# Clinical Criteria

| | | | |
|---|---|---|---|
| **Subject:** | Keytruda (pembrolizumab) | | |
| **Document #:** | ING-CC-0124 | **Publish Date:** | ~~12/01/2021~~01/31/2022 |
| **Status:** | Revised | **Last Review Date:** | ~~11/19/2021~~12/13/2021 |

## Table of Contents



## 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.

*Breast Cancer*

Keytruda is FDA 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. Keytruda is also approved for use in combination with chemotherapy as neoadjuvant treatment, followed by single agent use in the adjuvant setting after surgery.

*Cervical Cancer*

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. Keytruda is also indicated in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 CPS≥1.

*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.

Keytruda is FDA approved as first line therapy for patients with microsatellite instability-high or mismatch repair deficient colorectal cancer (MSIH/dMMR).

NCCN Drugs and Biologics Compendium and the NCCN Clinical Practice Guidelines (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.

*Cutaneous Squamous Cell Carcinoma (cSCC)*

Basal cell and cutaneous squamous cell cancers are together known as non-melanoma skin cancers (NMSCs) or keratinocyte carcinoma.

Keytruda is FDA approved to treat individuals with locally advanced, recurrent or metastatic cutaneous (skin) squamous cell carcinoma that is not curable by surgery or radiation.

*Endometrial Cancer*

Keytruda received accelerated FDA approval for the treatment of endometrial cancer in combination with lenvatinib (Lenvima) in those with advanced disease that is *not* microsatellite instability-high or mismatch repair deficient (MSI-H/dMMR) who have disease progression following prior systemic therapy and are not eligible for surgery or radiation. At the time of this review, the NCCN placed this indication in the 2B category, and the discussion update was in progress.

*Esophageal Cancer*

Esophageal cancer can be classified as squamous cell carcinoma or adenocarcinoma. Compared to adenocarcinoma, squamous cell carcinoma has a poorer prognosis.

Keytruda is FDA indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10], with disease progression after one or more prior lines of systemic therapy. Keytruda (pembrolizumab) is also FDA indicated for the treatment of 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 in combination with platinum- and fluoropyrimidine–based chemotherapy.

*Gastric or Gastroesophageal Junction Adenocarcinoma*

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. Keytruda is also indicated for use with trastuzumab plus platinum and fluoropyrimidine-based chemotherapy as first line treatment in locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma.

*Head and Neck Squamous Cell Cancer (HNSCC)*

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, unresectable, or metastatic head and neck squamous cell carcinoma (HNSCC) as first-line monotherapy whose tumors express PD-L1 with CPS greater than or equal to 1, as first-line in combination with platinum and fluorouracil, and as monotherapy in those with disease progression on or after platinum-containing chemotherapy. NCCN also provides similar recommendation for Keytruda in HNSCC, with an additional recommendation for use of Keytruda with platinum and fluorouracil as a subsequent therapy option. However, published studies are lacking at this time.

*Hepatocellular Carcinoma*

Hepatocellular carcinoma is the most common form of liver cancer. 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 with relapsed or refractory classical Hodgkin lymphoma (cHL), and pediatrics with refractory cHL, or those who have relapsed after 2 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. 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*

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 adult or pediatric patients 12 years of age or older with Stage IIB, Stage IIC or Stage III melanoma 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.”

NCCN also provides a category 2A recommendation for use of Keytruda (pembrolizumab) as single-agent treatment for brain metastases in patients with melanoma.

*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. 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. NCCN also offers a 2A recommendation for use of Keytruda in locoregional unresectable or metastatic adrenocortical carcinoma as single agent or in combination with mitotane.

*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. 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) ≥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 ≥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) ≥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 (≥ 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 ≥ 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. NCCN also provides a category 2A recommendation for use of Keytruda (pembrolizumab) as single-agent treatment for brain metastases in patients with PD-L1 positive NSCLC.

NCCN also provides a recommendation for use of Keytruda as treatment for recurrent, advanced, or metastatic NSCLC in combination with pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology, or carboplatin and either paclitaxel or albumin-bound paclitaxel for squamous cell histology as first line or subsequent therapy in those with BRAF, NTRK, MET, or ROS1 mutations. The recommendation was based on studies (Gandhi 2018, Paz-Ares 2018) that excluded individuals with EGFR and ALK mutations, but it is unknown if those with other sensitizing mutations were included to support such use.

*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. Keytruda is also FDA approved as adjuvant treatment in those with renal cell carcinoma at intermediate-high, or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

The NCCN provides similar recommendations, with an additional recommendation for subsequent therapy; however, published studies supporting this are lacking. NCCN also provides a recommendation for use of Keytruda for relapse or stage IV kidney cancer in combination with lenvatinib (preferred) as first-line therapy for clear cell histology and favorable or poor/intermediate risk

*Soft Tissue Sarcoma*
NCCN considers Keytruda useful in certain circumstances as first line or subsequent therapy for various types of soft tissue sarcoma, including of the extremity/body wall, head/neck, retroperitoneal/intra-abdominal, angiosarcoma, and alveolar soft part sarcoma.

*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/MSIH 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/MSIH only) with disease progression following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. The FDA approval was based on tumor response rate and durability of response. NCCN provides additional recommendations for certain solid tumors (occult primary, pancreatic, and small bowel adenocarcinoma) that are dMMR/MSIH for Keytruda as first-line therapy; however, supporting literature is lacking. The recommendation is based on a small phase II study (Le, 2017), which studied Keytruda's use as subsequent therapy.

Keytruda is also FDA approved for solid tumors with tumor mutational burden-high (TMB-H), defined as greater than or equal to 10 mutations per megabase (mut/Mb), as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory treatment options. This indication was approved under the FDA's accelerated approval program, and continued approval is contingent upon confirmation of clinical benefit.

*Thymic Carcinoma*

NCCN provides a 2A category recommendation for Keytruda as subsequent therapy for unresectable or metastatic thymic carcinoma. This is based on two phase II trials (Giaccone 2018, Cho 2019) which demonstrated positive overall response rate (22.5% and 15.4%, respectively). NCCN caveats this a warning that immunotherapy, including Keytruda, can be associated with a high rate of severe immune-related adverse events, including myocarditis. For this reason, Keytruda is not recommended in those with thymomas. Additionally NCCN also recommends use of Keytruda in individuals who cannot tolerate first-line combination regimens.

*Urothelial Carcinoma*

Urothelial carcinoma is the most common type of bladder cancer. The ACS estimates that in 201 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 any platinum-containing chemotherapy.
- 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.

**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.

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, 2017). Ott and colleagues (2017) 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 Primary Cutaneous 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. The recommendation was based on a small phase II trial of 24 patients (21 had stage III or IV), with an overall response rate of 38% (2 complete responses and 7 partial responses). The authors concluded that more studies are needed to determine potential biomarkers for response, and assess whether PD-1/PD-L1 therapy can actually negatively affect the disease since there is theoretical concern that PD-1 blockade could accelerate growth of the malignancy (Khodadoust 2020).

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."

In the 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.

NCCN also provides a category 2A recommendation for use of Keytruda as palliative therapy for patients with esophageal and esophagogastric junction cancer who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and Karnofsky performance score ≥60% or ECOG performance score of ≤2 and if no prior tumor progression while on therapy with a checkpoint inhibitor as preferred third-line or subsequent therapy as a single agent for esophageal and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥1. At this time, there is lack of supporting data to support such use.

NCCN provides a category 2A recommendation for use of Keytruda as useful in certain circumstances in those with salivary gland tumors as single-agent systemic therapy for tumor mutational burden high (TMB-H) recurrent disease with distant metastases in patients with a performance status (PS) of 0-3, or unresectable locoregional recurrence or second primary with prior radiation therapy. The recommendation was based on an ongoing study (Marabelle 2020) that included three patients with TMB-H salivary gland cancer. Therefore, there is lack of supporting data to support such use at this time.

NCCN provides a category 2A recommendation for use of Keytruda in combination with ipilimumab in cutaneous melanoma as preferred second-line or subsequent therapy* option for metastatic or unresectable disease** after progression or maximum clinical benefit from BRAF targeted therapy. This recommendation was based on an open-label, phase 1b study (Carlino 2020), which resulted in treatment related adverse effects of 96.1% (35.9% with drug discontinuation), of which 47.1% were grade 3 and higher. Therefore, further data is warranted to support such use.

NCCN provides a category 2A recommendation for use of Keytruda as useful in certain circumstances as a single agent for second-line treatment of advanced, recurrent, or metastatic squamous cell vulvar cancer if disease progression on or after chemotherapy in patients whose tumors express PD-L1 (Combined Positive Score ≥1). The recommendation was based on a small ongoing basket study that included individuals with cervical cancer (Chung 2018, Marabelle 2020). Therefore, there is lack of supporting data for such use at this time.

### 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 directions production of a protein in the regulating MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion.

Carcinoma in situ: A group of abnormal cells that stay in place where they were first formed, and have not spread, but may become cancerous. Also called stage 0 disease.

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).

Cystectomy: Surgery to remove all or part of the bladder. Also used to describe removal of a cyst.

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

Immune checkpoint inhibitor: A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. When these proteins are blocked, the "brakes" on the immune system are released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include programmed death (PD)-1, PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen (CTLA)-4/B7-1/B7-2 (NCI, 2018).

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.

Programmed death (PD)-1: PD-1 proteins are found on T-cells and attach to PD ligands (PD-L1) found on normal (and cancer) cells (see immune checkpoint inhibitor above). Normally, this process keeps T-cells from attacking other cells in the body. Examples of FDA approved PD-1 inhibitors include Keytruda (pembrolizumab), Opdivo (nivolumab), and Libtayo (cemiplimab).

Programmed death ligand (PD-L)-1: The ligands found on normal (and cancer) cells to which the PD-1 proteins attach (see immune checkpoint inhibitor above). Cancer cells can have large amounts of PD-L1 on their surface, which helps them to avoid immune attacks. Examples of FDA approved PD-L1 inhibitors include Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab).

Unresectable: Unable to be removed with surgery.

Urothelial carcinoma: A type of bladder cancer which occurs in the urinary tract system. Urothelial carcinoma is also known as transitional cell carcinoma of the bladder.

## 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 locoregional unresectable or metastatic Adrenocortical Carcinoma (NCCN 2A); **AND**
   A. Individual is using as single agent, or in combination with mitotane; **AND**
   B. Individual has a current ECOG performance status of 0-2; **AND**
   C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   D. 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 locally recurrent, unresectable, or metastatic Triple-Negative Breast Cancer (TNBC); **AND**
   A. Individual is using in combination with paclitaxel/nab-paclitaxel, ***or*** in combination with gemcitabine and a platinum agent); **AND**
   B. Individual has a tumor with PD-L1 gene expression with Combined Positive Score (CPS) of greater than or equal to 10; **AND**
   C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

III. Individual has a diagnosis of high risk early-stage Triple-Negative Breast Cancer (TNBC); **AND**
   A. Individual is using in combination with chemotherapy in the neoadjuvant setting; **AND**
   B. Individual will continue/is continuing Keytruda as single agent in the adjuvant setting after surgical intervention; **AND**
   C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

IV. Individual has a diagnosis of persistent, recurrent or metastatic Cervical Cancer; **AND**
   A. Individual is using in combination with paclitaxel and a platinum agent, with or without bevacizumab; **AND**
   B. Individual has a tumor with PD-L1 gene expression with Combined Positive Score (CPS) of greater than or equal to 1 (CPS ≥ 1); **AND**
   C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

V. 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 anti-PD-1 agent ; **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**

VI. Individual has a diagnosis of Colorectal Cancer (Label, NCCN 2A); **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 (deficient mismatch repair/high microsatellite instability [dMMR/MSIH] 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/MSIH only) following previous treatment with **one** of the following:
      a. Oxaliplatin-, irinotecan-, and/or fluoropyrimidine-based therapy;
         **OR**
   3. First line treatment as a single agent for unresectable or metastatic disease (dMMR/MSIH only);

**AND**

C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

VII. Individual has a diagnosis of locally advanced, recurrent or metastatic Cutaneous Squamous Cell Carcinoma (cSCC); **AND**
A. Individual is using as monotherapy; **AND**
B. Disease is not curable by surgery or radiation; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

VIII. Individual has a diagnosis of advanced Endometrial Cancer (*not* dMMR/MSIH); **AND**
A. Individual is using in combination with lenvatinib; **AND**
B. Individual has confirmed disease progression after one or more prior lines of systemic therapy; **AND**
C. Individual is not a candidate for curative surgery or radiation; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

IX. Individual has a diagnosis of recurrent locally advanced or metastatic squamous cell Esophageal Cancer; **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 10; **AND**
C. Individual has demonstrated disease progression after one or more prior lines of systemic therapy; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

X. Individual has a diagnosis of unresectable, recurrent locally advanced, or metastatic Esophageal Cancer (Label, NCCN 1, 2A); **AND**
A. Individual is using in combination with platinum and fluoropyrimidine-based chemotherapy; **AND**
B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. 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 recurrent locally advanced or metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (Label, NCCN 2A); **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 anti-PD-1 or anti-PD-L1 agent ; **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**

XII. Individual has a diagnosis of locally advanced unresectable or metastatic Gastric or Gastroesophageal Junction Adenocarcinoma; **AND**
A. Individual has HER2-positive disease and is using as first line treatment; **AND**
B. Individual is using in combination with trastuzumab, platinum- and fluoropyrimidine-based chemotherapy; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

XIII. Individual has a diagnosis of recurrent, unresectable, or metastatic Head and Neck Squamous Cell Carcinoma (HNSCC); **AND**
A. Individual is using as monotherapy; **AND**
1. Individual meets *one* of the following:
a. Individual is using as first-line treatment for tumor with PD-L1 gene expression with CPS of greater than or equal to 1; **OR**
b. Individual has demonstrated disease progression on or after platinum-containing chemotherapy;

**OR**

B. Individual is using as first-line treatment in combination with platinum-containing chemotherapy and fluorouracil regardless of PD-L1 expression; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

XIV. 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 anti-PD-1 or anti-PD-L1 agent; **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**

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

**OR**

XVI. 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 anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XVII. 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 anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XVIII. Individual has a diagnosis of Melanoma (cutaneous and uveal); **AND**
A. Individual has *resected, stage IIB, IIC or 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 anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XIX. Individual has a diagnosis of metastatic Melanoma with brain metastases (NCCN 2A); **AND**
- A. Individual has a primary diagnosis of melanoma; **AND**
- B. Individual is using as single agent for brain metastases; **AND**
- C. Individual has a current ECOG performance status of 0-2; **AND**
- D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XX. 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 anti-PD-1 or anti-PD-L1 agent; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XXI. Individual has a diagnosis of Non-Hodgkin Lymphoma, Primary Mediastinal Large B-Cell Lymphoma; **AND**
- 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 anti-PD-1 or anti-PD-L1 agent; **AND**
- E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XXII. Individual has a diagnosis of *advanced, recurrent, or metastatic* Non-Small Cell Lung Cancer (NSCLC) (Label, NCCN 2A); **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. Individual does not have presence of actionable molecular markers*; **AND**
- F. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent 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 or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XXIII. Individual has a diagnosis of *advanced, recurrent, or metastatic nonsquamous* NSCLC (Label, NCCN 2A); **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. Individual does not have presence of actionable molecular markers*; **AND**
- E. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent 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 or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XXIV. Individual has a diagnosis of advanced, recurrent, or metastatic *squamous* NSCLC (Label, NCCN 2A); **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 does not have presence of actionable molecular markers*; **AND**
- E. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent 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 or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XXV. Individual has a diagnosis of advanced, 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 anti-PD-1 or anti-PD-L1 agent ; **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**

XXVI. Individual has a diagnosis of advanced, 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 anti-PD-1 or anti-PD-L1 agent ; **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**

XXVII. Individual has a diagnosis of advanced, recurrent, 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 anti-PD-1 or anti-PD-L1 agent ; **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**

XXVIII. Individual has a diagnosis of metastatic NSCLC with brain metastases (NCCN 2A); **AND**
A. Individual has a primary diagnosis of non-small cell lung cancer; **AND**
B. Individual is using as single agent for brain metastases; **AND**
C. Individual has confirmed tumor with PD-L1 gene expression level greater than or equal to 1%; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

XXIX. Individual has diagnosis of advanced Renal Cell Carcinoma (RCC) (Label, NCCN 1); **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 or lenvatinib; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent ; **AND**
E. Individual has a current Karnofsky performance status of ≥ 70%; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

XXX. Individual has diagnosis of Renal Cell Carcinoma (RCC) (Label); **AND**
A. Individual is using as adjuvant treatment in those with intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions;

**OR**

~~XXX.~~ XXXI. Individual has a diagnosis of unresectable, recurrent, advanced, or metastatic Soft Tissue Sarcoma (NCCN 2A); **AND**
A. Individual is using as monotherapy for first line or subsequent therapy; **AND**
B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual has a current ECOG performance status of 0-2; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

**OR**

~~XXXI.~~ XXXII. 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 anti-PD-1 or anti-PD-L1 agent; **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**

~~XXXII.~~ XXXIII. Individual has a diagnosis of unresectable or metastatic solid tumors; **AND**
A. Individual is using as monotherapy; **AND**
B. Individual has high tumor mutation burden (TMB) (greater than or equal to 10 mutations per megabase) with test results confirmed; **AND**

C. Individual has confirmed disease progression following prior treatment with no other satisfactory alternative treatment options; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

~~XXIII.~~XXIV. Individual has a diagnosis of unresectable or metastatic Thymic Carcinoma (NCCN 2A); **AND**
A. Individual is using as monotherapy; **AND**
B. Individual has confirmed disease progression following chemotherapy, or intolerance to first-line combination regimens; **AND**
C. Individual does not have thymomas; **AND**
D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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**

~~XXIV.~~XXV. Individual has a diagnosis of locally advanced or metastatic Urothelial Carcinoma (Label, NCCN 1, 2A); **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; **OR**
2. Individual is using as subsequent therapy; **OR**
3. Individual has confirmed disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

**AND**
C. Individual has not received treatment with another anti PD-1 or anti-PD-L1 agent; **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**

~~XXV.~~XXVI. Individual has a diagnosis of high risk non-muscle invasive (T1, high grade Ta, and/or carcinoma in situ [CIS]) Urothelial Carcinoma of the Bladder with or without papillary tumors (Label, NCT02625961); **AND**
A. Individual has Bacillus Calmette-Guerin (BCG)- unresponsive disease defined as one of the following:
1. Persistent disease despite adequate BCG therapy (adequate defined as administration of at least 5 doses of an initial induction course *plus either* at least 2 doses of maintenance therapy or at least 2 doses of a second induction course); **OR**
2. Disease recurrence after an initial tumor-free state following adequate BCG therapy (adequate defined as administration of at least 5 doses of an initial induction course *plus either* at least 2 doses of maintenance therapy or at least 2 doses of a second induction course); **OR**
3. T1 disease (i.e., tumor has spread to the connective tissue, but not the muscle) following a single induction course of BCG; **AND**
B. Individual is ineligible for cystectomy; **AND**
C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **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.

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

Keytruda (pembrolizumab) may not be approved when the above criteria are not met and for all other indications.

## 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 |
| **C15.3-C15.5** | Malignant neoplasm of esophagus upper, middle, or lower third |
| **C15.8-C15.9** | Malignant neoplasm of overlapping sites of esophagus |
| **C15.9** | Malignant neoplasm of esophagus, unspecified |
| **C16.0** | Malignant neoplasm of stomach |
| **C17.0-C17.9** | Malignant neoplasm of small intestine |
| **C18.0-C18.9** | Malignant neoplasm of colon |
| **C19** | Malignant neoplasm of colon and rectum |
| **C20** | Malignant neoplasm of rectum |
| **C21.0-C21.8** | Malignant neoplasm of anus, unspecified |
| **C37** | Malignant neoplasm of thymus |
| **C43.0-C43.8** | Malignant melanoma of skin |
| **C49.9** | Malignant neoplasm of connective and soft tissue, unspecified |
| **C50.01-C50.919** | Malignant neoplasm of breast |
| **C54.1** | Malignant neoplasm of endometrium |
| **C64.1-C64.9** | Malignant neoplasm of kidney, except renal pelvis |
| **C74.00-C74.02** | Malignant neoplasm of cortex of adrenal gland |
| **C77.0-C79.9** | Secondary malignant neoplasms |
| **C78.00-C78.02** | Secondary malignant neoplasm of lung |
| **C78.6** | Secondary malignant neoplasm of retroperitoneum and peritoneum |
| **C78.7** | Secondary malignant neoplasm of liver and intrahepatic bile duct |
| **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 |
| **D09.0-D09.19** | Carcinoma in situ of bladder and urinary organs |
| **D37.8-D37.9** | Neoplasm of uncertain behavior of other specified digestive organs |
| **Z85.00-Z85.59** | Personal history of malignant neoplasms |
| **Z85.71** | Personal history of Hodgkin lymphoma |
| **Z85.810-Z85.9** | Personal history of malignant neoplasms |

## Document History

Revised: 12/13/2021
Document History:

- 12/13/2021 – Select Review: Update criteria to add FDA approval use in adjuvant treatment in Renal Cell Carcinoma at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. Also update FDA approved use in melanoma as adjuvant treatment in those with Stage IIB, IIC or III melanoma following complete resection (and not only stage III). Coding Reviewed: Added ICD-10-CM C43.0-C43.8.
- 11/19/2021 – Select Review: Update criteria to add use with paclitaxel and a platinum agent, with or without bevacizumab, in individuals with cervical cancer. No changes. Coding reviewed: No changes.
- 09/13/2021 – Select Review: Update criteria to remove requirement of cisplatin ineligibility and CPS expression in locally advanced or metastatic urothelial carcinoma per label. Coding reviewed: No changes.
- 08/20/2021 – Select Review: Update criteria for cSCC to include use in locally advanced disease. Update criteria to add use in TNBC in the neoadjuvant/adjuvant setting. Coding reviewed: No changes.
- 06/14/2021 – Select Review: Update criteria to add first line use in combination with lenvatinib for renal cell carcinoma per guidelines. Wording and formatting updates. Coding Review: No changes.
- 05/21/2021 – Annual Review: Update criteria to add use in adrenocortical carcinoma as single agent or with mitotane per guidelines. Update criteria for esophageal cancer for combination use with platinum and fluoropyrimidine-based chemotherapy per label. Add criteria for use in HER2 positive gastric and gastroesophageal junction cancer in

combination with trastuzumab, platinum agent, and fluoropyrimidine chemotherapy per label. Add criteria for brain metastases from melanoma or NSCLC per NCCN. Remove indication for SCLC per FDA withdrawal. Update use in urothelial carcinoma for subsequent therapy per NCCN. Update criteria to add use in soft tissue sarcoma per guidelines. Update NSCLC criteria to specify any actionable molecular marker with a note to further expand on definition and marker testing per NCCN. Clarify use in advanced and recurrent NSCLC disease per NCCN. Update criteria to allow use in thymic carcinomas for intolerance to first line regimens per NCCN. Coding Reviewed: Added ICD-10-CM C49.9, C74.00-C74.02.

- 12/14/2020 – Select Review: Update criteria to add new indication for triple-negative breast cancer per FDA label. Update criteria to remove restriction for interstitial lung disease for consistency. Coding Reviewed: Added ICD-10-CM C50.01-C50.919.
- 08/21/2020 – Select Review: Update criteria to add new indications for solid tumors with high tumor mutational burden, cutaneous squamous cell carcinoma, and first line therapy for dMMR/MSIH colorectal cancer per FDA label. Wording and formatting updates. Coding Reviewed: Added ICD-10-CM-C17.0-C17.9, C18.0-C18.9, C19, C20, C21.0-C21.8, C78.00-C78.02, C78.6, C78.7, C64.1-C64.9.
- 05/15/2020 – Annual Review: Add new criteria for thymic carcinoma per NCCN 2A. Update criteria to add ROS1 and BRAF mutations for NSCLC per NCCN. Coding Reviewed: Added ICD-10-Dx: C37
- 02/21/2020 – Select Review: Add new criteria per label for use of Keytruda in high risk non-muscle invasive (T1, high grade Ta, and/or carcinoma in situ [CIS]) Urothelial Carcinoma of the Bladder with or without papillary tumors. Clarify use in urothelial carcinoma as ineligible for any platinum-containing chemotherapy OR ineligible for cisplatin-containing chemotherapy with PD-L1 tumor testing. Wording and formatting changes. Coding Reviewed: Added ICD-10-CM D09.0-D09.19
- 11/15/2019 – Select Review: Add new criteria for use of Keytruda in endometrial cancer. Coding reviewed: Added ICD-10 C54.1
- 08/16/2019 – Select Review: Add new criteria for use in recurrent locally advanced or metastatic squamous cell esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 10], with disease progression after one or more prior lines of systemic therapy. Update HNSCC criteria to reflect FDA expansion for Keytruda as first-line monotherapy with CPS of 1% or greater, and first line in combination with platinum/FU regardless of PD-L1 expression. Update SCLC criteria to reflect new FDA indication for use as subsequent therapy. For consistency, wording update to restrict use in those with prior use of anti-PD-1/PD-L1 agents. Coding reviewed: Added ICD-10 C15.3-C15.5, C15.8, C15.9, C16.0, D37.8, D37.9 for esophageal cancer per FDA label. Remove duplicate codes ICD-10 C64.1-C64.9.
- 06/10/2019 – Select Review: Add new criteria for FDA update for use of Keytruda 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.

## References


1. American Cancer Society. Cancer facts & figures. Atlanta: American Cancer Society; Updated periodically. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf.
2. American Cancer Society. Key statistics for bladder cancer. Revised on January 5, 2017. Available at: https://www.cancer.org/cancer/bladder-cancer/about/key-statistics.html. Accessed on April 17, 2019.
3. Burtness B, Harrington KJ, Greil R, et al. KEYNOTE-048: phase III study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Presented at: the ESMO 2018 Congress;Munich, Germany: October 19-23, 2018. Abstract LBA8_PR. Available at: https://www.esmo.org/Press-Office/Press-Releases/KEYNOTE048-head-neck-cancer-immunotherapy-Burtness.
4. Burtness B, Harrington KJ, Greil R, et al; KEYNOTE-048 Investigators. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet.* 2019 Nov 23;394(10212):1915-1928. doi: 10.1016/S0140-6736(19)32591-7. Epub 2019 Nov 1. Erratum in: *Lancet.* 2020 Jan 25;395(10220):272. *Lancet.* 2020 Feb 22;395(10224):564.
5. Carlino MS, Menzies AM, Atkinson V, et al. Long-term Follow-up of Standard-Dose Pembrolizumab Plus Reduced-Dose Ipilimumab in Patients with Advanced Melanoma: KEYNOTE-029 Part 1B. *Clin Cancer Res*. 2020;26(19):5086-5091. doi:10.1158/1078-0432.CCR-20-0177 Available at: https://clincancerres.aacrjournals.org/content/26/19/5086.
6. Cho J, Kim HS, Ku BM, et al. Pembrolizumab for patients with refractory or relapsed thymic epithelial tumor: An open label phase II trial. J. Clin Oncol 2019; 37:2162-2170.
7. Chung HC, Lopez-Martin JA, Chuan-Hao-Kao S, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158 [abstract]. J Clin Oncol 2018;36(15):8506.
8. Chung HC, Schellens JH, Delord J-P, et al. Pembrolizumab treatment of advanced cervical cancer: updated results from the phase 2 KEYNOTE-158 study [abstract]. *J Clin Oncol.* 2018; 36. https://meetinglibrary.asco.org/record/160523/abstract.
9. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2020. URL: http://www.clinicalpharmacology.com. Updated periodically.
10. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: October 14, 2021.
11. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
12. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;378(22):2078-2092. doi:10.1056/NEJMoa1801005 Available at: https://www.nejm.org/doi/pdf/10.1056/NEJMoa1801005.

13. Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. Lancet Oncol 2018; 19:347-355.
14. Habra MA, Stephen B, Cambpell M, et al. Phase II clinical trial of pembrolizumab efficacy and safety in advanced adrenocortical carcinoma. J Immunother Cancer 2019;7:253.
15. Khodadoust MS, Rook AH, Porcu P, et al. Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sézary Syndrome: A Multicenter Phase II Study. *J Clin Oncol.* 2020 Jan 1; 38(1): 20-28.
16. Le DT, Durham JN, Smith KN, et al. Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017; 357(6349):409-413.
17. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015; 372(26):2509-2520.
18. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2020; Updated periodically.
19. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21(10):1353-1365. doi:10.1016/S1470-2045(20)30445-9.
20. National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/types/alphalist. Accessed on April 20, 2020.
21. NCCN Clinical Practice Guidelines in Oncology™. © 2021 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on October 14, 2021.
    a. Anal Carcinoma V1.2021. Revised February 16, 2021.
    b. B-Cell Lymphomas V3.2021. Revised March 16, 2021.
    c. Bladder Cancer V2.2021. Revised March 22, 2021.
    d. Bone Cancer V1.2021. Revised November 20, 2020.
    e. Breast Cancer V3.2021. Revised March 29, 2021.
    f. Central Nervous System Cancers V4.2020. Revised March 22, 2021.
    g. Cervical Cancer. V1.2021. Revised October 2, 2020.
    h. Colon Cancer V2.2021. Revised January 21, 2021.
    i. Cutaneous Melanoma V2.2021. Revised February 19, 2021.
    j. Esophageal and Esophagogastric Junction Cancers. V2.2021. Revised March 9, 2021.
    k. Gastric Cancer V2.2021. Revised March 9, 2021.
    l. Gestational Trophoblastic Neoplasia V2.2021. Revised March 31, 2021.
    m. Head and Neck Cancer V2.2021. Revised March 26, 2021.
    n. Hepatobiliary Cancers V1.2021. Revised March 5, 2021.
    o. Hodgkin Lymphoma V3.2021. Revised March 12, 2021.
    p. Kidney Cancer V4.2021. Revised April 19, 2021.
    q. Malignant Pleural Mesothelioma V2.2021. Revised February 16, 2021.
    r. Merkel Cell Carcinoma V1.2020. Revised October 2, 2019.
    s. Neuroendocrine and Adrenal Tumors V2.2020. Revised July 24, 2020.
    t. Non-Small Cell Lung Cancer. V4.2021. Revised March 3, 2021.
    u. Occult Primary. V2.2021. Revised February 8, 2021.
    v. Ovarian Cancer V1.2021. Revised February 26, 2021.
    w. Pancreatic Adenocarcinoma V2.2021. February 25, 2021.
    x. Pediatric Hodgkin Lymphoma. V3.2021. March 18, 2021.
    y. Penile Cancer V1.2021. Revised January 13, 2021.
    z. Primary Cutaneous Lymphomas. V2.2021. Revised March 4, 2021.
    aa. Prostate Cancer. V2.2021. Revised February 17, 2021.
    bb. Rectal Cancer V1.2021. Revised December 22, 2020.
    cc. Small Bowel Adenocarcinoma V1.2021. Revised February 16, 2021.
    dd. Small Cell Lung Cancer. V3.2021. Revised March 23, 2021.
    ee. Soft Tissue Sarcoma. V1.2021. Revised October 30, 2020.
    ff. Squamous Cell Skin Cancer. V1.2021. Revised February 5, 2021.
    gg. T-Cell Lymphomas V1.2021. Revised October 5, 2020.
    hh. Testicular cancer V1.2021. Revised November 5, 2020.
    ii. Thyroid Carcinoma. V3.2020. Revised February 2, 2021.
    jj. Thymomas and Thymic Carcinomas V1.2021. Revised December 4, 2020.
    kk. Uterine Neoplasms V1.2021. Revised October 20, 2020.
    ll. Uveal Melanoma V3.2020. Revised January 15, 2021.
    mm. Vulvar Cancer (Squamous Cell Carcinoma) V2.2021. Revised October 19, 2020.
22. NCT02625961. ClinicalTrials.gov. U.S. National Library of Medicine. Available at https://clinicaltrials.gov/ct2/show/NCT02625961?term=nct02625961&draw=2&rank=1.
23. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer; results from the phase Ib KEYNOTE-028 study. J Clin Oncol 2017;35:3823-9.
24. Ott PA, Pha-Paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. Am Oncol. 2017; 28(5):1036-1041.
25. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;379(21):2040-2051. doi:10.1056/NEJMoa1810865 Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1810865.
26. Raj N, Zheng Y, Kelly V, et al. PD-1 blockade in advanced adrenocortical carcinoma. J Clin Oncol 2020;38:71-80.
27. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Eng J Med. 2016; 375(19):1823-1833.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.