

Clinical Policy: Nivolumab (Opdivo)

Reference Number: PA.CP.PHAR.121

Effective Date: 01/18

Last Review Date: 01/19

[Coding Implications](#)

[Revision Log](#)

Description

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

FDA Approved Indication(s)

Opdivo is indicated for the treatment of:

- Patients with BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.
- Patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent.
- Patients with unresectable or metastatic melanoma, in combination with ipilimumab.
- Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- Patients with metastatic non-small cell lung cancer (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.
- Patients with metastatic small cell lung cancer (SCLC) with progression after platinum based chemotherapy and at least one other line of therapy.
- Patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy.
- Adult patients with classical [classic] Hodgkin lymphoma (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.
- Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after a platinum-based therapy.
- Patients with locally advanced or metastatic urothelial carcinoma (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.
- 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.
- Patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Policy/Criteria

It is the policy of health plans affiliated with Pennsylvania Health and 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;
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: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
 - b. In combination with Yervoy[®]: 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;
 - 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 metastatic NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Disease has progressed on or after systemic 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).

Approval duration: 6 months

C. Small Cell Lung Cancer (must meet all):

1. Diagnosis of SCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Failure of platinum-containing regimen (e.g. cisplatin, carboplatin), unless contraindicated or clinically significant adverse effects are experienced;
5. Request meets one of the following (a or b):
 - a. Dose does not exceed 240 mg every 2 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 \geq 18 years;
4. 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 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 \geq 18 years;
- 4. Disease has relapsed or progressed after autologous hematopoietic stem cell transplantation;
- 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 \geq 18 years;
- 4. Disease has progressed on or after 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 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 \geq 18 years;
- 4. Failure of a platinum-containing regimen (e.g., cisplatin, carboplatin), unless contraindicated or clinically significant adverse effects are experienced;
- 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*).

Approval duration: 6 months

H. Colorectal Cancer (must meet all):

1. Diagnosis of MSI-H or defective mismatch repair (dMMR) CRC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 12 years;
4. Disease is unresectable or metastatic;
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;
 - 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 \geq 18 years;
4. 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*).

Approval duration: 6 months

J. 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 Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy (e.g., no disease progression or significant toxicity);
3. If request is for a dose increase, request meets one of the following (a or b):
 - a. New dose does not exceed 3 mg/kg every 2 weeks;
 - 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 Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;

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

2. Refer to PA.CP.PHAR.53

Background

Description/Mechanism of Action:

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase

BRAF: B-Raf proto-oncogene,
serine/threonine kinase

CHL: classic Hodgkin lymphoma

CRC: colorectal cancer

dMMR: mismatch repair deficient

EGFR: epidermal growth factor receptor

FDA: Food and Drug Administration

HCC: hepatocellular carcinoma

HSCT: hematopoietic stem cell transplantation

MSI-H: microsatellite instability-high

NSCLC: non-small cell lung cancer

PD-1: programmed death receptor-1

RCC: renal cell carcinoma

SCLC: small cell lung cancer

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 cease or unacceptable toxicity occurs	800 mg/day
Cisplatin- or carboplatin-containing chemotherapy	SCLC, 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

IV. 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
<p>Melanoma - adjuvant treatment</p> <p>NSCLC</p> <p>RCC - advanced with previous anti-angiogenic therapy</p> <p>CHL, SCCHN, UC, HCC</p>	240 mg IV every 2 weeks or 480 mg IV every 4 weeks	480 mg/dose
MSI-H or dMMR CRC	<p>Monotherapy: 240 mg IV every 2 weeks</p> <p>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</p>	<p>Monotherapy: 240 mg/dose</p> <p>With ipilimumab: 3 mg/kg/dose</p>
RCC - advanced previously untreated	<p>Monotherapy: 240 mg IV every 2 weeks or 480 mg every 4 weeks</p> <p>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</p>	480 mg/dose

V. Product Availability

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

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.

HCPSC Codes	Description
J9299	Injection, nivolumab, 1 mg

Reviews, Revisions, and Approvals	Date	Approval 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.	02/18	
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.	01/19	

References

1. Opdivo Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; August 2018. Available at <https://www.opdivo.com/>. Accessed September 26, 2018.
2. Bavencio Prescribing Information. Rockland, MD: EMD Serono, Inc.; October 2017. Available at <https://www.emdserono.com/content/dam/web/corporate/non-images/country-specific/us/pi/bavencio-pi.pdf>. Accessed September 26, 2018.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at <http://www.nccn.org>. Accessed September 26, 2018.
4. Small cell lung cancer (Version 2.2018). National Comprehensive Cancer Network Guidelines. Available at <http://www.nccn.org>. Accessed September 26, 2018.
5. Non-small cell lung cancer (Version 6.2018) National Comprehensive Cancer Network. Available at <http://www.nccn.org>. Accessed September 26, 2018.