

UTILIZATION REVIEW MEDICAL POLICY

- POLICY:** Oncology (Injectable) – Keytruda Utilization Review Medical Policy
- Keytruda® (pembrolizumab for injection, for intravenous use and injection for intravenous use – Merck & Co., Inc.)

REVIEW DATE: 06/17/2020

OVERVIEW

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

- **Melanoma**, for the treatment of patients with unresectable or metastatic disease. Keytruda is also indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
- **Non-small cell lung cancer (NSCLC)**, in the following situations:
 - As a single agent for the first-line treatment of patients whose tumors have high programmed death-ligand 1 (PD-L1) expression (tumor proportion score [TPS] $\geq 1\%$) as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation or for metastatic disease; AND
 - As a single agent for the treatment of patients with metastatic disease whose tumors express PD-L1 (TPS $\geq 1\%$) 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
 - In combination with Alimta® (pemetrexed intravenous injection) and platinum-based chemotherapy, for the first-line treatment of patients with metastatic nonsquamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations; AND
 - In combination with carboplatin and either paclitaxel or Abraxane® (nab-paclitaxel injection), for first-line treatment in metastatic squamous NSCLC.
- **Head and neck squamous cell carcinoma (HNSCC)**, in the following situations:
 - As a single agent for the treatment of recurrent or metastatic disease with disease progression on or after platinum-containing chemotherapy; AND
 - In combination with platinum and fluorouracil (FU) for the first-line treatment of patients with metastatic or with unresectable, recurrent disease; AND
 - As a single agent, for the first line treatment of patients with metastatic or with unresectable, recurrent disease whose tumors express PD-L1 (combined positive score [CPS] ≥ 1) as determined by an FDA-approved test.
- **Classical Hodgkin lymphoma (cHL)**, for treatment of adult and pediatric patients with refractory disease, or who have relapsed after three or more prior lines of therapy.*
- **Primary mediastinal large B-cell lymphoma (PMBCL)**, for treatment of adult and pediatric patients with refractory disease, or who have relapsed after two or more prior lines of therapy.*
Limitation of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
- **Urothelial carcinoma**, in the following situations:
 - Treatment of 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) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status;* AND
- 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
 - Treatment of Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ 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)**, for 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.*

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

- **Gastric cancer**, for 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.*
- **Cervical cancer**, for 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.*
- **Hepatocellular carcinoma**, for treatment of patients who have been previously treated with Nexavar[®] (sorafenib tablets).*
- **Merkel cell carcinoma**, for adult and pediatric patients with recurrent, locally advanced, or metastatic disease.*
- **Small cell lung cancer**, for treatment of metastatic disease and disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.*
- **Renal cell carcinoma**, in combination with Inlyta (axitinib tablets), for the first-line treatment of patients with advanced disease.
- **Esophageal cancer**, treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.
- **Endometrial cancer**, in combination with Lenvima (lenvatinib capsules), for the treatment of patients with advanced disease that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

*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.

Dosing

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 or 400 mg given once every 6 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.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Keytruda. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication(s). Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Keytruda as well as the monitoring required for adverse events (AEs) and long-term efficacy, initial approval requires Keytruda to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Cervical Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
 - A) Patient has tried chemotherapy; AND
Note: Examples of chemotherapy are cisplatin, paclitaxel, bevacizumab, topotecan, carboplatin).
 - B) 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) The medication 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. Approve the following dosing regimens (A or B):

- A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

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2. **Classic Hodgkin Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):

- A) ONE the following conditions apply (i, ii, or iii):
 - i. Patient has had a hematopoietic stem cell transplantation (HSCT); OR
 - ii. Patient has tried three or more systemic regimens; OR
Note: Examples of systemic therapies include 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]). This includes an auto-HSCT as one line of therapy.
 - iii. Patient is not eligible for transplant according to the prescriber; AND
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B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimens (A, B, or C):

- A) 200 mg as an intravenous infusion given not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion given not more frequently than once every 6 weeks; OR
- C) 2 mg per kg (up to a maximum of 200 mg) given as an intravenous infusion given not more frequently than once every 3 weeks.

3. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

- A) Disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
- B) The medication is used in combination with Lenvima™ (lenvatinib capsules); AND
- C) Patient has progressed on at least one prior systemic therapy; AND
Note: Examples of systemic therapy are carboplatin, paclitaxel, docetaxel, cisplatin, doxorubicin, ifosfamide, everolimus, letrozole.
- D) Patient is not a candidate for curative surgery or radiation; AND
- E) The medication 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. Approve the following dosing regimens (A or B):

- A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

4. Esophageal and Esophagogastric Junction Cancer. Approve for 1 year if the patient meets the following (A and B):

- A) Patient meets one of the following criteria (i or ii):
 - i. Patient meets BOTH of the following criteria (a and b):
 - a) Patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 10 ; AND
 - b) Patient has tried at least one previous chemotherapy regimen; OR
Note: Examples of chemotherapy regimens are fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin, fluoropyrimidine and cisplatin, paclitaxel with cisplatin or carboplatin, docetaxel with cisplatin.
 - ii. Patient meets BOTH of the following criteria (a and b):
 - a) 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) Patient has tried at least two previous chemotherapy regimens; AND
Note: Examples of chemotherapy regimens are fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin, fluoropyrimidine and cisplatin, paclitaxel with cisplatin or carboplatin, docetaxel with cisplatin.
- B) The medication 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. Approve the following dosing regimens (A or B):

- A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

5. Gastric Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

- A) 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) Patient has tried at least two previous chemotherapy regimens; AND
Note: Examples of chemotherapy regimens are fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin, fluoropyrimidine and cisplatin, paclitaxel with cisplatin or carboplatin, docetaxel with cisplatin 5.
- C) If the patient's tumor is human epidermal growth factor receptor 2 (HER2) or HER2/neu positive, targeted therapy with trastuzumab has been tried; AND
- D) The medication 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. Approve the following dosing regimens (A or B):

- A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

6. Head and Neck Squamous Cell Carcinoma (HNSCC). Approve for 1 year if the patients meets the following (A, B, and C):

- A) Patient has recurrent or metastatic disease; AND
- B) Patient meets one of the following criteria (i or ii):
 - i. If the medication is used for first-line treatment, patient has to meet one of the following criteria (a or b):
 - a) Keytruda is used in combination with chemotherapy; OR
Note: Examples of chemotherapy are cisplatin, carboplatin, fluorouracil.
 - b) Keytruda is used as a single agent if the tumors are PD-L1-positive (combined positive score ≥ 1), as determined by an approved test.
 - ii. For subsequent therapy, patient has tried at least one platinum-containing chemotherapy regimen.
Note: Examples of platinum-contain chemotherapy regimens are: cisplatin or carboplatin with Erbitux[®] [cetuximab intravenous infusion], gemcitabine, or 5-fluorouracil [5-FU]; AND
- C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimens (A or B):

- A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

7. Hepatocellular Carcinoma, Including Hepatobiliary Cancers. Approve for 1 year if the patient meets the following conditions (A and B):

- A) Patient has tried at least one tyrosine kinase inhibitor; AND

Note: Examples of tyrosine kinase inhibitors include Nexavar (sorafenib tablets) and Lenvima (levatinib capsules).

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

Dosing. Approve the following dosing regimens (A or B):

A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

8. **Melanoma** [Note: This includes cutaneous melanoma, brain metastases due to melanoma and uveal melanoma]. Approve for the duration noted below if the patient meets BOTH of the following (A and B):

A) Patient meets ONE of the following (i or ii):

i. Approve for 1 year if the patient has unresectable, advanced, or metastatic melanoma; OR

ii. Approve for up to 1 year (total) if Keytruda will be used as adjuvant treatment; AND

Note: For example, in a patient with no evidence of disease following resection of node-positive disease, locoregional recurrence, or in transit recurrence.

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

Dosing. Approve if the dose is one of the following (A or B):

A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

9. **Merkel Cell Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has recurrent, locally advanced, or metastatic disease; AND

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

Dosing. Approve the following dosing regimens (A, B, or C):

A) 200 mg as an intravenous infusion given not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion given not more frequently than once every 6 weeks; OR

C) 2 mg per kg (up to a maximum of 200 mg) given as an intravenous infusion given not more frequently than once every 3 weeks.

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

Note: Examples of solid tumors with MSI-H or dMMR are breast, gastric, gastroesophageal or esophageal cancers, colon or rectal cancer, Ewing sarcoma, osteosarcoma, mesenchymal chondrosarcoma, poorly differentiated neuroendocrine tumor, pancreatic adenocarcinoma, endometrioid carcinomas, penile, adrenal gland, vulvar, cervical, ovarian, fallopian tube, primary peritoneal, small bowel adenocarcinoma, testicular cancer. Approve for 1 year if the patient meets BOTH of the following (A and B):

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

i. Patient has tried at least one prior systemic therapy for an MSI-H or dMMR solid tumor); OR

ii. Patient has unresectable or metastatic gallbladder cancer (including intra- and extra-hepatic cholangiocarcinoma); OR

iii. Patient has colon or rectal cancer, and ONE of the following apply (a or b):

a) Patient has tried chemotherapy; OR

Note: Examples of chemotherapy are a fluoropyrimidine such as fluorouracil (5-FU), capecitabine; an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

- b) Patient has metastatic disease and is not a candidate for intensive therapy, according to the prescriber; AND
- B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimens (A, B, or C):

- A) 200 mg as an intravenous infusion given not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion given not more frequently than once every 6 weeks; OR
- C) 2 mg per kg (up to a maximum of 200 mg) given as an intravenous infusion given not more frequently than once every 3 weeks.

11. Non-Small Cell Lung Cancer. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

- A) Patient has advanced or metastatic disease; AND
- B) The tumor proportion score (TPS) for PD-L1 as determined by an approved test is $\geq 1\%$; AND
- C) If the patient has non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) and the tumor is positive for a targetable mutation, the patient has previously received targeted drug therapy for the specific mutation; AND

Note: Examples of targetable mutations include sensitizing epidermal growth factor receptor [EGFR] mutation, anaplastic lymphoma kinase [ALK] fusions, RET rearrangement positive, MET exon 14 skipping, NTRK gene fusion positive, BRAF V600E mutation positive, and ROS1 rearrangement positive.

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

Dosing. Approve the following dosing regimens (A, B, or C):

- A) 200 mg as an intravenous infusion not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks; OR
- C) In brain metastases, the following regimens may also be approved:
 - i. 10 mg/kg every 2 weeks; OR
 - ii. 2 mg/kg every 3 weeks.

12. Primary Mediastinal Large B-Cell Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

- A) Patient has relapsed after, or is refractory to, at least two previous regimens; AND

Note: Examples of previous regimens include autologous hematopoietic stem cell transplant (auto-HSCT), EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab), RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), RCEPP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).

- B) The medication is prescribed by or in consultation with an oncologist

Dosing. Approve the following dosing regimens (A, B, or C):

- A) 200 mg as an intravenous infusion given not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion given not more frequently than once every 6 weeks; OR
- C) 2 mg per kg (up to a maximum of 200 mg) given as an intravenous infusion given not more frequently than once every 3 weeks.

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- 13. Renal Cell Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A, B, and C):
- A) Patient has advanced disease; AND
 - B) Keytruda is used in combination with Inlyta (axitinib tablets); AND
 - C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimens (A or B):

- A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

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- 14. Small Cell Lung Cancer.** Approve for 1 year if the patient meets BOTH of the following criteria (A and B):

- A) Patient has tried at least one other chemotherapy regimen; AND

Note: Examples of chemotherapy regimen are cisplatin, carboplatin, etoposide, irinotecan, topotecan, paclitaxel.

- B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimens (A or B):

- A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

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- 15. Urothelial Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):

- A) Patient meets ONE of the following conditions (i, ii, iii, or iv):

- i. Patient has tried at least one platinum-based chemotherapy; OR

Note: Cisplatin and carboplatin are platinum-based chemotherapies.

- ii. Patient meets both of the following (a and b):

- a) According to the prescriber, patient is not eligible for cisplatin-based chemotherapy, AND
 - b) The tumor expresses PD-L1, defined as a combined positive score (CPS) ≥ 10 ; OR

- iii. According to the prescriber, patient is not eligible for platinum-based chemotherapy (i.e., with cisplatin and carboplatin); OR

Note: This is regardless of PD-L1 status.

- iv. Patient meets both of the following (a and b):

- a) Patient has non-muscle invasive bladder cancer; AND

- b) Patient has tried Bacillus Calmette-Guerin (BCG) or intravesical chemotherapy.

Note: Examples of agents used as intravesical chemotherapy include mitomycin and gemcitabine.

- B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimens (A or B):

- A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR
- B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks.

Other Uses with Supportive Evidence

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- 16. Anal Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):

- A) Patient has received at least one other chemotherapy regimen; AND

Note: Examples of chemotherapy regimens are 5-fluorouracil (5-FU), cisplatin, carboplatin, paclitaxel, FOLFOX (oxaliplatin, leucovorin, and 5-FU).

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

Dosing. Approve the following dosing regimens (A, B, or C):

A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks; OR

C) 2 mg per kg as an intravenous infusion administered not more frequently than once every 3 weeks.

17. Gestational Trophoblastic Neoplasia. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient meets one of the following (i or ii):

i. Patient has tried at least one previous chemotherapy regimen for recurrent or progressive disease; OR

Note: Examples of chemotherapy regimens contain etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.

ii. Patient has methotrexate-resistant high-risk disease; AND

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

Dosing. Approve the following dosing regimens (A, B, or C):

A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks; OR

C) 2 mg per kg as an intravenous infusion administered not more frequently than once every 3 weeks.

18. Malignant Pleural Mesothelioma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient has tried first-line chemotherapy; AND

Note: Examples of chemotherapy are Alimta (pemetrexed intravenous injection) with or without cisplatin or carboplatin, gemcitabine plus cisplatin, vinorelbine.

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

Dosing. Approve the following dosing regimens (A, B, or C):

A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks; OR

C) 10 mg per kg as an intravenous infusion administered not more frequently than once every 2 weeks.

19. Mycosis Fungoides/Sezary Syndrome. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimens (A, B, or C):

A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks; OR

C) 2 mg per kg as an intravenous infusion administered not more frequently than once every 3 weeks.

20. Extranodal NK/T-Cell Lymphoma, Nasal Type. Approve for 1 year if the patient meets the following criteria (A and B):

A) The patient has received an asparaginase-based chemotherapy regimen; AND

Note: Examples of asparaginase-based chemotherapy are dexamethasone, ifosfamide, pegaspargase, etoposide; and gemcitabine, pegaspargase, oxaliplatin).

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

Dosing. Approve the following dosing regimens (A or B):

A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks

21. Thymic Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient has tried at least one other chemotherapy regimen; AND

Note: Examples of chemotherapy regimen are carboplatin, paclitaxel, cisplatin, doxorubicin, cyclophosphamide.

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

Dosing. Approve the following dosing regimens (A, B, or C):

A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks; OR

C) 2 mg per kg as an intravenous infusion administered not more frequently than once every 3 weeks.

22. Vulvar Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) The tumors are PD-L1-positive (combined positive score ≥ 1), as determined by an approved test; AND

B) Patient has tried at least one other chemotherapy regimen.

Note: Examples of chemotherapy regimen are cisplatin, carboplatin, fluorouracil, paclitaxel; AND

C) The medication 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. Approve the following dosing regimens (A, B, or C):

A) 200 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

B) 400 mg as an intravenous infusion administered not more frequently than once every 6 weeks; OR

C) 2 mg per kg as an intravenous infusion administered not more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Keytruda is not recommended in the following situations:

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

REFERENCES

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	<ul style="list-style-type: none"> • Cervical Cancer: New FDA approved indication was added. • cHL: Criteria were revised to include patients of all ages who have one of the following: the patient has had an auto-HSCT and post-transplant Adcetris therapy, the patient has had ≥ 3 lines of systemic therapy and this includes an auto-HSCT as one line of therapy, or the patient is ineligible for transplant. Previously, criteria were separated by age groups. • MSI-H or dMMR CRC: Removed criterion that CRC is MSI-H or dMMR since this is in the indication. • NSCLC: For the criterion of Keytruda will be used in combination with Alimta and carboplatin, cisplatin was added as an alternative to carboplatin. • PMBCL: New FDA approved indication was added. • Anal Carcinoma: New indication recommended by NCCN guidelines was added. • Brain Metastases Due to Melanoma or NSCLC: Criteria were revised to add patients newly diagnosed with asymptomatic metastases. • Melanoma, Uveal: New indication was added based on NCCN guidelines. • Extended Approval: Throughout the policy revised to add “or stable disease”. • Duration of Therapy: Throughout the policy revised so the patient has a response or stable disease as determined by the prescribing physician. • Other Cancer-Related Indications: Nasopharyngeal HNSCC (category 2B) was added. Cervical cancer and vulvar cancer were removed and added to the MSI-H or dMMR CRC discussion. 	06/20/2018
Update 06/21/18	<ul style="list-style-type: none"> • The indication for urothelial carcinoma in the overview was updated based on revised prescribing information. The wording of the indication for treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy was revised to add “and whose tumors express PD-L1 (CPS ≥ 10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.” 	Not applicable
Annual revision	<p>All Indications</p> <ul style="list-style-type: none"> • Changed approval duration to 1 year (previously was 6 months). • Removed response criteria for continuation of therapy (now must meet PA criteria for reauthorization). • Removed requirement in dosing section that Keytruda is infused over 30 minutes. <p>Brain Metastases Due to Melanoma or NSCLC, Uveal Melanoma, Patient has been Started on Keytruda</p> <ul style="list-style-type: none"> • Conditions were deleted and are now generally included under respective cancers (melanoma and NSCLC). For patients already started on Keytruda, patients must meet criteria and dosing for continuation of therapy. <p>Cervical Cancer</p> <ul style="list-style-type: none"> • Since chemotherapy is required, delete requirement that the patient has recurrent or metastatic disease (presumed to be recurrent or metastatic if chemotherapy has been tried). • Simplify list of therapies that may have been tried so as to clarify that specific regimens are not required to be tried prior to Keytruda but are examples that may be tried as part of a regimen for cervical cancer. • Remove criterion that requires Keytruda be administered as a single agent (not needed). <p>Classic Hodgkin Lymphoma</p> <ul style="list-style-type: none"> • Since multiple therapies or stem cell transplant is required, delete requirement that the patient has relapsed or progressive disease (presumed to be relapsed or recurrent if multiple therapies has been tried). • Remove criterion that requires Keytruda be administered as a single agent (not needed). • For an exception to the requirement that the patient is required to have tried 3 previous lines of therapy, remove requirement that patients undergoing stem cell transplantation must undergo an autologous procedure (allogeneic procedures also mentioned in guidelines). To align with guidelines, remove requirement that the patient received post-transplant therapy with Adcetris. <p>Gastric, Gastroesophageal Junction, or Esophageal Cancer</p>	12/19/2018

	<ul style="list-style-type: none"> • Since chemotherapy is required, delete requirement that the patient has locally advanced or metastatic disease (presumed to be locally advanced or metastatic if chemotherapy has been tried). • Remove criterion that requires Keytruda be administered as a single agent (not needed). <p>Head and Neck Squamous Cell Carcinoma (HNSCC)</p> <ul style="list-style-type: none"> • Since chemotherapy is required unless contraindicated, delete requirement that the patient has recurrent or metastatic disease (presumed to be recurrent or metastatic if chemotherapy has been tried). Since used in nasopharyngeal disease, remove requirement that the patient has non-nasopharyngeal HNSCC. • Remove criterion that required the patient has disease progression on or after trying platinum-containing chemotherapy. For the criterion that requires a previous trial of chemotherapy, add cisplatin and carboplatin to the list of examples. • Remove criterion that requires Keytruda be administered as a single agent (not needed). <p>Hepatocellular Carcinoma, Including Hepatobiliary Cancers</p> <ul style="list-style-type: none"> • Add criteria to approve for this FDA-approved indication if the patient has tried at least one tyrosine kinase inhibitor, and if prescribed by or in consultation with an oncologist. <p>Melanoma</p> <ul style="list-style-type: none"> • Add a note to clarify that the criteria apply to cutaneous melanoma, brain metastasis due to melanoma, and uveal melanoma. • Add a criterion to approve for use of Keytruda in the adjuvant setting. <p>Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors</p> <ul style="list-style-type: none"> • When chemotherapy is required, delete requirement that the patient has unresectable or metastatic disease (presumed to be unresectable or metastatic if chemotherapy has been tried). • Remove criterion that requires Keytruda be administered as a single agent (not needed). • Add criteria to approve in the first-line setting for unresectable or metastatic gallbladder cancer. • For colon or rectal cancer simplify criteria to require a previous trial of chemotherapy (previously required progression while on a fluoropyrimidine or adjuvant therapy with FOLFOX). Remove requirement that patients who progressed after treatment with a fluoropyrimidine have not previously been treated with Keytruda or Opdivo. • For other MSI-H or dMMR solid tumors, change wording to require a trial of at least one prior systemic therapy (previously required disease progression). Remove requirement that there are no satisfactory alternative treatment options (not in guidelines for majority of these tumors). • Remove criterion that does not cover Keytruda for children with central nervous system tumors. <p>Non-Small Cell Lung Cancer</p> <ul style="list-style-type: none"> • When chemotherapy is required, delete requirement that the patient has metastatic disease (presumed to be metastatic if chemotherapy has been tried). • For non-squamous cell carcinoma, change criteria so that patients with unknown status for targetable mutations are not required to undergo testing (aligns with guidelines). • For patients with a tumor proportion score of $\geq 1\%$ and $\geq 50\%$, remove criterion that requires Keytruda be administered as a single agent (not needed). For those with a tumor proportion score of at least 1%, remove criterion that excluded coverage if Keytruda, Opdivo, or Tecentiq have been used in the past. • To approve in the first-line setting, generally require use in combination with chemotherapy (applies to squamous and non-squamous histologies). Previously, use in the first-line setting only applied to non-squamous histology and required a specific regimen to be taken with Keytruda. • In the dosing section, clarify that dosing of 10 mg/kg given every 2 weeks and 2 mg/kg given every 3 weeks are approvable in patients with brain metastases. <p>Urothelial Carcinoma</p> <ul style="list-style-type: none"> • When chemotherapy is required, delete requirement that the patient has locally advanced or metastatic disease (presumed to be unresectable or metastatic if chemotherapy has been tried). • Remove criterion that requires Keytruda be administered as a single agent (not needed). • For patients that are not eligible for cisplatin, add that the tumor must express PD-L1. • Add criteria to allow an exception for patients who, according to the prescriber, are not eligible for platinum-based chemotherapy. Note that this is regardless of PD-L1 status. • Reword criteria to require a previous trial of at least one platinum-containing chemotherapy. Criteria previously required disease progression during or after trying one of these therapies. <p>Anal Carcinoma</p> <ul style="list-style-type: none"> • Since chemotherapy is required, delete requirement that the patient has metastatic disease (presumed to be metastatic if chemotherapy has been tried). 	
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	<ul style="list-style-type: none"> Remove criterion that requires Keytruda be administered as a single agent (not needed). <p>Malignant Pleural Mesothelioma</p> <ul style="list-style-type: none"> Remove criterion that requires Keytruda be administered as a single agent (not needed). In dosing, add criteria to approve 200 mg as an intravenous infusion given once every 3 weeks. <p>Merkel Cell Carcinoma</p> <ul style="list-style-type: none"> Move this condition to the FDA-Approved Uses section of the policy. Previously was approvable as an Other Uses With Supportive Evidence. Change criteria to approve for recurrent, locally advanced, or metastatic disease, which aligns with the approved labeling. Criteria previously approved for disseminated disease. Add 200 mg as an intravenous infusion given once every 3 weeks as an approvable dose. <p>Small Cell Lung Cancer</p> <ul style="list-style-type: none"> Add this off-label indication as an approval, if the patient has tried at least one other systemic therapy within the past 6 months, and if prescribed by or in consultation with an oncologist. The approvable dose is 200 mg as an intravenous infusion given once every 3 weeks. <p>Other Cancer-Related Indications</p> <ul style="list-style-type: none"> Remove nasopharyngeal head and neck cancer (included in criteria). Add T-cell lymphoproliferative disorders, chronic lymphocytic leukemia/small lymphocytic lymphoma, and gestational trophoblastic neoplasia to the list of oncology indications that are reviewed on a case-by-case basis by the Medical Director. 	
Selected revision	<p>Melanoma: For adjuvant treatment, criteria were changed to allow up to 1 year (total) of treatment. This aligns with the treatment duration for this use in the published study and for this indication in the Opdivo CC policy. Previously, criteria did not limit total treatment duration.</p>	01/30/2019
Annual revision	<p>All Indications. For Dosing, added “not more frequently than” with regards to frequency. If “e.g” are listed in criteria they were re-formatted to a Note. For criteria “Keytruda is prescribed by...” was changed to “The medication is prescribed by..” Where applicable, prescribing physician was changed to prescriber.</p> <p>Endometrial Carcinoma. New approval indication was added.</p> <p>Esophageal and Esophagogastric Junction Cancer. Previously was listed together with Gastric Cancer. Now, this indication is separated out since the guidelines are also separate for these conditions.</p> <p>Gastric Cancer. Deleted out “Gastroesophageal Junction (GEJ) Cancer, or Esophageal Cancer” from indication. Criteria regarding the patient has tried a fluoropyridine and platinum was changed to “at least two previous chemotherapy regimens”.</p> <p>Head and Neck Squamous Cell Carcinoma. The following criteria were added: the patient has recurrent or metastatic disease; for first-line setting, Keytruda is used in combination with chemotherapy or for use as single agent, the tumor has to be PD-L1-positive; for subsequent therapy, the wording was changed to at least one platinum-containing chemotherapy regimen has been tried. The other criteria providing exception for chemotherapy contraindication was deleted.</p> <p>Melanoma. Deleted criteria Keytruda will not be used in combination with Yervoy.</p> <p>Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors. Added a list of different solid tumors in a Note under the indication as examples. Deleted the examples from within criteria.</p> <p>Non-Small Cell Lung Cancer. Modified criteria with regards to tumor proportion score for PD-L1 to state ≥ 1 and $< 50\%$ and added criteria that Keytruda is used as a single agent for maintenance. For non-squamous cell carcinoma with regards to targeted mutations, deleted criteria, “tumor is negative or unknown for these targetable mutations.”</p> <p>Renal Cell Carcinoma. Added new approval condition and criteria.</p> <p>Small Cell Lung Cancer. Instead of systemic therapy, changed to “chemotherapy regimen”. Deleted criteria “within the past 6 months” with regards to trying chemotherapy.</p> <p>Anal Carcinoma. Added “at least one” with regards to trying chemotherapy “regimen”.</p> <p>Gestational Trophoblastic Neoplasia. Added new approval condition and criteria.</p> <p>Mycosis Fungoides/Sezary Syndrome. Added new approval condition and criteria.</p> <p>Thymic Carcinoma. Added new approval condition and criteria.</p> <p>Vulvar Cancer. Added new approval condition and criteria.</p> <p>Other Cancer-Related Indications. Deleted to be in-line with other policies.</p>	12/11/2019
Early annual revision	<p>All Indications: In accordance with the approved labeling, the dosing section was updated to include 400 mg an intravenous infusion administered not more frequently than once every 6 weeks.</p> <p>Classic Hodgkin Lymphoma: Examples of systemic therapies were moved to a Note (previously listed as examples within the criteria).</p>	06/17/2020

	<p>Endometrial Carcinoma: Criteria were modified to allow coverage for a patient with recurrent disease, if other conditions are met. Previously, criteria only addressed advanced disease.</p> <p>Hepatocellular Carcinoma, Including Hepatobiliary Cancers: Examples of tyrosine kinase inhibitors were moved to a Note (previously listed as examples within the criteria).</p> <p>Melanoma: Examples of adjuvant therapy uses were moved to a Note (previously listed as examples within the criteria).</p> <p>Non-Small Cell Lung Cancer: Criteria that applied specifically to patients with a tumor proportion score (TPS) \geq 1% and $<$ 50% were deleted from the policy. Now all criteria for NSCLC apply to any patient with a TPS \geq 1%. Criteria applying to a patient with non-squamous cell carcinoma were modified to be listed in a Note as examples of targetable mutations (previously listed as i.e. within the criteria). RET rearrangement positive, MET exon 14 skipping, NTRK gene fusion positive, BRAF V600E mutation positive, and ROS1 rearrangement positive were added to list of targetable mutations.</p> <p>Urothelial Carcinoma: Examples of platinum-based chemotherapies were moved to a Note (previously listed as examples within the criteria). Clarify in criteria that tumor expression of PD-L1 is defined by combined positive score (CPS) \geq 10 (previously CPS was listed as an i.e. in the criteria). Criteria were added to approve Keytruda if the patient has non-muscle invasive bladder cancer and has tried Bacillus Calmette-Guerin (BCG) or intravesical chemotherapy.</p> <p>Extranodal NK/T-Cell Lymphoma, Nasal Type: To align with NCCN recommendations, this indication was added as an Other Use With Supportive Evidence. Criteria approve for 1 year if the patient has tried asparaginase-based chemotherapy regimen and if prescribed by or in consultation with an oncologist. Dosing is aligned with dosing for FDA-approved uses.</p>	
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NSCLC – Non-small cell lung cancer; EGFR – Epidermal growth factor receptor; ALK – Anaplastic lymphoma kinase; cHL – Classic Hodgkin Lymphoma; HNSCC – Head and neck squamous cell carcinoma; MSI-H – Microsatellite Instability-High; dMMR – Mismatch Repair Deficient; PD-L1 – Programmed death-ligand 1; GEJ – Gastroesophageal Junction; NCCN – National Comprehensive Cancer Network; auto-HSCT – Autologous-hematopoietic stem cell transplantation; PMBCL – Primary Mediastinal Large B-Cell Lymphoma.