Medical Drug Clinical Criteria

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Overview

This document addresses the use of Opdivo, a programmed death receptor-1 (PD-1) blocking monoclonal antibody.

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

Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

According to the ACS, there will be an estimated 95,520 new cases of colon cancer and 39,910 new cases of rectal cancer diagnosed in 2017. It is expected that 50,620 persons will die from colon and rectal cancer combined in 2017.

Opdivo, as a single agent, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based chemotherapy.

Opdivo, in combination with ipilimumab, is indicated for the treatment of adults and pediatric patients 12 years and older with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

Esophageal Squamous Cell Carcinoma (ESCC)

Esophageal cancers can be classified as squamous cell carcinoma (SCC) or adenocarcinoma. Unlike adenocarcinoma, SCC is usually localized near the tracheal bifurcation, and associated with poorer prognosis.

Opdivo is indicated for treatment of unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior therapy with a fluoropyrimidine- and platinum-based regimen.

FDA has approved both Opdivo (nivolumab) in combination with fluoropyrimidine- and platinum-containing chemotherapy and Opdivo plus Yervoy (ipilimumab) as a first-line treatment for adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) regardless of PD-L1 status.

Esophageal and Gastroesophageal Junction Cancer

Opdivo is indicated for use in patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

Opdivo is indicated for use in advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

NCCN compendia also provides a NCCN 1 recommendation for use as primary treatment in those with surgically unresectable locoregional HER2 negative disease in combination with oxaliplatin and fluorouracil or capecitabine.

Opdivo (nivolumab) is recommended as primary treatment for medically fit patients with surgically unresectable locoregional HER2 overexpression negative disease in combination with Oxaliplatin and fluorouracil or capecitabine (PD-L1 CPS≥5).
Squamous Cell Carcinoma of the Head and Neck

Head and neck cancers account for nearly 3 percent (approximately 62,000 cases) of all cancers in the US, and an estimated 13,000 deaths, with nearly 90% form the squamous cell variety.

Opdivo is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

Hepatocellular Carcinoma (HCC)

HCC is the most common form of liver cancer with about 40,710 new cases of liver and intrahepatic bile duct cancer diagnosed in 2017 and nearly 28,920 deaths from the disease annually in the US.

Opdivo is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib, or as subsequent therapy (NCCN 2A).

Classical Hodgkin Lymphoma

Hodgkin lymphoma is a type of malignancy which starts in the lymphocytes. Hodgkin lymphoma most commonly affects people between the ages of 15 and 40 and people older than age 55. In developed countries, classical Hodgkin lymphoma accounts for approximately 95% of all Hodgkin disease (ACS, 2017).

Opdivo is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- 3 or more lines of systemic therapy that includes autologous HSCT.

As a single agent or in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma.

Malignant Pleural and Peritoneal Mesothelioma

Opdivo in combination with ipilimumab is FDA approved for use as first line therapy for unresectable malignant pleural mesothelioma (MPM), a highly aggressive cancer with poor prognosis and limited treatment options.

NCCN compendia also includes a category 2A recommendation for off-label use of nivolumab as monotherapy or in combination with Yervoy (ipilimumab) in the treatment of malignant pleural and peritoneal mesothelioma (MPM) as subsequent therapy.

Metastatic Melanoma with Brain Metastases

The NCCN Compendia and Clinical Practice Guideline (CPG) for central nervous system cancers offers a category 2A recommendation for nivolumab in combination with Yervoy (ipilimumab) in the treatment of asymptomatic patients with newly diagnosed or recurrent brain metastases secondary to melanoma and stable systemic disease or reasonable systemic treatment options (Long 2017, 2018, Tawbi 2017).

Adjuvant Treatment of Melanoma

The FDA has approved nivolumab (Opdivo) for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

The FDA approved nivolumab for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected stage IIB or IIC, Stage III, or Stage IV melanoma.

Cutaneous Melanoma

The NCCN Compendia and Clinical Practice Guideline (CPG) in cutaneous melanoma offers NCCN recommendations for nivolumab as preferred systemic therapy, option as a single agent for initial treatment of limited resectable in Stage III disease with clinical satellite/in-transit metastases (NCCN1) or local satellite/in-transit recurrence (NCCN 2A)

Unresectable or Metastatic Melanoma

The American Cancer Society (ACS) estimated that approximately 87,110 cases of melanoma (also referred to as malignant melanoma) will be diagnosed in the United States in 2017 (ACS, 2017).

The FDA has approved nivolumab (Opdivo) in combination with ipilimumab (Yervoy) for the treatment of those with unresectable or metastatic melanoma BRAF V600 wild-type.

The FDA has approved nivolumab (Opdivo) as a single agent or in combination with ipilimumab for the treatment of those with unresectable or metastatic melanoma.

Uveal Melanoma

The NCCN panel recommendation for use of Yervoy (ipilimumab) as a single agent is based on retrospective case series that evaluated nivolumab as a treatment option of uveal melanoma. The recommendation for combination therapy is based on unpublished data from a phase II multicenter, single arm, and open-label study of nivolumab in combination with ipilimumab as first line in adults with metastatic uveal melanoma (NCT02626962).

Merkel Cell Carcinoma

NCCN Compendia and CPG includes a category 2A recommendation for off-label use of nivolumab in the treatment of disseminated disease as clinical judgment dictates; the “preliminary data from non-randomized trials in patients with MCC demonstrate that rates of durable response are improved with PD-1/PD-L1 blockage compared with cytotoxic therapy.”

Metastatic Non-Small Cell Lung Cancer

Lung cancer is the leading cause of death from cancer worldwide, with advanced NSCLC representing 85% of these cases. According to the National Cancer Institute (NCI), in 2018 an estimated 222,500 new cases of lung cancer (NSCLC and SCLC) will be diagnosed in the US, and of these approximately 155,870 deaths (70%) will occur.

Opdivo is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo.

Opdivo is also FDA indicated for use in combination with ipilimumab for recurrent, advanced, or metastatic disease as first-line therapy for tumors expressing PD-L1 ≥ 1% that are EGFR, ALK, ROS1, BRAF negative. NCCN provides an additional category 2A recommendation for tumors with PD-L1 < 1%.

Opdivo, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is FDA indicated for first line treatment of recurrent or metastatic NSCLC for patients without EGFR or ALK genomic tumor aberrations.

Opdivo, in combination with platinum-doublet chemotherapy, is FDA indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC)

NCCN panel recommends that individuals with NSCLC be tested for actionable molecular markers, such as EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations, before initiating first line therapy to help guide 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.

Metastatic NSCLC with Brain Metastases

The NCCN Compendia and Clinical Practice Guideline (CPG) for central nervous system cancers offers a category 2A recommendation for nivolumab as single agent in individuals with brain metastases secondary to NSCLC who are PD-L1 positive (Gauvain 2019, Rizvi 2015, Goldman 2016).

Advanced Renal Cell Carcinoma

According to the NCI, in 2018 approximately 63,990 new cases of RCC will be diagnosed in the US with an estimated 14,400 deaths resulting from the diagnosis. Clear-cell is among the most prevalent type of RCC.

Opdivo as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

NCCN Compendia and CPG for kidney cancer includes a category 2A recommendation for use of nivolumab in combination with ipilimumab as a subsequent therapy for the treatment of advanced clear cell RCC.

Opdivo, in combination with ipilimumab, is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC).

Opdivo, in combination with cabozantinib, is indication for the treatment of patients with advanced RCC as first line treatment.

Small Bowel Adenocarcinoma (SBA)

Small bowel cancer is relatively rare compared to other cancers of the gastrointestinal tract, accounting for about 3% of cancers in this system. Due to the rarity of SBA, historically, treatment for SBA mimicked those for colorectal cancer. In 2019, NCCN developed the first guidelines in the U.S., and the second in the world, to address small bowel adenocarcinomas.

NCCN Compendia and CPG for SBA includes a category 2A recommendation for use of nivolumab as single agent or in combination with ipilimumab as subsequent therapy for the treatment of advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only). Data was extrapolated from studies for colorectal cancer (Overman 2017, 2018).

NCCN Compendia and CPG for SBA includes a category 2A recommendation for use of nivolumab as initial therapy as a single agent or in combination with ipilimumab for advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only), if no previous treatment with a checkpoint inhibitor

Urothelial Carcinoma

Urothelial carcinoma is the most common type of bladder cancer. The ACS estimates that in 2017 there will be approximately 76,030 new cases of bladder cancer (about 60,490 in men and 18,540 in women) and 16,870 deaths from bladder cancer in the US.

Opdivo is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who:

- has disease progression during or following platinum-containing chemotherapy
- has disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Opdivo is also indication as adjuvant treatment in those who are at high risk of recurrence after undergoing radical resection of UC.

NCCN also provides a 2A recommendation for use of Opdivo in upper GU tract tumors as adjuvant therapy for pathologic stage T2-4 or nodal disease (N+) of the renal pelvis or urothelial carcinoma of the ureter may be considered if platinum-based neoadjuvant chemo given and ypT2-ypT4 or ypN+

NCCN Compendia and CPG for Bladder cancer includes a category 2A recommendation for nivolumab in bladder cancer as adjuvant therapy

Other Uses

While NCCN in 2018 also provided 2A recommendations for the use of Opdivo as a single agent for second-line or subsequent treatment of metastatic squamous cell carcinoma of the anal canal if neither nivolumab or pembrolizumab was previously received. The recommendation is based on the results of an ongoing single-arm phase 2, multi-center trial. Of the 37 enrolled participants, 2 received a complete response and 7 received partial response with overall response rate of 24% (95% CI, 15-33) (Morris 2017).

NCCN also provides 2A recommendation for Opdivo for cervical cancer for second-line or subsequent therapy as a single agent if PD-L1 positive in recurrent or metastatic disease. NCCN 2023 guidelines moved this recommendation from

preferred to useful in certain circumstances. The one study to support this use showed an objective response rate of 26.3% (95%CI, 9.1 to 51.2) for cervical cancer. At a median follow-up of 19.2 months, median DOR was not reached in the five responding patients in the cervical cohort (Naumann et al 2019).

NCCN also provides 2A recommendation for Opdivo for gestational trophoblastic neoplasia as single-agent therapy for multiagent chemotherapy-resistant high-risk, recurrent, or progressive disease. However, there is insufficient published evidence to support the use of Opdivo for such conditions. The use is extrapolated as a PD-L1 class effect due to pembrolizumab data (Ghorani E et.al. 2017).

NCCN also provides a 2A recommendation for Opdivo with or without ipilimumab for small bowel adenocarcinoma as initial therapy for advanced or metastatic disease (dMMR/MSI-H only) in patients with prior oxaliplatin exposure in the adjuvant setting. However, there is insufficient published evidence to support the use of Opdivo for such situations.

NCCN also provides a 2A recommendation for the use of Opdivo in combination with Yervoy for central nervous system cancers in the treatment of *symptomatic* patients with newly diagnosed or recurrent brain metastases secondary to melanoma and stable systemic disease or reasonable systemic treatment options. However, while the evidence for asymptomatic patients was promising, the study results for patients with symptomatic disease showed little to no intracranial response (Long 2017, 2018, Tawbi 2017).

NCCN also provides a 2A recommendation for the use of Opdivo in combination with Yervoy for NSCLC for recurrent, advanced, or metastatic disease as first-line or subsequent therapy for tumors that are EGFR, ALK, ROS1, BRAF, NTRK, MET, and RET positive. There is insufficient evidence to support its use in these situations.

NCCN also provides a 2A recommendation for use of Opdivo as monotherapy in advanced or metastatic renal cell carcinoma with non-clear cell component. However, there is insufficient evidence to support its use in such situations. Additionally, the NCCN provides a 2A recommendation for use of Opdivo with Yervoy for “favorable” risk patients with advanced renal cell carcinoma; however, the panel notes the data has been conflicting for this population.

NCCN also provides a 2A recommendation for use of Opdivo as subsequent therapy in combination with cabozantinib for relapse or stage IV disease with clear cell histology. There is a single meeting abstract of a small cohort study (Apolo 2021)

NCCN provides a 2A recommendation for use of Opdivo as monotherapy or in combination with ipilimumab for individuals with MSI-H or dMMR metastatic CRC as primary treatment for individuals who have not received any previous chemotherapy. There is insufficient evidence to support its use in this situation.

NCCN provides a 2A recommendation for use of Opdivo as single agent for individuals relapsed or refractory T-cell lymphoma following additional therapy with an alternate combination chemotherapy regimen (asparaginase-based) not previously used, if a clinical trial is not available. The recommendation was based on a case report of 3 patients (Chan 2018). Therefore, at this time, there is insufficient evidence to support its use in this situation.

NCCN provides a 2A recommendation for use of Opdivo as useful in certain circumstances as a single agent second-line treatment for recurrent, metastatic, or high-risk mismatch repair deficient (dMMR) uterine tumors. The recommendation was based on a single-arm, phase 2 trial that included patients with high-risk mismatch repair deficient (dMMR), noncolorectal tumors. Of this population, 13 patients had endometrioid endometrial adenocarcinoma and 4 patients with uterine carcinosarcoma (Azad 2020). At this time, there is insufficient evidence to support Opdivo’s use in this situation.

NCCN provides a 2A recommendation for use of Opdivo as useful in certain circumstances as single agent for second-line or subsequent treatment of HPV-related advanced, recurrent, or metastatic squamous cell vulvar cancer. This recommendation was based on a small (n=24) phase I/II trial, of which 5 had vaginal/vulvar cancer). The authors concluded that use of Opdivo is this situation is promising and warrants additional investigation (Naumann 2019).

NCCN provides a 2A recommendation for use of Opdivo for urothelial carcinoma of the prostate as primary treatment for tumors with stromal invasion as adjuvant therapy and for primary carcinoma of the urethra as adjuvant treatment considered for pathologic stage T3-4 or N1-2 disease in the bulbar urethra. Both of these recommendations had no references or trial data.

NCCN provides a 2A recommendation for use of Opdivo for use in cancer of the nasopharynx as first-line systemic therapy or subsequent therapy in combination with cisplatin and gemcitabine for T1-4, N0-3, M1 disease. There are currently no studies or references for this use. The recommendation is extrapolated from two studies of two non-FDA approved PD-1 inhibitors.

NCCN provides a 2A recommendation for use of Opdivo in combination with cetuximab is recommended in non-nasopharyngeal, advanced head and neck cancer for resectable locoregional recurrence or persistent disease without prior radiation therapy. The Chung 2022 trial is an open-label, single-arm, phase 2 study to support this use. The OS was 11.4 months in the group with prior treatment and 20.2 months in the group with no prior treatment.

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.
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

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.

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.

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.

Primary treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.

Programmed death (PD)-1 proteins: 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. However, this can also prevent T-cells from attacking cancer cells in the body. Examples of FDA approved anti-PD-1 agents 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 anti-PD-L1 agents include Bavencio (avelumab), Tecentriq (atezolizumab), and Imfinzi (durvalumab).

Progression free survival (PFS): The length of time during and after treatment that an individual lives but does not get worse (usually measured by the size of a tumor or amount of cancer in the body).

Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.

Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus).

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Small bowel adenocarcinoma: Cancer originating in the small intestine (i.e., duodenum, jejunum, and ileum).

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.

Opdivo (nivolumab)

Requests for Opdivo (nivolumab) may be approved if the following criteria are met:

I. Individual is using for the treatment of Bone cancer, including osteosarcoma, Ewing Sarcoma, chondrosarcoma, and chordoma; **AND**
   A. Individual is using in combination with ipilimumab for unresectable or metastatic disease; **AND**
   B. Individual has failed and progression on prior treatment; **AND**
   C. Individual has no satisfactory alternative treatment options for tissue tumor mutation burden-high (TMB-H) tumors with 10 or more mutations per megabase;

OR

II. Individual has a diagnosis of Colorectal Cancer, including advanced Appendiceal Adenocarcinoma (Label, NCCN 2A); **AND**
   A. Individual meets one of the following criteria:
      1. Individual is using as monotherapy or in combination with ipilimumab in primary treatment for unresectable metachronous metastases (defective 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. Individual is using as monotherapy or in combination with ipilimumab as subsequent therapy for unresectable advanced or metastatic disease (defective mismatch repair/ high microsatellite instability [dMMR/MSIH] only) following previous treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan- based chemotherapy (Label, NCCN 2A);

   AND
   B. Individual has not received 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

III. Individual has a diagnosis of unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) (Label); AND
   A. Individual is using in one of the following ways:
      1. In combination with ipilmumab (Yervoy); OR
      2. In combination with fluoropyrimidine- and platinum-containing chemotherapy; AND
   B. Individual is using as first-line treatment; AND
   C. Individual has a current ECOG performance status of 0-1; AND
   D. Individual has not received prior treatment with anti-PD-1, anti-PD-L1, any antibody or drug specifically targeting T-cell co-stimulation, or checkpoint pathways; 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 unresectable locally advanced, recurrent, or metastatic Esophageal Squamous Cell Carcinoma (ESCC) (Label, NCCN 1); **AND**
   A. Individual is using as single agent for second line or subsequent therapy; **AND**
   B. Individual has confirmation of disease progression on or had intolerance to fluoropyrimidine- and platinum-based chemotherapy; **AND**
   C. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
   D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **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 completely resected Esophageal or Gastroesophageal Junction Cancer (Label, NCCN 1); **AND**
   A. Individual is using as single agent for residual pathologic disease; **AND**
   B. Individual has received neoadjuvant chemoradiotherapy (CRT); **AND**
   C. Individual has a current ECOG performance status of 0-2; **AND**
   D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **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 advanced or metastatic Gastric, Gastroesophageal Junction Cancer, or Esophageal Adenocarcinoma (Label, NCCN 1, 2A); **AND**
   A. Individual is using in combination with fluoropyrimidine and platinum-containing chemotherapy; **AND**
   B. Individual has HER2 negative disease; **AND**
   C. Individual has a current ECOG performance status of 0-2; **AND**
   D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or other checkpoint inhibitor; **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 advanced Hepatocellular Carcinoma and the following criteria are met (Label, NCCN 2A):
- A. Individual is using in combination with ipilimumab for subsequent therapy; **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-1 agent; **AND**
- D. 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 Hodgkin Lymphoma and the following criteria are met (Label, NCCN 2A):
- A. Individual is using for relapsed or refractory Hodgkin lymphoma except for those with lymphocyte-predominant Hodgkin lymphoma;

OR

IX. Individual has a diagnosis of relapsed/refractory advanced classic Kaposi Sarcoma and the following criteria are met (NCCN 2A):
- A. Individual is using in combination with ipilimumab (Yervoy); **AND**
- B. Individual is using as subsequent systemic therapy;

OR

X. Individual has a diagnosis of unresectable Malignant Pleural or Peritoneal Mesothelioma and using as first line therapy (Label, NCCN 2A); **AND**
- A. Individual is using in combination with ipilimumab (Yervoy); **AND**
- B. Individual has a ECOG performance status of 0-2; **AND**
- C. 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

XI. Individual has a diagnosis of Malignant Pleural or Peritoneal Mesothelioma (NCCN 2A); **AND**
- A. Individual is using as a single agent, or in combination with ipilimumab (Yervoy) for subsequent therapy; **AND**
- B. Individual has a ECOG performance status of 0-2; **AND**
- C. 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

XII. Individual has a diagnosis of Melanoma (Cutaneous or Uveal) and the following criteria are met (Label):
- A. Individual has unresectable or metastatic melanoma;
  AND
  1. Individual is using as a single agent, or in combination with ipilimumab;
  2. Current ECOG performance status of 0-2; **AND**
  3. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
  4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

  OR
- B. Individual has resected advanced melanoma (Label, NCCN 2A); **AND**
  1. Individual is using as a single agent for ~~up to 12 months of~~ adjuvant therapy; **AND**
  2. Individual has resected stage II~~I~~B, stage II~~I~~C, stage III, or stage IV disease; **AND**
  3. Current ECOG performance status of 0-2; **AND**
  4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
  5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

  OR
- C. Individual has Melanoma (Cutaneous or Uveal) (Label); **AND**
  1. One of the following:
     a. Individual has melanoma with involvement of lymph nodes; **OR**
     b. Individual has metastatic melanoma and has undergone complete resection;

  AND
  2. Individual is using as a single agent for adjuvant therapy;

OR

XIII. Individual has a diagnosis of metastatic Melanoma with brain metastases and the following criteria are met (NCCN 2A):
- A. Individual has a primary diagnosis of melanoma; **AND**
- B. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017); **AND**
- C. Individual is using as monotherapy or in combination with ipilimumab; **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

XIV. Individual has a diagnosis of Merkel Cell Carcinoma and the following criteria are met (Label, NCCN 2A):
- A. Individual is using as a single agent; **AND**
- B. Individual has presence of metastatic or recurrent locoregional MCC determined to be not amenable to definitive surgery or radiation therapy; **AND**
- C. Current ECOG performance status of 0-2; **AND**
- D. 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

XV. Individual has a diagnosis of Non-Small Cell Lung Cancer (NSCLC) and the following criteria are met (Label, NCCN 2A):
- A. Individual has metastatic NSCLC; **AND**
  1. Individual is using as a single agent; **AND**
  2. Confirmation of disease progression on or after platinum-containing chemotherapy; **AND**
  3. Current ECOG performance status of 0-2; **AND**
  4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
  5. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

- B. Individual has recurrent, advanced, or metastatic NSCLC and using as first-line therapy (Label, NCCN 1, 2A); **AND**
  1. Individual is using in combination with ipilimumab; **AND**
  2. Individual does not have presence of actionable molecular markers*; **AND**
  3. Individual has PD-L1 expression positive (≥1%) tumor; **AND**
  4. Current ECOG performance status of 0-2; **AND**
  5. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
  6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

- C. Individual has recurrent, advanced, or metastatic NSCLC and using as first-line therapy (Label, NCCN 1, 2A); **AND**
  1. Individual is using in combination with ipilimumab *and* 2 (two) cycles of platinum-doublet chemotherapy (i.e., platinum-based chemotherapy with pemetrexed, or carboplatin with paclitaxel); **AND**
  2. Individual does not have presence of actionable molecular markers*; **AND**
  3. Current ECOG performance status of 0-2; **AND**
  4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
  5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

- D. Individual is using for continuation treatment of recurrent, advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) (NCCN 1, 2A); **AND**
  1. Individual is using in combination with ipilimumab (Yervoy); **AND**
  2. Individual achieved a response or has stable disease following first line therapy of nivolumab + ipilimumab +/- chemotherapy given; **AND**
  3. Individual does not have presence of actionable molecular markers*; **AND**
  4. Current ECOG performance status of 0-2; **AND**
  5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

E. Individual has resectable NSCLC and using as neoadjuvant therapy (Label, NCCN 2A); **AND**
   1. Individual is using in combination with platinum-doublet chemotherapy (e.g. paclitaxel and carboplatin); **AND**
   2. Resectable is defined as tumors ≥ 4 cm or node positive; **AND**
   3. Current ECOG performance status of 0-2; **AND**
   4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XVI. Individual has a diagnosis of metastatic NSCLC with brain metastases and the following criteria are met (NCCN 2A):
   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 PD-L1 expression positive (≥ 1%) tumors; **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

XVII. Individual has a diagnosis of Renal Cell Carcinoma (RCC) (Label, NCCN 2A); **AND**
   A. Individual has advanced or metastatic RCC ; **AND**
      1. Individual is using as monotherapy; **AND**
      2. Histological confirmation of RCC with clear-cell component; **AND**
      3. Individual has confirmation of disease progression after one or two prior anti-angiogenic regimens (e.g. axitinib, bevacizumab [or bevacizumab biosimilar], pazopanib, sorafenib, sunitinib, etc.) for treatment of advanced or metastatic disease; **AND**
      4. Current ECOG performance status of 0-2; **AND**
      5. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
      6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

   OR

   B. Individual has intermediate - or poor-risk, advanced RCC; **AND**
      1. Individual is using in combination with ipilimumab for four cycles followed by single agent Opdivo (nivolumab), as first-line therapy for previously untreated RCC; **OR**
      2. Individual is using in combination with ipilimumab for four cycles followed by single agent Opdivo (nivolumab), as subsequent therapy, if no checkpoint blockade (PD-1, PD-L1, or CTLA-4) antibody treatment has been previously administered (NCCN 2A); **AND**
      3. Histological confirmation of RCC with clear-cell component; **AND**
      4. Current ECOG performance status of 0-2; **AND**
      5. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
      6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

   OR

   C. Individual has relapsed, recurrent, or advanced RCC (Label, NCCN 2A); **AND**
      1. Individual is using as first-line therapy in combination with cabozantinib tablets; **AND**
      2. Current ECOG performance status of 0-2; **AND**
      3. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
      4. 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 Small Bowel Adenocarcinoma (SBA) and meets the following criteria (NCCN 2A):
   A. Individual has advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only); **AND**
   B. Individual is using as monotherapy or in combination with ipilimumab as subsequent therapy; **AND**
   C. Current ECOG performance status of 0-2; **AND**
   D. 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

XIX. Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA)—Advanced ampullary cancer and meets the following criteria (NCCN 2A);

A. Individual has advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only); **AND**
B. Individual is using as initial or subsequent therapy as monotherapy or in combination with ipilimumab; **AND**
C. Current ECOG performance status of 0-2; **AND**
D. 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 Squamous Cell Carcinoma of the Head and Neck (SCCHN) and meet the following criteria:
A. Individual has recurrent, unresectable, or metastatic SCCHN; **AND**
1. Individual is using as monotherapy; **AND**
2. Individual has confirmation of disease progression on or after platinum-containing chemotherapy; **AND**
3. Current ECOG performance status of 0-2; **AND**
4. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXI. Individual has Urothelial carcinoma and meet the following criteria:
A. Individual has locally advanced or metastatic disease; **AND**
1. Individual is using as a single agent; **AND**
2. Individual meets one of the following criteria:
a. Confirmation of disease progression on or after platinum-containing chemotherapy; **OR**
b. Confirmation of disease progression within 12 months of receiving neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

OR

B. Individual is using as single agent for adjuvant therapy; **AND**
1. Individual is at high risk of recurrence after having radical resection; **AND**
C. Current ECOG performance status of 0-2; **AND**
D. 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 relapsed or refractory Primary Mediastinal Large B-Cell Lymphoma; **AND**
A. Individual is using as a single agent; **OR**
B. Individual is using in combination with brentuximab vedotin.

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET, RET, and ERBB2 (HER2) 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).

Opdivo (nivolumab) 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

J9299	Injection, Nivolumab, 1 mg [Opdivo]

ICD-10 Diagnosis

C00.0-C14.8	Malignant neoplasm of lip, oral cavity and pharynx
C15.3-C15.9	Malignant neoplasm of esophagus
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 rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0-C21.8	Malignant neoplasm of anus and anal canal
C22.0-C22.9	Malignant neoplasm of liver and intrahepatic bile ducts
C30.0-C33	Malignant neoplasm of nasal cavity, middle ear, accessory sinuses, larynx, trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C40.10-C40.82	Malignant neoplasm of bone and articular cartilage of limbs
C41.0-C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C38.4	Malignant neoplasm of pleura
C43.0-C43.9	Malignant melanoma of skin
C4A.0-C4A.9	Merkel cell carcinoma
C44.42	Squamous cell carcinoma of skin of scalp and neck
C45.0	Mesothelioma of pleura
C46.0-C46.9	Kaposi's sarcoma
C61	Malignant neoplasm of prostate [specified as urothelial carcinoma]
C64.1-C65.9	Malignant neoplasm of kidney, renal pelvis
C66.1-C66.9	Malignant neoplasm of ureter [specified as urothelial carcinoma]
C67.0-C67.9	Malignant neoplasm of bladder [specified as urothelial carcinoma]
C68.0	Malignant neoplasm of urethra [specified as urothelial carcinoma]
C69.30-C69.32	Malignant neoplasm of choroid
C69.40-C69.42	Malignant neoplasm of ciliary body
C76.0	Malignant neoplasm of head, face and neck
C78.00-C78.02	Secondary malignant neoplasm of lung
C79.31	Secondary malignant neoplasm of brain
C81.10-C81.99	Hodgkin lymphoma (classical)
C83.30-C83.37	Diffuse large B-cell lymphoma
D37.8-D37.9	Neoplasm of uncertain behavior of other specified digestive organs
Z85.00-Z85.01	Personal history of malignant neoplasm of unspecified digestive organ
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.51	Personal history of malignant neoplasm of bladder
Z85.528	Personal history of other malignant neoplasm of kidney
Z85.53	Personal history of malignant neoplasm of renal pelvis
Z85.71	Personal history of Hodgkin lymphoma
Z85.820	Personal history of malignant melanoma of skin
Z85.821	Personal history of Merkel cell carcinoma

Document History

Revised: 11/19/2023
Document History:

- 11/19/2023 – Select Review: Update criteria to clarify use in resected melanoma with FDA indication for adjuvant treatment with completely resected stage IIB, Stage IIC, Stage III, or Stage IV melanoma. Also removed 1 year criteria due to FDA label updates. Coding Reviewed: No changes.
- 08/18/2023 – Select Review: Update criteria to clarify use in NSCLC in first-line therapy. Coding Reviewed: No changes.

- 05/19/2023 – Select Review: Update criteria for gastric, esophageal, and esophagogastric junction cancers to those with HER2 negative disease only. Coding Reviewed: No changes.
- 03/13/2023- Select Review: Update criteria for melanoma due to FDA label updates. Coding Reviewed: No changes.
- 02/24/2023 – Annual Review: Update with NCCN 2A recommendations for use in bone cancer, Kaposi sarcoma, Primary Mediastinal Large B-cell lymphoma, and update existing criteria with NCCN 2A updates for adding advanced appendiceal adenocarcinoma to the colorectal cancer criteria. Additionally updated existing NSCLC criteria for use in first-line treatment by adding advanced to recurrent or metastatic disease. Also added continuation maintenance therapy criteria after first-line therapy A. Coding Reviewed: Added ICD-10-CM C40.10-C40.82, C41.0-C41.9, C46.0-C46.9, C83.30-C83.37.
- 06/13/2022 – Select Review: Update with FDA approval for use in unresectable advanced or metastatic esophageal squamous cell carcinoma. Coding Reviewed: Added C44.42.
- 03/14/2022 – Select Review: Update with new FDA indication for Opdivo's use in combination with platinum-doublet chemotherapy, for neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC). Coding Reviewed: No changes.
- 02/25/2022 – Annual Review: Add NCCN 2A recommendation for use in Small Bowel Adenocarcinoma in advanced ampullary cancer. Update Malignant Pleural Mesothelioma to include Malignant Peritoneal Mesothelioma. Clarify criteria language for "intermediate" vs Immediate advanced RCC. Updated references. Coding Reviewed: No changes.
- 09/13/2021 – Select Review: Update criteria to remove use as monotherapy in hepatocellular carcinoma per FDA withdrawal. Update criteria to add new indication as adjuvant therapy after radical resection for urothelial carcinoma per label. Coding reviewed: No changes.
- 06/14/2021 – Select Review: Update criteria to add new indication for completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease per label. Coding Reviewed: No changes.
- 05/21/2021 – Select Review: Update criteria to add new indication for advanced or metastatic gastric, gastroesophageal junction cancer, or esophageal adenocarcinoma per label. Coding Reviewed: No changes.
- 03/15/2021 – Select Review: Update renal cell carcinoma criteria to allow use with cabozantinib as first line therapy per label. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: Update hepatocellular criteria to allow use as subsequent therapy in general per guidelines. Update NSCLC criteria to specify any actionable molecular marker with a note to further expand on definition and marker testing. Update criteria to add indication for NSCLC with brain metastases. Remove indication for small cell lung cancer per label and NCCN recommendation downgrade. Wording, formatting, and reference updates. Coding Reviewed: No changes.
- 11/20/2020 – Select Review: Update criteria to add indication for first line treatment with ipilimumab in unresectable malignant pleural mesothelioma per label. Clarify use as subsequent therapy in malignant pleural mesothelioma. Coding Reviewed: No changes.
- 08/21/2020 – Select Review: Update criteria to add indication for esophageal squamous cell carcinoma per label. Remove indication for use with ipilimumab as first line therapy in NSCLC in those with high tumor mutational burden. Wording and formatting updates. Coding review: Added ICD-10-CM: C15.3-C15.9, C16.0, C21.0-C21.8, D37.8-D37.9, Z85.00-Z85.01.
- 06/08/2020 – Select Review: Update criteria to add first line use in combination use with ipilimumab and platinum-doublet chemotherapy for NSCLC per label. Coding Reviewed: No changes.
- 05/15/2020 – Select Review: Clarify use in NSCLC regarding mutations. Coding reviewed: No changes
- 03/16/2020 – Select Review: Update criteria to add combination use with ipilimumab for hepatocellular carcinoma per FDA label. Coding reviewed: No changes.
- 02/21/2020 – Annual Review: Update criteria to add indication for metastatic melanoma with brain metastases in asymptomatic patients per NCCN 2A. Update criteria to add indication for first line therapy in combination with ipilimumab in NSCLC per NCCN 2A. Add indication for SBA as subsequent therapy per NCCN 2A. Clarify previous therapy use in colorectal cancer as subsequent therapy. Clarify use in renal cell cancer with ipilimumab as subsequent therapy. Add notation in criteria for interchangeability with bevacizumab biosimilar for renal cell cancer indication. Wording and formatting changes for non-approvable criteria for conciseness. Coding Reviewed: No changes
- 08/16/2019 – Select Review: Update criteria to restrict use in those with prior anti- PD-1/PD-L1 agents for consistency. Update renal cell criteria to notate single agent use after 4 cycles of combination therapy with ipilimumab per FDA label. Coding Reviewed: No changes.
- 05/17/2019 – Annual Review: Initial review of Opdivo (nivolumab). Update Opdivo criteria for NCCN 2A recommendation use in combination with Yervoy (ipilimumab) for malignant pleural mesothelioma. Coding reviewed. No changes.

References

1. Apolo AB, da Motta Girardi D, Niglio SA, et al. Final results from a phase I trial and expansion cohorts of cabozantinib and nivolumab (CaboNivo) alone or with ipilimumab (CaboNivoIpi) for metastatic genitourinary tumors. ASCO; 2021. Available at: https://meetinglibrary.asco.org/record/194730/abstract.

2. Azad NS, Gray RJ, Overman MJ, et al. Nivolumab Is Effective in Mismatch Repair-Deficient Noncolorectal Cancers: Results From Arm Z1D-A Subprotocol of the NCI-MATCH (EAY131) Study. *J Clin Oncol*. 2020;38(3):214-222. doi:10.1200/JCO.19.00818 Available at: https://ascopubs.org/doi/10.1200/JCO.19.00818.
3. Chan TSY, Li J, Loong F, Khong PL, Tse E, Kwong YL. PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety. *Ann Hematol*. 2018;97(1):193-196. doi:10.1007/s00277-017-3127-2.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: http://www.clinicalpharmacology.com. Updated periodically.
5. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
6. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
7. Gauvain C, Vauléon E, Chouaid C, et al. Intracerebral efficacy and tolerance of nivolumab in non-small-cell lung cancer patients with brain metastases [published correction appears in Lung Cancer. 2019 Oct;136:159]. Lung Cancer. 2018;116:62-66. doi:10.1016/j.lungcan.
8. Ghorani E, Kaur B, Fisher RA, et al. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. Lancet 2017;390:2343- 2345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29185430.
9. Goldman JW, Crino L, Vokes EE, et al. Nivolumab (nivo) in patients (pts) with advanced (adv) NSCLC and central nervous system (CNS) metastases (mets). J Thorac Oncol. 2016;34(15):9038. Doi:10.1200/JCO.2016.34.15_supple.9038. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.9038.
10. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018; 378(22):2093-2104.
11. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Eng J Med.* 2019;381:2020-31.
12. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2021; Updated periodically.
13. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicenter randomized phase 2 study. *Lancet Oncol.* 2018;19:672-81.
14. Long GV, Atkinson V, Menzies AM, et al. A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients with melanoma brain metastases: the Anti-PD1 Brain Collaboration. *J Clin Oncol.* 2017;35:9508[abstract]. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9508.
15. Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. Lancet Oncol 2017;18:446-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28223062.
16. Moehler M, Shitara K, Garrido M, et al. Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: first results of the CheckMate 649 study. [abstract]. Presented at the Oral Presentation presented at the ESMO 2020 Annual Meeting; September 19-21, 2020; Virtual Meeting. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/nivolumab-nivo-plus-chemotherapy-chemo-versus-chemo-as-first-line-1l-treatment-for-advanced-gastric-cancer-gastroesophageal-junction-cancer.
17. Naumann RW, Hollebecque A, Meyer T, et al. Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results From the Phase I/II CheckMate 358 Trial. *J Clin Oncol*. 2019;37(31):2825-2834. doi:10.1200/JCO.19.00739 Available at: https://ascopubs.org/doi/full/10.1200/JCO.19.00739.
18. NCCN Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. January 24, 2023
    a. Ampullary Adenocarcinoma. V2.2022. Revised December 6, 2022.
    b. Anal Carcinoma V1.2023. Revised January 9, 2023.
    c. B-Cell Lymphomas. V5.2022. Revised July 12, 2022.
    d. Bladder Cancer V3.2022. Revised December 21, 2022.
    e. Bone Cancer. V2.2023. Revised September 28, 2022.
    f. Central Nervous System Cancers V2.2022. Revised September 29, 2022.
    g. Cervical Cancer. V1.2023. Revised January 6, 2023.
    h. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V1.2023. Revised August 30, 2022.
    i. Colon Cancer V2.2022. Revised October 27, 2022.
    j. Cutaneous Melanoma. V1.2023. December 22, 2022.
    k. Esophageal and Esophagogastric Junction Cancers. V5.2022. Revised December 5, 2022.
    l. Gastric Cancer. V2.2022. Revised January 11, 2022.
    m. Gestational Trophoblastic Neoplastic. V1.2023. Revised December 20, 2022.
    n. Head and Neck Cancer V1.2023. Revised December 20, 2022.
    o. Hepatobiliary Cancers V5.2022. Revised January 13, 2023.
    p. Hodgkin Lymphoma V2.2023. Revised November 8, 2022.
    q. Kaposi Sarcoma. V1.2023. Revised December 20, 2022.
    r. Kidney Cancer. V4.2023. Revised January 18, 2023.
    s. Merkel Cell Carcinoma. V2.2022. Revised March 24, 2022.
    t. Malignant Pleural Mesothelioma V1.2023. Revised December 15, 2022.
    u. Malignant Peritoneal Mesothelioma. V1.2023. Revised December 15, 2022.
    v. Cutaneous Melanoma V1.2022. Revised December 3, 2021.

w. Neuroendocrine and Adrenal Tumors. V2.2022. Revised December 21, 2022.
x. Non-Small Cell Lung Cancer. V1.2023. Revised December 22, 2022.
y. Pediatric Aggressive Mature B-Cell Lymphomas. V3.2022. Revised October 19, 2022.
z. Pediatric Central Nervous System Cancers. V2.2023. Revised October 31, 2022.
aa. Pediatric Hodgkin Lymphoma. V1.2023. Revised January 12, 2023.
bb. Rectal Cancer V3.2022. Revised October 27, 2022.
cc. Small Bowel Adenocarcinoma V1.2023. Revised January 9, 2023.
dd. Small Cell Lung Cancer. V3.2023. Revised December 21, 2022.
ee. T-Cell Lymphomas. V1.2023. Revised January 5, 2023.
ff. Uterine Neoplasms. V1.2023. Revised December 22, 2022.
gg. Uveal Melanoma V2.2022. Revised April 5, 2022.
hh. Vulvar Cancer (Squamous Cell Carcinoma). V1.2023. Revised December 22, 2022.

19. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol.* 2018;36:773-9. Available at: https://ascopubs.org/doi/pdf/10.1200/JCO.2017.76.9901.
20. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicenter, phase 2 study. *Lancet Oncol.* 2017;18:1182-91.
21. Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015;16(3):257-265. doi:10.1016/S1470-2045(15)70054-9 Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)70054-9/fulltext.
22. Tawbi HA, Forsyth AJ, Algazi AP, et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: results of the phase II study CheckMate 204. *J Clin Oncol.* 2017;35:9507-9507[abstract]. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9507.

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.