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Section:	Prescription Drugs	**Effective Date:**	January 1, 2025
Subsection:	Antineoplastic Agents	**Original Policy Date:**	January 16, 2015
Subject:	Opdivo	**Page:**	1 of 15

Last Review Date: December 13, 2024

Opdivo

Description

Opdivo (nivolumab)

Background
Opdivo (nivolumab) is a monoclonal antibody indicated for the treatment of patients with melanoma, non-small cell lung cancer (NSCLC), malignant pleural mesothelioma, renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma, colorectal cancer, esophageal cancer, gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma. Opdivo works by binding to the programmed cell death-1 (PD-1) receptor, and blocking its interaction with PD-1 ligands, PD-L1 and PD-L2. This interaction releases the inhibitory effects of PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response, resulting in decreased tumor growth (1).

Regulatory Status
FDA-approved indications: 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. Adjuvant treatment of patients with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma
2. Non-Small Cell Lung Cancer (NSCLC)
    a. Resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting, in combination with platinum-doublet chemotherapy

   b. Resectable (tumors ≥4 cm or node positive) NSCLC and no known EGFR mutations or ALK rearrangements, for neoadjuvant treatment, in combination with platinum-doublet chemotherapy, followed by single-agent Opdivo as adjuvant treatment after surgery
   c. 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, as first-line treatment in combination with ipilimumab
   d. 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
   e. Metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on an FDA-approved therapy for these aberrations prior to receiving Opdivo
3. Malignant Pleural Mesothelioma
   a. 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 advanced renal cell carcinoma, as a first-line treatment 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 of 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. Adjuvant treatment of patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC
   b. Patients with unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine
   c. Patients with 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, in combination with ipilimumab
10. Esophageal Cancer
    a. Completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT)
    b. Unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) as first-line treatment in combination with fluoropyrimidine- and platinum-containing chemotherapy
    c. Unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) as first-line treatment in combination with ipilimumab
    d. Unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy
11. Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
    a. Advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy

Off-Label Uses: (2)

1. Small cell lung cancer
2. Metastatic anal cancer
3. Merkel cell carcinoma

Opdivo carries warnings for immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT) and embryo-fetal toxicity. 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 (1).

The safety and effectiveness of Opdivo have not been established in pediatric patients age less than 12 years of age with melanoma or microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) or in pediatric patients less than 18 years of age for the other approved indications (1).

Related Policies
Bavencio, Keytruda, Loqtorzi, Opdualag, Tecentriq, Yervoy, Zynyz

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** if the conditions indicated below are met.

Opdivo may be considered **investigational** 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
   a. Stage IIB, Stage IIC, Stage III, or Stage IV melanoma

3. Resectable non-small cell lung cancer (NSCLC)
   a. Tumors ≥4 cm **OR** node positive

b. Used in combination with platinum-doublet chemotherapy in the neoadjuvant setting

4. 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

5. 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

6. 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 as first-line treatment in combination with ipilimumab

7. 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 of systemic therapy that includes autologous HSCT

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

9. Urothelial carcinoma with **ONE** of the following:
   a. Patient is at high risk of recurrence after undergoing radical resection
      i. Used as adjuvant treatment

b. Unresectable or metastatic urothelial carcinoma
    i. Used as first-line treatment in combination with cisplatin and gemcitabine
c. Locally advanced or metastatic urothelial carcinoma with **ONE** of the following:
    i. Disease must have progressed while on or after platinum-based chemotherapy
    ii. Disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

10. Hepatocellular carcinoma
    a. Prior treatment with sorafenib
    b. Used in combination with ipilimumab

11. Completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease
    a. Patient has received neoadjuvant chemoradiotherapy (CRT)

12. Unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC)
    a. Used as first-line treatment
    b. Used in combination with **ONE** of the following:
        i. Fluoropyrimidine- and platinum-containing chemotherapy
        ii. Ipilimumab

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

14. 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

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

16. Advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma
    a. Used in combination with fluoropyrimidine- and platinum-containing chemotherapy

17. Small cell lung cancer

18. Metastatic anal carcinoma

19. 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**
    a. Stage IIB, Stage IIC, Stage III, or Stage IV melanoma

3. Resectable non-small cell lung cancer (NSCLC)
    a. Used as a single agent after surgery as adjuvant treatment
    b. **NO** known EGFR mutations or ALK rearrangements

4. Metastatic non-small cell lung cancer
    a. **IF** used in combination with ipilimumab: one renewal **only**

5. Recurrent non-small cell lung cancer
    a. Used in combination with ipilimumab: one renewal **only**

6. Advanced renal cell carcinoma
    a. **IF** used in combination with cabozantinib: one renewal **only**

7. Relapsed or progressed classical Hodgkin lymphoma

8. Recurrent or metastatic squamous cell carcinoma of the head and neck

9. Urothelial carcinoma
    a. **IF** used as adjuvant treatment in patients at high risk of recurrence after radical resection: one renewal **only**
    b. **IF** used for unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine: one renewal **only**

10. Hepatocellular carcinoma

11. Completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease: one renewal **only**

12. Unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC)
    a. Used in combination with **ONE** of the following:
        i. Fluoropyrimidine- and platinum-containing chemotherapy: one renewal **only**
        ii. Ipilimumab: one renewal **only**

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

14. Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer

15. Unresectable malignant pleural mesothelioma
    a. Used in combination with ipilimumab: one renewal **only**

16. Advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma
    a. Used in combination with fluoropyrimidine- and platinum-containing chemotherapy: one renewal **only**

17. Small cell lung cancer

18. Metastatic anal carcinoma

19. Merkel cell carcinoma

AND ALL of 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*

Indication	Renewal PA Duration*	Number of Renewals Allowed
Adjuvant treatment of melanoma post resection	**6** months	One renewal only
Adjuvant treatment of urothelial carcinoma (patients at high risk of recurrence after radical resection)	**6** months	One renewal only
Completely resected esophageal or gastroesophageal junction cancer with residual pathological disease	**6** months	One renewal only
Resectable non-small cell lung cancer (NSCLC) as adjuvant treatment after surgery	**12** months	One renewal only

Advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma	**18** months	One renewal only
Unresectable malignant pleural mesothelioma	**18** months	One renewal only
Unresectable or metastatic urothelial carcinoma (first-line, in combination with cisplatin and gemcitabine)	**18** months	One renewal only
Metastatic non-small cell lung cancer (NSCLC) **	**18** months	Used with ipilimumab One renewal only
		As a single agent Until disease progression or unacceptable toxicity
Recurrent non-small cell lung cancer (NSCLC)**	**18** months	One renewal only
Unresectable malignant pleural mesothelioma	**18** months	One renewal only
Esophageal squamous cell carcinoma	**18** months	Used with ipilimumab or fluoropyrmidine- and platinum-containing chemotherapy: One renewal only
		Prior treatment with fluoropyrimidine- and platinum-based chemotherapy: Until disease progression or unacceptable toxicity
Advanced renal cell carcinoma	**18** months	Used with cabozantinib: One renewal only

		NOT being used with cabozantinib: Until disease progression or unacceptable toxicity
All other indications	**18** months	Until disease progression or unacceptable toxicity

****NO** renewal for Resectable non-small cell lung cancer (NSCLC) used as neoadjuvant treatment

Rationale

Summary

Opdivo (nivolumab) is a monoclonal antibody indicated for the treatment of various types of cancers. Opdivo works by binding to the programmed cell death-1 (PD-1) receptor, and blocking its interaction with PD-1 ligands, PD-L1 and PD-L2. This interaction releases the inhibitory effects of PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response, resulting in decreased tumor growth. Opdivo carries warnings for immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic HSCT and embryo-fetal toxicity. The safety and effectiveness of Opdivo have not been established in pediatric patients age less than 12 years of age with melanoma or microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) or in pediatric patients less than 18 years of age for the other approved indications (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; October 2024.
2. NCCN Drugs & Biologics Compendium® Nivolumab 2024. National Comprehensive Cancer Network, Inc. Accessed on October 24, 2024.

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

May 2021	Addition of indication: advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma
June 2021	Addition of indication: completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease. Added renewal duration chart for clarity
September 2021	Annual editorial review and reference update. Removed indication: hepatocellular carcinoma as a single agent. Addition of indication: adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection
March 2022	Annual editorial review and reference update
April 2022	Addition of indication per PI update: neoadjuvant treatment of resectable NSCLC
June 2022	Annual review and reference update. Addition of indication per PI update: unresectable advanced or metastatic esophageal squamous cell carcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy or in combination with ipilimumab
September 2022	Annual review and reference update
December 2022	Revised quantity limits chart to separate out metastatic NSCLC when used with ipilimumab
March 2023	Annual review and reference update
September 2023	Annual review and reference update
November 2023	Per PI update, added requirement of Stage IIB, IIC, III, or IV melanoma for adjuvant treatment of completely resected patients
December 2023	Annual review and reference update
March 2024	Annual review and reference update
April 2024	Per PI update, added indication of unresectable or metastatic urothelial carcinoma, as first-line treatment in combination with cisplatin and gemcitabine
June 2024	Annual review and reference update
September 2024	Annual review and reference update
October 2024	Per PI update, added indication of resectable NSCLC as adjuvant treatment as a single agent after surgery. Updated advanced RCC indication to require use with ipilimumab to be first-line
December 2024	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 13, 2024 and is effective on January 1, 2025.