Clinical Policy: Pembrolizumab (Keytruda)

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Line of Business: Commercial, HIM, Medicaid

Coding Implications
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	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	
Off-label uses		
Mycosis fungoides	X	
Sezary syndrome	X	
Anal carcinoma	X	
Gestational trophoblastic neoplasia	X	
Extranodal NK/T-cell lymphoma	X	
Vulvar carcinoma	X	
Adrenocortical carcinoma	X	
Alveolar soft part sarcoma	X	
Thymic carcinoma	X	
Anaplastic large cell lymphoma	X	
Small cell lung cancer	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 adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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.
  - As a single agent for the adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC.
- **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.
- **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 any platinum-containing chemotherapy, or

        - 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, 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 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 as determined by an FDA-approved test.
- **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.*
- **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**
    - In combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
    - As a single agent 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)**
  - In combination with axitinib, for the first-line treatment of patients with advanced RCC.
  - In combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
  - For the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.
- **Endometrial carcinoma**
  - In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
  - As a single agent for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting 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 (CPS ≥ 10) as determined by an FDA approved test.
- **Adult cHL and adult PMBCL**
  - For use at an additional recommended dosage of 400 mg every 6 weeks for cHL and PMBCL in adults.**

** 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.

It is the policy of health plans affiliated with Centene Corporation® 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 ≥ 12 years;
4. Disease is Stage IIB, IIC, III, recurrent, unresectable, or metastatic;
5. Prescribed as a single agent or in combination with Lenvima® or Yervoy®;
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 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:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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. Request meets one of the following (a, b, c, d, e, or f):
   a. Disease mutation status is negative for actionable biomarkers (EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 [HER2]);
   b. Disease mutation status is positive for EGFR S768I, L861Q, and/or G719X, and member has received prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib;*
   c. Disease mutation status is positive for EGFR exon 19 deletion or L858R, and member has received prior erlotinib ± (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, or dacomitinib;*
   d. Disease mutation status is positive for ROS1 rearrangement, and member has received prior crizotinib, entrectinib, or ceritinib;*
   e. Disease mutation status is positive for ALK rearrangement, and member has received prior crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib;*
   f. Disease mutation status is positive for EGFR exon 20, KRAS G12C, NRTK1/2/3, BRAF V600E, MET exon 14 skipping, RET rearrangement, or ERBB2 (HER2);

   **Prior authorization may be required*
6. Keytruda is prescribed in one of the following ways (a, b, c, or d):
   a. For PD-L1 positive disease (TPS ≥ 1%);
   b. In combination with a chemotherapy regimen *(see Appendix B)*;
   c. As single-agent continuation maintenance therapy if previously given first line as part of a chemotherapy regimen;
   d. As single-agent adjuvant treatment following resection and platinum-based chemotherapy (e.g., cisplatin, carboplatin) for adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA disease;
7. Member does not have contraindications to PD-1/PD-L1 inhibitor therapy (e.g., Opdivo®, Yervoy, Tecentriq®, Imfinzi®) (*see Appendix F*);
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 duration of one of the following (i or ii):
      i. 24 months;
      ii. 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*).

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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 either FU, docetaxel, or gemcitabine;
   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)*.

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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 (*adults or pediatrics*) or in combination with GVD (gemcitabine, vinorelbine, liposomal doxorubicin) (*adults only*) 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)*.

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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. Prescribed as a single agent;
6. 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)*.

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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 ways (a or b):
   a. As a single agent 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*).

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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 MSI-H 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 or b):
   a. As first-line or subsequent therapy for ampullary adenocarcinoma, CRC, gallbladder cancer, intrahepatic/extrahepatic cholangiocarcinoma, non-

nasopharyngeal head and neck cancer, occult primary tumor, pancreatic adenocarcinoma, or small bowel adenocarcinoma;
   b. As subsequent therapy for other solid tumors;
5. Prescribed as a single agent;
6. 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*).

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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, or b):
   a. In combination with trastuzumab, fluoropyrimidine- and platinum-containing or platinum- and fluoropyrimidine-based chemotherapy;
   b. 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)*.

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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. Tumor expresses PD-L1 (CPS ≥ 1);
5. Prescribed in one of the following ways (a or b):
   a. As a single agent, and (i and ii):
      i. Disease is recurrent or metastatic;

ii. Disease has progressed on or after ≥ 1 line of systemic therapy *(see Appendix B)*;

b. In combination with chemotherapy (e.g., paclitaxel/cisplatin, paclitaxel/carboplatin) with or without bevacizumab, and (i):
   i. Disease is persistent, recurrent, or metastatic;

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*).

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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, Opdivo);
6. Prescribed as a single agent;
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)*.

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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*).

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L. Renal Cell Carcinoma (must meet all)**:**
1. Diagnosis of RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Keytruda is prescribed in one of the following ways (a, b, or c):
   a. In combination with Inlyta® or Lenvima*, and disease is advanced (i.e., relapsed or stage IV);
      **Prior authorization may be required for Inlyta and Lenvima.*
   b. As single-agent adjuvant treatment, and member is at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions;
   c. As a single agent for relapsed or stage IV disease with non-clear cell histology (off-label);
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 (combination therapy) or 12 months (monotherapy);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

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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 pMMR or not MSI-H;*
   **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*).

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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;
5. One of the following (a or b):
   a. Disease has progressed following prior treatment;
   b. Prescribed as a first-line therapy for ampullary adenocarcinoma or pancreatic adenocarcinoma;
6. Prescribed as a single agent;
7. 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*).

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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. Prescribed as a single agent;
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*).

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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*).

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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 IIB or III mycosis fungoides;
      ii. Stage IV Sezary syndrome;
      iii. Unresectable or metastatic adrenocortical carcinoma;
      iv. Alveolar soft part sarcoma;
      v. Metastatic or unresectable thymic carcinoma, and prescribed as a single agent;
   b. Keytruda is prescribed as single-agent subsequent therapy:
      i. Metastatic anal carcinoma, and member has not previously received Keytruda or Opdivo;
      ii. Gestational trophoblastic neoplasia;
      iii. Extranodal NK/T-cell lymphoma;
      iv. Advanced, recurrent, or metastatic PD-L1-positive (CPS ≥ 1) vulvar carcinoma;
      v. Relapsed or refractory cutaneous anaplastic large cell lymphoma;
      vi. Relapsed or primary progressive small cell lung cancer;
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:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

R. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit, 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, iii, iv, or v):
      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. RCC monotherapy: New dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks for a maximum of 12 months;
      iv. NSCLC: New dose does not exceed 200 mg every 3 weeks or 400 mg every 6 weeks for a maximum duration of one of the following (a or b):
         a) 24 months;
         b) 12 months if adjuvant treatment;
      v. 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 (i or ii):
      i. cHL, PMBCL, MSI-H or dMMR 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;
      ii. Melanoma: New dose does not exceed 2 mg/kg up to 200 mg every 3 weeks for a maximum of 12 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:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents;

B. Pediatric patients with MSI-H or TMB-H central nervous 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 protein 1
PD-L1: programmed death-ligand 1
PMBCL: primary mediastinal large B-cell lymphoma
pMMR: mismatch repair proficient
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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Section I.B: Non-Small Cell Lung Cancer Examples of drugs used in combination with Keytruda: • Carboplatin, cisplatin, pemetrexed, paclitaxel Examples of targeted therapies: • EGFR S768I, L861Q, and/or G719X targeted therapies: afatinib, osimertinib, erlotinib, gefitinib, dacomitinib • EGFR exon 19 deletion or L858R targeted therapies: erlotinib ± (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, dacomitinib • ROS1 targeted therapies: crizotinib, entrectinib, ceritinib • ALK rearrangement targeted therapies: crizotinib, ceritinib, alectinib, brigatinib, lorlatinib	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:	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
• Bendamustine, brentuximab vedotin, carboplatin, cisplatin, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, gemcitabine, ibrutinib, ifosfamide, lenalidomide, mesna, mitoxantrone, methylprednisolone, oxaliplatin, prednisone, procarbazine, rituximab, vincristine, vinorelbine* **Various combinations of the listed drugs are components of the following chemotherapy regimens: CEOP, CEPP, DHAP, DHAX, EPOCH-R, ESHAP, GDP, GemOx, ICE, MINE, RCDOP, RCEOP, RCEPP, RCHOP, RGCVP*		
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 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.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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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 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*: Adrenal tumor, ampullary adenocarcinoma, breast cancer, chondroma, cutaneous angiosarcoma, Ewing sarcoma, myxofibrosarcoma, nasopharynx cancer, occult primary carcinoma, osteosarcoma, pancreatic cancer, prostate cancer, testicular cancer, undifferentiated sarcoma or pleomorphic sarcoma
Sarcoma	
Thyroid cancer	
Retroperitoneal adenocarcinoma	
Small cell lung cancer	
Renal cell cancer	
Additional examples – NCCN compendium: Adrenal tumor, ampullary adenocarcinoma, cervical / vulvar / ovarian / fallopian tube / primary peritoneal cancer, chondroma, Ewing sarcoma, occult primary carcinoma, osteosarcoma, penile cancer, small bowel adenocarcinoma, testicular cancer, vulvar 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.
- Although Keytruda's approval for small cell lung cancer was withdrawn due to lack improvement in overall survival in phase 3 randomized trial data, the NCCN continues to recommend this use, stating that "pembrolizumab [is] just as effective as, and sometimes better than, the other subsequent therapy options."
- Per NCCN, contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or presence of an oncogene (i.e., EGFR exon 19 deletion or exon 21 L858R, ALK rearrangements), which has been shown to be associated with less benefit.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Pediatrics		
cHL, PMBCL, MSI-H or dMMR cancer, MCC, TMB-H cancer	2 mg/kg IV every 3 weeks up to 24 months	200 mg every 3 weeks
Melanoma	2 mg/kg IV every 3 weeks up to 12 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	200 mg IV every 3 weeks OR 400 mg every 6 weeks up to 24 months* OR up to 12 months for adjuvant treatment** _____ **As single-agent therapy or in combination with chemotherapy* ***As single-agent therapy*	200 mg every 3 weeks OR 400 mg every 6 weeks
HNSCC, cHL, PMBCL, urothelial carcinoma, MSI-H or dMMR cancer (including endometrial carcinoma), gastric cancer, esophageal squamous cell carcinoma, cervical cancer, HCC, MCC, TMB-H cancer, cSCC	200 mg IV every 3 weeks OR 400 mg every 6 weeks up to 24 months* _____ **For cervical cancer, esophageal cancer, gastric cancer, or HNSCC: as single-agent therapy or in combination with chemotherapy.*	200 mg every 3 weeks OR 400 mg every 6 weeks
RCC (combination therapy)	200 mg IV every 3 weeks OR 400 mg every 6 weeks in combination with axitinib or lenvatinib up to 24 months	200 mg every 3 weeks OR 400 mg every 6 weeks
RCC (monotherapy)	200 mg IV every 3 weeks OR 400 mg every 6 weeks for up to 12 months	200 mg every 3 weeks OR 400 mg every 6 weeks
Non-MSI-H/pMMR endometrial carcinoma (combination therapy)	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	200 mg every 3 weeks OR 400 mg every 6 weeks

Indication	Dosing Regimen	Maximum Dose
	_____ **In combination with chemotherapy for high-risk early-stage TNBC when used as neoadjuvant treatment and for locally recurrent unresectable or metastatic TNBC.*	

VI. Product Availability

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

VII. References

1. Keytruda Prescribing Information. Whitehouse Station, NJ: Merck and Co.; January 2023. Available at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed February 8, 2023.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at https://www.nccn.org/professionals/drug_compendium/content/. Accessed February 8, 2023.
3. 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/

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, 1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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 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.	11.27.18	02.19
No clinical changes: off-label designation removed for MCC as it is now FDA approved.	01.31.19	02.19
Criteria added for new FDA indications: 1) melanoma for adjuvant treatment is incorporated by adding lymph node positive disease;	04.23.19	05.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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 additional NCCN directed requirement of prior ROS1 targeted therapy; subsequent therapy requirement for platinum-based chemotherapy when TPS ≥ 1% is removed since Keytruda is now FDA-approved as first-line therapy when TPS ≥ 1%. 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. 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 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	07.09.19	08.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
regimen must be FDA-approved or recommended by NCCN"; references reviewed and updated.		
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; HIM line of business added; 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	
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 cutaneous squamous cell carcinoma, 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;	05.11.21	08.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
added Legacy WellCare with 12 month initial approval durations (WCG.CP.PHAR.322 to be retired); updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.		
RT4: criteria added for new FDA approved indication: RCC in combination with lenvatinib.	08.20.21	
RT4: updated FDA Approved Indication(s) section to reflect revised indication for metastatic urothelial carcinoma (removal of use in patients "who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test") – no change to criteria required.	09.15.21	
RT4: criteria added for new FDA approved indication: cervical cancer in combination with chemotherapy with or without bevacizumab.	10.19.21	
RT4: criteria added for new FDA approved indication: adjuvant treatment of RCC.	12.01.21	
RT4: for melanoma criteria added per updated prescribing information for pediatric extension in stage III disease and new indications for both adults and pediatrics for stage IIB and IIC; for RCC clarified maximum dosing for initial and continued approvals to distinguish length of therapy for 12 months in monotherapy and 24 months for combination therapy.	12.20.21	
RT4: removal of previously approved indication for usage as third-line monotherapy for PD-L1 positive gastric/GEJ cancer patients per updated prescribing information.	02.25.22	
3Q 2022 annual review: RT4: updated FDA Approved Indication(s) section to include newly approved indication for use as monotherapy for MSI-H or dMMR endometrial carcinoma (no change to criteria required); revisions per NCCN – melanoma: added requirement for use as a single agent or in combination with Lenvima or Yervoy; NSCLC: added requirement for no contraindications to PD-1/PD-L1 inhibitors, clarified criteria regarding disease mutation status (disease should be negative for actionable biomarkers and prior targeted therapy is now required only for ROS1 and EGFR S768I, L861Q, and/or G719X mutations), added pathway for use as single-agent continuation maintenance therapy if previously given first line as part of a chemotherapy regimen; HNSCC: added pathway for combination use with docetaxel or gemcitabine; cHL: added pathway for combination use with GVD in adults; cSCC, HCC, PMBCL: added requirement for use as a single agent; urothelial carcinoma: added requirement for use as a single agent for locally advanced or metastatic disease in members who are ineligible for or have previously received platinum-containing chemotherapy; MSI-H/dMMR cancers: added additional cancers for which Keytruda may	05.03.22	08.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
be used first line (ampullary adenocarcinoma, non-nasopharyngeal head and neck cancer, pancreatic adenocarcinoma), removed requirement for oxaliplatin contraindication for small bowel adenocarcinoma, added requirement for use as a single agent; RCC: added requirement for use as a single agent for adjuvant treatment; TMB-H cancer: added pathway for use as first-line for ampullary adenocarcinoma or pancreatic adenocarcinoma, added requirement for use as a single agent; off-label uses: added additional coverable cancers (adrenocortical carcinoma, alveolar soft part sarcoma, anaplastic large cell lymphoma, small cell lung cancer), added pathway for use as first line for thymic carcinoma, removed use for malignant pleural mesothelioma, updated mycosis fungoides to allow stage IIB, updated anal carcinoma to require no prior treatment with Keytruda or Opdivo, updated cancers where Keytruda is to be used only as subsequent therapy to require use as a single agent, updated extranodal NK/T-cell lymphoma to remove nasal type specification; revised legacy WellCare Medicaid initial approval durations from 12 months to 6 months to align with CNC Medicaid; references reviewed and updated.		
RT4: for endometrial carcinoma for use in combination with Lenvima, revised dMMR to pMMR per updated FDA approved indication. Template changes applied to other diagnoses/indications.	08.23.22	
RT4: added criteria for newly FDA approved indication of single-agent adjuvant therapy for NSCLC, added "as determined by an FDA-approved test" for MSI-H/dMMR cancer and microsatellite instability-high or mismatch repair deficient CRC, and revised "adult indications: additional dosing regimen" to apply only to adult cHL and PMBCL per updated PI; revised NSCLC criteria to include additional requirements related to mutation status per NCCN compendium; references reviewed and updated.	02.08.23	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.