Utilization Review Policy 177

POLICY: Oncology (Injectable – Programmed Death Receptor-1) – Opdivo
- Opdivo® (nivolumab intravenous infusion – Bristol-Myers Squibb)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 09/16/2024

COVERAGE CRITERIA FOR: ALL UCARE PLANS

OVERVIEW
Opdivo, a human programmed death receptor-1 (PD-1) blocking antibody, is indicated for the following uses:[1]

1) **Classical Hodgkin lymphoma**, for adults who have relapsed or progressed after autologous hematopoietic stem cell transplantation (auto-HSCT) and Adcetris® (brentuximab vedotin intravenous infusion) OR after three or more lines of systemic therapy that includes auto-HSCT.*
2) **Colorectal cancer**, with or without Yervoy® (ipilimumab intravenous infusion) for patients ≥ 12 years of age with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic disease that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.*
3) **Esophageal carcinoma**, in the following situations:
   - For adults with unresectable advanced, recurrent, or metastatic squamous cell disease after prior fluoropyrimidine- and platinum-based chemotherapy.
   - Adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adults who have received neoadjuvant chemoradiotherapy.
   - First-line treatment of adults with unresectable advanced or metastatic esophageal squamous cell carcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.
   - First-line treatment of adults with unresectable advanced or metastatic esophageal squamous cell carcinoma in combination with Yervoy.
4) **Gastric cancer, esophagogastric junction cancer, and esophageal adenocarcinoma**, for adults with advanced or metastatic disease, in combination with fluoropyrimidine- and platinum-containing chemotherapy.
5) **Head and neck squamous cell carcinoma**, in adults with recurrent or metastatic disease with disease progression on or after platinum-based therapy.
6) **Hepatocellular carcinoma**, in adults who have been previously treated with Nexavar® (sorafenib tablets), in combination with Yervoy.*
7) **Malignant pleural mesothelioma**, for first-line treatment, in combination with Yervoy in adults with unresectable disease.
8) **Melanoma**, in patients ≥ 12 years of age with:
   - Unresectable or metastatic disease as a single agent.

- Unresectable or metastatic disease in combination with Yervoy.
- Adjuvant treatment for Stage IIB to Stage IV disease in patients who have undergone complete resection.

9) **Non-small cell lung cancer**:
   i. As first-line treatment in combination with Yervoy, in adults with metastatic disease expressing programmed death-ligand 1 (≥ 1%) as determined by an FDA-approved test, without epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.
   ii. As first-line treatment in combination with Yervoy and two cycles of platinum-doublet chemotherapy, in adults with recurrent or metastatic disease without *EGFR* or *ALK* genomic tumor aberrations.
   iii. In adults with metastatic disease and progression on or after platinum-based chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo.
   iv. In combination with platinum-doublet chemotherapy, as neoadjuvant treatment of adults with resectable (tumors ≥ 4 cm or node positive) disease.

10) **Renal cell carcinoma**:
   i. In adults with advanced disease who have received prior anti-angiogenic therapy.
   ii. In combination with Yervoy, for adults with intermediate or poor risk advanced disease, as first-line therapy.
   iii. In combination with Cabometyx® (cabozantinib tablets), for the first-line treatment of adults with advanced disease.

11) **Urothelial carcinoma**, in the following situations:
- In adults with unresectable or metastatic disease, as first-line treatment in combination with cisplatin and gemcitabine.
- In adults with advanced or metastatic disease who have disease progression during or following platinum-containing chemotherapy.
- In adults with advanced or metastatic disease who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- Adjuvant treatment of adults at high risk of recurrence after undergoing radical resection of urothelial carcinoma.

* This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Opdivo. 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. Because of the specialized skills required for evaluation and diagnosis of patients treated with Opdivo as well as the monitoring required for adverse events and long-term

efficacy, approval requires Opdivo to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Opdivo is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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1. Classic Hodgkin Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
Note: For pediatric patients, see Pediatric Hodgkin Lymphoma criteria.
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i, ii, or iii):
i. Patient has had a hematopoietic stem cell transplantation (HSCT); OR
ii. Patient has tried three or more systemic regimens AND this includes an auto-HSCT as one line of therapy; OR
Note: Examples of systemic regimens are ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), Sanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone), escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).
iii. Patient has relapsed or refractory disease and the medication is used in combination with Adcetris (brentuximab intravenous infusion) or ICE (ifosfamide, carboplatin, and etoposide);
AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks.

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2. Colon, Rectal, or Appendiceal Cancer. Approve for 1 year 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; AND
C) Patient meets ONE of the following (i, ii, or iii):
i. Patient has tried chemotherapy; OR

Note: Examples of chemotherapy are fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine, oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

ii. Patient has unresectable, advanced, or metastatic disease; OR

iii. The medication is used for neoadjuvant therapy; AND

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

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) 240 mg administered as an intravenous infusion not more frequently than once every 2 weeks; OR

B) 480 mg administered as an intravenous infusion not more frequently than once every 4 weeks; OR

C) 3 mg/kg administered as an intravenous infusion not more frequently than once every 2 weeks.

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3. Esophageal and Esophagogastric Junction Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND

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

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

i. Patient has received preoperative chemotherapy; AND
Note: Examples of chemotherapy include 5-fluorouracil plus either cisplatin or oxaliplatin; and paclitaxel plus carboplatin.

ii. According to the prescriber, the patient has residual disease; OR

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

i. Patient has squamous cell carcinoma; AND

ii. Patient meets ONE of the following [(1) or (2)]:

1. According to the prescriber, the patient is not a surgical candidate; OR
2. Patient has unresectable locally advanced, recurrent, or metastatic disease; OR

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

i. Patient has adenocarcinoma; AND

ii. Patient meets ONE of the following [(1) or (2)]:

1. According to the prescriber, the patient is not a surgical candidate; OR
2. Patient has unresectable locally advanced, recurrent, or metastatic disease; AND

iii. The disease is negative for human epidermal growth factor receptor 2 (HER2) overexpression; AND

iv. The tumor expression for programmed death ligand-1 (PD-L1) has a combined positive score (CPS) ≥ 5; AND

v. The medication is used in combination with fluoropyrimidine and oxaliplatin; OR
Note: Examples of fluoropyrimidines include 5-fluorouracil and capecitabine.

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

i. Patient meets ONE of the following [(1) or (2)]:

1. According to the prescriber, the patient is not a surgical candidate; OR

2. Patient has unresectable locally advanced, recurrent, or metastatic disease; AND

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

iii. The medication will be used in combination with ONE of the following [(1) or (2)]:

1. Fluoropyrimidine and oxaliplatin containing chemotherapy; OR
   Note: Examples of fluoropyrimidines include 5-fluorouracil and capecitabine.
2. Yervoy (ipilimumab intravenous infusion); OR

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

i. Patient has adenocarcinoma; AND

ii. Tumor is MSI-H or dMMR; AND

iii. The medication is used as neoadjuvant or perioperative immunotherapy; AND

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

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):

A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR

B) 360 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

C) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR

D) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

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4. Gastric Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND

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

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

1. Patient has locoregional disease; AND
2. Tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR); AND
3. The medication is used as neoadjuvant or perioperative immunotherapy; OR

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

1. Patient meets ONE of the following [(1) or (2)]:
   (1) Patient has unresectable locally advanced, recurrent, or metastatic disease; OR
   (2) According to the prescriber, the patient is not a surgical candidate; AND
2. The disease is negative for human epidermal growth factor receptor 2 (HER2) overexpression; AND
3. The medication is used in combination with fluoropyrimidine and oxaliplatin; OR
   Note: Examples of fluoropyrimidines include fluorouracil and capecitabine.

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

1. Patient meets ONE of the following [(1) or (2)]:
   (1) Patient has unresectable locally advanced, recurrent, or metastatic disease; OR
   (2) According to the prescriber, the patient is not a surgical candidate; AND
2. Tumor is MSI-H or dMMR; AND

3. Patient meets ONE of the following [(1) or (2)]:
   a. The medication is used in combination with Yervoy (ipilimumab intravenous infusion); OR
   b. The medication is used in combination with a fluoropyrimidine and oxaliplatin; AND
      Note: Examples of fluoropyrimidines include fluorouracil and capecitabine.

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

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 360 mg as an intravenous infusion administered not more frequently than once every 3 weeks.

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5. Head and Neck Squamous Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
   ~~a.~~ Patient has non-nasopharyngeal disease; OR
   b. Patient meets ALL of the following conditions (a, b, and c):
      i. Patient has nasopharyngeal disease; AND
      ii. Patient has recurrent, unresectable, oligometastatic, or metastatic disease; AND
      iii. Opdivo is used in combination with cisplatin and gemcitabine; AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks.

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6. Hepatocellular 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 ONE of the following (i, ii, or iii):
   a. Unresectable disease and is not a transplant candidate; OR
   b. Liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease; OR
   c. Metastatic disease or extensive liver tumor burden; AND
C) If the medication is used first-line, patient meets BOTH of the following (i and ii):
   a. Patient has Child-Pugh Class B liver disease; AND
   b. The medication is used as a single agent; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR
C) 1 mg/kg as an intravenous infusion administered not more frequently than once every 3 weeks.

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7. 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 ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
  i. Approve for 1 year if the patient has unresectable, advanced, or metastatic melanoma; OR
  ii. Approve for up to 1 year of treatment (total) if Opdivo will be used as adjuvant treatment; AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, C, D, or E):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR
C) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
D) 1 mg/kg as an intravenous infusion not more frequently than once every 3 weeks; OR
E) 6 mg/kg as an intravenous infusion not more frequently than once every 4 weeks.

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8. 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) If used as first-line therapy, the medication is used in combination with Yervoy (ipilimumab 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) 360 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR
B) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

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9. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i, ii, iii, iv, v, or vi):
i. Opdivo is used as first-line or continuation maintenance therapy and the patient meets ALL of the following (a, b, and c):
Note: This is regardless of programmed death-ligand-1 (PD-L1) status.
a) Patient has recurrent, advanced, or metastatic disease; AND
b) Opdivo will be used in combination with Yervoy (ipilimumab intravenous infusion); AND
c) 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. *KRAS G12C* is not considered an actionable mutation (the tumor may be *KRAS G12C* mutation positive).
ii. Opdivo is used as first-line or subsequent therapy and the patient meets ALL of the following (a, b, and c):
Note: This is regardless of PD-L1 status.
i. Patient has recurrent, advanced, or metastatic disease; AND
ii. 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
iii. The medication will be used in combination with Yervoy; OR
iii. Opdivo is used as first-line therapy and the patient meets ALL of the following (a, b, and c):
Note: This is regardless of PD-L1 status.
i. Patient has recurrent, advanced, or metastatic disease; AND
ii. 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*); AND
iii. The medication will be used in combination with Yervoy; OR
iv. Opdivo is used as subsequent therapy and the patient meets ALL of the following (a, b, c, and d):
a) Patient has recurrent, advanced, or metastatic disease; AND
b) The tumor is positive for ONE of the following mutations [(1), (2), (3), or (4)]:
1. Epidermal growth factor receptor (*EGFR*) *S768I*, *L861Q*, and/or *G719X* mutation positive; OR

2. *EGFR* exon 19 deletion or exon 21 L858R; OR
3. Anaplastic lymphoma kinase (*ALK*) rearrangement positive; OR
4. *ROS1* rearrangement positive; AND

c) 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), Vizimpro (dacomitinib tablets), Xalkori (crizotinib capsules), Rozlytrek (entrectinib capsules), or Zykadia (ceritinib tablets).

d) Opdivo is used in combination with Yervoy; OR

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

a) Patient has recurrent, advanced, or metastatic disease; AND

b) Patient has tried systemic chemotherapy; AND
Note: Examples of systemic chemotherapy include cisplatin, carboplatin, Alimta (pemetrexed injection), Abraxane (paclitaxel albumin-bound injection), gemcitabine, paclitaxel.

c) Patient has not progressed on prior therapy with a programmed death-1 (PD-1)/PD-L1 inhibitor; AND
Note: This includes previous therapy with either one of Opdivo, Keytruda (pembrolizumab intravenous infusion), or Tecentriq (atezolizumab intravenous infusion).

d) If tumor is positive for an actionable mutation, the patient has received targeted drug therapy for the specific mutation; AND
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; OR

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

a) Patient has resectable disease; AND
Note: Resectable disease is defined as tumors ≥ 4 cm or node positive.

b) Opdivo is used as neoadjuvant therapy; AND

c) Opdivo is used in combination with platinum-doublet chemotherapy; AND
Note: Examples of platinum-doublet chemotherapy include carboplatin plus paclitaxel, cisplatin plus pemetrexed, and cisplatin plus gemcitabine.

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

Dosing. Approve ONE of the following dosing regimens (A, B, C, or D):

A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR

B) 360 mg as an intravenous infusion administered not more frequently than once every 3 weeks; OR

C) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR

D) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

10. Renal Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has advanced, relapsed, or metastatic disease; AND
- **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)** 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
- **B)** 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR
- **C)** 3 mg/kg as an intravenous infusion administered not more frequently than once every 3 weeks.

11. Urothelial Carcinoma. Approve for 1 year 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 ONE of the following dosing regimens (A or B):
- **A)** 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
- **B)** 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks.

Other Uses with Supportive Evidence

12. Ampullary 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 microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease; AND
- **C)** Patient meets ONE of the following (i or ii):
  - **i.** The medication is used first-line and the patient has ONE of the following (a, b, or c):
    - **a)** Unresectable localized disease; OR
    - **b)** Stage IV resected disease; OR
    - **c)** Metastatic disease at initial presentation; OR
  - **ii.** The medication is used for subsequent therapy; AND
- **D)** The medication is used in combination with Yervoy (ipilimumab intravenous infusion); AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR
C) 3 mg/kg as an intravenous infusion administered not more frequently than once every 3 weeks.

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13. Anal Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least one chemotherapy regimen; AND
Note: Examples of chemotherapy are 5-fluorouracil (5-FU), cisplatin, carboplatin plus paclitaxel, FOLFOX (oxaliplatin, leucovorin, and 5-FU).
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) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR
C) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

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14. Biliary Tract Cancers. 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 ONE of the following (i, ii, or iii):
i. Unresectable disease; OR
ii. Resected gross residual disease; OR
iii. Metastatic disease; AND
C) Tumor is tumor mutational burden-high (TMB-H); AND
D) The medication is used as subsequent therapy; AND
E) The medication is used in combination with Yervoy (ipilimumab intravenous infusion); AND
F) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR
C) 1 mg/kg as an intravenous infusion administered not more frequently than once every 3 weeks.

14. Bone Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, F, G, and H):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has ONE of the following conditions (i, ii, iii, iv, or v):
  - **i.** Chondrosarcoma; OR
  - **ii.** Chordoma; OR
  - **iii.** Ewing sarcoma; OR
  - **iv.** Osteosarcoma; OR
  - **v.** High-grade undifferentiated pleomorphic sarcoma; AND
- **C)** Patient has unresectable or metastatic disease; AND
- **D)** Patient has tumor mutational burden-high (TMB-H) disease; AND
- **E)** Patient has progressed following prior treatment; AND
- **F)** Patient has no satisfactory alternative treatment options; AND
- **G)** The medication is used in combination with Yervoy (ipilimumab intravenous infusion); AND
- **H)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks.

15. 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)** Patient has programmed death ligand-1 (PD-L1) positive disease (combined positive score [CPS] ≥ 1); AND
- **D)** The medication is used as second-line or subsequent therapy; AND
- **E)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks.

17. Diffuse High-Grade Gliomas. 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 hypermutant tumor diffuse high-grade glioma; AND
- **C)** Patient meets ONE of the following (i or ii):
  - **i.** The medication is used for adjuvant treatment; OR
  - **ii.** The medication is used for recurrent or progressive disease; AND
- **D)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR
C) 3 mg/kg as an intravenous infusion administered not more frequently than once every 3 weeks.

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18. Endometrial 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 tried at least one prior systemic therapy; AND
Note: Examples of systemic therapy are carboplatin, paclitaxel, docetaxel, cisplatin, doxorubicin, topotecan, ifosfamide, everolimus/letrozole.
C) Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease; AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR
C) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

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19. Extranodal NK/T-Cell Lymphomas. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has received an asparaginase-based chemotherapy regimen; AND
Note: Examples of asparaginase-based chemotherapy are dexamethasone, ifosfamide, pegaspargase, etoposide; and gemcitabine, pegaspargase, oxaliplatin.
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks.

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20. Gestational Trophoblastic Neoplasia. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) Patient has multiagent chemotherapy-resistant disease; AND
Note: Examples of chemotherapy regimens contain etoposide, cisplatin/carboplatin, paclitaxel, bleomycin, ifosfamide, methotrexate.

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

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks.

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

Dosing. Approve 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks.

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22. Merkel Cell Carcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i or ii):
  i. Patient has disseminated Merkel cell carcinoma; OR
  ii. The medication is used as neoadjuvant therapy; AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks.

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23. 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 or ii):
  i. Patient has well differentiated, Grade 3 disease; OR
  ii. Patient has poorly differentiated, large or small cell disease (other than lung); AND
D) The medication is used in combination with Yervoy (ipilimumab intravenous infusion); AND
E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

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24. Pediatric Hodgkin Lymphoma. 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 tried at least one prior systemic chemotherapy; AND
Note: Examples of chemotherapy are AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide), ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), OEPA (vincristine, etoposide, prednisone, doxorubicin).

C) If used for re-induction therapy, the medication is used in combination with Adcetris (brentuximab intravenous infusion); AND

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

Dosing. Approve ONE of the following dosing regimens (A, B, or C):

A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR

B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR

C) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

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25. Primary Mediastinal Large B-Cell Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient has relapsed or refractory disease; AND

B) Patient meets ONE of the following (i or ii):

i. The medication is used as a single agent; OR

ii. The medication is used in combination with Adcetris (brentuximab intravenous infusion) after a partial response to therapy for relapsed or refractory disease; AND

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

Dosing. Approve ONE of the following dosing regimens (A or B):

A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR

B) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

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26. Small Bowel Adenocarcinoma. 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 or metastatic disease; AND

C) The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); AND
D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A, B, or C):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks; OR
C) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

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27. Small Cell Lung Cancer. Approve for 1 year 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 as second-line or subsequent therapy; AND
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) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
B) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks; OR
C) 1 mg/kg as an intravenous infusion administered not more frequently than once every 3 weeks.

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28. Soft Tissue Sarcoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has ONE of the following (i or ii):
  i. Patient has advanced or metastatic disease and has ONE of the following (a, b, c, d, e, or f):
    a) Myxofibrosarcoma; OR
    b) Undifferentiated pleomorphic sarcoma; OR
    c) Dedifferentiated liposarcoma; OR
    d) Cutaneous angiosarcoma; OR
    e) Undifferentiated sarcoma; OR
    f) Tumor mutation burden-high (TMB-H); OR
  ii. Angiosarcoma; AND
C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve ONE of the following dosing regimens (A or B):
A) 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks; OR

B) 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks.

29. Vulvar 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 human papilloma virus (HPV)-related disease; AND
- **C)** Patient has tried at least one prior systemic therapy; AND
  Note: Examples of systemic therapy are cisplatin, carboplatin, fluorouracil, paclitaxel, bevacizumab.
- **D)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Opdivo 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	**Classic Hodgkin Lymphoma:** Added ICE (ifosfamide, carboplatin, and etoposide) to requirement that the patient has relapsed or refractory disease and the medication will be used in combination with Adcetris. **Colon, Rectal, or Appendiceal Cancer:** Added Appendiceal to the condition of approval. Added medication is used for adjuvant therapy as an additional option for approval. **Esophageal and Esophagogastric Junction Carcinoma:** For squamous cell carcinoma, added according to the prescriber, the patient is not a surgical candidate, as an option of approval. Added locally and recurrent to patient has unresectable locally advanced,	02/08/2023

	recurrent, or metastatic disease. Added requirement that the disease is negative for human epidermal growth factor 2 overexpression. **Head and Neck Squamous Cell Carcinoma:** Patient has progressed on or following platinum based chemotherapy was removed as an option for approval. **Mesothelioma:** For first-line therapy, added patient has unresectable disease as a requirement. **Non-Small Cell Lung Cancer:** Added first-line use in patients with recurrent, advanced, or metastatic disease with *BRAF V600E* mutation, *NTRK1/2/3* gene fusion, *MET* exon 14 skipping mutation, or *RET* rearrangement, in combination with Yervoy® (ipilimumab intravenous infusion) as an option of approval. Removed *BRAF V600E* mutation, *NTRK1/2/3* gene fusion, *MET* exon 14 skipping mutation, or *RET* rearrangement as options for approval for first-line or subsequent therapy. **Renal Cell Carcinoma:** Removed Stage IV from requirement that the patient has advanced, relapsed, or metastatic disease. For first-line therapy, added patient has clear cell histology as a requirement. **Ampullary Adenocarcinoma:** Added new condition of approval. **Anal Carcinoma:** Added 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks as another dosing option. **Bone Cancer:** Added new condition of approval. **Cervical Cancer:** Removed 480 mg as an intravenous infusion administered not more frequently than once every 4 weeks as a dosing option. **Diffuse High-Grade Gliomas:** Added new condition of approval. **Endometrial Carcinoma:** Added 3 mg/kg as an intravenous infusion administered not more frequently than once every 2 weeks as a dosing option. **Extranodal NK/T-Cell Lymphomas:** Removed nasal type from the condition of approval. **Kaposi Sarcoma:** Added new condition of approval. **Merkel Cell Carcinoma:** Added 240 mg as an intravenous infusion administered not more frequently than once every 2 weeks as another dosing option. **Primary Mediastinal Large B-Cell Lymphoma:** Added new condition of approval. **Vulvar Cancer:** Removed 480 mg as an intravenous infusion administered not more frequently than once every 3 weeks as a dosing option.	
Selected Revision	**Renal Cell Carcinoma:** Removed requirement "If used as first line therapy, the patient meets the following: the patient has clear cell histology; AND the medication is used in combination with	08/23/2023

	Yervoy (ipilimumab intravenous infusion) or Cabometyx (cabozantinib tablets).".	
Annual Revision	**Classic Hodgkin Lymphoma:** Removed "patient is not eligible for transplant" as an option for approval. **Colon, Rectal, or Appendiceal Cancer:** Added the tumor is polymerase epsilon/delta (POLE/POLD1) mutation positive as a new option for approval. **Esophageal and Esophagogastric Junction Carcinoma:** For option of approval Bii, removed requirement that patient has tried chemotherapy. For option of approval Biv, removed requirement that the patient has squamous cell carcinoma, that the tumor is negative for human epidermal growth factor receptor 2 overexpression, and the medication will be used for first-line therapy. Added requirement that the tumor is microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR). Revised fluoropyrimidine and platinum containing chemotherapy to fluoropyrimidine and oxaliplatin containing chemotherapy. Added additional option of approval for patient with adenocarcinoma, tumor is MSI-H or dMMR, and the medication is used for neoadjuvant or perioperative therapy. **Gastric Cancer:** Added option of approval for patient with locoregional disease, tumor is MSI-H or dMMR, and medication is used as neoadjuvant or perioperative therapy. Added option of approval for patient with unresectable locally advanced, recurrent, or metastatic disease, OR patient is not a surgical candidate, tumor is MSI-H or dMMR, and the medication will be used in combination with Yervoy (ipilimumab intravenous infusion) or with a fluoropyrimidine and oxaliplatin. Removed requirement that the tumor expression for programmed death-ligand 1 has a combined score ≥ 5. **Hepatocellular Carcinoma:** Removed "including hepatobiliary cancers" from the condition of approval. Added requirement that the patient has ONE of the following: unresectable disease and is not a transplant candidate; liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease; OR metastatic disease or extensive liver tumor burden. Added requirement that if the medication is used for first-line therapy, the patient has Child-Pugh Class B liver disease and the medication is used as a single agent. **Melanoma:** Added 1 mg/kg as an intravenous (IV) infusion no more frequently than once every 3 weeks and 6 mg/kg as an IV infusion no more frequently than once every 4 weeks as additional dosing regimens. Removed Note from adjuvant treatment criterion. **Mesothelioma:** Removed patient has unresectable disease as a requirement for the first-line use of Opdivo.	01/31/2024

	Non-Small Cell Lung Cancer: Added the following to the Note for first-line or continuation maintenance therapy: *KRAS G12C* is not considered an actionable mutation (the tumor may be *KRAS G12C* mutation positive). Revised Bii: Opdivo is used as first-line therapy and the patient meets ALL of the following to Opdivo is used as first-line or subsequent therapy and the patient meets ALL of the following. Revised Biii: Opdivo is used as first-line or subsequent therapy to Opdivo is used as first-line therapy; and removed *KRAS G12C* from list of mutations. **Biliary Tract Cancers:** Added new condition of approval. **Cervical Cancer:** Added requirement that the patient has recurrent or metastatic disease. **Gestational Trophoblastic Neoplasia:** Removed patient has tried at least one previous chemotherapy regimen for recurrent or progressive disease and patient has methotrexate resistant high-risk disease as options for approval. Added requirement that the patient has multiagent chemotherapy-resistant disease. **Small Cell Lung Cancer:** Added 1 mg/kg as an IV infusion not more frequently than once every 3 weeks and 3 mg/kg as an IV infusion not more frequently than once every 2 weeks as additional dosing regimens. Remove 480 mg as an IV infusion not more frequently than once every 4 weeks as a recommended dosing regimen. **Soft Tissue Sarcoma:** Added new condition of approval.	
Selected Revision	**Urothelial Carcinoma:** The requirement that the patient has tried at least one other chemotherapy regimen or the patient is at high risk of recurrence after radical resection of the tumor has been removed.	03/20/2024
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024