Reference number
1980-A

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 ≥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 ≥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. 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.

4. Classical Hodgkin Lymphoma

i. Keytruda is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).
ii. Keytruda is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more prior lines of therapy.

5. 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.

6. 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 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.

7. 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) solid tumors 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 MSI-H central nervous system cancers have not been established.

8. Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer
Keytruda is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

9. Gastric Cancer
Keytruda is indicated as a single agent for the treatment of patients with recurrent locally advanced, 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.

Keytruda is indicated in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma.

10. Esophageal Cancer
Keytruda is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

i. in combination with platinum- and fluoropyrimidine-based chemotherapy, or
ii. as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test.

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

16. 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) [≥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.

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

18. Triple-Negative Breast Cancer
Keytruda is indicated for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

Keytruda is indicated in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.

B. Compendial Uses[2]

1. Cutaneous melanoma
2. Non-small cell lung cancer
3. Head and neck cancer
4. Classical Hodgkin lymphoma
5. Urothelial carcinoma
6. Solid tumors
7. Adrenocortical carcinoma
8. Anaplastic thyroid carcinoma
9. Follicular, hurthle cell, or papillary thyroid carcinoma
10. Medullary thyroid carcinoma
11. Colorectal cancer
12. Small bowel adenocarcinoma, including advanced ampullary cancer
13. Malignant pleural mesothelioma
14. Merkel cell carcinoma
15. Gastric cancer and esophagogastric junction cancer
16. Esophageal cancer
17. Cervical cancer
18. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
19. Uveal melanoma
20. Testicular cancer
21. Endometrial carcinoma
22. Anal carcinoma
23. Central Nervous System (CNS) brain metastases
24. Primary mediastinal large B-cell lymphoma
25. Pancreatic adenocarcinoma
26. Hepatobiliary cancers
27. Hepatocellular carcinoma
28. Vulvar cancer
29. Renal cell carcinoma
30. Thymic carcinoma
31. Mycosis Fungoides/Sezary syndrome
32. Extranodal NK/T-cell lymphoma, nasal type
33. Gestational trophoblastic neoplasia
34. Poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma
35. Prostate cancer
36. Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders
37. Alveolar soft part sarcoma
38. Undifferentiated pleomorphic sarcoma
39. Diffuse large B-cell lymphoma
40. Occult primary cancer

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

E. 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.

F. 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.

G. Adrenocortical carcinoma
Authorization of 12 months may be granted for treatment of adrenocortical carcinoma.

H. Anaplastic Thyroid Carcinoma
Authorization of 12 months may be granted for treatment of anaplastic thyroid carcinoma for tumor mutational burden-high (≥10 mutations/megabase) tumors.

I. Follicular, Hurthle Cell, or Papillary Thyroid Carcinoma
Authorization of 12 months may be granted for treatment of follicular, hurthle cell, or papillary thyroid carcinoma for tumor mutational burden-high (≥10 mutations/megabase) tumors.

J. Medullary Thyroid Carcinoma
Authorization of 12 months may be granted for treatment of medullary thyroid carcinoma for tumor mutational burden-high (≥10 mutations/megabase) tumors.

K. Colorectal Cancer (CRC)
Authorization of 12 months may be granted for treatment of colorectal cancer when both of the following criteria are met:
1. Disease is unresectable, advanced, or metastatic.
2. Tumor is microsatellite instability-high or mismatch repair deficient.

L. Malignant Pleural Mesothelioma

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

M. Merkel Cell Carcinoma (MCC)
Authorization of 12 months may be granted for treatment of Merkel cell carcinoma.

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

O. Esophageal Cancer and Esophagogastric Junction Cancer
Authorization of 12 months may be granted for treatment of esophageal cancer, including esophagogastric junction (EGJ) cancer, in members who are not surgical candidates or who have recurrent, locally advanced, or metastatic disease.

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

Q. 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.

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

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

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

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

V. 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).

W. Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
Authorization of 12 months may be granted for the treatment of primary mediastinal large B-cell lymphoma.

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

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

Z. Hepatocellular Carcinoma (HCC)
Authorization of 12 months may be granted for treatment of members with hepatocellular carcinoma.

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

BB. Renal Cell Carcinoma (RCC)
Authorization of 12 months may be granted for treatment of renal cell carcinoma when Keytruda will be used in combination with axitinib or lenvatinib.

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

DD. Mycosis Fungoides/Sezary Syndrome
Authorization of 12 months may be granted for treatment of mycosis fungoides or Sezary syndrome.

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

FF. Gestational Trophoblastic Neoplasia
Authorization of 12 months may be granted for treatment of gestational trophoblastic neoplasia.

GG. 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 that have progressed following prior treatment and who have no satisfactory alternative treatment options when either of the following criteria are met:
1. Keytruda will be used for microsatellite instability-high or mismatch repair deficient tumors.
2. Keytruda will be used for tumor mutational burden-high tumors (≥10 mutations/megabase).

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

II. Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders
Authorization of 12 months may be granted for treatment of primary cutaneous anaplastic large cell lymphoma (ALCL).

JJ. Alveolar Soft Part Sarcoma
Authorization of 12 months may be granted for treatment of alveolar soft part sarcoma (ASPS).

KK. Undifferentiated Pleomorphic Sarcoma
Authorization of 12 months may be granted for treatment of undifferentiated pleomorphic sarcoma.

LL. Diffuse Large B-Cell Lymphoma
Authorization of 12 months may be granted for treatment of diffuse large B-cell lymphoma.

MM. Cutaneous Squamous Cell Carcinoma (cSCC)
Authorization of 12 months may be granted for treatment of recurrent, metastatic, or locally advanced cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.

NN. Occult Primary
Authorization of 12 months may be granted for treatment of occult primary cancer in members with microsatellite instability-high or mismatch repair deficient tumors.

OO. Small Bowel Adenocarcinoma
Authorization of 12 months may be granted for treatment of small bowel adenocarcinoma, including advanced ampullary cancer, when both of the following criteria are met:
1. Disease is advanced or metastatic.
2. Tumor is microsatellite-instability high or mismatch repair deficient.

PP. Triple-Negative Breast Cancer

Authorization of 12 months may be granted for treatment of triple-negative breast cancer when any of the following criteria are met:

1. The member meets both of the following criteria:
    i. The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for ALL of the following receptors:
        a. Human epidermal growth factor receptor 2 (HER-2)
        b. Estrogen
        c. Progesterone
    ii. Tumor must express PD-L1 (CPS ≥10).
2. The member meets all of the following criteria:
    i. The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for ALL of the following receptors:
        a. Human epidermal growth factor receptor 2 (HER-2)
        b. Estrogen
        c. Progesterone
    ii. The requested drug will be used for high-risk early-stage disease.
    iii. The requested drug will be used as either:
        a. Neoadjuvant treatment in combination with chemotherapy; or
        b. Continued adjuvant therapy after surgery, as a single agent.

IV. CONTINUATION OF THERAPY

A. Adjuvant Treatment of Melanoma or high-risk early-stage TNBC

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, OR Keytruda is being used for high-risk early-stage TNBC.
3. Keytruda has been effective for treating the diagnosis or condition.

B. NSCLC, head and neck cancer, cHL, PMBCL, MSI-H or dMMR Cancers, Gastric Cancer, Esophageal Cancer (including EGJ), Cervical Cancer, urothelial carcinoma, HCC, MCC, RCC, Endometrial carcinoma, cSCC, TNBC with PD-L1 tumors, TMB-H Cancer

Authorization for 12 months (up to 24 months of continuous use) 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 NSCLC, head and neck cancer, cHL, PMBCL, MSI-H or dMMR cancers, gastric cancer, esophageal cancer (including EGJ), cervical cancer, urothelial carcinoma, HCC, MCC, RCC, endometrial carcinoma, cSCC, TNBC with PD-L1 tumors, and TMB-H cancers.
3. Keytruda has been effective for treating the diagnosis or condition.

C. 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.; August 2021.
2. The NCCN Drugs & Biologics Compendium® © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 31, 2021.