Clinical Policy: Pembrolizumab (Keytruda)

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

Coding Implications
Revision Log

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

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

- **Melanoma**
  - For the treatment of patients with unresectable or metastatic melanoma.
- **Non-Small Cell Lung Cancer (NSCLC)**
  - As a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations
  - 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
  - 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
- **Head and Neck Squamous Cell Cancer (HNSCC)**
  - For the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy*
- **Classical Hodgkin Lymphoma (cHL)**
  - For the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy*
- **Urothelial Carcinoma**
  - For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status*
  - For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- **Microsatellite Instability-High Cancer**
  - For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)*
    - Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or

    - Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
  - Limitation(s) of use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established
- **Gastric Cancer**
  - For the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy.*
- **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*
- **Primary Mediastinal Large B-Cell Lymphoma (PMBCL)**
  - For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy*
  - Limitation(s) of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy
- **Hepatocellular Carcinoma (HCC)**
  - For the treatment of patients with HCC who have been previously treated with sorafenib*

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

Policy/Criteria

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

I. Initial Approval Criteria

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

1. Diagnosis of recurrent or metastatic cervical cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Tumors express PD-L1 [CPS ≥ 1];
5. Disease has progressed on or after at least one chemotherapy regimen (e.g., single-agent cisplatin, carboplatin, paclitaxel, or combination regimens containing these agents);
6. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

B. Melanoma (must meet all):

1. Diagnosis of unresectable or metastatic melanoma (including uveal melanoma [off-label]);
2. Prescribed by or in consultation with an oncologist;
3. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

C. Non-Small Cell Lung Cancer (must meet all):
1. Diagnosis of non-small cell lung cancer (NSCLC);
2. Prescribed by or in consultation with an oncologist;
3. Disease is recurrent or metastatic;
4. Meets on of the following (a, b, or c):
   a. EGFR, ALK, ROS1, and BRAF mutation status is negative or unknown and one of the following (i or ii):
      i. Disease is non-squamous and Keytruda is prescribed in combination with pemetrexed and platinum chemotherapy (e.g., carboplatin, cisplatin);
      ii. Tumor PD-L1 expression ≥ 50% (TPS);
   b. Tumor PD-L1 expression ≥ 1% (TPS) and disease has progressed on or after previous line therapy (*see Appendix F*);
   c. Disease is squamous and Keytruda is prescribed in combination with carboplatin and either paclitaxel or nab-paclitaxel;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

D. Head and Neck Squamous Cell Carcinoma (must meet all):
1. Diagnosis of head and neck squamous cell carcinoma (HNSCC) (see Appendix B for subtypes by location);
2. Disease has progressed on or after platinum-containing chemotherapy;
3. Meets a or b:
   a. FDA approved use:
      i. Disease is recurrent or metastatic;
   b. Off-label NCCN recommended use:
      i. Prescribed as a single agent (a, b or c):
         a) Disease or other factors preclude surgery;
         b) Very advanced (T4b*) nonmetastatic disease;
         c) Unresectable disease with the following characteristics (1 or 2):
            1) Nodal disease with no metastases;
            2) Second primary tumor and member has received prior radiation therapy.

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

**American Joint Committee on Cancer () TNM staging classification (7th ed., 2010) as reported in NCCN Head and Neck Cancers: T (primary tumor characteristics); N (regional lymph nodes); M (metastatic disease).*

Approval duration: 6 months

E. Classical Hodgkin Lymphoma (must meet all):
1. Diagnosis of classical Hodgkin lymphoma (cHL);
2. Meets one of the following (a or b):
    a. FDA approved use (i or ii):
        i. Disease is refractory (defined as disease that does not improve or go away in response to treatment);
        ii. Member has relapsed (defined as worsening or return of cancer after a period of improvement) after 3 or more prior lines of therapy;
    b. Off-label NCCN recommended use (i or ii):
        i. Age ≥ 18 years, and member has relapsed after treatment with brentuximab vedotin;
        ii. Age > 60 years, and Keytruda will be used as palliative therapy for relapsed or refractory disease;
3. Request meets one of the following (a or b):
    a. Dose does not exceed 200 mg (2 mg/kg [maximum 200 mg] if age < 18 years) every 3 weeks;
    b. Requested dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

F. Urothelial Carcinoma (must meet all):
1. Diagnosis of urothelial carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Meets one of the following (a or b):
    a. Member is not eligible for platinum-containing chemotherapy;
    b. Disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;
4. Request meets one of the following (a or b):
    a. Dose does not exceed 200 mg every 3 weeks;
    b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

G. Microsatellite Instability-High Cancer (must meet all):
1. Diagnosis of MSI-H or dMMR cancer;
2. Prescribed by or in consultation with an oncologist;
3. Disease is unresectable or metastatic;
4. Meets one of the following (a, b or c):
   a. Colorectal cancer (*colon cancer, rectal cancer, or both*);
   b. Other solid tumors (*see Appendix E for examples*): Disease progressed following prior treatment;
   c. Hepatobiliary cancer (gallbladder, intra/extra-hepatic cholangiocarcinoma) [off-label];
5. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

H. Gastric Cancer (must meet all):
1. Diagnosis of recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Tumors express PD-L1 [Combined Positive Score (CPS) ≥1];
4. Disease has progressed on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy;
5. Request meets any of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

I. Primary Mediastinal Large B-Cell Lymphoma (must meet all)**:**
5. Diagnosis of PMBCL;
6. Prescribed by or in consultation with an oncologist or hematologist;
7. Age ≥ 2 years;
8. Disease is refractory or member has relapsed after one or more chemotherapy regimens (e.g., EPOCH-R, RCHOP, RCHOP followed by ICE);
9. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

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 has progressed on or after therapy with Nexavar®;
   **Prior authorization is required for Nexavar*
5. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration: 6 months

K. Merkel Cell Carcinoma (off-label) (must meet all)**:**
1. Diagnosis of Merkel cell carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

L. Other diagnoses/indications: Refer to CP.PMN.53.

II. Continued Approval

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PA.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
   a. New dose does not exceed 200 mg every 3 weeks;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

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

Background

Description/Mechanism of Action:

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase
cHL: classical Hodgkin lymphoma
CPS: combined positive score
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
EPOCH-R: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin + rituximab
FDA: Food and Drug Administration
HCC: hepatocellular carcinoma
HER2: human epidermal growth factor receptor 2
HNSCC: head and neck squamous cell carcinoma
ICE: ifosfamide, carboplatin, etoposide
MSI-H: microsatellite instability-high
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer
PD-1: programmed cell death protein 1
PD-L1/2: programmed death-ligand 1/2
RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
ROS1: ROS proto-oncogene 1, receptor tyrosine kinase
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
Various chemotherapy regimens	PMBCL first-line therapy: EPOCH-R, RCHOP, RCHOP followed by ICE PMBCL – intend to proceed to high-dose therapy: • DHAP (dexamethasone, cisplatin, cytarabine) ± R • ESHAP (etoposide (Toposar®), methylprednisolone, cytarabine, cisplatin) ± R • GDP (gemcitabine (Gemzar®), dexamethasone, cisplatin/carboplatin) ± R • GemOx (gemcitabine (Gemzar®), oxaliplatin_± R	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	• ICE (ifosfamide (Ifex®), carboplatin, etoposide (Toposar)) ± R • MINE (mesna (Mesnex®), ifosfamide (Ifex®), mitoxantrone, etoposide (Toposar®)) ± R PMBCL – non-candidates for high-dose therapy: • Bendamustine ± R • CEPP (cyclophosphamide, etoposide (Toposar®), prednisone, Matulane® (procarbazine)) ± R • CEOP (cyclophosphamide, etoposide (Toposar®), vincristine (Vincasar®), prednisone) ± R • DA-EPOCH ± R • GDP ± R • GemOx ± R	
cisplatin, carboplatin, paclitaxel, or combination regimens containing these agents	Cervical Cancer: Varies	Varies
Xalkori® (crizotinib)	NSCLC: 250 mg PO BID	500 mg/day
Zykadia® (ceritinib)	NSCLC: 450 mg PO QD	450 mg/day
Tafinlar® (dabrafenib) with Mekinist® (trametinib)	NSCLC: Tafinlar: 150 mg PO BID Mekinist: 2 mg PO QD	Tafinlar: 300 mg/day Mekinist: 2 mg/day
Alecensa® (alectinib)	NSCLC: 600 mg PO BID	1200 mg/day
Alunbrig® (brigatinib)	NSCLC: 90 mg PO QD for 7 days, if tolerated increase to 180 mg PO QD	180 mg/day
Tarceva® (erlotinib)	NSCLC: 150 mg PO QD	150 mg/day
Gilotrif® (afatinib)	NSCLC: 40 mg PO QD	40 mg/day
Iressa® (gefitinib)	NSCLC: 250 mg PO QD	250 mg/day
Tagrisso® (osimertinib)	NSCLC: 80 mg PO QD	80 mg/day
Nexavar (sorafenib)	HCC: 400 mg PO BID	800 mg/day

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.

R = Rituxan® (rituximab)

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: Head and Neck Squamous Cell Cancers by Location[*5]
- Paranasal sinuses (ethmoid, maxillary)
- Larynx (glottis, supraglottis)
- Pharynx (nasopharynx, oropharynx, hypopharynx)
- Lip and oral cavity
- Major salivary glands (parotid, submandibular, sublingual)
- Occult primary

_____
**Squamous cell carcinoma, or a variant, is the histologic type in more than 90% of head and neck cancers.*

Appendix E: Examples of Solid Tumors
- Adrenal gland tumors
- Cervical cancer
- Endometrial cancer
- Biliary cancer
- Gastric/gastroesophageal junction cancer
- Hepatobiliary cancer
- Ovarian, fallopian tube, primary peritoneal cancer
- Pancreatic cancer
- Penile cancer
- Small intestinal cancer
- Breast cancer
- Prostate cancer
- Vulvar cancer
- Bladder cancer
- Esophageal cancer
- Sarcoma
- Testicular cancer
- Thyroid cancer
- Rectal cancer
- Retroperitoneal adenocarcinoma
- Small cell lung cancer
- Renal cell carcinoma

Appendix F: General Information
- NCCN Compendium recommend Keytruda for the treatment of Merkel cell carcinoma for disseminated, clinical M1 disease with or without surgery and/or radiation therapy.
- NCCN Compendium recommend Keytruda for the treatment of unresectable or metastatic MSI-H or dMMR colorectal cancer for the following: disease progression following treatment with a fluoropyrimidine (e.g., fluorouracil, capecitabine), oxaliplatin, and irinotecan; following adjuvant therapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOx (capecitabine and oxaliplatin) within the past 12 months; as a single agent for members in which intensive therapy is not appropriate.
- Keytruda may be used as subsequent therapy following disease progression on or after the following:
  - Platinum-containing chemotherapy if EGFR, ALK, ROS1 and BRAF mutation status is negative or unknown
  - FDA-approved therapy for EGFR mutation positive disease (e.g., Tarceva, Gilotrif, Iressa, Tagrisso)

- FDA-approved therapy for ALK mutation positive disease (e.g., Xalkori, Zykadia, Alecensa, Alunbrig)
- FDA-approved or NCCN-supported therapy for ROS1 mutation positive disease (e.g., Xalkori, Zykadia)
- FDA-approved therapy for BRAF V600E mutation positive disease (e.g., Tafinlar with Mekinist)

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Cervical cancer, cHL, HCC, HNSCC, melanoma, MSI-H cancer, gastric cancer, NSCLC, PMBCL, urothelial carcinoma	Adults: 200 mg IV every 3 weeks	200 mg every 3 weeks
cHL, melanoma, MSI-H cancer, PMBCL	Pediatrics: 2 mg/kg IV every 3 weeks	200 mg every 3 weeks

All regimens are an intravenous infusion over 30 minutes

V. Product Availability

- Powder, single-dose vial: 50 mg

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

Coding Implications

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

HCPCS Codes	Description
J9271	Injection, Pembrolizumab, 1mg

Reviews, Revisions, and Approvals	Date	Approval Date
Added max dose requirement to both initial and re-auth criteria. Increased all approval durations from 3/6 months to 6/12 months. Removed reasons to discontinue. Added requirement for documentation of positive response to therapy. References reviewed and updated.	02/18	
1Q 2019 Criteria added for new FDA indications HCC and as first-line therapy for metastatic squamous NSCLC in combination with chemotherapy; re-added criteria for PMBCL as previously approved; referenced reviewed and updated.	01/19	

References

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2. Pembrolizumab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed June 19, 2018.
3. Melanoma (Version 2.2018). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed June 21, 2018.
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9. National Comprehensive Cancer Network. Cervical Cancer Version 1.2018. Available at: http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed June 19, 2018.
10. National Comprehensive Cancer Network. B-Cell Lymphomas Version 4.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed June 19, 2018.
11. National Comprehensive Cancer Network. Hepatobiliary Cancers Version 5.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed November 27, 2018.