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: 09/23/2026

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 MSI-H dMMR disease as determined by an FDA-authorized test.
- **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 programmed death ligand-1 (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**:
  - Unresectable or metastatic disease in patients ≥ 12 years of age, as a single agent or in combination with Opdivo.
  - 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 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.
  - 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**, in combination with Opdivo for the first-line treatment of patients with intermediate or poor risk advanced disease.

Guidelines

The use of Yervoy is recommended across multiple National Comprehensive Cancer Network (NCCN) guidelines and the NCCN Compendium.[2-22,24-32,34,35] Recommendations with a category of evidence of 2B or higher support the approval criteria outlined below.

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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. 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

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.

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); 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.

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3. Hepatocellular Carcinoma. Approve for 4 months if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **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 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 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.

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.

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, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** The tumor is negative for the following actionable biomarkers: epidermal growth factor receptor (*EGFR*) exon 19 deletion or exon 21 L858R, anaplastic lymphoma kinase *(ALK), RET*, and *ROS1*; AND
- **C)** The medication is used in combination with Opdivo (nivolumab intravenous infusion); AND

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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.

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

8. **Ampullary Adenocarcinoma.** 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 mismatch repair deficient (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 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, 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.

10. **Bone 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 has unresectable or metastatic disease; 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, iii, iv, or v):
      i. Chondrosarcoma; OR
      Note: Includes mesenchymal chondrosarcoma and dedifferentiated chondrosarcoma.

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ii. Chordoma; OR
iii. Ewing sarcoma; OR
iv. High-grade undifferentiated pleomorphic sarcoma; OR
v. Osteosarcoma; 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.

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 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. Gastrointestinal Stromal Tumors. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
A) Patient is ≥ 12 years of age; AND
B) Patient has tumor mutation burden-high (TMB-H) tumors; AND

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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.

15. Gestational Trophoblastic Neoplasia. 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 multiagent chemotherapy-resistant disease; AND
Note: Examples of chemotherapy regimens include etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.
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.

16. Head and Neck Cancers. 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, metastatic, recurrent, persistent, or unresectable disease; AND
C) Patient has non-nasopharyngeal 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.

17. 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.

18. 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.

19. Neuroendocrine Tumors. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):

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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.

20. Ovarian/Fallopian Tube/Peritoneal 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 has platinum-resistant, persistent, or recurrent 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.

21. 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.

22. 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) 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
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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23. 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; 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.

24. Thyroid Carcinoma. 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 progressive, recurrent, or metastatic 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.

25. 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 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.

26. 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.

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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
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	07/16/2025

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	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. **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

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HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Esophageal and Esophagogastric Junction Cancer:** When the patient has programmed death ligand-1 (PD-L1) positive disease (combined positive score [CPS] ≥ 1), the options that the patient has unresectable locally advanced, recurrent, or metastatic disease; according to the prescriber, the patient is not a surgical candidate; OR the medication is used as induction therapy in patients planned for esophagectomy were removed. When the tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR), the options that the patient has 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 patients planned for esophagectomy were removed. **Hepatocellular Carcinoma:** The options that the medication is being used as first line and according to the prescriber, the patient has ONE of the following: Liver-confined, unresectable disease and is deemed ineligible for transplant OR extrahepatic/metastatic disease and is deemed ineligible for resection, transplant, or locoregional therapy were removed. The option that the medication is being used for subsequent therapy was removed. **Non-Small Cell Lung Cancer – Recurrent, Advanced, or Metastatic Disease:** The option that the medication is used as first-line therapy and the tumor is positive for ONE of the following mutations: *EGFR* exon 20 mutation; *ERBB2* (*HER2*) mutation; or *NRG1* gene fusion was removed. The option that the medication is used as first-line or subsequent therapy and the tumor is positive for ONE of the following mutations: *BRAF* V600E mutation; *NTRK*1/2/3 gene fusion; or *MET* exon 14 skipping mutation was removed. The options that the medication is used as subsequent therapy and the tumor is *EGFR* S768I, L861Q, and/or G719X mutation positive were removed. The option that the medication is used as first-line or continuation maintenance therapy and has the tumor has no actionable mutations along with the corresponding Note was removed. **Ampullary Adenocarcinoma:** The options that the medication is used first-line for metastatic disease OR the medication is used as subsequent therapy were removed. **Bone:** The requirement that the patient has progressed following prior treatment was removed. **Cervical Cancer:** The requirement that the medication is used as second line or subsequent therapy was modified to the medication is used as subsequent therapy. **Gastrointestinal Stromal Tumors:** This was added as a new condition of approval under "Other Uses with Supportive Evidence." **Gestational Trophoblastic Neoplasia:** The requirement that the patient is ≥ 18 years of age was added. **Head and Neck Cancers:** The requirement that the medication is used in combination with Opdivo (nivolumab intravenous infusion) was added. **Ovarian/Fallopian Tube/Peritoneal Cancer.** This was added as a new condition of approval under "Other Uses with Supportive Evidence." **Thyroid Carcinoma:** This was added as a new condition of approval under "Other Uses with Supportive Evidence." **Vaginal Cancer:** The requirement that the medication is used as second-line or subsequent therapy was modified to the medication is used as subsequent therapy.	09/23/2026

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