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Section:	Prescription Drugs	**Effective Date:**	April 1, 2021
Subsection:	Antineoplastic Agents	**Original Policy Date:**	January 16, 2015
Subject:	Opdivo	**Page:**	1 of 10

Last Review Date: March 12, 2021

Opdivo

Description

Opdivo (nivolumab)

Background
Opdivo is a monoclonal antibody for the treatment of patients with unresectable (cannot be removed by surgery), metastatic (advanced) melanoma, adjuvant treatment of melanoma and metastatic non-small cell lung cancer, unresectable malignant pleural mesothelioma, renal cell carcinoma, hepatocellular carcinoma, relapsed or progressed classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, locally advanced or metastatic urothelial carcinoma, or microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer who are no longer responding to other drugs, and esophageal squamous cell carcinoma. Opdivo works by inhibiting the PD-1 protein on cell surfaces, which blocks the immune system from attacking melanoma tumors (1).

Regulatory Status
FDA-approved indication: Opdivo is a human programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with: (1)

1. Melanoma
    a. Unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab
    b. Melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting
2. Non-Small Cell Lung Cancer (NSCLC)
    a. In combination with ipilimumab, for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1

(≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations
   b. Metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy
   c. Metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on a FDA-approved therapy for these aberrations prior to receiving Opdivo
3. Malignant Pleural Mesothelioma
   a. Adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab
4. Renal Cell Carcinoma (RCC)
   a. Advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy
   b. First-line treatment of patients with advanced RCC, in combination with cabozantinib
   c. Intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab
5. Classical Hodgkin Lymphoma (cHL)
   a. Classical Hodgkin lymphoma that has relapsed or progressed after:
      i. Autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin, OR
      ii. 3 or more lines systemic therapy that includes autologous HSCT
6. Squamous Cell Carcinoma of the Head and Neck (SCCHN)
   a. Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy
7. Urothelial Carcinoma
   a. Locally advanced or metastatic urothelial carcinoma who:
      i. Have disease progression during or following platinum-containing chemotherapy
      ii. Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
8. Colorectal Cancer
   a. Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab
9. Hepatocellular Carcinoma

   a. Hepatocellular carcinoma that has been previously treated with sorafenib, as a single agent or in combination with ipilimumab
10. Esophageal Squamous Cell Carcinoma (ESCC)
   a. Unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy

Off-Label Uses: (2)
1. Small cell lung cancer
2. Metastatic anal cancer
3. Merkel cell carcinoma

Clinically significant immune-mediated adverse reactions may occur with Opdivo therapy including pneumonitis, colitis, hepatitis, nephritis, renal dysfunction, hyperthyroidism, and hypothyroidism. Patients should be monitored for signs and symptoms of adverse reactions and based on the severity, Opdivo should be withheld or discontinued and corticosteroids administered. Opdivo may cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised of the potential hazard to a fetus. Opdivo is administered every 2 weeks until disease progression or unacceptable toxicity (1).

The safety and effectiveness of Opdivo have been established in pediatric patients age 12 years and older (1).

Related Policies
Bavencio, Keytruda, Tecentriq, Yervoy

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Opdivo may be considered **medically necessary** in patients 12 years of age or older for unresectable or metastatic melanoma, adjuvant treatment of melanoma, metastatic non-small cell lung cancer, renal cell carcinoma, relapsed or progressed classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma, locally advanced or metastatic urothelial carcinoma, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, hepatocellular carcinoma, esophageal squamous cell carcinoma, malignant pleural mesothelioma, small cell lung cancer, metastatic anal carcinoma, or Merkel cell carcinoma ; and if the conditions indicated below are met.

Opdivo is considered **investigational** in all other patients and for all other indications.

Prior-Approval Requirements

Age 12 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Unresectable or metastatic melanoma
   a. Used as a single agent **OR** in combination with ipilimumab

2. Adjuvant treatment of melanoma post resection

3. Metastatic non-small cell lung cancer (NSCLC) with **ONE** of the following:
   a. **NO** EGFR or ALK genomic tumor aberrations with **ONE** of the following:
      i. Disease progressed on or after platinum-based chemotherapy
      ii. Tumors express PD-L1 as determined by an FDA-approved test **AND** used as first-line treatment in combination with ipilimumab
      iii. Used as first-line treatment in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy
   b. Positive for EGFR or ALK genomic tumor aberrations
      i. Disease must have progressed while on or after platinum-based chemotherapy
      ii. Patient had disease progression on FDA approved therapy

4. Recurrent non-small cell lung cancer (NSCLC)
   a. **NO** EGFR or ALK genomic tumor aberrations
   b. Used as first-line treatment in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy

5. Advanced renal cell carcinoma with **ONE** of the following:
   a. First-line treatment in combination with cabozantinib
   b. Prior treatment with anti-angiogenic therapy
   c. Patient is considered to have an intermediate or poor prognosis
      i. Used In combination with ipilimumab

6. Relapsed or progressed classical Hodgkin lymphoma with **ONE** of the following:

   a. Patient has had autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation therapy with brentuximab vedotin
   b. Patient has had 3 or more lines systemic therapy that includes autologous HSCT

7. Recurrent or metastatic squamous cell carcinoma of the head and neck
   a. Disease must have progressed while on or after platinum-based chemotherapy

8. Locally advanced or metastatic urothelial carcinoma with **ONE** of the following:
   a. Disease must have progressed while on or after platinum-based chemotherapy
   b. Disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

9. Hepatocellular carcinoma
   a. Prior treatment with sorafenib
   b. Used as a single agent or in combination with ipilimumab

10. Unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC)
   a. Prior treatment with fluoropyrimidine- and platinum-based chemotherapy

11. Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
   a. Progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan
   b. Diagnosis has to be confirmed by PCR-based assay genetic testing
   c. Used as a single agent **OR** in combination with ipilimumab

12. Unresectable malignant pleural mesothelioma
   a. Used as first-line treatment in combination with ipilimumab

13. Small cell lung cancer

14. Metastatic anal carcinoma

15. Merkel cell carcinoma

Prior – Approval *Renewal* Requirements

Age 12 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Unresectable or metastatic melanoma
2. Adjuvant treatment of melanoma post resection: one renewal **only**
3. Metastatic non-small cell lung cancer
    a. **IF** used in combination with ipilimumab: one renewal **only**
4. Recurrent non-small cell lung cancer
    a. Used in combination with ipilimumab: one renewal **only**
5. Advanced renal cell carcinoma
    a. **IF** used in combination with cabozantinib: one renewal **only**
6. Relapsed or progressed classical Hodgkin lymphoma
7. Recurrent or metastatic squamous cell carcinoma of the head and neck
8. Locally advanced or metastatic urothelial carcinoma
9. Hepatocellular carcinoma
10. Unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC)
11. Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
12. Unresectable malignant pleural mesothelioma
    a. Used in combination with ipilimumab
13. Small cell lung cancer
14. Metastatic anal carcinoma
15. Merkel cell carcinoma

AND the following for **ALL** indications:

a. **NO** disease progression or unacceptable toxicity
b. Prescriber agrees to discontinue treatment for any immune mediated adverse reaction (encephalitis, nephritis, rash, decreased renal function and endocrinopathies) or disease progression

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits

Duration 6 months

Prior – Approval *Renewal* Limits

Duration 6 months for adjuvant treatment of melanoma post resection
18 months for all other diagnoses

ONE renewal **ONLY** for: metastatic/recurrent NSCLC when used with ipilimumab; for adjuvant treatment of melanoma post resection; for malignant pleural mesothelioma; and for advanced renal cell carcinoma when used in combination with cabozantinib

Rationale

Summary
Opdivo is a monoclonal antibody indicated for the treatment of various types of cancers. Opdivo works by inhibiting the PD-1 protein on cell surfaces, which blocks the immune system from attacking melanoma tumors. Opdivo may cause fetal harm when administered to a pregnant woman (1).

Prior authorization is required to ensure the safe, clinically appropriate and cost-effective use of Opdivo while maintaining optimal therapeutic outcomes.

References
1. Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; January 2021.
2. The NCCN Drugs & Biologics Compendium® © 2021 National Comprehensive Cancer Network, Inc. http://www.nccn.org.

Policy History

Date	Action
January 2015	Addition to PA
March 2015	Annual editorial review and reference update Addition of Metastatic squamous non-small cell lung cancer
June 2015	Annual review

October 2015	Addition of BRAF V600 wild-type, the patient must use in combination with ipilimumab, and metastatic non-small cell lung cancer with the squamous cell requirement along with disease must have progressed after FDA-approved therapy if patient has EGFR or ALK tumor expression option.
December 2015	Annual review Addition of new indication of renal cell carcinoma after prior treatment with an anti-angiogenic therapy
March 2016	Annual review Removal of requirements: disease progression following Yervoy (ipilimumab) if BRAF V600 mutation positive, a BRAF inhibitor, BRAF V600 wild-type the patient must use in combination with ipilimumab Policy number change from 5.04.53 to 5.21.53
June 2016	Annual review Addition of relapsed or progressed classical Hodgkin lymphoma in patients who have had autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation therapy with brentuximab vedotin (Adcetris). Addition of Prescriber agrees to discontinue treatment for any immune mediated adverse reaction (encephalitis, nephritis, rash, decreased renal function and endocrinopathies) or disease progression in renewal section per SME
September 2016	Annual review
December 2016	Addition of recurrent or metastatic squamous cell carcinoma of the head and neck with progression on or after platinum-based chemotherapy
February 2017	Addition of locally advanced or metastatic urothelial carcinoma with one of the following: disease progression during or following platinum-containing chemotherapy, or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
June 2017	Annual editorial review Addition to the relapsed or progressed classical Hodgkin lymphoma: patient has had 3 or more lines systemic therapy that includes autologous HSCT
August 2017	Addition of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
September 2017	Annual review
October 2017	Addition of hepatocellular carcinoma
December 2017	Annual review
January 2018	Addition of melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting
March 2018	Annual review
May 2018	Addition of indication: Intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab; malignant pleural mesothelioma, small cell lung cancer, metastatic anal carcinoma, and Merkel cell carcinoma; and changed the age from 18 to 12 yrs of age

June 2018	Annual review
July 2018	Addition of indication: metastatic colorectal cancer as a single agent or in combination with ipilimumab
August 2018	Addition of metastatic small cell lung cancer, progression after platinum-based chemotherapy and at least one other line of therapy
September 2018	Annual editorial review and reference update
November 2018	Annual review
March 2019	Change to indication: unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab
June 2019	Annual review
April 2020	Revised indication: hepatocellular carcinoma as a single agent or in combination with ipilimumab
May 2020	Addition of indication: metastatic NSCLC whose tumors express PD-L1, as first-line treatment used in combination with ipilimumab, with no EGFR or ALK genomic tumor aberrations. Revised metastatic NSCLC indication so they need to have both disease progression after platinum-based chemotherapy and disease progression after therapy for EGFR or ALK tumor aberration, if present. Addition of indication: metastatic or recurrent NSCLC with no EGFR or ALK tumor aberrations as first-line treatment with ipilimumab and 2 cycles of platinum-doublet chemotherapy. Changed renewal duration from 12 months to 18 months. Added “ONE renewal ONLY for metastatic/recurrent NSCLC when used with ipilimumab and for adjuvant treatment of melanoma post resection”
June 2020	Annual review. Addition of indication: esophageal squamous cell carcinoma (ESCC)
September 2020	Annual review
October 2020	Per FEP, revised malignant pleural mesothelioma indication: removed it from the off-label section, included the requirement that it must be unresectable and used as first-line treatment in combination with ipilimumab. Added “no disease progression or unacceptable toxicity” renewal requirement
December 2020	Annual review
January 2021	Removed metastatic small cell lung cancer indication per PI. Small cell lung cancer remains a recommended indication per NCCN
February 2021	Addition of indication: advanced renal cell carcinoma in combination with cabozantinib as first-line treatment
March 2021	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.