Clinical Criteria

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Overview

This document address 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.

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.

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 Mesothelioma

NCCN compendia and CPG 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 mesothelioma (MPM), a highly aggressive cancer with poor prognosis and limited treatment options.

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.

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.

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 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 indicated for first line treatment of recurrent or metastatic NSCLC for patients without EGFR or ALK genomic tumor aberrations.

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).

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).

Small Cell Lung Cancer

Opdivo is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy.

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 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.

Other Uses

While NCCN also provides 2A recommendations for the use of Opdivo as subsequent treatment of metastatic squamous cell carcinoma of the anal canal. 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).

NCCN also provides 2A recommendation for Opdivo for gestational trophoblastic neoplasia following treatment with a platinum/etoposide-containing regimen and as a single agent for individuals with methotrexate-resistant high-risk disease. However, there is insufficient published evidence to support the use of Opdivo for such conditions.

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 positive. NCCN also provides a 2A recommendation for the use of Opdivo in stage IV or recurrent NSCLC as first line monotherapy. There is insufficient evidence to support its use in these situations. While the NCCN also provides a 2A recommendation for use of Opdivo with Yervoy for first line treatment of NSCLC in those with high tumor mutational burden, overall survival resulted in non-statistical significance.

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.

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 Colorectal Cancer ~~and *one* of the following is met~~ (Label, NCCN 2A)~~:~~ **AND**
   A. Individual meets one of the following criteria:
      ~~A.~~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**
      ~~B.~~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;

   AND
   ~~II.~~B. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   ~~III.~~C. Individual has a current ECOG performance status of 0-2; **AND**
   ~~IV.~~D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

II. Individual has a diagnosis of 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.~~III. Individual has a diagnosis of advanced Hepatocellular Carcinoma and the following criteria are met:
   A. Individual is using as monotherapy or in combination with ipilimumab; **AND**
   B. Confirmation of disease progression on or had intolerance to sorafenib; **AND**
   C. Individual has a current ECOG performance status of 0-2; **AND**
   D. Individual has not received treatment with another anti-PD-1 or anti-PD-1 agent; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

~~VI.~~IV. 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

~~VII.~~V. Individual has a diagnosis of Malignant Pleural Mesothelioma and the following criteria are met (NCCN 2A):
   A. Individual is using as subsequent therapy;
   OR
   B. Individual is ineligible for platinum-based chemotherapy, defined as having one or more of the following risk factors for platinum-based chemotherapy toxicity:
      1. ECOG performance status equal to 2;
      2. Glomerular filtration rate less than 60 mL/min;
      3. Hearing loss (measured at audiometry) of 25dB at two contiguous frequencies;
      4. Grade 2 or greater peripheral neuropathy;

   AND
   C. Individual is using as monotherapy; **AND**
   D. Current ECOG performance status of 0-2; **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

~~VIII.~~VI. Individual is using for the treatment of Malignant Pleural Mesothelioma (NCCN 2A); **AND**
   A. Individual is using 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

~~IX.~~VII. Individual has a diagnosis of Melanoma (Cutaneous or Uveal) and the following criteria are met:

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A. Individual has unresectable or metastatic melanoma;
AND
1. Individual is using as a single agent, or in combination with ipilimumab, as first-line therapy for untreated melanoma;
OR
2. Individual is using as a single agent, or in combination with ipilimumab, as second-line or subsequent therapy for confirmed disease progression while receiving or since completing most recent therapy, if anti-PD-1 or anti-PD-L1 not previously used;
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

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 IIIB, IIIC, 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

~~X.~~VIII. 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

~~XI.~~IX. Individual has a diagnosis of Merkel Cell Carcinoma and the following criteria are met:
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

~~XII.~~X. Individual has a diagnosis of Non-Small Cell Lung Cancer (NSCLC) and the following criteria are met:
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 stage IV or recurrent NSCLC and using as first-line therapy (NCCN 2A); **AND**~~
~~1. Individual is using in combination with ipilimumab; **AND**~~
~~2. Cytological confirmation of stage IV or recurrent NSCLC disease; **AND**~~
~~3. Individual has high tumor mutation burden (greater than or equal to 10 mutations per megabase); **AND**~~
~~4. Individual does not have sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translations in nonsquamous carcinoma; **AND**~~
~~5. Individual has not received prior systemic therapy as primary therapy for advanced or metastatic NSCLC; prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior; **AND**~~
~~6. Current ECOG performance status of 0-2; **AND**~~
~~7. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**~~
~~8. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;~~

OR

~~C.~~B. Individual has recurrent, advanced, or metastatic NSCLC and using as first-line therapy (NCCN 2A); **AND**
1. Individual is using in combination with ipilimumab; **AND**
2. Individual does not have presence of EGFR, ALK, ROS1, or BRAF mutations; **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.~~C. Individual has recurrent or metastatic NSCLC and using as first-line therapy; **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 EGFR, ALK, ROS1, or BRAF mutations; **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

~~XIII.~~XI. 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 immediate- 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

~~XIV.~~XII. 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

~~XV.~~XIII. Individual has a diagnosis of Small Cell Lung Cancer (SCLC) and meets the following criteria:

A. Individual is using as monotherapy or in combination with ipilimumab, as subsequent therapy and meets *one* of the following (Label, NCCN 2A):
   1. Confirmation of disease relapse within 6 months following complete or partial response or stable disease with initial treatment;
      OR
   2. Individual has no response with initial treatment;
      OR
   3. Individual has primary progressive 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

~~XVI.~~XIV. 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

~~XVII.~~XV. Individual has Urothelial carcinoma and meet the following criteria:

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

Requests for 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
C21.8	Malignant neoplasm of overlapping sites of rectum, 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
C38.4	Malignant neoplasm of pleura
C43.0-C43.9	Malignant melanoma of skin
C4A.0-C4A.9	Merkel cell carcinoma
C45.0	Mesothelioma of pleura
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)
D37.8-D37.9	Neoplasm of uncertain behavior of other specified digestive organs
Z85.00	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: 08/21/2020
Document History:

- 08/21/2020 – Select Review: Update critiera 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, D37.8-D37.9, Z85.00
- 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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a. Anal Carcinoma V1.2020. Revised November 19, 2019.
b. Bladder Cancer V1.2020. Revised November 27, 2019.
c. Central Nervous System Cancers V3.2019. Revised October 18, 2019.
d. Colon Cancer V1.2020. Revised December 19, 2019.
e. Esophageal and Esophagogastric Junction Cancers. V3.2020. Revised July 7, 2020.
f. Gestational Trophoblastic Neoplastic. V1.2020. Revised December 11, 2019.
g. Head and Neck Cancer V3.2019. Revised September 16, 2019.
h. Hepatobiliary Cancers V3.2019. Revised August 1, 2019
i. Hodgkin Lymphoma V2.2019. Revised July 15, 2019.
j. Kidney Cancer. V2.2020. Revised August 5, 2019.
k. Malignant Pleural Mesothelioma V1.2020. Revised November 27, 2019.
l. Cutaneous Melanoma V1.2020. Revised December 19, 2019
m. Non-Small Cell Lung Cancer. V5.2020. Revised May 27, 2020.
n. Rectal Cancer V1.2020. Revised December 19, 2019.
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p. Small Cell Lung Cancer. V2.2020. Revised November 15, 2019.
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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.