Utilization Review Policy 188

POLICY: Oncology (Injectable – CTLA-4 Antibody) – Yervoy Utilization Management Medical Policy

- Yervoy® (ipilimumab intravenous infusion – Bristol-Myers Squibb)

EFFECTIVE DATE: 1/1/2021
LAST REVISION DATE: 12/04/2024; selected revision 04/30/2025

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

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.
- **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; if Yervoy is withheld then Opdivo should also be 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):
     a. The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); OR
     b. The tumor is polymerase epsilon/delta (POLE/POLD1) mutation positive; 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.

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):

a. Patient meets ALL of the following (a, b, c, and d):

a) Patient has squamous cell carcinoma; AND

b) Patient has unresectable, advanced, or metastatic disease; AND

c) According to the prescriber, the patient is not a surgical candidate; AND

d) The medication will be used for first-line therapy; OR

ii. The tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR); 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.

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) According to the prescriber, the patient has ONE of the following (i or ii):

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; 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.

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 Yervoy 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 Yervoy 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.

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):

1. Patient is ≥ 18 years of age; AND
2. 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
3. The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
4. 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). Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

1. Patient is ≥ 18 years of age; AND
2. Patient has recurrent, advanced, or metastatic disease; AND
3. Patient meets ONE of the following (i, ii, iii, or iv):
   a. Yervoy is used as first-line or continuation maintenance therapy and the patient meets BOTH of the following (a and b):
   Note: This is regardless of PD-L1 status.
      i. The medication will be used in combination with Opdivo (nivolumab intravenous infusion); AND
      ii. The tumor is negative for actionable mutations; OR

Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *NTRK* gene fusion-positive, *ROS1, BRAF V600E, MET 14* skipping mutation, *RET* rearrangement.

b. Yervoy is used as first-line therapy and the patient meets BOTH of the following (a and b):
   a) The tumor is positive for ONE of the following mutations [(1) or (2)]:
      (1) Epidermal growth factor receptor (*EGFR*) exon 20 mutation; OR
      (2) *ERBB2* (HER2) mutation; AND
   b) The medication will be used in combination with Opdivo (nivolumab intravenous infusion); OR

c. Yervoy is used as first-line or subsequent therapy and the patient meets BOTH of the following (a and b):
   a) The tumor is positive for ONE of the following mutations [(1), (2), (3), or (4)]:
      (1) *BRAF V600E* mutation; OR
      (2) *NTRK1/2/3* gene fusion; OR
      (3) *MET* exon 14 skipping mutation; OR
      (4) *RET* rearrangement; AND
   b) The medication will be used in combination with Opdivo (nivolumab intravenous infusion); OR

iv. Yervoy is used as subsequent therapy and the patient meets ALL of the following (a, b, and c):
   a) Tumor is positive for ONE of the following [(1), (2), (3), or (4)]:
      (1) *EGFR* exon 19 deletion or exon 21 *L858R* mutation; OR
      (2) *EGFR S768I*, *L861Q*, and/or *G719X* mutation; OR
      (3) *ALK* rearrangement positive; OR
      (4) *ROS1* rearrangement positive; AND
   b) The patient has received targeted drug therapy for the specific mutation; AND
   Note: Examples of targeted drug therapy include Gilotrif (afatinib tablets), Tagrisso (osimertinib tablets), erlotinib, Iressa (gefitinib tablets), Xalkori (crizotinib capsules), Zykadia (ceritinib capsules), Alecensa (alectinib capsules), Alunbrig (brigatinib tablets), Lorbrena (lorlatinib tablets), Rozlytrek (entrectinib capsules), or Vizimpro (dacomitinib tablets).
   c) Yervoy is used in combination with Opdivo (nivolumab intravenous infusion); AND

4. 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.

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 advanced 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

8. **Ampullary Adenocarcinoma.** Approve for 4 months if the patient meets ALL of the following (A, B, C, D, E, and F):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has intestinal type disease; AND
   C) Patient has progressive, unresectable, or metastatic disease; AND
   D) The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
   E) The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND
   F) 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.

9. **Biliary Tract Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. Patient has unresectable, resected with gross residual, or metastatic disease; OR
      ii. Patient meets ALL of the following (a, b, and c):
         i. Patient has gallbladder cancer; AND
         ii. Patient has resectable locoregionally advanced disease; AND
         iii. The medication is used for neoadjuvant therapy; AND
   C) Patient has tumor mutation burden-high (TMB-H) disease; AND
   Note: TMB-H is defined as 10 or more mutations per megabase.
   D) Patient has ONE of the following (i, ii, or iii):
      i. Gallbladder cancer; OR

ii. Intrahepatic cholangiocarcinoma; OR
iii. Extrahepatic cholangiocarcinoma; AND

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

F) 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. 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):

1. Approve 1 mg/kg administered intravenously not more frequently than once every 6 weeks; OR
2. Approve 3 mg/kg administered intravenously not more frequently than once every 3 weeks.

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12. Kaposi Sarcoma. 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 classic Kaposi sarcoma; AND

C) Patient has relapsed or refractory 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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13. 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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14. 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 advanced or metastatic disease; AND

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

- **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; 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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15. 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 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; 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.

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16. Soft Tissue Sarcoma. 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, unresectable, or metastatic disease; AND

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

- **i.** Extremity/body wall, head/neck disease; OR
- **ii.** Retroperitoneal/intra-abdominal disease; OR
- **iii.** Rhabdomyosarcoma; OR
- **iv.** Angiosarcoma; 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 Appendiceal to the condition of approval. **Esophageal and Esophagogastric Junction Cancer:** Added Esophagogastric Junction to the condition of approval. Added requirement that the tumor is human epidermal growth factor overexpression negative. Added option for approval that according to the prescriber, the patient is not a surgical candidate. **Melanoma:** Added "recurrent" to the requirement that the patient has unresectable, recurrent, or metastatic melanoma. **Non-Small Cell Lung Cancer (NSCLC):** Added option for approval for first-line therapy in patients with epidermal growth factor receptor (EGFR) exon 20 mutation, KRAS G12C mutation, or ERBB2 (HER2) mutation; and Yervoy used in combination with Opdivo (nivolumab intravenous infusion). Revised first-line and subsequent therapy option of approval by removing EGFR exon 20 and KRAS G12C mutation from list of mutations. Revised subsequent therapy option for approval by adding EGFR exon 19 deletion or L858R mutation; and ALK rearrangement to the list of mutations. Moved ROS1 rearrangement to the list of mutations. Added examples of targeted drug therapies to the Note. **Ampullary Adenocarcinoma:** Added new condition of approval. **Bone Cancer:** Added new condition of approval. **Neuroendocrine Tumors:** Revised option for approval to patient has extrapulmonary poorly differentiated neuroendocrine carcinoma. Revised option for approval to patient has large or small cell carcinoma. Added option for approval if patient has mixed neuroendocrine-non-neuroendocrine neoplasm. **Small Bowel Adenocarcinoma:** Revised dosing from 3 mg/kg to 1 mg/kg.	11/16/2022
Annual Revision	**Colon, Rectal, or Appendiceal Cancer:** Removed requirement that the patient has either tried chemotherapy; OR has unresectable, advanced, or metastatic disease. **Esophageal or Esophagogastric Junction Cancer:** Removed requirement that the tumor is human epidermal growth factor receptor 2 overexpression negative. Added tumor is microsatellite instability-high or deficient mismatch repair, as an additional option for approval. Added 3 mg/kg administered intravenously not more frequently than once every 3 weeks as an addition dosing regimen. **Hepatocellular Carcinoma:** Added requirement that the patient has Child-Pugh Class A liver function. Added requirement that the patient has one of the following: unresectable disease and are not a transplant candidate; OR liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease; OR metastatic disease or extensive liver tumor burden. **Non-Small Cell Lung Cancer:** Added descriptor "exon 21" to criterion Epidermal growth factor (*EGFR*) exon 19 deletion or exon 21 *L858R* mutation. **Renal Cell Carcinoma:** Removed descriptor "Stage IV" from criterion Patient has advanced, relapsed, or metastatic disease. **Biliary Tract Cancer:** Added new condition of approval. **Bone Cancer:** Moved Tumor mutation burden-high is defined as 10 or more mutations per megabase to a Note. **Gastric Cancer:** Added new condition of approval. **Kaposi Sarcoma:** Added new condition of approval. **Merkel Cell Carcinoma:** Added new condition of approval. **Soft Tissue Sarcoma:** Added new condition of approval.	12/06/2023
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/16/2024
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.	12/04/2024

	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.	
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. **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.	04/30/2025