Medical Drug Clinical Criteria

Subject:	Opdivo (nivolumab)		
Document #:	CC-0125	**Publish Date:**	04/01/2025
Status:	Revised	**Last Review Date:**	02/21/2025

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Overview

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

Note, the subcutaneous Opdivo Qvantig formulation may be substituted for intravenous nivolumab (Opdivo). However, Opdivo Qvantig is not indicated in combination with intravenous ipilimumab (Yervoy).

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

Ampullary Adenocarcinoma
The NCCN Compendia and Clinical Practice Guideline (CPG) provide 2A recommendations as first-line therapy in combination with ipilimumab (useful in certain circumstances) in patients with intestinal type disease if microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) for metastatic disease OR as therapy for disease progression in combination with ipilimumab (useful in certain circumstances) if no prior immunotherapy and if microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

Anal Carcinoma

The NCCN Compendia and CPG provide 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).

Biliary Tract Cancers

The NCCN CPG provides a 2A recommendation in combination with Yervoy for progression on or after systemic therapy in unresectable/resected gross residual or metastatic disease that is Tumor Mutation Burden-High (TMB-H).

Central Nervous System Cancers

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).

Cervical Cancer

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).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

NCCN also provides a 2A recommendation for Opdivo for CLL/SLL as a single agent or in combination with ibrutinib for histologic (Richter) transformation to diffuse large B-cell lymphoma in those with del (17p)/TP53 mutation or who are chemotherapy refractory or unable to receive chemoimmunotherapy. The NCCN panel acknowledged that there are limited published data supporting the use of PD-1 inhibitors. Few panel members felt that monotherapy with PD-1 inhibitors is not an effective treatment option for relapsed or refractory Richter transformation.

Colorectal Cancer

The FDA indicates Opdivo, as a single agent or in combination with ipilimumab, 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 irinotecan.

NCCN also provides a 2A recommendation for use of Opdivo:

- Systemic therapy for advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) as a single agent or in combination with ipilimumab if candidate for immunotherapy and no prior immunotherapy received
- Therapy as a single agent or in combination with ipilimumab (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) (candidate for immunotherapy and no prior immunotherapy received)
- For resectable disease as neoadjuvant therapy or as initial treatment as a single agent or in combination with ipilimumab for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only or polymerase epsilon/delta [POLE/POLD1] mutation.

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.

The FDA has indicated Opdivo for the following:

- for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).
- in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
- for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

NCCN also provides multiple 1 and 2A recommendations for use in Esophageal and Esophagogastric Junction Cancers. The recommendations are for use in relieving dysphagia in those medically fit and planned for esophagectomy, as primary and maintenance treatment for MSI-H/dMMR individuals for neoadjuvant or perioperative immunotherapy, and use as palliative therapy when patients are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease as first-line therapy or second-line therapy/subsequent therapy if individual has a Karnofsky performance score ≥60% or ECOG performance score ≤2.

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

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).

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 Opdivo as preferred postoperative therapy for patients who have received preoperative chemoradiation and R0 resection and residual disease (yp T positive and/or N positive).

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).

Gestational Trophoblastic Neoplasia (GTN)

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).

Head and Neck Cancer

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.

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.

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).

Opdivo in combination with platinum-doublet chemotherapy is FDA indicated as neoadjuvant treatment, followed by single-agent nivolumab after surgery as adjuvant treatment, for adults with resectable (tumors ≥ 4 cm and/or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.

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.

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.

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.

NCCN also provides a 2A recommendation for use of Opdivo as monotherapy in advanced or metastatic renal cell carcinoma with non-clear cell component.

NCCN provides a 2A recommendation for use of Opdivo with Yervoy for “favorable” risk patients with advanced renal cell carcinoma, the NCCN 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)

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.

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.

T-cell Lymphomas

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.

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

Opdivo is also FDA indicated in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

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

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.

Uterine Sarcoma

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).

Vulvar Cancer

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).

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 has a diagnosis of Ampullary Adenocarcinoma (NCCN 2A):**AND**
   A. Using in one of the following ways:
      1. As first-line therapy for metastatic intestinal type disease; **OR**

B. For disease progression; **AND**
C. Individual has deficient mismatch repair or microsatellite instability-high [dMMR or MSI-H] disease; **AND**
D. Individual is using in combination with ipilimumab; **AND**
E. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
F. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
G. 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 Anal carcinoma (NCCN 2A); **AND**
A. Individual is using as second-line and subsequent therapy; **AND**
B. Individual is using in metastatic disease; **AND**
C. Individual is using as a single agent; **AND**
D. Individual has not received 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

III. Individual is using for the treatment of Bone cancer, including osteosarcoma, Ewing Sarcoma, chondrosarcoma, and chordoma (NCCN 2A); **AND**
A. Individual is using in combination with ipilimumab for unresectable or metastatic disease; **AND**
B. Individual has failed and progressed 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; **AND**
D. Individual has not received 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

IV. Individual has a diagnosis of Biliary Tract Cancers (NCCN 2A); **AND**
A. Individual is using in combination with ipilimumab; **AND**
B. Meets one of the following:
1. Individual is using for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease that is tumor mutational burden-high (TMB-H); **OR**
2. Individual is using as neoadjuvant systemic therapy for resectable locoregionally advanced disease and does not have jaundice;

AND

C. Individual has not received 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

V. Individual has a diagnosis of Cervical Cancer (NCCN 2A); **AND**
A. Individual is using as a single agent; **AND**
B. Individual is using for second-line or subsequent therapy; **AND**
C. Individual has CPS ≥ 1 for local/regional recurrence or stage IVB or recurrence with distant metastases; **AND**
D. Individual has not received 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

VI. Individual has a diagnosis of Colorectal Cancer, including advanced Appendiceal Adenocarcinoma (NCCN 2A); **AND**
A. Individual is using as monotherapy or in combination with ipilimumab; **AND**
B. Meets one of the following:
1. Individual has resectable disease for neoadjuvant or initial treatment (NCCN 2A); **AND**
2. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) (NCCN 2A);

OR

3. Individual has disease progression from prior treatment for advanced or metastatic disease (NCCN 2A); **AND**
4. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) (NCCN 2A);

OR

5. Individual is using as neoadjuvant therapy in clinical T4b disease (NCCN 2A); **AND**
6. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H];

AND

C. Individual has not received 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

VII. Individual has a diagnosis of Colorectal Cancer, including advanced Appendiceal Adenocarcinoma (Label, NCCN 2A); **AND**

A. Meets one of the following:
   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] or polymerase epsilon/delta [POLE/POLD1] mutation) 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] or polymerase epsilon/delta [POLE/POLD1] mutation) 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

VIII. Individual has a diagnosis of Endometrial carcinoma (NCCN 2A); **AND**

A. Individual has a diagnosis of recurrent MSI-H/dMMR disease; **AND**
B. Individual is using as a single agent; **AND**
C. Individual is using as second-line or subsequent therapy; **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

IX. Individual has Esophageal and Esophagogastric junction cancer (NCCN 1, 2A); **AND**

A. Individual is using for induction systemic therapy; **AND**
B. Individual is using to relieve dysphagia; **AND**
C. Individual is medically fit and planned for esophagectomy; **AND**
D. Meets one of the following:
   1. Using in combination with platinum-containing chemotherapy and capecitabine or fluorouracil; **OR**
   2. Using in combination with ipilimumab; **OR**
   3. If positive MSI-H/dMMR tumor, using in combination with ipilimumab OR in combination with oxaliplatin and capecitabine or fluorouracil;

AND

E. Individual has not received 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

X. Individual has a diagnosis of unresectable locally advanced, recurrent 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

XI. Individual has a diagnosis of unresectable locally advanced, recurrent, or metastatic Esophageal Squamous Cell Carcinoma (ESCC) (Label); **AND**
- A. Individual is using as single agent or in combination with ipilimumab 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 is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XII. Individual has a diagnosis of completely resected Esophageal and Esophagogastric Junction Cancers (Label); **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

XIII. Individual has a diagnosis of Gastric or Esophageal and Esophagogastric Junction Cancers and has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (NCCN 2A); **AND**
- A. One of the following:
  1. Individual is using as a single agent for adenocarcinoma as postoperative management following completely resected disease in those who received preoperative therapy with intravenous nivolumab (Opdivo) + ipilimumab; **OR**
  2. Individual Is using in combination with ipilimumab for primary treatment of adenocarcinoma as neoadjuvant or perioperative immunotherapy;

  AND
- B. 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 advanced or metastatic Gastric, or Esophageal and Esophagogastric Junction Cancers (Label); **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

XV. Individual has a diagnosis of Esophageal and Esophagogastric Junction Cancers; **AND**
- A. Individual is using for palliative care (NCCN 1, 2A); **AND**
- B. Individual is not a surgical candidate OR has unresectable locally advanced, recurrent, or metastatic disease; **AND**
- C. Meets one of the following:
  1. Has HER2 negative disease; **AND**
  2. Using as first-line therapy in combination with fluoropyrimidine- and oxaliplatin; **AND**
  3. Individual has PD-L1 CPS ≥ 5;

  OR
  4. Has MSI-H/dMMR tumors; **AND**
  5. Using as first-line therapy in combination with ipilimumab or in combination with fluoropyrimidine- and oxaliplatin;

  OR
  6. Has Squamous cell carcinoma; **AND**
  7. Using as first-line therapy in combination with ipilimumab OR fluoropyrimide- and platinum-containing chemotherapy;

OR

8. Using as second-line or subsequent therapy; **AND**
9. Using as a single agent or in combination with ipilimumab;

AND

D. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
E. Individual does not have prior tumor progression while on therapy with a checkpoint inhibitor; **AND**
F. 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 Gastric Cancer (NCCN 1); **AND**

A. Individual is medically fit for surgery but with surgically unresectable disease; **AND**
B. Meets one of the following:
   1. Has HER2 negative disease; **AND**
   2. Individual is using in combination with fluoropyrimidine and oxaliplatin.

   OR

   3. Has MSI-H or dMMR tumors; **AND**
   4. Individual is using in combination with ipilimumab or in combination with fluoropyrimidine and oxaliplatin;

AND

C. Individual has a PD-L1 CPS ≥ 5; **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 multi-agent chemotherapy-resistant gestational trophoblastic neoplasia (NCCN 2A); **AND**

A. Individual has intermediate trophoblastic tumor or high-risk disease; **AND**
B. Individual is using as single-agent therapy or in combination with ipilimumab; **AND**
C. Individual has not received 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

XVIII. Individual has a diagnosis of advanced Hepatocellular Carcinoma (Label, NCCN 2A); **AND**

A. Individual is using in one of the following ways:
   1. Individual is using as a single agent in those classified as Child-Pugh Class B; **OR**
   2. Individual is using in combination with ipilimumab for subsequent therapy; **OR**
   3. Individual is using in combination with ipilimumab for progressive disease and classified as Child-Pugh Class A;

   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

XIX. Individual has a diagnosis of Hodgkin Lymphoma t (Label, NCCN 1, 2A); **AND**

A. Individual is using for relapsed or refractory Hodgkin lymphoma except for those with lymphocyte-predominant Hodgkin lymphoma; **AND**
B. Using in one of the following ways:
   1. Individual is as a single agent; **OR**
   2. Individual is using in combination with brentuximab vedotin or with ifosfamide, carboplatin, etoposide (ICE) as primary systemic therapy or second-line therapy; **OR**
   3. Individual is using in combination with AVD (doxorubicin, vinblastine, dacarbazine) for primary treatment;

AND

C. Individual has not received 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

XX. Individual has a diagnosis of Pediatric Classic Hodgkin Lymphoma (NCCN 2A); **AND**

A. Individual is using for relapsed or refractory Hodgkin lymphoma except for those with lymphocyte-predominant Hodgkin lymphoma; **AND**

B. Using in one of the following ways:
    1. Individual is as a single agent; **OR**
    2. Individual is using in combination with brentuximab vedotin or with ifosfamide, carboplatin, etoposide (ICE);

AND

C. Individual has not received 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

XXI. Individual has a diagnosis of relapsed/refractory advanced classic Kaposi Sarcoma (NCCN 2A); **AND**
A. Individual is using as a single agent or in combination with ipilimumab (Yervoy); **AND**
B. Individual is using as subsequent systemic therapy; **AND**
C. Individual does not have multicentric Castleman Disease (MCD) or KSHV-associated inflammatory cytokine syndrome (KICS);

OR

XXII. 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

XXIII. 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

XXIV. Individual has a diagnosis of Malignant Pleural Mesothelioma (NCCN 1); **AND**
A. Individual has epithelioid histology; **AND**
B. Individual is using as induction systemic therapy; **AND**
C. Individual is using in combination with ipilimumab; **AND**
D. Individual uses prior to surgical exploration for stage I disease; **AND**
E. 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

XXV. Individual has a diagnosis of Melanoma (Cutaneous or Uveal); **AND**
A. Individual has unresectable or metastatic melanoma (Label, NCCN 1, 2A);
AND
    1. Individual is using as a single agent, or in combination with ipilimumab; **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

B. Individual has resected advanced melanoma (Label, NCCN 1, 2A); **AND**
    1. Individual is using as a single agent for adjuvant therapy; **AND**
    2. Individual has resected stage IIB, stage IIC, 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, NCCN 1, 2A)); **AND**
    1. Meets 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

D. Individual has metastatic or unresectable melanoma (Cutaneous or Uveal) (NCCN 1, 2A); **AND**
   1. Individual is using as second-line or subsequent systemic therapy; **AND**
   2. Using in combination with ipilimumab for disease progression on single-agent anti-PD-1 therapy; **OR**
   3. Using as a single agent or in combination with ipilimumab if disease control occurred with prior anti-PD-1 immunotherapy as re-induction therapy;

OR

XXVI. Individual has a diagnosis of metastatic Melanoma with brain metastases (NCCN 2A); **AND**
   A. Individual has a primary diagnosis of melanoma; **AND**
   B. Using in one of the following way:
      1. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017); **OR**
      2. Individual has BRAF non-specific asymptomatic brain metastases; **AND**
      3. Individual is using as monotherapy or in combination with ipilimumab; **AND**
      4. Individual 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

XXVII. Individual has a diagnosis of Merkel Cell Carcinoma (Label, NCCN 2A) **AND**
   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**
   F. Individual is using as a single agent or in combination with ipilimumab (NCCN 2A); **AND**
   G. Individual has M1 disseminated disease if anti-PD-L1 or anti-PD-1 therapy is contraindicated or disease has progressed on anti-PD-L1 or anti-PD-1 monotherapy; **AND**
   H. 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 Non-Small Cell Lung Cancer (NSCLC) (Label, NCCN 2A); **AND**
   A. Individual has recurrent, advanced, or 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. 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 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 intravenous nivolumab (Opdivo) + 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

F. Individual has resectable NSCLC (Label, NCCN 1); **AND**
   1. Resectable is defined as tumors ≥ 4 cm and/or node positive; **AND**
   2. Individual has no known EGFR mutations or ALK rearrangements; **AND**
   3. Using as adjuvant therapy post-surgery; **AND**
   4. Individual is using Opdivo as a single agent after prior combination use of Opdivo and platinum-doublet chemotherapy; **AND**
   5. Current ECOG performance status of 0-2; **AND**
   6. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
   7. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIX. 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 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

XXX. Individual has a diagnosis of Primary Mediastinal Large B-Cell Lymphoma (NCCN 2A); **AND**
   A. Individual is using for pediatric aggressive mature B-cell lymphoma; **AND**
      1. Individual is using for relapsed or refractory disease as a single agent; **OR**
      2. Individual is using for consolidation/additional therapy in combination with brentuximab vedotin after partial response achieved after therapy for relapsed or refractory disease;

   AND

   B. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; AND
   C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXI. 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 its 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 (Label, NCCN 1, 2A); **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 1, 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

D. Individual has relapsed, recurrent, or advanced RCC (NCCN 2A); **AND**
   1. Individual is using as subsequent therapy in combination with cabozantinib or ipilimumab; **AND**
   2. Individual has a current ECOG performance status of 0-2; **AND**
   3. Individual has had prior immune-oncology therapy (e.g. pembrolizumab); **AND**
   4. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

E. Individual has relapse or metastatic non-clear cell RCC (nccRCC) [including hereditary leiomyomatosis and renal cell carcinoma (HLRCC)] (NCCN 2A); **AND**
   1. Individual is using as systemic therapy as a single agent or in combination with cabozantinib; **AND**
   2. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   3. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXXII. Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA) including Ampullary Adenocarcinoma (NCCN 2A); **AND**
   A. Individual has advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation); **AND**
   B. Individual is using 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

XXXIII. Individual has a diagnosis of Extranodal NK/T-cell lymphomas (NCCN 2A); **AND**
   A. Individual has relapsed/refractory disease; **AND**
   B. Individual is using following treatment with asparaginase-based regimen; **AND**
   C. Individual is using as monotherapy; **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

XXXIV. Individual has a diagnosis of advanced or metastatic Soft Tissue Sarcoma and Aggressive Soft Tissue Neoplasms (NCCN 2A); **AND**
   A. Individual is using in combination with ipilimumab; **OR**
   B. Individual is using as a single agent; **AND**
   C. Has not received 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

XXXV. Individual has a diagnosis of Squamous Cell Carcinoma of the Head and Neck (SCCHN) (Label, NCCN 1); **AND**
   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 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

XXXVI. Individual has a diagnosis of Head and Neck cancers (NCCN 1, 2A); **AND**

A. Using for one of the following types of cancers:
   1. Individual has recurrent, unresectable, oligometastatic, or metastatic Nasopharyngeal Cancers (INCCN 2A); **AND**
   2. Individual has no surgery or radiotherapy (RT) options; **AND**
      a. Individual is using nivolumab in combination with cisplatin and gemcitabine; **OR**
      b. Individual is using nivolumab as monotherapy for first-line or systemic therapy if previously treated;

   AND

   3. Has not received another anti-PD-1 or anti-PD-L1 agent;

OR

B. Individual has squamous recurrent, unresectable, or metastatic non-nasopharyngeal cancer; **AND**
   1. Individual has no surgery or radiotherapy options; **AND**
   2. Individual is using as monotherapy or in combination with cetuximab;

OR

XXXVII. Individual has metastatic Anaplastic Thyroid carcinoma (NCCN 2A); **AND**

A. Individual is using as a single agent; **AND**
B. Current ECOG performance status of 0-2; **AND**
C. Has not received 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

XXXVIII. Individual has Urothelial carcinoma (Label, NCCN 1, 2A); **AND**

A. Individual has locally advanced, recurrent, 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 chemotherapy; **OR**
      b. Confirmation of disease progression within 12 months of receiving neoadjuvant or adjuvant treatment with platinum-containing chemotherapy;

   OR

   3. Individual is using as single agent for adjuvant therapy; **AND**
   4. Individual is at high risk of recurrence after having radical resection;

AND

B. Current ECOG performance status of 0-2; **AND**
C. Has not received 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

XXXIX. Individual has Urothelial carcinoma (Label, NCCN 1, 2A); **AND**

A. Individual has unresectable, recurrent, or metastatic disease; **AND**
B. Individual is using in combination with cisplatin and gemcitabine; **AND**
C. Individual is using as first-line treatment; **AND**
D. Current ECOG performance status of 0-2; **AND**
E. Has not received 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

XL. Individual has a diagnosis of Urothelial carcinoma of the Prostate (NCCN 2A); **AND**

A. Individual is using as adjuvant therapy; **AND**
B. Individual is using for tumors with stromal invasion if platinum-based neoadjuvant chemotherapy not given and pT3, pT4a, pN+; **AND**
C. Individual is using as a single agent;

OR

XLI. Individual has a diagnosis of Central Nervous System Cancers- Pediatric Diffuse High-Grade Gliomas (NCCN 2A); **AND**

A. Individual is using as single agent for hypermutant tumor; **AND**
B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XLII. Individual has a diagnosis of recurrent or metastatic Vaginal Cancer (NCCN 2A); **AND**
A. Individua is using a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has PD-L1 expression positive (CPS ≥ 1%) tumor; **AND**
D. Individual has not received 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

XLIII. Individual has a diagnosis of recurrent or metastatic Vulvar Cancer (NCCN 2A); **AND**
A. Individual is using as a single agent; **AND**
B. Individual is using as second-line or subsequent therapy; **AND**
C. Individual has HPV-related tumor; **AND**
D. Individual has not received 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.

***Note:** Actionable molecular markers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK, MET, RET, ERBB2 (HER2), and NRG1 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-C06.9	Malignant neoplasm of parts of lip and oral cavity
C09.0-C13.9	Malignant neoplasm of tonsil, pharynx, pyriform sinus
C14.0-C14.8	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15.3-C15.9	Malignant neoplasm of esophagus
C16.0-C16.9	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	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C23	Malignant neoplasm of gallbladder

C24.0-C24.9	Malignant neoplasm of other and unspecified parts of biliary tract
C30.0	Malignant neoplasm of nasal cavity
C31.0-C31.1	Malignant neoplasm of accessory sinuses
C32.0-C32.9	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C38.4	Malignant neoplasm of pleura
C40.00-C40. 92	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
C43.0-C43.9	Malignant melanoma of skin
C44.02	Squamous cell carcinoma of skin of lip
C44.42	Squamous cell carcinoma of skin of scalp and neck
C45.0-C45.9	Mesothelioma
C46.0-C46.9	Kaposi's sarcoma
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C4A.0-C4A.9	Merkel cell carcinoma
C51.0-C51.9	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53.0-C53.9	Malignant neoplasm of cervix uteri
C54.0-C54.9	Malignant neoplasm of corpus uteri
C58	Malignant neoplasm of placenta
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
C71.0-C71.9	Malignant neoplasm of brain
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C72.9	Malignant neoplasm of central nervous system, unspecified
C73	Malignant neoplasm of thyroid gland
C76.0	Malignant neoplasm of head, face and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes 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)
C84.90-C84.99	Mature T/NK-cell lymphomas, unspecified
C84.Z0-C84.Z9	Other mature T/NK-cell lymphomas
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C86.00	Extranodal NK/T-cell lymphoma, nasal type not having achieved remission
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: 02/21/2025
Document History:

- 02/21/2025 – Annual Review: Update NCCN criteria for use in Ampullary adenocarcinoma as first-line therapy in MSI-H/dMMR disease in combination with Yervoy. Update existing NCCN use in biliary tract cancer for use in neoadjuvant therapy for resectable advanced disease. Update use in bladder cancer/urothelial cancer for recurrent disease. Update NCCN recommendation for use in Bone cancer with "progressed" language. Update NCCN recommendations for use in Colorectal cancer for use in resectable and unresectable disease, include POLE/POLD1 mutation in criteria where applicable, clarify continuation use of Opdivo, and use in T4b disease. Add NCCN 2A recommendation for use in Endometrial cancer with MSI-H/dMMR mutation. Update existing Esophageal Esophagogastric Junction cancer criteria. Add recommendations from NCCN for use in Esophageal or Esophagogastric Junction cancer in relieving dysphagia in those medically fit and planned for esophagectomy, and as use in palliative care when patients are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease as first-line therapy or second-line/subsequent therapy if individual has a Karnofsky performance score ≥60% or ECOG performance score ≤2. Clarify use in palliative care in HER2 negative disease. Update existing gastric cancer criteria with NCCN 1 use in HER2 negative disease. Include use in palliative care for gastric cancer. Update Gestational Trophoblastic Neoplasia NCCN criteria to include combination use with Yervoy and clarify intermediate disease as intermediate trophoblastic tumor. Add NCCN 2A recommendation for Opdivo monotherapy use in Head and Neck cancer. Add use in combination with AVD for existing Hodgkin Lymphoma criteria. Add NCCN 1 criteria for use in Pleural Mesothelioma. Add recommendation for use in relapsed/refractory Pediatric Classic Hodgkin Lymphoma as a single agent or in combination with brentuximab or ICE. Add recommendation for use in relapsed/refractory Primary Mediastinal Large B-Cell Lymphoma as a single agent or in combination with brentuximab for consolidation therapy. Clarify use in Renal cell carcinoma for relapsed, recurrent, or advanced disease when used as subsequent therapy with prior immune-oncology. Add POLE/POLD1 mutation for use in SBA. Add 2A recommendation for use in urothelial cancer of the prostate as primary treatment for tumors with stromal invasion as adjuvant therapy. Add recommendation for use in Thyroid cancer as a single agent. Add NCCN 2A recommendation for use in vaginal cancer. Update actionable molecular markers list according to NCCN. Wording and formatting updates. Coding Reviewed: Added ICD-10-CM C48.0-C48.8, C49.0-C49.9, C52, C54.0-C54.9, C72.0, C72.1, C73, C85.20-C85.29.
- 11/15/2024 – Select Review: Add new FDA approval for Opdivo's use in combination with platinum-doublet chemotherapy as neoadjuvant treatment, followed by single-agent nivolumab after surgery as adjuvant treatment, for adults with resectable (tumors ≥ 4 cm and/or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements Coding Reviewed: Removed ICD-10-CM C07 and C08.0-C08.9 from the range C00.0-C14.8 and updated descriptions. Removed ICD-10-CM C22.2-C22.7 from the range C22.0-C22.9 and updated descriptions. Removed ICD-10-CM C30.1 and C31.2-C31.9 from the range C30.0-C33 and updated descriptions. Removed ICD-10-CM C83.30-C83.37. Added ICD-10-CM C16.1-C16.9, C23, C24.0-C24.9, C40.00-C40.02, C40.90-C40.92, C44.02, C51.0-C51.9, C53.0-C53.9, C58, C71.0-C71.9, C72.9, C77.0, C84.90-C84.99, C84.Z0-C84.Z9, C86.00. Added ICD-10-CM C45.1-C45.9 to C45.0 and updated description for the range.
- 3/11/2024 – Select Review: Add new FDA approval for use in first-line treatment in unresectable or metastatic urothelial carcinoma in combination with cisplatin and gemcitabine. Remove NCCN use in Primary mediastinal B-cell lymphoma as recommendation changed from 2A to 2B when used in combination with brentuximab vedotin. Wording and formatting updates. Coding Reviewed: No changes.
- 02/23/2024 – Annual Review: ADD NCCN category 2A recommendation for Anal Carcinoma in second-line and subsequent therapy as a single agent for metastatic disease if no prior immunotherapy received. Add NCCN category 2A recommendation for Biliary Tract Cancers in combination with ipilimumab. Update existing NCCN criteria for use in ESCC for second-line/subsequent therapy with combination use of Yervoy and removing criteria language restricting use of prior PD-1, PD-L1 agents or checkpoint inhibitors. Add NCCN category 2A recommendation for Cervical cancer in second-line or subsequent therapy as a single agent if CPS ≥ 1 for local/regional recurrence or stage IVB or recurrence with distant metastases. Update existing NCCN 2A criteria

in Gastric or Esophageal and Esophagogastric Junction Cancers by adding criteria for disease states and use in MSI-H/dMMR tumor as a single agent or in combination with ipilimumab. Add NCCN 2A recommendation for use in Gestational Trophoblastic Neoplasia in multiagent chemotherapy-resistant Gestational Trophoblastic Neoplasia that is high or intermediate risk. Update existing NCCN 2A criteria in Hepatocellular carcinoma for use as a single agent vs. in combination with ipilimumab. Update existing NCCN 2A criteria for use in Hodgkin Lymphoma as a single agent or in combination with brentuximab vedotin or ICE. Update existing NCCN 2A criteria for use in classic Kaposi sarcoma for appropriate population usage. Update existing NCCN 2A criteria to include use as a single agent or combination use with ipilimumab for use in BRAF-non-specific asymptomatic brain metastases from melanoma. Add NCCN 2A recommendation for use in metastatic or unresectable melanoma in combination with ipilimumab if disease progression occurred on prior single-agent anti-PD-1 therapy. Also continue as a single agent or in combination with ipilimumab if disease control occurred with prior anti-PD-1 therapy as re-induction therapy. Add NCCN 2A recommendation for use in Merkel Cell Carcinoma as a single agent or in combination with ipilimumab in M1 disseminated disease if progression on anti-PD-1 or anti-PD-L1 monotherapy or anti-PD-1 or anti-PD-L1 is contraindicated. Add NCCN 2A recommendation for use in relapse, recurrent, or advanced RCC when used as subsequent therapy in combination with cabozantinib and individual had prior immune-oncology therapy (e.g. pembrolizumab). Add NCCN 2A recommendation for use in non-clear cell RCC as a single agent or in combination with cabozantinib. Clarify existing Small Bowel Adenocarcinoma criteria and Ampullary Adenocarcinoma criteria from NCCN guidelines. Add NCCN 2A recommendation for use in relapsed/refractory extranodal NK-T cell lymphoma. Add NCCN 2A recommendation for use in metastatic soft tissue sarcoma as a single agent or in combination with ipilimumab. Add NCCN 2A recommendation for use in nasopharyngeal and non-nasopharyngeal cancers. Add NCCN 2A recommendation for use in Pediatric Diffuse High-Grade gliomas as a single agent for use in hypermutant tumors. Add NCCN 2A recommendation for use in recurrent or metastatic vulvar cancer as a single agent in HPV-related tumor. Wording and formatting updates. Coding Reviewed: No changes.

- 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.

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18. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. January 17, 2025.
    a. Ampullary adenocarcinoma. V2.2025. Revised January 10, 2025.
    b. Anal Carcinoma. V1.2025. Revised December 4, 2024.
    c. Biliary Tract Cancers. V6.2024. Revised January 10, 2024.
    d. B-Cell Lymphomas. V1.2025. Revised December 20, 2024.
    e. Bladder cancer. V5.2024. Revised October 28, 2024.
    f. Bone cancer. V1.2025. Revised August 20, 2024.
    g. Central Nervous System Cancers V3.2024. Revised September 30, 2024.
    h. Cervical Cancer. V1.2025. Revised December 19, 2024.
    i. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V1.2025. Revised October 1, 2024.
    j. Colon Cancer V6.2024. Revised January 17, 2025.
    k. Cutaneous Melanoma. V1.2025. December 20. 2024.
    l. Esophageal and esophagogastric junction cancers. V5.2024. Revised December 20, 2024.
    m. Gastric cancer. V5.2024. Revised December 20, 2024.
    n. Gestational Trophoblastic Neoplastic. V1.2025. Revised December 17, 2024.
    o. Head and neck cancers. V1.2025. Revised November 26, 2024
    p. Hepatocellular Carcinoma. V4.2024. Revised January 10, 2025.
    q. Hodgkin Lymphoma V1.2024. Revised October 12, 2023.
    r. Kaposi Sarcoma. V2.2025. Revised January 14, 2025.
    s. Kidney Cancer. V3.2025. Revised January 9, 2025
    t. Merkel Cell Carcinoma. V1.2024. Revised November 22, 2023.
    u. Malignant Pleural Mesothelioma V2.2025. Revised January 14, 2025.
    v. Malignant Peritoneal Mesothelioma. V2.2025. Revised January 14, 2025.
    w. Cutaneous Melanoma V3.2023. Revised October 27, 2023.
    x. Neuroendocrine and Adrenal Tumors. V1.2023. Revised August 2, 2023.
    y. Non-Small Cell Lung Cancer. V3.2025. Revised January 14, 2025.
    z. Pediatric Aggressive Mature B-Cell Lymphomas. V2.2024. Revised September 3, 2024.
    aa. Pediatric Central Nervous System Cancers. V1.2025. Revised November 8, 2024.
    bb. Pediatric Hodgkin Lymphoma. V1.2024. Revised May 14, 2024.
    cc. Rectal Cancer V4.2024. Revised August 22, 2024.
    dd. Small Bowel Adenocarcinoma. V1.2025. Revised December 4, 2024.
    ee. Small cell lung cancer. V4.2025. Revised January 13, 2025.
    ff. Soft Tissue Sarcoma. V4.2024. Revised November 21, 2024.
    gg. T-Cell Lymphomas. V1.2025. Revised November 11, 2024.
    hh. Thyroid Carcinoma. V5.2024. Revised January 15, 2025.
    ii. Uterine neoplasms. V1.2025. Revised December 16, 2024.
    jj. Vaginal Cancer V3.2025. Revised December 16, 2024.
    kk. Uveal Melanoma. V1.2024. Revised May 23, 2024.
    ll. Vulvar Cancer. V4.2024. Revised May 1, 2024.
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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.