Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM117	**Last Approval:**	03/26/2019
Title:	Pembrolizumab (Keytruda®)		
Approved By:	UM Pharmacy Subcommittee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Pembrolizumab (Keytruda): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Age -Medication list (current and past) including all biologic agents -Labs/diagnostics.

BACKGROUND

Keytruda, a human programmed death receptor-1 (PD-1) blocking antibody, is indicated for the treatment of the following indications:[1]

1) Melanoma, for the treatment of patients with unresectable or metastatic disease; AND
2) Non-small cell lung cancer (NSCLC), in the following situations:
    a. As a single agent for the first-line treatment of patients with metastatic disease whose tumors have high programmed death-ligand 1 (PD-L1) expression (tumor proportion score [TPS] ≥ 50%) as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations; AND
    b. As a single agent for the treatment of patients with metastatic disease whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test and 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; AND
    c. In combination with Alimta® (pemetrexed intravenous injection) and platinum-based chemotherapy, for the first-line treatment of patients with metastatic disease with no EGFR or ALK genomic tumor aberrations; AND
    d. In combination with carboplatin and either paclitaxel or Abraxane® (nab-paclitaxel injection), for first-line treatment in metastatic squamous NSCLC; AND
3) Head and neck squamous cell carcinoma (HNSCC), for the treatment of recurrent or metastatic disease with disease progression on or after platinum-containing chemotherapy;* AND
4) Classical Hodgkin lymphoma (cHL), treatment of adult and pediatric patients with refractory disease, or who have relapsed after three or more prior lines of therapy;* AND
5) Primary mediastinal large B-cell lymphoma (PMBCL), treatment of adult and pediatric patients with refractory disease, or who have relapsed after two or more prior line of therapy;* AND

Limitation of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

6) Urothelial carcinoma, in the following situations:

a. Treatment locally advanced or metastatic disease in patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status;* OR
b. 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; AND

7) Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), treatment of adult and pediatric patients with unresectable or metastatic disease, in the following situations:
   - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options;* OR
   - colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan;* AND

Limitation of Use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system (CNS) cancers have not been established.

8) Gastric cancer, treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) 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 lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy;* AND
9) Cervical cancer, treatment of patients with recurrent or metastatic disease with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test;* AND
10) Hepatocellular carcinoma, treatment of patients who have been previously treated with Nexavar® (sorafenib tablets);*
11) Merkel cell carcinoma, for adults and pediatric patients with recurrent, locally advanced, or metastatic disease.*

*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.

The recommended dose of Keytruda is 200 mg (for pediatric patients, 2 mg/kg up to 200 mg) administered as an intravenous infusion once every 3 weeks. It is given until disease progression or unacceptable toxicity, (or up to 24 months in patients with non-melanoma indications without disease progression). There are no recommended dose reductions in the prescribing information. Management of adverse events may require that Keytruda be withheld or permanently discontinued as determined by the prescribing physician.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

Coverage of Keytruda is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Cervical Cancer.

Criteria. *The patient must meet the following criteria (A, B, and C):*

A) The patient has tried chemotherapy (e.g., cisplatin, paclitaxel, Avastin [bevacizumab intravenous injection], topotecan, carboplatin); AND

B) The patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 1; AND

C) Keytruda is prescribed by or in consultation with an oncologist.

Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

Dosing in Cervical Cancer in Adults. *Dosing must meet the following*: Approve if the dose is 200 mg as an intravenous infusion administered once every 3 weeks.

Initial Approval/Extended Approval.

A) *Initial Approval*: Approve for 12 months.

B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Cervical Cancer in Adults. Treatment may continue until disease progression or unacceptable toxicity.

2. Classical Hodgkin Lymphoma (cHL).

Criteria. *The patient must meet the following criteria (A and B):*

A) ONE of the following conditions apply (i, ii, or iii):

i. The patient has had a hematopoietic stem cell transplantation (HSCT); OR

ii. The patient has tried three or more systemic regimens (e.g., ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine], Sanford V [doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone], escalated BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone]) AND this includes an auto-HSCT as one line of therapy; OR

iii. The patient is not eligible for transplant according to the prescribing physician; AND

B) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in cHL. *Dosing must meet ONE of the following (A OR B)*:

- **A)** 200 mg as an intravenous infusion given once every 3 weeks; OR
- **B)** 2 mg per kg (up to a maximum of 200 mg) given as an intravenous infusion given once every 3 weeks.

Initial Approval/Extended Approval.

- **A)** *Initial Approval*: Approve for 12 months.
- **B)** *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in cHL. Treatment may continue until disease progression or unacceptable toxicity.

3. Gastric Cancer, Gastroesophageal Junction (GEJ) Cancer, or Esophageal Cancer.

Criteria. *The patient must meet the following criteria (A, B, C, and D):*

- **A)** The patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 1; AND
- **B)** The patient has tried therapy with a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine) and platinum (e.g., cisplatin, carboplatin); AND
- **C)** If the patient's tumor is human epidermal growth factor receptor 2 (HER2) or HER2/neu positive, targeted therapy with trastuzumab intravenous infusion (Herceptin®) has been tried; AND
- **D)** Keytruda is prescribed by or in consultation with an oncologist.

Note: also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

Dosing in Gastric Cancer, Gastroesophageal Junction (GEJ) Cancer, or Esophageal Cancer in Adults. *Dosing must meet the following*: 200 mg as an intravenous infusion every 3 weeks.[1, 28-29]

Initial Approval/Extended Approval.

- **A)** *Initial Approval*: Approve for 12 months.
- **B)** *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Gastric Cancer, Gastroesophageal Junction (GEJ) Cancer, or Esophageal Cancer in Adults. Treatment may continue until disease progression or unacceptable toxicity.

4. Head and Neck Squamous Cell Carcinoma (HNSCC).

Criteria. *The patient must meet the following criteria (A and B):*

A) The patient meets ONE of the following conditions (i or ii):
  - **i.** The patient has tried chemotherapy (e.g., cisplatin, carboplatin, Erbitux® [cetuximab intravenous infusion], 5-fluorouracil [5-FU], capecitabine, paclitaxel, docetaxel, methotrexate [MTX]); OR
  - **ii.** A platinum-containing chemotherapy regimen or other chemotherapy is contraindicated, according to the prescribing physician; AND

B) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in Recurrent or Metastatic HNSCC in Adults. *Dosing must meet the following*: 200 mg as an intravenous infusion given once every 3 weeks.[1]

Initial Approval/Extended Approval.
A) *Initial Approval*: Approve for 12 months.
B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Recurrent or Metastatic HNSCC Adults. Treatment may continue until disease progression or unacceptable toxicity.

Labs/Diagnostics. None required.

5. Hepatocellular Carcinoma, Including Hepatobiliary Cancers.

Criteria. *The patient must meet the following criteria (A and B):*

A) The patient has tried at least one tyrosine kinase inhibitor (TKI) [e.g., Nexavar {sorafenib tablets}, Lenvima {levatinib capsules}]; AND
B) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in Hepatocellular Carcinoma, Including Hepatobiliary Cancers. *Dosing must meet the following*: 200 mg as an intravenous infusion given every 3 weeks.

Initial Approval/Extended Approval.
A) *Initial Approval*: Approve for 12 months.
B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Hepatocellular Carcinoma, Including Hepatobiliary Cancers in Adults. Treatment may continue until disease progression or unacceptable toxicity.

6. Melanoma [Note: This include cutaneous melanoma, brain metastases due to melanoma and uveal melanoma].

Criteria. *The patient must meet the following criteria (A, B, AND C):*

A) The patient meets ONE of the following (i or ii):
  i. The patient has unresectable, advanced, or metastatic melanoma; OR
  ii. Keytruda will be used as adjuvant treatment (e.g., in a patient with no evidence of disease following resection of node-positive disease, locoregional recurrence, or in transit recurrence); AND
B) Keytruda will not be used in combination with Yervoy® (ipilimumab intravenous infusion); AND
C) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in Advanced, Unresectable or Metastatic Melanoma in Adults. *Dosing must meet the following*: 200 mg as an intravenous infusion given once every 3 weeks.

Initial Approval/Extended Approval.
C) *Initial Approval*: Approve for 12 months.
D) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Advanced, Unresectable or Metastatic Melanoma in Adults. Treatemnt many continue until disease progression or unacceptable toxicity.

7. Merkel Cell Carcinoma.

Criteria. *The patient must meet the following criteria (A AND B):*

A) The patient has recurrent, locally advanced, or metastatic disease; AND
B) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in Merkel Cell Carcinoma. *Dosing must meet one of the following*:

A) 2 mg/kg (up to 200 mg) as an intravenous infusion given once every 3 weeks; OR
B) 200 mg as an intravenous infusion given once every 3 weeks.

Initial Approval/Extended Approval.
A) *Initial Approval*: Approve for 12 months.
B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Merkel Cell Carcinoma. Treatment may continue until disease progression or unacceptable toxicity.

8. Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.

Criteria. *The patient must meet the following criteria (A and B):*

A) One of the following conditions apply (i, ii, or iii):
- **i.** The patient has tried at least one prior systemic therapy for an MSI-H or dMMR solid tumor (for example, gastric, gastroesophageal or esophageal cancers, Ewing sarcoma, osteosarcoma, mesenchymal chondrosarcoma, pancreatic adenocarcinoma, endometrioid carcinomas, penile, adrenal gland, vulvar, cervical, ovarian, fallopian tube, primary peritoneal, testicular); OR
- **ii.** The patient has unresectable or metastatic gallbladder cancer (including intra- and extra-hepatic cholangiocarcinoma); OR
- **iii.** The patient has colon or rectal cancer, and ONE of the following apply (a or b):
  - **a)** The patient has tried chemotherapy (e.g., a fluoropyrimadine such as fluorouracil [5-FU], capecitabine; an adjunctive chemotherapy regimen such as FOLFOX [5-FU, leucovorin, and oxaliplatin] or CapeOX [capecitabine and oxaliplatin]); OR
  - **b)** The patient has metastatic disease and is not a candidate for intensive therapy,[15-16] according to the prescribing physician; AND

B) Keytruda is prescribed by or in consultation with an oncologist

Dosing in MSI-H or dMMR Solid Tumors. *Dosing must meet the following (A OR B)*:

A) 200 mg as an intravenous infusion given once every 3 weeks; OR
B) 2 mg per kg (up to a maximum of 200 mg) as an intravenous infusion given once every 3 weeks.

Initial Approval/Extended Approval.
A) *Initial Approval*: Approve for 12 months.
B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in MSI-H or dMMR Solid Tumors Solid Tumors. Treatment may continue until disease progression or unacceptable toxicity.

9. Non-Small Cell Lung Cancer.

Criteria. *The patient must meet the following criteria (A, B, AND C):*

A) Keytruda is prescribed by or in consultation with an oncologist; AND
B) The patient meets ONE of the following (i, ii, or iii):
i. The patient has advanced or metastatic disease and a tumor proportion score (TPS) for PD-L1 as determined by an approved test is ≥ 50%; OR
ii. The patient's tumor proportion score (TPS) for PD-L1 as determined by an approved test is ≥ 1% AND systemic chemotherapy has been tried (e.g., cisplatin, carboplatin, Alimta [pemetrexed for intravenous injection], gemcitabine, paclitaxel); OR
iii. Keytruda will be used in combination with chemotherapy (e.g., Alimta [pemetrexed] and carboplatin or cisplatin, paclitaxel, albumin-bound paclitaxel); AND

C) If non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) the patient must also meet ONE of the following conditions (i or ii):

i. The patient's tumor is positive for a targetable mutation (i.e., sensitizing epidermal growth factor receptor [*EGFR*] mutation, anaplastic lymphoma kinase [*ALK*] fusions) AND the patient has received targeted drug therapy for the specific mutation; OR

ii. The tumor is negative or unknown for these targetable mutations (i.e., *EGFR, ALK)*.

Dosing in NSCLC in Adults. *Dosing must meet the following*:

A) 200 mg as an intravenous infusion every 3 weeks; OR,

B) In brain metastatses, the following regimens may also be approved:

i. 10 mg/kg every 2 weeks; OR

ii. 2 mg/kg every 3 weeks.

Initial Approval/Extended Approval.

A) *Initial Approval*: Approve for 12 months.

B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Adults. Treatment may continue until disease progression or unacceptable toxicity.

10. Primary Mediastinal Large B-Cell Lymphoma (PMBCL).

Criteria. *The patient must meet the following criteria (A AND B):*

A) The patient has relapsed after, or is refractory to, at least two previous regimens (e.g., autologous hematopoietic stem cell transplant [auto-HSCT], EPOCH-R [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, Rituxan {rituximab injection}], RCHOP [Rituxan, cyclophosphamide, doxorubicin, vincristine, prednisone], RCEPP [Rituxan, cyclophosphamide, doxorubicin, vincristine, prednisone]); AND

B) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in PMBCL. *Dosing must meet ONE of the following (A OR B)*:[1]

A) 200 mg as an intravenous infusion given once every 3 weeks; OR

B) 2 mg per kg (up to a maximum of 200 mg) as an intravenous infusion given once every 3 weeks.

Initial Approval/Extended Approval.

A) *Initial Approval*: Approve for 12 months.

B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in PMBCL. Treatment may continue until disease progression or unacceptable toxicity.

11. Urothelial Carcinoma.

Criteria. *The patient must meet the following criteria (A and B):*

A) The patient meets ONE of the following conditions (i, ii, or iii):
- **i.** The patient has tried at least one platinum- (cisplatin, carboplatin) containing chemotherapy; OR
- **ii.** According to the prescribing physician, the patient is not eligible for cisplatin-based chemotherapy, AND the tumor expresses PD-L1 (i.e., has a combined positive score [CPS] ≥ 10); OR
- **iii.** According to the prescribing physician, the patient is not eligible for platinum-based chemotherapy (i.e., with cisplatin and carboplatin) [Note: this is regardless of PD-L1 status]; AND

B) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in Urothelial Carcinoma in Adults. *Dosing must meet the following*: 200 mg as an intravenous once every 3 weeks.

Initial Approval/Extended Approval.

A) *Initial Approval*: Approve for 12 months.

B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Adults. Treatment may continue until disease progression or unacceptable toxicity.

Other Uses with Supportive Evidence

12. Anal Carcinoma.

Criteria. *The patient must meet the following criteria (A, B, C, AND D):*

A) The patient has received other chemotherapy (e.g., 5-fluorouracil [5-FU], cisplatin, carboplatin, paclitaxel, FOLFOX [oxaliplatin, leucovorin, and 5-FU]); AND

B) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in Anal Carcinoma in Adults. *Dosing must meet ONE of the following (A OR B)*:

A) 200 mg as an intravenous infusion given once every 3 weeks; OR

B) 2 mg per kg as an intravenous infusion once every 3 weeks.

Initial Approval/Extended Approval.

A) *Initial Approval*: Approve for 12 months.

B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Anal Carcinoma in Adults. Treatment may continue until disease progression or unacceptable toxicity.

Labs/Diagnostics. None required.

13. Malignant Pleural Mesothelioma.

Criteria. *The patient must meet the following criteria (A and B):*

A) The patient has tried first-line chemotherapy (e.g., Alimta [pemetrexed intravenous injection] with or without cisplatin or carboplatin, gemcitabine plus cisplatin, vinorelbine); AND
B) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in Malignant Pleural Mesothelioma in Adults. *Dosing must meet one of the following*:
A) 10 mg per kg as an intravenous infusion given once every 2 weeks; OR
B) 200 mg as an intravenous infusion given once every 3 weeks.

Initial Approval/Extended Approval.
A) *Initial Approval*: Approve for 12 months.
B) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy in Adults. Treatment many continue until disease progression or unacceptable toxicity.

14. Small Cell Lung Cancer.

Criteria. *The patient must meet the following criteria (A AND B):*

A) The patient has tried at least one other systemic therapy (e.g., cisplatin, carboplatin, etoposide) within the past 6 months; AND
B) Keytruda is prescribed by or in consultation with an oncologist.

Dosing in Small Cell Lung Cancer. *Dosing must meet the following*:
200 mg as an intravenous infusion given once every 3 weeks.

Initial Approval/Extended Approval.
C) *Initial Approval*: Approve for 12 months.
D) *Extended Approval*: Extended approvals are allowed for 12 months if the patient continues to meet the criteria and dosing (see above).

Duration of Therapy Small Cell Lung Cancer. Treatment may continue until disease progression or unacceptable toxicity.

15. **Other Cancer-Related Indications.** Forward to the Medical Director for review on a case-by-case basis. Other indications supported in the *NCCN Compendium*, include include mycosis fungoides/Sezary syndrome (category 2A); T-cell lymphoproliferative disorders (2B); extranodal NK/T-cell lymphoma, nasal type (category 2A), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) [2B], gestational trophoblastic neoplasia (2A).

Conditions Not Recommended for Approval

Keytruda has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References	1. Keytruda® injection for intravenous use and injection for intravenous use [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc; December 2018. 2. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (Version 3.2018 – April 16, 2018). © 2018 National Comprehensive Cancer

Network, Inc. Available at: http://www.nccn.org. Accessed on December 16, 2018.
3. The NCCN Drugs & Biologics Compendium. © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 16, 2018. Search term: pembrolizumab.
4. PDQ® Pediatric Treatment Editorial Board. PDQ Childhood Hodgkin Lymphoma Treatment. Bethesda, MD: National Cancer Institute. Updated 12/1/2017. Available at: https://www.cancer.gov/types/lymphoma/hp/child-hodgkin-treatment-pdq. Accessed on June 8, 2018. [PMID: 26389170]
5. Chen R, Zinzani PL, Fanale MA, et al; for the KEYNOTE-087 investigators. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol*. 2017;35(19):2125-2132.
6. Armand P, Shipp MA, Ribrag V, et al. Programmed Death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. *J Clin Oncol*. 2016;34(31):3733-3739.
7. The NCCN Head and Neck Cancers Clinical Practice Guidelines in Oncology (Version 2.2018 – June 20 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 3, 2018.
8. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol*. 2016;17:956-965.
9. Chow LQ, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. *J Clin Oncol*. 2016;34:3838-3845.
10. Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. *J Clin Oncol*. 2017;35(14):1542-1549.
11. The NCCN Melanoma Clinical Practice Guidelines in Oncology (Version 1.2019 – November 1, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 20, 2018.
12. Robert C, Schachter J, Long GV, et al; KEYNOTE-006 investigators. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015; 372:2521-2532.
13. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med.* 2013;369:134-144.
14. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. 2015;16:908-918.
15. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 4.2018 – October 19, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 13, 2018.
16. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 3.2018 – August 7, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 17, 2018.
17. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509-2520.
18. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – November 21, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 4, 2018.

19. Reck M, Rodríguez-Abreu D, Robinson AG, et al; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823-1833.
20. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540-1550.
21. Langer CJ, Gadgeel SM, Borghaei H, et al; for KEYNOTE-021 investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomized, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17(11):1497-1508.
22. The NCCN Bladder Cancer Clinical Practice Guidelines in Oncology (Version 5.2018 – July 3, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 7, 2018.
23. Bellmunt J, de Wit R, Vaughn DJ, et al; KEYNOTE-045 Investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015-1026.
24. The NCCN Merkel Cell Carcinoma Clinical Practice Guidelines in Oncology (Version 1.2019 – August 31, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 7, 2018.
25. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. *N Engl J Med*. 2016;374(26):2542-2552.
26. The NCCN Malignant Pleural Mesothelioma Clinical Practice Guidelines in Oncology (Version 2.2018 – February 26, 2018) © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 7, 2018.
27. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol*. 2017;18(5):623-630.
28. The NCCN Gastric Cancer Clinical Practice Guidelines in Oncology (Version 2.2018 – May 22, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 3, 2018.
29. The NCCN Esophageal and Esophagogastric Junction Cancers Clinical Practice Guidelines in Oncology (Version 2.2018 – May 22, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 3, 2018.
30. Fuchs CS, Doi T, Jang RW, et al. Efficacy and safety of pembrolizumab monotherapy in patients with previously treated gastric and gastroesophageal junction cancer. Phase 2 clinical Keynote-059 trial. *JAMA Oncol*. 2018 May 10. [Epub ahead of print].
31. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (Version 1.2019 – August 3, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 16,, 2018.
32. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (Version 1.2019 – November 8, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 13, 2018.
33. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (Version 1.2019 – October 17, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 16, 2018.
34. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (Version 2.2018 – November 26, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 7, 2018.

35. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:976-983.
36. Anderson ES, Postow MA, Wolchok JD, et al. Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression; efficacy and safety of combined treatment. *J Immunother Cancer*. 2017;5(1):76.
37. Parakh S, Park JJ, Mendis S, et al. Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases. *Br J Cancer*. 2017;116(12):1558-1563.
38. Doi T, Piha-Paul SA, Jalal SI, et al. Safety and antitumor activity of the anti -programmed death-1 antibody pembrolizumab in patients with advanced esophageal carcinoma. *J Clin Oncol*. 2018;36:61-67.
39. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 1.2019 – November 30, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. December 16, 2018.
40. Zinzani PL, Thieblemont C, Melnichenko V, et al. Efficacy and safety of pembrolizumab in relapsed/refractory primary mediastinal large B-cell lymphoma (rrPMBCL): Updated analysis of the Keynote-170 phase 2 trial [abstract]. *Blood*. 2017;130(suppl 1):2833. Available at: http://www.bloodjournal.org/content/130/Suppl_1/2833. Accessed on June 5, 2018.
41. Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. *Blood*. 2017;130(3):267-270.
42. The NCCN Anal Carcinoma Clinical Practice Guidelines in Oncology (Version 2.2018 – June 8, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 16, 2018.
43. Ott PA, Piha-Paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. *Ann Oncol*. 201;28(5):1036-1041.
44. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018 Apr 15. [Epub ahead of print].
45. The NCCN Uveal Melanoma Clinical Practice Guidelines in Oncology (Version 1.2018 – March 15, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 20, 2018.
46. The NCCN Cervical Cancer Clinical Practice Guidelines in Oncology (Version 2.2019 – October 12, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 19, 2018.
47. Frenel JS, Le Tourneau C, O'Neil B, et al. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: results from the phase Ib KEYNOTE-028 trial. *J Clin Oncol*. 2017;35(36):4035-4041.
48. Karydis I, Chan PY, Wheater M, et al. Clinical activity and safety of pembrolizumab in ipilimumab pre-treated patients with uveal melanoma. *Oncoimmunology*. 2016;5:e1143997.
49. Kottschade LA, McWilliams RR, Markovic SN, et al. The use of pembrolizumab for the treatment of metastatic uveal melanoma. *Melanoma Res*. 2016;26:300-303.
50. Algazi AP, Tsai KK, Shoushtari AN, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. *Cancer*. 2016;122:3344-3353.
51. Heppt MV, Heinzerling L, Kähler KC, et al. Prognostic factors and outcomes in metastatic uveal melanoma treated with programmed cell death-1 or combined PD-1/cytotoxic T-lymphocyte antigen-4 inhibition. *Eur J Cancer*. 2017;82:56-65.

52. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078-2092.
53. Alimta® for injection [prescribing information]. Indianapolis, IN: Eli Lilly and Company; June 2018.
54. The NCCN Hepatobiliary Cancer Clinical Practice Guidelines in Oncology (Version 5.2018 – November 19, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 7, 2018.
55. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 1.2019 – October 10, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 16, 2018.
56. The NCCN Vulvar Cancer Clinical Practice Guidelines in Oncology (Version 1.2019 – August 30, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 16, 2018.
57. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 4.2018 – August 15, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 16, 2018.
58. The NCCN Neuroendocrine and Adrenal Cancer Clinical Practice Guidelines in Oncology (Version 3.2018 – September 11, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 16, 2018.

OTHER REFERENCES UTILIZED

- Rekhtman N, Leighl NB, Somerfield MR. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American society of clinical oncology endorsement of the college of American pathologists/international association for the study of lung cancer/association for molecular pathology guideline. *J Oncol Pract*. 2015;11:135-136.
- Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline update. *J Clin Oncol*. 2017;35(30):3484-3515.
- Muro K, Chung HC, Shankaran V, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial. *Lancet Oncol*. 2016;17:717-726.
- Schadendorf D, Dummer R, Hauschild A, et al. Health-related quality of life in the randomised KEYNOTE-002 study of pembrolizumab versus chemotherapy in patients with ipilimumab-refractory melanoma. *Eur J Cancer*. 2016;67:46-54.
- Garon EB, Rizvi NA, Hui R, et al; KEYNOTE-001 investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med.* 2015;372:2018-2028.
- Shoushtari AN, Munhoz RR, Kuk D, et al. The efficacy of anti-PD-1 agents in acral and mucosal melanoma. *Cancer*. 2016;122:3354-3362.
- Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017;18(3):1493-1501.

	• US Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Updated June 13, 2018. Available at: http://www.fda.gov/CcompanionDiagnostics. Accessed on June 18, 2018. • Kwong YL, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. *Blood*. 2017;129(17):2437-2442.
CFR	
WAC	WAC 284-43-2050
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Contract Citation	☐ WAH ☐ IMC ☐ MA
Other Requirements	
NCQA Elements	

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
01/12/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM to PM	Cindy Bush
04/25/2018	Transferred to new template	Cindy Bush
05/16/18	Revised	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee
08/03/2018	Revised	Jennifer Farley, PharmD
02/27/2019	Significant revisions, including added indications, updated existing indications, changed initial/extended approval from 6 to 12 months, and added dosing regimens	Ivan Figueira, PharmD
03/26/2019	Approval	UM Pharmacy Subcommittee