Medical Drug Clinical Criteria

Subject:	Yervoy (ipilimumab)		
Document #:	CC-0119	**Publish Date:**	~~04/01/2025~~07/01/2025
Status:	Revised	**Last Review Date:**	~~02/21/2025~~05/16/2025

Table of Contents

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, and non-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 ≥ 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.

The NCCN panel recommends that individuals with NSCLC be tested for actionable molecular markers, such as EGFR, ALK, ROS1, BRAF, NTRK, MET and RET mutations, before initiating first line therapy to help guide treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

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 (CRC) 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.

NCCN provides a 2A recommendation for use of Yervoy in combination with Opdivo for individuals with MSI-H or dMMR metastatic colorectal cancers as primary treatment for individuals who have not received any previous chemotherapy.

Yervoy has an 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 also gives a 2A recommend for the combination use as subsequent therapy or progressive disease.

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

FDA has approved Opdivo (nivolumab) plus Yervoy (ipilimumab) as a first-line treatment for adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

NCCN provides a 2A recommendation for the use of Yervoy in combination with Opdivo in biliary tract cancers.
NCCN provides a 2A recommendation for the use of Yervoy in combination with Opdivo for malignant peritoneal mesothelioma.

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).

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 2018, 2021). 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 use in Gastric or Esophageal and Esophagogastric Junction cancers in second-line or subsequent therapy and MSI-H/dMMR tumors in unresectable locally advanced, recurrent or metastatic disease or neoadjuvant/perioperative immunotherapy.

NCCN also provides a 2A recommendation for use in relapsed or refractory advanced classic Kaposi Sarcoma when used in combination with Opdivo as subsequent systemic therapy (when multicentric Castleman disease or KSHV-associated inflammatory cytokine syndrome is not involved).

NCCN also provides a 2A recommendation for use in M1 disseminated disease if anti-PD-L1 or anti-PD-1 therapy is contraindicated or disease has progressed on them. Yervoy can be uses as a single or agent or in combination with Opdivo.

NCCN also provides a 2A recommendation for Yervoy in combination with Opdivo for small bowel adenocarcinoma, including advanced ampullary cancer as therapy for advanced or metastatic disease with dMMR/MSI-H.

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.

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

NCCN provides a 2A recommendation for the use of Yervoy in combination with Opdivo in advanced or metastatic soft tissue sarcoma.

NCCN provides a 2A recommendation for the use of Yervoy as second-line or subsequent systemic therapy option for metastatic or unresectable disease after disease progression, intolerance, and/or projected risk of progression with BRAF-targeted therapy at a low-dose in combination with pembrolizumab for disease progression following single-agent anti-PD-1 therapy (preferred if not previously used alone or in combination with anti-PD-1 therapy) or systemic therapy is preferred for unresectable or widely disseminated distant metastatic disease

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 has a diagnosis of Ampullary Adenocarcinoma (NCCN 2A); **AND**
   A. Individual is using in combination with nivolumab (Opdivo) for unresectable or metastatic disease; **AND**
   B. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] disease; **AND**
   C. Individual is using for first-line therapy or disease progression; **AND**
   D. Individual has an Eastern Cooperative Oncology Group (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

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

OR

III. Individual has a diagnosis of Biliary Tract Cancers (NCCN 2A); **AND**
   A. Individual is using in combination with nivolumab; **AND**
   B. Individual has tumor mutational burden-high (TMB-H) disease; **AND**
   ~~B.~~C. Individual is using for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease ~~that is tumor mutational burden-high (TMB-H)~~; **AND**
   ~~C.~~D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   ~~D.~~E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IV. Individual is using for the treatment of Colorectal Cancer~~, including advanced Appendiceal Adenocarcinoma~~; **AND**
   ~~A. Individual meets *one* of the following:~~
      ~~1. Primary treatment used in combination with nivolumab (Opdivo) for unresectable metachronous metastases (deficient mismatch repair or microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months (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 (MSI-H), or polymerase epsilon/delta [POLE/POLD1] mutations that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan- based chemotherapy (Label, NCCN 2A); **AND**~~
   ~~B. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**~~
   ~~C. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**~~
   A. Individual is using in combination with nivolumab in unresectable or metastatic disease with defective mismatch repair (dMMR) or high microsatellite instability (MSI-H) mutation (Label, NCCN 2A); **AND**
   ~~D.~~B. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

Formatted: Font: Bold

Formatted: Indent: Left: 0.63", Hanging: 0.13"

Formatted: Font: Bold

OR

V. Individual has a diagnosis of advanced metastatic Colorectal Cancer (NCCN 2A), including advanced Appendiceal Adenocarcinoma; **AND**
   A. Individual meets one of the following:
      1. Individual is using for resectable disease as either neoadjuvant or initial therapy, or disease progression; **OR**
      ~~2. Individual Is using for disease progression from prior treatment for advanced or metastatic treatment; **OR**~~
      ~~3.~~2. Individual is using for neoadjuvant therapy in clinical T4b disease;
      AND
   B. Individual is using in combination with nivolumab; **AND**
   C. Individual has deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation); **AND**
   D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;
   ~~D. Individual has a current ECOG performance status of 0-2;~~

OR

VI. Individual has Esophageal and Esophagogastric Junction Cancer (NCCN 2A); **AND**
   A. Individual is using for induction systemic therapy in combination with nivolumab (Opdivo); **AND**
   B. Individual is using for relieving dysphagia; **AND**
   C. Individual is medically fit and planned for esophagectomy; **AND**
   D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VII. Individual has a diagnosis of unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) (Label); **AND**
   A. Individual is using in combination with nivolumab (Opdivo); **AND**
   B. Individual is using as first-line treatment; **AND**
   C. Individual has a current ECOG performance status of 0-~~1~~2; **AND**
   ~~D. Individual has not received prior treatment with anti-PD-1, anti-PD-L1, any antibody or drug specifically targeting T-cell co-stimulation, or checkpoint pathways; **AND**~~
   D. Individual has no prior checkpoint inhibitor therapy or no tumor progression while on therapy with a checkpoint inhibitor; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VIII. Individual has a diagnosis of unresectable locally advanced, recurrent, or metastatic Esophageal Squamous Cell Carcinoma (NCCN 2A); **AND**
   A. Individual is using in combination with nivolumab; **AND**
   B. Individual is using as second line or subsequent therapy; **AND**
   C. Individual has confirmation of disease progression on or had intolerance to fluoropyrimidine- and platinum-based chemotherapy; **AND**
   D. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
   E. Individual has not received another anti-PD-1 or anti-PD-L1; **AND**
   F. 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 unresectable locally advanced, recurrent or metastatic Gastric, Esophageal and Esophagogastric Junction Cancers (NCCN 2A); **AND**
   A. Individual has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor; **AND**
   B. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
   C. Using In combination with nivolumab; **AND**
   D. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

X. Individual has a diagnosis of Gastric or Esophageal and Esophagogastric Junction Cancers and has microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumor (NCCN 2A); **AND**
   A. Individual Is using in combination with nivolumab for primary treatment of adenocarcinoma as neoadjuvant or perioperative immunotherapy; **AND**

Formatted: Indent: Left: 0.75", No bullets or numbering

Formatted: Font: Bold

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

OR

XI. Individual has a diagnosis of Gastric or Esophageal and Esophagogastric Junction Cancers (NCCN 2A); **AND**
A. Individual is using for palliative care; **AND**
B. Individual is not a surgical candidate or has unresectable locally advanced, recurrent or metastatic disease; **AND**
C. Meets one of the following
1. Has squamous cell carcinoma; **OR**
2. Individual has MSI-H or dMMR tumors; **OR**
~~3. Is using as second-line or subsequent therapy;~~

AND
D. Individual has a current ECOG performance status of 0-2 or Karnofsky performance score of 60-100; **AND**
E. Individual is using in combination with nivolumab (Opdivo);

OR

XII. Individual has a diagnosis of Gastric Cancer (NCCN 2A); **AND**
A. Individual is medically fit for surgery, but with surgically unresectable disease; **AND**
B. Individual has MSI-H or dMMR tumors; **AND**
C. Individual is using in combination with nivolumab (Opdivo); **AND**
~~D. Individual has a PD-L1 CPS ≥ 5; **AND**~~
~~E.~~D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; AND
~~F.~~E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XIII. Individual has a diagnosis of advanced Hepatocellular Carcinoma and the following criteria are met (Label, NCCN 2A):
A. Individual is using in combination with nivolumab (Opdivo); **AND**
~~B. Individual is using as subsequent therapy for progressive disease; **AND**~~
~~C.~~B. Individual has a current ECOG performance status of 0-2; **AND**
~~D.~~C. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
~~E.~~D. 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 relapsed/refractory advanced classic Kaposi Sarcoma and the following criteria are met (NCCN 2A):
A. Individual is using in combination with nivolumab (Opdivo); **AND**
B. Individual is using as subsequent systemic therapy; **AND**
C. Individual does not have multicentric Castleman Disease (MCD) or KSHV-associated inflammatory cytokine syndrome (KICS);

OR

XV. Individual has a diagnosis of unresectable Malignant Pleural or Peritoneal Mesothelioma and using as first line therapy (Label, NCCN 2A); **AND**
A. Individual is using in combination with 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

XVI. Individual has a diagnosis of Malignant Pleural or Peritoneal 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

XVII. Individual has a diagnosis of Malignant Pleural Mesothelioma (NCCN 1); **AND**
A. Individual has epithelioid histology; **AND**
B. Individual is using as induction systemic therapy; **AND**
C. Individual is using in combination with nivolumab (Opdivo); **AND**
D. Individual uses prior to surgical exploration for stage I disease; **AND**
E. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

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

OR

XVIII. Individual has a diagnosis of metastatic Melanoma with brain metastases (NCCN 2A); **AND**
A. Individual has a primary diagnosis of melanoma; **AND**
B. Using in one of the following ways:
1. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017); **OR**
2. Individual has BRAF-non-specific asymtopmatic brain metastases; **AND**
C. Individual is using as a single agent or 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

XIX. 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) (Label, NCCN 1, 2A);

OR

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);

OR

D. In cutaneous melanoma, low-dose Yervoy (1 mg/kg every 3 weeks) used for a total of four doses in combination with pembrolizumab, followed by pembrolizumab every 3 weeks as monotherapy for 2 years; **AND**
1. The combination is used as second-line or subsequent therapy for progression following anti-PD-1 therapy in advanced melanoma; **AND**
2. Individual has not received treatment with another anti-CTLA-4 agent; **AND**
3. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XX. Individual is using ~~as a single agent~~ in combination with Opdivo 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 (~~Label,~~ NCCN 2A));

OR

XXI. Individual has a diagnosis of Merkel Cell Carcinoma (NCCN 2A); **AND**
A. Individual is using as a single agent or in combination with nivolumab; **AND**
B. Individual has M1 disseminated disease if anti-PD-L1 or anti-PD-1 therapy is contraindicated or disease has progressed on anti-PD-L1 or anti-PD-1 monotherapy; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXII. Individual is using for first line treatment of recurrent, advanced, or metastatic Non-Small Cell Lung Cancer (NSCLC) (Label, NCCN 1); **AND**
A. Individual is using in combination with nivolumab; **AND**
B. Individual does not have presence ofactionable molecular markers*; **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

XXIII. Individual is using for continuation treatment of recurrent, advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) (NCCN 1, 2A); **AND**
A. Individual is using ~~I~~in combination with nivolumab (Opdivo); **AND**

B. Individual achieved a response or has stable disease following first line therapy of nivolumab + ipilimumab +/- chemotherapy given; **AND**
C. Individual does not have presence of actionable molecular markers*; **AND**
D. Current ECOG performance status of 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXIV. Individual is using for first line treatment of recurrent, advanced, or metastatic Non-Small Cell Lung Cancer (NSCLC) (Label, NCCN 1, 2A); **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 ofactionalbe molecular markers*; **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

XXV. Individual is using for the treatment of intermediate- or poor-risk advanced Renal Cell Carcinoma (RCC) (Label, NCCN 1, 2A); **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;

OR

XXVII. 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] or polymerase epsilon/delta [POLE/POLD1]); **AND**
B. Individual is using in combination with nivolumab; **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**
A. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

XXVIII. Individual has a diagnosis of advanced or metastatic soft tissue sarcoma (NCCN 2A); **AND**
A. Individual is using in combination with nivolumab; **AND**
B. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

***Note:** Actionable molecular markers include EGFR, ALK, ROS1, BRAF, NTRK, MET, RET, ERBB2 (HER2), and NRG1 mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes (NCCN 1, 2A).

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. Individual is using in combination with Opdivo Qvantig (nivolumab hyaluronidase); **OR**
III. 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]

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-C16.9	Malignant neoplasm of stomach
C17.0-C17.9	Malignant neoplasm of small intestine
C18.0-C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C23	Malignant neoplasm of gallbladder
C24.0-24.9	Malignant neoplasm of other and unspecified parts of biliary tract
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C38.4	Malignant neoplasm of pleura
C40.00-C40.92	Malignant neoplasm of bone and articular cartilage of limbs
C41.0-C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C44.42	Squamous cell carcinoma of skin of scalp and neck
C43.0-C43.9	Malignant melanoma of skin
C45.0-C45.9	Mesothelioma
C46.0-C46.9	Kaposi's sarcoma
C48.1-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C4A.0-C4A.9	Merkel cell carcinoma
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
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
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: 05/16/2025
Document History:

- 05/16/2025 – Select Review: Align with Opdivo's updates when used in combination with Yerovy due to FDA indication updates and NCCN recommendations. Coding Reviewed: No changes.
- 02/21/2025 – Annual Review: For Ampullary Adenocarcinoma add NCCN category 2A recommendation in combination with nivolumab in unresectable or metastatic MSI-H/dMMR tumors. For Esophageal and Esophagogastric Junction Cancers add NCCN 2A recommendation in combination with nivolumab for relieving dysphagia in those medically fit and planned for esophagectomy. Add NCCN 2A recommendation for use in combination with nivolumab for palliative care who are not surgical candidates or has unresectable, locally advanced, recurrent, or metastatic disease .For Gastric Cancer add NCCN 2A recommendation for use in combination with nivolumab in those medically fit for surgery, but with surgically unresectable disease with MSI-H or dMMR tumors. For Malignant Pleural Mesothelioma add NCCN 1 recommendation for use in combination with nivolumab as induction systemic therapy in epithelioid histology disease. Update Existing NCCN 2A recommendations for Bone Cancer to clarify existing NCCN 2A recommendation. Update Colorectal cancer including Appendiceal Adenocarcinoma by adding POLE/POLD1 mutation. Update Non-Small Cell Lung Cancer by removing tumor requirement in first-line treatment of recurrent, advanced, or metastatic disease for PDL1 expression positive (≥ 1%). Update Small Bowel Adenocarcinoma with addition of POLE/POLD1 mutation. Remove Ampullary cancer from the small bowel adenocarcinoma criteria. Coding Reviewed: Added ICD-10-CM C16.0-C16.9, C23, C24.0-24.9, C33, C49.0-C49.9, C4A.0-C4A.9, C72.0, C72.1. Added C48.8 to existing range of C48.0-C48.2 and updated description. Added C45.1-C45.9 to C45.0 and updated description. Removed C22.2-C22.7 from range C22.0-C22.9 to only include C22.0, C22.1, C22.8, C22.9.
- 02/23/2024 – Annual Review: Add NCCN category 2A recommendation for Biliary Tract Cancers in combination with nivolumab. Update existing NCCN 2A recommendation for use in colorectal cancer criteria when used in combination with nivolumab. Added criteria to ensure no prior immunotherapy received. Update existing NCCN 2A recommendations for use in Gastric or Esophageal and Esophagogastric Junction cancers in second-line or subsequent therapy and MSI-H/dMMR tumors in unresectable locally advanced, recurrent or metastatic disease or neoadjuvant/perioperative immunotherapy. Update existing NCCN 2A criteria in Hepatocellular carcinoma for use in combination with nivolumab. Update existing NCCN 2A criteria for use in classic Kaposi sarcoma for appropriate population usage. Update existing NCCN 2A criteria to include single agent or combination use with nivolumab for use in BRAF-non-specific asymptomatic brain metastases from melanoma. Add NCCN 2A recommendation for use in Merkel Cell Carcinoma in combination with nivolumab in M1 disseminated disease if progression on anti-PD-1 or anti-PD-L1 monotherapy or anti-PD-1 or anti-PD-L1 is contraindicated. Clarify existing Small Bowel Adenocarcinoma criteria and Ampullary Adenocarcinoma criteria from NCCN guidelines. Add NCCN 2A recommendation for use in metastatic soft tissue sarcoma in combination with nivolumab. Wording and formatting updates. Coding Reviewed: No changes.
- 08/18/2023 – Select Review: Update existing first line use criteria for NSCLC to clarify use in combination with nivolumab and with or without platinum therapy. Coding Reviewed: No changes.
- 03/13/2023 – Annual Review: Update existing criteria due to FDA label update in melanoma when used in combination with Opdivo. Correct Mesothelioma criteria to remove "first-line therapy" in RN 7 as language is redundant for RN 6. Coding Reviewed: No changes.
- 02/24/2023 – Annual Review: Add new NCCN 2A recommendations for use in Bone cancer, Kaposi Sarcoma, and Malignant Peritoneal disease. Clarify existing criteria with NCCN 2A updates in colorectal cancer with the addition of advanced appendiceal adenocarcinoma. For the NSCLC criteria, clarify use in first-line treatment with the inclusion of advanced to recurrent or metastatic disease. Also added criteria for continuation maintenance therapy after first-line use. Clarified existing Small bowel adenocarcinoma criteria. Coding Reviewed: Added ICD-10-CM C40.00-C40.92, C41.0-C41.9, C46.0-C46.9, C48.1-C48.2.
- 06/13/2022 – Select Review: Add FDA approval for use in unresectable advanced or metastatic esophageal squamous cell carcinoma. Coding Reviewed: Added ICD-10-CM C00.0-C14.8, C15.3-C15.9, C44.42.
- 05/20/2022 – Select Review: Correct use in Advanced ampullary cancer as combination therapy only. Coding Reviewed: No changes.
- 02/25/2022 – Annual Review: Add NCCN 2A recommendation for use Advanced Ampullary Cancer. Update Malignant Peritoneal Mesothelioma (MPM) to include Peritoneal Mesothelioma (MPeM). Update references. Coding Reviewed: No changes.
- 02/19/2021 – Annual Review: Update hepatocellular criteria to allow use as subsequent therapy in general per guidelines. Update NSCLC criteria to specify any actionable molecular marker with a note to further expand on definition and marker testing. Remove indication for small cell lung cancer per label and NCCN recommendation downgrade. Wording, formatting, and reference updates. Coding Reviewed: No changes.
- 11/20/2020 – Select Review: Update criteria to add indication for first line treatment with 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.

References

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2024. URL: http://www.clinicalpharmacology.com. Updated periodically DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm..
2. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med. 2022 Feb 3;386(5):449-462. doi: 10.1056/NEJMoa2111380. Available at: pubmed.ncbi.nlm.nih.gov/35108470/
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018; 378(22):2093-2104.
5. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Eng J Med.* 2019;381:2020-31.
6. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2024; Updated periodically.
7. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicenter randomized phase 2 study. *Lancet Oncol.* 2018;19:672-81.
8. Long GV, Atkinson V, Menzies AM, et al. A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients with melanoma brain metastases: the Anti-PD1 Brain Collaboration. *J Clin Oncol.* 2017;35:9508[abstract]. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9508.
9. NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed January 17, 2024.
    a. Ampullary adenocarcinoma. V1.2024. Revised December 13, 2023.
    b. Biliary Tract Cancers. V3.2023. Revised November 8, 2023.
    c. Bone cancer. V1.2024. Revised August 7, 2023.
    d. Central Nervous System Cancers V.2023. Revised March 24, 2023.
    e. Colon Cancer V4.2023. Revised November 16, 2023.
    f. Esophageal and esophagogastric junction cancers. V3.2023. Revised August 29, 2023.
    g. Kaposi Sarcoma. V1.2024. Revised November 7, 2023.
    h. Kidney Cancer. V2.2024. Revised January 3, 2024.
    i. Malignant Pleural Mesothelioma V1.2024. Revised November 21, 2023.
    j. Malignant Peritoneal Mesothelioma. V1.2024. Revised November 21, 2023.
    k. Cutaneous Melanoma V3.2023. Revised October 27, 2023.
    l. Neuroendocrine and Adrenal Tumors. V1.2023. Revised August 2, 2023.
    m. Non-Small Cell Lung Cancer. V1.2024. Revised December 21, 2023.
    n. Rectal Cancer V6.2023. Revised November 16, 2023.
    o. Small Bowel Adenocarcinoma. V1.2024. Revised December 20, 2023.
    p. Uveal Melanoma. V1.2023. Revised May 4, 2023.
10. Margolin K, Ernstoff MS, Hamid O. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012; 13(5):459-465.
11. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol.* 2018;36:773-9. Available at: https://ascopubs.org/doi/pdf/10.1200/JCO.2017.76.9901.
12. Tawbi HA, Forsyth AJ, Algazi AP, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. *N Engl J Med* 2018;379:722-730. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1805453?query=recirc_curatedRelated_article.
13. Tawbi, HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (Checkmate 204): final results of an open-label, multicentre, phase 2 study. Lancet Oncol 2021; 22: 1692-1704. Available at: https://pubmed.ncbi.nlm.nih.gov/34774225/.

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.