Clinical Policy: Nivolumab (Opdivo)
Reference Number: ERX.SPA.302
Effective Date: 03.01.19
Last Review Date: 02.19

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

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 epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (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.
- Patients with intermediate or poor risk, previously untreated advanced RCC, in combination with ipilimumab.
- Adult patients with classical [classic] Hodgkin lymphoma (CHL) that has relapsed or progressed after
do 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, as a single agent or in combination with ipilimumab.
- Patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

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 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: 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 ≥ 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 ≥ 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 RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request meets one of the following (a, b, or c):
   a. Monotherapy: Dose does not exceed 240 mg every 2 weeks or 480 mg every 4 weeks;
   b. In combination with Yervoy: Dose does not exceed 3 mg/kg every 3 weeks for 4 doses, followed by 240 mg every 2 weeks or 480 mg every 4 weeks;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration: 6 months

E. Classical Hodgkin Lymphoma (must meet all):
1. Diagnosis of cHL;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. 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 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**

**F. Squamous Cell Carcinoma of the Head and Neck** (must meet all):
1. Diagnosis of SCCHN;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. 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*).  

**Approval duration: 6 months**

**G. Urothelial Carcinoma** (must meet all):
1. Diagnosis of UC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. 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 unresectable or metastatic CRC;
2. Tumor is characterized as MSI-H or dMMR;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 12 years;
5. Dose does not exceed one of the following (a, b, or c):
   a. Monotherapy: 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 ≥ 18 years;
4. Member has had disease progression following treatment with Nexavar®;
   *Prior authorization may be required for Nexavar.*
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**

**J. Off-label NCCN Compendium Recommended Indications** (must meet all):
1. Diagnosis of one of the following (a, b, or c):
   a. Metastatic squamous cell anal carcinoma;
b. Metastatic Merkel cell carcinoma;
c. Gestational trophoblastic neoplasia;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**K. 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 or b):
   a. New dose does not exceed 480 mg every 4 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 (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**

<table>
<thead>
<tr>
<th>Abbreviation/Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>anaplastic lymphoma kinase</td>
</tr>
<tr>
<td>BRAF</td>
<td>B-Raf proto-oncogene, serine/threonine kinase</td>
</tr>
<tr>
<td>cHL</td>
<td>classic Hodgkin lymphoma</td>
</tr>
<tr>
<td>CRC</td>
<td>colorectal cancer</td>
</tr>
<tr>
<td>dMMR</td>
<td>mismatch repair deficient</td>
</tr>
<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
</tr>
<tr>
<td>HSCT</td>
<td>hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>MSI-H</td>
<td>microsatellite instability-high</td>
</tr>
<tr>
<td>NSCLC</td>
<td>non-small cell lung cancer</td>
</tr>
<tr>
<td>PD-1</td>
<td>programmed death receptor-1</td>
</tr>
<tr>
<td>RCC</td>
<td>renal cell carcinoma</td>
</tr>
<tr>
<td>SCLC</td>
<td>small cell lung cancer</td>
</tr>
<tr>
<td>UC</td>
<td>urothelial carcinoma</td>
</tr>
</tbody>
</table>

**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.*

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nexavar (sorafenib)</td>
<td>HCC: 400 mg PO BID until clinical benefit ceases or unacceptable toxicity occurs</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/ Maximum Dose</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>cisplatin- or carboplatin-containing chemotherapy</td>
<td>SCLC, UC, SCCHN: Varies</td>
<td>Varies</td>
</tr>
</tbody>
</table>

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

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma - unresectable or metastatic</td>
<td>Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</td>
<td>480 mg/dose</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Melanoma - adjuvant treatment NSCLC</td>
<td>240 mg IV every 2 weeks or 480 mg IV every 4 weeks</td>
<td>480 mg/dose</td>
</tr>
<tr>
<td>RCC - advanced with previous anti-angiogenic therapy CHL, SCCHN, UC, HCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSI-H or dMMR CRC</td>
<td>Monotherapy: 240 mg IV every 2 weeks</td>
<td>240 mg/dose</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>RCC - advanced previously untreated</td>
<td>Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</td>
<td>480 mg/dose</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

VI. Product Availability
Single-dose vials: 40 mg/4 mL, 100 mg/10 mL, 240 mg/24 mL

VII. References
Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>11.13.18</td>
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<tr>
<td></td>
<td>02.19</td>
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</tbody>
</table>

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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