: Combined positive score

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Non-Small Cell Lung Cancer Examples of drugs used in combination with pembrolizumab: • 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
Classical Hodgkin Lymphoma Examples of chemotherapy regimens: • ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) • Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone) • BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) • AVD (doxorubicin, vinblastine, dacarbazine) • BV (brentuximab vedotin)	Varies	Varies
Primary Mediastinal Large B-Cell Lymphoma Examples of drugs used in single or multi-drug chemotherapy regimens:	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
• 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.		
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
Cervical Cancer 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	Varies	Varies
Hepatocellular Carcinoma Nexavar® (sorafenib)	400 mg PO BID	800 mg/day
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

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue pembrolizumab based on the severity of reaction.
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective method of contraception.
- Immune-Mediated Adverse Reactions:
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction.
- **Examples of Solid Tumors***
  - Adrenal gland tumor
  - Anal cancer
  - Biliary tract cancer
  - 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)

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

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Background updated 2. Dosing information updated. 3. Continued Therapy approval was updated 4. Clinical policy (length of duration) was updated. 5. Appendices updated. 6. References were updated.	06/2020	09/14/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Background was updated. 3. Dosing information was updated. 4. Initial Approval Criteria was updated. 5. Duration of approve continued therapy was updated. 6. References were updated.	05/10/2021	06/10/2021