Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Other: TYPE B DRUG

Service Description

This document addresses the use of Yervoy® (ipilimumab), a recombinant human cytotoxic T-lymphocyte antigen 4 (CTLA-4)- blocking monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of advanced melanoma (cutaneous and uveal), renal cell carcinoma, colorectal cancer, and non-small cell lung cancer.

Background Information

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.

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

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 an 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.

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 in general.

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 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).

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

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 housework, 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 can 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.

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

- 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.

Approved Indications

Yervoy (ipilimumab) FDA Approved Indications
Melanoma • Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older as a single agent or in combination with nivolumab. • Adjuvant treatment of adult patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.
Renal Cell Carcinoma (RCC) Treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma, as first-line treatment in combination with nivolumab.
Colorectal Cancer Treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab. **This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Hepatocellular Carcinoma Treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab. **This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Non-Small Cell Lung Cancer (NSCLC) • Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab. • Treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy.
Malignant Pleural Mesothelioma Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab.
Esophageal Cancer Treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, as first line treatment in combination with nivolumab

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 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 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.

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

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.

NCCN provides a 2A recommendation for use of Yervoy in combination with Opdivo for individuals with MSI-H or dMMR metastatic CRC as primary treatment for individuals who have not received any previous chemotherapy. There is insufficient evidence to support its use in this situation.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9228	Injection, ipilimumab, 1 mg [Yervoy]

ICD-10	Description
C00.0-C14.8	Malignant neoplasm of lip, oral cavity and pharynx
C15.3-C15.9	Malignant neoplasm of esophagus
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
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	Mesothelioma of pleura
C46.0-C46.9	Kaposi's sarcoma
C48.1-C48.2	Malignant neoplasm of peritoneum
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

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

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

Medical Necessity Guidelines

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.

Ipilimumab (Yervoy®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. 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; **AND**
   - B. Individual has failed and progression 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

ii. Individual has a diagnosis of Biliary Tract Cancers (NCCN 2A); **AND**
   - A. Individual is using in combination with nivolumab; **AND**
   - B. 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. Individual has not received another anti-PD-1 or anti-PD-L1 agent; **AND**
   - D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

iii. 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/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 (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**
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 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; **AND**
D. Individual has not received prior treatment with anti-PD-1, anti-PD-L1, any antibody or drug specifically targeting T-cell co- stimulation, or checkpoint pathways; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

v. 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

vi. 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

vii. 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**
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

viii. 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. 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

ix. 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

x. 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

xi. 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

xii. 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

xiii. 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);
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**
4. 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

xiv. Individual is using as a single agent 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);

OR

xv. 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

xvi. 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 of actionable molecular markers*; **AND**
C. Individual has PD-L1 expression positive (≥ 1%) tumor; **AND**
D. Current ECOG performance status of 0-2; **AND**
E. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
F. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

xvii. 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 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

xviii. 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 of actionable 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

xix. 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;

OR

xx. Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA) including Advanced Ampullary cancer (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; **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

xxi. Individual has a diagnosis of advanced or metastatic soft tissue sarcoma and (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, and ERBB2 (HER2) 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 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).

B. Criteria For Continuation of Therapy

i. MMM considers continuation of ipilimumab (Yervoy) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:
   A. A current oncology note documenting the patient's response to treatment showing no progression of disease.
   B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results (every six months).

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

C. Authorization Duration

Diagnosis	Initial Approval Duration	Reauthorization Approval Duration	Recommended Treatment Duration
• Unresectable or Metastatic Melanoma • Renal Cell Carcinoma • Colorectal Cancer • Hepatocelullar Carcinoma	Up to 3 months	If needed to complete a total of 3 months of therapy	3 months
• Adyuvant treatment of melanoma	Up to 3 months	Up to 6 months	3 years
• Non-Small Cell Lung Cancer (NSCLC) • Malignant Pleural Mesothelioma • Esophageal Cancer	Up to 6 months	Up to 6 months	2 years

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Individual has an autoimmune disease which requires treatment with immunosuppressant drugs.
ii. When the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.

Limits or Restrictions

A. Quantity Limitations
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

FDA Approved Indication	Dosing	Duration of Therapy
Melanoma	<u>Unresectable or metastatic melanoma</u> • Yervoy 3 mg/kg every 3 weeks for a maximum of 4 doses. • Yervoy 3 mg/kg immediately following nivolumab 1 mg/kg on the same day, every 3 weeks for 4 doses. After completing 4 doses of	<u>Unresectable or metastatic melanoma</u> 3 months (one dose every 3 weeks for 4 doses)

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

	the combination, administer nivolumab as a single agent. Adjuvant Treatment of Melanoma: Yervoy 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years.	Adjuvant Treatment of Melanoma Every 3 weeks up to a maximum of 4 doses, then Every 12 weeks for up to 3 years
Renal Cell Carcinoma (RCC)	1 mg/kg immediately following nivolumab 3 mg/kg on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab.	3 months (one dose every 3 weeks for 4 doses)
Colorectal Cancer	Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer Yervoy 1 mg/kg intravenously over 30 minutes immediately following nivolumab 3 mg/kg intravenously over 30 minutes on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer nivolumab as a single agent.	3 months (one dose every 3 weeks for 4 doses)
Hepatocellular Carcinoma	Yervoy 3 mg/kg intravenously over 30 minutes immediately following nivolumab 1 mg/kg intravenously over 30 minutes on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer nivolumab as a single agent.	3 months (one dose every 3 weeks for 4 doses)
Non-Small Cell Lung Cancer (NSCLC)	• Yervoy 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks. • Yervoy 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks and 2 cycles of platinum-doublet chemotherapy.	Until disease progression, unacceptable toxicity, or up to 2 years.
Malignant Pleural Mesothelioma	Yervoy 1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks.	Until disease progression, unacceptable toxicity, or up to 2 years.
Esophageal Cancer	1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks or 360 mg every 3 weeks.	Until disease progression, unacceptable toxicity, or up to 2 years.
Exceptions		
None		

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

Reference Information

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2023. 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.; 2023; 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™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed January 17, 2023.
    a. Ampullary Adenocarcinoma. V2.2022. Revised December 6, 2022.
    b. Bone Cancer. V2.2023. Revised September 28, 2022.
    c. Central Nervous System Cancers. V1.2023. Revised September 29, 2022.
    d. Colon Cancer. V2.2022. Revised October 27, 2022.
    e. Esophageal and Esophagogastric Junction Cancers. V5.2022. Revised December 5, 2022.
    f. Hepatobiliary Cancers. V5.2022. Revised January 13, 2023.
    g. Kaposi Sarcoma. V1.2023. Revised December 20, 2022.
    h. Kidney Cancer. V4.2023. Revised January 18, 2023.
    i. Malignant Peritoneal Mesothelioma. V1.2023. Revised December 15, 2022
    j. Malignant Pleural Mesothelioma. V1.2022. Revised December 22, 2021.
    k. Cutaneous Melanoma. V1.2023. Revised December 22, 2022.
    l. Neuroendocrine and Adrenal Tumors. V2. 2022. Revised December 21, 2022.
    m. Non-Small Cell Lung Cancer. V3.2023. Revised April 13, 2023.
    n. Rectal Cancer. V3.2022. Revised October 27, 2022.
    o. Small Bowel Adenocarcinoma V1.2023. Revised January 9, 2023.
    p. Uveal Melanoma. V2.2022. Revised December 22, 2022.

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.

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
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.	11/18/2024	12/17/2024
Select Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024
Policy Inception	Elevance Health's Medical Policy adoption	N/A	11/30/2023

Revised: 09/23/2024

Policy Name	Policy Number	Scope
Ipilimumab (Yervoy®)	MP-RX-FP-106-23	☒ MMM MA ☒ MMM Multihealth