

Clinical Policy: Nivolumab (Opdivo), Nivolumab/Hyaluronidase-nvhy (Opdivo Qvantig)

Reference Number: PA.CP.PHAR.121

Effective Date: 01/2018

Last Review Date: 01/2026

Description

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

Nivolumab/hyaluronidase-nvhy (Opdivo Qvantig[™]) is a combination of nivolumab and hyaluronidase, an endoglycosidase.

FDA Approved Indication(s)

Opdivo is indicated for the treatment of:

Indications	Description	Opdivo	Opdivo Qvantig	
Melanoma	Unresectable or metastatic melanoma	As a single agent	X (Age ≥ 12 years)	X (Age ≥ 12 years)
		In combination with ipilimumab [‡]	X (Age ≥ 12 years)	
		Following combination treatment with intravenous nivolumab and ipilimumab		X (Age ≥ 12 years)
	Completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma, in the adjuvant setting	X (Age ≥ 12 years)	X (Age ≥ 12 years)	
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	X	X	
	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 or Opdivo Qvantig as adjuvant treatment after surgery	X	X	
	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 [‡]	X		
	Adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor	X		

Indications	Description	Opdivo	Opdivo Qvantig
	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 or Opdivo Qvantig	X	X
Malignant pleural mesothelioma	Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab	X	
Renal cell carcinoma (RCC)	Adult patients with advanced RCC who have received prior antiangiogenic therapy	X	X
	Adult patients with advanced RCC, as a first-line treatment in combination with cabozantinib	X	X
	Adult patients with intermediate or poor risk advanced RCC, as a first-line treatment	In combination with ipilimumab† Following combination treatment with nivolumab with ipilimumab	X X
Classical Hodgkin lymphoma (cHL)*	Adult patients with cHL that has relapsed or progressed after: <ul style="list-style-type: none"> autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT. 	X	
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	X	X
Urothelial carcinoma (UC)	Adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC	X	X
	Adult patients with unresectable or metastatic UC, as first-line treatment in combination with cisplatin and gemcitabine	X	X
	Adult patients with locally advanced or metastatic UC who: <ul style="list-style-type: none"> have disease progression during or following platinum-containing chemotherapy, or 	X	X

Indications	Description	Opdivo	Opdivo Qvantig	
	<ul style="list-style-type: none"> have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy 			
Colorectal cancer (CRC)	Patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC in combination with ipilimumab	X (Age ≥ 12 years)		
	Patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan as monotherapy†	X (Age ≥ 12 years)		
	Patients with unresectable or metastatic MSI-H or dMMR CRC following combination treatment with intravenous nivolumab and ipilimumab* as monotherapy†		X (Age ≥ 12 years)	
Hepatocellular carcinoma (HCC)	Adult patients with unresectable or metastatic HCC, as first-line treatment in combination with ipilimumab	X		
	Adult patients with unresectable or metastatic HCC, as first-line treatment following combination treatment with intravenous nivolumab and ipilimumab		X	
	Adult patients with HCC who have been previously treated with sorafenib	In combination with ipilimumab†	X	
		Following combination treatment with intravenous nivolumab and ipilimumab*		X
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)	X	X	
	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) whose tumor expresses PD-L1 (≥ 1)	X	X	
	In combination with ipilimumab for the first-line treatment of adult patients with unresectable advanced or metastatic ESCC whose tumors express PD-L1 (≥ 1)†	X		

Indications	Description	Opdivo	Opdivo Qvantig
	Adult patients with unresectable advanced, recurrent, or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy	X	X
Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma	In combination with fluoropyrimidine- and platinum-containing chemotherapy for adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma whose tumors express PD-L1 (≥ 1)	X	X

*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.

‡ Limitation(s) of use: Opdivo Qvantig is not indicated in combination with ipilimumab for the treatment of RCC, unresectable or metastatic melanoma, metastatic NSCLC, MSI-H or dMMR metastatic CRC, HCC, or unresectable advanced or metastatic ESCC.

Policy/Criteria

It is the policy of PA Health & Wellness that Opdivo and Opdivo Qvantig are **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 one of the following (a, b, c or d):
 - a. Unresectable or metastatic;
 - b. Resected stage IIB, IIC, III, or IV;
 - c. Resectable stage III or limited local satellite/in-transit recurrence or nodal recurrence (off-label)
 - d. Other NCCN recommendations listed as category 1, 2A, or 2B;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. For Opdivo Qvantig requests, both of the following (a and b):
 - a. Member weight ≥ 30 kg;
 - b. Prescribed as a single agent;
5. For Opdivo requests, prescribed in one of the following ways (a or b):
 - a. For use as a single agent;
 - b. For use in combination with Yervoy[®];
**Prior authorization may be required for Yervoy.*
6. Request meets one of the following (a or b):
 - a. Dose does not exceed the maximum indicated regimen in section V (*see Appendix E for dose rounding guidelines*);
 - b. 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. 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 \geq 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, ii or iii):
 - i. Neoadjuvant treatment in combination with platinum-doublet chemotherapy;
 - ii. Adjuvant treatment as a single agent, and both of the following (1 and 2):
 - 1) Prescribed following neoadjuvant treatment in combination with platinum-doublet chemotherapy;
 - 2) Disease mutation status is negative for EGFR and ALK;
 - iii. Other NCCN recommendations listed as category 1, 2A, or 2B;
 - b. Tumors \geq 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 (1, 2, or 3):
 - 1) 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;
 - 2) 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;
 - 3) Disease is positive for a RET rearrangement;
 - ii. Request meets one of the following (1 or 2):
 - 1) Member has PD-L1 tumor expression of \geq 1%;
 - 2) Opdivo is being used in combination with Yervoy \pm a platinum-based regimen (*see Appendix B*);
 - c. Other NCCN recommendations listed as category 1, 2A, or 2B;
7. Request meets one of the following (a or b):
 - a. Dose does not exceed the maximum indicated regimen in section V;
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

**Prior authorization may be required for Yervoy*

Approval duration: 12 months

C. Malignant Pleural Mesothelioma (must meet all):

1. Diagnosis of malignant pleural mesothelioma;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. For Opdivo requests: 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*);

**Prior authorization may be required for Yervoy.*

5. For Opdivo Qvantig requests: Prescribed as subsequent therapy as a single agent (*off-label*);
6. Request meets one of the following (a or b):
 - a. Dose does not exceed 360 mg every 3 weeks;
 - b. 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: 12 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 \geq 18 years;
4. One of the following (a or b):
 - a. Disease is relapsed, recurrent, metastatic, surgically unresectable stage IV;
 - b. Member has hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC (*off-label*);
5. For Opdivo requests: Prescribed in one of the following ways (a-d):
 - a. For use as a single agent;
 - b. For use in combination with Cabometyx[®];
 - c. For use in combination with Yervoy;
**Prior authorization may be required for Yervoy.*
 - d. Other NCCN recommendations listed as category 1, 2A, or 2B;
6. For Opdivo Qvantig requests: Prescribed in one of the following ways (a-d):
 - a. For use as first-line treatment as a single agent, following combination treatment with Opdivo and Yervoy;
 - b. For use as subsequent therapy as a single agent;
 - c. For use in combination with Cabometyx;
 - d. Other NCCN recommendations listed as category 1, 2A, or 2B;
7. Request meets one of the following (a or b):
 - a. Dose does not exceed the maximum indicated regimen in section V (*see Appendix E for dose rounding guidelines*);
 - b. 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

E. Classical Hodgkin Lymphoma (must meet all):

1. Diagnosis of cHL;
2. Request is for Opdivo;
3. Prescribed by or in consultation with an oncologist;
4. Age \geq 18 years;
5. Prescribed as one of the following (a-d):
 - a. Disease is relapsed, refractory or progressive: one of the following (i or ii):
 - i. Prescribed as subsequent therapy as a single agent or in combination with Adcentris[®] or ICE (ifosfomide, carboplatin, etoposide);
 - ii. Palliative therapy (*off-label*);
 - b. For primary treatment, one of the following (i or ii):

- i. Prescribed in combination with AVD (doxorubicin, vinblastine, dacarbazine) (*off-label*);
- ii. Member is not a candidate for anthracycline (e.g., doxorubin) and prescribed as a single agent or in combination with Adcentris[®];
- c. Post allogenic hematopoietic cell transplant, as a single agent;
- d. Other NCCN recommendations listed as category 1, 2A, or 2B;
6. 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: 12 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 \geq 18 years;
4. Opdivo is prescribed in one of the following ways (a-e):
 - 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 Opdivo requests: For use in combination with Yervoy as first-line therapy (*off-label*);
 - e. Other NCCN recommendations listed as category 1, 2A, or 2B;
5. For nasopharyngeal carcinoma, one of the following (a or b):
 - a. Failure of Loqtorzi[®] at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
 - b. Request is for Stage IV or metastatic cancer;
6. Request meets one of the following (a, b or c):
 - a. Opdivo: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
 - b. Opdivo Qvantig: Dose does not exceed 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units 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: 12 months

G. Urothelial Carcinoma (must meet all):

1. Diagnosis of UC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. One of the following (a- 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 or b):
 - a. Dose does not exceed the maximum indicated regimen in section V;
 - b. 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

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 \geq 12 years;
- 5. For Opdivo requests, prescribed in one of the following ways (a or b):
 - a. As a single agent;
 - b. In combination with Yervoy;
**Prior authorization may be required for Yervoy.*
- 6. For Opdivo Qvantig requests, both of the following (a and b):
 - a. Member weight \geq 30 kg;
 - b. Prescribed as a single agent;
- 7. Dose does not exceed one of the following (a or b):
 - a. Dose does not exceed the maximum indicated regimen in section V (*see Appendix E for dose rounding guidelines*);
 - b. 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

I. Hepatocellular Carcinoma (must meet all):

- 1. Diagnosis of HCC;
- 2. Prescribed by or in consultation with an oncologist;
- 3. Age \geq 18 years;
- 4. One of the following:
 - a. Disease is unresectable or metastatic;
 - b. Other NCCN recommendations listed as category 1, 2A, or 2B;
- 5. For first-line systemic therapy, prescribed in one of the following ways (a, b or c):
 - a. For Opdivo requests: In combination with Yevoy*;
 - b. For Opdivo Qvantig requests: As a single agent following combination treatment with Opdivo and Yervoy*;
**Prior authorization may be required for Yervoy.*
 - c. Member is deemed ineligible for resection, transplant, or locoregional therapy
- 6. For subsequent-line systemic therapy, one of the following (a, b or c):
 - a. For Opdivo requests, one of the following (i or ii):
 - i. Prescribed as a single agent, and member has not been previously treated with a checkpoint inhibitor (PD-L1/PD-1, e.g., Keytruda);
 - ii. Prescribed in combination with Yervoy*, and member has not been previously treated with anti-CTLA4-based combinations (e.g., tremelimumab-actl plus

durvalumab);

**Prior authorization may be required for Yervoy.*

- b. For Opdivo Qvantig requests: Prescribed as a single agent following combination treatment with Opdivo and Yervoy;
 - c. Other NCCN recommendations listed as category 1, 2A, or 2B;
7. Dose does not exceed one of the following (a, b, or c):
- a. Opdivo 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*);
 - b. Opdivo Qvantig: 600 mg/10,000 units every 2 weeks or 1,200 mg/20,000 units 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: 12 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 \geq 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 and b):
 - a. One of the following (i, ii or iii):
 - i. For unresectable locally advanced, recurrent or metastatic disease, prescribed in one of the following ways (1 or 2):
 1. In combination or with fluoropyrimidine- and platinum-containing chemotherapy;
 2. For Opdivo requests: in combination with Yervoy;
**Prior authorization may be required for Yervoy.*
 - ii. 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;
 - iii. Other NCCN recommendations listed as category 1, 2A, or 2B;
 - b. One of the following (i or ii)
 - i. Failure of Tevimbra[®] at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
 - ii. Request is for Stage IV or metastatic cancer;
7. For MSI-H or dMMR cancers, prescribed in one of the following ways (a-d):
 - a. As a single agent for perioperative therapy;
 - b. In combination with fluoropyrimidine-containing chemotherapy (e.g., 5-fluorouracil, capecitabine) and oxaliplatin as induction or palliative therapy;

- c. For Opdivo requests: In combination with Yervoy as induction, neoadjuvant, perioperative, or palliative therapy;
- d. Other NCCN recommendations listed as category 1, 2A, or 2B;
- 8. Request meets one of the following (a or b):
 - a. Dose does not exceed the maximum indicated regimen in section V;
 - b. 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

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 \geq 18 years;
- 5. For unresectable locally advanced, recurrent, or metastatic disease, all of the following (a - e):
 - a. Prescribed in combination with a fluoropyrimidine- (e.g., 5-fluorouracil, capecitabine) and platinum-containing (e.g., carboplatin, cisplatin, oxaliplatin) chemotherapy;
 - b. Disease is HER2-negative;
 - c. Tumor expresses PD-L1 (CPS \geq 1);
 - d. One of the following (i or ii):
 - i. Failure of Tevimbra[®] at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
 - ii. Request is for Stage IV or metastatic cancer;
 - e. Other NCCN recommendations listed as category 1, 2A, or 2B;
- 6. For MSI-H or dMMR cancers, prescribed in one of the following was (a-d):
 - a. In a single agent;
 - b. In combination with fluoropyrimidine-containing chemotherapy (e.g., 5-fluorouracil, capecitabine) and oxaliplatin;
 - c. For Opdivo requests: in combination with Yervoy;
**Prior authorization may be required for Yervoy.*
 - d. Other NCCN recommendations listed as category 1, 2A, or 2B;
- 7. Request meets one of the following (a or b):
 - a. Dose does not exceed the maximum indicated regimen in section V;
 - b. 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

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

- 1. Diagnosis of one of the following (a-y):

- 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;
- g. Vulvar cancer - HPV-related advanced, recurrent, or metastatic disease, as second-line treatment;
- h. Cervical cancer, as second-line or subsequent therapy;
- i. Endometrial carcinoma or uterine sarcoma 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-iv):
 - i. Ampullary adenocarcinoma;
 - ii. Appendiceal neoplasms and cancers;
 - iii. Small bowel adenocarcinoma that is advanced or metastatic;
 - iv. Endometrial carcinoma that is recurrent or metastatic, as subsequent therapy;
- p. Squamous cell skin cancer;
- q. Small bowel adenocarcinoma or appendiceal neoplasms and cancers with POLE/POLD1 mutation;
- r. 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;
- s. Classic Kaposi sarcoma, as subsequent therapy;
- t. 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;
- u. Anaplastic thyroid carcinoma that is metastatic;
- v. Vaginal cancer, as second-line or subsequent therapy;
- w. Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with histologic (Richter) transformation to diffuse B-cell lymphoma;
- x. One of the following mesothelioma (i, ii, or iii):
 - i. Peritoneal mesothelioma;
 - ii. Pericardial mesothelioma;
 - iii. Tunica vaginalis testis mesothelioma

- y. Other NCCN recommendations listed as category 1, 2A, or 2B;
2. Prescribed by or in consultation with an oncologist;
3. Member meets one of the following (a or b):
 - a. Opdivo: Age \geq 12 years;
 - b. Opdivo Qvantig: Age \geq 18 years;
4. One of the following (a-i):
 - a. 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);
 - b. For gestational trophoblastic neoplasia: prescribed as a single agent for multi-agent chemotherapy-resistant disease (*see Appendix B*) in one of the following settings (i or ii):
 - i. Recurrent or progressive intermediate trophoblastic tumor;
 - ii. High-risk disease (*see Appendix D*);
 - c. For primary mediastinal large B-cell lymphoma: prescribed as one of the following (i or ii):
 - i. As a single agent;
 - ii. Combination with brentuximab vedotin as consolidation/additional therapy;
 - d. For pediatric diffuse high-grade gliomas: prescribed as one of the following (i or ii):
 - i. As a single agent;
 - ii. For Opdivo requests: in combination with Yervoy;
**Prior authorization may be required for Yervoy.*
 - e. For bone cancer, prescribed in one of the following ways (i or ii):
 - i. For Opdivo requests: In combination with Yervoy;
 - ii. For dedifferentiated chondrosarcoma, as a single agent or in combination with Sutent[®];
**Prior authorization may be required for Sutent;*
 - f. For ampullary adenocarcinoma, request is for Opdivo prescribed in combination with Yervoy*,
**Prior authorization may be required for Yervoy;*
 - g. For CLL or SLL, prescribed as a single agent or in combination with Imbruvica[®];
**Prior authorization may be required for Imbruvica.*
 - h. For endometrial carcinoma, squamous cell skin cancer, anaplastic thyroid carcinoma, vaginal cancer, SCLC: prescribed as a single agent;
 - i. Other NCCN recommendations listed as category 1, 2A, or 2B;
5. 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: 12 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 in combination with Yervoy, malignant pleural mesothelioma, advanced RCC in combination with Cabometyx, unresectable or metastatic UC, ESCC in combination with chemotherapy, gastric cancer, EGJ, esophageal adenocarcinoma, first-line HCC, and unresectable or metastatic CRC, maximum duration of therapy does not exceed 2 years;
5. If request is for a dose increase, request meets one of the following (a or b):
 - a. Dose does not exceed the maximum indicated regimen in section V (*see Appendix E for dose rounding guidelines*);
 - b. 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	HL: hereditary leiomyomatosis
AVD: doxorubicin, vinblastine, dacarbazine	HSCT: hematopoietic stem cell transplantation
BRAF: B-Raf proto-oncogene, serine/threonine kinase	MET: mesenchymal-epithelial transition
cHL: classic Hodgkin lymphoma	MSI-H: microsatellite instability-high
CLL: chronic lymphocytic leukemia	NSCLC: non-small cell lung cancer
CNS: central nervous system	PD-1: programmed death receptor-1
CPS: combined positive score	PD-L1: programmed death-ligand 1
CRC: colorectal cancer	POLE: polymerase epsilon
dMMR: mismatch repair deficient	POLD: polymerase delta
EGFR: epidermal growth factor receptor	RCC: renal cell carcinoma
EGJ: esophagogastric junction	ROS1: ROS proto-oncogene 1
ESCC: esophageal squamous cell carcinoma	SCCHN: squamous cell carcinoma of the head and neck
FDA: Food and Drug Administration	SCLC: small cell lung cancer
G/GEJ: gastric or gastroesophageal junction adenocarcinoma	SLL: small lymphocytic lymphoma
HCC: hepatocellular carcinoma	TMB: tumor mutational burden
HER-2: human epidermal growth factor	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
Loqtorzi (toripalimab-tpzi)	Nasopharyngeal carcinoma First-line treatment: 240 mg IV every three weeks up to 24 months in combination with cisplatin and gemcitabine Previously treated, unresectable or metastatic: 3 mg/kg IV every two weeks	First-line treatment: 240 mg/3 weeks Previously treated, unresectable or metastatic: 3 mg/kg every two weeks
Tevimbra (tislelizumab-jsgr)	ESCC and G/GEJ: 200 mg IV on Day 1 of every 3-week cycle	See regimen
Lenvima (lenvatinib)	HCC: 12 mg PO QD (patients \geq 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	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	NSCLC – nonsquamous cell carcinoma: 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.

*Off-label

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	≥ 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

Drug Name	Indication	Dosing Regimen	Maximum Dose
Opdivo	Melanoma (unresectable or metastatic)	<u>Monotherapy:</u>	See regimen

Drug Name	Indication	Dosing Regimen	Maximum Dose
		<ul style="list-style-type: none"> Adult and pediatric patients weighing \geq 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 <p><u>With ipilimumab:</u></p> <ul style="list-style-type: none"> Adult and pediatric patients weighing \geq 40 kg: 1 mg/kg IV, followed by ipilimumab 3 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 Pediatric patients weighing $<$ 40 kg: 1 mg/kg IV, followed by ipilimumab 3 mg/kg IV 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)	<ul style="list-style-type: none"> Adult and pediatric patients weighing \geq 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 <p>Until disease recurrence or unacceptable toxicity for up to 1 year</p>	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	<p><u>Monotherapy or with cabozantinib:</u> 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</p> <p><u>With ipilimumab:</u> 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</p>	See regimen

Drug Name	Indication	Dosing Regimen	Maximum Dose
	UC	<p><u>Monotherapy:</u> 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</p> <p><u>With cisplatin and gemcitabine:</u> 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 mg IV every 4 weeks until disease progression, unacceptable toxicity, or up to 2 years from first dose</p>	See regimen
	MSI-H/dMMR CRC	<p><u>Monotherapy:</u></p> <ul style="list-style-type: none"> • Adult and pediatric patients weighing \geq 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 <p><u>With ipilimumab:</u></p> <ul style="list-style-type: none"> • Adult and pediatric patients weighing \geq 40 kg: 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 • Pediatric patients weighing $<$ 40 kg: 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day, every 3 weeks for 4 doses, then nivolumab 3 mg/kg IV every 2 weeks 	See regimen
	HCC	<u>With ipilimumab:</u> 1 mg/kg IV, followed by ipilimumab 3 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	See regimen
	NSCLC	<p><u>Monotherapy:</u> 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</p> <p><u>With ipilimumab:</u> 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</p>	See regimen

Drug Name	Indication	Dosing Regimen	Maximum Dose
		<p><u>With ipilimumab and platinum-doublet chemotherapy:</u> 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 toxicity, or up to 2 years in patients without disease progression</p> <p><u>With platinum-doublet chemotherapy:</u></p> <ul style="list-style-type: none"> • Neoadjuvant: 360 mg IV every 3 weeks with platinum-doublet chemotherapy on the same day every 3 weeks for up to 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	<p><u>Adjuvant treatment of resected esophageal or GEJ cancer:</u> 240 mg IV every 2 weeks or 480 mg IV every 4 weeks for a total treatment duration of 1 year</p> <p><u>ESCC:</u> until disease progression, unacceptable toxicity, or up to 2 years:</p> <ul style="list-style-type: none"> • As a single agent or in combination with fluoropyrimidine- and platinum-containing chemotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks • In combination with ipilimumab: 3 mg/kg IV every 2 weeks or 360 mg IV every 3 weeks with ipilimumab 1 mg/kg IV every 6 weeks 	See regimen
	Gastric cancer, EGJ cancer, and esophageal adenocarcinoma	<u>With fluoropyrimidine- and platinum-containing chemotherapy:</u> 240 mg IV every 2 weeks or 360 mg IV every 3 weeks	360 mg/dose
	Malignant pleural mesothelioma	<u>With ipilimumab:</u> nivolumab 360 mg IV every 3 weeks and ipilimumab 1 mg/kg IV every 6 weeks	360 mg/dose

Drug Name	Indication	Dosing Regimen	Maximum Dose
Opdivo Qvantig	RCC	<u>Monotherapy or with cabozantinib:</u> 600 mg/10,000 units SC every 2 weeks or 1,200 mg/20,000 units SC every 4 weeks until disease progression, unacceptable toxicity, or if administered with Cabometyx, up to 2 years	See regimen
	Melanoma	<u>Monotherapy:</u> <ul style="list-style-type: none"> • Adult and pediatrics age ≥ 12 years and weighing ≥ 40 kg: 600 mg/10,000 units SC every 2 weeks or 1,200 mg/20,000 units SC every 4 weeks until disease progression or unacceptable toxicity OR for adjuvant treatment, until disease recurrence or unacceptable toxicity for up to 1 year • Pediatrics age ≥ 12 years and weighing ≥ 30 kg but < 40 kg: 300 mg/5,000 units SC every 2 weeks or 600 mg /10,000 units SC every 4 weeks until disease progression or unacceptable toxicity OR for adjuvant treatment, until disease recurrence or unacceptable toxicity for up to 1 year 	1,200 mg/ 20,000 units per dose
	SCCHN	<u>Monotherapy:</u> 600 mg/10,000 units SC every 2 weeks or 1,200 mg/20,000 units SC every 4 weeks until disease progression or unacceptable toxicity	1,200 mg/ 20,000 units per dose
	CRC	<u>Monotherapy:</u> <ul style="list-style-type: none"> • Adult and pediatrics age ≥ 12 years and weighing ≥ 40 kg: 600 mg/10,000 units SC every 2 weeks or 1,200 mg/20,000 units SC every 4 weeks until disease progression or unacceptable toxicity OR if treatment for first-line CRC up to 2 years Pediatrics age ≥ 12 years and weighing ≥ 30 kg but < 40 kg: 300 mg/5,000 units SC every 2 weeks or 600 mg /10,000 units SC every 4 weeks until disease progression or unacceptable toxicity OR if treatment for first-line CRC up to 2 years	1,200 mg/ 20,000 units per dose
	HCC	<u>Monotherapy:</u> 600 mg/10,000 units SC every 2 weeks or 1,200 mg/20,000 units SC every 4 weeks until disease progression	1,200 mg/ 20,000 units per dose

Drug Name	Indication	Dosing Regimen	Maximum Dose
		or unacceptable toxicity OR if treatment for first-line HCC up to 2 years	
	NSCLC	<p><u>Monotherapy:</u> 600 mg/10,000 units SC every 2 weeks or 1,200 mg/20,000 units SC every 4 weeks until disease progression or unacceptable toxicity</p> <p><u>With platinum-doublet chemotherapy</u></p> <ul style="list-style-type: none"> • Neoadjuvant: 900 mg/15,000 units SC with platinum-doublet chemotherapy on the same day every 3 weeks until disease progression or unacceptable toxicity, for up to 4 cycles • Adjuvant: 1,200 mg/20,000 units SC as a single agent every 4 weeks after surgery until disease progression, recurrence, or unacceptable toxicity, for up to 13 cycles (up to 1 year) 	See regimen
	UC	<p><u>Monotherapy:</u> 600 mg/10,000 units SC every 2 weeks or 1,200 mg/20,000 units SC every 4 weeks until disease progression, disease recurrence, unacceptable toxicity, or if prescribed as adjuvant treatment, up to 1 year</p> <p><u>With cisplatin and gemcitabine:</u> 900 mg/15,000 units SC every 3 weeks with cisplatin and gemcitabine on the same day for up to 6 cycles, then 600 mg/10,000 units SC as a single agent every 2 weeks or 1,200 mg/20,000 units SC every 4 weeks until disease progression, unacceptable toxicity, or up to 2 years from first dose</p>	See regimen
Esophageal cancer	<p>Adjuvant treatment of resected esophageal or GEJ cancer:</p> <p><u>Monotherapy:</u> 600 mg/10,000 units SC every 2 weeks or 1,200 mg/20,000 units SC every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year</p> <p>ESCC: <u>Monotherapy or with fluoropyrimidine- and platinum- containing chemotherapy:</u> 600 mg/10,000 units SC every 2 weeks or</p>	See regimen	

Drug Name	Indication	Dosing Regimen	Maximum Dose
		1,200 mg/20,000 units SC every 4 weeks until disease progression, disease recurrence, unacceptable toxicity, or if prescribed as combination therapy, up to 2 years	
	Gastric cancer, EGJ cancer, and esophageal adenocarcinoma	<u>With fluoropyrimidine- and platinum-containing chemotherapy:</u> 600 mg/10,000 units every 2 weeks or 900 mg/15,000 units every 3 weeks until disease progression, unacceptable toxicity, or up to 2 years	See regimen

V. Product Availability

Drug Name	Availability
Nivolumab (Opdivo)	Single-dose vials: 40 mg/4 mL, 100 mg/10 mL, 120 mg/12 mL, 240 mg/24 mL
Nivolumab/hyaluronidase-nvhy (Opdivo Qvantig)	Single-dose vial: 300 mg nivolumab/5,000 units hyaluronidase/2.5 mL, 600 mg nivolumab/10,000 units hyaluronidase/5 mL

VI. References

1. Opdivo Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; May 2025. Available at <https://www.opdivo.com/>. Accessed November 6, 2025.
2. Opdivo Qvantig Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; November 2025. Available at: https://packageinserts.bms.com/pi/pi_opdivo-qvantig.pdf. Accessed December 2, 2025.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at <http://www.nccn.org>. Accessed December 2, 2025.

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
J9289	Injection, nivolumab, 2 mg and hyaluronidase-nvhy
J9299	Injection, nivolumab, 1 mg

Reviews, Revisions, and Approvals	Date
<p>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.</p>	02/2018
<p>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.</p>	01/2019
<p>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.</p>	01/2020
<p>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 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.</p>	01/2021
<p>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</p>	01/2022

Reviews, Revisions, and Approvals	Date
<p>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.</p>	
<p>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.</p>	01/2023
<p>RT4: updated criteria for melanoma to reflect FDA approved pediatric age extension; updated Appendix B.</p>	04/2023
<p>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.</p>	01/2024
<p>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 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</p>	04/2024

Reviews, Revisions, and Approvals	Date
<p>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.</p>	
<p>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.</p> <p>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, dactinomycin) 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 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</p>	<p>12/2024</p>

Reviews, Revisions, and Approvals	Date
<p>following treatment with platinum-based regimen per NCCN; references reviewed and updated.</p>	
<p>RT4: added new SC formulation Opdivo Qvantiq to policy; clarified maximum duration of therapy limit does not exceed 2 years in continued therapy for NSCLC applies when in combination with Yervoy and for ESCC in combination with chemotherapy; for melanoma and colorectal cancer, added criterion prescribed as a single agent and for Opdivo in combination with Yervoy; for RCC – for Opdivo, added prescribed as a single agent or in combination with Cabometyx or Yervoy; for RCC – Opdivo Qvantig, added prescribed as first-line treatment as a single agent following combination treatment with Opdivo and Yervoy, subsequent therapy as a single agent, or in combination with Cabometyx; Per March SDC, for SCCHN, added redirection for nasopharyngeal carcinoma to Loqtorzi. Per March SDC, for SCCHN, added redirection for nasopharyngeal carcinoma to Loqtorzi.</p> <p>RT4: for CRC: updated FDA Approved Indication(s) section to include combination use with Yervoy for unresectable or metastatic MSI-H or dMMR CRC and to reflect conversion from accelerated approval to full approval for MSI-H or dMMR CRC that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan per PI, clarified criteria for Opdivo Qvantig requests is prescribed as subsequent-line systemic therapy per PI, updated Section V for adult and pediatric patients weighing ≥ 40 kg from "3 mg/kg" to "240 mg" IV followed by ipilimumab on the same day and added option for 6 mg/kg every 4 weeks after combination with ipilimumab for pediatric patients weighing < 40 kg per PI; for HCC: updated FDA Approved Indication(s) section with addition of first-line treatment in combination with ipilimumab and conversion from accelerated approval to full approval for those who has progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan per PI and updated criteria with the following: added disease is unresectable or metastatic, added criteria for usage in first-line systemic therapy setting and additional criteria for subsequent-line systemic therapy setting per NCCN. HCPCS code added [J9289]; RT4: updated FDA Approved Indication(s) section and criteria to reflect revised indication that limits use to tumors expressing PD-L1 (≥ 1) in combination with chemotherapy for unresectable advanced or metastatic ESCC in first-line setting and gastric cancer, GEJ cancer and esophageal adenocarcinoma (previously approved regardless of PD-L1 status); also for MSI-H or dMMR esophageal cancers, specified usage as perioperative therapy when prescribed as a single agent, as induction or palliative therapy when prescribed combination with fluoropyrimidine-containing chemotherapy, and as induction, neoadjuvant, perioperative, or palliative when prescribed in combination with Yervoy; updated</p>	<p>06/2025</p>

Reviews, Revisions, and Approvals	Date
Per June SDC: for ESCC and gastric/GEJ adenocarcinoma, added redirection to Tevimbra.	
<p>1Q 2026 annual review: for melanoma, added option for resectable stage III or limited local satellite/in-transit recurrence or nodal recurrence; for malignant pleural mesothelioma, removed requirement for unresectable; for RCC, added option to be prescribed for HLRCC-associated RCC; for cH: added request is for Opdivo as NCCN does not included recommended use in this setting, for primary treatment, removed staging requirement (III-IV) and added option if member is not candidate for anthracycline; added option for use post allogenic hematopoietic cell transplant; for relapsed/refractory/or progressive disease, added option for combo use with Adcentris or ICE; added off-label indications for appendiceal neoplasms and cancers, squamous cell skin cancer, and uterine sarcoma per NCCN; for bone cancer, added option for combination use with Sutent for dedifferentiated chondrosarcoma; for CLL/SLL, removed combo use with Yervoy and added single agent or combination with Imbruvica; for vaginal cancer, added prescribed as a single agent or in combination with Yervoy; for pediatric Hodgkin lymphoma, removed requirement for re-induction therapy or subsequent therapy; extended initial approval duration from 6 to 12 months for this maintenance medication for a chronic condition; references reviewed and updated.</p> <p>RT4: for Opdivo Qvantig: for CRC added new indication for use that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan and converted from accelerated approval to full approval for use following combination treatment; for HCC, added new indication for use as first-line treatment following combination treatment and converted from accelerated approval to full approval for those who have been previously treated with sorafenib and removed requirement that member is deemed ineligible for resection, transplant, or locoregional therapy; for Opdivo Qvantig, for melanoma and CRC added pediatric extension to age \geq 12 years (previously approved in adults) and new dosage strength (300 mg/5,000 units).</p>	01/2026