

STANDARD MEDICARE PART B MANAGEMENT

KEYTRUDA (pembrolizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Melanoma
 - i. Keytruda (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.
 - ii. Keytruda is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.
2. Non-Small Cell Lung Cancer
 - i. Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
 - ii. Keytruda, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.
 - iii. Keytruda, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 (Tumor Proportion Score [TPS $\geq 1\%$]) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
 - a..stage III where patients are not candidates for surgical resection or definitive chemoradiation,
 - or
 - b.metastatic.
 - iv. Keytruda, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS $\geq 1\%$) 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

Keytruda is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.
4. Head and Neck Cancer Squamous Cell Cancer
 - i. Keytruda, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).
 - ii. Keytruda, as a single agent, is indicated 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.

iii. Keytruda, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

5. Classical Hodgkin Lymphoma

Keytruda is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after three or more prior lines of therapy.

6. Primary Mediastinal Large B-cell Lymphoma

Keytruda is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphomas (PMBCL), or who have relapsed after 2 or more prior lines of therapy.

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

7. Urothelial Carcinoma

- i. Keytruda is indicated 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 (CPS \geq 10) as determined by an FDA-approved test, or in patients who are not eligible for platinum-containing chemotherapy regardless of PD-L1 status.
- ii. Keytruda is indicated 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.
- iii. Keytruda is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

8. Microsatellite Instability-High or Mismatch Repair Deficient Cancer

Keytruda is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)

- i. Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- ii. Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

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

9. Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

Keytruda is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

10. Gastric Cancer

Keytruda is indicated for the treatment of patients with recurrent locally advanced, metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS \geq 1) as determined by an FDA approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

11. Esophageal Cancer

Keytruda is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS \geq 10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

12. **Cervical Cancer**
Keytruda is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumor express PD-L1 (CPS \geq 1) as determined by an FDA-approved test.
13. **Hepatocellular Carcinoma**
Keytruda is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.
14. **Merkel Cell Carcinoma**
Keytruda is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).
15. **Renal Cell Carcinoma**
Keytruda, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).
16. **Endometrial Carcinoma**
Keytruda, in combination with lenvatinib, is indicated 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.
17. **Tumor Mutational Burden-High Cancer**
Keytruda is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [\geq 10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Limitations of use: The safety and effectiveness of Keytruda in pediatric patients with TMB-H central nervous system cancers have not been established.

18. **Cutaneous Squamous Cell Carcinoma**
Keytruda is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.

B. Compendial Uses

1. Cutaneous melanoma
2. Non-small cell lung cancer
3. Head and neck cancer
4. Classical Hodgkin lymphoma
5. Small cell lung cancer
6. Urothelial carcinoma
7. Solid tumors
8. Colorectal cancer
9. Malignant pleural mesothelioma
10. Merkel cell carcinoma
11. Gastric cancer and esophagogastric junction cancer
12. Esophageal cancer
13. Cervical cancer
14. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
15. Uveal melanoma
16. Testicular cancer

17. Endometrial carcinoma
18. Anal carcinoma
19. Central Nervous System (CNS) brain metastases
20. Primary mediastinal large B-cell lymphoma
21. Pancreatic adenocarcinoma
22. Hepatobiliary cancers
23. Hepatocellular carcinoma
24. Vulvar cancer
25. Kidney cancer
26. Thymic carcinoma
27. Mycosis Fungoides/Sezary syndrome
28. T-cell lymphomas
29. Gestational trophoblastic neoplasia
30. Poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma
31. Prostate cancer
32. Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders
33. Alveolar soft part sarcoma
34. Undifferentiated pleomorphic sarcoma
35. Diffuse large B-cell lymphoma

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:

- A. Pediatric members with microsatellite instability-high (MSI-H) central nervous system cancers.
- B. Pediatric members with TMB-H central nervous system cancers.

III. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous Melanoma

Authorization of 12 months may be granted for the treatment of cutaneous melanoma in either of the following settings:

1. Treatment of unresectable or metastatic disease.
2. Keytruda will be used as adjuvant treatment following complete lymph node resection or complete resection of metastatic disease.

B. Non-small Cell Lung Cancer (NSCLC)

Authorization of 12 months may be granted for treatment of recurrent, advanced, or metastatic NSCLC.

C. Head and Neck Cancer

Authorization of 12 months may be granted for treatment of head and neck cancer.

D. Classical Hodgkin Lymphoma

Authorization of 12 months may be granted for treatment of classical Hodgkin lymphoma.

E. Small Cell Lung Cancer

Authorization of 12 months may be granted for treatment of relapsed, primary progressive, or metastatic small cell lung cancer.

F. Urothelial Carcinoma

Authorization of 12 months may be granted for treatment of urothelial carcinoma, including bladder cancer, upper genitourinary tract tumors, urothelial carcinoma of the prostate, and primary carcinoma of the urethra.

G. Solid Tumors

Authorization of 12 months may be granted for treatment of solid tumors in members with unresectable or metastatic disease that has progressed following prior treatment and have no satisfactory alternative treatment options when either of the following criteria is met:

1. Keytruda will be used for microsatellite instability-high or mismatch repair deficient solid tumors.
2. Keytruda will be used for tumor mutational burden-high (≥ 10 mutations/megabase) solid tumors.

H. Colorectal Cancer

Authorization of 12 months may be granted for treatment of colorectal cancer when both of the following criteria are met:

1. Disease is unresectable or metastatic.
2. Tumor is microsatellite instability-high or mismatch repair deficient.

I. Malignant Pleural Mesothelioma

Authorization of 12 months may be granted for treatment of malignant pleural mesothelioma.

J. Merkel Cell Carcinoma

Authorization of 12 months may be granted for treatment of Merkel cell carcinoma.

K. Gastric Cancer and Esophagogastric Junction Cancer

Authorization of 12 months may be granted for treatment of gastric cancer, including esophagogastric junction cancer, in members who are not surgical candidates or who have recurrent, locally advanced, or metastatic disease.

L. Esophageal Cancer

Authorization of 12 months may be granted for treatment of esophageal cancer in members who are not surgical candidates or who have recurrent, locally advanced, or metastatic disease.

M. Cervical Cancer

Authorization of 12 months may be granted for treatment of recurrent or metastatic cervical cancer.

N. Epithelial Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Cancer

Authorization of 12 months may be granted for the treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.

O. Uveal Melanoma

Authorization of 12 months may be granted for treatment of uveal melanoma.

P. Testicular Cancer

Authorization of 12 months may be granted for the treatment of testicular cancer.

Q. Endometrial Carcinoma

Authorization of 12 months may be granted for the treatment of endometrial carcinoma.

R. Anal Carcinoma

Authorization of 12 months may be granted for the treatment of anal carcinoma.

S. CNS Brain Metastases

Authorization of 12 months may be granted for the treatment of CNS brain metastases in members with melanoma or non-small cell lung cancer (NSCLC).

T. Primary Mediastinal Large B-Cell Lymphoma

Authorization of 12 months may be granted for the treatment of primary mediastinal large B-cell lymphoma.

U. Pancreatic Adenocarcinoma

Authorization of 12 months may be granted for the treatment of pancreatic adenocarcinoma.

V. Hepatobiliary Cancers

Authorization of 12 months may be granted for the treatment of hepatobiliary cancers, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer.

W. Hepatocellular Carcinoma

Authorization of 12 months may be granted for treatment of members with hepatocellular carcinoma.

X. Vulvar Cancer

Authorization of 12 months may be granted for treatment of vulvar cancer.

Y. Kidney Cancer

Authorization of 12 months may be granted for the treatment of members with kidney cancer, including renal cell carcinoma, when Keytruda will be used in combination with axitinib.

Z. Thymic Carcinoma

Authorization of 12 months may be granted for treatment of thymic carcinoma.

AA. Mycosis Fungoides/Sezary Syndrome

Authorization of 12 months may be granted for treatment of Mycosis Fungoides or Sezary syndrome.

BB. T-Cell Lymphomas

Authorization of 12 months may be granted for treatment of extranodal NK/T-cell lymphoma, nasal type.

CC. Gestational Trophoblastic Neoplasia

Authorization of 12 months may be granted for treatment of gestational trophoblastic neoplasia.

DD. Poorly Differentiated Neuroendocrine Carcinoma/Large or Small Cell Carcinoma

Authorization of 12 months may be granted for treatment of poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma in members with microsatellite instability-high or mismatch repair deficient tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

EE. Prostate Cancer

Authorization of 12 months may be granted for treatment of prostate cancer.

FF. Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

Authorization of 12 months may be granted for treatment of primary cutaneous anaplastic large cell lymphoma (ALCL).

GG. Alveolar Soft Part Sarcoma

Authorization of 12 months may be granted for treatment of alveolar soft part sarcoma (ASPS).

HH. Undifferentiated Pleomorphic Sarcoma

Authorization of 12 months may be granted for treatment of undifferentiated pleomorphic sarcoma.

II. Diffuse Large B-Cell Lymphoma

Authorization of 12 months may be granted for treatment of diffuse large B-cell lymphoma.

JJ. Cutaneous Squamous Cell Carcinoma

Authorization of 12 months may be granted for treatment of recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.

IV. CONTINUATION OF THERAPY**A. Adjuvant Treatment of Melanoma**

Authorization for 12 months total therapy may be granted for all members (including new members) who are continuing with Keytruda therapy when all of the following criteria are met:

1. The member is currently receiving therapy with Keytruda.
2. Keytruda is being used as adjuvant treatment for a member with melanoma following complete lymph node resection or complete resection of metastatic disease.
3. Keytruda has been effective for treating the diagnosis or condition.

B. All Other Indications

Authorization for 12 months may be granted for all members (including new members) who are continuing with Keytruda therapy when all of the following criteria are met:

1. The member is currently receiving therapy with Keytruda.
2. Keytruda is being used to treat any other diagnosis or condition enumerated in Section III.
3. Keytruda has been effective for treating the diagnosis or condition.

V. REFERENCES

1. Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; June 2020.
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3. Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2017. <http://www.clinicalpharmacology-ip.com/default.aspx>. Accessed July 10, 2019.
4. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; <http://online.lexi.com/lco/action/home>. Accessed July 10, 2019.