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: 08/01/2021**
Policy Number: PA.CP.PHAR.322	**Effective Date: 01/2018** **Revision Date: 07/2021**
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.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

3Q 2021 annual review: FDA cHL label updated from relapsed disease after 3 lines of therapy to after 1 line of therapy (adults) or 2 lines of therapy (pediatrics); new NCCN pediatric cHL guideline added to reference section; new FDA-approved TNBC indication added; for HCC, Lenvima added as a prior therapy option per NCCN. Newly approved indication of esophageal/GEJ junction carcinoma and new indication for combo use for 1st line gastric or GEJ adenocarcinoma were added AND removal of SCLC indication; references reviewed and updated.

Name of Authorized Individual (Please type or print): **Venkateswara R. Davuluri, MD**	**Signature of Authorized Individual:**

Clinical Policy: Pembrolizumab (Keytruda)

Reference Number: PA.CP.PHAR.322
Effective Date: 01/18
Last Review Date: 07/2021~~0~~

Coding Implications
Revision Log

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

FDA Approved Indication(s)

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Indication	Adults	Pediatrics
Melanoma	X	
Non-small cell lung cancer	X	
Head and neck squamous cell carcinoma	X	
Classical Hodgkin lymphoma	X	X
Primary mediastinal large B-cell lymphoma	X	X
Urothelial carcinoma	X	
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer *(First-line treatment for colorectal cancer limited to adults.)*	X	X *(excludes CNS tumor)*
Gastric cancer	X	
Esophageal cancer	X	
Cervical cancer	X	
Hepatocellular carcinoma	X	
Merkel cell carcinoma	X	X
Renal cell carcinoma	X	
Endometrial carcinoma	X	
Tumor mutational burden-high (TMB-H) cancer	X	X *(excludes CNS tumor)*
Cutaneous squamous cell carcinoma	X	
Triple-negative breast cancer (TNBC)	X	
Adult indications - additional dosing regimens	X	
Off-label uses		
Mycosis fungoides	X	
Sezary syndrome	X	
Anal carcinoma	X	
Gestational trophoblastic neoplasia	X	
Pleural mesothelioma	X	
Extranodal NK/T-cell lymphoma, nasal type	X	
Vulvar carcinoma	X	

**If a solid tumor is characterized as MSI-H, dMMR, or TMB-H, see criteria at Sections I.H or I.P respectively.*

Keytruda is indicated:

- **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 patients with relapsed or refractory cHL.
  - For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.~~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 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, 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
- **Microsatellite Instability-High Cancer or Mismatch Repair Deficient Colorectal Cancer**
  - For the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC.
- **Gastric Cancer**
  - In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.
  - 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 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
    - ~~o~~ 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 ≥10) as determined by an FDA approved test.~~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*

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- **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.*
- **Tumor Mutational Burden-High (TMB-H) Cancer**
  - For the treatment of adult and pediatric patients with unresectable or metastatic TMB-H [≥10 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 Keytruda in pediatric patients with TMB-H central nervous system cancers have not been established.
- **Cutaneous Squamous Cell Carcinoma (cSCC)**
  - For the treatment of patients with recurrent of metastatic cSCC that is not curable by surgery or radiation.
- **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 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.**

Adult indications

- For use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.***
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* 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.

** *This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.*

*** *This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing 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 or 400 mg every 6 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.~~A. **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 or 400 mg every 6 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.~~B. **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. Keytruda is prescribed in one of the following ways (a or b):
   a. For PD-L1 positive disease (TPS ≥ 1%);
   b. In combination with a chemotherapy regimen *(see Appendix B)*;
7. 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 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;~~

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~~3. Age ≥ 18 years;~~
~~4. Disease is unresectable or metastatic;~~
~~5. Keytruda is prescribed in one of the following ways (a or b):~~
~~a. For relapsed disease if no progression on PD-L1 checkpoint inhibitor therapy (e.g., Tecentriq® (atezolizumab), Imfinzi® (durvalumab));~~
~~b. For disease that 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 or 400 mg every 6 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.~~C. 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. Keytruda is prescribed in one of the following ways (a, b, or c):
   a. In combination with platinum-containing chemotherapy and FU;
   b. As a first-line single agent and the tumor expresses PD-L1 with a CPS of ≥ 1;
   c. 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 or 400 mg every 6 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.~~D. 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. Keytruda is prescribed as single-agent therapy in one of the following ways (a, b, c, or d):
   a. After hematopoietic stem cell transplant;
   b. For disease that is refractory to ≥ 1 line of systemic therapy (*see Appendix B*);
   c. Age ≥ 18 years: for disease that has relapsed after ≥ 1 line of systemic therapy (*see Appendix B*);

~~4.~~ Age ≥ 2 years to < 18 years: for disease that has relapsed after ≥ 2 lines of systemic therapy (*see Appendix B*);~~Keytruda is prescribed as single-agent therapy in one of the following ways (a or b):~~

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~~a. For disease that is refractory to ≥ 1 line of systemic therapy or has relapsed after ≥ 3 lines of systemic therapy (*see Appendix B*);~~
~~b.~~d. ~~After hematopoietic stem cell transplant;~~
5. Request meets one of the following (a, b, or c):
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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

E. 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 systemic therapy *(see Appendix B)*
5. Request meets one of the following (a, b, or c):
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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

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~~G.~~**F. 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);
   a. For BCG-unresponsive, high-risk, NMIBC with CIS, member is ineligible for or has elected not to undergo cystectomy (*see Appendix D for BCG shortage information*);
5. 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 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.~~G. **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 E for examples of solid tumors)*;
2. Prescribed by or in consultation with an oncologist;
3. Member meets one of the following (a or b):
   a. Age ≥ 2 years to < 18 years and request is not for first-line therapy;
   b. Age ≥ 18 years;
4. Keytruda is prescribed in one of the following ways (a, b, or c):
   a. As first-line or subsequent therapy for colorectal cancer, gallbladder cancer, intrahepatic/extrahepatic cholangiocarcinoma, occult primary tumor;
   b. As first-line therapy for small bowel adenocarcinoma if oxaliplatin contraindication, otherwise subsequent therapy;
   c. As subsequent therapy for other solid tumors;
5. Request meets one of the following (a or b):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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.~~H. **Gastric Cancer or Esophageal Cancer or Gastroesophageal Junction Adenocarcinoma ~~Gastric, EGJ, and Esophageal Adenocarcinoma Cancer~~** (must meet all):
1. Diagnosis of gastric or esophageal cancer or gastroesophageal junction adenocarcinoma~~, 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. Keytruda is prescribed in one of the following ways (a or b or c):
   a. In combination with trastuzumab, fluoropyrimidine- and platinum-containing or platinum- and fluoropyrimidine-based chemotherapy;
   b. As a single agent for the treatment of patients whose tumors express PD-L1 (CPS ≥ 1) and disease has progressed on or after ≥ 2 lines of systemic therapy *(see Appendix B)*;

~~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.~~6. Request meets any of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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

I. 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):
   c. Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks for a maximum of 24 months;
   d. 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 ≥ 1 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 or 400 mg every 6 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.**~~**A. ~~Primary Mediastinal Large B-Cell Lymphoma~~** (must meet all)**:**
1. Diagnosis of PMBCL;
2.1. Prescribed by or in consultation with an oncologist or hematologist;
3.1. Age ≥ 2 years;
4.1. Disease is refractory to or has relapsed after ≥ 1 line of therapy *(see Appendix B)*
6.1. Request meets one of the following (a, b, or c):
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks for a maximum of 24 months;
   b.a. Pediatrics: Dose does not exceed 2 mg/kg (up to 200 mg) every 3 weeks for a maximum of 24 months;
   c.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

~~**L.**~~**J. Hepatocellular Carcinoma** (must meet all):
1. Diagnosis of HCC;

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2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is classified as Child-Pugh Class A and has progressed on or after therapy with Nexavar® or Lenvima®~~;~~
   **Prior authorization is required for Nexavar and Lenvima*
5. Member has not previously been treated with immune checkpoint inhibitor therapy (PD-L1/PD-1, e.g., Tecentriq (atezolizumab), Opdivo (nivolumab));
6. 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 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

~~M.~~K. **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 or 400 mg every 6 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.~~L. **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 or 400 mg every 6 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.~~M. **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*
***See criteria set I.G. for MSI-H/dMMR endometrial carcinoma*

~~b. Disease is MSI-H or dMMR (i.e., disease is indicative of MMR gene mutation or loss of expression);~~

5. Disease has progressed on or after ≥ 1 line of 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 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*).

Approval duration: 6 months

~~P.~~N. **Tumor Mutational Burden-High Cancer** (must meet all):
1. Diagnosis of a solid tumor classified as TMB-H (i.e., ≥ 10 mutations/megabase [mut/Mb]) (*see Appendix E for examples of TMB-H solid tumors*);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 2 years;
4. Disease is unresectable or metastatic, and has progressed following prior treatment;
5. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 200 mg every 3 weeks or 400 mg every 6 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

~~Q.~~O. **Cutaneous Squamous Cell Carcinoma** (must meet all):
1. Diagnosis of cSCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member is not a candidate for curative surgery or radiation;
5. 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 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

P. Triple Negative Breast Cancer (must meet all):
1. Diagnosis of locally recurrent unresectable or metastatic TNBC (i.e., estrogen receptor/progesterone receptor (ER/PR) negative, human epidermal growth factor receptor 2 (HER2)-negative));

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2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Tumor expresses PD-L1 (CPS ≥ 10);
5. Prescribed in combination with chemotherapy (e.g., paclitaxel, paclitaxel protein-bound, gemcitabine and carboplatin);
6. 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 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

~~R.~~Q. **NCCN Recommended Uses (off-label)** (must meet all)**:**

1. Diagnosis of one of the following (a, b, or c)~~One of the following diagnoses~~:
   a. Keytruda is prescribed as first-line 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;
   ~~vi.~~c. Other category 1, 2A, or 2B NCCN-recommended uses not listed;
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

~~S.~~R. **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.PHAR~~A~~.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, or c):*
   a. Adults (i~~, ii,~~ or ~~i~~ii):
      i. Melanoma: New dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks (for a maximum of 12 months if adjuvant treatment);
      ~~ii. Endometrial carcinoma: New dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks;~~

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~~iii.~~ii. All other FDA-approved indications: New dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks for a maximum of 24 months;

b. Pediatrics: cHL, PMBCL, MSI-H cancer, MCC, TMB-H cancer: New dose does not exceed 2 mg/kg up to 200 mg every 3 weeks for a maximum of 24 months;

c. 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.PHAR~~A~~.01) applies; or
2. Refer to PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PMN.53;

B. Pediatric patients with MSI-H or TMB-H central nervous cancers

~~III.~~IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase
BCG: Bacillus Calmette-Guerin
cHL: classical Hodgkin lymphoma
CIS: carcinoma in situ
CNS: central nervous system
CPS: combined positive score
cSCC: cutaneous squamous cell carcinoma
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~~
TMB-H: tumor mutational burden-high
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.

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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.DE: Classical Hodgkin Lymphoma Adults: Examples of chemotherapy regimens: • ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) • Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone) • BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, probarbazine, prednisone) • Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine) Pediatrics: Examples of chemotherapy regimens • AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide) • ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) • Brentuximab vedotin + bendamustine ICE (ifosfamide, carboplatin, etoposide)~~Examples of chemotherapy regimens:~~ ~~• 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)~~	Varies	Varies
Section I.EF: 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*	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
**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*		
Section I.FG: 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 and at Appendix D: 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.HI 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.IK: 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
Section I.JL: Hepatocellular Carcinoma Nexavar (sorafenib)	400 mg PO BID	800 mg/day
Section I.J: Hepatocellular Carcinoma Lenvima (lenvatinib)	12 mg PO QD (patients ≥ 60 kg) or 8 mg PO QD (patients < 60 kg)	12 mg/day
Section I.MO: Endometrial Carcinoma Examples of chemotherapy regimens:*	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
• 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)*		

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: Keytruda Therapy for Urinary Bladder CIS in the Event of a BCG Shortage
- National Comprehensive Cancer Network (NCCN) information and recommendations:
  - Standard urinary bladder CIS therapy includes lesion resection followed by intravesical BCG.
  - The NCCN advises that in the event of a BCG shortage, BCG should be prioritized for induction of high-risk patients (e.g., high-grade T1 and CIS) and that, if feasible, the dose of BCG may be split (1/3 or 1/2 dose) so that multiple patients may be treated with a single vial in the event of a shortage.
  - If BCG is unavailable, the NCCN recommends the following alternatives:
    - Intravesical chemotherapy agents as first-line and subsequent therapy (e.g., gemcitabine, mitomycin, epirubicin, valrubicin, docetaxel, sequential gemcitabine/docetaxel, gemcitabine/mitomycin);
    - Initial radical cystectomy if patient is a surgical candidate.
  - The NCCN recommendations do not include off-label use of Keytruda as first-line or subsequent therapy in the absence of BCG failure.
- In its BCG June 2020 supply update sent to providers, Merck confirms a path forward to expand BCG manufacturing but cautions that the expansion could take years to fully realize. Merck directs providers to their wholesalers and distributors for supply questions and also provides its National Service Center number (800-672-6372) for additional information.

_____
1. *National Comprehensive Cancer Network Guidelines. Bladder Cancer Version 5.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed July 10, 2020.*
2. *Merck Supply Update: TICE BCG BCG LIVE (for intravesical use). June 2020.*

Appendix E: Examples of Solid Tumors per Pivotal Trials by "N" (descending)

MSI-H Solid Tumors	TMB-H Solid Tumors
CRC	SCLC
Endometrial cancer	Cervical cancer
Biliary cancer	Endometrial cancer

MSI-H Solid Tumors	TMB-H Solid Tumors
Gastric or GE junction cancer	Anal cancer
Pancreatic cancer	Vulvar cancer
Small intestinal cancer	Neuroendocrine cancer
Breast cancer	Salivary cancer
Prostate cancer	Thyroid cancer
Bladder cancer	Mesothelioma cancer
Esophageal cancer	*Additional examples - NCCN compendium*: Not currently available.
Sarcoma	
Thyroid cancer	
Retroperitoneal adenocarcinoma	
Small cell lung cancer	
Renal cell cancer	
Additional examples - NCCN compendium: adrenal gland tumor, cervical / vulvar / ovarian / fallopian tube / primary peritoneal cancer, penile cancer, testicular cancer.	

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Pediatrics		
cHL, PMBCL, MSI-H cancer, MCC, TMB-H cancer	2 mg/kg IV every 3 weeks up to 24 months	200 mg every 3 weeks
Adults		
Melanoma	200 mg IV every 3 weeks OR 400 mg every 6 weeks If adjuvant therapy up to 12 months	200 mg every 3 weeks OR 400 mg every 6 weeks
NSCLC, HNSCC, cHL, PMBCL, urothelial carcinoma, MSI-H cancer, gastric cancer, esophageal squamous cell carcinoma, cervical cancer, HCC, MCC, cSCC	200 mg IV every 3 weeks OR 400 mg every 6 weeks up to 24 months* **For NSCLC or HNSCC, single-agent therapy or in combination with chemotherapy.*	200 mg every 3 weeks OR 400 mg every 6 weeks
RCC	200 mg IV every 3 weeks OR 400 mg every 6 weeks in combination with axitinib up to 24 months	200 mg every 3 weeks OR 400 mg every 6 weeks
Endometrial carcinoma	200 mg IV every 3 weeks OR 400 mg every 6 weeks in combination with lenvatinib up to 24 months	200 mg every 3 weeks OR 400 mg every 6 weeks
TNBC	200 mg IV every 3 weeks OR 400 mg every 6 weeks up to 24 months* **In combination with chemotherapy.*	200 mg every 3 weeks OR 400 mg every 6 weeks

~~IV.~~

V. Indication	VI. Dosing Regimen	VII. Maximum Dose
VIII. Melanoma **IX.**	**X.** Adults: 200 mg IV every 3 weeks OR 400 mg every 6 weeks **XI.** If adjuvant therapy, up to 12 months	**XII.** 200 mg every 3 weeks OR 400 mg every 6 weeks
XIII. NSCLC, SCLC, HNSCC, cHL, PMBCL, urothelial carcinoma, MSI-H cancer, gastric cancer, esophageal squamous cell carcinoma, cervical cancer, HCC, MCC, cSCC	**XIV.** Adults: 200 mg IV every 3 weeks OR 400 mg every 6 weeks up to 24 months	**XV.** 200 mg every 3 weeks OR 400 mg every 6 weeks
XVI. cHL, PMBCL, MSI-H cancer, MCC , TMB-H cancer	**XVII.** Pediatrics: 2 mg/kg IV every 3 weeks up to 24 months	**XVIII.** 200 mg every 3 weeks
XIX. RCC	**XX.** Adults: 200 mg IV every 3 weeks OR 400 mg every 6 weeks in combination with axitinib up to 24 months	**XXI.** 200 mg every 3 weeks OR 400 mg every 6 weeks
XXII. Endometrial carcinoma	**XXIII.** Adults: 200 mg IV every 3 weeks OR 400 mg every 6 weeks in combination with lenvatinib	**XXIV.** 200 mg every 3 weeks OR 400 mg every 6 weeks

XXV.

XXVI.VI. Product Availability

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

XXVII.VII. References

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6. National Comprehensive Cancer Network Guidelines. Head and Neck Cancers Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed April 17, 2021.
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~~1.~~ Salem ME, Puccini A, Grothey A, et al. Landscape of tumor mutation load, mismatch repair deficiency, and PD-L1 expression in a large patient cohort of gastrointestinal cancers. Molecular cancer research : MCR. 2018;16(5):805-812. https://pubmed.ncbi.nlm.nih.gov/29523759/~~Keytruda Prescribing Information. Whitehouse Station, NJ: Merck and Co.; June 2020. Available at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed July 10, 2020.~~

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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: o Added age restriction to 18 yr and older o Added advanced disease for coverage	04/2020	

Reviews, Revisions, and Approvals	Date	Approval Date
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 o Disease characteristics (e.g., metastatic) are removed to encompass NCCN recommended uses • Gastric, EGJ, or esophageal adenocarcinoma criteria changes:		

Reviews, Revisions, and Approvals	Date	Approval Date
○ 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		
3Q 2020 annual review: new FDA approved dosing of 400 mg every 6 weeks added to all labeled adult indications; NSCLC: first-line removed from combination with chemotherapy per NCCN; brain metastasis moved under PD-L1 positive disease per NCCN; SCLC: relapsed disease added per NCCN; cHL: Keytruda as single-agent therapy added per NCCN; HNSCC: first-line therapy requirement removed from combination platinum/FU therapy per NCCN; MSI-H/dMMR tumors: first-line therapy for occult primary tumor and small bowel added per NCCN; HCC: Child-Pugh Class A added per NCCN/pivotal trial with no prior checkpoint inhibitor therapy caveat per NCCN; three new FDA approved indications added: 1) MSI-H/dMMR CRC first-line (adults), 2) TMB-H (adults/pediatrics), 3) cSCC (adults); NCCN off-label Keytruda use as first-line for MSI-H tumors is limited to adults; NCCN off-label criteria set is limited to adults; endometrial carcinoma criteria set is limited to 24 months of therapy; MSI-H/TMB-H CNS tumors excluded	07/2020	

Reviews, Revisions, and Approvals	Date	Approval Date
for pediatrics per PI; indication table added with directives to MSI-H/TMB-H criteria sets for appropriate cancers; BCG appendix D added; TMB-H solid tumor examples added to appendix E; references reviewed and updated; references reviewed and updated.		
3Q 2021 annual review: FDA cHL label updated from relapsed disease after 3 lines of therapy to after 1 line of therapy (adults) or 2 lines of therapy (pediatrics); new NCCN pediatric cHL guideline added to reference section; new FDA-approved TNBC indication added; for HCC, Lenvima added as a prior therapy option per NCCN. Newly approved indication of esophageal/GEJ junction carcinoma and new indication for combo use for 1st line gastric or GEJ adenocarcinoma were added AND removal of SCLC indication; references reviewed and updated.	07/2021	

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