

Clinical Criteria

Subject: Yervoy (ipilimumab)

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Overview

This document addresses the use of Yervoy (ipilimumab). Yervoy is a recombinant human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking monoclonal antibody used to treat advanced melanoma (cutaneous and uveal), renal cell carcinoma, colorectal cancer, non-small cell lung cancer and small cell lung cancer.

The Food and Drug Administration (FDA) approved indications for Yervoy include treatment of unresectable or metastatic melanoma. The National Comprehensive Cancer Network (NCCN) recommends that for unresectable or metastatic disease, Yervoy may be used with Opdivo as first-line therapy, or as a single drug or with Opdivo as second-line or subsequent treatment if the individual has disease progression. Additionally, NCCN indicates that Yervoy may be used as a single-agent for re-induction therapy in certain individuals who did not have significant systemic toxicity during prior Yervoy therapy and who relapse after initial clinical response or progress after stable disease greater than 3 months.

Yervoy is FDA indicated for use in combination with nivolumab for recurrent, advanced, or metastatic non-small cell lung cancer (NSCLC) as first-line therapy for tumors expressing PD-L1 $\geq 1\%$ that are EGFR, ALK, ROS1, BRAF negative. NCCN provides an additional category 2A recommendation for tumors with PD-L1 $< 1\%$.

Yervoy, in combination with nivolumab 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.

Yervoy is also FDA approved as adjuvant treatment of individuals with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

Recently, there has been increasing interest in the use of Yervoy for another form of metastatic melanoma. NCCN provides a 2A recommendation for use of Yervoy as a single agent or in combination with Opdivo for the treatment of unresectable or metastatic uveal melanoma.

Yervoy has a FDA approved indication for use in combination with Opdivo for the treatment of individuals with intermediate- or poor-risk previously untreated advanced renal cell carcinoma (RCC). NCCN includes a 2A recommendation for use of Yervoy in combination with Opdivo as a subsequent therapy for the treatment of advanced clear cell RCC. NCCN also provides a 2A recommendation for use in combination with Opdivo for favorable risk groups with advanced clear cell RCC but notes the phase I and III clinical trial data supporting this use showed conflicting results.

Yervoy has a FDA approved indication for use in combination with Opdivo for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan. NCCN includes a 2A recommendation for Yervoy in combination with Opdivo as primary treatment for metachronous metastases (dMMR/MSI-H only) and previous adjuvant fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CapeOX) within the past 12 months.

Yervoy has a FDA approved indication for use in combination with Opdivo for the treatment of hepatocellular carcinoma who have previously been treated with sorafenib. This was approved under the FDA accelerated program, and continued approval is contingent upon confirmatory trials.

NCCN provides a 2A recommendation for the use of Yervoy in combination with Opdivo as a new treatment option for small cell lung cancer (SCLC) in individuals with ECOG performance status of 0-2. The recommendation is for use as subsequent therapy for

treatment of primary progressive disease or use after disease relapse (6 months or less) after complete or partial response or stable disease with primary therapy.

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

NCCN provides a 2A recommendation for the use of Yervoy in combination with Opdivo for central nervous system cancers 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).

NCCN Compendia and CPG for small bowel adenocarcinoma includes a category 2A recommendation for use of nivolumab as single agent or in combination with Yervoy 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).

Other Uses

NCCN also provides a 2A recommendation for the use of Yervoy in combination with Opdivo 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 2A recommendations for Yervoy as a single agent in this patient population. The evidence behind this recommendation is weak and based on a small phase II trial (Margolin, 2012) which did not include a comparator arm, and no patients had a complete response.

NCCN also provides a 2A recommendation for Yervoy with or without Opdivo 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 Yervoy in combination with Opdivo for NSCLC recurrent, advanced, or metastatic disease as first-line or subsequent therapy for tumors that are EGFR, ALK, ROS1, BRAF positive. However, there is insufficient published evidence to support the use of Yervoy for such situations. While the NCCN also provides a 2A recommendation for use of Yervoy with Opdivo for first line treatment of NSCLC in those with high tumor mutational burden, overall survival resulted in non-statistical significance.

the NCCN provides a 2A recommendation for use of Yervoy with Opdivo for "favorable" risk patients with advanced renal cell carcinoma; however, the panel notes the data has been conflicting for this population.

Yervoy has a black box warning for severe and fatal immune-mediated adverse reactions. The most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy, but the reactions can involve any organ system. The majority of the immune-mediated reactions manifested during treatment; however, a minority occurred weeks to months after discontinuation. Assess individuals for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy, and evaluate clinical chemistries including liver function tests, adrenocorticotrophic hormone (ACTH) level, and thyroid function tests at baseline and before each dose. Permanently discontinue Yervoy and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

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.

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

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).

Cytotoxic: Treatment that is destructive to cells, preventing their reproduction or growth.

Disease Progression: Cancer that continues to grow or spread.

ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

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

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.

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.

Partial response (PR): A decrease in the size of a tumor, or in the amount of cancer in the body, resulting from treatment; also called partial remission.

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.

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

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).

Stable disease: Cancer that is not decreasing or increasing in extent or severity.

Unresectable: Unable to be removed with surgery.

Urothelial carcinoma: A type of bladder cancer which occurs in the urinary tract system.

Vascular endothelial growth factor (VEGF): A substance made by cells that stimulates new blood vessel formation.

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.

Yervoy (ipilimumab)

Requests for Yervoy (ipilimumab) may be approved if the following criteria are met:

- I. Individual is using for the treatment of Colorectal Cancer; **AND**
 - A. Individual meets *one* of the following:
 1. Primary treatment used in combination with nivolumab (Opdivo) for unresectable metachronous metastases (deficient mismatch repair/high microsatellite instability [dMMR/MSIH] only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months (NCCN 2A);
OR
 2. Used in combination with nivolumab (Opdivo) as subsequent therapy for unresectable advanced or metastatic colorectal cancer with deficient mismatch repair (dMMR) or high microsatellite instability (MSIH) mutations that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan- based chemotherapy; **AND**
 - B. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
 - C. 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 advanced Hepatocellular Carcinoma and the following criteria are met:
 - A. Individual is using in combination with nivolumab (Opdivo); **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-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 has a diagnosis of unresectable Malignant Pleural Mesothelioma and using as first line therapy; **AND**
 - A. Individual is using in combination with nivolumab (Opdivo); **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**
- IV. Individual has a diagnosis of Malignant Pleural Mesothelioma (NCCN 2A); **AND**
 - A. Individual is using in combination with nivolumab (Opdivo) for subsequent therapy; **AND**
 - B. Individual has an ECOG performance status of 0-2; **AND**
 - C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.
- OR**
- III-V. Individual has a diagnosis of metastatic Melanoma with brain metastases (NCCN 2A); **AND**
 - 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 in combination with nivolumab; **AND**
 - D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or anti-CTLA-4 agent; **AND**
 - E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;
- OR**
- IV-VI. Individual is using for the treatment of unresectable or metastatic Melanoma (Cutaneous and Uveal); **AND**
 - A. Individual has an ECOG performance status of 0-2; **AND**
 - B. Yervoy is used in combination with nivolumab (Opdivo) as:
 1. First-line therapy (NCCN 1);
OR
 2. Second-line or subsequent therapy for disease progression if nivolumab (Opdivo) was not previously used (NCCN 2A);
 - C. Yervoy is used as a single agent for *one* of the following:
 1. First line therapy as a single course of 4 treatments; **OR**
 2. Second-line or subsequent lines of therapy as a single course of 4 treatments (NCCN 2A); **OR**
 3. Retreatment, consisting of a 4-dose limit, for an individual who had no significant systemic toxicity during prior Yervoy therapy, and whose disease progressed after being stable for greater than 3 months following completion of a prior course of Yervoy, and for whom no intervening therapy has been administered (NCCN 2A);

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OR
~~V-VII.~~ Individual is using for the adjuvant treatment of Melanoma (cutaneous and uveal) in individuals with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including lymphadenectomy;

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OR
~~VI-VIII.~~ Individual is using for first line treatment of recurrent, advanced, or metastatic Non-Small Cell Lung Cancer (NSCLC) (Label, NCCN 2A); **AND**
A. Individual is using in combination with nivolumab; **AND**
B. Individual does not have presence of EGFR, ALK, ROS1, or BRAF mutations; **AND**
C. 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;

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OR
~~VIII-IX.~~ Individual is using for first line treatment of recurrent or metastatic Non-Small Cell Lung Cancer (NSCLC); **AND**
A. Individual is using in combination with nivolumab *and* 2 (two) cycles of platinum-doublet chemotherapy (i.e., platinum-based chemotherapy with pemetrexed, or carboplatin with paclitaxel); **AND**
B. Individual does not have presence of EGFR, ALK, ROS1, or BRAF mutations; **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;

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OR
~~VII-X.~~ Individual is using for the treatment of intermediate- or poor-risk advanced Renal Cell Carcinoma (RCC); **AND**
A. Yervoy is used in combination with nivolumab (Opdivo) for four cycles followed by single agent nivolumab (Opdivo), as first-line therapy for previously untreated RCC; **OR**
B. Yervoy is used in subsequent therapy with nivolumab (Opdivo) for four cycles followed by single agent nivolumab (Opdivo), if no checkpoint blockade (PD-1, PD-L1, or CTLA-4) antibody treatment has been previously administered (NCCN 2A); **AND**
C. Histologic confirmation of RCC with clear-cell component; **AND**
D. Individual has an ECOG performance status 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

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OR
~~IX-XI.~~ Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA) (NCCN 2A); **AND**
A. Individual has advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only); **AND**
B. Individual is using in combination with nivolumab as subsequent therapy; **AND**
C. 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;

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OR
~~X-XII.~~ Individual is using for the treatment of Small Cell Lung Cancer (NCCN 2A); **AND**
A. Individual has an ECOG performance status of 0-2; **AND**
B. Yervoy is used in combination with nivolumab (Opdivo) as subsequent therapy for one of the following (NCCN 2A):
1. Demonstrated disease relapse within 6 months following complete or partial response or stable disease with initial treatment; **OR**
2. No response with initial treatment; **OR**
3. Primary progressive disease;:

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OR
~~XI.~~ Individual is using for the treatment of Malignant Pleural Mesothelioma (NCCN 2A); **AND**
A. Individual is using in combination with nivolumab (Opdivo) for subsequent therapy; **AND**
B. Individual has an ECOG performance status of 0-2; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

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Requests for Yervoy (ipilimumab) may not be approved for the following:

- I. Individual has an autoimmune disease which requires treatment with immunosuppressant drugs; **OR**
- II. 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

J9228	Injection, ipilimumab, 1 mg [Yervoy]
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ICD-10 Diagnosis

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, primary, unspecified as to type
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C38.4	Malignant neoplasm of pleura
C43.0-C43.9	Malignant melanoma of skin
C45.0	Mesothelioma of pleura
C64.1-C65.9	Malignant neoplasm of kidney, renal pelvis
C69.30-C69.32	Malignant neoplasm of choroid
C69.40-C69.42	Malignant neoplasm of ciliary body
C78.00-C78.02	Secondary malignant neoplasm of lung
C79.2	Secondary malignant neoplasm of skin
C79.31	Secondary malignant neoplasm of brain
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.528	Personal history of other malignant neoplasm of kidney
Z85.53	Personal history of malignant neoplasm of renal pelvis
Z85.820	Personal history of malignant melanoma of skin

Document History

Revised: 11/20/2020

Document History:

- 11/20/2020 – Select Review: Update criteria to add indication for first line treatment with nivolumab in unresectable malignant pleural mesothelioma per label. Wording and formatting changes. Coding Reviewed: No changes.
- 08/21/2020 – Select Review: Remove indication for use with nivolumab as first line therapy in NSCLC in those with high tumor mutational burden. Coding Reviewed: No changes
- 06/08/2020 – Select Review: Update criteria to add first line use in combination use with nivolumab 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 nivolumab for hepatocellular carcinoma per FDA label. Coding Reviewed: Added ICD-10 C22.0-C22.9
- 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 NSCLC per NCCN 2A. Add indication for SBA as subsequent therapy per NCCN 2A. Update criteria for retreatment in melanoma in those who progressed after being stable for 3 months (replaces 6 months). Clarify previous therapy use in colorectal cancer as subsequent therapy. Wording and formatting changes for non-approvable criteria for conciseness. Coding Review: No changes.

- 08/16/2019 – Select Review: Update renal cell criteria to notate single agent use of nivolumab after 4 cycles of combination therapy with ipilimumab per FDA label. Coding Reviewed: No changes
- 05/17/2019 – Annual Review: Initial review of ipilimumab (Yervoy). Add criteria for malignant pleural mesothelioma based on new NCCN 2A recommendation. Wording and formatting changes. Coding Reviewed: Added ICD-10 C38.4 and C45.0.

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 - a. Central Nervous System Cancers. V3.2019. Revised October 18, 2019.
 - b. Colon Cancer. V1.2020. Revised December 19, 2019.
 - c. Kidney Cancer. V2.2020. Revised August 5, 2019.
 - d. Malignant Pleural Mesothelioma. V2.2020. Revised October 15, 2020.
 - e. Cutaneous Melanoma. V1.2020. Revised December 19, 2019.
 - f. Non-Small Cell Lung Cancer. V5.2020. Revised May 27, 2020.
 - g. Rectal Cancer. V1.2020. Revised December 19, 2019.
 - h. Small Bowel Adenocarcinoma V1.2020. Revised July 30, 2019.
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 - j. Uveal Melanoma. V1.2019. Revised June 14, 2019.
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