# Keytruda

## Description

**Keytruda (pembrolizumab)**

### Background

Keytruda is a monoclonal antibody for the treatment of patients with advanced or unresectable melanoma, melanoma with involvement of lymph node(s) following complete resection, metastatic non-small cell lung cancer (NSCLC), metastatic nonsquamous and squamous non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), refractory classical Hodgkin lymphoma (cHL), refractory mediastinal large B-cell lymphoma (PMBCL), recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus, microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatments, patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA approved test, hepatocellular carcinoma, Merkel cell carcinoma (MCC), renal cell carcinoma (RCC), and endometrial carcinoma. Keytruda blocks a cellular pathway known as PD-1, human programmed death receptor-1, which restricts the body’s immune system from attacking cancer cells (1-3).

### Regulatory Status

FDA-approved indication: Keytruda is a human programmed death receptor-1 (PD-1)-blocking antibody indicated: (3)

1. Melanoma
   a. For the treatment of patients with unresectable or metastatic melanoma
   b. For the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection
2. Non-Small Cell Lung Cancer (NSCLC)
   a. 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
   b. In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC
   c. As a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA approved test with no EGFR or ALK genomic tumor aberrations, and is:
      i. Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
      ii. Metastatic.
   d. 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.

3. Small cell lung cancer (SCLC)
   a. For the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-containing chemotherapy and at least one other prior line of therapy.

4. Head and Neck Squamous Cell Cancer (HNSCC)
   a. In combination with platinum and fluorouracil (FU), for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
   b. As a single agent, for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.
   c. As a single agent, for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

5. Classical Hodgkin Lymphoma (cHL)
   a. For the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior line of therapy

6. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
   a. For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy
   b. Limitations of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

7. Urothelial Carcinoma
a. 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.

b. 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.

8. Microsatellite Instability-High Cancer
   a. For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient 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.
   b. Limitations of Use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.

9. Gastric Cancer
   a. 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 and FDA-approved test, with disease progression on or after two or more lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

10. Esophageal Cancer
    a. For the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

11. Cervical Cancer
    a. For the treatment of patients with recurrent of metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

12. Hepatocellular Carcinoma (HCC)
    a. For the treatment of patients with HCC who have been previously treated with sorafenib.

13. Merkel Cell Carcinoma (MCC)
a. For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma

14. Renal Cell Carcinoma (RCC)
   a. In combination with axitinib, for the first-line treatment of patients with advanced RCC

15. Endometrial carcinoma
   a. In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation

Clinically significant immune-mediated adverse reactions may occur with Keytruda therapy including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, hypothyroidism, skin adverse reaction, infusion-related reactions, and other immune-mediated adverse reactions. Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued and corticosteroids administered. Patients should be monitored for signs and symptoms of pneumonitis, colitis, hypophysitis, thyroid disorders, and changes in liver and renal function. Keytruda may cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised of the potential hazard to a fetus (3).

Keytruda in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to Keytruda alone (3).

Safety and effectiveness of Keytruda have been established in pediatric patients (3).

**Related Policies**
Bavencio, Imfinzi, Opdivo, Tecentriq

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Keytruda may be considered **medically necessary** in patients with unresectable or metastatic melanoma, melanoma with involvement of lymph node(s) following complete resection, for metastatic non-small cell lung cancer (NSCLC), for metastatic nonsquamous and squamous non-small cell lung cancer (NSCLC), for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), patients with refractory classical Hodgkin lymphoma (cHL), for refractory primary mediastinal large B-cell lymphoma (PMBCL), advanced or metastatic urothelial
carcinoma, recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus, microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumors, or recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, or recurrent or metastatic cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, or endometrial carcinoma; and if the conditions indicated below are met.

Keytruda is considered investigational in patients with all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have ONE of the following:

1. Unresectable or metastatic melanoma

2. Melanoma with involvement of lymph node(s) following complete resection
   a. Used as adjuvant treatment

3. Metastatic non-small cell lung cancer (NSCLC)
   a. Used as a single agent
   b. PD-L1 tumor expression with Tumor Proportion Score (TPS) ≥ 1%
      determined by a FDA-approved test with ONE of the following:
      i. Negative for EGFR or ALK tumor expression and ONE of the following:
         1) Disease progression on or after platinum-containing chemotherapy
         2) First-line treatment
      ii. Positive EGFR or ALK tumor expression
          1) Disease progression after targeted FDA-approved therapy

4. Metastatic nonsquamous non-small cell lung cancer (NSCLC)
   a. Used in combination with pemetrexed and platinum chemotherapy as first-line treatment
   b. Negative for EGFR or ALK tumor expression

5. Stage III non-small cell lung cancer (NSCLC)
a. Patient is not a candidate for surgical resection or definitive chemoradiation
b. PD-L1 tumor expression with Tumor Proportion Score (TPS) ≥ 1% as determined by an FDA-approved test
c. Negative for EGFR or ALK tumor aberrations
d. Used as a single agent for first-line treatment

6. Metastatic squamous non-small cell lung cancer (NSCLC)
   a. Used in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment

7. Metastatic small cell lung cancer (SCLC)
   a. Disease progression on or after platinum-based chemotherapy AND at least one other prior line of therapy

8. Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) and ONE of the following:
   a. Used in combination with platinum and fluorouracil (FU) as first-line treatment
   b. PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as determined by an FDA-approved test
      i. Used as a single agent for first-line treatment
   c. Disease progression on or after platinum-containing chemotherapy
      i. Used as a single agent

9. Refractory classical Hodgkin lymphoma (cHL)
   a. Patient has relapsed after 3 or more prior lines of therapy

10. Refractory primary mediastinal large B-cell lymphoma (PMBCL)
    a. Patient has relapsed after 2 or more lines of therapy

11. Advanced or metastatic urothelial carcinoma with ONE of the following:
    a. Patient is NOT eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with combined positive score (CPS) ≥ 10 as determined by an FDA-approved test
    b. Patient is NOT eligible for any platinum-containing chemotherapy
    c. Disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
12. Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers with ONE of the following:
   a. Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
      i. NOT for use in pediatric patients with MSI-H central nervous system cancers
   b. Colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan

AND the following for MSI-H or dMMR cancers:
   a. Diagnosis has to be confirmed by PCR-based assay genetic testing

13. Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma
   a. PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as determined by an FDA-approved test
   b. Disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy

14. Recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus
   a. PD-L1 tumor expression with combined positive score (CPS) ≥ 10 as determined by an FDA-approved test
   b. Disease progression after one or more prior lines of systemic therapy

15. Recurrent or metastatic cervical cancer
   a. Disease progression on or after chemotherapy
   b. PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as determined by an FDA-approved test

16. Hepatocellular carcinoma (HCC)
   a. Patient has previously been treated with Nexavar (sorafenib)

17. Recurrent locally advanced or metastatic Merkel cell carcinoma (MCC)

18. Advanced renal cell carcinoma (RCC)
   a. First-line treatment
   b. Used in combination with Inlyta (axitinib)
   c. Prescriber agrees to monitor for hepatotoxicity
19. Advanced endometrial carcinoma  
   a. Used in combination with Lenvima (lenvatinib)  
   b. NOT MSI-H or dMMR  
   c. Disease progression following prior systemic therapy  
   d. NOT a candidate for curative surgery or radiation  

Prior – Approval Renewal Requirements  

Diagnoses  

Patient must have ONE of the following:  
1. Unresectable or metastatic melanoma  
2. Melanoma with involvement of lymph node(s) following complete resection  
3. Metastatic non-small cell lung cancer (NSCLC)  
4. Metastatic nonsquamous non-small cell lung cancer (NSCLC)  
5. Stage III non-small cell lung cancer (NSCLC)  
6. Metastatic squamous non-small cell lung cancer (NSCLC)  
7. Metastatic small cell lung cancer (SCLC)  
8. Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)  
9. Refractory classical Hodgkin lymphoma (cHL)  
10. Refractory primary mediastinal large B-cell lymphoma (PMBCL)  
11. Advanced or metastatic urothelial carcinoma  
12. Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers  
   a. NOT for use in pediatric patients with MSI-H central nervous system cancers  
13. Recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma  
14. Recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus  
15. Recurrent or metastatic cervical cancer  
16. Hepatocellular carcinoma (HCC)  
17. Recurrent locally advanced or metastatic Merkel cell carcinoma (MCC)  
18. Advanced renal cell carcinoma (RCC)  
   a. Used in combination with Inlyta (axitinib)  
   b. Prescriber agrees to monitor for hepatotoxicity  
19. Advanced endometrial carcinoma  
   a. Used in combination with Lenvima (lenvatinib)
a. Prescriber agrees to discontinue treatment for any immune mediated adverse reaction (encephalitis, nephritis, rash, decreased renal function and endocrinopathies) or disease progression.

**Policy Guidelines**

**Pre - PA Allowance**

None

**Prior - Approval Limits**

Duration 6 months

**Prior – Approval Renewal Limits**

Duration 12 months

**Rationale**

**Summary**

Keytruda is a monoclonal antibody indicated for the treatment of patients with advanced or unresectable melanoma, melanoma with involvement of lymph node(s) following complete resection, metastatic non-small cell lung cancer (NSCLC), metastatic nonsquamous and squamous non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), refractory classical Hodgkin lymphoma (cHL) who are no longer responding to other drugs, refractory primary mediastinal large B-cell lymphoma (PMBCL), locally advanced or metastatic urothelial carcinoma, recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus, microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatments, recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, and endometrial carcinoma. Clinically significant immune-mediated adverse reactions may occur with Keytruda therapy including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, hypothyroidism, skin adverse reaction, infusion-related reactions, and other immune-mediated adverse reactions. Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued and corticosteroids administered. Keytruda may cause fetal harm when administered to a pregnant woman. Safety and effectiveness of Keytruda have been established in pediatric patients (1-4).
Prior authorization is required to ensure the safe, clinically appropriate and cost-effective use of Keytruda while maintaining optimal therapeutic outcomes.

References


Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>September 2014</td>
<td>New Policy</td>
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<tr>
<td>December 2014</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>June 2015</td>
<td>Annual editorial review</td>
</tr>
<tr>
<td>October 2015</td>
<td>Addition of Metastatic non-small cell lung cancer (NSCLC) if the patient has PD-L1 tumor expression determined by a FDA-approved test and has disease progression on or after platinum-containing chemotherapy; or the patient has EGFR or ALK tumor expression and has disease progression after FDA-approved therapy</td>
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<tr>
<td>December 2015</td>
<td>Annual review</td>
</tr>
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<td>Removal of disease progression following Yervoy (ipilimumab) and, if BRAF V600 mutation positive, a BRAF inhibitor and no concurrent therapy with other agents for the treatment of unresectable or metastatic melanoma</td>
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<tr>
<td>March 2016</td>
<td>Annual editorial review</td>
</tr>
<tr>
<td></td>
<td>Policy number change from 5.04.50 to 5.21.50</td>
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<tr>
<td>June 2016</td>
<td>Annual editorial review</td>
</tr>
<tr>
<td></td>
<td>Addition of Prescriber agrees to discontinue treatment for any immune mediated adverse reaction (encephalitis, nephritis, rash, decreased renal function and endocrinopathies) or disease progression in renewal section per SME</td>
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<td>Event</td>
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<tr>
<td>August 2016</td>
<td>Addition of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy</td>
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<tr>
<td>September 2016</td>
<td>Annual review</td>
</tr>
<tr>
<td>November 2016</td>
<td>Addition of (NSCLC) PD-L1 tumor expression with Tumor Proportion Score (TPS) ≥ 50% determined by a FDA-approved test with no prior treatment needed</td>
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<tr>
<td>December 2016</td>
<td>Annual review</td>
</tr>
<tr>
<td>March 2017</td>
<td>Addition of refractory classical Hodgkin lymphoma (cHL), who have relapsed after 3 or more prior lines of therapy</td>
</tr>
<tr>
<td>June 2017</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>July 2017</td>
<td>Addition of the requirement to MSI-H: diagnosis has to be confirmed by PCR-based genetic testing</td>
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<tr>
<td>September 2017</td>
<td>Annual review</td>
</tr>
<tr>
<td>October 2017</td>
<td>Addition of recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma</td>
</tr>
<tr>
<td>December 2017</td>
<td>Annual review</td>
</tr>
<tr>
<td>June 2018</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>July 2018</td>
<td>Addition of the diagnosis of recurrent or metastatic cervical cancer</td>
</tr>
<tr>
<td>August 2018</td>
<td>Addition of diagnosis of refractory primary mediastinal large B-cell lymphoma (PMBCL)</td>
</tr>
<tr>
<td>September 2018</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>January 2019</td>
<td>Addition of indication: recurrent locally advanced or metastatic Merkel cell carcinoma (MCC)</td>
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March 2019  
Annual review and reference update. Addition of indication of melanoma with involvement of lymph node(s) following complete resection as adjuvant treatment

April 2019  
Addition of indication: Stage III NSCLC  
Addition of indication: Advanced renal cell carcinoma (RCC)

May 2019  
Revised Metastatic NSCLC indication to include first-line therapy with TPS ≥1% and negative for EGFR or ALK tumor expression. Added hepatotoxicity monitoring requirement to RCC diagnosis

June 2019  
Annual review. Added HNSCC indication used in combination with platinum and fluorouracil as first-line treatment and HNSCC as a single agent for first-line treatment with CPS >1. Added small cell lung cancer indication

August 2019  
Addition of indication: Recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus. Revised Metastatic NSCLC indication

September 2019  
Annual review. Addition of indication: endometrial carcinoma

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 13, 2019 and is effective on October 1, 2019.