| Reference number(s) |
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| 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 (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.
   ii. Keytruda is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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 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 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.

6. Urothelial Carcinoma
   i. Keytruda is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma:
      a. who are not eligible for any platinum-containing chemotherapy, or
      b. who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
   ii. 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 Cancer 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, 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 MSI-H central nervous system cancers have not been established.

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

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

   ii. Keytruda, as a single agent, 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 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 that express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test

11. Cervical Cancer
    i. Keytruda is indicated in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
    ii. Keytruda, as a single agent, 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
    iii. Keytruda is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions

15. Endometrial Carcinoma
    i. 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.
    ii. Keytruda, as a single agent, is indicated for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting 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

i. Keytruda, in combination with chemotherapy, is indicated 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.
ii. Keytruda is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery

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. Anaplastic thyroid carcinoma
8. Follicular, hürthle cell, or papillary thyroid carcinoma
9. Medullary thyroid carcinoma
10. Colorectal cancer
11. Small bowel adenocarcinoma
12. Malignant pleural mesothelioma
13. Gastric cancer and esophagogastric junction cancer
14. Esophageal cancer
15. Cervical cancer
16. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
17. Uveal melanoma
18. Testicular cancer
19. Endometrial carcinoma
20. Anal carcinoma
21. Central Nervous System (CNS) brain metastases
22. Primary mediastinal large B-cell lymphoma
23. Pancreatic adenocarcinoma
24. Hepatobiliary cancers
25. Vulvar cancer
26. Renal cell carcinoma
27. Thymic carcinoma
28. Primary Cutaneous Lymphomas
    i. Mycosis Fungoides/Sezary syndrome
    ii. Anaplastic Large Cell Lymphoma (ALCL)
29. Extranodal NK/T-cell lymphoma
30. Gestational trophoblastic neoplasia
31. Neuroendocrine and Adrenal Tumors
    i. Well Differentiated Grade 3 Tumors
    ii. Adrenal Gland Tumors
    iii. Poorly Differentiated/Large or Small Cell Tumors
    iv. Adrenocortical carcinoma
32. Soft tissue sarcomas: alveolar soft part sarcoma (ASPS), myxofibrosarcoma, undifferentiated pleomorphic sarcoma (UPS), cutaneous angiosarcoma, and undifferentiated sarcoma.

33. Occult primary cancer
34. Prostate cancer
35. Bone Cancer
    i. Chondrosarcoma
    ii. Chordoma
    iii. Ewing Sarcoma
    iv. Osteosarcoma
36. Breast Cancer
37. Salivary Gland Tumors
38. Merkel Cell Carcinoma
39. Penile Cancer
40. Uterine Sarcoma
41. Small cell lung cancer

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.
C. Documentation of laboratory report confirming high tumor mutational burden (≥10 mutations/megabase [mut/Mb]), where applicable.
D. Documentation of laboratory report confirming that the cancer cells are negative for the following receptors, where applicable:
    1. human epidermal growth factor receptor 2 (HER-2)
    2. estrogen
    3. progesterone
E. Documentation of the presence of EGFR, ALK, ROS1, and RET genomic aberration, 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. Pediatric members with TMB-H central nervous system cancers.
C. Members who have experienced disease progression while on programmed death receptor-1 (PD-1) or PD-L1 inhibitor therapy (other than when used as second-line or subsequent therapy for metastatic or unresectable melanoma in combination with ipilimumab following progression on single agent anti-PD-1 immunotherapy).

## IV. CRITERIA FOR INITIAL APPROVAL

### A. Cutaneous Melanoma

Authorization of 6 months may be granted for treatment of cutaneous melanoma in any of the following settings:

1. For unresectable, recurrent, or metastatic disease as a single agent.

2. As subsequent therapy for disease progression of metastatic or unresectable tumors, as a single agent or in combination with ipilimumab.
3. As adjuvant treatment following complete lymph node resection or complete resection of stage IIB, IIC, III, or metastatic disease as a single agent.

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

Authorization of 6 months may be granted for treatment of NSCLC when the tumor is negative for EGFR, ALK, and RET gene mutations (unless testing is not feasible due to insufficient tissue or if used in single agent subsequent therapy) and any of the following criteria are met:

1. Keytruda will be used in combination with pemetrexed plus carboplatin or cisplatin for nonsquamous cell histology, as first-line or subsequent treatment for recurrent, advanced, or metastatic disease (subsequent therapy only for ROS1 rearrangement positive tumors and prior crizotinib, entrectinib, or ceritinib therapy)
2. Keytruda will be used in combination with carboplatin plus paclitaxel or albumin-bound paclitaxel for squamous cell histology, as first-line or subsequent treatment for recurrent, advanced, or metastatic disease (subsequent therapy only for ROS1 rearrangement positive tumors and prior crizotinib, entrectinib, or ceritinib therapy)
3. Keytruda will be used in combination with pemetrexed if there is tumor response or stable disease following first-line pembrolizumab and pemetrexed plus cisplatin or carboplatin regimen for nonsquamous cell histology, as maintenance therapy
4. Keytruda will be used as a single agent if PD-L1 ≥50% as first-line treatment for recurrent, advanced, or metastatic disease
5. Keytruda will be used as a single agent if PD-L1 ≥1% as subsequent treatment for recurrent, advanced, or metastatic disease
6. Keytruda will be used as a single agent if there is tumor response or stable disease following first-line monotherapy or pembrolizumab and carboplatin plus paclitaxel or albumin-bound paclitaxel regimen, as maintenance therapy

**C. Head and Neck Squamous Cell Cancer**

Authorization of 6 months may be granted for treatment of members with very advanced 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 in members whose tumors express PD-L1 (CPS ≥1) or are microsatellite instability-high (MSI-H).
2. Keytruda will be used as a single agent for subsequent therapy (regardless of PD-L1 status).
3. Keytruda will be used in combination with fluorouracil and either carboplatin or cisplatin (regardless of PD-L1 status).

**D. Salivary Gland Tumors**

Authorization of 6 months may be granted for treatment as a single agent for tumor mutational burden high (TMB-H) (≥10 mutations/megabase [mut/Mb]) recurrent disease.

**E. Classical Hodgkin Lymphoma**

Authorization of 6 months may be granted as a single agent for treatment of relapsed, refractory or progressive classical Hodgkin lymphoma.

**F. 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. Stage IIIB disease as downstaging systemic therapy or following partial response or progression after primary treatment with concurrent chemoradiotherapy.
   iii. Locally advanced or metastatic disease.
   iv. Metastatic or local recurrence post-cystectomy.
   v. Muscle invasive local recurrence or persistent disease in a preserved bladder.
2. Keytruda will be used as subsequent therapy 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.
   ii. Stage IIIB disease following partial response or progression after primary treatment with concurrent chemoradiotherapy
   iii. Locally advanced or metastatic disease.
   iv. Metastatic or local recurrence post-cystectomy.
   v. Muscle invasive local recurrence or persistent disease in a preserved bladder.
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.

**G. 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 or metastatic disease.

**H. 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 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 metastatic disease.

**I. Solid Tumors**

Authorization of 6 months may be granted as a single agent for treatment of solid tumors in members with unresectable or metastatic disease that has progressed following prior treatment and who 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 [mut/Mb]) solid tumors.

**J. Anaplastic Thyroid Carcinoma**

Authorization of 6 months may be granted as a single agent for treatment of metastatic anaplastic thyroid carcinoma for tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]) tumors.

**K. Follicular, Hürthle Cell, or Papillary Thyroid Carcinoma**

Authorization of 6 months may be granted for treatment of unresectable or metastatic follicular, hürthle cell, or papillary thyroid carcinoma for tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]) tumors not amenable to radioactive iodine therapy.

**L. Medullary Thyroid Carcinoma**
Authorization of 6 months may be granted for treatment of unresectable, recurrent, or metastatic medullary thyroid carcinoma for tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]) tumors.

**M. Colorectal Cancer**
Authorization of 6 months may be granted as a single agent for the treatment of inoperable, advanced, or metastatic colorectal cancer, including appendiceal carcinoma, for microsatellite instability-high or mismatch repair deficient tumors.

**N. Small Bowel Adenocarcinoma**
Authorization of 6 months may be granted as a single agent for treatment of advanced or metastatic small bowel adenocarcinoma, including advanced ampullary cancer, for microsatellite instability-high or mismatch repair deficient tumors.

**O. Malignant Pleural Mesothelioma**
Authorization 6 months may be granted as a single agent for subsequent treatment of malignant pleural mesothelioma.

**P. Merkel Cell Carcinoma**
Authorization of 6 months may be granted for treatment of Merkel cell carcinoma in members with recurrent or metastatic disease.

**Q. Gastric Cancer**
Authorization of 6 months may be granted for treatment of gastric cancer in members who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease when any 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 or tumor mutational burden (TMB) high (≥10 mutations/megabase (mut/Mb)).
2. Keytruda will be used as third-line or subsequent therapy as a single agent for a PD-L1 positive tumor (CPS ≥ 1).
3. Keytruda will be used in combination with trastuzumab, platinum and fluoropyrimidine-based chemotherapy in HER2 overexpression positive adenocarcinoma.

**R. Esophageal Cancer and Esophagogastric Junction Cancer**
Authorization of 6 months may be granted for treatment of esophageal cancer (including esophagogastric junction (EGJ) cancer) in members who are not surgical candidates or have unresectable 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 or tumor mutational burden (TMB) high (≥10 mutations/megabase (mut/Mb)).
2. Keytruda will be used as second-line or subsequent therapy with PD-L1 tumor expression by CPS ≥ 10 for squamous cell carcinoma.
3. Keytruda will be used as third-line or subsequent therapy as a single agent with PD-L1 tumor expression by CPS ≥ 1.
4. Keytruda will be used in combination with platinum and fluoropyrimidine-based chemotherapy for HER2 overexpression negative members.

5. Keytruda will be used in combination with trastuzumab, platinum and fluoropyrimidine-based chemotherapy for HER2 overexpression positive members.

**S. Cervical Cancer**
Authorization of 6 months may be granted for the treatment of cervical cancer when any of the following criteria are met:
1. Persistent, recurrent or metastatic disease in combination with chemotherapy in members whose tumors express PD-L1 (CPS ≥1).
2. Persistent, recurrent or metastatic disease as single agent subsequent therapy in members whose tumors express PD-L1 (CPS ≥1) or are microsatellite instability-high or mismatch repair deficient.
3. Recurrent or metastatic disease and the member has experienced disease progression on or after chemotherapy for tumors that express PD-L1 (CPS ≥ 1), as a single agent.

**T. 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, primary peritoneal cancer, carcinosarcoma (malignant mixed Mullerian tumors), clear cell carcinoma, mucinous carcinoma, grade 1 endometrioid carcinoma, low-grade serous carcinoma/ovarian borderline epithelial tumors (low malignant potential with invasive implants) for recurrent or persistent microsatellite instability-high or mismatch repair deficient tumors or tumor mutational burden-high (TMB-H) (tumors ≥10 mutations/megabase [mut/Mb]) and no satisfactory alternative treatment options.

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

**V. 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 or tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors.

**W. Endometrial Carcinoma**
Authorization of 6 months may be granted for treatment of endometrial carcinoma when the member meets any 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 systemic therapy
2. Keytruda will be used in combination with lenvatinib for advanced or recurrent 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.
3. Keytruda will be used as a single agent for unresectable or metastatic tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors that have progressed following prior treatment and the patient has no satisfactory alternative treatment.

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

**Y. 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.

**Z. Primary Mediastinal Large B-Cell Lymphoma**

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

**AA. 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 any of the following settings:

1. Keytruda will be used as subsequent therapy for locally advanced or metastatic disease and disease progression.
2. For local recurrence in the pancreatic operative bed after resection or recurrent metastatic disease.
3. Keytruda will be used as first-line therapy for metastatic disease in members with poor performance status.

**BB. Hepatobiliary Cancers**

Authorization of 6 months may be granted as a single agent for progression of and treatment of unresectable or metastatic hepatobiliary cancers, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer for disease that is microsatellite instability-high or mismatch repair deficient.

**CC. Hepatocellular Carcinoma**

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

**DD. Vulvar Cancer**

Authorization of 6 months may be granted as a single agent for second-line or subsequent 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 ≥ 1).
3. Keytruda will be used in members with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors that have progressed following prior treatment and there are no satisfactory alternative treatment options,

**EE. Renal Cell Carcinoma**

Authorization of 6 months may be granted for treatment of renal cell carcinoma, when any of the following criteria are met:

1. Keytruda will be used as first-line treatment in combination with axitinib or lenvatinib for advanced, relapsed or stage IV disease.
2. Keytruda will be used as subsequent therapy in combination with axitinib or lenvatinib for relapsed or stage IV disease with clear cell histology.
3. Keytruda will be used as a single agent for relapsed or stage IV disease with non-clear cell histology.
4. Keytruda will be used for the adjuvant treatment of members with RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

**FF. Thymic Carcinoma**

Authorization of 6 months may be granted as a single agent for treatment of thymic carcinoma for unresectable, locally advanced, or metastatic disease, or as postoperative therapy for residual tumor in members who cannot tolerate first-line combination regimens.

**GG. Primary Cutaneous Lymphomas**

Authorization of 6 months may be granted for treatment of primary cutaneous lymphomas when either of the following is met:
1. Member has a diagnosis of mycosis fungoides/Sezary syndrome.
2. Member has a diagnosis of relapsed or refractory anaplastic large cell lymphoma (ALCL) and the requested medication will be used as a single agent.

**HH. Extranodal NK/T-cell lymphoma**

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

**II. Gestational Trophoblastic Neoplasia**

Authorization of 6 months may be granted as a single agent for treatment of gestational trophoblastic neoplasia for multi-agent chemotherapy-resistant disease 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 high-risk disease.

**JJ. Neuroendocrine and Adrenal Tumors**

1. Authorization of 6 months may be granted for treatment of poorly differentiated/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:
   i. Keytruda will be used for microsatellite instability-high or mismatch repair deficient tumors.
   ii. Keytruda will be used for tumor mutational burden-high tumors (≥10 mutations/megabase [mut/Mb]).
2. Authorization of 6 months may be granted for treatment of locally advanced or metastatic well differentiated grade 3 neuroendocrine tumors that are tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]) and the disease has progressed following prior treatment and there is no satisfactory alternative treatment options.
3. Authorization of 6 months may be granted for treatment of unresectable or metastatic adrenocortical carcinoma.

**KK. Cutaneous Squamous Cell Carcinoma**

Authorization of 6 months may be granted as a single agent for treatment of cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

**LL. Soft Tissue Sarcoma**

Authorization of 6 months may be granted for treatment of the following types of soft tissue sarcoma when either of the following criteria are met:
1. The member has alveolar soft part sarcoma (ASPS) and the requested medication will be used as a single agent or in combination with axitinib (Inlyta).
2. The member has unresectable, recurrent, advanced, or metastatic myxofibrosarcoma, undifferentiated pleomorphic sarcoma (UPS), cutaneous angiosarcoma, or undifferentiated sarcoma that is tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] and the requested medication will be used as a single agent.

**MM. Occult Primary Cancer**

Authorization of 6 months may be granted as a single agent for treatment of occult primary cancer in members with microsatellite instability-high or mismatch repair deficient tumors or tumor mutational burden-high (TMB-H) (≥10 mutations/megabase (mut/Mb) tumors).

**NN. Breast Cancer**

1. Authorization of 6 months may be granted for treatment of locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) when all of the following criteria are met:
   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).
   iii. The requested medication will be used in combination with chemotherapy.

2. Authorization of 6 months may be granted for treatment of high-risk early-stage triple-negative breast cancer (TNBC) when all of the following criteria are met:
   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 medication will be used as either:
      a. Neoadjuvant treatment in combination with chemotherapy; or
      b. Continued adjuvant treatment after surgery, as a single agent.

3. Authorization of 6 months may be granted for treatment of breast cancer as a single agent for recurrent unresectable or metastatic tumors when both of the following criteria are met:
   i. The disease has progressed following prior treatment and the patient has no satisfactory alternative treatment options.
   ii. The tumors are microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tissue tumor mutation burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]).

**OO. Prostate Cancer**

Authorization of 6 months may be granted as subsequent therapy as a single agent for treatment of castration-resistant distant metastatic prostate cancer in members with microsatellite instability-high, mismatch repair deficient, or tumor mutational burden (TMB) ≥10 mutations/megabase tumors.

**PP. Bone Cancer – Chondrosarcoma, Chordoma, Ewing Sarcoma, Osteosarcoma**

1. Authorization of 6 months may be granted as a single agent for unresectable or metastatic tumors when both of the following criteria are met:
   i. The disease has progressed following prior treatment and the patient has no satisfactory alternative treatment options.
   ii. The tumors are microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tissue tumor mutation burden-high (TMB-H) (≥10 mutations/megabase (mut/Mb)

**QQ. Penile Cancer**

Authorization of 6 months may be granted as a single agent for subsequent therapy of unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors that have progressed following prior treatment and there are no satisfactory alternative treatment options.

**RR. Uterine Sarcoma**

Authorization of 6 months may be granted as a single agent for subsequent therapy for unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors that have progressed following prior treatment and there are no satisfactory alternative treatment options.

**SS. Small Cell Lung Cancer**

Authorization of 6 months may be granted as a single agent for subsequent therapy of relapsed or progressive disease.

## V. CONTINUATION OF THERAPY

**A. Treatment of adjuvant melanoma, adjuvant high-risk early-stage TNBC, or adjuvant RCC**
Authorization of 6 months may be granted (up to 12 months total) for continued treatment in members requesting reauthorization for adjuvant treatment of cutaneous melanoma, high-risk early-stage TNBC, or RCC who have not experienced disease recurrence or an unacceptable toxicity.

**B. NSCLC, HNSCC, cHL, PMBCL, MSI-H or dMMR Cancers, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, RCC, Endometrial carcinoma, cSCC, locally recurrent unresectable or metastatic TNBC, TMB-H Cancer**
Authorization of 6 months may be granted (up to 24 months of continuous use) for continued treatment in members requesting reauthorization for NSCLC, HNSCC, cHL, PMBCL, MSI-H or dMMR cancers, gastric cancer, esophageal cancer, cervical cancer, HCC, MCC, RCC, endometrial carcinoma, cSCC, locally recurrent unresectable or metastatic TNBC, and TMB-H cancers 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.; March 2022.
2. The NCCN Drugs & Biologics Compendium® © 2022 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed April 19, 2022.