

Clinical Criteria

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Table of Contents

Overview	Coding	References
Clinical criteria	Document history	

Overview

This document addresses the use of Keytruda (pembrolizumab), a human programmed death receptor-1 (PD-1) blocking antibody, for treatment of various cancers.

The following are the FDA indications and NCCN compendia uses for Keytruda.

Cervical Cancer

Cervical cancer is the fourth most common cancer among women worldwide. The National Cancer Institute (NCI) estimates 13,240 new cases in 2018 and 4170 deaths from cervical cancer in the United States. The majority of cases of cervical cancer are preventable by routine screening and treatment of precancerous lesions.

Keytruda is FDA indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 Combined Positive Score (CPS) ≥ 1 as determined by an FDA-approved test.

Colorectal Cancer

Colorectal cancer refers to malignancies originating from the large intestine (colon) or the rectum. The term colorectal cancer does not include anal cancer. According to the American Cancer Society (ACS), there will be an estimated 97,220 new cases of colon cancer and 43,030 new cases of rectal cancer diagnosed in 2017. It is expected that 50,630 persons will die from colon and rectal cancer combined in 2018.

NCCN Drugs and Biologics Compendium and the NCCN CPG on colon cancer and rectal cancer lists off-label use of Keytruda for individuals with unresectable metachronous metastases or unresectable advanced or metastatic colorectal cancer. The recommendations were based on 2A category of evidence and uniform consensus.

The NCCN panel recommends use of Keytruda or nivolumab as treatment options in patients with metastatic MMR-deficient colorectal cancer in second- or third-line therapy. Patients progressing on either of these drugs should not be offered the other.

Gastric or Gastroesophageal Junction Adenocarcinoma

Gastric and esophageal cancers are rare. The NCI estimates 26,240 new cases and 10,800 deaths from gastric cancer in the United States in 2018. For esophageal cancer, the NCI estimates 17,290 new cases and 15,850 deaths will occur in 2018. Gastroesophageal junction adenocarcinoma, a form of cancer that is located in the region where the esophagus joins the stomach, is also rare, but equally lethal. Five-year survival rates for both cancers are relatively low for esophageal cancer and for gastric cancer. Treatments are aimed at extending OS, while also providing palliative and supportive care.

Keytruda is FDA indicated for the treatment of patients with recurrent locally advanced or 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.

Head and Neck Squamous Cell Cancer (HNSCC)

Head and neck cancers account for nearly 3 percent (approximately 62,000 cases) of all cancers in the United States, and an estimated 13,000 deaths, with nearly 90% from the squamous cell variety. Head and neck cancer usually begins in the squamous cells that line moist, mucosal surfaces inside the head and neck (for example, inside the mouth, nose and throat), and is commonly referred to as squamous cell carcinoma of the head and neck. Head and neck cancers can also begin in the salivary glands, but these are much less common (NCI, 2018).

Keytruda is FDA 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.

The NCCN Drugs and Biologics Compendium and the NCCN CPG on head and neck cancer include Category 2A off-label recommendations for use of Keytruda as a treatment of recurrent, unresectable or metastatic disease HNSCC as a single agent for disease progression on or after platinum-containing chemotherapy based on panel consensus and preliminary findings reported from two phase 1b studies

Hepatocellular Carcinoma

Hepatocellular carcinoma is the most common form of liver cancer. About 42,220 new cases of liver and intrahepatic bile duct cancer will be diagnosed in 2018, with nearly 30,200 deaths from the disease annually in the U.S. Chronic infections with hepatitis B virus (HBV) or hepatitis C virus are the most common causes of liver cancer. (ACS, 2018).

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

Hodgkin Lymphoma

Hodgkin lymphoma is a type of malignancy which starts in the lymphocytes, a type of white blood cell that fights infection. Hodgkin lymphoma most commonly affects people between the ages of 15 and 40 and people older than age 55. In Hodgkin lymphoma, cells in the lymphatic system grow abnormally and may spread beyond the lymphatic system. As the disease progresses, it compromises the body's ability to fight infection. Many initial signs and symptoms may be similar to those of influenza, such as fever, fatigue and night sweats. Eventually, tumors develop. Hodgkin lymphoma is distinguished by the presence of abnormal Reed-Sternberg cells with the majority of cases expressing CD15 and CD30 on immunohistochemistry testing of tissue. In developed countries, classical Hodgkin lymphoma accounts for approximately 95% of all Hodgkin disease (ACS, 2018).

Keytruda is FDA 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.

NCCN Drugs and Biologics Compendium and the NCCN CPG for Hodgkin disease includes a 2A recommendation for off-label use of Keytruda as an additional therapy option when used as a single agent for individuals with relapsed or refractory cHL.

Malignant Pleural Mesothelioma

Malignant mesothelioma is a rare cancer where malignant cells are found in the lining of the chest or abdominal cavity, occurs in approximately 2,500 individuals in the U.S annually. Malignant pleural mesothelioma is the most common type, difficult to treat because the majority of individuals have advanced disease at presentation. The NCCN CPG for malignant pleural mesothelioma (2019) reported the median overall survival for the disease to be approximately 1 year, with cure rare.

The recently updated NCCN CPG for malignant pleural mesothelioma (2019) includes a category 2A recommendation for use of Keytruda as subsequent systemic therapy for the treatment of malignant pleural mesothelioma, a highly aggressive cancer with poor prognosis and limited treatment options. The recommendation is based on preliminary results from the KEYNOTE-028 study, a non-randomized, open-label, phase 1b trial that evaluated the clinical safety and activity of Keytruda in individuals with malignant pleural mesothelioma

Melanoma

The American Cancer Society (ACS) estimated that approximately 91,271 cases of melanoma (also referred to as malignant melanoma) will be diagnosed in the United States in 2017 (ACS, 2018). While melanoma accounts for only approximately 5% of skin cancer cases, it is estimated to be responsible for the vast majority of skin cancer deaths, with 9,320 deaths projected in 2017. BRAF gene mutations are seen most commonly in melanoma, occurring in approximately 50% of cutaneous melanomas. Mutations of the BRAF gene have been associated with shorter progression-free intervals and overall decreased survival. When discovered early, melanoma can usually be cured with surgery. Once metastasis occurs, the prognosis is usually poor. In the metastatic stage of melanoma (stage IV), the average survival rate is about 6 months with a 1-year mortality rate of 75%. Treatment of metastatic melanoma may include lymphadenectomy, immunotherapy, radiation therapy, chemotherapy or participation in a clinical trial.

Keytruda is FDA indicated for the treatment of patients with unresectable or metastatic melanoma and for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

NCCN Drugs and Biologics Compendium and the NCCN CPG on cutaneous melanoma include Category 2A recommendations for use of Keytruda as a single agent in first-line, second-line or subsequent therapy for disease progression or following maximal clinical benefit from BRAF targeted therapy for individuals with a performance status of 0-2.

NCCN Drug and Biologics Compendium and the NCCN CPG for uveal melanoma, the NCCN panel offers recommendations (category 2A) for use of Keytruda in the treatment of unresectable disease. The NCCN panel recommendation for use of Keytruda as a single agent is based on case series that evaluated Keytruda as a treatment option for uveal melanoma. Eggermont and colleagues reported results from the KEYNOTE-054 study (NCT02362594), a randomized phase 3 trial designed to evaluate Keytruda versus placebo after completion of resection of high-risk stage III melanoma. In summary, the authors concluded that: "as adjuvant therapy for high-risk stage III melanoma, 200 mg of Keytruda administered every 3 weeks for up to 1 year resulted in significantly longer recurrence-free survival than placebo, with no new toxic effects identified."

Merkel Cell Carcinoma

MCC is an uncommon type of skin cancer, also known as neuroendocrine carcinoma with up to 97% of cases primarily in the epidermis of the skin. According to the ACS (2018) there are approximately 1500 cases diagnosed in the United States each year with more than 9 out of 10 individuals diagnosed older than 50 years of age. An overall 5-year survival rate for MCC was reported at nearly 60%.

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

Microsatellite Instability-High Cancer

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

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

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

NCCN Drugs and Biologics Compendium and the NCCN CPG for bone cancer – Ewing sarcoma and osteosarcoma offers NCCN 2A recommendation for use of Keytruda when used as a single agent for unresectable or metastatic, MSI-H or dMMR tumors with disease progression with prior treatment or when the individual has no satisfactory alternative treatment options, in line with current FDA approval.

In the recent NCCN Drugs and Biologics Compendium and the NCCN CPG for ovarian cancer the NCCN panel lists NCCN 2A recommendations for use of Keytruda as a single-agent therapy for persistent disease or recurrence if MSI-H or dMMR, based on preliminary analysis from the KEYNOTE-028 study which led to the FDA approval for treatment of unresectable or metastatic solid tumors (dMMR/MSI-H only).

Neuroendocrine and Adrenal Tumors

NCCN 2A considers Keytruda for the management of mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable/metastatic adrenocortical tumors that have progressed following prior treatment and have no satisfactory alternative treatment options

Non-Hodgkin Lymphoma, Primary Mediastinal Large B-Cell Lymphoma

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

Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the leading cause of death from cancer worldwide, with advanced NSCLC representing the majority (85%) of these cases. According to the National Cancer Institute, in 2018, an estimated 234,030 new cases of lung cancer will be diagnosed in the United States, and of these, approximately 154,050 deaths (65.8%) will occur because of the disease. It has been estimated that only 15.7% of all individuals with lung cancer will survive 5 years or more following diagnosis (NCI, 2018).

Keytruda is FDA indicated

- In combination with pemetrexed and platinum chemotherapy, for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
- In combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.
- As a single agent, is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) $\geq 50\%$] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
- 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.

- As a single agent, is indicated for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 [Tumor Proportion Score (TPS) $\geq 1\%$] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations

The updated NCCN Drugs and Biologics Compendium and the NCCN CPG on NSCLC offers recommendations for use of Keytruda for use as first-line therapy for PD-L1 positive NSCLC with PD-L1 expression positive ($\geq 50\%$) and EGFR, ALK, ROS1 negative or unknown disease (Category 1) (Reck, 2016). The panel includes category 1 recommendations for use of Keytruda as a subsequent therapy for disease progression in individuals with NSCLC tumors with PD-L1 expression levels $\geq 1\%$, when Keytruda not previously given. The panel recommendations are based on preliminary results from one phase 1 study (KEYNOTE-001) and a phase 2/3 trial (KEYNOTE-010) that evaluated use of Keytruda as subsequent therapy for metastatic NSCLC. In the NCCN clinical practice guideline for NSCLC the panel defines continuation maintenance therapy as "the use of at least one of the agents that was given in the first-line regimen". The NCCN panel includes category 1 recommendations for nonsquamous NSCLC continuation maintenance therapy for use of Keytruda in combination with pemetrexed if given first-line as part of pembrolizumab/carboplatin/pemetrexed or pembrolizumab/cisplatin/pemetrexed regimen. For squamous cell NSCLC the panel offers a category 2A recommendation for use of Keytruda as a single agent as continuation maintenance therapy, if given first-line as part of pembrolizumab/carboplatin/paclitaxel regimen.

Penile Cancer

NCCN 2A recommendation to use as a single agent (preferred) as subsequent-line systemic therapy if unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor that has progressed following prior treatment and no satisfactory alternative treatment options. There are no randomized clinical trials due to the rarity of penile cancer in industrialized countries. The NCCN Panel strongly recommends consideration of clinical trial participation as data are limited in the second-line setting

Renal Cell Carcinoma

Keytruda received FDA approval for use in combination with axitinib (Inlyta), as first-line treatment of those with advanced renal cell carcinoma.

Small Cell Lung Cancer

NCCN Drugs and Biologics Compendium and the NCCN CPG on small cell lung cancer offers recommendations for use of Keytruda as a single agent as subsequent systemic therapy for individuals with disease relapse within 6 months following complete or partial response, or stable disease with initial treatment (category 2A). The panel also recommends use of Keytruda as a single agent for the treatment of primary progressive disease (category 2A). The recommendations are based on uniform consensus and unpublished data from the KEYNOTE-158 study (NCT02628067), a phase 2, multicenter, non-randomized, open-label, multi-cohort trial that used Keytruda in the treatment of advanced SCLC.

Solid Tumors

Keytruda is FDA granted accelerated approval for expanded use in adults or children for the treatment of unresectable or metastatic solid tumors (dMMR/MSI-H only) (which can be found in biliary, bladder, breast, colorectal, endometrial, esophageal, gastric/gastroesophageal junction, pancreatic, prostate, renal cell, retroperitoneal adenocarcinoma, sarcoma, small cell lung, small intestine and thyroid) with *disease progression following prior treatment* and no other satisfactory alternative treatment options identified. The approval included coverage in treatment of individuals with unresectable or metastatic colorectal cancer (dMMR/MSI-H only) with disease progression following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. The FDA approval was based on tumor response rate and durability of response.

Urothelial Carcinoma

Urothelial carcinoma is the most common type of bladder cancer. The ACS estimates that in 2019 there will be approximately 80,470 new cases of bladder cancer (incidence about four times higher in men than in women) and 17,670 deaths from bladder cancer (about 12,870 in men and 4800 in women) in the United States (ACS, 2019).

Keytruda is FDA 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.
- 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 [Combined Positive Score (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.

Other Uses

Keytruda is currently being studied in clinical trials for a variety of other cancers. Keytruda is also currently being studied in ongoing clinical trials for other uses including, but not limited to other malignancies and solid tumors. However for these off-label uses, currently there is insufficient published evidence to support the use of Keytruda for such conditions.

Anal Cancer

The NCCN Drugs and Biologics Compendia and the NCCN CPG for anal cancer offered a NCCN 2A recommendation for the use of Keytruda as a single agent for subsequent treatment of metastatic squamous cell carcinoma of the anal canal as a treatment option. The NCCN Panel recommendation is based on unpublished preliminary results reported from the KEYNOTE-28 trial, a multi-cohort, phase 1b trial for PD-1 positive squamous cell carcinoma of the anal canal (Ott, 2015). Ott and colleagues (2015) concluded that further studies of PD-1 and PD-L1 inhibitors is warranted for treatment of squamous cell carcinoma of the anal canal.

In the NCCN Drugs and Biologics Compendia and the NCCN CPG for B-Cell lymphomas the panel includes a NCCN 2A recommendation for use as systemic therapy of Keytruda as primary treatment in stage III Mycosis Fungoides or stage IV Sezary Syndrome. At this time there is insufficient published evidence supporting use in this condition and the updates to the discussion within the NCCN CPG for B-Cell lymphomas is still in progress.

Based on the recent NCCN Drugs and Biologics Compendia and NCCN CPG for hepatobiliary cancer the NCCN panel included a category 2A recommendation for use of Keytruda as primary treatment of unresectable or metastatic disease hepatobiliary (extrahepatic, gallbladder and intrahepatic) adenocarcinoma (MSI-H only). The recommendation is based on unpublished preliminary results from the 1-PREDICT study (NCT0253467). In summary, the authors concluded that "there is limited clinical data to support Keytruda in this setting."

The NCCN Drug and Biologics Compendia and the NCCN CPG for gestational trophoblastic neoplasia offer a category 2A recommendation for Keytruda as a single agent in the treatment of recurrent or progressive intermediate trophoblastic tumor following treatment with a platinum/etoposide-containing regimen and as a single agent for individuals with methotrexate-resistant high-risk disease. However, there is insufficient published evidence to support the use of Keytruda for such condition.

In the NCCN CPG for T-Cell Lymphomas the NCCN panel included a category 2A recommendation for extranodal NK/T-Cell lymphoma as a treatment option for Keytruda in relapsed or refractory disease following therapy in a clinical trial. The NCCN Panel concluded that use of Keytruda in "clinical trial is the preferred relapsed/refractory option in the absence of a clinical trial, Keytruda is an appropriate option."

The recently updated NCCN Drugs and Biologics and NCCN CPG for testicular cancer offer a category 2A recommendation for use of Keytruda as a single agent as palliative treatment in individuals with MSI-H/dMMR tumors and progression after treatment with high dose chemotherapy or third-line therapy. The recommendation is based on a small phase II study (Le, 2015; Le, 2017). In summary, the authors conclude that Keytruda may be a treatment option, however, they suggest participation in a clinical trial as the preferred treatment option.

Definitions and Measures

Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.

Anal cancer: Cancer originating in the tissues of the anus; the anus is the opening of the rectum (last part of the large intestine) to the outside of the body.

BRAF: The oncogene which directs production of a protein in the regulating MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion.

Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.

Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).

ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

Karnofsky Performance Status: A scale and criteria used by doctors and researchers to assess an individual's prognosis, measure changes in their function and abilities, and determine their ability to tolerate therapies. The lower the score (from 0-100), the worse the likelihood of survival.

- 100 = Normal, no complaints
- 90 = Able to carry on normal activities
- 80 = Normal activity with effort
- 70 = Care for self. Unable to carry on normal activity or to do active work
- 60 = Requires occasional assistance, but able to care for most of his needs
- 50 = Requires considerable assistance and frequent medical care
- 40 = Disabled. Requires special care and assistance
- 30 = Severely disabled. Hospitalization indicated though death nonimminent
- 20 = Very sick. Hospitalization necessary. Active supportive treatment necessary
- 10 = Moribund
- 0 = Dead

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Melanoma: A type of cancer that begins in the melanocytes. Melanoma is also referred to as malignant melanoma and cutaneous melanoma.

Merkel cell carcinoma: A rare, aggressive skin cancer.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Monoclonal antibody: A protein developed in the laboratory that can locate and bind to specific substances in the body and on the surface of cancer cells.

Multiple myeloma: A type of cancer that begins in plasma cells (white blood cells that produce antibodies).

Mutation: A permanent, transmissible change in genetic material.

Neoadjuvant therapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.

Non-small cell lung cancer: A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.

Non-Hodgkin Lymphoma (NHL): A group of malignant solid tumors or lymphoid tissues.

Phase I trial: A study to test a new drug or treatment in a small group of participants for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

Unresectable: Unable to be removed with surgery.

Urothelial carcinoma: A type of bladder cancer which occurs in the urinary tract system.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Keytruda (pembrolizumab)

Requests for Keytruda (pembrolizumab) may be approved if the following criteria are met:

- I. Individual has a diagnosis of recurrent or metastatic Cervical Cancer; **AND**

- A. Individual is using as monotherapy; **AND**
- B. Individual has a tumor with PD-L1 gene expression with Combined Positive Score (CPS) of greater than or equal to 1; **AND**
- C. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
- D. Individual has a current Eastern Cooperative Group (ECOG) performance status of 0-2; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

- II. Individual has a diagnosis of Colorectal Cancer; **AND**
 - A. Individual is using as monotherapy; **AND**
 - B. Individual meets *one* of the following:
 - 1. Primary treatment as a single agent for unresectable metachronous metastases (defective mismatch repair/high microsatellite instability [dMMR/MSI-H] only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; **OR**
 - 2. Subsequent therapy as a single agent (if nivolumab or pembrolizumab not previously given) for unresectable advanced or metastatic disease (dMMR/MSI-H only) following previous treatment with **one** of the following:
 - 1. Oxaliplatin-irinotecan and fluoropyrimidine-based therapy;
 - 2. Oxaliplatin-irinotecan;
 - C. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
 - D. Individual has a current ECOG performance status of 0-2; **AND**
 - E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

- III. Individual has a diagnosis for the recurrent locally advanced or metastatic Gastric or Gastroesophageal Junction Adenocarcinoma; **AND**
 - A. Individual is using as monotherapy; **AND**
 - B. Individual has a tumor with PD-L1 gene expression with CPS of greater than or equal to 1; **AND**
 - C. Individual has demonstrated disease progression on or after two or more prior lines of therapy including fluoropyrimidine and platinum-containing chemotherapy, if appropriate HER2/neu-targeted therapy; **AND**
 - D. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
 - E. Individual has a current ECOG performance status of 0-2; **AND**
 - F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

- IV. Individual has a diagnosis of recurrent, unresectable, or metastatic Head and Neck Squamous Cell Carcinoma (HNSCC); **AND**
 - A. Individual is using as monotherapy; **AND**
 - B. Individual has demonstrated disease progression on or after platinum-containing chemotherapy; **AND**
 - C. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
 - D. Individual has a current ECOG performance status of 0-2; **AND**
 - E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

- V. Individual has a diagnosis of Hepatocellular Carcinoma (HCC); **AND**
 - A. Individual has Child-Pugh Class A advanced HCC ; **AND**
 - B. Individual is using as monotherapy; **AND**
 - C. Individual has demonstrated disease progression or intolerance on or after treatment with an approved first-line agent; **AND**
 - D. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
 - E. Individual has a current ECOG performance status of 0-2; **AND**
 - F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

- VI. Individual has a diagnosis of relapsed or refractory Hodgkin Lymphoma except for those with lymphocyte-predominant Hodgkin lymphoma (L-1, NCCN 2A);

OR

- VII. Individual has a diagnosis of Malignant Pleural Mesothelioma; **AND**
 - A. Individual is using as subsequent therapy;
 - OR**

B. Individual is ineligible for platinum-based chemotherapy, defined as having *one or more* of the following risk factors for platinum-based chemotherapy toxicity:

1. ECOG performance status equal to 2;
2. Glomerular filtration rate less than 60 mL/min;
3. Hearing loss (measured at audiometry) of 25 dB at two contiguous frequencies;
4. Grade 2 or greater peripheral neuropathy;

AND

C. Individual is using as monotherapy; **AND**
D. Individual has a current ECOG performance status of 0-2; **AND**
E. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VIII. Individual has a diagnosis of Melanoma (cutaneous and uveal); **AND**

A. Individual has confirmed presence of *unresectable or metastatic melanoma*; **AND**
B. Individual is using as monotherapy; **AND**
C. Individual meets one of the following:

1. Individual is using as first-line therapy in untreated disease;
OR
2. Individual is using as second-line or subsequent therapy for confirmed disease progression while receiving or since completing most recent therapy; **AND**

D. Individual has current ECOG performance status of 0-2; **AND**
E. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IX. Individual has a diagnosis of Melanoma (cutaneous and uveal); **AND**

A. Individual has *resected, high-risk stage III disease*; **AND**
B. Individual is using as monotherapy; **AND**
C. Individual is using as adjuvant therapy for up to 12 months; **AND**
D. Individual has a current ECOG performance status of 0-2; **AND**
E. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

X. Individual has a diagnosis of Merkel Cell Carcinoma (MCC); **AND**

A. Individual is using as monotherapy; **AND**
B. Individual has presence of metastatic or advanced locoregional MCC determined to be not amenable to definitive surgery or radiation therapy; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XI. Individual has a diagnosis of Non-Hodgkin Lymphoma, Primary Mediastinal Large B-Cell Lymphoma;

A. Individual is using as monotherapy; **AND**
B. Individual is using to treat refractory disease or subsequent therapy for disease relapse after receiving two or more prior lines of therapy; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XII. Individual has a diagnosis of *locally advanced or metastatic* Non-Small Cell Lung Cancer (NSCLC); **AND**

A. Individual is using for the first-line treatment; **AND**
B. Individual's disease is confirmed cytologically as stage III or IV NSCLC; **AND**
C. Individual is using as monotherapy; **AND**
D. Confirmation tumor expresses PD-L1 gene on at least 1% or greater of tumor cells; **AND**
E. Confirmation there are no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations in nonsquamous carcinoma; **AND**
F. Individual has not received treatment with another PD-1 agent (for example, nivolumab) and has not undergone previous systemic therapy for metastatic disease; **AND**
G. Individual has a current ECOG performance status of 0-2; **AND**

H. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

XIII. Individual has a diagnosis of *advanced or metastatic nonsquamous NSCLC*; **AND**

- A. Individual is using for first-line treatment; **AND**
- B. Disease is confirmed cytologically as stage IIIb or IV NSCLC; **AND**
- C. Individual is using in combination with pemetrexed and a platinum agent; **AND**
- D. Confirmation there are no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations; **AND**
- E. Individual has not received treatment with another PD-1 agent (for example, nivolumab) and has not undergone previous systemic therapy for metastatic disease; **AND**
- F. Individual has a current ECOG performance status of 0-2; **AND**
- G. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

XIV. Individual has a diagnosis of *metastatic squamous NSCLC*; **AND**

- A. Individual is using for first line treatment; **AND**
- B. Disease is confirmed cytologically as stage IV NSCLC; **AND**
- C. Individual is using in combination with carboplatin plus paclitaxel or nab-paclitaxel; **AND**
- D. Individual has not received treatment with another PD-1 agent (for example, nivolumab) and has not undergone previous systemic therapy for metastatic disease; **AND**
- E. Individual has a current ECOG performance status of 0-2; **AND**
- F. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

XV. Individual has a diagnosis of *recurrent or metastatic nonsquamous NSCLC*; **AND**

- A. Individual is using in combination with pemetrexed as *continuation maintenance therapy*, if given first-line as part of pembrolizumab/pemetrexed and platinum-based regimen; **AND**
- B. Individual has confirmed achievement of tumor response or stable disease following initial cytotoxic therapy; **AND**
- C. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
- D. Individual has a current ECOG performance status of 0-2; **AND**
- E. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

XVI. Individual has a diagnosis of *recurrent or metastatic squamous cell NSCLC*; **AND**

- A. Individual is using as monotherapy as *continuation maintenance therapy*, if given first-line as part of pembrolizumab/carboplatin/paclitaxel (or nab-paclitaxel) regimen; **AND**
- B. Individual has confirmed achievement of tumor response or stable disease following initial cytotoxic therapy; **AND**
- C. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
- D. Individual has a current ECOG performance status of 0-2; **AND**
- E. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

XVII. Individual has a diagnosis of *metastatic NSCLC*; **AND**

- A. Individual is using as monotherapy in second or subsequent line of therapy; **AND**
- B. Individual has confirmed tumor with PD-L1 gene expression level greater than or equal to 1% with disease progression on or after platinum-containing chemotherapy; **AND**
- C. If individual has anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR) genomic tumor aberrations present, they must have confirmed disease progression on U.S. Food and Drug Administration (FDA) approved therapy for the aberrations prior to receiving pembrolizumab (Keytruda); **AND**
- D. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
- E. Individual has a current ECOG performance status of 0-2; **AND**
- F. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

XVIII. Individual has diagnosis of *advanced Renal Cell Carcinoma (RCC) (Label, NCCN 2A)*; **AND**

- A. Individual has histological confirmation of RCC with clear cell component; **AND**
- B. Individual is using as first-line therapy; **AND**
- C. Individual is using in combination with axitinib; **AND**
- D. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
- E. Individual has a current Karnofsky performance status of $\geq 70\%$; **AND**
- F. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

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OR

XVIII-XIX. Individual has a diagnosis of Small Cell Lung Cancer (NCCN 2A); **AND**

- A. Individual is using as monotherapy as subsequent therapy; **AND**
- B. Individual confirms treatment is for disease relapse within 6 months following complete or partial response or stable disease with initial treatment; **OR**
- C. Individual confirms treatment is for primary progressive disease; **AND**
- D. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
- E. Individual has a current ECOG performance status of 0-2; **AND**
- F. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

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OR

XIX-XX.

Individual has a diagnosis of unresectable or metastatic solid tumors (dMMR/MSIH only); **AND**

- A. Individual is using as monotherapy; **AND**
- B. Individual has confirmed disease progression following prior treatment with no other satisfactory alternative treatment options; **AND**
- C. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
- D. Individual has a current ECOG performance status of 0-2; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XX-XXI.

Individual has a diagnosis of locally advanced or metastatic Urothelial Carcinoma; **AND**

- A. Individual is using as monotherapy; **AND**
- B. Individual meets *one* of the following:
 - 1. Individual is not eligible for any platinum-containing chemotherapy, and if cisplatin-ineligible, tumor expresses PD-L1 with CPS of greater than or equal to 10; **OR**
 - 2. Individual has confirmed disease progression on or after platinum-containing chemotherapy; **OR**
 - 3. Individual has confirmed disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;
- C. Individual has not received treatment with another PD-1 agent (for example, nivolumab); **AND**
- D. Individual has a current ECOG performance status of 0-2; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

Requests for Keytruda (pembrolizumab) may not be approved for the following:

- I. When the above criteria are not met; **OR**
- II. Individual requests use for *first-line* therapy, except as described above; **OR**
- III. Individual requests reason for treatment other than for a diagnosis with accompanied criteria noted above.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9271 Injection, pembrolizumab, 1 mg [Keytruda]

ICD-10 Diagnosis

C00.0-C76.8	Malignant neoplasms
C7B.00-C7B.8	Secondary neuroendocrine tumors
C64.1-C64.9	Malignant neoplasm of kidney, except renal pelvis
C77.0-C79.9	Secondary malignant neoplasms
C80.0-C80.2	Malignant neoplasm without specification of site
C81.10-C81.99	Hodgkin lymphoma (classical)
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
Z85.00-Z85.59	Personal history of malignant neoplasms
Z85.71	Personal history of Hodgkin lymphoma

Document History

Revised: 06/10/2019

Document History:

- 06/10/2019 – Select Review: Add new criteria for FDA update for use of pembrolizumab in advanced renal cell carcinoma. Coding Reviewed: Added ICD-10 C64.1-C64.9
- 05/17/2019– Annual Review: Initial review of Keytruda (pembrolizumab). Add new criteria for FDA update for use of pembrolizumab in those with locally advanced or metastatic stage 3 NSCLC and PD-L1 TPS of 1% or greater in those without EGFR and ALK genomic tumor aberrations. Wording and formatting changes. Coding Reviewed: No changes.

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 - b. B-Cell Carcinoma V2.2019. Revised March 6, 2019.
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 - d. Bone Cancer V2. 2019. Revised April 10, 2019.
 - e. Central Nervous System Cancers V1.2019. Revised March 5, 2019.
 - f. Colon Cancer V1.2019. Revised March 15, 2019.
 - g. Head and Neck Cancer V1.2019. Revised March 6, 2019.
 - h. Hepatobiliary Cancers V2.2019. Revised March 6, 2019
 - i. Hodgkin Lymphoma V1.2019. Revised April 9, 2019.
 - j. Kidney Cancer V4.2019. Revised April 25, 2019.
 - k. Malignant Pleural Mesothelioma V2.2019. Revised April 1, 2019.
 - l. Cutaneous Melanoma V2.2019. Revised March 12, 2019
 - m. Merkel Cell Carcinoma V2.2019. Revised January 18, 2019.
 - n. Non-Small Cell Lung Cancer. V3.2019. Revised January 18, 2019.
 - o. Ovarian Cancer V1.2019. Revised March 8, 2019.
 - p. Rectal Cancer V1.2019. Revised March 15, 2019.
 - q. Small Cell Lung Cancer. V1.2019. Revised April 9, 2019.
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