Clinical Policy: Pembrolizumab (Keytruda)

Reference Number: ERX.SPA.263
Effective Date: 12.01.18
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Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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

FDA Approved Indication(s)

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.G or I.N 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

- **Head and neck squamous cell cancer (HNSCC)**
  - In combination with platinum and 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.
- **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*
  - Limitations 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 (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 (MSI-H) or mismatch repair deficient (dMMR) cancer**
  - For the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR* solid tumors 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 MSI-H central nervous system cancers have not been established
- **Microsatellite instability-high or mismatch repair deficient colorectal cancer (CRC)**
  - For the 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 GEJ (esophagogastric junction; EGJ) adenocarcinoma whose tumors express PD-L1 (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 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 ≥ 10) 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 ≥ 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**
  - 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 tumor mutational burden-high (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 or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.
- **Triple-negative breast cancer (TNBC)**
  - For the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery
  - 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.*

Contents:

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Keytruda is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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)*.

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

Approval duration: 6 months

B. Non-Small Cell Lung Cancer (must meet all)**:**
1. Diagnosis of 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 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: 6 months

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. 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: 6 months

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

1. Diagnosis of 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*);
   d. Age ≥ 2 years to < 18 years: for disease that has relapsed after ≥ 2 lines 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)*.

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

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*).

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

Approval duration: 6 months

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. Keytruda is prescribed in one of the following way (a or b):
   a. For locally advanced or metastatic disease, and member is ineligible for or has previously received platinum-containing chemotherapy (e.g., cisplatin, carboplatin);
   b. For BCG-unresponsive, high-risk, NMIBC with CIS, and 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*).

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

Approval duration: 6 months

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 CRC, 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, 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*).

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

Approval duration: 6 months

H. Gastric Cancer, Esophageal Cancer, or Gastroesophageal Junction Adenocarcinoma (must meet all)**:**
1. Diagnosis of gastric cancer, esophageal cancer, or GEJ 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, 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)*;
c. 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) *(see Appendix B)*;

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)*.

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

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. Tumor expresses PD-L1 (CPS ≥ 1);
6. Disease has progressed on or after ≥ 1 line of systemic therapy *(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 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: 6 months

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

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

Approval duration: 6 months

K. Merkel Cell Carcinoma (must meet all)**:**
1. Diagnosis of MCC;
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*).

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

Approval duration: 6 months

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*).

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

Approval duration: 6 months

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

1. Diagnosis of endometrial carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in combination with Lenvima®* ;
   **Prior authorization may be required for Lenvima*
5. Disease is not MSI-H or dMMR* (i.e., disease is not indicative of MMR gene mutation or loss of expression);
   **See criteria set I.G for MSI-H/dMMR endometrial carcinoma*
6. Disease has progressed following prior systemic therapy (e.g., carboplatin/paclitaxel);
7. Member is not a candidate for curative surgery or radiation;
8. 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*).

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

Approval duration: 6 months

N. Tumor Mutation 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*).

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

Approval duration: 6 months

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*).

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

Approval duration: 6 months

P. Triple Negative Breast Cancer (must meet all)**:**
1. Diagnosis of TNBC (i.e., estrogen receptor/progesterone receptor (ER/PR) negative and human epidermal growth factor receptor 2 (HER2)-negative);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. Disease is high-risk early-stage (*see Appendix F*), and:
      i. Prescribed in combination with chemotherapy (e.g., carboplatin, paclitaxel, doxorubicin, cyclophosphamide) as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery;
   b. Disease is locally recurrent unresectable or metastatic, and both of the following (i and ii):
      i. Tumor expresses PD-L1 (CPS ≥ 10);
      ii. Prescribed in combination with chemotherapy (e.g., paclitaxel, paclitaxel protein-bound, gemcitabine and carboplatin);
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 (i or ii)
      i. High-risk, early-stage TNBC: 24 weeks as neoadjuvant therapy and 27 weeks as adjuvant therapy;
      ii. Locally recurrent unresectable or metastatic TNBC: 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: 6 months

Q. NCCN Recommended Uses (off-label) (must meet all)**:**
1. Diagnosis of one of the following (a or b):
   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;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. 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*).*

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

Approval duration: 6 months

R. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Keytruda for a covered indication and has received this medication for at least 30 days;
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 iii):
      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. High-risk, early-stage TNBC: New dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks for a maximum of 24 weeks as neoadjuvant therapy and 27 weeks as adjuvant therapy;
      iii. 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*).

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

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 or evidence of coverage documents;

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

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
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
mut/Mb: mutations/megabase
NCCN: National Comprehensive Cancer Network
NMIBC: non-muscle invasive bladder cancer
NSCLC: non-small cell lung cancer
PD-1: programmed death 1
PD-L1: programmed death ligand 1

RCC: renal cell carcinoma
ROS1: ROS proto-oncogene 1
TMB-H: tumor mutational burden-high
TNBC: triple-negative breast 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 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.D: 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)	Varies	Varies
Section I.E: 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.F: 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	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
3. Centers for Disease Control's current shortages page: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages		
Section I.H: 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.I: 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.J: 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.M: 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: 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	Small cell lung cancer
Endometrial cancer	Cervical cancer
Biliary cancer	Endometrial cancer
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.	

Appendix F: General Information

- High-risk early-stage TNBC was defined as tumor size > 1 cm but ≤ 2 cm in diameter with nodal involvement or tumor size > 2 cm in diameter regardless of nodal involvement in the pivotal KEYNOTE-522 study.

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	200 mg IV every 3 weeks OR 400 mg every 6 weeks up to 24 months*	200 mg every 3 weeks OR 400 mg every 6 weeks

Indication	Dosing Regimen	Maximum Dose
squamous cell carcinoma, cervical cancer, HCC, MCC, cSCC	**For NSCLC or HNSCC, single-agent therapy or in combination with chemotherapy.*	
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* for the following durations: • High-risk early-stage TNBC – neoadjuvant: 24 weeks • High-risk early-stage TNBC – adjuvant: 27 weeks • Locally recurrent unresectable metastatic TNBC: 24 months _____ **In combination with chemotherapy for high-risk early-stage TNBC when used as neoadjuvant treatment and for locally recurrent unresectable or metastatic TNBC.*	200 mg every 3 weeks OR 400 mg every 6 weeks

VI. Product Availability

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

VII. References

1. Keytruda Prescribing Information. Whitehouse Station, NJ: Merck and Co.; July 2021. Available at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed July 28, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at https://www.nccn.org/professionals/drug_compendium/content/. Accessed April 17, 2021.
3. National Comprehensive Cancer Network Guidelines. Cutaneous Melanoma Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed April 17, 2021.
4. National Comprehensive Cancer Network Guidelines. Uveal Melanoma Version 3.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf. Accessed April 17, 2021.
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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.
7. National Comprehensive Cancer Network Guidelines. Hodgkin Lymphoma Version 3.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed April 17, 2021.
8. National Comprehensive Cancer Network. Pediatric Hodgkin Lymphoma Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/ped_hodgkin.pdf. Accessed April 17, 2021.
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10. National Comprehensive Cancer Network Guidelines. Bladder Cancer Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed April 17, 2021.
11. National Comprehensive Cancer Network Guidelines. Gastric Cancer Version 2.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed April 17, 2021.
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13. National Comprehensive Cancer Network. Cervical Cancer Version 1.2021. Available at www.nccn.org. Accessed April 17, 2021.
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20. 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/

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	08.07.18	11.18
Added requirement for negative or unknown EGFR, ALK, ROS1, or BRAF tumor status per updated FDA indication and NCCN compendium for first-line use in metastatic nonsquamous NSCLC in combo with platinum chemotherapy and pemetrexed; streamlined criteria for subsequent use in NSCLC; references reviewed and updated.	10.02.18	02.19
Criteria added for new FDA indications HCC, MCC, and as first-line therapy for metastatic squamous NSCLC in combination with chemotherapy; re-added criteria for PMBCL as previously approved; references reviewed and updated.	01.11.19	02.19
Criteria added for new FDA indications: 1) melanoma for adjuvant treatment is incorporated by adding lymph node positive disease; complete resection is not required given additional NCCN recommended uses; age is adjusted from 2 to 18 years and older per the FDA label's indication and pediatric sections; 2) renal cell carcinoma; 3) advanced (stage III) NSCLC. NSCLC: single-agent therapy for brain metastasis is added per NCCN; removal of histology requirements; mutational status requirements are limited to EGFR and ALK per the FDA label for primary therapy and to the 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%. HNSCC: locations as examples are incorporated into the criteria set; oxaliplatin is removed as an example as it is not listed as an NCCN recommendation for this cancer. cHL and PMBCL: refractory disease is clarified by specifying at least one line of therapy; transplantation is included as a line of therapy option. Urothelial carcinoma: progression as a response to platinum therapy is removed as response may include persistence or partial response. MSI-H cancer: appendix updated to include solid tumors listed in the NCCN compendium and FDA label; subsequent therapy requirement is removed where recommended per NCCN; disease characteristics (e.g., metastatic) are removed to encompass NCCN recommended uses.	04.23.19	05.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Gastric cancer: esophageal cancer and unresectable disease are added; systemic therapy examples are expanded per NCCN. Cervical cancer: chemotherapy examples are expanded per NCCN. Additional NCCN recommended uses are added as a new Section L with notation of primary versus subsequent therapy requirements. Appendix B and references are reviewed and updated.		
Added pediatric maximum dosing recommendations for all indications applicable to pediatrics: cHL, PMBCL, MSI-H cancer, and MCC.	05.06.19	
Criteria added for new FDA indications: 1) SCLC (previously included per NCCN as subsequent therapy; updated criteria maintains subsequent therapy but specifies prior platinum therapy; 2) HNSCC (previously post platinum therapy only; new indications 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; 3) dosing for all indications is limited to 24 months per the PI with the exception of melanoma and off-label uses in section I.N; 4) dosing for adjuvant melanoma therapy is limited to 12 months per the PI; 5) boilerplate language is added to all dosing sections: "Prescribed regimen must be FDA-approved or recommended by NCCN"; references reviewed and updated.	07.09.19	08.19
4Q 2019 annual review: criteria added for new FDA indication for esophageal squamous cell carcinoma; criteria added for new FDA indication in endometrial carcinoma; added chondrosarcomas as another example of an NCCN-supported MSI-H/dMMR tumor type in *Appendix D*; references reviewed and updated.	10.15.19	11.19
Criteria added for new FDA indication: NMIBC-CIS; urologist added for UC; removed 50 mg powder single-dose vial formulation; references reviewed and updated.	02.11.20	05.20
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 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.	07.14.20	08.20
RT4: 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. Ad hoc change: for HCC, Lenvima added as a prior therapy option per NCCN.	11.16.20	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2021 annual review: RT4: criteria added for newly approved indications of 1) esophageal/GEJ junction carcinoma, 2) combo use for 1st line gastric or GEJ adenocarcinoma, 3) locally advanced cSCC, and 4) high-risk early-stage TNBC; removed SCLC indication and criteria; updated FDA labeled indication for endometrial carcinoma to remove accelerated approval language and modified criteria to be consistent with FDA language; updated FDA labeled indication language for MSI-H/dMMR cancer; references reviewed and updated.	05.11.21	08.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.