

SPECIALTY GUIDELINE 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 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 3 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 lymphoma (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 ≥ 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.
 - 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 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. Gastric Cancer
Keytruda is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.
- 10. 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 ≥ 10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.
- 11. 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 ≥ 1) as determined by an FDA-approved test.

12. Hepatocellular Carcinoma

Keytruda is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

13. Merkel Cell Carcinoma

Keytruda is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

14. Renal Cell Carcinoma

Keytruda, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

15. 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.

B. Compendial Uses

1. Cutaneous melanoma
2. Non-small cell lung cancer
3. Head and neck squamous cell cancer
4. Classical Hodgkin Lymphoma
5. Urothelial carcinoma
 - i. Bladder cancer
 - ii. Primary carcinoma of the urethra
 - iii. Upper genitourinary tract tumors
 - iv. Urothelial carcinoma of the prostate
6. Solid tumors
7. Colorectal cancer
8. Malignant pleural mesothelioma
9. Gastric cancer and esophagogastric junction cancer
10. Esophageal cancer
11. Cervical cancer
12. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
13. Uveal melanoma
14. Testicular cancer
15. Endometrial carcinoma
16. Anal carcinoma
17. Central Nervous System (CNS) brain metastases
18. Primary mediastinal large B-cell lymphoma
19. Pancreatic adenocarcinoma
20. Hepatobiliary cancers
21. Vulvar cancer
22. Kidney cancer
23. Thymic carcinoma
24. Mycosis Fungoides/Sezary syndrome
25. T-cell lymphomas
26. Gestational trophoblastic neoplasia

- 27. Small cell lung cancer
- 28. Poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma

All other indications are considered experimental/investigational and not medically necessary.

II. DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review:

- A. Documentation of programmed death ligand 1 (PD-L1) tumor expression, where applicable.
- B. Documentation of laboratory report confirming MSI-H or mismatch repair deficient (dMMR) tumor status, where applicable.

III. EXCLUSIONS

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

- A. Pediatric members with MSI-H central nervous system cancers.
- B. Members who have experienced disease progression while on programmed death receptor-1 (PD-1) or PD-L1 inhibitor therapy.

IV. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous Melanoma

Authorization of 6 months may be granted as a single agent for treatment of cutaneous melanoma in either of the following settings:

- 1. For 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 6 months may be granted for treatment of NSCLC in any of the following settings:

- 1. Treatment of recurrent, advanced or metastatic nonsquamous NSCLC:
 - i. Keytruda will be used following EGFR or ALK therapy if EGFR or ALK positive, AND
 - ii. Keytruda will be used in combination with both of the following:
 - a. Pemetrexed
 - b. Carboplatin or cisplatin.
- 2. Treatment of recurrent, advanced or metastatic squamous NSCLC:

Keytruda will be used in combination with carboplatin or cisplatin and paclitaxel or paclitaxel protein-bound.
- 3. Treatment of recurrent, advanced or metastatic NSCLC expressing PD-L1 (TPS $\geq 1\%$):
 - i. Keytruda will be used as a single agent, AND
 - ii. Keytruda will be used following EGFR or ALK therapy if EGFR or ALK positive.
- 4. Continuation maintenance therapy may be granted in the following settings when tumor response or stable disease is achieved:
 - i. Keytruda will be used in combination with pemetrexed if given first-line as part of a Keytruda/pemetrexed and either cisplatin or carboplatin regimen for recurrent, advanced or metastatic disease for nonsquamous cell histology.
 - ii. Keytruda will be used as a single agent if:
 - a. Keytruda monotherapy was given for first-line recurrent, advanced or metastatic disease for nonsquamous cell histology.

- b. Keytruda was given as monotherapy or as part of a regimen with cisplatin or carboplatin and either paclitaxel or albumin bound paclitaxel for recurrent, advanced or metastatic squamous cell histology.

C. Head and Neck Squamous Cell Cancer

Authorization of 6 months may be granted for treatment of members with head and neck squamous cell carcinoma (HNSCC) when any of the following criteria is met:

1. Keytruda will be used as a single agent for first-line treatment of unresectable, metastatic, or second primary HNSCC in members whose tumors express PD-L1 (CPS ≥ 1).
2. Keytruda will be used as a single agent for subsequent therapy for unresectable, metastatic, or second primary HNSCC (regardless of PD-L1 status).
3. Keytruda will be used in combination with fluorouracil and either carboplatin or cisplatin for the treatment of members with unresectable, metastatic, or second primary HNSCC (regardless of PD-L1 status).

D. Classical Hodgkin Lymphoma

Authorization of 6 months may be granted as a single agent for treatment of classical Hodgkin lymphoma when any of the following criteria is met:

1. Member has refractory disease.
2. Member has relapsed after 2 or more prior lines of therapy or following hematopoietic stem cell transplant.
3. Member has relapsed disease and is transplant-ineligible.

E. Urothelial Carcinoma – Bladder Cancer

Authorization of 6 months may be granted as a single agent for treatment of bladder cancer when any of the following criteria is met:

1. Keytruda will be used as first-line therapy in cisplatin ineligible members whose tumors express PD-L1 (CPS ≥ 10), or in members who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression for any of the following:
 - i. Stage II or Stage IIIA disease, if tumor is present following reassessment of tumor status 2-3 months after primary treatment with concurrent chemoradiotherapy.
 - ii. Locally advanced or metastatic disease.
 - iii. Metastatic or local recurrence post-cystectomy.
2. Keytruda will be used as subsequent therapy following platinum-containing chemotherapy for either of the following:
 - i. Locally advanced or metastatic disease.
 - ii. Metastatic or local recurrence post-cystectomy.
3. Keytruda will be used as subsequent therapy for the treatment of members with high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) when both of the following criteria are met:
 - i. Disease is Bacillus Calmette-Guerin (BCG)-unresponsive.
 - ii. Member is ineligible for or has elected not to undergo cystectomy.

F. Urothelial Carcinoma – Primary Carcinoma of the Urethra

Authorization of 6 months may be granted as a single agent for treatment of primary carcinoma of the urethra when either of the following criteria is met:

1. Keytruda will be used as first-line therapy for recurrent, locally advanced, or metastatic disease in cisplatin ineligible members whose tumors express PD-L1 (CPS ≥ 10), or in members who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression.
2. Keytruda will be used as subsequent therapy for recurrent, locally advanced or metastatic disease following platinum-containing chemotherapy.

G. Urothelial Carcinoma – Upper Genitourinary Tract Tumors or Urothelial Carcinoma of the Prostate

Authorization of 6 months may be granted as a single agent for treatment of upper genitourinary (GU) tract tumors or urothelial carcinoma of the prostate when either of the following criteria is met:

1. Keytruda will be used as first-line therapy for locally advanced or metastatic disease in cisplatin ineligible members whose tumors express PD-L1 (CPS $\geq$ 10), or in members who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression.
2. Keytruda will be used as subsequent therapy for locally advanced or metastatic disease following platinum-containing chemotherapy.

H. Solid Tumors

Authorization of 6 months may be granted for treatment of solid tumors in members with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

I. Colorectal Cancer

Authorization of 6 months may be granted as a single agent for the treatment of colorectal cancer, including small bowel adenocarcinoma, appendiceal carcinoma, and anal adenocarcinoma for microsatellite instability-high or mismatch repair deficient tumors when any of the following criteria is met:

1. Keytruda will be used as primary treatment for unresectable metachronous metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months.
2. Keytruda will be used as initial therapy for unresectable advanced or metastatic disease who are not appropriate for intensive therapy.
3. Keytruda will be used as subsequent therapy for unresectable advanced or metastatic disease following previous oxaliplatin- irinotecan- and/or fluoropyrimidine-based therapy.

J. Malignant Pleural Mesothelioma

Authorization 6 months may be granted as a single agent for subsequent treatment of malignant pleural mesothelioma.

K. Merkel Cell Carcinoma

Authorization of 6 months may be granted for treatment of Merkel cell carcinoma in members with recurrent locally advanced or metastatic disease.

L. Gastric Cancer and Esophagogastric Junction Cancer

Authorization of 6 months may be granted for treatment of gastric cancer, including esophagogastric junction (EGJ) cancer, in members who are not surgical candidates or have locally advanced, recurrent, or metastatic disease when either of the following criteria is met:

1. Keytruda will be used as second-line or subsequent therapy as a single agent for a tumor with microsatellite instability-high or deficient mismatch repair.
2. Keytruda will be used as third-line or subsequent therapy as a single agent for a PD-L1 positive tumor (CPS $\geq$ 1).

M. Esophageal Cancer

Authorization of 6 months may be granted for treatment of esophageal cancer in members who are not surgical candidates or have for locally advanced, recurrent, or metastatic disease when any of the following conditions are met:

1. Keytruda will be used as second-line or subsequent therapy as a single agent for a tumor with microsatellite instability-high or deficient mismatch repair.
2. Keytruda will be used as second-line therapy for a PD-L1 positive tumor (CPS $\geq$ 10) for squamous cell carcinoma.

3. Keytruda will be used as third-line or subsequent therapy as a single agent for a PD-L1 positive tumor (CPS ≥ 1).

N. Cervical Cancer

Authorization of 6 months may be granted as a single agent for second-line therapy for the treatment of recurrent or metastatic cervical cancer when either of the following criteria is met:

1. Microsatellite instability-high or mismatch repair deficient tumors.
2. Member has experienced disease progression on or after chemotherapy for tumors that express PD-L1 (CPS ≥ 1).

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

Authorization of 6 months may be granted as a single agent for treatment of epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer for recurrent or persistent microsatellite instability-high or mismatch repair deficient tumors.

P. Uveal Melanoma

Authorization of 6 months may be granted as a single agent for treatment of uveal melanoma for distant metastatic disease.

Q. Testicular Cancer

Authorization of 6 months may be granted as a single agent for third-line therapy for treatment of testicular cancer in members with microsatellite instability-high or mismatch repair deficient tumors.

R. Endometrial Carcinoma

Authorization of 6 months may be granted for treatment of endometrial carcinoma when the member meets either of the following criteria:

1. Keytruda will be used for recurrent, metastatic, or high-risk microsatellite instability-high or mismatch repair deficient tumors that have progressed following prior cytotoxic chemotherapy.
2. Keytruda will be used in combination with lenvatinib for advanced endometrial carcinoma that is not microsatellite instability-high or mismatch repair deficient when the member has disease progression following prior systemic therapy and is not a candidate for curative surgery or radiation.

S. Anal Carcinoma

Authorization of 6 months may be granted as a single agent for treatment of anal carcinoma for metastatic disease as second-line or subsequent therapy.

T. CNS Brain Metastases

Authorization of 6 months may be granted as a single agent for treatment of CNS brain metastases in members with melanoma or PD-L1 positive non-small cell lung cancer.

U. Primary Mediastinal Large B-Cell Lymphoma

Authorization of 6 months may be granted for treatment of primary mediastinal large B-cell lymphoma in members with relapsed or refractory disease.

V. Pancreatic Adenocarcinoma

Authorization of 6 months may be granted as a single agent for treatment of pancreatic adenocarcinoma in members with microsatellite instability-high or mismatch repair deficient tumors in either of the following settings:

1. Keytruda will be used as subsequent therapy for locally advanced or metastatic disease.
2. For local recurrence in the pancreatic operative bed after resection.

W. Hepatobiliary Cancers

Authorization of 6 months may be granted as a single agent for treatment of hepatobiliary cancers, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer when either of the following criteria is met:

1. Keytruda will be used as primary treatment for unresectable or metastatic disease that is microsatellite instability-high or mismatch repair deficient.
2. Keytruda will be used as adjuvant treatment for resected gross residual disease that is microsatellite instability-high or mismatch repair deficient.

X. Hepatocellular Carcinoma

Authorization of 6 months may be granted for treatment of members with hepatocellular carcinoma who have been previously treated with sorafenib.

Y. Vulvar Cancer

Authorization of 6 months may be granted as a single agent for second-line treatment of advanced, recurrent or metastatic disease in members with squamous cell vulvar cancer when either of the following criteria is met:

1. Member has microsatellite instability-high or mismatch repair deficient tumor.
2. Member has experienced disease progression on or after chemotherapy and whose tumor expresses PD-L1 (CPS $\geq$ 1).

Z. Kidney Cancer

Authorization of 6 months may be granted for treatment of members with kidney cancer, including renal cell carcinoma, when either of the following criteria is met:

1. Keytruda will be used as first-line treatment in combination with axitinib for advanced, relapsed or stage IV disease.
2. Keytruda will be used as subsequent therapy in combination with axitinib for relapsed or stage IV disease with clear cell histology.

AA. Thymic Carcinoma

Authorization of 6 months may be granted as a single agent for treatment of thymic carcinoma as a second-line agent for unresectable, locally advanced, or metastatic disease.

BB. Mycosis Fungoides/Sezary Syndrome

Authorization of 6 months may be granted for treatment of stage III Mycosis Fungoides or Stage IV Sezary syndrome.

CC. T-Cell Lymphomas

Authorization of 6 months may be granted for treatment of extranodal NK/T-cell lymphoma, nasal type, in members with relapsed or refractory disease.

DD. Gestational Trophoblastic Neoplasia

Authorization of 6 months may be granted as a single agent for treatment of gestational trophoblastic neoplasia when either of the following criteria is met:

1. Member has recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor) following treatment with a platinum/etoposide-containing regimen.
2. Member has methotrexate-resistant high-risk disease.

EE. Small Cell Lung Cancer

Authorization of 6 months may be granted as a single agent for treatment of small cell lung cancer when any of the following criteria is met:

1. Disease has relapsed within 6 months following complete or partial response or stable disease with initial treatment.
2. Member has primary progressive disease.
3. Disease is metastatic and has progressed on or after platinum-based chemotherapy and at least one other prior line of therapy.

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

Authorization of 6 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.

V. CONTINUATION OF THERAPY

A. Adjuvant treatment of melanoma

Authorization of 6 months may be granted (up to 12 months total) for continued treatment in members requesting reauthorization for cutaneous melanoma who have not experienced disease recurrence or an unacceptable toxicity.

B. NSCLC, SCLC, HNSCC, cHL, PMBCL, MSI-H Cancers, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, RCC, Endometrial carcinoma

Authorization of 6 months may be granted (up to 24 months of continuous use) for continued treatment in members requesting reauthorization for NSCLC, SCLC, HNSCC, cHL, PMBCL, MSI-H cancers, gastric cancer, esophageal cancer, cervical cancer, HCC, MCC, RCC, and endometrial carcinoma who have not experienced disease progression or unacceptable toxicity.

C. Urothelial Carcinoma

Authorization of 6 months may be granted (up to 24 months of continuous use) for continued treatment in members requesting reauthorization for urothelial carcinoma when both of the following criteria are met:

1. Member has not experienced disease progression or unacceptable toxicity.
2. For high-risk BCG-unresponsive non-muscle invasive bladder cancer only: disease is not persistent or recurrent.

D. All other indications

Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section IV who have not experienced disease progression or an unacceptable toxicity.

VI. REFERENCES

1. Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; January 2020.
2. The NCCN Drugs & Biologics Compendium® © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed July 9, 2019.
3. The NCCN Clinical Practice Guidelines in Oncology® Neuroendocrine and Adrenal Tumors 1.2019. ©2019 National Comprehensive Cancer Network, Inc. <http://www.nccn.org>. Accessed July 26, 2019.