Yervoy® (ipilimumab)
(Intravenous)

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I. Length of Authorization Δ 1,5,6,8-12,17-19,20,24,27-29,31,33,39-42,44,46-49,53,54

- Initial: Prior authorization validity will be provided initially for 6 months, unless otherwise specified.
  - Cutaneous Melanoma (neoadjuvant treatment in combination with nivolumab): Prior authorization validity will be provided for a maximum of 6 weeks of therapy (2 doses).
  - Prior authorization validity will be provided for a maximum of 12 weeks (2 doses) for the following indications:
    - ❖ Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (neoadjuvant/perioperative adenocarcinoma)
    - ❖ Gastric Cancer (neoadjuvant or perioperative)
  - Prior authorization validity will be provided up to a maximum of 12 weeks (4 doses) of therapy (validity may be extended to 16 weeks if 4 doses were not administered within the 12-week time frame) for the following indications:
    - ❖ Ampullary Adenocarcinoma
    - ❖ Appendiceal Adenocarcinoma
    - ❖ CNS Cancer (in combination with nivolumab)
    - ❖ Colorectal Cancer
    - ❖ Cutaneous Melanoma (first-line therapy, subsequent therapy, OR adjuvant therapy in combination with nivolumab)*
    - ❖ Hepatocellular Carcinoma
    - ❖ Merkel Cell Carcinoma (every 3 weeks dosing regimen)
    - ❖ Renal Cell Carcinoma
    - ❖ Small Bowel Adenocarcinoma

- Uveal Melanoma

** Requests for Cutaneous Melanoma first-line and subsequent therapy may be renewed if the patient meets the provisions for re-induction therapy.*

- Renewal: Prior authorization validity may be renewed every 6 months thereafter, unless otherwise specified.
  - Cutaneous Melanoma (single agent adjuvant therapy): Prior authorization validity will be provided for 60 weeks of therapy (8 total doses).
  - Prior authorization validity may NOT be renewed for the following indications:
    - Ampullary Adenocarcinoma
    - Appendiceal Adenocarcinoma
    - CNS Cancer (in combination with nivolumab)
    - Colorectal Cancer
    - Cutaneous Melanoma (first-line, subsequent, or neoadjuvant/adjuvant therapy in combination with nivolumab)*
    - Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (excluding PD-L1 squamous cell carcinoma)
    - Gastric Cancer
    - Hepatocellular Carcinoma
    - Merkel Cell Carcinoma (every 3 weeks dosing regimen)
    - Renal Cell Carcinoma
    - Small Bowel Adenocarcinoma
    - Uveal Melanoma

    ** Requests for Cutaneous Melanoma first-line and subsequent therapy may be renewed if the patient meets the provisions for re-induction therapy.*
  - Prior authorization validity may be renewed up to a maximum of 2 years of therapy (18 doses) for the following:
    - Biliary Tract Cancers (subsequent therapy)
    - Bone Cancer
    - Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (PD-L1 squamous cell carcinoma)
    - Kaposi Sarcoma
    - Non-Small Cell Lung Cancer
    - Peritoneal Mesothelioma (first-line therapy)**
    - Pleural Mesothelioma (first-line/induction therapy)**

    *** Including pericardial mesothelioma and tunica vaginalis testis mesothelioma*

II. Dosing Limits

Max Units (per dose and over time) [HCPCS Unit]:

Indication	Billable Units (BU)	Per unit time (days)
Renal Cell Carcinoma (RCC), Small Bowel Adenocarcinoma (SBA), Ampullary Adenocarcinoma, Colorectal Cancer (CRC), Appendiceal Adenocarcinoma	150 billable units	21 days x 4 doses
Pleural Mesothelioma (PM), Peritoneal Mesothelioma (PeM), Soft Tissue Sarcoma, Gastric Cancer, Biliary Tract Cancers, Bone Cancer, Kaposi Sarcoma, Esophageal and Esophagogastric/ Gastroesophageal Junction Cancer, NSCLC, Gestational Trophoblastic Neoplasia	150 billable units	42 days
Merkel Cell Carcinoma	*Initial* 350 billable units	21 days x 4 doses
	Maintenance 150 billable units	42 days
Hepatocellular Carcinoma (HCC)	350 billable units	21 days x 4 doses
CNS Cancers	*Initial* 1150 billable units	21 days x 4 doses
	Maintenance 1150 billable units	84 days
Cutaneous Melanoma	*Initial* 350 billable units	21 days x 4 doses
	Maintenance 350 billable units	84 days x 4 doses
Uveal Melanoma	1150 billable units	21 days x 4 doses

III. Initial Approval Criteria [1]

Prior authorization validity is provided in the following conditions:

- Patient is at least 18 years of age, unless otherwise indicated; **AND**

Ampullary Adenocarcinoma ‡ [2,120e]

- Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used in combination with nivolumab; **AND**
- Patient has intestinal type disease; **AND**
    - Used as first-line therapy for metastatic disease; **OR**

- Used as subsequent therapy; **AND**
  - Patient progressed on or was intolerant to a prior line of treatment that included a fluoropyrimidine AND oxaliplatin or irinotecan, unless contraindicated

Biliary Tract Cancers (Gallbladder Cancer or Intra-/Extra-Hepatic Cholangiocarcinoma) ‡ [2,46,115e]

- Used in combination with nivolumab; **AND**
- Patient has tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used as subsequent treatment for progression on or after systemic treatment for unresectable, gross residual (R2), or metastatic disease; **AND**
- Disease is refractory to standard therapies or there are no standard treatment options available; **AND**

• Use of ipilimumab will be restricted to patients with a contraindication or intolerance to pembrolizumab

Bone Cancer ‡ [2,46,115e]

- Patient has one of the following: Ewing sarcoma*, Chondrosarcoma *(excluding mesenchymal chondrosarcoma)*, Osteosarcoma, or Chordoma; **AND**
- Patient has tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used in combination with nivolumab; **AND**
- Patient has unresectable or metastatic disease that progressed following prior treatment; **AND**
- Patient has no satisfactory alternative treatment options; **AND**

• Use of ipilimumab will be restricted to patients with a contraindication or intolerance to pembrolizumab

**Other primary round cell tumors of the bone (eg, CIC::DUX4, BCOR::CCNB3) can be treated like Ewing Sarcoma*

Central Nervous System (CNS) Cancer ‡ [2,4,8,10,11,27,81e]

- Used for the treatment of brain metastases in patients with BRAF non-specific melanoma; **AND**
- Used in combination with nivolumab; **AND**
  - Used as initial treatment in patients with small asymptomatic limited brain metastases for newly diagnosed or stable systemic disease or if reasonable systemic treatment options exist; **OR**

- Used for recurrent limited brain metastases; **OR**
- Used as primary treatment in patients with small asymptomatic extensive brain metastases; **OR**
- Used for recurrent extensive brain metastases with stable systemic disease or reasonable systemic treatment options

Colorectal Cancer (CRC) † ‡ [1,2,19,31,42,84e-86e,93e,122e]

- Patient is at least 12 years of age; **AND**
- Patient has microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used in combination with nivolumab; **AND**
  - Used as primary/initial treatment for unresectable or medically inoperable, recurrent, advanced, or metastatic disease; **OR**
  - Used as subsequent therapy for unresectable or medically inoperable, advanced, or metastatic disease; **AND**
    - Disease progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based chemotherapy, unless contraindicated; **OR**
  - Used as neoadjuvant therapy for advanced or metastatic disease

Appendiceal Adenocarcinoma – Colon Cancer ‡ [2,3,109e]

- Patient has microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used in combination with nivolumab; **AND**
- Used for advanced or metastatic disease; **AND**
  - Used as primary or initial treatment; **OR**
  - Used as subsequent treatment; **AND**
    - Disease progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based chemotherapy, unless contraindicated

Esophageal Cancer and Esophagogastric/Gastroesophageal Junction Cancers † ‡ [1,2,45,53,104e]

- Used in combination with nivolumab; **AND**
- Used as first-line therapy; **AND**
  - Patient has squamous cell carcinoma; **AND**
  - Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**

- Tumor expresses PD-L1 (CPS ≥1) as determined by an FDA-approved or CLIA compliant test❖; **AND**

- Use of ipilimumab in combination with nivolumab will be restricted to patients with a contraindication or intolerance to one of the following:
  - Nivolumab/(fluorouracil or capecitabine)/(cisplatin or oxaliplatin)
  - Pembrolizumab/(fluorouracil or capecitabine)/(cisplatin or oxaliplatin); **OR**

- Used as neoadjuvant or perioperative therapy; **AND**
  - Patient has adenocarcinoma; **AND**
  - Used as primary treatment for patients who are medically fit for surgery with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, Any N disease; **AND**
  - Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test❖

Gastric Cancer ‡ [2,54]

- Used in combination with nivolumab; **AND**
- Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used as neoadjuvant or perioperative therapy; **AND**
- Used as primary treatment prior to surgery for potentially resectable locoregional disease (cT2 or higher, any N) in patients who are medically fit for surgery

Hepatocellular Carcinoma (HCC) † ‡ [1,2,29e,30e,31e,33e]

- Patient does not have Child-Turcotte-Pugh (CTP) Class C liver disease; **AND**
- Used in combination with nivolumab; **AND**
  - Used as first-line therapy; **AND**
    - Patient has unresectable or metastatic disease; **AND**
    - Use of ipilimumab in combination with nivolumab will be restricted to patients with a contraindication or intolerance to tremelimumab/durvalumab; **OR**
  - Used as subsequent therapy; **AND**
    - Used for one of the following:
      - Patient was previously treated with sorafenib †
      - Patient had disease progression on or after systemic therapy and has not previously been treated with anti-CTLA4-based combinations; **AND**

Patients with AFP ≥ 400 ng/mL ONLY:

- Use of ipilimumab in combination with nivolumab will be restricted to patients with a contraindication or intolerance to ramucirumab

Kaposi Sarcoma ‡ [2,47]

- Used in combination with nivolumab as subsequent therapy; **AND**
- Used for relapsed/refractory advanced cutaneous, oral, visceral, or nodal disease; **AND**
- Disease progressed on or did not respond to first-line therapy; **AND**
- Disease progressed on alternate first-line therapy

Renal Cell Carcinoma (RCC) † ‡ [1,2,18]

- Used in combination with nivolumab for clear cell histology; **AND**
- Used as first-line therapy; **AND**
  - Patient has poor or intermediate risk advanced disease †; **OR**
  - Patient has relapsed or stage IV (M1 or unresectable T4, M0) disease

Peritoneal Mesothelioma (PeM)* ‡ [2,56]

- Used in combination with nivolumab; **AND**
  - Used as subsequent therapy (if platinum chemotherapy was administered first-line); **OR**
  - Used as first-line therapy; **AND**
    - Patient has medically inoperable disease and/or complete cytoreduction not achievable, or presence of any high-risk features**; **OR**
    - Patient has disease progression following CRS + HIPEC if no prior adjuvant systemic therapy was given

**Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.*

*** High-risk features include: biphasic/sarcomatoid histology, nodal metastasis, Ki-67 >9%, thrombocytosis, PS=2, bicavitary disease, high disease burden/incomplete cytoreduction (Peritoneal Cancer Index [PCI] >17, completeness of cytoreduction (cc) score >1)*

Pleural Mesothelioma (PM)* † ‡ Φ [1,2,5,25,26,34,37]

- Used in combination with nivolumab; **AND**
  - Used as subsequent therapy (if platinum chemotherapy was administered first-line); **OR**
  - Used as first-line therapy in patients with medically inoperable or unresectable disease; **OR**
  - Used as induction therapy prior to surgical exploration; **AND**
    - Patient has clinical stage I disease and epithelioid histology

**Note: May also be used for pericardial mesothelioma and tunica vaginalis testis mesothelioma.*

Cutaneous Melanoma † ‡ Φ [1,2,6,17,43,4e,5e,10e,11e,20e-22e,98e,99e]

- Used as first-line therapy for unresectable or metastatic* disease †; **AND**
  - Patient is at least 12 years of age; **AND**
  - Used as a single agent or in combination with nivolumab; **OR**
- Used as subsequent therapy for unresectable or metastatic* disease; **AND**
  - Used after disease progression, intolerance, and/or projected risk of progression with BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); **AND**
    - Used as a single agent in patients at least 12 years of age; **AND**

      ➢ Patient must demonstrate an inadequate response to one of the following, unless there is a contraindication or intolerance, prior to approval of ipilimumab:
      - Pembrolizumab (patients ≥ 18 years of age)
      - Nivolumab; **OR**

    - Used in combination with nivolumab in patients at least 12 years of age; **OR**
    - Used in combination with pembrolizumab for disease progression following anti-PD-1 therapy; **OR**
  - Used as re-induction therapy in patients who experienced disease control *(i.e., complete or partial response or stable disease)* and no residual toxicity from prior use, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; **AND**
    - Used as a single agent ; **AND**
    - Patient has completed initial induction ipilimumab therapy (i.e., completion of 4 cycles within a 16 week period); **OR**
- Used as adjuvant treatment; **AND**
  - Used as a single agent; **AND**
    - Patient has stage III disease with pathologic involvement of regional lymph nodes of more than 1 mm and has undergone complete resection including total lymphadenectomy †; **AND**

    - Use of ipilimumab for adjuvant therapy will be restricted to patients with a contraindication or intolerance to pembrolizumab or nivolumab; **OR**

  - Used in combination with nivolumab; **AND**
    - Patient has oligometastatic disease and no evidence of disease (NED) following metastasis-directed therapy (i.e., complete resection, stereotactic ablative therapy or T-VEC/intralesional therapy) OR following systemic therapy followed by resection; **OR**

- Used as neoadjuvant therapy; **AND**
  - Used in combination with nivolumab; **AND**
    - Patient has stage III disease; **AND**
      - Used as primary treatment for clinically positive, resectable nodal disease; **OR**
      - Used for limited resectable disease with clinical satellite/in-transit metastases; **OR**
    - Patient has limited resectable local satellite/in-transit recurrence; **OR**
    - Patient has resectable disease limited to nodal recurrence

**Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in-transit metastases, as well as unresectable/borderline resectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease.*

Uveal Melanoma ‡ [2,20-23,32]

- Used as a single agent or in combination with nivolumab; **AND**
- Patient has metastatic or unresectable disease; **AND**

Merkel Cell Carcinoma ‡ [2,50,51,66]

- Used for M1 disseminated disease; **AND**
  - Used in combination with nivolumab; **OR**
- Used for recurrent N+ regional disease if curative surgery and curative radiation therapy (RT) are not feasible; **AND**
  - Used in combination with nivolumab

Non-Small Cell Lung Cancer (NSCLC) † ‡ [1,2,12,16,24,36,34e-36e,42e,49e,88e,109e]

- Used for recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
  - Used as first-line therapy; **AND**
    - Used for one of the following:
      - Patients with tumors that are negative for actionable molecular biomarkers** (may be KRAS G12C mutation positive)
      - Patients who are positive for one of the following molecular biomarkers: EGFR exon 20, KRAS G12C, BRAF V600E, NTRK1/2/3 gene fusion, MET exon 14 skipping, NRG1 gene fusion, or ERBB2 (HER2); **AND**
    - Used in combination with one of the following:
      - Nivolumab

- Nivolumab and platinum-doublet chemotherapy (e.g., pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology, or paclitaxel and carboplatin for squamous cell histology, etc.); **AND**

Squamous NSCLC:

- Use of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to cemiplimab/paclitaxel/(carboplatin or cisplatin); **OR**

Nonsquamous NSCLC:

- Use of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to cemiplimab/(paclitaxel or pemetrexed)/(carboplatin or cisplatin); **OR**

- Used as subsequent therapy; **AND**
  - Used for one of the following:
    - Patients who are positive for one of the following molecular biomarkers and have received prior targeted therapy**§**: EGFR S768I, L861Q, and/or G719X
    - Patients who are positive for one of the following molecular biomarkers: BRAF V600E, NTRK1/2/3 gene fusion, MET exon 14 skipping; **AND**
  - Used in combination with one of the following:
    - Nivolumab
    - Nivolumab and platinum-doublet chemotherapy (e.g., pemetrexed and either carboplatin or cisplatin for non-squamous cell histology, or paclitaxel and carboplatin for squamous cell histology, etc.); **AND**

Squamous NSCLC:

- Use of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to cemiplimab/paclitaxel/(carboplatin or cisplatin); **OR**

Nonsquamous NSCLC:

- Use of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to cemiplimab/(paclitaxel or pemetrexed)/(carboplatin or cisplatin); **OR**

- Used as continuation maintenance therapy in combination with nivolumab; **AND**
  - Patient has achieved a response or stable disease following first-line therapy with nivolumab and ipilimumab with or without chemotherapy

*** Note: Actionable molecular genomic biomarkers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, NRG1, and ERBB2 (HER2). Complete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, NRG1, and ERBB2 (HER2) via biopsy and/or plasma testing. If a clinically actionable marker is found, it is reasonable to start*

therapy based on the identified marker. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
§ *Genomic Aberration/Mutational Driver Targeted Therapies: Refer to guidelines for appropriate use.*

Small Bowel Adenocarcinoma (SBA) ‡ [2,19,29,91e,120e]

- Used in combination with nivolumab; **AND**
- Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as detected by an FDA or CLIA compliant test❖; **AND**
    - Patient has advanced or metastatic disease; **AND**
        - Used as primary treatment; **OR**
    - Patient has locally unresectable or medically inoperable disease; **AND**
        - Used as primary treatment

Soft Tissue Sarcoma ‡ [2,46,52,150e]

- Used in combination with nivolumab; **AND**
- Used for one of the following disease subtypes:
    - Extremity/Body Wall* or Head/Neck*
        - Used as subsequent therapy for advanced/metastatic disease with disseminated metastases; **AND**
            - Patient has myxofibrosarcoma, dedifferentiated liposarcoma, or undifferentiated sarcomas; **AND**
                - Use of ipilimumab in combination with nivolumab will be restricted to patients with a contraindication or intolerance to pembrolizumab; **OR**
            - Patient has cutaneous angiosarcoma
    - Retroperitoneal/Intra-Abdominal**
        - Used as one of the following:
            - Alternative systemic therapy for unresectable or progressive disease after initial therapy for unresectable localized disease; **OR**
            - Palliative subsequent therapy for stage IV disease with disseminated metastases; **AND**
        - Used for one of the following:
            - Patient has myxofibrosarcoma, dedifferentiated liposarcoma, or undifferentiated sarcomas; **AND**

- Use of ipilimumab in combination with nivolumab will be restricted to patients with a contraindication or intolerance to pembrolizumab; **OR**

➢ Patient has cutaneous angiosarcoma

- Angiosarcoma
  - Patient must demonstrate an inadequate response to a generically available agent/regimen (e.g., paclitaxel, doxorubicin, etc. *[see NCCN Soft Tissue Sarcoma guideline for complete list of alternatives]*), unless there is a contraindication or intolerance prior to approval of ipilimumab

**For atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS) of the extremity, abdominal wall, trunk that was initially diagnosed as ALT/WDLPS and shows evidence of de-differentiation, treat as other soft tissue sarcomas.*

***For well-differentiated liposarcoma (WDLPS-retroperitoneum, paratesticular) with or without evidence of de-differentiation, treat as other soft tissue sarcomas.*

Gestational Trophoblastic Neoplasia ‡ [2,64,137e,138e]

- Used in combination with nivolumab; **AND**
- Patient has multiagent chemotherapy-resistant disease; **AND**
  - Patient has intermediate placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT); **AND**
    - Patient has recurrent or progressive disease; **OR**
  - Patient has high risk disease (i.e., ≥7 Prognostic score or stage IV disease); **AND**

- Use of ipilimumab will be restricted to patients with a contraindication or intolerance to avelumab

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

Enhanced Oncology Value (EOV) Program – Redacted indications
Uses not listed above have inadequate data to support efficacy and are excluded from prior authorization validity. Other treatment options including, but are not limited to, the following may be appropriate: radiation therapy, surgery, traditional chemotherapy (e.g., platinum, taxane), compassionate use/expanded access programs, clinical trials, supportive care, integrative and complementary therapies.

❖ *If confirmed using an FDA approved assay – http://www.fda.gov/CompanionDiagnostics*

✝ FDA Approved Indication(s); ‡ Compendia Recommended Indication; Φ Orphan Drug

IV. Renewal Criteria Δ 1,2,6,9-12,17-29,39-41,46-49,53,54,60-61

Prior authorization validity may be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Duration of authorization has not been exceeded *(refer to Section I)*; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe immune-mediated adverse reactions (e.g., colitis, hepatitis, dermatitis/rash, pneumonitis, nephritis/renal dysfunction, endocrinopathies, etc.), severe infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), etc.; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread

Δ Notes:

- Patients responding to therapy who relapse ≥ 6 months after discontinuation due to duration (i.e., receipt of 24 months of PD-directed therapy) are eligible to re-initiate checkpoint inhibitor therapy.
- Patients who complete adjuvant therapy and progress ≥ 6 months after discontinuation are eligible to re-initiate checkpoint inhibitor therapy for metastatic disease.
- Patients whose tumors, upon re-biopsy, demonstrate a change in actionable mutation (e.g., MSS initial biopsy; MSI-H subsequent biopsy) may be eligible to re-initiate checkpoint inhibitor therapy and will be evaluated on a case-by-case basis.

V. Dosage/Administration Δ 1,5,6,8-12,17-29,31,33,34,38-42,44,46-55,57-62,66,69

Indication	Dose
Renal Cell Carcinoma (RCC), Small Bowel Adenocarcinoma (SBA) & Ampullary Adenocarcinoma	Administer 1 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab on the same day, then follow with nivolumab monotherapy)
Biliary Tract Cancers	Subsequent therapy: ○ Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks) until disease progression or unacceptable toxicity for up to 2 years
Bone Cancer & Kaposi Sarcoma	Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks) until disease progression or unacceptable toxicity for up to 2 years
CNS Cancers	In combination with nivolumab: ○ Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with nivolumab on the same day, then follow with nivolumab monotherapy)
Colorectal Cancer (CRC)	Neoadjuvant therapy ○ Administer 1 mg/kg intravenously every 3 weeks for 4 doses (given in combination with nivolumab on the same day) Primary/initial treatment and Subsequent therapy ○ Administer 1 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab on the same day, then follow with nivolumab monotherapy)
Appendiceal Adenocarcinoma	Administer 1 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab on the same day, then follow with nivolumab monotherapy)
Esophageal and Esophagogastric/ Gastroesophageal Junction Cancer	Squamous cell carcinoma: ○ PD-L1 ≥ 1 (first line): Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab) until disease progression or unacceptable toxicity for up to 2 years Adenocarcinoma (MSI-H/dMMR): ○ Neoadjuvant/perioperative therapy: Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab) for 12 weeks, followed by surgery and then postoperative therapy with nivolumab
Gastric Cancer	Neoadjuvant/perioperative therapy: Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks) for 12 weeks, followed by surgery and then postoperative therapy with nivolumab
Hepatocellular Carcinoma (HCC)	Administer 3 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab on the same day, then follow with nivolumab monotherapy)
Pleural Mesothelioma (PM) & Peritoneal Mesothelioma (PeM)	Subsequent therapy: ○ Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks) until disease progression or unacceptable toxicity All other lines of therapy:

(including pericardial mesothelioma and tunica vaginalis testis mesothelioma)	○ Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 or 3 weeks) until disease progression or unacceptable toxicity for up to 2 years
Cutaneous Melanoma	Single agent as first-line or subsequent therapy: ○ Administer 3 mg/kg intravenously every 3 weeks for a maximum of 4 doses In combination with nivolumab as first-line or subsequent therapy: ○ Administer 1 mg/kg intravenously or 3 mg/kg intravenously every 3 weeks for a maximum of 4 doses (when given in combination with nivolumab on the same day, follow with nivolumab monotherapy) In combination with pembrolizumab as subsequent therapy: ○ Administer 1 mg/kg intravenously every 3 weeks for a maximum of 4 doses (given in combination with pembrolizumab on the same day, then follow with pembrolizumab monotherapy) In combination with nivolumab as neoadjuvant therapy: ○ Administer 1 mg/kg intravenously every 3 weeks for a maximum of 2 doses (given in combination with nivolumab on the same day) Single agent as adjuvant therapy: ○ Initial: Administer 3 mg/kg intravenously every 3 weeks for up to a maximum of 4 doses ○ Maintenance: Administer 3 mg/kg intravenously every 12 weeks for up to an additional 4 doses In combination with nivolumab as adjuvant therapy: ○ Administer 1 mg/kg intravenously or 3 mg/kg intravenously every 3 weeks for a maximum of 4 doses (given in combination with nivolumab on the same day)
Uveal Melanoma	Single agent: ○ Administer 3 mg/kg or 10mg/kg intravenously every 3 weeks for 4 doses In combination with nivolumab: ○ Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with nivolumab on the same day, then follow with nivolumab monotherapy)
Merkel Cell Carcinoma	In combination with nivolumab: ○ Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks) until disease progression or unacceptable toxicity OR ○ Administer 1 mg/kg intravenously OR 3 mg/kg intravenously every 3 weeks for a maximum of 4 doses (given with nivolumab every 3 weeks, may follow with nivolumab monotherapy)
Non-Small Cell Lung Cancer (NSCLC)	In combination with nivolumab: ○ Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 3 weeks), until disease progression or unacceptable toxicity for up to 2 years In combination with nivolumab and platinum-doublet chemotherapy: ○ Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 3 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles) until disease progression or unacceptable toxicity for up to 2 years

Soft Tissue Sarcoma & Gestational Trophoblastic Neoplasia (GTN)	Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks) until disease progression or unacceptable toxicity
Note: All treatments given for a maximum of 4 doses must be administered within 16 weeks of the first dose.	

VI. Billing Code/Availability Information

HCPCS Code:

- J9228 – Injection, ipilimumab, 1 mg; 1 billable unit = 1 mg

NDC(s):

- Yervoy 50 mg/10 mL injection (single-dose vial): 00003-2327-xx
- Yervoy 200 mg/40 mL injection (single-dose vial): 00003-2328-xx

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant

ICD-10	ICD-10 Description
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
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
C22.3	Angiosarcoma of liver
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	Malignant neoplasm of extrahepatic bile duct
C24.1	Malignant neoplasm of ampulla of Vater
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung

ICD-10	ICD-10 Description
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
C40.01	Malignant neoplasm of scapula and long bones of right upper limb
C40.02	Malignant neoplasm of scapula and long bones of left upper limb
C40.10	Malignant neoplasm of short bones of unspecified upper limb
C40.11	Malignant neoplasm of short bones of right upper limb
C40.12	Malignant neoplasm of short bones of left upper limb
C40.20	Malignant neoplasm of long bones of unspecified lower limb
C40.21	Malignant neoplasm of long bones of right lower limb
C40.22	Malignant neoplasm of long bones of left lower limb
C40.30	Malignant neoplasm of short bones of unspecified lower limb
C40.31	Malignant neoplasm of short bones of right lower limb
C40.32	Malignant neoplasm of short bones of left lower limb
C40.80	Malignant neoplasm of overlapping sites of bone and articular cartilage of unspecified limb
C40.81	Malignant neoplasm of overlapping sites of bone and articular cartilage of right limb
C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of left limb
C40.90	Malignant neoplasm of unspecified bones and articular cartilage of unspecified limb
C40.91	Malignant neoplasm of unspecified bones and articular cartilage of right limb
C40.92	Malignant neoplasm of unspecified bones and articular cartilage of left limb
C41.0	Malignant neoplasm of bones of skull and face
C41.1	Malignant neoplasm of mandible
C41.2	Malignant neoplasm of vertebral column
C41.3	Malignant neoplasm of ribs, sternum and clavicle
C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
C43.0	Malignant melanoma of lip
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal

ICD-10	ICD-10 Description
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites
C45.9	Mesothelioma, unspecified
C46.0	Kaposi's sarcoma of skin
C46.1	Kaposi's sarcoma of soft tissue
C46.2	Kaposi's sarcoma of palate
C46.3	Kaposi's sarcoma of lymph nodes
C46.4	Kaposi's sarcoma of gastrointestinal sites
C46.50	Kaposi's sarcoma of unspecified lung
C46.51	Kaposi's sarcoma of right lung
C46.52	Kaposi's sarcoma of left lung
C46.7	Kaposi's sarcoma of other sites
C46.9	Kaposi's sarcoma, unspecified
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C47.10	Malignant neoplasm of peripheral nerves of unspecified upper limb, including shoulder
C47.11	Malignant neoplasm of peripheral nerves of right upper limb, including shoulder
C47.12	Malignant neoplasm of peripheral nerves of left upper limb, including shoulder

ICD-10	ICD-10 Description
C47.20	Malignant neoplasm of peripheral nerves of unspecified lower limb, including hip
C47.21	Malignant neoplasm of peripheral nerves of right lower limb, including hip
C47.22	Malignant neoplasm of peripheral nerves of left lower limb, including hip
C47.3	Malignant neoplasm of peripheral nerves of thorax
C47.4	Malignant neoplasm of peripheral nerves of abdomen
C47.5	Malignant neoplasm of peripheral nerves of pelvis
C47.6	Malignant neoplasm of peripheral nerves of trunk, unspecified
C47.8	Malignant neoplasm of overlapping sites of peripheral nerves and autonomic nervous system
C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system, unspecified
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.10	Malignant neoplasm of connective and soft tissue of unspecified upper limb, including shoulder
C49.11	Malignant neoplasm of connective and soft tissue of right upper limb, including shoulder
C49.12	Malignant neoplasm of connective and soft tissue of left upper limb, including shoulder
C49.20	Malignant neoplasm of connective and soft tissue of unspecified lower limb, including hip
C49.21	Malignant neoplasm of connective and soft tissue of right lower limb, including hip
C49.22	Malignant neoplasm of connective and soft tissue of left lower limb, including hip
C49.3	Malignant neoplasm of connective and soft tissue of thorax
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.6	Malignant neoplasm of connective and soft tissue of trunk, unspecified
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C58	Malignant neoplasm of placenta
C4A.0	Merkel cell carcinoma of lip
C4A.10	Merkel cell carcinoma of eyelid, including canthus
C4A.111	Merkel cell carcinoma of right upper eyelid, including canthus
C4A.112	Merkel cell carcinoma of right lower eyelid, including canthus
C4A.121	Merkel cell carcinoma of left upper eyelid, including canthus
C4A.122	Merkel cell carcinoma of left lower eyelid, including canthus
C4A.20	Merkel cell carcinoma of unspecified ear and external auricular canal
C4A.21	Merkel cell carcinoma of right ear and external auricular canal
C4A.22	Merkel cell carcinoma of left ear and external auricular canal

ICD-10	ICD-10 Description
C4A.30	Merkel cell carcinoma of unspecified part of face
C4A.31	Merkel cell carcinoma of nose
C4A.39	Merkel cell carcinoma of other parts of face
C4A.4	Merkel cell carcinoma of scalp and neck
C4A.51	Merkel cell carcinoma of anal skin
C4A.52	Merkel cell carcinoma of skin of breast
C4A.59	Merkel cell carcinoma of other part of trunk
C4A.60	Merkel cell carcinoma of unspecified upper limb, including shoulder
C4A.61	Merkel cell carcinoma of right upper limb, including shoulder
C4A.62	Merkel cell carcinoma of left upper limb, including shoulder
C4A.70	Merkel cell carcinoma of unspecified lower limb, including hip
C4A.71	Merkel cell carcinoma of right lower limb, including hip
C4A.72	Merkel cell carcinoma of left lower limb, including hip
C4A.8	Merkel cell carcinoma of overlapping sites
C4A.9	Merkel cell carcinoma, unspecified
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum

ICD-10	ICD-10 Description
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain
C7B.1	Secondary Merkel cell carcinoma
D37.1	Neoplasm of uncertain behavior of stomach
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
D39.2	Neoplasm of uncertain behavior of placenta
O01.9	Hydatidiform mole, unspecified
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.09	Personal history of malignant neoplasm of other digestive organs
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.820	Personal history of malignant melanoma of skin
Z85.821	Personal history of Merkel cell carcinoma
Z85.830	Personal history of malignant neoplasm of bone
Z85.831	Personal history of malignant neoplasm of soft tissue

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC