| Reference number(s) |
|---|
| 1889-A |

# 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 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, as a single agent, is indicated for the first-line treatment of patients with stage III non-small cell lung cancer (NSCLC), who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
   ii. Keytruda, as a single agent, is indicated 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.
   iii. Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
   iv. Keytruda, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.

3. Head and Neck Squamous Cell Cancer
   Keytruda is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

4. 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.

5. Urothelial Carcinoma (Bladder cancer, Upper Genitourinary tract tumors, Urothelial carcinoma of the prostate, Primary carcinoma of the urethra)
   Keytruda is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

i. 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
ii. Are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or
iii. Have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

6. 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
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.

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

7. Gastric Carcinoma
Keytruda is indicated for the treatment of patients with recurrent, locally advanced, metastatic gastric or gastroesophageal junction 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 prior lines of therapy including fluoropyrimidine and platinum containing chemotherapy and if appropriate, HER2/neu targeted therapy.

8. 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 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA approved test

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

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

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

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

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

B. <u>Compendial Uses</u>
1. Non-small cell lung cancer
2. Unresectable advanced or metastatic microsatellite instability-high colorectal cancer

3. Malignant pleural mesothelioma
4. Gastric carcinoma
5. Colorectal cancer
6. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
7. Uveal melanoma
8. Esophageal and Esophagogastric Junction cancers
9. Bone cancer
    i. Ewing's sarcoma
    ii. Osteosarcoma
10. Testicular cancer
11. Endometrial carcinoma
12. Anal carcinoma
13. Adrenal gland tumors
14. Penile cancer
15. Central Nervous System (CNS) brain metastases in patients with melanoma or NSCLC
16. Non-Hodgkin's lymphoma
17. Pancreatic adenocarcinoma
18. Hepatobiliary cancers
    i. Extrahepatic cholangiocarcinoma
    ii. Intrahepatic cholangiocarcinoma
    iii. Gallbladder cancer
19. Squamous cell vulvar cancer

All other indications are considered experimental/investigational and are not a covered benefit.

## II. EXCLUSIONS

Coverage will not be provided for pediatric members with microsatellite instability-high (MSI-H) central nervous system cancers.

## III. CRITERIA FOR INITIAL APPROVAL

### A. Melanoma

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

1. Treatment of unresectable or metastatic melanoma.
2. Adjuvant treatment of members with melanoma with involvement of lymph node(s) following complete resection.

### B. Non-small Cell Lung Cancer (NSCLC)

1. Authorization of 12 months may be granted for treatment of metastatic NSCLC in any of the following settings:
    i. First-line treatment of nonsquamous NSCLC:
        a. The member's EGFR, ALK and ROS1 genomic tumor markers are negative or unknown, AND
        b. Keytruda will be used as a single agent or in combination with both of the following:
            1. Pemetrexed
            2. Carboplatin or cisplatin
    ii. First-line treatment of squamous NSCLC:
        a. Keytruda will be used in combination with carboplatin and paclitaxel or albumin-bound paclitaxel, OR

b. Member meets both of the following:
   1. The member's EGFR, ALK and ROS1 genomic tumor markers are negative or unknown
   2. Keytruda will be used as a single agent or in combination with both of the following:
      a. Carboplatin or cisplatin
      b. Paclitaxel or albumin-bound paclitaxel

iii. Maintenance therapy: Keytruda was used as part of first-line chemotherapy.

iv. Subsequent therapy
   1. Following targeted therapy if any of the following genomic tumor markers are positive: EGFR, ALK, or ROS1, OR
   2. Following cytotoxic chemotherapy.

2. Authorization of 12 months may be granted for the first-line treatment of stage III NSCLC which is not appropriate for surgical resection or definitive chemoradiation when Keytruda will be used as a single agent and the member's EGFR, ALK and ROS1 genomic tumor markers are negative or unknown.

**C. Head and Neck Cancer**
Authorization of 12 months may be granted for the treatment of members with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

**D. Classical Hodgkin Lymphoma**
Authorization of 12 months may be granted for treatment of refractory or relapsed classical Hodgkin lymphoma.

**E. Urothelial Carcinoma (Bladder cancer, upper genitourinary tract tumors, urothelial carcinoma of the prostate, primary carcinoma of the urethra)**
Authorization of 12 months may be granted for treatment of locally advanced or metastatic urothelial carcinoma when any of the following criteria is met:
1. Member is not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10].
2. Member is not eligible for platinum-containing chemotherapy.
3. Member experienced disease progression during or following platinum-containing chemotherapy.
4. Member experienced disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

**F. Microsatellite Instability-High Cancer**
Authorization of 12 months may be granted for treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors when either of the following criteria are met:
1. The member has colorectal cancer
2. For other solid tumors: Member experienced disease progression following prior treatment and has no satisfactory alternative treatment options.

**G. Malignant Pleural Mesothelioma**
Authorization 12 months may be granted for treatment of malignant pleural mesothelioma.

**H. Merkel Cell Carcinoma**
Authorization of 12 months may be granted for treatment of Merkel cell carcinoma.

**I. Gastric Carcinoma**

Authorization of 12 months may be granted for treatment of recurrent locally advanced, metastatic gastric or gastroesophageal junction adenocarcinoma when either of the following criteria are met:

1. Keytruda is being used as second-line or subsequent therapy for a tumor with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR), OR
2. Keytruda is being used as third-line or subsequent therapy for a PD-L1 positive tumor [Combined Positive Score (CPS) ≥ 1].

**J. Cervical Cancer**

Authorization of 12 months may be granted for the treatment of recurrent or metastatic cervical cancer when all of the following criteria are met:

1. Tumor expresses PD-L1 [Combined Positive Score (CPS) greater than or equal to 1].
2. Member has experienced disease progression on or after chemotherapy.

**K. 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.

**L. Uveal Melanoma**

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

**M. Esophageal and Esophagogastric Junction Cancers**

Authorization of 12 months may be granted for treatment of esophageal and esophagogastric junction cancer.

**N. Bone Cancer**

Authorization of 12 months may be granted for the treatment of Ewing's sarcoma and osteosarcoma.

**O. Testicular Cancer**

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

**P. Endometrial Carcinoma**

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

**Q. Anal Carcinoma**

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

**R. Adrenal Gland Tumors**

Authorization of 12 months may be granted for the treatment of adrenal gland tumors.

**S. Penile Cancer**

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

**T. 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).

**U. Non-Hodgkin's Lymphoma (including Primary Mediastinal Large B-Cell Lymphoma)**

Authorization of 12 months may be granted for the treatment of non-Hodgkin's lymphoma.

**V. Pancreatic Adenocarcinoma**

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

**W. Hepatobiliary Cancers**
Authorization of 12 months may be granted for the treatment of intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer.

**X. Hepatocellular Carcinoma (HCC)**
Authorization of 12 months may be granted for the treatment of members with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

**Y. Squamous Cell Vulvar Cancer**
Authorization of 12 months may be granted for the treatment of members with squamous cell vulvar cancer.

**Z. Renal Cell Carcinoma**
Authorization of 12 months may be granted for the treatment of members with renal cell carcinoma when Keytruda will be used in combination with axitinib.

## IV. CONTINUATION OF THERAPY

**A. Adjuvant treatment of melanoma**
Authorization of up to 12 months total may be granted for all members (including new members) who meet all initial authorization criteria.

**B. All other indications**
Authorization of 12 months may be granted for all members (including new members) who meet all initial authorization criteria.

## V. REFERENCES

1. Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; April 2019.
2. The NCCN Drugs & Biologics Compendium® © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 20, 2019.