This document address the use of Opdivo (a recombinant humanized monoclonal antibody that targets the human epidermal growth factor receptor 2 protein (HER2). Perjeta interrupts the communication pathway involved in the growth and progression of the cancer cells in the tumor.

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

Central Nervous System Cancer

The NCCN Compendia and Clinical Practice Guideline (CPG) for central nervous system cancers (2019) offers a category 2A recommendation for nivolumab in combination with Yervoy (ipilimumab) in the treatment of newly diagnosed or recurrent brain metastases secondary to melanoma and stable systemic disease or reasonable systemic treatment options.

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.

**Adjuvant Treatment of Melanoma**

NCCN compendia includes a category 2A recommendation 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.

**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 irinotecan.

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.

**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 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.

**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
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.

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.

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):
   A. Individual is using as monotherapy or in combination with ipilimumab in primary treatment for unresectable metachronous metastases (defective mismatch repair/ high microsatellite instability [dMMR/MSI-H] only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
B. Individual is using as monotherapy in subsequent therapy (if nivolumab or pembrolizumab not previously given) for unresectable advanced or metastatic disease (defective mismatch repair/high microsatellite instability [dMMR/MSIH] only) following previous treatment with oxaliplatin–irinotecan; OR
C. Individual is using in combination with ipilimumab as subsequent therapy for unresectable advanced or metastatic colorectal cancer with dMMR or MSI-H mutations that has progressed following treatment with fluoropyrimidine and oxaliplatin or irinotecan;

AND

II. Individual has not received another PD-1 agent (e.g. pembrolizumab); AND
III. Individual has a current Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; AND
IV. 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 advanced Hepatocellular Carcinoma and the following criteria are met:
A. Individual is using as monotherapy; AND
B. Confirmation of disease progression on or had intolerance to sorafenib (Label, NCCN 2A); AND
C. Individual has a current ECOG performance status of 0-2; AND
D. Individual has not received treatment with another PD-1 agent (e.g. pembrolizumab); 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 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. 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;
C. Individual is using as monotherapy; AND
D. Current ECOG performance status of 0-2; AND
E. Has not received treatment with another PD-1 agent (e.g. pembrolizumab); AND
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VIII. 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 PD-1 agent (e.g. pembrolizumab); AND
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IX. Individual has a diagnosis of Melanoma (Cutaneous or Uveal) and the following criteria are met:
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 PD-1 not previously used; AND
   3. Current ECOG performance status of 0-2; AND
   4. Has not received treatment with another PD-1 agent (e.g. pembrolizumab); 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 PD-1 agent (e.g. pembrolizumab); AND
   5. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;
X. 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 PD-1 agent (e.g. pembrolizumab); **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XI. Individual has a diagnosis of Non-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 PD-1 agent (e.g. pembrolizumab); **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 (Label, 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 PD-1 agent (e.g. pembrolizumab); **AND**
      8. Individual is not receiving therapy for an autoimmune disease, chronic condition, or interstitial lung disease with a systemic immunosuppressant;

OR

XII. 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, 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 PD-1 agent (e.g. pembrolizumab); **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, as first-line therapy for previously untreated RCC; **OR**
      2. Individual is using in combination with ipilimumab if no checkpoint blockade (PD-1, PD-L1, or CTLA-4) antibody treatment has been previously administered; **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 PD-1 agent (e.g. pembrolizumab); **AND**
      6. 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 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 PD-1 agent (e.g. pembrolizumab); **AND**
      5. 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 Small Cell Lung Cancer (SCLC) and meets the following the 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;
3. Individual has primary progressive disease;

AND

4. Current ECOG performance status of 0-2; AND

5. Has not received treatment with another PD-1 agent (e.g. pembrolizumab); AND

6. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

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 PD-1 agent (e.g. pembrolizumab); 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 for the following:

I. Treatment used as first line therapy, except as described above; OR

II. The reason for treatment is other than for a diagnosis with accompanied criteria noted above; OR

III. The above criteria are not met.

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
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
C44A.0-C44A.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)
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

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Document History:

References

   g. Hepatobiliary Cancers V2.2019. Revised March 6, 2019
   k. Cutaneous Melanoma V2.2019. Revised March 12, 2019

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