RXADVANCE
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Clinical Policy Title:	nivolumab
Policy Number:	RxA.431
Drug(s) Applied:	Opdivo®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2020
Line of Business Policy Applies to:	All lines of business

Background

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

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.
- Adult patients with metastatic non-small cell lung cancer (NSCLC) expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab.
- Adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC) 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 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
  - 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, as a single agent or in combination with ipilimumab.
- Patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
Nivolumab (Opdivo®)	Melanoma - unresectable or metastatic, HCC	Monotherapy: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks With ipilimumab: 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	480 mg/dose with ipilimumab: 1 mg/kg/dose
Nivolumab (Opdivo®) + ipilimumab	Metastatic NSCLC expressing PD-L1	3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks	with ipilimumab: 3 mg/kg/dose
Nivolumab (Opdivo®) + ipilimumab	Metastatic or recurrent NSCLC	360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and histology-based platinum doublet chemotherapy every 3 weeks	360 mg/dose
Nivolumab (Opdivo®)	Melanoma - adjuvant treatment NSCLC RCC - advanced with previous anti-angiogenic therapy CHL, SCCHN, UC, ESCC	240 mg IV every 2 weeks or 480 mg IV every 4 weeks	480 mg/dose
Nivolumab (Opdivo®)	MSI-H or dMMR crc	Monotherapy: Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks. Pediatric patients age 12 years and older and	monotherapy: 480 mg/dose

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		weighing less than 40 kg: 3 mg/kg every 2 weeks With ipilimumab: 3 mg/kg IV, followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, followed by nivolumab monotherapy.	with ipilimumab: 3 mg/kg/dose
Nivolumab (Opdivo®)	RCC- advanced previously untreated	Monotherapy: 240 mg IV every 2 weeks or 480 me 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 with ipilimumab: 3 mg/kg/dose

Dosage Forms

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

Clinical Policy

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

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
Commercial: 6 months
Medicaid: 6 months
HIM: 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. Request is for one of the following (a or b):
    a. First-line treatment of patient with metastatic NSCLC with tumors express PD-L1(≥1%), or patient with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations.
    b. Disease has progressed on or after a platinum-containing regimen (e.g., cisplatin, carboplatin);
5. 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. Metastatic NSCLC expressing PD-L1: 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks,
    c. Metastatic or recurrent NSCLC: 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and histology-based platinum doublet chemotherapy 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).

Approval Duration
Commercial: 6 months
Medicaid: 6 months
HIM: 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
Commercial: 6 months
Medicaid: 6 months
HIM: 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
Commercial: 6 months
Medicaid: 6 months

HIM: 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
Commercial: 6 months
Medicaid: 6 months
HIM: 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
Commercial: 6 months
Medicaid: 6 months
HIM: 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
Commercial: 6 months
Medicaid: 6 months
HIM: 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 for one of the following (a, b, or c):
    a. Monotherapy: For adult and pediatric patient weighing 40 kg or more 480 mg every 4 weeks;
    b. In combination with Yervoy®: 3 mg/kg every 3 weeks for 4 doses, then followed by monotherapy;
    c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence).*

Approval Duration
Commercial: 6 months
Medicaid: 6 months
HIM: 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, b or c):
    a. 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
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

J. Esophageal Squamous Cell Carcinoma (must meet all):
1. Diagnosis of unresectable advanced, recurrent or metastatic ESCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Failure of at least one fluoropyrimidine- and platinum-based chemotherapy 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:
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

K. 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. Cutaneous Melanoma;
e. Brain metastases;
f. Malignant Pleural Mesothelioma;
g. Small Bowel Adenocarcinoma;
h. Extra-nodal NK/T-Cell Lymphoma, nasal type;

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
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

II. Continued Therapy Approval

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

1. Currently receiving medication that has been authorized by RxAdvance, 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
Commercial: 12 months
Medicaid: 12 months
HIM: 12 months

III. Appendices

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
ESCC: Esophageal Squamous Cell Carcinoma
PD-L1: Programmed death-ligand 1

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
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

- Contraindication(s):
  - None reported
- Boxed Warning(s):
  - None reported

APPENDIX D: General Information

- Not applicable

References

1. Opdivo Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; June 2020. Available at https://www.opdivo.com/. Accessed July 31, 2020.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at http://www.nccn.org. Accessed September 26, 2018.
3. Small cell lung cancer (Version 4.2020). National Comprehensive Cancer Network Guidelines. Available at https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed July 31, 2020.
4. Non-small cell lung cancer (Version 6.2020) National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed July 31, 2020.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Drug(s) applied was updated. 3. Line of Business Policy Applies to was updated to "All lines of business". 4. Updated background for NSCLC, HCC and added ESCC information. 5. Updated Dosing regimen for NSCLC, HCC, CRC and added ESCC regimen. 6. Initial and Continued approval duration was updated to specify Medicaid, Commercial & HIM approval duration. 7. Initial therapy criteria was updated to include new indication ESCC. 8. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 9. Appendix B was updated: added ESCC & PD-L1. 10. References were reviewed and updated.	07/31/2020	09/14/2020