CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Oncology (Injectable – CTLA-4 Antibody) – Yervoy Utilization Management Medical Policy
- Yervoy® (ipilimumab intravenous infusion – Bristol-Myers Squibb)

REVIEW DATE: 01/28/2026

OVERVIEW

Yervoy, a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody, is indicated for the following uses:[1]

- **Colorectal cancer, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)**, in combination with Opdivo® (nivolumab intravenous infusion) for the treatment of patients ≥ 12 years of age with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease.
- **Esophageal cancer**, in combination with Opdivo for the first-line treatment of adults with unresectable advanced or metastatic esophageal squamous cell carcinoma whose tumors express PD-L1 (≥1).
- **Hepatocellular carcinoma**:
  - First-line treatment of adults with unresectable or metastatic disease in combination with Opdivo.
  - In combination with Opdivo, for the treatment of adults who have been previously treated with Nexavar® (sorafenib tablets).
- **Malignant pleural mesothelioma**, in combination with Opdivo, for the first-line treatment of adults with unresectable disease.
- **Melanoma**, for unresectable or metastatic disease in patients ≥ 12 years of age, as a single agent or in combination with Opdivo.
- **Melanoma**, for adjuvant treatment of cutaneous disease in patients with pathologic involvement of regional lymph nodes of > 1 mm who have undergone complete resection, including total lymphadenectomy.
- **Non-small cell lung cancer (NSCLC)**, in combination with Opdivo, for the first-line treatment of adults with metastatic disease whose tumors express programmed death ligand-1 (PD-L1) [≥ 1%], as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.
- **NSCLC**, in combination with Opdivo and two cycles of platinum-doublet chemotherapy, for the first-line treatment of adults with metastatic or recurrent NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations.
- **Renal cell carcinoma (RCC),**in combination with Opdivo for the first-line treatment of patients with intermediate or poor risk advanced disease.

Dosing

- For "Other Uses with Supportive Evidence", limited dosing is available regarding use of Yervoy for these conditions; however, doses of up to 3 mg/kg administered once every 3 weeks are recommended in the product labeling for the majority of approved uses.
- In general, if Yervoy is administered in combination with Opdivo, both agents should be withheld if Yervoy is withheld.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Yervoy. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Yervoy as well as the monitoring required for adverse events and long-term efficacy, approval requires Yervoy to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Yervoy is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. **Colon, Rectal, or Appendiceal Cancer.** Approve for 4 months if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); OR
     - **ii.** The tumor is polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype (tumor mutation burden > 50 mutations/megabase); AND
   - **C)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
   - **D)** The medication is prescribed by or in consultation with an oncologist.

   Dosing: Approve 1 mg/kg administered intravenously not more frequently than once every 3 weeks.

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2. **Esophageal and Esophagogastric Junction Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has programmed death ligand-1 (PD-L1) positive disease (combined positive score [CPS] ≥ 1) and meets ONE of the following (a, b or c):
       - **a)** Patient has unresectable locally advanced, recurrent, or metastatic disease; OR
       - **b)** According to the prescriber, the patient is not a surgical candidate; OR
       - **c)** The medication is used as induction therapy in patients planned for esophagectomy; OR
     - **ii.** The tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) and meets ONE of the following (a, b, c, or d):
       - **a)** Patient has unresectable locally advanced, recurrent, or metastatic disease; OR
       - **b)** According to the prescriber, the patient is not a surgical candidate; OR
       - **c)** The medication is used as neoadjuvant or perioperative immunotherapy; OR
       - **d)** The medication is used as induction therapy in patients planned for esophagectomy; AND
   - **C)** The medication will be used in combination with Opdivo (nivolumab intravenous infusion); AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve ONE of the following dosing regimens (A or B):
A) Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks; OR
B) Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

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3. Hepatocellular Carcinoma. Approve for 4 months if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) The patients meets ONE of the following (i or ii):
- **i.** The medication is being used as first line and according to the prescriber, the patient has ONE of the following (a or b):
  - **a)** Liver-confined, unresectable disease and is not a transplant candidate; OR
  - **b)** Extrahepatic/metastatic disease and are deemed ineligible for resection, transplant, or locoregional therapy; OR
- **ii.** The medication is being used for subsequent therapy; AND

C) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

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4. Melanoma. Approve for the duration noted if the patient meets ALL of the following (A, B, and C):
Note: This includes cutaneous melanoma, brain metastases due to melanoma, and uveal melanoma.
A) Patient is ≥ 12 years of age; AND
B) Patient meets ONE of the following (i, ii, or iii):
- **i.** Approve for 2 months if the medication is used as neoadjuvant treatment; OR
- **ii.** Approve for 4 months if the patient has unresectable, recurrent, or metastatic melanoma; OR
- **iii.** Approve for 1 year if the medication is used as adjuvant treatment; AND
  Note: For example, in patients with cutaneous melanoma who have undergone complete resection, including total lymphadenectomy.

C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) Adjuvant treatment: Approve up to 10 mg/kg administered intravenously once every 3 weeks or 12 weeks; OR
B) Neoadjuvant treatment: Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks; OR
C) Unresectable or Metastatic Melanoma: Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

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5. Mesothelioma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has ONE of the following (i, ii, iii, or iv):
- **i.** Malignant pleural mesothelioma; OR
- **ii.** Malignant peritoneal mesothelioma; OR
- **iii.** Pericardial mesothelioma; OR

iv. Tunica vaginalis testis mesothelioma; AND

C) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

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6. Non-Small Cell Lung Cancer (NSCLC) – Recurrent, Advanced, or Metastatic Disease. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

A) Patient is ≥ 18 years of age; AND

B) The tumor is negative for the following actionable biomarkers: epidermal growth factor receptor (*EGRF) exon 19* deletion or *exon 21 L858R*, anaplastic lymphoma kinase *(ALK), RET*, and *ROS1*; AND

C) Patient meets ONE of the following (i, ii, iii, or iv):

i. Patient meets BOTH of the following (a and b):

a) The medication is used as first-line therapy; AND

b) The tumor is positive for ONE of the following mutations [(1), (2), or (3)]:

(1) Epidermal growth factor receptor (*EGFR*) exon 20 mutation; OR

(2) *ERBB2* (HER2) mutation; OR

(3) *NRG1* gene fusion; OR

ii. Patient meets BOTH of the following (a and b):

a) The medication is used as first-line or subsequent therapy; AND

b) The tumor is positive for ONE of the following mutations [(1), (2), or (3)]:

(1) *BRAF V600E* mutation; OR

(2) *NTRK1/2/3* gene fusion; OR

(3) *MET* exon 14 skipping mutation; OR

iii. Patient meets BOTH of the following (a and b):

a) The medication is used as subsequent therapy; AND

b) Tumor is positive for *EGFR S768I*, *L861Q*, and/or *G719X* mutation; OR

iv. Patient meets BOTH of the following (a and b):

a) The medication is used as first-line or continuation maintenance therapy; AND

b) The tumor has no actionable mutations; AND

Note: The tumor does NOT have the following mutations: *EFGR exon 19* deletion, *EFGR exon 21 L858R. EFGR S768I, EGFR L861Q, EGFR G719X, EGFR exon 20* insertion, *ALK* rearrangement, *ROS1* rearrangement, *BRAF V600E, NTRK 1/2/3* gene fusion, *METex14* skipping, *RET* rearrangement, *ERBB2 (HER2)*, and *NRG1* gene fusion.

D) The medication with is used in combination with Opdivo (nivolumab intravenous infusion); AND

E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

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7. Renal Cell Carcinoma. Approve for 4 months if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has relapsed or Stage IV disease; AND

C) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 3 weeks.

Other Uses with Supportive Evidence

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8. Ampullary Adenocarcinoma. Approve for 4 months if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
- **C)** Patient meets ONE of the following (i or ii):
  - **i.** The medication is used first-line for metastatic disease; OR
  - **ii.** The medication is used for subsequent therapy; AND
- **D)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

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9. Biliary Tract Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has tumor mutation burden-high (TMB-H) disease; AND
  Note: TMB-H is defined as 10 or more mutations per megabase.
- **C)** Patient meets ONE of the following (i or ii):
  - **i.** Unresectable, resected with gross residual, or metastatic disease; OR
  - **ii.** Resectable locoregionally advanced disease; AND
- **D)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

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10. Bone Cancer. Approve for 1 year if the patient meets the ALL of following (A, B, C, D, E, F, and G):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable or metastatic disease; AND
- **C)** Patient has progressed following prior treatment; AND
- **D)** Patient has tumor mutation burden-high (TMB-H) disease; AND
  Note: TMB-H is defined as 10 or more mutations per megabase.
- **E)** Patient has ONE of the following (i, ii, iii, iv, or v):
  - **i.** Chondrosarcoma; OR
    Note: Includes mesenchymal chondrosarcoma and dedifferentiated chondrosarcoma.
  - **ii.** Chordoma; OR
  - **iii.** Ewing sarcoma; OR
  - **iv.** High-grade undifferentiated pleomorphic sarcoma; OR
  - **v.** Osteosarcoma; AND
- **F)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **G)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

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11. Cervical Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent or metastatic disease; AND
- **C)** The medication is used as second-line or subsequent therapy; AND
- **D)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
- **A)** Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks; OR
- **B)** Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

12. Endometrial Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, unresectable, or metastatic disease; AND
- **C)** Patient has tumor mutation burden-high (TMB-H) tumors; AND
  Note: TMB-H is defined as 10 or more mutations per megabase.
- **D)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

13. Gastric Cancer. Approve for 4 months if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR); AND
- **C)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
- **A)** Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks; OR
- **B)** Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

14. Gestational Trophoblastic Neoplasia. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient has multiagent chemotherapy-resistant disease; AND
  Note: Examples of chemotherapy regimens include etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.
- **B)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **C)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

15. Head and Neck Cancers. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND

B) Patient has advanced, metastatic, recurrent, persistent, or unresectable disease; AND
C) Patient has non-nasopharyngeal disease; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

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16. Kaposi Sarcoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has relapsed or refractory disease; AND
C) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

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17. Merkel Cell Carcinoma. Approve for 4 months if the patient meets BOTH of the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

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18. Neuroendocrine Tumors. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has locoregional unresectable, advanced, or metastatic disease; AND
C) Patient meets ONE of the following (i, ii, iii, iv, or v):
  i. Patient has well differentiated, Grade 3 disease; OR
  ii. Patient has extrapulmonary poorly differentiated neuroendocrine carcinoma; OR
  iii. Patient has large or small cell carcinoma; OR
  iv. Patient has mixed neuroendocrine-non-neuroendocrine neoplasm; OR
  v. Patient has adrenocortical carcinoma; AND
D) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

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19. Pancreatic Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 18 years of age; AND
B) Patient has locally advanced, metastatic, or recurrent disease; AND
C) Tumor is tumor mutational burden-high (TMB-H); AND
  Note: TMB-H is defined as 10 or more mutations per megabase.
D) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

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20. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has locally unresectable, medically inoperable, advanced, or metastatic disease; AND
- **C)** Patients meets ONE of the following (i or ii):
  - **i.** The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); OR
  - **ii.** The tumor is polymerase epsilon/delta (POLE/POLD1) mutation positive with ultra-hypermutated phenotype (tumor mutation burden > 50 mutations/megabase); AND
- **D)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 3 weeks.

21. Soft Tissue Sarcoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has ONE of the following (i or ii):
  - **i.** Patient has advanced, unresectable, progressive, or metastatic disease and has ONE of the following (a, b, c, d, e, f, or g):
    - **a)** Myxofibrosarcoma; OR
    - **b)** Undifferentiated pleomorphic sarcoma; OR
    - **c)** Dedifferentiated liposarcoma; OR
    - **d)** Cutaneous angiosarcoma; OR
    - **e)** Undifferentiated sarcoma; OR
    - **f)** Rhabdomyosarcoma; OR
    - **g)** Tumor mutation burden-high (TMB-H); OR
      Note: TMB-H is defined as 10 or more mutations per megabase.
  - **ii.** Angiosarcoma
- **C)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

22. Vaginal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent or metastatic disease; AND
- **C)** The medication is used as second-line or subsequent therapy; AND
- **D)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
- **A)** Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks; OR
- **B)** Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

23. Vulvar Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND

B) Patient has advanced, recurrent, or metastatic disease; AND
C) The medication is used as subsequent therapy; AND
D) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Yervoy is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Colon, Rectal, or Appendiceal Cancer:** Added the tumor is polymerase epsilon/delta (POLE/POLD1) mutation positive as new option for approval. **Hepatocellular Carcinoma:** Removed requirements that the patient has Child-Pugh Class A liver function and patient has tried at least one tyrosine kinase inhibitor. Added requirement that the medication is used for subsequent therapy. Removed option for approval that the patient has liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease. Added "liver-confined" to liver-confined, unresectable disease and is not a transplant candidate. Revised metastatic disease or extensive liver tumor burden to extrahepatic/metastatic disease and are deemed ineligible for resection, transplant, or locoregional therapy. **Melanoma:** Added approve for 2 months if Yervoy is used as neoadjuvant treatment as new option for approval. Added neoadjuvant dosing. **Non-Small Cell Lung Cancer:** Added the tumor may be *KRAS G12C* mutation positive to the Note for the tumor is negative for actionable mutations. Removed *KRAS G12C* as an option for approval. **Biliary Tract Cancer:** Removed requirement that the medication is used as subsequent therapy. Added patient has gallbladder cancer, has resectable locoregionally advanced disease, and the medication is used for neoadjuvant therapy as an option for approval. **Bone Cancer:** Revised requirement that the patient is ≥ 12 years of age to patient is ≥ 18 years of age. **Small Bowel Adenocarcinoma:** Added the tumor is polymerase epsilon/delta (POLE/POLD1) mutation positive as new option for approval.	12/04/2024
Update	04/08/2025: The policy name was changed from "Oncology (Injectable) – Yervoy UM Medical Policy" to "Oncology (Injectable – CTLA-4 Antibody) – Yervoy UM Medical Policy".	N/A
Selected Revision	**Hepatocellular Carcinoma:** Removed requirement that the medication is used as subsequent therapy.	04/30/2025

	Melanoma: Revised dosing for adjuvant treatment to approve up to 10 mg/kg administered intravenously once every 3 weeks or 12 weeks. Previously, approval was for 10 mg/kg administered intravenously once every 3 weeks or 12 weeks. **Non-Small Cell Lung Cancer:** The note was updated to remove "The tumor may be *KRAS G12C* mutation positive." **Renal Cell Carcinoma:** Removed relapsed or metastatic from patient has advanced disease.	
Early Annual Revision	**Colon, Rectal, or Appendiceal Cancer:** The requirement that the tumor is polymerase epsilon/delta (POLE/POLD1) mutation was changed to also require ultra-hypermutated phenotype (tumor mutation burden > 50 mutations/megabase). **Esophageal and Esophagogastric Junction Cancer:** A requirement that the patient has programmed death ligand-1 (PD-L1) positive disease (combined positive score [CPS] ≥ 1) was added as an approval option. The requirement for unresectable, advanced, or metastatic disease was expanded to include locally-advanced and recurrent disease; requirements that the patient has squamous cell carcinoma and that the medication will be used for first-line therapy were removed. Added that the medication will be used as induction therapy in patients planned for esophagectomy as an approval a patient with PD-L1 positive disease (combined positive score [CPS] ≥ 1). For a tumor that is microsatellite instability-high or deficient mismatch repair, a requirement for one of the following was added: unresectable, locally advanced, recurrent, or metastatic disease; according to the prescriber, the patient is not a surgical candidate; the medication is used as neoadjuvant or perioperative immunotherapy; or the medication is used as induction therapy in a patient planned for esophagectomy. **Hepatocellular Carcinoma:** For liver-confined, unresectable disease in a patient who is not a transplant candidate or extrahepatic/metastatic disease deemed ineligible for resection, transplant, or locoregional therapy, added a requirement that the medication is being used in the first line setting. Added use as subsequent therapy as an approval option. **Non-Small Cell Lung Cancer – Recurrent, Advanced, or Metastatic Disease:** Indication was changed to as listed. Previously, all non-small cell lung cancer (NSCLC) was addressed more generally under NSCLC. Added a requirement that the tumor is negative for the following actionable biomarkers: epidermal growth factor receptor (EGRF) exon 19 deletion or exon 21 L858R, anaplastic lymphoma kinase (ALK), RET, and ROS1. For first-line therapy, added NRG1 gene fusion as an approval option. For first-line or subsequent therapy, removed RET rearrangement as an approval option. For subsequent therapy, EGFR exon 19 deletion or exon 21 L858R mutation, ALK rearrangement positive, ROS1 rearrangement, and the requirement that the patient has received targeted drug therapy for the specific mutation was removed. For use as first-line or continuation maintenance therapy, changed the requirement that "the tumor is negative for actionable mutations" to "the tumor has no actionable mutations; a Note was added to clarify that the tumor does not have the following mutations: EFGR exon 19 deletion, EFGR exon 21 L858R, EFGR S768I, EGFR L861Q, EGFR G719X, EGFR exon 20 insertion, ALK rearrangement, ROS1 rearrangement, BRAF V600E, NTRK 1/2/3 gene fusion, METex14 skipping, RET rearrangement, ERBB2 (HER2), and NRG1 gene fusion. **Renal Cell Carcinoma:** The requirement for advanced disease was changed to be relapsed or Stage IV disease. **Ampullary Adenocarcinoma:** The requirements that the patient has intestinal type disease and progressive, unresectable or metastatic disease were removed. A requirement that the medication is used first-line for metastatic disease or as subsequent therapy was added. **Biliary Tract Cancer:** For a patient with resectable locoregionally advanced disease, the requirements that the patient has gallbladder cancer and that the medication is used for neoadjuvant therapy were removed. The requirement that the patient has gallbladder cancer, intrahepatic cholangiocarcinoma, or extrahepatic cholangiocarcinoma was removed. **Gestational Trophoblastic Neoplasia:** This was added as a new condition of approval. **Head and Neck Cancers:** This was added as a new condition of approval. **Kaposi Sarcoma:** The requirement that the patient has classic Kaposi sarcoma was removed.	07/16/2025

	Neuroendocrine Tumors: Locoregional or unresectable disease was added as an approval option. Adrenocortical carcinoma was added as an approval option. **Pancreatic Cancer:** This was added as a new condition of approval. **Small Bowel Adenocarcinoma:** Locally unresectable and medically inoperable disease were added as options for approval. The requirement that the tumor is polymerase epsilon/delta (POLE/POLD1) mutation was changed to also require ultra-hypermutated phenotype (tumor mutation burden > 50 mutations/megabase). **Soft Tissue Sarcoma:** Progressive disease was added as an option for approval. For a patient with advanced, unresectable, progressive, or metastatic disease, a requirement was added that the patient has one of the following: myxofibrosarcoma; undifferentiated pleomorphic sarcoma; dedifferentiated liposarcoma; cutaneous angiosarcoma; undifferentiated sarcoma; and tumor mutation burden-high (TMB-H). Extremity/body wall, head/neck disease, retroperitoneal/intra-abdominal disease, and rhabdomyosarcoma were removed as options for approval.	
Early Annual Revision	**Cervical Cancer:** Added new condition of approval. **Endometrial Carcinoma:** Added new condition of approval. **Soft Tissue Sarcoma:** Rhabdomyosarcoma was added as an approval option when the patient has advanced, unresectable, progressive or metastatic disease. The Note: TMB-H is defined as 10 or more mutations per megabase was added to the option of approval that the tumor is mutation burden-high (TMB-H). **Vaginal Cancer:** Added new condition of approval. **Vulvar Cancer:** Added new condition of approval.	01/28/2026