Clinical Policy: Nivolumab (Opdivo)

Reference Number: PA.CP.PHAR.121
Effective Date: 01/2018
Last Review Date: 12/2024

Description
Nivolumab (Opdivo®) is a programmed death receptor-1 (PD-1) blocking antibody.

FDA Approved Indication(s)
Opdivo is indicated for the treatment of:

- **Melanoma**
  - Patients and pediatric (12 years and older) with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
  - Patients and pediatric (12 years and older) with melanoma with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma, in the adjuvant setting.
- **Non-small cell lung cancer (NSCLC)**
  - Adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy.
  - Adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, for neoadjuvant treatment in combination with platinum-doublet chemotherapy, followed by single-agent Opdivo as adjuvant treatment after surgery.
  - Adult patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab.
  - Adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
  - Adult patients with metastatic NSCLC 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.
- **Malignant pleural mesothelioma**
  - Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab.
- **Renal cell carcinoma (RCC)**
  - Adult patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy.
  - Adult patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib.
  - Adult patients with intermediate or poor risk, previously untreated advanced RCC, in combination with ipilimumab.
- **Classical Hodgkin lymphoma (cHL)**
  - Adult patients with cHL that has relapsed or progressed after:*
    - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
    - 3 or more lines of systemic therapy that includes autologous HSCT.

- **Squamous cell carcinoma of the head and neck (SCCHN)**
  - Adult patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.
- **Urothelial carcinoma (UC)**
  - Adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC.
  - Adult patients with unresectable or metastatic UC, as first-line treatment in combination with cisplatin and gemcitabine.
  - Adult Patients with locally advanced or metastatic UC who:
    - have disease progression during or following platinum-containing chemotherapy, or
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- **Colorectal cancer**
  - Adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.*
- **Hepatocellular carcinoma (HCC)**
  - Adult patients with HCC who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab.*
- **Esophageal cancer**
  - As adjuvant treatment in adult patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy (CRT).
  - In combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).
  - In combination with ipilimumab for the first-line treatment of adult patients with unresectable advanced or metastatic ESCC.
  - Adult patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.
- **Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma**
  - Adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

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

Policy/Criteria

It is the policy of PA Health & Wellness that Opdivo is **medically necessary** when one of the following criteria are met:

I. Initial Approval Criteria

A. Melanoma (must meet all):

1. Diagnosis of melanoma that is either (a or b):

a. Unresectable or metastatic;
b. Resected stage IIB, IIC, III, or IV
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Request meets one of the following (a, b, or c):
   a. If prescribed as monotherapy (unresectable or metastatic disease, or adjuvant treatment): Dose does not exceed any of the following (i or ii):
      i. Adult and pediatric members weighing ≥ 40 kg: 240 mg every 2 weeks or 480 mg every 4 weeks;
      ii. Pediatric members weighing < 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks (*see Appendix E for dose rounding guidelines*);
   b. If prescribed in combination with Yervoy® (unresectable or metastatic disease), any of the following (i or ii; *see Appendix E for dose rounding guidelines*):
      i. Adult and pediatric members weighing ≥ 40 kg:Dose does not exceed 1 mg/kg every 3 weeks for 4 doses, followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
      ii. Pediatric members weighing < 40 kg: 1 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration: 6 months

B. Non-Small Cell Lung Cancer (must meet all):
1. Diagnosis of resectable, recurrent, advanced, or metastatic NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member has not previously progressed on a PD-1/PD-L1 inhibitor (e.g., Keytruda®, Tecentriq®, Imfinzi®);
5. For resectable NSCLC: Both of the following (a and b):
   a. Prescribed in one of the following ways (i or ii):
      i. Neoadjuvant treatment in combination with platinum-doublet chemotherapy;
      ii. Adjuvant treatment as a single agent, and both of the following (a and b):
         a) Prescribed following neoadjuvant treatment in combination with platinum-doublet chemotherapy;
         b) Disease mutation status is negative for EGFR and ALK;
   b. Tumors ≥ 4 cm or node positive disease;
6. For recurrent, advanced, or metastatic NSCLC: Opdivo is prescribed in one of the following ways (a, b or c):
   a. For use as a single agent, and disease has progressed on or after systemic therapy;
   b. For use in combination with Yervoy, and both of the following (i and ii):
      i. Request meets one of the following (a, b, or c):
         a. Disease mutation status is unknown or negative for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, and RET, and member has not received prior systemic therapy for advanced disease;

b. Disease mutation status is positive for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, RET, or NTRK gene fusion, and member has received mutation-specific treatment;
c. Disease is positive for a RET rearrangement;

ii. Request meets one of the following (a or b):
a. Member has PD-L1 tumor expression of ≥ 1%;
b. Opdivo is being used in combination with Yervoy ± a platinum-based regimen (*see Appendix B*);

**Prior authorization may be required for Yervoy*

c. Other NCCN recommendations listed as category 1, 2A, or 2B;

7. Request meets one of the following (a, b, c, d or e):
a. Monotherapy: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
b. In combination with Yervoy: Dose does not exceed 360 mg every 3 weeks (*see Appendix E for dose rounding guidelines*);
c. In combination with Yervoy and platinum-doublet chemotherapy: Dose does not exceed 360 mg every 3 weeks;
d. In combination with platinum-doublet chemotherapy, both of the following are met (i and ii):
i. Dose does not exceed 360 mg every 3 weeks;
ii. Request does not exceed 4 cycles;
e. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration: 6 months *(up to 12 weeks for neoadjuvant)*

C. Malignant Pleural Mesothelioma (must meet all)**:**
1. Diagnosis of unresectable malignant pleural mesothelioma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a or b):
a. As first-line therapy in combination with Yervoy;
b. If not administered first-line, as subsequent therapy in combination with Yervoy or as a single agent (off-label);
5. Request meets one of the following (a or b):
a. Dose does not exceed 360 mg every 3 weeks;
b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

D. Renal Cell Carcinoma (must meet all):
1. Diagnosis of renal cell carcinoma (RCC);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request meets one of the following (a, b, or c):
a. Monotherapy or in combination with cabozantinib: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;

b. In combination with Yervoy: Dose does not exceed 3 mg/kg every 3 weeks for 4 doses, followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

E. Classical Hodgkin Lymphoma (must meet all):
1. Diagnosis of cHL;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as one of the following (a or b):
   a. Disease is relapsed, refractory or progressive: Prescribed as subsequent therapy or palliative therapy (*off-label*);
   b. Disease is stage III-IV: Primary treatment in combination with AVD (doxorubicin, vinblastine, dacarbazine) (*off-label*);
5. Request meets one of the following (a or b):
   a. Dose does not exceed 240 mg every 2 weeks or 480mg every 4 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

F. Squamous Cell Carcinoma of the Head and Neck (must meet all):
1. Diagnosis of SCCHN;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Opdivo is prescribed in one of the following ways (a, b, c or d):
   a. For use as a single agent;
   b. For use in combination with cisplatin and gemcitabine;
   c. For use in combination with Erbitux® (cetuximab) as first-line therapy or subsequent-line therapy (*off-label*);
   d. For use in combination with Yervoy as first-line therapy (*off-label);*
5. Request meets one of the following (a or b):
   a. Dose does not exceed 240 mg every 2 weeks or 480mg every 4 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

G. Urothelial Carcinoma (must meet all):
1. Diagnosis of UC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a, b, c, d or e):
   a. Failure of a platinum-containing regimen (e.g., cisplatin, carboplatin), unless clinically significant adverse effects are experienced or all are contraindicated;
   b. Prescribed as adjuvant treatment and member is at high risk of recurrence after undergoing resection of UC;

c. Member is at high risk of recurrence and did not previously receive a platinum-containing regimen;
d. Prescribed as first-line treatment in combination with cisplatin and gemcitabine;
e. Other NCCN recommendations listed as category 1, 2A, or 2B;

5. Request meets one of the following (a, b or c):
   a. Monotherapy: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
   b. In combination with cisplatin and gemcitabine: Dose does not exceed 360 mg every 3 weeks (for up to 6 cycles), followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

H. Colorectal Cancer (must meet all):
1. Diagnosis of CRC;
2. Tumor is characterized as MSI-H, dMMR or polymerase epsilon/delta (POLE/POLDI) (off-label);
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 12 years;
5. Dose does not exceed one of the following (a, b, or c):
   a. Monotherapy, dose does not exceed either of the following (i or ii):
      i. Adult and pediatric members weighing ≥ 40 kg: 240 mg every 2 weeks or 480 mg every 4 weeks;
      ii. Pediatric members weighing < 40 kg: 3 mg/kg every 2 weeks *(see Appendix E for dose rounding guidelines)*;
   b. In combination with Yervoy, dose does not exceed either of the following (i or ii)
      i. Adult and pediatric members weighing ≥ 40 kg: 3 mg/kg every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks;
      ii. Pediatric members weighing < 40 kg: 3 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 2 weeks;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

I. Hepatocellular Carcinoma (must meet all):
1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as subsequent line systemic therapy;
5. Opdivo is prescribed in one of the following ways (a or b):
   a. As a single agent (*off-label*);
   b. In combination with Yervoy;
6. Member has not been previously treated with immune checkpoint inhibitor therapy (PD-L1/PD-1, e.g., Keytruda), unless following atezolizumab and bevacizumab if prescribed in combination with Yervoy;

7. Dose does not exceed one of the following (a, b, or c):
    a. Monotherapy: 240 mg every 2 weeks or 480 mg every 4 weeks;
    b. In combination with Yervoy: 1 mg/kg every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks (*see Appendix E for dose rounding guidelines*);
    c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

J. Esophageal Cancer (must meet all)**:**
1. Diagnosis of one of the following (a, b, c or d):
    a. Completely resected or planned esophagectomy esophageal cancer or gastroesophageal junction (esophagogastric junction; EGJ) cancer;
    b. Unresectable advanced, recurrent, or metastatic ESCC;
    c. MSI-H or dMMR esophageal cancer or EGJ cancer (off-label);
    d. Other NCCN recommendations listed as category 1, 2A, or 2B;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. For completely resected esophageal cancer or EGJ cancer, member meets both of the following (a or b):
    a. Member has residual pathologic disease and previously received CRT;
    b. Other NCCN recommendations listed as category 1, 2A, or 2B;;
5. For ESCC, one of the following (a, b or c):
    a. For unresectable advanced or metastatic disease: Prescribed in combination with Yervoy or with fluoropyrimidine- and platinum-containing chemotherapy;
    b. For unresectable advanced, recurrent, or metastatic disease: Member has had previous treatment with a fluoropyrimidine-based (e.g., 5-fluorouracil, capecitabine) and platinum-based (e.g., carboplatin, cisplatin, oxaliplatin) chemotherapy;
    c. Other NCCN recommendations listed as category 1, 2A, or 2B;
6. For MSI-H or dMMR cancers, prescribed in combination with Yervoy or with fluoropyrimidine-containing chemotherapy (e.g., 5-fluorouracil, capecitabine) and oxaliplatin;
7. Request meets one of the following (a, b or c):
    a. ESCC in combination with Yervoy: Dose does not exceed 3 mg/kg every 2 weeks or 360 mg every 3 weeks;
    b. Other indications: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
    c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

K. Gastric and Esophageal Adenocarcinomas (must meet all)**:**
1. Diagnosis of gastric cancer, EGJ cancer, or esophageal adenocarcinoma;
2. Member meets one of the following (a, b, c or d):
    a. Disease is unresectable, advanced, recurrent, or metastatic;

b. For EGJ cancer or esophageal adenocarcinoma: member meets one of the following (i, ii or iii):
   i. Member is post-operative following chemoradiation;
   ii. Member has planned esophagectomy;
   iii. Disease is advanced, recurrent, or metastatic;
c. Tumor is characterized as MSI-H or dMMR (off-label);
d. Other NCCN recommendations listed as category 1, 2A, or 2B;

3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For advanced, recurrent, or metastatic disease, prescribed in combination with (a or b):
   a. A fluoropyrimidine- (e.g., 5-fluorouracil, capecitabine) and platinum-containing (e.g., carboplatin, cisplatin, oxaliplatin) chemotherapy;
   b. Ipilimumab;
6. For MSI-H or dMMR cancers, prescribed in one of the following was (a, b or c):
   a. In a single agent;
   b. In combination with Yervoy;
   c. In combination with fluoropyrimidine-containing chemotherapy (e.g., 5-fluorouracil, capecitabine) and oxaliplatin;
7. Request meets one of the following (a or b):
   a. Dose does not exceed 240 mg every 2 weeks or 360 mg every 3 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 6 months

L. Off-label NCCN Compendium Recommended Indications (must meet all)**:**

1. Diagnosis of one of the following (a-x):
   a. Squamous cell anal carcinoma;
   b. Merkel cell carcinoma;
   c. Gestational trophoblastic neoplasia;
   d. Uveal melanoma that is metastatic or unresectable;
   e. Extranodal NK/T-cell lymphoma, nasal type, that is relapsed or refractory;
   f. Pediatric Hodgkin lymphoma, as re-induction therapy or subsequent therapy;
   g. Vulvar cancer - HPV-related advanced, recurrent, or metastatic disease, as second-line treatment;
   h. Cervical cancer;
   i. Endometrial carcinoma that is recurrent or metastatic;
   j. Small cell lung cancer (SCLC), as subsequent therapy;
   k. Bone cancer (e.g., Ewing Sarcoma, chordoma, osteosarcoma, chondrosarcoma);
   l. Central nervous system (CNS) cancer (e.g., brain metastases);
   m. Primary mediastinal large B-cell lymphoma that is relapsed or refractory;
   n. Pediatric diffuse high-grade gliomas;
   o. One of the following MSI-H or dMMR cancers (i, ii, or iii):
      i. Ampullary adenocarcinoma;
      ii. Small bowel adenocarcinoma that is advanced or metastatic;

iii. Endometrial carcinoma that is recurrent or metastatic, as subsequent therapy;

p. Small bowel adenocarcinoma with POLE/POLD1 mutation;
q. One of the following biliary tract cancers that is unresectable, resected gross residual (R2), advanced, or metastatic (i, ii, or iii):
   i. Extrahepatic cholangiocarcinoma;
   ii. Intrahepatic cholangiocarcinoma;
   iii. Gallbladder cancer;
r. Classic Kaposi sarcoma, as subsequent therapy;
s. One of the following unresectable or metastatic soft tissue sarcomas (i – vii):
   i. Tumor classified as TMB high (TMB-H) (i.e., ≥ 10 mutations/megabase [mut/Mb]);
   ii. Angiosarcoma;
   iii. Myxofibrosarcoma;
   iv. Undifferentiated pleomorphic sarcoma;
   v. Dedifferentiated liposarcoma;
   vi. Undifferentiated sarcomas;
   vii. Pleomorphic rhabdomyosarcoma, as subsequent therapy;
t. Anaplastic thyroid carcinoma that is metastatic;
u. Vaginal cancer, as second-line or subsequent therapy;
v. Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with histologic (Richter) transformation to diffuse B-cell lymphoma;
w. One of the following mesothelioma (i, ii, or iii):
   i. Peritoneal mesothelioma;
   ii. Pericardial mesothelioma;
   iii. Tunica vaginalis testis mesothelioma
x. Other NCCN recommendations listed as category 1, 2A, or 2B;

2. Prescribed by or in consultation with an oncologist;
3. For anal carcinoma: prescribed prior to resection or as second line or subsequent therapy (examples of prior therapy include 5-FU/cisplatin, carboplatin/paclitaxel, FOLFOX, FOLFCIS);
4. For gestational trophoblastic neoplasia: prescribed as a single agent for multi-agent chemotherapy-resistant disease (*see Appendix B*) in one of the following settings (a or b):
   a. Recurrent or progressive intermediate trophoblastic tumor;
   b. High-risk disease (*see Appendix D*);
5. For primary mediastinal large B-cell lymphoma: prescribed as one of the following (a or b):
   a. As a single agent;);
   b. Combination with brentuximab vedotin as consolidation/additional therapy;
6. For pediatric diffuse high-grade gliomas: prescribed as a single agent or in combination with temozolomide for adjuvant therapy or for recurrent/progressive disease;
7. For Merkel call carcinoma, uveal melanoma, CNS cancer, hepatobiliary cancer, small bowl adenocarcinoma, soft tissue sarcoma, Kaposi sarcoma, mesotheliomas: prescribed as a single agent or in combination with Yervoy;
   **Prior authorization may be required for Yervoy.*

8. For bone cancer, ampullary adenocarcinoma, CLL or SLL: prescribed in combination with Yervoy;
9. For endometrial carcinoma, anaplastic thyroid carcinoma, vaginal cancer, SCLC: prescribed as a single agent;
10. For cervical cancer: prescribed as second line or subsequent therapy for PD-L1 tumor expression of ≥ 1%;
11. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration: 6 months

M. Other diagnoses/indications: Refer to PA.CP.PHAR.53

II. Continued Approval

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy;
3. If request is for adjuvant treatment, maximum duration of therapy does not exceed one of the following (a or b):
    a. For NSCLC: 13 cycles;
    b. All other FDA-approved adjuvant indications: up to 1 year;
4. If request is for metastatic or recurrent NSCLC, malignant pleural mesothelioma, advanced RCC in combination with cabozantinib, unresectable or metastatic UC, ESCC, gastric cancer, EGJ, and esophageal adenocarcinoma, maximum duration of therapy does not exceed 2 years;
5. If request is for a dose increase, request meets one of the following (a-h):
    a. NSCLC and malignant pleural mesothelioma in combination with Yervoy: New dose does not exceed 360 mg every 3 weeks;
    b. Gastric, EGJ cancer and esophageal adenocarcinomas: New dose does not exceed 360 mg every 3 weeks or 240 mg every 2 weeks;
    c. ESCC in combination with Yervoy: New dose does not exceed 3 mg/kg every 2 weeks or 360 mg every 3 weeks;
    d. Melanoma (i or ii):
        i. If prescribed as monotherapy (unresectable or metastatic disease, or adjuvant treatment), new dose does not exceed any of the following (a or b):
            a) Adult and pediatric members weighing ≥ 40 kg: 240 mg every 2 weeks or 480 mg every 4 weeks;
            b) Pediatric members weighing < 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks;
        ii. If prescribed in combination with Yervoy (unresectable or metastatic disease), new dose does not exceed any of the following (a or b):

a) Adult and pediatric members weighing ≥ 40kg: 1 mg/kg every 3 weeks for 4 doses, followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
b) Pediatric members weighing < 40 kg: 1 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks;

e. UC (i or ii):
   i. If prescribed as monotherapy, new dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
   ii. If prescribed in combination with cisplatin and gemcitabine, new dose does not exceed 360 mg every 3 weeks (for up to 6 cycles), followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
f. CRC (i or ii):
   i. If prescribed as monotherapy, new dose does not exceed either of the following (a or b):
      a) Adult and pediatric members weighing ≥ 40 kg: 240 mg every 2 weeks or 480 mg every 4 weeks;
      b) Pediatric members weighing < 40 kg: 3 mg/kg every 2 weeks (*see Appendix E for dose rounding guidelines*);
   ii. If prescribed in combination with Yervoy, new dose does not exceed either of the following (a or b; *see Appendix E for dose rounding guidelines*):
      a) Adult and pediatric members weighing ≥ 40 kg: 3 mg/kg every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks;
      b) Pediatric members weighing < 40 kg: 3 mg/kg every 3 weeks for 4 doses, followed by 3 mg/kg every 2 weeks;
g. Other indications: New dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
h. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval duration: 12 months

B. Other diagnoses/indications (1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PHAR.53

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase
AVD: doxorubicin, vinblastine, dacarbazine
BRAF: B-Raf proto-oncogene, serine/threonine kinase
cHL: classic Hodgkin lymphoma
CLL: chronic lymphocytic leukemia
CNS: central nervous system
CRC: colorectal cancer
dMMR: mismatch repair deficient
EGFR: epidermal growth factor receptor
EGJ: esophagogastric junction
ESCC: esophageal squamous cell carcinoma

FDA: Food and Drug Administration
HCC: hepatocellular carcinoma
HER-2: human epidermal growth factor
HSCT: hematopoietic stem cell transplantation
MET: mesenchymal-epithelial transition
MSI-H: microsatellite instability-high
NSCLC: non-small cell lung cancer
PD-1: programmed death receptor-1
PD-L1: programmed death-ligand 1
POLE: polymerase epsilon
POLD: polymerase delta
RCC: renal cell carcinoma
ROS1: ROS proto-oncogene 1
SCLC: small cell lung cancer
SLL: small lymphocytic lymphoma
TMB: tumor mutational burden
UC: urothelial carcinoma

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Nexavar (sorafenib)	HCC: 400 mg PO BID until clinical benefit ceases or unacceptable toxicity occurs	800 mg/day
Lenvima (lenvatinib)	HCC: 12 mg PO QD (patients ≥ 60 kg) or 8 mg PO QD (patients < 60 kg) until disease progression or unacceptable toxicity	12 mg/day
Tecentriq (atezolizumab) + bevacizumab (Avastin®, Mvasi, Zirabev)	HCC Tecentriq: 840 mg IV every 2 weeks, 1,200 mg IV every 3 weeks, or 1,680 mg IV every 4 weeks Bevacizumab: 15 mg/kg IV every 3 weeks	See regimen
Imfinzi (durvalumab)*	HCC Varies	Varies
First-line therapies (e.g., 5-FU/cisplatin, carboplatin/paclitaxel, FOLFOX, FOLFCIS)	Metastatic anal carcinoma: Varies	Varies
First-line therapies (e.g., platinum/etoposide-containing regimen)	Gestational trophoblastic neoplasia: Varies	Varies
platinum-containing regimens	NSCLC – squamous cell carcinoma: paclitaxel + carboplatin dose varies NSCLC – nonsquamous cell carcinoma:	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	pemetrexed + [carboplatin or cisplatin] dose varies	
Multiagent chemotherapy regimens examples: EMA/CO (etoposide, methotrexate, dactinomycin/cyclophosphamide, vincristine), EMA/EP (etoposide, methotrexate, dactinomycin/etoposide, cisplatin)	Gestational Trophoblastic Neoplasia: Varies	Varies
Yervoy (ipilimumab)	Melanoma, HCC: 3 mg/kg IV every 3 weeks for a maximum of 4 doses RCC, CRC: 1 mg/kg IV every 3 weeks for a maximum of 4 doses NSCLC, malignant pleural mesothelioma, ESCC: 1 mg/kg IV every 6 weeks	See regimen

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- High-risk disease in gestational trophoblastic neoplasia is defined as having a FIGO stage II to III and ≥ 7 prognostic score or stage IV
  - FIGO staging system:

Stage	Criteria
I	Tumor confined to uterus
II	Tumor extends to other genital structures (ovary, tube, vagina, broad ligaments) by metastasis or direct extension
III	Lung metastasis
IV	All other distant metastases

  - Prognostic Scoring Index
    - The total score is obtained by adding the individual scores for each prognostic factor (low risk is indicated by a score < 7 and high risk is indicated by a score ≥ 7)

Prognostic factor	Risk score

	0	1	2	4
Age (years)	< 40	≥ 40	--	--
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	--
Interval from index pregnancy (months)	< 4	4 to 6	7 to 12	>12
Pretreatment hCG (IU/L)	$< 10^3$	10^3 to $< 10^4$	10^4 to 10^5	$\geq 10^5$
Largest tumor size, including uterus (cm)	< 3	3 to 5	> 5	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	0	1 to 4	5 to 8	> 8
Previous failed chemotherapy	--	--	Single drug	Two or more drugs
Total score	--	--	--	--

*Appendix E: Dose Rounding Guidelines**

Weight-based Dose Range	Vial Quantity Recommendation
≤ 41.99 mg	1 vial of 40 mg/4 mL
42 mg-104.99 mg	1 vial of 100 mg/10 mL
105 mg-146.99 mg	1 vial of 40 mg/4 mL and 100 mg/10 mL
147 mg-209.99 mg	2 vials of 100 mg/10 mL
210 mg-251.99 mg	1 vial of 240 mg/24 mL
260 mg-293.99 mg	1 vial of 40 mg/4 mL and 240 mg/24 mL
294 mg-356.99 mg	1 vial of 100 mg/4 mL and 240 mg/24 mL
357 mg-503.99 mg	2 vials of 240 mg/24 mL

***This is part of a dose rounding guideline on select drug classes as part of an initiative conducted on a larger scale with multiple references and prescriber feedback.*

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Melanoma (unresectable or metastatic)	Monotherapy: • Adult and pediatric patients weighing ≥ 40 kg: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Pediatric patients weighing < 40 kg: 3 mg/kg IV every 2 weeks or 6 mg/kg IV every 4 weeks	See regimen

Indication	Dosing Regimen	Maximum Dose
	With ipilimumab: • Adult and pediatric patients weighing ≥ 40 kg: 1 mg/kg IV, followed by ipilimumab 3 mg/kg on the same day, every 3 weeks for 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Pediatric patients weighing < 40 kg: 1 mg/kg IV, followed by ipilimumab 3 mg/kg on the same day, every 3 weeks for 4 doses, then nivolumab 3 mg/kg IV every 3 weeks or 6 mg/kg mg IV every 6 weeks	
Melanoma (adjuvant treatment)	• Adult and pediatric patients weighing ≥ 40 kg: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Pediatric patients weighing < 40 kg: 3 mg/kg IV every 2 weeks or 6 mg/kg IV every 4 weeks Until disease recurrence or unacceptable toxicity for up to 1 year	See regimen
RCC - advanced with previous anti-angiogenic therapy, cHL, SCCHN	240 mg IV every 2 weeks or 480 mg IV every 4 weeks	480 mg/dose
RCC – advanced previously untreated	Monotherapy or with cabozantinib: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks With ipilimumab: 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day every 3 weeks for 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	See regimen
UC	Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks With cisplatin and gemcitabine: 360 mg IV every 3 weeks, followed by cisplatin and gemcitabine on the same day every 3 weeks for up to 6 cycles, then nivolumab 240 mg IV every 2 weeks or 480	See regimen

Indication	Dosing Regimen	Maximum Dose
	mg IV every 4 weeks until disease progression, unacceptable toxicity, or up to 2 years from first dose	
MSI-H/dMMR CRC	Monotherapy: • Adult and pediatric patients weighing ≥ 40 kg: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Pediatric patients weighing < 40 kg: 3 mg/kg IV every 2 weeks With ipilimumab: • Adult and pediatric patients weighing ≥ 40 kg: 3 mg/kg IV, followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • Pediatric patients weighing < 40 kg: 3 mg/kg IV, followed by ipilimumab 1 mg/kg on the same day, every 3 weeks for 4 doses, then nivolumab 3 mg/kg IV every 2 weeks	Monotherapy: 480 mg/dose With ipilimumab: 3 mg/kg/dose
HCC	With ipilimumab: 1 mg/kg IV, followed by ipilimumab 3 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses, nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	See regimen
NSCLC	Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks With ipilimumab: 360 mg IV every 3 weeks and ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression With ipilimumab and platinum-doublet chemotherapy: 360 mg IV every 3 weeks and ipilimumab 1 mg/kg IV every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles until disease progression, unacceptable	See regimen

Indication	Dosing Regimen	Maximum Dose
	toxicity, or up to 2 years in patients without disease progression With platinum-doublet chemotherapy: • Neoadjuvant: 360 mg IV every 3 weeks with platinum-doublet chemotherapy on the same day every 3 weeks for 4 cycles or until disease progression or unacceptable toxicity • Adjuvant: 480 mg IV every 4 weeks as a single agent after surgery for up to 13 cycles (approximately 1 year) or until disease recurrence or unacceptable toxicity	
Esophageal cancer	Adjuvant treatment of resected esophageal or GEJ cancer: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks for a total treatment duration of 1 year ESCC: until disease progression, unacceptable toxicity, or up to 2 years: • As a single agent or in combination with fluoropyrimidine- and platinum-containing chemotherapy: 240 mg every 2 weeks or 480 mg every 4 weeks • In combination with ipilimumab: 3 mg/kg every 2 weeks or 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks	480 mg/dose
Gastric cancer, EGJ cancer, and esophageal adenocarcinoma	With fluoropyrimidine- and platinum-containing chemotherapy: 240 mg every 2 weeks or 360 mg every 3 weeks	360 mg/dose
Malignant pleural mesothelioma	With ipilimumab: nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks	360 mg/dose

V. Product Availability

Single-dose vials: 40 mg/4 mL, 100 mg/10 mL, 120 mg/12 mL, 240 mg/24 mL

VI. References

1. Opdivo Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; October 2024. Available at https://www.opdivo.com/. Accessed November 1, 2024.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at http://www.nccn.org. Accessed November 7, 2024.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9299	Injection, nivolumab, 1 mg

Reviews, Revisions, and Approvals	Date
Added requirement for being prescribed by or in consultation with an oncologist; added requirement for Child-Pugh classification to for HCC indication; updated melanoma criteria set to reflect expanded indication for the adjuvant treatment of patients with melanoma: removed "unresectable or metastatic" from the diagnosis. Added coverage criteria for the new FDA-approved indication of hepatocellular carcinoma. Updated off-label usage requirements for NSCLC, RCC, Classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck and urothelial carcinoma to reflect off-label NCCN recommendations for use. Added coverage criteria for the new FDA-approved indication of MSI-H/dMMR colorectal cancer and for the NCCN-recommended off-label usages of malignant pleural mesothelioma and small cell lung cancer. References reviewed and updated.	02/2018
1Q 2019 annual review; ages adjusted per PI to 18 and older for all indications except CRC; melanoma - brain metastasis is deleted and incorporated under a diagnosis of melanoma; for NSCLC, progression on platinum therapy changed to progression on systemic therapy to encompass progression on first-line targeted therapy per PI and NCCN; removed malignant pleural mesothelioma due to NCCN 2B recommendation status; off-label NCCN recommended trophoblastic tumor is added; dMMR/MSI-H metastatic rectal cancer removed from off-label section as it is represented under the CRC labeled use; for RCC, combination dosing with Yervoy added per PI; references reviewed and updated.	01/2019
1Q 2020 annual review: added off-label use in malignant pleural mesothelioma per NCCN recommendation update from category 2B to category 2A; added requirement for use in anal carcinoma as second line or subsequent therapy; added requirement for use in gestational trophoblastic neoplasia following a platinum/etoposide-containing regimen or in methotrexate-resistant, high-risk disease; references reviewed and updated.	01/2020
1Q 2021 annual review: FDA approved pleural mesothelioma added; per FDA/NCCN as follows: for melanoma, unresectable, metastatic, or lymph node positive disease added; for NSCLC, single-agent therapy	01/2021

Reviews, Revisions, and Approvals	Date
for TMB positive tumor added, combination therapy for RET rearrangement added, combination therapy changed from Yervoy and platinum doublet therapy to Yervoy plus/minus a platinum based regimen; for cHL, relapsed, refractory or progressive disease added, post HSCT replaced with prescribed as subsequent therapy; for HCC, Lenvima added as a prior therapy option; off-label pediatric Hodgkin lymphoma and vulvar cancer added; references reviewed and updated.	
1Q 2022 annual review: updates made per NCCN: for urothelial carcinoma removed requirement for resection to be radical as NCCN also supports partial resection prior to adjuvant therapy and added treatment option of high-risk recurrence as an optional criterion; added cervical cancer as off-label indication; updated gestational trophoblastic neoplasia treatment settings; added criterion for use as single-agent therapy for SCCHN; clarified uveal melanoma to be metastatic; removed "metastatic" designation for Merkel cell carcinoma; clarified small bowel adenocarcinoma be advanced or metastatic; clarified extranodal NK/T-cell lymphoma to be relapsed or refractory; added new FDA-approved indications of gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma; added new FDA-approved indication of completely resected esophageal or gastroesophageal junction cancer; references reviewed and updated.	01/2022
1Q 2023 annual review: added for new FDA approved indication for first-line use in ESCC in combination with Yervoy or with fluoropyrimidine- and platinum-containing chemotherapy; for HCC, added additional options for prior use of Tecentriq+bevacizumab or Imfinzi and removed requirement for no previous treatment with a checkpoint inhibitor per latest NCCN guidelines; added new FDA-approved indication of neoadjuvant use in NSCLC; added off-label criteria for bone cancer, central nervous system cancers, pediatric primary mediastinal large B-cell lymphoma, pediatric diffuse high-grade gliomas per NCCN 2A recommendations; removed age restriction from off-label criteria; references reviewed and updated.	01/2023
RT4: updated criteria for melanoma to reflect FDA approved pediatric age extension; updated Appendix B.	04/2023
1Q 2024 annual review: HCC, added option for Child-Pugh Class B and prescribed as a single agent per NCCN 2A recommendation; references reviewed and updated. RT4: updated indication and criteria for the treatment of melanoma in the adjuvant setting.	01/2024
RT4: for UC, updated indication and criteria for the first-line treatment of UC in combination with cisplatin and gemcitabine; converted advanced/metastatic UC from accelerated approval to full FDA-approval. Ad hoc: for NSCLC, revised dose limit for use in combination with Yervoy from 3 mg/kg every 2 weeks to 360 mg every 3 weeks per PI, removed criteria for use in tumors positive for tumor mutation burden	04/2024

Reviews, Revisions, and Approvals	Date
biomarkers- per NCCN No Longer Recommended Uses; for CRC, clarified weight-based dose limit for pediatric members per PI; added off-label criteria per NCCN compendium: for malignant pleural mesothelioma as subsequent therapy, cHL as palliative therapy, SCCHN in combination with Erbitux or with cisplatin and gemcitabine, CRC characterized with POLE/POLED1 mutation, esophageal cancer or EGJ cancer characterized with MSI-H or dMMR mutations, gastric cancer characterized with MSI-H or dMMR mutations, adult relapsed or refractory primary mediastinal large B-cell lymphoma, MSI-H or dMMR mutational cancers (e.g., ampullary adenocarcinoma, small bowel adenocarcinoma, endometrial carcinoma), biliary tract cancers, classic Kaposi sarcoma in combination with Yervoy, soft tissue sarcomas, anaplastic thyroid carcinoma as a single agent, anal carcinoma prior to resection, and merkel cell carcinoma; removed off-label criteria per NCCN compendium: failure of induction therapy/initial treatment for primary mediastinal large B-cell lymphoma, and bone cancer as a single agent.	
1Q 2025 annual review: RT4: added new FDA-approved indication for neoadjuvant treatment followed by single-agent Opdivo as adjuvant treatment after surgery for NSCLC; increased maximum duration allowed for neoadjuvant therapy from 3 cycles/9 weeks to 4 cycles/12 weeks. Ad hoc: for continued therapy: added criterion for maximum duration of therapy limit of 13 cycles for adjuvant NSCLC, up to 1 year for all other adjuvant treatment, and up to 2 years for metastatic or recurrent NSCLC, malignant pleural mesothelioma, advanced RCC in combination with cabozatinib, unresectable or metastatic UC, ESCC, gastric cancer, EGJ, and esophageal adenocarcinoma; revised dose limit for NSCLC in combination with Yervoy to 360 mg every 3 weeks; added additional dose limit option of 240 mg every 2 weeks for gastric cancer, EGJ cancer, and esophageal adenocarcinoma. for melanoma, added resected stage IV melanoma per PI; for cHL, added option for disease stage III-IV prescribed as primary treatment in combination with AVD (doxorubicin, vinblastine, darcarbazine) per NCC; for SCCHN, for combination with Erbitux added option for subsequent-line therapy option and added option to be prescribed in combination with Yervoy as first-line therapy per NCCN; for HCC, removed child-pugh classifications, removed specific treatment regimens member has had disease progression following from and revised to prescribed as subsequent line systemic therapy, added member has not been previously treated with immune checkpoint inhibitor therapy, unless following atezolizumab and bevacizumab if prescribed in combination with Yervoy per NCCN; for esophageal cancer, EGJ cancer or esophageal adenocarcinoma, added option for planned esophagectomy and to be prescribed as a single agent for MSI-H or dMMR cancers per	12/2024

Reviews, Revisions, and Approvals	Date
NCCN; added off-label criteria per NCCN: for pediatric cHL – option to be used as re-induction therapy, vaginal cancer for second-line or subsequent therapy as a single agent, chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with histologic (Richter) transformation to diffuse B-cell lymphoma – prescribed as a single agent for SCLC, peritoneal, pericardial and tunica vaginalis testis mesothelioma – as single agent or in combination with Yervoy, single agent usage for Kaposi sarcoma; clarified small bowel adenocarcinoma be advanced or metastatic per NCCN; for off-label recurrent or progressive intermediate trophoblastic tumor, removed requirement for following treatment with platinum-based regimen per NCCN; references reviewed and updated.	