

## Clinical Policy: Nivolumab (Opdivo)

Reference Number: ERX.SPA.302

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Line of Business: Commercial, Medicaid

[Revision Log](#)

See **Important Reminder** at the end of this policy for important regulatory and legal information.

### Description

Nivolumab (Opdivo<sup>®</sup>) is a programmed death receptor-1 (PD-1) blocking antibody.

### FDA Approved Indication(s)

Opdivo is indicated for the treatment of:

- **Melanoma**
  - Patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
  - Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- **Non-small cell lung cancer (NSCLC)**
  - Adult patients with metastatic NSCLC expressing PD-L1 ( $\geq 1\%$ ) 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 non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
  - 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)**
  - Patients with advanced RCC who have received prior antiangiogenic therapy.
  - Patients with advanced RCC, as a first-line treatment in combination with cabozantinib.
  - 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)**
  - Patients with recurrent or metastatic SCCHN with disease progression on or after a platinum-based therapy.
- **Urothelial carcinoma (UC)**
  - 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)**
  - Patients with HCC who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab.\*
- **Esophageal cancer**
  - Patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy (CRT) as adjuvant treatment.
  - Patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.
- **Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma**
  - 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

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Opdivo is **medically necessary** when the following criteria are met:

#### I. Initial Approval Criteria

##### A. Melanoma (must meet all):

1. Diagnosis of unresectable, metastatic, or lymph node positive melanoma;
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 (unresectable or metastatic disease, or adjuvant treatment): Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
  - b. In combination with Yervoy® (unresectable or metastatic disease): 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 (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).

\*Prescribed regimen must be FDA-approved or recommended by NCCN

##### Approval duration: 6 months

##### B. Non-Small Cell Lung Cancer (must meet all):

1. Diagnosis of 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. 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 as a single agent or in combination with Yervoy for tumors positive for the Tumor Mutation Burden (TMB) biomarker;

- c. 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  $\geq 1\%$ ;
      - b) Opdivo is being used in combination with Yervoy  $\pm$  a platinum-based regimen (see *Appendix B*);
- \*Prior authorization may be required for Yervoy*
6. Request meets one of the following (a, b, c, or d):\*
    - 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 3 mg/kg every 2 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. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

**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  $\geq 18$  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;
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*).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

**D. Renal Cell Carcinoma** (must meet all):

1. Diagnosis of RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq 18$  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 (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*).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

**E. Classical Hodgkin Lymphoma (must meet all):**

1. Diagnosis of relapsed, refractory or progressive cHL;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  18 years;
4. Prescribed as subsequent therapy;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 240 mg every 2 weeks or 480 mg 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*).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**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  $\geq$  18 years;
4. Disease has progressed on or after a platinum-containing regimen (e.g., cisplatin, carboplatin);
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 240 mg every 2 weeks or 480 mg 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*).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**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  $\geq$  18 years;
4. Failure of a platinum-containing regimen (e.g., cisplatin, carboplatin), unless clinically significant adverse effects are experienced or all are contraindicated;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 240 mg every 2 weeks or 480 mg 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*).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

**H. Colorectal Cancer (must meet all):**

1. Diagnosis of unresectable or metastatic CRC;
2. Tumor is characterized as MSI-H or dMMR;
3. Prescribed by or in consultation with an oncologist;
4. Age  $\geq$  12 years;
5. Dose does not exceed one of the following (a, b, or c): \*
  - a. Monotherapy: 240 mg every 2 weeks;
  - b. In combination with Yervoy: 3 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*).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**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  $\geq$  18 years;

4. Member has had disease progression following treatment with Nexavar® or Lenvima®;  
*\*Prior authorization may be required for Nexavar and Lenvima.*
5. Member has not had previous treatment with a checkpoint inhibitor (e.g., Yervoy, Keytruda, Tecentriq, Imfinzi);
6. 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*).*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

**J. Esophageal Cancer (must meet all):**

1. Diagnosis of one of the following (a or b):
  - a. Completely resected esophageal cancer or gastroesophageal junction (esophagogastric junction; EGJ) cancer
  - b. Unresectable advanced, recurrent, or metastatic ESCC;
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 and b):
  - a. Member has residual pathologic disease;
  - b. Member has previously received CRT;
5. For unresectable advanced, recurrent, or metastatic ESCC: Member has had previous treatment with a fluoropyrimidine-based (e.g., 5-fluorouracil, capecitabine) and platinum-based (e.g., carboplatin, cisplatin, oxaliplatin) chemotherapy;
6. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 240 mg every 2 weeks or 480 mg 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*).*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**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 or b):
  - a. Disease is advanced, recurrent, or metastatic;
  - b. For EGJ cancer or esophageal adenocarcinoma: member meets one of the following (i or ii):
    - i. Member is post-operative following chemoradiation;
    - ii. Disease is advanced, recurrent, or metastatic;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For advanced, recurrent, or metastatic disease: both of the following are met (a and b):
  - 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;
6. 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*).*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

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

1. Diagnosis of one of the following (a, b, c, d, e, f, g, or h):
  - a. Metastatic squamous cell anal carcinoma;
  - b. Metastatic Merkel cell carcinoma;
  - c. Gestational trophoblastic neoplasia;
  - d. Uveal melanoma;
  - e. Small bowel adenocarcinoma;
  - f. Extranodal NK/T-cell lymphoma, nasal type;
  - g. Pediatric Hodgkin lymphoma;
  - h. Vulvar cancer - HPV-related advanced, recurrent, or metastatic disease;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  18 years;
4. For anal carcinoma: prescribed as second line or subsequent therapy (examples of prior therapy include 5-FU/cisplatin, carboplatin/paclitaxel, FOLFOX, FOLFICIS);
5. For gestational trophoblastic neoplasia: prescribed as one of the following (a or b):
  - a. Following treatment with a platinum/etoposide-containing regimen;
  - b. Disease is methotrexate-resistant and high-risk (*see Appendix D*);
6. For uveal melanoma: prescribed as a single agent or in combination with Yervoy;  
*\*Prior authorization may be required for Yervoy*
7. For pediatric Hodgkin lymphoma and vulvar cancer: prescribed as subsequent therapy;
8. 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).\*

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

**M. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Opdivo for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, c, or d):\*
  - a. NSCLC in combination with Yervoy: New dose does not exceed 3 mg/kg every 2 weeks;
  - b. Malignant pleural mesothelioma in combination with Yervoy, and gastric and esophageal adenocarcinomas: New dose does not exceed 360 mg every 3 weeks;
  - c. Other indications: New dose does not exceed 480 mg every 4 weeks;
  - d. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

*\*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 12 months**

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.  
**Approval duration: Duration of request or 6 months (whichever is less);** or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).



**III. Diagnoses/Indications for which coverage is NOT authorized:**

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

ALK: anaplastic lymphoma kinase	receptor-2
BRAF: B-Raf proto-oncogene, serine/threonine kinase	HSCT: hematopoietic stem cell transplantation
CHL: classic Hodgkin lymphoma	MET: mesenchymal-epithelial transition
CRC: colorectal cancer	MSI-H: microsatellite instability-high
dMMR: mismatch repair deficient	NSCLC: non-small cell lung cancer
EGFR: epidermal growth factor receptor	PD-1: programmed death receptor-1
EGJ: esophagogastric junction	PD-L1: programmed death-ligand 1
ESCC: esophageal squamous cell carcinoma	RCC: renal cell carcinoma
FDA: Food and Drug Administration	ROS1: ROS proto-oncogene 1
HCC: hepatocellular carcinoma	TMB: Tumor Mutational Burden
HER2: 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
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
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: pemetrexed + [carboplatin or cisplatin] dose varies  UC, SCCHN: Varies	Varies

*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 <sup>3</sup>	10 <sup>3</sup> to < 10 <sup>4</sup>	10 <sup>4</sup> to 10 <sup>5</sup>	≥ 10 <sup>5</sup>
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.*

**V. Dosage and Administration**

Indication	Dosing Regimen	Maximum Dose
Melanoma (unresectable or metastatic)	<p>Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</p> <p>With ipilimumab: 1 mg/kg IV, followed by ipilimumab 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>	480 mg/dose



Indication	Dosing Regimen	Maximum Dose
Melanoma (adjuvant treatment) RCC - advanced with previous anti-angiogenic therapy, CHL, SCCHN, UC	240 mg IV every 2 weeks or 480 mg IV every 4 weeks	480 mg/dose
MSI-H/dMMR CRC	Monotherapy: 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 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	Monotherapy: 480 mg/dose  With ipilimumab: 3 mg/kg/dose
RCC - advanced previously untreated	Monotherapy or with cabozantinib: 240 mg IV every 2 weeks or 480 mg 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	480 mg/dose
HCC	Monotherapy: 240 mg IV every 2 weeks or 480 mg every 4 weeks until disease progression or unacceptable toxicity  With ipilimumab: nivolumab 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 as single-agent nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks until disease progression or unacceptable toxicity	480 mg/dose
NSCLC	Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks until disease progression or unacceptable toxicity  With ipilimumab: nivolumab 3 mg/kg IV every 2 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: nivolumab 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	Monotherapy: 480 mg/dose  With ipilimumab: 3 mg/kg/dose  With ipilimumab and platinum-doublet: 360 mg/dose
Esophageal cancer	240 mg IV every 2 weeks or 480 mg IV every 4 weeks until disease progression or unacceptable toxicity	480 mg/dose
Gastric cancer, EGJ cancer, and esophageal adenocarcinoma - advanced or metastatic	240 mg every 2 weeks or 360 mg every 3 weeks	360 mg/dose

Indication	Dosing Regimen	Maximum Dose
Malignant pleural mesothelioma	With ipilimumab: nivolumab 360 mg every 3 weeks and ipilimumab 1 mg/kg every 6 weeks	With ipilimumab: 360 mg/dose

#### VI. Product Availability

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

#### VII. References

1. Opdivo Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; May 2021. Available at <https://www.opdivo.com/>. Accessed June 30, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at <http://www.nccn.org>. Accessed July 6, 2021.
3. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 8.2020. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf). Accessed November 17, 2020.
4. National Comprehensive Cancer Network. Kidney Cancer, Version 2.2021. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/kidney.pdf](https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf). Accessed February 3, 2021.
5. Hellman MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med. 2019 November; 381(21):2020-2031

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	11.13.18	02.19
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.	11.26.19	02.20
Added appendix E: dose rounding guidelines; added reference to appendix E within criteria; added FDA-labeled indication of HCC in combination with Yervoy; added NCCN compendium-supported indication of uveal melanoma as a single agent or in combination with Yervoy.	04.04.20	05.20
Updated HCC criteria to include no previous treatment with a checkpoint inhibitor based on NCCN recommendation; added criteria for FDA-labeled indications of NSCLC & ESCC; updated SCLC indication for optional use in combination with ipilimumab per updated NCCN compendium; added NCCN compendium-supported indications of small bowel adenocarcinoma and T-cell lymphoma	06.23.20	08.20
1Q 2021 annual review: RT4: FDA approved malignant 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; removed SCLC criteria per label update; RT4: added new FDA approved indication of use in combination with cabozantinib as first-line therapy for advanced RCC; references reviewed and updated.	11.20.20	02.21
RT4: added new FDA-approved indications of gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma	05.11.21	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
RT4: added new FDA-approved indication of completely resected esophageal or gastroesophageal junction cancer.	06.30.21	

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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