Bristol Myers Squibb®
Access Support®

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# A digital reference guide to Reimbursement & Coding for OPDIVO® (nivolumab)

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

**Please see Important Safety Information for OPDIVO and YERVOY® (ipilimumab), and US Full Prescribing Information for OPDIVO and YERVOY.**
**For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday-Friday, or visit www.BMSAccessSupport.com.**

1506-US-2400460 09/2024 OPDIVO Reimbursement & Coding Digital Reference Guide 2024

## Welcome

Use the buttons on the far right to switch between different sections of this guide.

Links will appear in this area below to subsections of each indication.

OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Introduction

## INDICATIONS AND SELECT IMPORTANT SAFETY INFORMATION

### Indications

OPDIVO® (nivolumab), as a single agent, is indicated for the treatment of adult and pediatric patients 12 years of age and older with unresectable or metastatic melanoma.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of adult and pediatric patients 12 years of age and older with unresectable or metastatic melanoma.

OPDIVO® (nivolumab) is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

OPDIVO® (nivolumab), in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

OPDIVO® (nivolumab) in combination with platinum-doublet chemotherapy, is indicated for neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by single-agent OPDIVO® as adjuvant treatment after surgery.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated 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.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab) and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with 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.

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**Please see Important Safety Information for OPDIVO and YERVOY® (ipilimumab), and US Full Prescribing Information for OPDIVO and YERVOY.**
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OPDIVO® (nivolumab)
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# Introduction

## INDICATIONS AND SELECT IMPORTANT SAFETY INFORMATION

### Indications (continued)

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM).

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

OPDIVO® (nivolumab), in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin or after 3 or more lines of systemic therapy that includes autologous HSCT. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma 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.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Introduction

## INDICATIONS AND SELECT IMPORTANT SAFETY INFORMATION

### Indications (continued)

OPDIVO® (nivolumab), in combination with cisplatin and gemcitabine, is indicated as first-line treatment for adult patients with unresectable or metastatic urothelial carcinoma.

OPDIVO® (nivolumab), as a single agent, is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.

OPDIVO® (nivolumab), as a single agent, is indicated for the treatment of 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. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of adults and pediatric patients 12 years and older 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. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

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OPDIVO® (nivolumab)
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# Introduction

## INDICATIONS AND SELECT IMPORTANT SAFETY INFORMATION

### Indications (continued)

OPDIVO® (nivolumab) is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).

OPDIVO® (nivolumab), in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

OPDIVO® (nivolumab), in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

**Please see Important Safety Information for OPDIVO and YERVOY® (ipilimumab), and US Full Prescribing Information for OPDIVO and YERVOY.**
**For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday-Friday, or visit www.BMSAccessSupport.com.**



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OPDIVO® (nivolumab) INJECTION FOR INTRAVENOUS USE 10 mg/mL

# HEALTHCARE COMMON PROCEDURE CODING SYSTEM (HCPCS) AND REVENUE CODES FOR OPDIVO® (nivolumab) AND YERVOY® (ipilimumab)

Healthcare providers should code healthcare claims based upon the service that is rendered, the patient's medical record, the coding requirements of each health insurer, and the best coding practices. The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.

## Recommended HCPCS Code for OPDIVO[1]

| HCPCS Code | Description | Billing Units |
|---|---|---|
| J9299 | Injection, nivolumab, 1 mg | 1 mg = 1 billing unit |

## Recommended HCPCS Code for YERVOY[1]

| HCPCS Code | Description | Billing Units |
|---|---|---|
| J9228 | Injection, ipilimumab, 1 mg | 1 mg = 1 billing unit |

Use the following claim formats when OPDIVO or OPDIVO + YERVOY is administered to patients on an outpatient basis and billed to health plans:

- Physician office: CMS-1500 (paper format) or ASC 837P (electronic format)
- Hospital outpatient: UB-04 (CMS-1450) [paper format] or ASC 837I (electronic format)
- **JW modifier** – Providers and suppliers are required to report the JW modifier on Part B drug claims for discarded drugs and biologicals. Also, providers and suppliers must document the amount of discarded drugs or biologicals in Medicare beneficiaries' medical records[2]
- **JZ modifier** – Starting no later than July 1, 2023, providers and suppliers are required to attest if there were no discarded amounts of drugs and biologicals[3]
- **JG modifier** – To be used by hospital outpatient to identify if the drug was obtained through 340B pricing. Note that use of this modifier will not trigger any differentiated payment[4]

All the coding information presented is applicable to outpatient procedures only. Please see pages 2.5-2.8 for more information.

## Revenue Codes[5] (for Use in the Hospital Outpatient Setting)

| Revenue Code | Description |
|---|---|
| 0636 | Drugs requiring detailed coding |
| 0335 | Chemotherapy administration, IV |
| 0260 | IV therapy |







OPDIVO® (nivolumab)
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# General Codes

## CURRENT PROCEDURAL TERMINOLOGY (CPT)* CODES FOR OPDIVO® (nivolumab) AND YERVOY® (ipilimumab)

The CPT codes that may be appropriate when administering OPDIVO or OPDIVO + YERVOY appear in the tables below.

### Recommended CPT Code for OPDIVO[6]

| CPT Code | Description |
|---|---|
| 96413 | Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug |

### Recommended CPT Codes for YERVOY[6]

| CPT Code | Description |
|---|---|
| 96417 | Chemotherapy administration, IV infusion; each additional sequential infusion (different substance/drug), up to 1 hour (list separately in addition to code for primary procedure). (Use 96417 in conjunction with 96413) |
| 96415 | Chemotherapy administration, IV infusion; each additional hour (list separately in addition to code for primary procedure). (Report 96415 for infusion intervals of greater than 30 minutes beyond 1-hour increments) |

**Please contact the payer for additional coding information regarding OPDIVO and OPDIVO + YERVOY.**



IV=intravenous.

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OPDIVO® (nivolumab)
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# General Codes

## NATIONAL DRUG CODES (NDCs) INFORMATION FOR OPDIVO® (nivolumab) AND YERVOY® (ipilimumab)

The NDCs for OPDIVO and YERVOY, listed in the tables below, are often necessary in addition to the appropriate J-code when filing a claim for reimbursement.

### NDC Codes for OPDIVO[7]

100 mg/10 mL (10 mg/mL) solution in a single-dose vial

0003-3774-12


40 mg/4 mL (10 mg/mL) solution in a single-dose vial

0003-3772-11

120 mg/12 mL (10 mg/mL) solution in a single-dose vial

0003-3756-14


240 mg/24 mL (10 mg/mL) solution in a single-dose vial

0003-3734-13


### NDC Codes for YERVOY[8]

One 200-mg (5-mg/mL), single-use vial

200-mg vial = 200 billable units

0003-2328-22


One 50-mg (5-mg/mL), single-use vial

50-mg vial = 50 billable units

0003-2327-11




### Storage Information

Store under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the original package until time of use. Do not freeze or shake.

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# General Codes

## 5010 ELECTRONIC TRANSACTION CODING FOR OPDIVO® (nivolumab) AND YERVOY® (ipilimumab)

- For electronic transactions, including 837P and 837I, the 11-digit NDC is to be preceded by the qualifier N4 for payers that require it[9]
- This is typically followed by the quantity qualifier, such as UN (units), F2 (international units), GR (gram), or ML (milliliter), and the quantity administered[9]

### 5010 Transaction Coding for OPDIVO[9]

| How Supplied | 11-Digit NDC | NDC Qualifier | NDC Basis of Measurement | Sample NDC 5010 Format |
|---|---|---|---|---|
| 40 mg/4 mL (10 mg/mL) solution in a single-dose vial | 00003-3772-11 | N4 | ML | N400003377211ML4 |
| 100 mg/10 mL (10 mg/mL) solution in a single-dose vial | 00003-3774-12 | N4 | ML | N400003377412ML10 |
| 120 mg/12 mL (10 mg/mL) solution in a single-dose vial | 00003-3756-14 | N4 | ML | N400003375614ML12 |
| 240 mg/24 mL (10 mg/mL) solution in a single-dose vial | 00003-3734-13 | N4 | ML | N400003373413ML24 |

### 5010 Transaction Coding for YERVOY[9]

| How Supplied | 11-Digit NDC | NDC Qualifier | NDC Basis of Measurement | Sample NDC 5010 Format |
|---|---|---|---|---|
| 50-mg/10-mL (5 mg/mL) single-use vial | 00003-2327-11 | N4 | ML | N400003232711ML10 |
| 200-mg/40-mL (5 mg/mL) single-use vial | 00003-2328-22 | N4 | ML | N400003232822ML40 |

The example given in the far right column demonstrates NDC quantity reporting for 1 vial of OPDIVO or YERVOY. The actual amount of drug used can vary based on factors such as indication or patient weight. Currently, reporting NDC quantity varies from payer to payer, so the provider should consult each specific payer to determine the required format.

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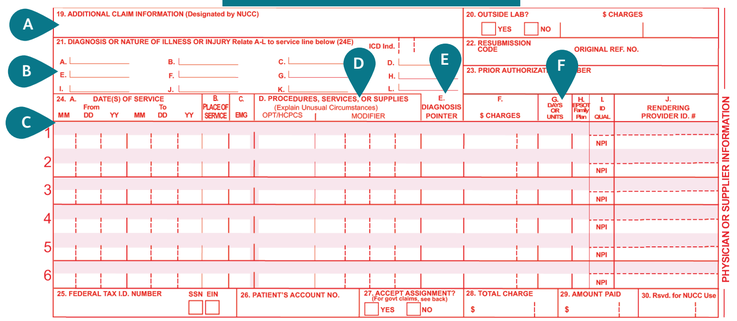
# General Codes

## CODING AND BILLING UNITS FOR OPDIVO® (nivolumab)

Please contact the payer or BMS Access Support® for additional information on coding and billing units.

CMS-1500 Form




This sample form is for informational purposes only.

### Physician Office

**A** **Item 19:** Many payers require detailed information about the drug in Item 19[9]:

- Drug name: OPDIVO
- Total dosage and strength
- Method of administration
- 11-digit NDC
- Basis of measurement

**B** **Item 21:** Enter site-specific ICD-10-CM codes in priority order.[9]

**C** **Item 24A:** NDC information is required in the red shaded area. The NDC is preceded by the qualifier N4 and followed by the quantity qualifier (ML) and the quantity administered.[9] *See table below for a full list of NDCs formatted for 24A.*

**D** **Item 24D:** Enter HCPCS code J9299 and *CPT* code* 96413.[1,6,9] In addition, it is required that you enter J9299-JW on next line to record waste.[2] Alternatively, if no wastage, enter J9299-JZ to attest there were no discarded amounts.[10]

**E** **Item 24E:** Enter the relevant diagnosis code reference letter or number from Item 21 to relate the date of service and the services or procedures performed that is entered on the same line under 24D.[9]

**F** **Item 24G:**

- Billing units are reported here[9]
- For OPDIVO, 1 mg = 1 billing unit

**NDC Information for OPDIVO[7]**

| How Supplied (Single-Dose Vial) | NDC Format |
|---|---|
| 40 mg/4 mL (10mg/mL) solution | N400003377211ML4 |
| 100 mg/10 mL (10 mg/mL) solution | N400003377412ML10 |
| 120 mg/12 mL (10 mg/mL) solution | N400003375614ML12 |
| 240 mg/24 mL (10 mg/mL) solution | N400003373413ML24 |

Healthcare providers should code healthcare claims based upon the service that is rendered, the patient's medical record, the coding requirements of each health insurer, and the best coding practices. The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.

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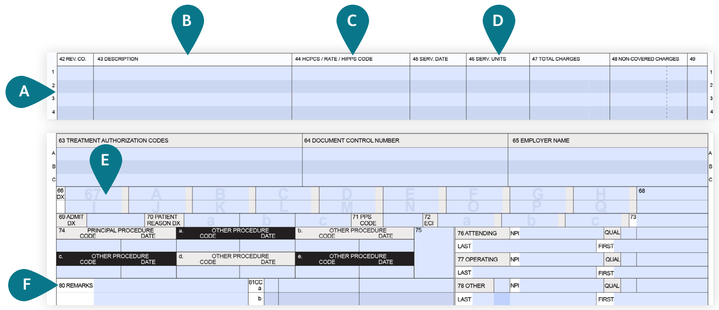
# General Codes

## CODING AND BILLING UNITS FOR OPDIVO® (nivolumab) (continued)

UB-04 Form




This sample form is for informational purposes only.

### Outpatient Hospital

**A Form Locator (FL) 42:**

- Enter the 4-digit revenue code for service provided in accordance with hospital billing policy.[11]
- For chemotherapy administration, revenue codes 0260 (IV therapy) or 0335 (radiology–therapeutic: chemotherapy–IV) could be used.[5]
- CMS recommends using 0636 (drugs requiring detailed coding).[5,12]

**B FL 43:**

- Enter the qualifier "N4" followed by 11-digit NDC in positions 01–13.[11]
- Report quantity qualifier (ML) followed by quantity administered (40 mg/**4** mL, 100 mg/**10** mL, 120 mg/**12** mL, or 240 mg/**24** mL) beginning in position 14.[7,11] *See table below for a full list of NDCs formatted for FL43.*

**C FL 44:**

- Enter HCPCS code J9299 and CPT code* 96413.[1,6,11]
- In addition, it is required that you enter J9299-JW on the next claim line to record waste.[2]
- Alternatively, if no wastage, enter J9299-JZ to attest there were no discarded amounts. Include the JG modifier if the drug was obtained through 340B pricing.[4,10]

**D FL 46:**

- Billing units (service units) are entered here[11]
- 1 mg = 1 billing unit

**E FLs 67A-67Q:** Enter site-specific ICD-10-CM diagnosis codes for malignancy being treated.[11]

**F FL 80:** Some payers require detailed information about the drug.[11]
Enter the following:

- Drug name: OPDIVO
- Total dosage and strength
- Method of administration
- 11-digit NDC
- Basis of measurement

**NDC Information for OPDIVO[7]**

| How Supplied (Single-Dose Vial) | NDC Format |
|---|---|
| 40 mg/4 mL (10mg/mL) solution | N400003377211ML4 |
| 100 mg/10 mL (10 mg/mL) solution | N400003377412ML10 |
| 120 mg/12 mL (10 mg/mL) solution | N400003375614ML12 |
| 240 mg/24 mL (10 mg/mL) solution | N400003373413ML24 |

Healthcare providers should code healthcare claims based upon the service that is rendered, the patient's medical record, the coding requirements of each health insurer, and the best coding practices. The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.





OPDIVO® (nivolumab)
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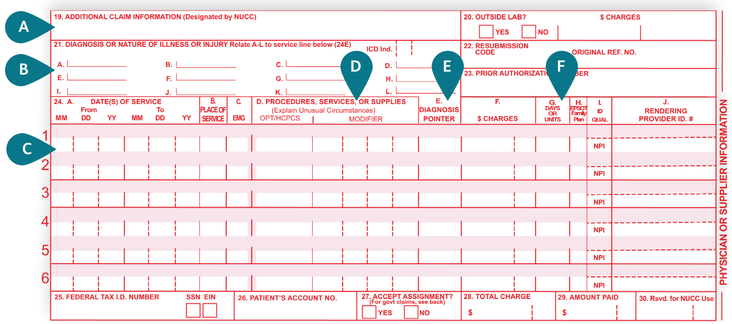
# CODING AND BILLING UNITS FOR OPDIVO® (nivolumab) + YERVOY® (ipilimumab)

Please contact the payer or BMS Access Support® for additional information on coding and billing units

CMS-1500 Form




This sample form is for informational purposes only.

## Physician Office

**A** **Item 19:**
Many payers require detailed information about the drug in Item 19[9]:

- Drug name: OPDIVO and YERVOY
- Total dosage and strength
- Method of administration
- 11-digit NDC
- Basis of measurement

**B** **Item 21:** Enter site-specific ICD-10-CM codes in priority order.[9]

**C** **Item 24A:** NDC information is required in the red shaded area.[9] The NDC is preceded by the qualifier N4 and followed by the quantity qualifier (ML) and the quantity administered.[9] See tables below for a full listing of NDCs formatted for 24A.[9]

**D** **Item 24D:** Enter HCPCS code J9299 for OPDIVO and J9228 for YERVOY.[1] Enter CPT code* 96413 for OPDIVO, 96417 for YERVOY, and 96415 (if needed) for time of treatment infusion.[6] In addition, it is required that you enter J9299-JW and J9228-JW on the next line to record waste. Alternatively, if no wastage, enter J9299-JZ and J9228-JZ to attest there were no discarded amounts.[10]

**E** **Item 24E:** Enter the relevant diagnosis code reference letter or number from Item 21 to relate the date of service and the services or procedures performed that is entered on the same line under 24D.[9]

**F** **Item 24G:**

- Billing units are reported here[9]
- For OPDIVO and YERVOY, 1 mg = 1 billing unit

### NDC Information for OPDIVO[7]

| How Supplied (Single-Dose Vial) | NDC Format |
|---|---|
| 40 mg/4 mL (10mg/mL) solution | N400003377211ML4 |
| 100 mg/10 mL (10 mg/mL) solution | N400003377412ML10 |
| 120 mg/12 mL (10 mg/mL) solution | N400003375614ML12 |
| 240 mg/24 mL (10 mg/mL) solution | N400003373413ML24 |

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OPDIVO® (nivolumab)
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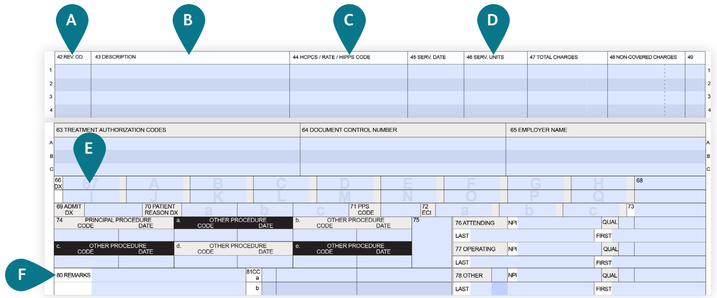
# CODING AND BILLING UNITS FOR OPDIVO® (nivolumab) + YERVOY® (ipilimumab) (continued)

## UB-04 Form

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### NDC Information for OPDIVO[7]

| How Supplied (Single-Dose Vial) | NDC Format |
|---|---|
| 40 mg/4 mL (10mg/mL) solution | N400003377211ML4 |
| 100 mg/10 mL (10 mg/mL) solution | N400003377412ML10 |
| 120 mg/12 mL (10 mg/mL) solution | N400003375614ML12 |
| 240 mg/24 mL (10 mg/mL) solution | N400003373413ML24 |

## Outpatient Hospital

**A Form Locator (FL) 42:**

- Enter the 4-digit revenue code for service provided in accordance with hospital billing policy.[11]
- For chemotherapy administration, revenue codes 0260 (IV therapy) or 0335 (radiology–therapeutic: chemotherapy–IV) could be used.[5]
- CMS recommends using 0636 (drugs requiring detailed coding).[5,12]

**B FL 43:**

- For each product administered, enter the qualifier "N4" followed by 11-digit NDC in positions 01–13.[11] Report the quantity qualifier (ML) followed by the quantity administered (40 mg/4 mL, 100 mg/10 mL, 120 mg/12 mL, or 240 mg/24 mL for OPDIVO and 50 mg/10 mL or 200 mg/40 mL for YERVOY) beginning in position 14.[7,8,10] See table below for a full listing of NDCs formatted for FL43.

**C FL 44:**

- Enter the relevant HCPCS and CPT codes* here.[11] The HCPCS codes are J9299 for OPDIVO and J9228 for YERVOY.[6] The CPT codes are 96413 for OPDIVO, 96417 for YERVOY, and 96415 (if needed) for time of treatment infusion.[4]
- In addition, it is required that you enter J9299-JW and J9228-JW on the next line to record waste.[2]
- Alternatively, if no wastage, enter J9299-JZ and J9228-JZ to attest there were no discarded amounts. Include the JG modifier if the drug was obtained through 340B pricing.[4,10]

**D FL 46:**

- Billing units (service units) are entered here[11]
- 1 mg = 1 billing unit

**E FLs 67A-67Q:** Enter site-specific ICD-10-CM diagnosis codes for malignancy being treated.[11]

**F FL 80:** Some payers require detailed information about the drug.[11]
Enter the following:

- Drug name: OPDIVO and YERVOY
- Total dosage and strength
- Method of administration
- 11-digit NDC
- Basis of measurement

Healthcare providers should code healthcare claims based upon the service that is rendered, the patient's medical record, the coding requirements of each health insurer, and the best coding practices. The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.

**References: 1.** American Medical Association. 2019 HCPCS Level II. Professional ed. Chicago, IL: American Medical Association; 2019. **2.** Centers for Medicare & Medicaid Services. MLN Matters, Number MM9603 Revised. Revised June 10, 2016. Accessed June 20, 2022. https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/MM9603.pdf **3.** Centers for Medicare & Medicaid Services. Calendar Year (CY) 2023 Medicare Physician Fee Schedule Final Rule. Published November 1, 2022. Accessed December 20, 2022. https://www.cms.gov/newsroom/fact-sheets/calendar-year-cy-2023-medicare-physician-fee-schedule-final-rule **4.** Centers for Medicare & Medicaid Services. CMS Manual System: Pub 100-04 Medicare Claims Processing. Published December 8, 2022. Accessed December 21, 2022. https://www.cms.gov/files/document/r11737cp.pdf **5.** National Uniform Billing Committee (NUBC). Official UB-04 Data Specifications Manual 2020. Chicago, IL: American Hospital Association; 2020. **6.** American Medical Association. CPT Professional 2022. Professional ed. Chicago, IL: American Medical Association; 2022. **7.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. July 2022. **8.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. May 2022. **9.** Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 26 – Completing and Processing Form CMS-1500 Data Set. Revision 4388. September 6, 2020. Accessed June 20, 2022. https://www.cms.gov/ Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c26.pdf **10.** Centers for Medicare & Medicaid Services. Medicare-FFS Program, Billing 340B Modifiers under the Hospital Outpatient Prospective Payment System (OPPS). March 3, 2023. Accessed February 13, 2024. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c01.pdf **11.** Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 25 – Completing and Processing the Form CMS-1450 Data Set. Revision 4194. January 11, 2020. Accessed June 20, 2022. http://www.cms.gov/Regulationsand-Guidance/Guidance/Manuals/downloads/clm104c25.pdf **12.** Centers for Medicare & Medicaid Services. Medicare Claims Processing Manual. Chapter 17 – Drugs and Biologicals. Revision 4233. February 8, 2020. Accessed June 20, 2022. https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/clm104c17.pdf

# General Reimbursement Information

## MEDICARE DRUG REIMBURSEMENT FOR OPDIVO® (nivolumab)

### What is the Medicare reimbursement allowable for OPDIVO?

**Physicians***

- The payment limit is 106% of average sales price (ASP), not including sequestration, and represents one billing unit of OPDIVO, which is billed for each 1 mg[1,2†]
- The amount paid to physicians for OPDIVO HCPCS code J9299 (and in the case of OPDIVO + YERVOY® (ipilimumab), YERVOY HCPCS code J9228) is published at the beginning of each calendar quarter in "Payment Allowance Limits for Medicare Part B Drugs,"[2] which can be downloaded at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice
- Medicare Part B will pay physicians 80% of the allowed price for OPDIVO HCPCS code J9299 (and in the case of OPDIVO + YERVOY, YERVOY HCPCS code J9228); the patient is responsible for 20% co-insurance, which may be covered by secondary insurance (private supplemental coverage, Medicaid, etc)[3]

**Hospital outpatient facilities***

Drugs paid separately under the hospital outpatient fee schedule are based on 106% of average sales price (ASP), not including sequestration, for one billing unit for the corresponding HCPCS code. This is 1 mg for OPDIVO HCPCS code J9299 (and in the case of OPDIVO + YERVOY, 1 mg for YERVOY HCPCS code J9228)[1,2†]

- The Payment Allowance Limits[2] are published each quarter at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice

**Hospital inpatient settings**

- Reimbursement in the inpatient setting is bundled into the Medicare Diagnosis Related Groups called MS-DRGs[4,5]
- This prospective rate changes on October 1 each year and does not allow for drugs to be paid separately[6,7]

*While the statutory amount that Medicare will reimburse for a Part B Drug in a physician office will remain at ASP +6%, sequestration has resulted in a reduction to the Medicare portion of the payment to Medicare providers. Essentially, all payments from Medicare carriers to the providers (including physician offices, hospitals, etc) will be reduced by 2%.[8]

†See the Centers for Medicare & Medicaid Services' (CMS) Internet Only Manual (IOM) Publication 100-04, Chapter 17-20.1.3.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# General Reimbursement Information

## COMMERCIAL INSURANCE REIMBURSEMENT FOR OPDIVO® (nivolumab)

### Physicians

- Drug reimbursement, like service reimbursement, is usually based on a fee schedule[9]
- The fee schedules are based on the ASP or AWP, as published by a credible source,[10,11] or an average costing methodology as determined by the payer, such as usual, customary, and reasonable (UC&R)[12]

### Hospital outpatient facilities

- In this setting, reimbursement is most commonly based on percentage of charges[11]
- Alternatively, some hospitals use the same ASP or AWP methodologies typically used by physician offices[11]
- Other methodologies include capitated model, cost minus submitted charges, or discount off submitted charges[11]

### Hospital inpatient settings

- Inpatient rates are prospective, meaning they are predetermined per discharge[4]
- There are private payers that pay on a version of the DRGs[5]
- There are also payers that pay on a negotiated and fixed rate per day called a "per diem."[5] There are capitated rates for inpatients as well[5]
- New drugs may be carved out of per diems or capitated rates, if the hospital negotiates to do so[13]

**References**: **1.** Centers for Medicare & Medicaid Services. 2020 ASP drug pricing files. Updated September 19, 2022. Accessed November 4, 2022. https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2022-asp-drug-pricing-files **2.** Centers for Medicare & Medicaid Services. Payment allowance limits for Medicare Part B drugs. Accessed November 4, 2022. https://www.cms.gov/apps/ama/license.asp?file=/files/zip/october-2022-asp-pricing-file.zip **3.** Centers for Medicare & Medicaid Services. Medicare & You 2023. Accessed November 4, 2022. https://www.medicare.gov/Pubs/pdf/10050-medicare-and-you.pdf **4.** Centers for Medicare & Medicaid Services. Acute inpatient PPS. Updated August 2, 2022. Accessed November 4, 2022. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/index.html?redirect=/acuteinpatientpps **5.** AMCP Task Force on Drug Payment Methodologies. AMCP guide to pharmaceutical payment methods, executive edition. *J Managed Care Pharm*. 2007;13(8 suppl C):S1-S39. **6.** Centers for Medicare & Medicaid Services. Drug coverage under different parts of Medicare. Accessed November 4, 2022. https://www.cms.gov/outreach-and-education/outreach/partnerships/downloads/11315-p.pdf **7.** CMS.gov. MS-DRG Classifications and Software. Updated November 2, 2022. Accessed November 4, 2022. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/MS-DRG-Classifications-and-Software **8.** Centers for Medicare & Medicaid Services. CMS Medicare FFS Provider e-news. March 8, 2013. Accessed November 4, 2022. https://www.cms.gov/Outreach-and-Education/Outreach/FFSProvPartProg/Downloads/2013-03-08-standalone.pdf **9.** Robinson JC. Insurers' strategies for managing the use and cost of biopharmaceuticals. *Health Aff (Millwood)*. 2006;25(5):1205-1217. **10.** American Society of Clinical Oncology. Payment reform glossary. ASCO website. Accessed November 4, 2022. https://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/pdf/Payment-Reform-Glossary.pdf **11.** Magellan Rx Management. Medical Pharmacy Trend Report 2020. Published 2021. Accessed November 4, 2022. http://www.magellanrxinsights.com **12.** US Bureau of Labor Statistics. Definitions of health insurance terms. Accessed November 4, 2022. http://www.bls.gov/ncs/ebs/sp/healthterms.pdf **13.** Academy of Managed Care Pharmacy. Managed care glossary. AMCP website. Accessed November 4, 2022. https://www.amcp.org/about/managed-care-pharmacy-101/managed-care-glossary.

# Melanoma: Adjuvant Therapy and Advanced Disease

## INDICATIONS

OPDIVO® (nivolumab), as a single agent, is indicated for the treatment of adult and pediatric patients 12 years of age and older with unresectable or metastatic melanoma.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of adult and pediatric patients 12 years of age and older with unresectable or metastatic melanoma.

OPDIVO® (nivolumab) is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

# Melanoma: Adjuvant Therapy and Advanced Disease

## RECOMMENDED DOSING

### Unresectable or Metastatic (Advanced) Melanoma[1]

**Dosing for adult and pediatric patients aged 12 years and older and weighing 40 kg or more‡**

| OPDIVO® (nivolumab) monotherapy | |
|---|---|
| **DOSING & SCHEDULE*†** | **DURATION** |
| **240 mg of OPDIVO** IV infusion over 30 minutes q2w **OR** **480 mg of OPDIVO** IV infusion over 30 minutes q4w | Until disease progression or unacceptable toxicity |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

**‡For pediatric patients age 12 years and older and weighing less than 40 kg, OPDIVO to be dosed 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks infused IV over 30 minutes until disease progression or unacceptable toxicity.**

(continued on next page)







OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Melanoma: Adjuvant Therapy and Advanced Disease

## RECOMMENDED DOSING (continued)

### Unresectable or Metastatic (Advanced) Melanoma[1,3]

**Dosing for adult and pediatric patients aged 12 years and older and weighing 40 kg or more[§]**

| OPDIVO® (nivolumab) + YERVOY® (ipilimumab) | | | |
|---|---|---|---|
| **DOSING & SCHEDULE*†‡** | | | **DURATION** |
| **Induction phase (weight-based)** | | | |
| **1 mg/kg of OPDIVO**<br>IV infusion over<br>30 minutes q3w | **WITH** | **3 mg/kg of YERVOY**<br>IV infusion over<br>30 minutes q3w | In combination with YERVOY for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier |
| **Maintenance phase** | | | |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | **OR** | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease progression or unacceptable toxicity |

**Administer OPDIVO first, followed by YERVOY on the same day.**

**After completing 4 doses of the combination in the induction phase, administer OPDIVO as a single agent.**

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO or OPDIVO + YERVOY in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

**§For pediatric patients age 12 years and older and weighing less than 40 kg, OPDIVO to be dosed with YERVOY according to induction phase shown above, and OPDIVO dosed for the maintenance phase 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks infused IV over 30 minutes until disease progression or unacceptable toxicity.**

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# Melanoma: Adjuvant Therapy and Advanced Disease

## RECOMMENDED DOSING (continued)

### Completely Resected Stage IIB, Stage IIC, Stage III, or Stage IV Melanoma[1]

**Dosing for adult and pediatric patients aged 12 years and older and weighing 40 kg or more‡**

| OPDIVO® (nivolumab) monotherapy | |
|---|---|
| **DOSING & SCHEDULE*†** | **DURATION** |
| **240 mg of OPDIVO** IV infusion over 30 minutes q2w **OR** **480 mg of OPDIVO** IV infusion over 30 minutes q4w | Until disease recurrence or unacceptable toxicity for up to 1 year |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

**‡For pediatric patients age 12 years and older and weighing less than 40 kg, OPDIVO to be dosed 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks infused IV over 30 minutes until disease recurrence or unacceptable toxicity for up to 1 year.**

IV=intravenous; q2w=every 2 weeks; q3w=every 3 weeks; q4w=every 4 weeks.

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Melanoma: Adjuvant Therapy and Advanced Disease

## ICD-10-CM CODES[4]

| C43 | Malignant melanoma of skin |
|---|---|
| C43.0 | Malignant melanoma of lip |
| C43.1 | Malignant melanoma of eyelid, including canthus* |
| C43.10 | Malignant melanoma of unspecified eyelid, including canthus |
| C43.11 | Malignant melanoma of right eyelid, including canthus* |
| C43.111 | Malignant melanoma of right upper eyelid, including canthus |
| C43.112 | Malignant melanoma of right lower eyelid, including canthus |
| C43.12 | Malignant melanoma of left eyelid, including canthus* |
| C43.121 | Malignant melanoma of left upper eyelid, including canthus |
| C43.122 | Malignant melanoma of left lower eyelid, including canthus |
| C43.2 | Malignant melanoma of ear and external auricular canal* |
| C43.20 | Malignant melanoma of unspecified ear and external auricular canal |
| C43.21 | Malignant melanoma of right ear and external auricular canal |
| C43.22 | Malignant melanoma of left ear and external auricular canal |
| C43.3 | Malignant melanoma of other and unspecified parts of face* |
| C43.30 | Malignant melanoma of unspecified part of face |
| C43.31 | Malignant melanoma of nose |
| C43.39 | Malignant melanoma of other parts of face |
| C43.4 | Malignant melanoma of scalp and neck |
| C43.5 | Malignant melanoma of trunk* |
| C43.51 | Malignant melanoma of anal skin |
| C43.52 | Malignant melanoma of skin of breast |
| C43.59 | Malignant melanoma of other part of trunk |

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Melanoma: Adjuvant Therapy and Advanced Disease

## ICD-10-CM CODES[4] (continued)

| | |
|---|---|
| C43.6 | Malignant melanoma of upper limb, including shoulder* |
| C43.60 | Malignant melanoma of unspecified upper limb, including shoulder |
| C43.61 | Malignant melanoma of right upper limb, including shoulder |
| C43.62 | Malignant melanoma of other parts of face |
| C43.7 | Malignant melanoma of lower limb, including hip* |
| C43.70 | Malignant melanoma of unspecified lower limb, including hip |
| C43.71 | Malignant melanoma of right lower limb, including hip |
| C43.72 | Malignant melanoma of left lower limb, including hip |
| C43.8 | Malignant melanoma of overlapping sites of skin |
| C43.9 | Malignant melanoma of skin, unspecified |

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

(continued on next page)

The code C43 has an Excludes 2 note under it. Per ICD-10-CM official guidelines, an Excludes 2 note under a code represents "Not included here." An Excludes 2 note indicates that the condition excluded is not part of the condition represented by the code, but a patient may have both conditions at the same time. When an Excludes 2 note appears under a code, it is acceptable to use both the code and the excluded code together, when appropriate.[4]

Under code C43, the Excludes 2 note lists the following[4]:

- Malignant melanoma of skin of genital organs (C51-C52, C60.-, C63.-)
- Merkel cell carcinoma (C4A.-)
- Sites other than skin – code to malignant neoplasm of the site







OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Melanoma: Adjuvant Therapy and Advanced Disease

## ICD-10-CM CODES[4] (continued)

| | |
|---|---|
| C21 | Malignant neoplasm of anus and anal canal |
| C21.0 | Malignant neoplasm of anus, unspecified |
| C21.1 | Malignant neoplasm of anal canal |
| C51 | Malignant neoplasm of vulva |
| C51.0 | Malignant neoplasm of labium majus |
| C51.1 | Malignant neoplasm of labium minus |
| C51.2 | Malignant neoplasm of clitoris |
| C51.9 | Malignant neoplasm of vulva, unspecified |
| C52 | Malignant neoplasm of vagina |
| C57 | Malignant neoplasm of other and unspecified female genital organs |
| C57.7 | Malignant neoplasm of other specified female genital organs |
| C57.8 | Malignant neoplasm of overlapping sites of female genital organs |
| C57.9 | Malignant neoplasm of female genital organ, unspecified |
| C60 | Malignant neoplasm of penis |
| C60.0 | Malignant neoplasm of prepuce |
| C60.1 | Malignant neoplasm of glans penis |
| C60.8 | Malignant neoplasm of overlapping sites of penis |
| C60.9 | Malignant neoplasm of penis, unspecified |
| C63 | Malignant neoplasm of other and unspecified male genital organs |
| C63.0 | Malignant neoplasm of epididymis* |
| C63.00 | Malignant neoplasm of unspecified epididymis |
| C63.01 | Malignant neoplasm of right epididymis |
| C63.02 | Malignant neoplasm of left epididymis |

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

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# Melanoma: Adjuvant Therapy and Advanced Disease

## ICD-10-CM CODES[4] (continued)

| | |
|---|---|
| C63.1 | Malignant neoplasm of spermatic cord* |
| C63.10 | Malignant neoplasm of unspecified spermatic cord |
| C63.11 | Malignant neoplasm of right spermatic cord |
| C63.12 | Malignant neoplasm of left spermatic cord |
| C63.2 | Malignant neoplasm of scrotum |
| C63.7 | Malignant neoplasm of other specified male genital organs |
| C63.8 | Malignant neoplasm of overlapping sites of male genital organs |
| C63.9 | Malignant neoplasm of male genital organ, unspecified |

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[4]:

| | |
|---|---|
| Z51.12 | Encounter for antineoplastic immunotherapy |

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.





OPDIVO® (nivolumab)
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# Melanoma: Adjuvant Therapy and Advanced Disease

## IMPORTANT SAFETY INFORMATION

**Severe and Fatal Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 7% (31/456) of patients, including Grade 4 (0.2%), Grade 3 (2.0%), and Grade 2 (4.4%).

Immune-Mediated Colitis

OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated colitis occurred in 25% (115/456) of patients, including Grade 4 (0.4%), Grade 3 (14%) and Grade 2 (8%).

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Melanoma: Adjuvant Therapy and Advanced Disease

## IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 15% (70/456) of patients, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%).

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%).

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, adrenal insufficiency occurred in 8% (35/456), including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypophysitis occurred in 9% (42/456), including Grade 3 (2.4%) and Grade 2 (6%).

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hyperthyroidism occurred in 9% (42/456) of patients, including Grade 3 (0.9%) and Grade 2 (4.2%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypothyroidism occurred in 20% (91/456) of patients, including Grade 3 (0.4%) and Grade 2 (11%).

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OPDIVO® (nivolumab)
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# Melanoma: Adjuvant Therapy and Advanced Disease

## IMPORTANT SAFETY INFORMATION (continued)

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO and YERVOY can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%).

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated rash occurred in 28% (127/456) of patients, including Grade 3 (4.8%) and Grade 2 (10%).

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal*: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

## IMPORTANT SAFETY INFORMATION (continued)

unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular*: blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal*: pancreatitis (1.3%); *other (hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

**Infusion-Related Reactions**

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients.

**Complications of Allogeneic Hematopoietic Stem Cell Transplantation**

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

**Embryo-Fetal Toxicity**

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of

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OPDIVO® (nivolumab)
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## IMPORTANT SAFETY INFORMATION (continued)

the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

**Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone**

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**Lactation**

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

**Serious Adverse Reactions**

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In Checkmate 067, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). In Checkmate 238, serious adverse reactions occurred in 18% of patients receiving OPDIVO (n=452). Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. In Checkmate 76K, serious adverse reactions occurred in 18% of patients receiving OPDIVO (n=524). Adverse reactions which resulted in permanent discontinuation of OPDIVO in >1% of patients included arthralgia (1.7%), rash (1.7%), and diarrhea (1.1%). A fatal adverse reaction occurred in 1 (0.2%) patient (heart failure and acute kidney injury). The most frequent Grade 3-4 lab abnormalities

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OPDIVO® (nivolumab)
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# Melanoma: Adjuvant Therapy and Advanced Disease

## IMPORTANT SAFETY INFORMATION (continued)

reported in ≥1% of OPDIVO- treated patients were increased lipase (2.9%), increased AST (2.2%), increased ALT (2.1%), lymphopenia (1.1%), and decreased potassium (1.0%).

### Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (62%), diarrhea (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea (30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%). In Checkmate 238, the most common adverse reactions (≥20%) reported in OPDIVO-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%). In Checkmate 76K, the most common adverse reactions (≥20%) reported with OPDIVO (n=524) were fatigue (36%), musculoskeletal pain (30%), rash (28%), diarrhea (23%), and pruritus (20%).

### Clinical Trials and Patient Populations

Checkmate 238–adjuvant treatment of patients with completely resected Stage III or Stage IV melanoma; Checkmate 76K–adjuvant treatment of patients 12 years of age and older with completely resected Stage IIB or Stage IIC melanoma; Checkmate 037–previously treated metastatic melanoma; Checkmate 066—previously untreated metastatic melanoma; Checkmate 067–previously untreated metastatic melanoma, as a single agent or in combination with YERVOY

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March, 2024. **2.** Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol*. 2018;29(11):2208-2213. **3.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March, 2024. **4.** American Medical Association. 2024 ICD-10-CM: The Complete Official Codebook. Chicago, IL: *American Medical Association*; 2024.







OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## INDICATIONS

OPDIVO® (nivolumab), in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

OPDIVO® (nivolumab) in combination with platinum-doublet chemotherapy, is indicated for neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by single-agent OPDIVO® as adjuvant treatment after surgery.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated 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.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab) and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with 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.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## RECOMMENDED DOSING FOR OPDIVO® (NIVOLUMAB)

OPDIVO, in combination with platinum-doublet chemotherapy, is indicated for neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by single-agent OPDIVO as adjuvant treatment after surgery.

### OPDIVO® (nivolumab) used in the perioperative setting

| DOSING & SCHEDULE* | DURATION |
|---|---|
| **OPDIVO + platinum-doublet chemotherapy as neoadjuvant treatment** | |
| **360 mg of OPDIVO**<br>IV infusion over 30 minutes<br>q3w followed on the same day by<br>platinum-doublet chemotherapy q3w | **In combination with chemotherapy for up to 4 cycles or until disease progression or unacceptable toxicity** |
| **OPDIVO as a single agent in the adjuvant setting after surgical resection** | |
| **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | **For up to 13 (approximately 1 year) cycles or until disease recurrence or unacceptable toxicity** |

*Administer OPDIVO first, followed by platinum-doublet chemotherapy on the same day.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## RECOMMENDED DOSING (continued)

### 1L Metastatic Non-Small Cell Lung Cancer (PD-L1 ≥1%)[1,2]

| OPDIVO® (nivolumab) + YERVOY® (ipilimumab) | | | |
|---|---|---|---|
| **DOSING & SCHEDULE*** | | | **DURATION** |
| **360 mg of OPDIVO**<br>IV infusion over<br>30 minutes q3w | **WITH** | **1 mg/kg of YERVOY**<br>IV infusion over<br>30 minutes q6w | In combination with YERVOY, until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression |
| **Administer OPDIVO first, followed by YERVOY on the same day.** | | | |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO or OPDIVO + YERVOY in patients with severe or life-threatening infusion-related reactions.[1]

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Please see Important Safety Information for OPDIVO and YERVOY® (ipilimumab), and US Full Prescribing Information for OPDIVO and YERVOY.
For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday-Friday, or visit www.BMSAccessSupport.com.





OPDIVO® (nivolumab)
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# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## RECOMMENDED DOSING (continued)

### 1L Metastatic or Recurrent Non-Small Cell Lung Cancer[1,2]

**OPDIVO® (nivolumab) + YERVOY® (ipilimumab) with 2 cycles of histology-based platinum-doublet chemotherapy**

| DOSING & SCHEDULE* | | | DURATION |
|---|---|---|---|
| **OPDIVO + YERVOY** | | | |
| **360 mg of OPDIVO**<br>IV infusion over<br>30 minutes q3w | WITH | **1 mg/kg of YERVOY**<br>IV infusion over<br>30 minutes q6w | In combination with YERVOY, until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression |
| **AND platinum-doublet chemotherapy** | | | |
| **Histology-based platinum-doublet chemotherapy q3w** | | | **2 cycles of histology-based platinum-doublet chemotherapy** |

**Administer OPDIVO first, followed by YERVOY on the same day.**

Histology-based chemo; SQ patients: carboplatin AUC 6 + paclitaxel 200 mg/m$^2$ q3w; NSQ patients: carboplatin AUC 5 or 6 or cisplatin 75 mg/m$^2$ + pemetrexed 500 mg/m$^2$ q3w with optional pemetrexed maintenance therapy.[1]

For the r/m NSCLC dosing regimen in combination with chemo: on the first week, 4 agents will be administered (OPDIVO 360 mg + YERVOY 1 mg/kg + histology-based chemo) followed by 3 agents (OPDIVO + histology-based chemo) on the third week, 2 agents (OPDIVO + YERVOY) on the sixth week, and OPDIVO monotherapy on the ninth week, followed by maintenance therapy of OPDIVO + YERVOY.[1]

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO or OPDIVO + YERVOY in patients with severe or life-threatening infusion-related reactions.[1]

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# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## RECOMMENDED DOSING (continued)

### 2L Metastatic Non-Small Cell Lung Cancer[1]

| OPDIVO® (nivolumab) monotherapy | |
|---|---|
| **DOSING & SCHEDULE*†** | **DURATION** |
| **240 mg of OPDIVO** IV infusion over 30 minutes q2w **OR** **480 mg of OPDIVO** IV infusion over 30 minutes q4w | Until disease progression or unacceptable toxicity |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[3]

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**

1L=first-line; 2L=second-line; ALK=anaplastic lymphoma kinase; AUC=area under the curve; EGFR=epidermal growth factor receptor; FDA=US Food and Drug Administration; IV=intravenous; NSQ=nonsquamous; r/m=recurrent or metastatic; PD-L1=programmed death-ligand 1; q2w=every 2 weeks; q3w=every 3 weeks; q4w=every 4 weeks; q6w=every 6 weeks; SQ=squamous.





OPDIVO® (nivolumab)
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# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## ICD-10-CM CODES[4]

| | |
|---|---|
| **C33** | **Malignant neoplasm of trachea** |
| **C34** | **Malignant neoplasm of bronchus and lung** |
| C34.0 | Malignant neoplasm of main bronchus, carina, and hilus of lung* |
| C34.00 | Malignant neoplasm of unspecified main bronchus |
| C34.01 | Malignant neoplasm of right main bronchus |
| C34.02 | Malignant neoplasm of left main bronchus |
| C34.1 | Malignant neoplasm of upper lobe, bronchus or lung* |
| C34.10 | Malignant neoplasm of upper lobe, unspecified bronchus or lung |
| C34.11 | Malignant neoplasm of upper lobe, right bronchus or lung |
| C34.12 | Malignant neoplasm of upper lobe, left bronchus or lung |
| C34.2 | Malignant neoplasm of middle lobe, bronchus or lung |
| C34.3 | Malignant neoplasm of lower lobe, bronchus or lung* |
| C34.30 | Malignant neoplasm of lower lobe, unspecified bronchus or lung |
| C34.31 | Malignant neoplasm of lower lobe, right bronchus or lung |
| C34.32 | Malignant neoplasm of lower lobe, left bronchus or lung |
| C34.8 | Malignant neoplasm of overlapping sites of bronchus and lung* |
| C34.80 | Malignant neoplasm of overlapping sites of unspecified bronchus and lung |
| C34.81 | Malignant neoplasm of overlapping sites of right bronchus and lung |
| C34.82 | Malignant neoplasm of overlapping sites of left bronchus and lung |
| C34.9 | Malignant neoplasm of unspecified part of bronchus or lung* |
| C34.90 | Malignant neoplasm of unspecified part of bronchus or lung |
| C34.91 | Malignant neoplasm of unspecified part of right bronchus or lung |
| C34.92 | Malignant neoplasm of unspecified part of left bronchus or lung |

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

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The accurate completion and submission of reimbursement and coverage-related documentation to the patient's insurance is the responsibility of the provider and patient. Bristol Myers Squibb and its agents cannot guarantee coverage for any treatment.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## ICD-10-CM CODES[4] (continued)

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[4]:

| | |
|---|---|
| Z51.12 | Encounter for antineoplastic immunotherapy |

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.

# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## IMPORTANT SAFETY INFORMATION

**Severe and Fatal Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune- mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune- mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%). In NSCLC patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, immune-mediated pneumonitis occurred in 9% (50/576) of patients, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%). Four patients (0.7%) died due to pneumonitis.

Immune-Mediated Colitis

OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

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# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## IMPORTANT SAFETY INFORMATION (continued)

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%).

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO and YERVOY can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%).

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%).

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal:* pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular*: blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal*: pancreatitis (1.3%); *other*

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## IMPORTANT SAFETY INFORMATION (continued)

*(hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

**Infusion-Related Reactions**

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30- minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

**Complications of Allogeneic Hematopoietic Stem Cell Transplantation**

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

**Embryo-Fetal Toxicity**

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

**Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone**

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**Lactation**

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

**Serious Adverse Reactions**

In Checkmate 816, serious adverse reactions occurred in 30% of patients (n=176) who were treated with OPDIVO in combination with platinum-doublet chemotherapy. Serious adverse reactions in >2% included pneumonia and vomiting. No fatal adverse reactions occurred in patients who received OPDIVO in combination with platinum-doublet chemotherapy. In Checkmate 77T, serious adverse reactions occurred in 21% of patients who received OPDIVO in combination with platinum-doublet chemotherapy as neoadjuvant treatment (n=228). The most frequent (≥2%) serious adverse reactions was pneumonia. Fatal adverse reactions occurred in 2.2% of patients, due to cerebrovascular accident, COVID-19 infection, hemoptysis, pneumonia, and pneumonitis (0.4% each). In the adjuvant phase of Checkmate 77T,

(continued on next page)





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Non-Small Cell Lung Cancer (NSCLC): Metastatic/Recurrent or Early-Stage

## IMPORTANT SAFETY INFORMATION (continued)

22% of patients experienced serious adverse reactions (n=142). The most frequent serious adverse reaction was pneumonitis/ILD (2.8%). One fatal adverse reaction due to COVID-19 occurred. In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. In Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 057, fatal adverse reactions occurred; these included events of infection (7 patients, including one case of *Pneumocystis jirovecii* pneumonia), pulmonary embolism (4 patients), and limbic encephalitis (1 patient).

### Common Adverse Reactions

In Checkmate 816, the most common (>20%) adverse reactions in the OPDIVO plus chemotherapy arm (n=176) were nausea (38%), constipation (34%), fatigue (26%), decreased appetite (20%), and rash (20%). In Checkmate 77T, the most common adverse reactions (reported in ≥20%) in patients receiving OPDIVO in combination with chemotherapy (n= 228) were anemia (39.5%), constipation (32.0%), nausea (28.9%), fatigue (28.1%), alopecia (25.9%), and cough (21.9%). In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

### Surgery Related Adverse Reactions

In Checkmate 77T, 5.3% (n=12) of the OPDIVO-treated patients who received neoadjuvant treatment, did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery in OPDIVO- treated patients were cerebrovascular accident, pneumonia, and colitis/diarrhea (2 patients each) and acute coronary syndrome, myocarditis, hemoptysis, pneumonitis, COVID-19, and myositis (1 patient each).

Please see US Full Prescribing Information for OPDIVO and YERVOY

### Clinical Trials and Patient Populations

Checkmate 227—previously untreated metastatic non-small cell lung cancer, in combination with YERVOY; Checkmate 9LA–previously untreated recurrent or metastatic non-small cell lung cancer in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy by histology; Checkmate 017–second-line treatment of metastatic squamous non-small cell lung cancer; Checkmate 057–second-line treatment of metastatic non- squamous non-small cell lung cancer; Checkmate 816–neoadjuvant non-small cell lung cancer, in combination with platinum-doublet chemotherapy; Checkmate 77T–Neoadjuvant treatment with platinum-doublet chemotherapy for non-small cell lung cancer followed by single-agent OPDIVO as adjuvant treatment after surgery.

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March 2024. **2.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. May 2022. **3.** Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol.* 2018;29(11):2208-2213. **4.** American Medical Association. 2020 ICD-10-CM: The Complete Official Codebook. Chicago, IL: *American Medical Association*; 2024.







OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# 1L Unresectable Malignant Pleural Mesothelioma (uMPM)

## INDICATION

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM).

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

# 1L Unresectable Malignant Pleural Mesothelioma (uMPM)

## RECOMMENDED DOSING

### 1L Unresectable Malignant Pleural Mesothelioma[1,2]

| OPDIVO® (nivolumab) + YERVOY® (ipilimumab) | | | |
|---|---|---|---|
| **DOSING & SCHEDULE*†** | | | **DURATION** |
| **360 mg of OPDIVO**<br>IV infusion over<br>30 minutes q3w | **WITH** | **1 mg/kg of YERVOY**<br>IV infusion over<br>30 minutes q6w | In combination with YERVOY until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression |
| **Administer OPDIVO first, followed by YERVOY on the same day.** | | | |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO or OPDIVO + YERVOY in patients with severe or life-threatening infusion-related reactions.[1]

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**

IV=intravenous; q3w=every 3 weeks; q6w=every 6 weeks.

# 1L Unresectable Malignant Pleural Mesothelioma (uMPM)

## ICD-10-CM CODES[3]

| C45 | Mesothelioma |
|---|---|
| C45.0 | Malignant mesothelioma of pleura |

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[3]:

| Z51.12 | Encounter for antineoplastic immunotherapy |
|---|---|

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.







OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# 1L Unresectable Malignant Pleural Mesothelioma (uMPM)

## IMPORTANT SAFETY INFORMATION

**Severe and Fatal Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-Mediated Colitis

OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis.

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# 1L Unresectable Malignant Pleural Mesothelioma (uMPM)

## IMPORTANT SAFETY INFORMATION (continued)

or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO and YERVOY can cause immune-mediated nephritis.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal*: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular:* blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal:* pancreatitis (1.3%); *other (hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# 1L Unresectable Malignant Pleural Mesothelioma (uMPM)

## IMPORTANT SAFETY INFORMATION (continued)

### Infusion-Related Reactions

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In MPM patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, infusion-related reactions occurred in 12% (37/300) of patients.

### Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

### Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

### Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

### Lactation

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

### Serious Adverse Reactions

In Checkmate 743, serious adverse reactions occurred in 54% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis, and encephalitis.

### Common Adverse Reactions

In Checkmate 743, the most common adverse reactions (≥20%) in patients receiving OPDIVO plus YERVOY were fatigue (43%), musculoskeletal pain (38%), rash (34%), diarrhea (32%), dyspnea (27%), nausea (24%), decreased appetite (24%), cough (23%), and pruritus (21%).

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March 2024. **2.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. May 2022. **3.** American Medical Association. 2024 ICD-10-CM: The Complete Official Codebook. Chicago, IL: *American Medical Association*; 2024.







OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Renal Cell Carcinoma (RCC): Advanced

## INDICATIONS

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

OPDIVO® (nivolumab), in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Renal Cell Carcinoma (RCC): Advanced

## RECOMMENDED DOSING

### Advanced Renal Cell Carcinoma[1,2]

| OPDIVO® (nivolumab) + YERVOY® (ipilimumab) | | | |
|---|---|---|---|
| **DOSING & SCHEDULE*†** | | | **DURATION** |
| **Induction phase*† (weight-based)** | | | |
| **3 mg/kg of OPDIVO**<br>IV infusion over<br>30 minutes q3w | **WITH** | **1 mg/kg of YERVOY**<br>IV infusion over<br>30 minutes q3w | In combination with YERVOY for 4 doses, or<br>until disease progression or unacceptable toxicity |
| **Maintenance phase** | | | |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | **OR** | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease progression or unacceptable toxicity |
| **After completing 4 doses of the combination in the induction phase, administer OPDIVO as a single agent.** | | | |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO or OPDIVO + YERVOY in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[3]

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# Renal Cell Carcinoma (RCC): Advanced

## RECOMMENDED DOSING (continued)

### Advanced Renal Cell Carcinoma[1]

| OPDIVO® (nivolumab) + cabozantinib | |
|---|---|
| **DOSING & SCHEDULE**[*†] | **DURATION** |
| **OPDIVO** | |
| **240 mg of OPDIVO** IV infusion over 30 minutes q2w **OR** **480 mg of OPDIVO** IV infusion over 30 minutes q4w | Until disease progression, unacceptable toxicity, or up to 2 years |
| **Cabozantinib** | |
| ADMINISTER OPDIVO IN COMBINATION WITH **40 mg cabozantinib orally once daily without food** | Until disease progression or unacceptable toxicity |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[3]

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# Renal Cell Carcinoma (RCC): Advanced

## RECOMMENDED DOSING (continued)

### Advanced Renal Cell Carcinoma[1]

**OPDIVO® (nivolumab) monotherapy**

| DOSING & SCHEDULE*† | | | DURATION |
|---|---|---|---|
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | OR | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease progression or unacceptable toxicity |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[3]

IV=intravenous; q2w=every 2 weeks; q3w=every 3 weeks; q4w=every 4 weeks.

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Renal Cell Carcinoma (RCC): Advanced

## ICD-10-CM CODES[4]

| | |
|---|---|
| **C64** | **Malignant neoplasm of kidney, except renal pelvis** |
| C64.1 | Malignant neoplasm of right kidney, except renal pelvis |
| C64.2 | Malignant neoplasm of left kidney, except renal pelvis |
| C64.9 | Malignant neoplasm of unspecified kidney, except renal pelvis |
| **C65** | **Malignant neoplasm of renal pelvis** |
| C65.1 | Malignant neoplasm of right renal pelvis |
| C65.2 | Malignant neoplasm of left renal pelvis |
| C65.9 | Malignant neoplasm of unspecified renal pelvis |

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[4]:

| | |
|---|---|
| Z51.12 | Encounter for antineoplastic immunotherapy |

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Renal Cell Carcinoma (RCC): Advanced

## IMPORTANT SAFETY INFORMATION

### Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

#### Immune-Mediated Pneumonitis

OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 3.9% (26/666) of patients, including Grade 3 (1.4%) and Grade 2 (2.6%).

#### Immune-Mediated Colitis

OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated colitis occurred in 9% (60/666) of patients, including Grade 3 (4.4%) and Grade 2 (3.7%).

#### Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 7% (48/666) of patients, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%).

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# Renal Cell Carcinoma (RCC): Advanced

## IMPORTANT SAFETY INFORMATION (continued)

OPDIVO in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to OPDIVO alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. In patients receiving OPDIVO and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% of patients.

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, adrenal insufficiency occurred in 7% (48/666) of patients, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%). In patients receiving OPDIVO and cabozantinib, adrenal insufficiency occurred in 4.7% (15/320) of patients, including Grade 3 (2.2%) and Grade 2 (1.9%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).

In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypophysitis occurred in 4.4% (29/666) of patients, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%).

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, thyroiditis occurred in 2.7% (22/666) of patients, including Grade 3 (4.5%) and Grade 2 (2.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hyperthyroidism occurred in 12% (80/666) of patients, including Grade 3 (0.6%) and Grade 2 (4.5%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypothyroidism occurred in 18% (122/666) of patients, including Grade 3 (0.6%) and Grade 2 (11%).

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, diabetes occurred in 2.7% (15/666) of patients, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2 (0.9%).

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OPDIVO® (nivolumab)
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# Renal Cell Carcinoma (RCC): Advanced

## IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO and YERVOY can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated nephritis with renal dysfunction occurred in 4.1% (27/666) of patients, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%).

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated rash occurred in 16% (108/666) of patients, including Grade 3 (3.5%) and Grade 2 (4.2%).

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal*: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular:* blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal*: pancreatitis (1.3%); *other (hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%),

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## IMPORTANT SAFETY INFORMATION (continued)

erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

### Infusion-Related Reactions

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, infusion-related reactions occurred in 5.1% (28/547) of patients.

### Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

### Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

### Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

### Lactation

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the

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## IMPORTANT SAFETY INFORMATION (continued)

potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

### Serious Adverse Reactions

In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis. In Checkmate 9ER, serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib (n=320). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia.

### Common Adverse Reactions

In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), dyspnea (20%), and vomiting (20%). In Checkmate 9ER, the most common adverse reactions (≥20%) in patients receiving OPDIVO and cabozantinib (n=320) were diarrhea (64%), fatigue (51%), hepatotoxicity (44%), palmar-plantar erythrodysaesthesia syndrome (40%), stomatitis (37%), rash (36%), hypertension (36%), hypothyroidism (34%), musculoskeletal pain (33%), decreased appetite (28%), nausea (27%), dysgeusia (24%), abdominal pain (22%), cough (20%), and upper respiratory tract infection (20%). In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were fatigue (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%).

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March 2024. **2.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. May 2022. **3.** Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol.* 2018;29(11):2208-2213. **4.** American Medical Association. *2024 ICD-10-CM: The Complete Official Codebook.* Chicago, IL: American Medical Association; 2024.







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# Relapsed or Progressed Classical Hodgkin Lymphoma (cHL)

## INDICATION

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin or after 3 or more lines of systemic therapy that includes autologous HSCT. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO is associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.





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# Relapsed or Progressed Classical Hodgkin Lymphoma (cHL)

## RECOMMENDED DOSING

### Relapsed or Progressed Classical Hodgkin Lymphoma[1]

| OPDIVO® (nivolumab) monotherapy | | | |
|---|---|---|---|
| DOSING & SCHEDULE*† | | | DURATION |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | OR | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease progression or unacceptable toxicity |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**

IV=intravenous; q2w=every 2 weeks; q4w=every 4 weeks.

# Relapsed or Progressed Classical Hodgkin Lymphoma (cHL)

## ICD-10-CM CODES[3]

| C81 | Hodgkin lymphoma |
|---|---|
| C81.1 | Nodular sclerosis Hodgkin lymphoma* |
| C81.10 | Nodular sclerosis Hodgkin lymphoma, unspecified site |
| C81.11 | Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck |
| C81.12 | Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes |
| C81.13 | Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes |
| C81.14 | Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb |
| C81.15 | Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb |
| C81.16 | Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes |
| C81.17 | Nodular sclerosis Hodgkin lymphoma, spleen |
| C81.18 | Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites |
| C81.19 | Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites |
| C81.2 | Mixed cellularity Hodgkin lymphoma* |
| C81.20 | Mixed cellularity Hodgkin lymphoma, unspecified site |
| C81.21 | Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck |
| C81.22 | Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes |
| C81.23 | Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes |
| C81.24 | Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb |
| C81.25 | Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb |
| C81.26 | Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes |
| C81.27 | Mixed cellularity Hodgkin lymphoma, spleen |
| C81.28 | Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites |
| C81.29 | Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites |

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

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The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.





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# Relapsed or Progressed Classical Hodgkin Lymphoma (cHL)

## ICD-10-CM CODES[3] (continued)

| | |
|---|---|
| C81.3 | Lymphocyte-depleted Hodgkin lymphoma* |
| C81.30 | Lymphocyte-depleted Hodgkin lymphoma, unspecified site |
| C81.31 | Lymphocyte-depleted Hodgkin lymphoma, lymph nodes of head, face, and neck |
| C81.32 | Lymphocyte-depleted Hodgkin lymphoma, intrathoracic lymph nodes |
| C81.33 | Lymphocyte-depleted Hodgkin lymphoma, intra-abdominal lymph nodes |
| C81.34 | Lymphocyte-depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb |
| C81.35 | Lymphocyte-depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb |
| C81.36 | Lymphocyte-depleted Hodgkin lymphoma, intrapelvic lymph nodes |
| C81.37 | Lymphocyte-depleted Hodgkin lymphoma, spleen |
| C81.38 | Lymphocyte-depleted Hodgkin lymphoma, lymph nodes of multiple sites |
| C81.39 | Lymphocyte-depleted Hodgkin lymphoma, extranodal and solid organ sites |
| C81.4 | Lymphocyte-rich Hodgkin lymphoma* |
| C81.40 | Lymphocyte-rich Hodgkin lymphoma, unspecified site |
| C81.41 | Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck |
| C81.42 | Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes |
| C81.43 | Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes |
| C81.44 | Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb |
| C81.45 | Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb |
| C81.46 | Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes |
| C81.47 | Lymphocyte-rich Hodgkin lymphoma, spleen |
| C81.48 | Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites |
| C81.49 | Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites |

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

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# Relapsed or Progressed Classical Hodgkin Lymphoma (cHL)

## ICD-10-CM CODES[3] (continued)

| | |
|---|---|
| C81.7 | Other Hodgkin lymphoma* |
| C81.70 | Other Hodgkin lymphoma, unspecified site |
| C81.71 | Other Hodgkin lymphoma, lymph nodes of head, face, and neck |
| C81.72 | Other Hodgkin lymphoma, intrathoracic lymph nodes |
| C81.73 | Other Hodgkin lymphoma, intra-abdominal lymph nodes |
| C81.74 | Other Hodgkin lymphoma, lymph nodes of axilla and upper limb |
| C81.75 | Other Hodgkin lymphoma, lymph nodes of inguinal region and lower limb |
| C81.76 | Other Hodgkin lymphoma, intrapelvic lymph nodes |
| C81.77 | Other Hodgkin lymphoma, spleen |
| C81.78 | Other Hodgkin lymphoma, lymph nodes of multiple sites |
| C81.79 | Other Hodgkin lymphoma, extranodal and solid organ sites |

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

For patients who have had a stem cell transplant, add the following as a secondary code[3]:

| | |
|---|---|
| Z94.84 | Stem cells transplant status |

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[3]:

| | |
|---|---|
| Z51.12 | Encounter for antineoplastic immunotherapy |

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.

# Relapsed or Progressed Classical Hodgkin Lymphoma (cHL)

## IMPORTANT SAFETY INFORMATION

**Severe and Fatal Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO. Early identification and management are essential to ensure safe use of OPDIVO. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment with OPDIVO. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%).

In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO, including Grade 3 (n=1) and Grade 2 (n=12).

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

Immune-Mediated Endocrinopathies

OPDIVO can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and

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# Relapsed or Progressed Classical Hodgkin Lymphoma (cHL)

## IMPORTANT SAFETY INFORMATION (continued)

symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%).

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis.

### Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%).

### Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%).

### Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular:* uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal:* pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine:* hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Relapsed or Progressed Classical Hodgkin Lymphoma (cHL)

## IMPORTANT SAFETY INFORMATION (continued)

### Infusion-Related Reactions

OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

### Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO prior to or after an allogeneic HSCT.

### Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose.

### Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

### Lactation

There are no data on the presence of OPDIVO in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

### Serious Adverse Reactions

In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT.

### Common Adverse Reactions

In Checkmate 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%).

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March 2024. **2.** Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol*. 2018;29(11):2208-2213. **3.** American Medical Association. *2024 ICD-10-CM: The Complete Official Codebook.* Chicago, IL: American Medical Association; 2024.

**Please see Important Safety Information for OPDIVO and YERVOY® (ipilimumab), and US Full Prescribing Information for OPDIVO and YERVOY.**
**For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday-Friday, or visit www.BMSAccessSupport.com.**





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## INDICATION

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO is associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## RECOMMENDED DOSING

### Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck[1]

| OPDIVO® (nivolumab) monotherapy | |
|---|---|
| **DOSING & SCHEDULE*†** | **DURATION** |
| **240 mg of OPDIVO** IV infusion over 30 minutes q2w **OR** **480 mg of OPDIVO** IV infusion over 30 minutes q4w | Until disease progression or unacceptable toxicity |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**

IV=intravenous; q2w=every 2 weeks; q4w=every 4 weeks.

# Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## ICD-10-CM CODES[3]

| | |
|---|---|
| **C00** | **Malignant neoplasm of lip** |
| C00.0 | Malignant neoplasm of external upper lip |
| C00.1 | Malignant neoplasm of external lower lip |
| C00.2 | Malignant neoplasm of external lip, unspecified |
| C00.3 | Malignant neoplasm of upper lip, inner aspect |
| C00.4 | Malignant neoplasm of lower lip, inner aspect |
| C00.5 | Malignant neoplasm of lip, unspecified, inner aspect |
| C00.6 | Malignant neoplasm of commissure of lip, unspecified |
| C00.8 | Malignant neoplasm of overlapping sites of lip |
| C00.9 | Malignant neoplasm of lip, unspecified |
| **C01** | **Malignant neoplasm of base of tongue** |
| **C02** | **Malignant neoplasm of other and unspecified parts of tongue** |
| C02.0 | Malignant neoplasm of dorsal surface of tongue |
| C02.1 | Malignant neoplasm of border of tongue |
| C02.2 | Malignant neoplasm of ventral surface of tongue |
| C02.3 | Malignant neoplasm of anterior two-thirds of tongue, part unspecified |
| C02.4 | Malignant neoplasm of lingual tonsil |
| C02.8 | Malignant neoplasm of overlapping sites of tongue |
| C02.9 | Malignant neoplasm of tongue, unspecified |
| **C03** | **Malignant neoplasm of gum** |
| C03.0 | Malignant neoplasm of upper gum |
| C03.1 | Malignant neoplasm of lower gum |
| C03.9 | Malignant neoplasm of gum, unspecified |

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# Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## ICD-10-CM CODES[3] (continued)

| | |
|---|---|
| **C04** | **Malignant neoplasm of floor of mouth** |
| C04.0 | Malignant neoplasm of anterior floor of mouth |
| C04.1 | Malignant neoplasm of lateral floor of mouth |
| C04.8 | Malignant neoplasm of overlapping sites of floor of mouth |
| C04.9 | Malignant neoplasm of floor of mouth, unspecified |
| **C05** | **Malignant neoplasm of palate** |
| C05.0 | Malignant neoplasm of hard palate |
| C05.1 | Malignant neoplasm of soft palate |
| C05.2 | Malignant neoplasm of uvula |
| C05.8 | Malignant neoplasm of overlapping sites of palate |
| C05.9 | Malignant neoplasm of palate, unspecified |
| **C06** | **Malignant neoplasm of other and unspecified parts of mouth** |
| C06.0 | Malignant neoplasm of cheek mucosa |
| C06.1 | Malignant neoplasm of vestibule of mouth |
| C06.2 | Malignant neoplasm of retromolar area |
| C06.8 | Malignant neoplasm of overlapping sites of other and unspecified parts of the mouth* |
| C06.80 | Malignant neoplasm of overlapping sites of unspecified parts of mouth |
| C06.89 | Malignant neoplasm of overlapping sites of other parts of mouth |
| C06.9 | Malignant neoplasm of mouth, unspecified |
| **C09** | **Malignant neoplasm of tonsil** |
| C09.0 | Malignant neoplasm of tonsillar fossa |
| C09.1 | Malignant neoplasm of tonsillar pillar (anterior) (posterior) |
| C09.8 | Malignant neoplasm of overlapping sites of tonsil |
| C09.9 | Malignant neoplasm of tonsil, unspecified |

*This is a category code and is invalid for stand-alone use. Please select one of the expanded codes listed below.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## ICD-10-CM CODES[3] (continued)

| | |
|---|---|
| **C10** | **Malignant neoplasm of oropharynx** |
| C10.0 | Malignant neoplasm of vallecula |
| C10.1 | Malignant neoplasm of anterior surface of epiglottis |
| C10.2 | Malignant neoplasm of lateral wall of oropharynx |
| C10.3 | Malignant neoplasm of posterior wall of oropharynx |
| C10.4 | Malignant neoplasm of branchial cleft |
| C10.8 | Malignant neoplasm of overlapping sites of oropharynx |
| **C12** | **Malignant neoplasm of pyriform sinus** |
| **C13** | **Malignant neoplasm of hypopharynx** |
| C13.0 | Malignant neoplasm of postcricoid region |
| C13.1 | Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect |
| C13.2 | Malignant neoplasm of posterior wall of hypopharynx |
| C13.8 | Malignant neoplasm of overlapping sites of hypopharynx |
| C13.9 | Malignant neoplasm of hypopharynx, unspecified |
| **C14** | **Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx** |
| C14.0 | Malignant neoplasm of pharynx, unspecified |
| C14.2 | Malignant neoplasm of Waldeyer's ring |
| C14.8 | Malignant neoplasm of overlapping sites of lip, oral cavity and pharynx |

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# Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## ICD-10-CM CODES[3] (continued)

| | |
|---|---|
| **C32** | **Malignant neoplasm of larynx** |
| C32.0 | Malignant neoplasm of glottis |
| C32.1 | Malignant neoplasm of supraglottis |
| C32.2 | Malignant neoplasm of subglottis |
| C32.3 | Malignant neoplasm of laryngeal cartilage |
| C32.8 | Malignant neoplasm of overlapping sites of larynx |
| C32.9 | Malignant neoplasm of larynx, unspecified |
| **C76** | **Malignant neoplasm of other and ill-defined sites** |
| C76.0 | Malignant neoplasm of head, face and neck |

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[3]:

| | |
|---|---|
| Z51.12 | Encounter for antineoplastic immunotherapy |

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.

# Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## IMPORTANT SAFETY INFORMATION

**Severe and Fatal Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO. Early identification and management are essential to ensure safe use of OPDIVO. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment with OPDIVO. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%).

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid- refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

Immune-Mediated Endocrinopathies

OPDIVO can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune- mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## IMPORTANT SAFETY INFORMATION (continued)

treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%).

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%).

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%).

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; n*ervous system:* meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal:* pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune):* hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

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# Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

## IMPORTANT SAFETY INFORMATION (continued)

### Infusion-Related Reactions

OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

### Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO prior to or after an allogeneic HSCT.

### Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose.

### Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

### Lactation

There are no data on the presence of OPDIVO in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

### Serious Adverse Reactions

In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=236). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis.

### Common Adverse Reactions

In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO (n=236) were cough (14%) and dyspnea (14%) at a higher incidence than investigator's choice.

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March 2024. **2.** Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol*. 2018;29(11):2208-2213. **3.** American Medical Association. *2024 ICD-10-CM: The Complete Official Codebook*. Chicago, IL: American Medical Association; 2024.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Urothelial Carcinoma (UC): Locally Advanced or Metastatic and Adjuvant Therapy

## INDICATIONS

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma 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.

OPDIVO® (nivolumab), as a single agent, is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.

OPDIVO® (nivolumab), in combination with cisplatin and gemcitabine, is indicated as first-line treatment for adult patients with unresectable or metastatic urothelial carcinoma.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO is associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Urothelial Carcinoma (UC): Locally Advanced or Metastatic and Adjuvant Therapy

## RECOMMENDED DOSING

### Locally Advanced or Metastatic Urothelial Carcinoma[1]

| OPDIVO® (nivolumab) monotherapy | | | |
|---|---|---|---|
| DOSING & SCHEDULE*† | | | DURATION |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | OR | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease progression or unacceptable toxicity |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Urothelial Carcinoma (UC): Locally Advanced or Metastatic and Adjuvant Therapy

## RECOMMENDED DOSING (continued)

### Adjuvant Treatment of Urothelial Carcinoma[1]

| OPDIVO® (nivolumab) monotherapy | | |
|---|---|---|
| DOSING & SCHEDULE*† | | DURATION |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | OR | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease recurrence or unacceptable toxicity for up to 1 year |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**

IV=intravenous; q2w=every 2 weeks; q4w=every 4 weeks.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Urothelial Carcinoma (UC): Locally Advanced or Metastatic and Adjuvant Therapy

## RECOMMENDED DOSING

### 1L Unresectable or Metastatic Urothelial carcinoma.[1]

**OPDIVO® + Cisplatin and Gemcitabine**
Dosing for adult patients

| DOSING & SCHEDULE*†‡ | | | DURATION |
|---|---|---|---|
| **Combination phase** | | | |
| **360 mg of OPDIVO**<br>IV infusion over<br>30 minutes q3w | WITH | **Cisplatin and Gemcitabine**<br>on the same day q3w | In combination with cisplatin and gemcitabine for up to 6 cycles |
| **Maintenance phase** | | | |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | OR | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | After completing up to 6 cycles of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years from first dose |

Please see Important Safety Information for OPDIVO and YERVOY® (ipilimumab), and US Full Prescribing Information for OPDIVO and YERVOY.
For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday-Friday, or visit www.BMSAccessSupport.com.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Urothelial Carcinoma (UC): Locally Advanced or Metastatic and Adjuvant Therapy

## ICD-10-CM CODES[3]

| | |
|---|---|
| **C65** | **Malignant neoplasm of renal pelvis** |
| C65.1 | Malignant neoplasm of the right renal pelvis |
| C65.2 | Malignant neoplasm of the left renal pelvis |
| C65.9 | Malignant neoplasm of unspecified renal pelvis |
| **C66** | **Malignant neoplasm of ureter** |
| C66.1 | Malignant neoplasm of the right ureter |
| C66.2 | Malignant neoplasm of the left ureter |
| C66.9 | Malignant neoplasm of unspecified ureter |
| **C67** | **Malignant neoplasm of bladder** |
| C67.0 | Malignant neoplasm of trigone of bladder |
| C67.1 | Malignant neoplasm of dome of bladder |
| C67.2 | Malignant neoplasm of lateral wall of bladder |
| C67.3 | Malignant neoplasm of anterior wall of bladder |
| C67.4 | Malignant neoplasm of posterior wall of bladder |
| C67.5 | Malignant neoplasm of bladder neck |
| C67.6 | Malignant neoplasm of ureteric orifice |
| C67.8 | Malignant neoplasm of overlapping sites of bladder |
| C67.9 | Malignant neoplasm of bladder, unspecified |
| **C68** | **Malignant neoplasm of other and unspecified urinary organ** |
| C68.0 | Malignant neoplasm of urethra |
| C68.8 | Malignant neoplasm of overlapping sites of urinary organs |
| C68.9 | Malignant neoplasm of urinary organ, unspecified |

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[3]:

| | |
|---|---|
| Z51.12 | Encounter for antineoplastic immunotherapy |

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.





OPDIVO® (nivolumab)
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# Urothelial Carcinoma (UC): Locally Advanced or Metastatic and Adjuvant Therapy

## IMPORTANT SAFETY INFORMATION

### Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO. Early identification and management are essential to ensure safe use of OPDIVO. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment with OPDIVO. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%).

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

Immune-Mediated Endocrinopathies

OPDIVO can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).

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OPDIVO® (nivolumab)
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# Urothelial Carcinoma (UC): Locally Advanced or Metastatic and Adjuvant Therapy

## IMPORTANT SAFETY INFORMATION (continued)

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%).

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%).

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

Withhold or permanently discontinue OPDIVO depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%).

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or were reported with the use of other PD- 1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal*: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

**Infusion-Related Reactions**

OPDIVO can cause severe infusion-related reactions. Discontinue OPDIVO in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-

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OPDIVO® (nivolumab)
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# Urothelial Carcinoma (UC): Locally Advanced or Metastatic and Adjuvant Therapy

## IMPORTANT SAFETY INFORMATION (continued)

experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

**Complications of Allogeneic Hematopoietic Stem Cell Transplantation**

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO prior to or after an allogeneic HSCT.

**Embryo-Fetal Toxicity**

Based on its mechanism of action and findings from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose.

**Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone**

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**Lactation**

There are no data on the presence of OPDIVO in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

**Serious Adverse Reactions**

In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. In Checkmate 274, serious adverse reactions occurred in 30% of patients receiving OPDIVO (n=351). The most frequent serious adverse reaction reported in ≥2% of patients receiving OPDIVO was urinary tract infection. Fatal adverse reactions occurred in 1% of patients; these included events of pneumonitis (0.6%). In Checkmate 901, serious adverse reactions occurred in 48% of patients receiving OPDIVO in combination with chemotherapy. The most frequent serious adverse reactions reporting in ≥2% of patients who received OPDIVO with chemotherapy were urinary tract infection (4.9%), acute kidney injury (4.3%), anemia (3%), pulmonary embolism (2.6%), sepsis (2.3%), and platelet count decreased (2.3%). Fatal adverse reactions occurred in 3.6% of patients who received OPDIVO in combination with chemotherapy; these included sepsis (1%). OPDIVO and/or chemotherapy were discontinued in 30% of patients and were delayed in 67% of patients for an adverse reaction.

**Common Adverse Reactions**

In Checkmate 275, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). In Checkmate 274, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=351) were rash (36%), fatigue (36%), diarrhea (30%), pruritus (30%), musculoskeletal pain (28%), and urinary tract infection (22%). In Checkmate 901, the most common adverse reactions (≥20%) were nausea, fatigue, musculoskeletal pain, constipation, decreased appetite, rash, vomiting, and peripheral neuropathy.

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March 2024. **2.** Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol.* 2018;29(11):2208-2213. **3.** American Medical Association. *2024 ICD-10 CM: The Complete Official Codebook.* Chicago, IL: American Medical Association; 2024.

**Please see Important Safety Information for OPDIVO and YERVOY® (ipilimumab), and US Full Prescribing Information for OPDIVO and YERVOY.**
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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# MSI-H/dMMR Metastatic Colorectal Cancer

## INDICATIONS

OPDIVO® (nivolumab), as a single agent, is indicated for the treatment of 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. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of adults and pediatric patients 12 years and older 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. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# MSI-H/dMMR Metastatic Colorectal Cancer

## RECOMMENDED DOSING

### MSI-H/dMMR Metastatic Colorectal Cancer[1]

**Dosing for adult and pediatric patients aged 12 and older and weighing 40 kg or more**

| OPDIVO® (nivolumab) + YERVOY® (ipilimumab) | | | |
|---|---|---|---|
| **DOSING & SCHEDULE*†‡** | | | **DURATION** |
| **Induction phase (weight-based)** | | | |
| **3 mg/kg of OPDIVO**<br>IV infusion over<br>30 minutes q3w | **WITH** | **1 mg/kg of YERVOY**<br>IV infusion over<br>30 minutes q3w | In combination with YERVOY for 4 doses |
| **Maintenance phase** | | | |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | **OR** | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease progression or unacceptable toxicity |

**Administer OPDIVO first, followed by YERVOY on the same day.**
**After completing 4 doses of the combination in the induction phase, administer OPDIVO as a single agent.**

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO or OPDIVO + YERVOY in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# MSI-H/dMMR Metastatic Colorectal Cancer

## RECOMMENDED DOSING (continued)

### MSI-H/dMMR Metastatic Colorectal Cancer[1]

**Dosing for adult and pediatric patients aged 12 and older and weighing 40 kg or more**

| OPDIVO® (nivolumab) monotherapy | | | |
|---|---|---|---|
| DOSING & SCHEDULE*† | | | DURATION |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | OR | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease progression or unacceptable toxicity |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO or OPDIVO + YERVOY in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

IV=intravenous; q2w=every 2 weeks; q3w=every 3 weeks; q4w=every 4 weeks.

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**





OPDIVO® (nivolumab)
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# MSI-H/dMMR Metastatic Colorectal Cancer

## ICD-10-CM CODES[3]

| | |
|---|---|
| **C18** | **Malignant neoplasm of colon** |
| C18.0 | Malignant neoplasm of cecum |
| C18.1 | Malignant neoplasm of appendix |
| C18.2 | Malignant neoplasm of ascending colon |
| C18.3 | Malignant neoplasm of hepatic flexure |
| C18.4 | Malignant neoplasm of transverse colon |
| C18.5 | Malignant neoplasm of splenic flexure |
| C18.6 | Malignant neoplasm of descending colon |
| C18.7 | Malignant neoplasm of sigmoid colon |
| C18.8 | Malignant neoplasm of overlapping sites of colon |
| C18.9 | Malignant neoplasm of colon, unspecified |
| **C19** | **Malignant neoplasm of rectosigmoid junction** |
| **C20** | **Malignant neoplasm of rectum** |

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[3]:

| | |
|---|---|
| Z51.12 | Encounter for antineoplastic immunotherapy |

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.





OPDIVO® (nivolumab)
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# MSI-H/dMMR Metastatic Colorectal Cancer

## IMPORTANT SAFETY INFORMATION

**Severe and Fatal Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 3.9% (26/666) of patients, including Grade 3 (1.4%) and Grade 2 (2.6%).

Immune-Mediated Colitis

OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated colitis occurred in 9% (60/666) of patients, including Grade 3 (4.4%) and Grade 2 (3.7%).

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients

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## IMPORTANT SAFETY INFORMATION (continued)

receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 7% (48/666) of patients, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%).

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, adrenal insufficiency occurred in 7% (48/666) of patients, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).

In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypophysitis occurred in 4.4% (29/666) of patients, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%).

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, thyroiditis occurred in 2.7% (22/666) of patients, including Grade 3 (4.5%) and Grade 2 (2.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hyperthyroidism occurred in 12% (80/666) of patients, including Grade 3 (0.6%) and Grade 2 (4.5%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypothyroidism occurred in 18% (122/666) of patients, including Grade 3 (0.6%) and Grade 2 (11%).

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OPDIVO® (nivolumab)
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# MSI-H/dMMR Metastatic Colorectal Cancer

## IMPORTANT SAFETY INFORMATION (continued)

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, diabetes occurred in 2.7% (15/666) of patients, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2 (0.9%).

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO and YERVOY can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated nephritis with renal dysfunction occurred in 4.1% (27/666) of patients, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%).

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated rash occurred in 16% (108/666) of patients, including Grade 3 (3.5%) and Grade 2 (4.2%).

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal:* pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine:* hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

## IMPORTANT SAFETY INFORMATION (continued)

purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular*: blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal*: pancreatitis (1.3%); *other (hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

### Infusion-Related Reactions

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, infusion-related reactions occurred in 4.2% (5/119) of patients.

### Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# MSI-H/dMMR Metastatic Colorectal Cancer

## IMPORTANT SAFETY INFORMATION (continued)

### Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

### Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

### Lactation

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

### Serious Adverse Reactions

In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=119), serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration.

### Common Adverse Reactions

In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent (n=74), the most common adverse reactions (≥20%) were fatigue (54%), diarrhea (43%), abdominal pain (34%), nausea (34%), vomiting (28%), musculoskeletal pain (28%), cough (26%), pyrexia (24%), rash (23%), constipation (20%), and upper respiratory tract infection (20%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=119), the most common adverse reactions (≥20%) were fatigue (49%), diarrhea (45%), pyrexia (36%), musculoskeletal pain (36%), abdominal pain (30%), pruritus (28%), nausea (26%), rash (25%), decreased appetite (20%), and vomiting (20%).

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March 2024. **2.** Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol.* 2018;29(11):2208-2213. **3.** American Medical Association. *2024 ICD-10 CM: The Complete Official Codebook.* Chicago, IL: American Medical Association; 2024.







OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Advanced Hepatocellular Carcinoma (HCC)

## INDICATION

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Advanced Hepatocellular Carcinoma (HCC)

## RECOMMENDED DOSING

### Advanced Hepatocellular Carcinoma[1]

| OPDIVO® (nivolumab) + YERVOY® (ipilimumab) | | | |
|---|---|---|---|
| **DOSING & SCHEDULE*†‡** | | | **DURATION** |
| **Induction phase (weight-based)** | | | |
| **1 mg/kg of OPDIVO**<br>IV infusion over<br>30 minutes q3w | **WITH** | **3 mg/kg of YERVOY**<br>IV infusion over<br>30 minutes q3w | In combination with YERVOY for 4 doses |
| **Maintenance phase** | | | |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | **OR** | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease progression or unacceptable toxicity |
| **Administer OPDIVO first, followed by YERVOY on the same day.**<br>**After completing 4 doses of the combination in the induction phase, administer OPDIVO as a single agent.** | | | |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO or OPDIVO + YERVOY in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

IV=intravenous; q2w=every 2 weeks; q3w=every 3 weeks; q4w=every 4 weeks.

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Advanced Hepatocellular Carcinoma (HCC)

## ICD-10-CM CODES[3]

| C22 | Malignant neoplasm of liver and intrahepatic bile ducts |
|---|---|
| C22.0 | Liver cell carcinoma (hepatocellular carcinoma, hepatoma) |
| C22.8 | Malignant neoplasm of liver, primary, unspecified as to type |

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[3]:

| Z51.12 | Encounter for antineoplastic immunotherapy |
|---|---|

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.







OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Advanced Hepatocellular Carcinoma (HCC)

## IMPORTANT SAFETY INFORMATION

**Severe and Fatal Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 7% (31/456) of patients, including Grade 4 (0.2%), Grade 3 (2.0%), and Grade 2 (4.4%).

Immune-Mediated Colitis

OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated colitis occurred in 25% (115/456) of patients, including Grade 4 (0.4%), Grade 3 (14%) and Grade 2 (8%).

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 15% (70/456) of patients, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%).

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Advanced Hepatocellular Carcinoma (HCC)

## IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, adrenal insufficiency occurred in 8% (35/456), including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%).

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypophysitis occurred in 9% (42/456), including Grade 3 (2.4%) and Grade 2 (6%).

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hyperthyroidism occurred in 9% (42/456) of patients, including Grade 3 (0.9%) and Grade 2 (4.2%).

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypothyroidism occurred in 20% (91/456) of patients, including Grade 3 (0.4%) and Grade 2 (11%).

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO and YERVOY can cause immune-mediated nephritis.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated rash occurred in 28% (127/456) of patients, including Grade 3 (4.8%) and Grade 2 (10%).

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

## IMPORTANT SAFETY INFORMATION (continued)

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system:* meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; ocular: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal*: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine:* hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular*: blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal*: pancreatitis (1.3%); *other (hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

### Infusion-Related Reactions

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 8% (4/49) of patients.

### Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Advanced Hepatocellular Carcinoma (HCC)

## IMPORTANT SAFETY INFORMATION (continued)

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

### Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

### Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

### Lactation

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

### Serious Adverse Reactions

In Checkmate 040, serious adverse reactions occurred in 59% of patients receiving OPDIVO with YERVOY (n=49). Serious adverse reactions reported in ≥4% of patients were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.

### Common Adverse Reactions

In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO with YERVOY (n=49), were rash (53%), pruritus (53%), musculoskeletal pain (41%), diarrhea (39%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (22%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decreased (20%).

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. March 2024. **2.** Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol.* 2018;29(11):2208-2213. **3.** American Medical Association. *2024 ICD-10 CM: The Complete Official Codebook.* Chicago, IL: American Medical Association; 2024.







OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Gastroesophageal Cancers: Metastatic and Adjuvant

## INDICATIONS

OPDIVO® (nivolumab) is indicated for the treatment of adult patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

OPDIVO® (nivolumab) is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult patients who have received neoadjuvant chemoradiotherapy (CRT).

OPDIVO® (nivolumab), in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC).

OPDIVO® (nivolumab), in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of adult patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

## SELECT IMPORTANT SAFETY INFORMATION

### Summary of Warnings and Precautions

OPDIVO and YERVOY are associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Gastroesophageal Cancers: Metastatic and Adjuvant

## RECOMMENDED DOSING

### Advanced Esophageal Squamous Cell Carcinoma[1]

| OPDIVO® (nivolumab) monotherapy | | | |
|---|---|---|---|
| DOSING & SCHEDULE*† | | | DURATION |
| **240 mg of OPDIVO**<br>IV infusion over<br>30 minutes q2w | OR | **480 mg of OPDIVO**<br>IV infusion over<br>30 minutes q4w | Until disease progression or unacceptable toxicity |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Gastroesophageal Cancers: Metastatic and Adjuvant

## RECOMMENDED DOSING (continued)

### Adjuvant Treatment of Resected Esophageal Carcinoma or Gastroesophageal Junction Cancer[1]

| OPDIVO® (nivolumab) monotherapy | |
|---|---|
| **DOSING & SCHEDULE*†** | **DURATION** |
| **240 mg of OPDIVO** IV infusion over 30 minutes q2w **OR** **480 mg of OPDIVO** IV infusion over 30 minutes q4w | Until disease progression or unacceptable toxicity for a total treatment duration of 1 year |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure-response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Gastroesophageal Cancers: Metastatic and Adjuvant

## RECOMMENDED DOSING (continued)

### Metastatic Esophageal Squamous Cell Carcinoma[1]

| OPDIVO® (nivolumab) with fluoropyrimidine- and platinum-containing chemotherapy | |
|---|---|
| **OPDIVO** | |
| **DOSING & SCHEDULE*†** | **DURATION** |
| **240 mg of OPDIVO** IV infusion over 30 minutes q2w‡ **OR** **480 mg of OPDIVO** IV infusion over 30 minutes q4w‡ | OPDIVO: Until disease progression, unacceptable toxicity, or up to 2 years |
| **Chemotherapy** | |
| Administer OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy | Chemotherapy: Until disease progression or unacceptable toxicity |
| **Administer OPDIVO first, followed by fluoropyrimidine- and platinum-containing chemotherapy on the same day.[1]** | |

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

†Based on exploratory dose-exposure–response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.[2]

‡30-minute intravenous infusion on the same day.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Gastroesophageal Cancers: Metastatic and Adjuvant

## RECOMMENDED DOSING (continued)

### Metastatic Esophageal Squamous Cell Carcinoma[1] (continued)

**OPDIVO® (nivolumab) + YERVOY® (ipilimumab)**

| DOSING & SCHEDULE*†‡ | | DURATION |
|---|---|---|
| **3 mg/kg of OPDIVO**<br>IV infusion over<br>30 minutes q2w‡<br>**OR**<br>**360 mg of OPDIVO**<br>IV infusion over<br>30 minutes q3w‡ | **WITH** | **1 mg/kg of YERVOY**<br>IV infusion over<br>30 minutes q6w | In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years |

**Administer OPDIVO first, followed by YERVOY, on the same day.**

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO or OPDIVO + YERVOY in patients with severe or life-threatening infusion-related reactions.[1]

‡30-minute intravenous infusion on the same day.

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OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Gastroesophageal Cancers: Metastatic and Adjuvant

## RECOMMENDED DOSING (continued)

### Advanced or Metastatic Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinoma[1]

**OPDIVO® (nivolumab) with fluoropyrimidine- and platinum-containing chemotherapy**

| DOSING & SCHEDULE* | | | DURATION |
|---|---|---|---|
| **240 mg of OPDIVO** IV infusion over 30 minutes with fluoropyrimidine- and platinum-containing chemotherapy q2w | OR | **360 mg of OPDIVO** IV infusion over 30 minutes with fluoropyrimidine- and platinum-containing chemotherapy q3w | Until disease progression, unacceptable toxicity, or up to 2 years |

**Administer OPDIVO first, followed by fluoropyrimidine- and platinum-containing chemotherapy on the same day.[1]**

*Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.[1]

IV=intravenous; q2w=every 2 weeks; q3w=every 3 weeks; q4w=every 4 weeks.

**Please see the US Full Prescribing Information, Section 2, Dosing & Administration, for information on Dose Modifications, including interruption and discontinuation.**





OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

# Gastroesophageal Cancers: Metastatic and Adjuvant

## ICD-10-CM CODES[4]

| Code | Diagnosis | Advanced ESCC | Adjuvant Treatment of EC or GEJC | 1L Metastatic ESCC | Advanced or Metastatic Gastric, GEJ, and Esophageal Adenocarcinoma |
|---|---|---|---|---|---|
| **C15** | Malignant neoplasm of esophagus | ✓ | ✓ | ✓ | ✓ |
| C15.3 | Malignant neoplasm of upper third of esophagus | ✓ | ✓ | ✓ | |
| C15.4 | Malignant neoplasm of middle third of esophagus | ✓ | ✓ | ✓ | |
| C15.5 | Malignant neoplasm of lower third of esophagus | ✓ | ✓ | ✓ | ✓ |
| C15.8 | Malignant neoplasm of overlapping sites of esophagus | ✓ | ✓ | ✓ | ✓ |
| C15.9 | Malignant neoplasm of esophagus, unspecified | ✓ | ✓ | ✓ | ✓ |
| **C16** | Malignant neoplasm of stomach | | ✓ | | ✓ |
| C16.0 | Malignant neoplasm of cardia | | ✓ | | ✓ |
| C16.1 | Malignant neoplasm of fundus of stomach | | | | ✓ |
| C16.2 | Malignant neoplasm of body of stomach | | | | ✓ |
| C16.3 | Malignant neoplasm of pyloric antrum | | | | ✓ |
| C16.4 | Malignant neoplasm of pylorus | | | | ✓ |
| C16.5 | Malignant neoplasm of lesser curvature of stomach, unspecified | | | | ✓ |
| C16.6 | Malignant neoplasm of greater curvature of stomach, unspecified | | | | ✓ |
| C16.8 | Malignant neoplasm of overlapping sites of stomach | | | | ✓ |
| C16.9 | Malignant neoplasm of stomach, unspecified | | | | ✓ |

**Note:** If infusion for antineoplastic immunotherapy is the only reason for the patient encounter, physicians and hospitals may report the code below as the primary diagnosis[4]:

| | |
|---|---|
| Z51.12 | Encounter for antineoplastic immunotherapy |

The accurate completion of reimbursement or coverage-related documentation is the responsibility of the healthcare provider and the patient. Bristol Myers Squibb and its agents make no guarantee regarding reimbursement for any service or item.







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## IMPORTANT SAFETY INFORMATION

**Severe and Fatal Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%).

Immune-Mediated Colitis

OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and Grade 2 (1%).

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%).

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency,

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## IMPORTANT SAFETY INFORMATION (continued)

initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%).

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO and YERVOY can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%).

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%).

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# Gastroesophageal Cancers: Metastatic and Adjuvant

## IMPORTANT SAFETY INFORMATION (continued)

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular:* myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal*: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular*: blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal*: pancreatitis (1.3%); *other (hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

### Infusion-Related Reactions

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

### Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after

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## IMPORTANT SAFETY INFORMATION (continued)

being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

### Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

### Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

### Lactation

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

### Serious Adverse Reactions

In Attraction-3, serious adverse reactions occurred in 38% of patients receiving OPDIVO (n=209). Serious adverse reactions reported in ≥2% of patients who received OPDIVO were pneumonia, esophageal fistula, interstitial lung disease, and pyrexia. The following fatal adverse reactions occurred in patients who received OPDIVO: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%). In Checkmate 577, serious adverse reactions occurred in 33% of patients receiving OPDIVO (n=532). A serious adverse reaction reported in ≥2% of patients who received OPDIVO was pneumonitis. A fatal reaction of myocardial infarction occurred in one patient who received OPDIVO. In Checkmate 648, serious adverse reactions occurred in 62% of patients receiving OPDIVO in combination with chemotherapy (n=310). The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were pneumonia (11%), dysphagia (7%), esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with chemotherapy; these included pneumonitis, pneumatosis intestinalis, pneumonia, and acute kidney injury. In Checkmate 648, serious adverse reactions occurred in 69% of patients receiving OPDIVO in combination

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## IMPORTANT SAFETY INFORMATION (continued)

with YERVOY (n=322). The most frequent serious adverse reactions reported in ≥2% who received OPDIVO in combination with YERVOY were pneumonia (10%), pyrexia (4.3%), pneumonitis (4.0%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with YERVOY; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome. In Checkmate 649, serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy (n=782). The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation.

### Common Adverse Reactions

In Attraction-3, the most common adverse reactions (≥20%) in OPDIVO-treated patients (n=209) were rash (22%) and decreased appetite (21%). In Checkmate 577, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=532) were fatigue (34%), diarrhea (29%), nausea (23%), rash (21%), musculoskeletal pain (21%), and cough (20%). In Checkmate 648, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=310) were nausea (65%), decreased appetite (51%), fatigue (47%), constipation (44%), stomatitis (44%), diarrhea (29%), and vomiting (23%). In Checkmate 648, the most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with YERVOY were rash (31%), fatigue (28%), pyrexia (23%), nausea (22%), diarrhea (22%), and constipation (20%). In Checkmate 649, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=782) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), diarrhea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), and musculoskeletal pain (20%).

### Clinical Trials and Patient Populations

Checkmate 649–previously untreated advanced or metastatic gastric cancer, gastroesophageal junction and esophageal adenocarcinoma; Checkmate 577–adjuvant treatment of esophageal or gastroesophageal junction cancer; Attraction-3–esophageal squamous cell carcinoma; Checkmate 648—previously untreated, unresectable advanced recurrent or metastatic esophageal squamous cell carcinoma; Checkmate 648—previously untreated, unresectable advanced recurrent or metastatic esophageal squamous cell carcinoma

**References: 1.** OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. July 2022. **2.** Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol*. 2018;29(11):2208-2213. **3.** YERVOY [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. May 2022. **4.** American Medical Association. *2020 ICD-10-CM: The Complete Official Codebook*. Chicago, IL: American Medical Association; 2020.







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# BMS Access Support®

## BMS ACCESS SUPPORT ONCOLOGY CO-PAY ASSISTANCE PROGRAM

BMS supports access to prescribed BMS medications through the BMS Access Support Co-Pay Assistance Program. This program helps commercially insured patients who have been prescribed select BMS medications with out-of-pocket deductibles, co-pays, or co-insurance requirements.

## HOW DOES THIS PROGRAM WORK?

- **Enrolled patients** may pay as little as **$0** per infusion, per product
- **BMS will cover** the remaining amount up to a maximum benefit of **$25,000** per patient, per product, per calendar year

### Looking for support? We're here for you.

Patient access support, reimbursement resources, and financial support options may be available through **BMS Access Support®**

**Call a Patient Access Specialist at 1-800-861-0048, 8 AM to 8 PM ET, Monday - Friday**

**Visit www.BMSAccessSupport.com**

**Schedule a meeting with a BMS Access and Reimbursement Manager on the BMS Access Support website**

Other restrictions apply. Final determination of Program eligibility is based on review of a completed application. Please see full Terms and Conditions on the following page.

**Please note**: The Program will cover the out-of-pocket expenses of BMS products only. It does not cover the costs of any other healthcare provider charges, or any other treatment costs. Patients may be responsible for non drug-related out-of-pocket costs, depending on their specific healthcare benefits.

# BMS Access Support®

## BMS ACCESS SUPPORT CO-PAY ASSISTANCE PROGRAM TERMS & CONDITIONS

**[Program only available for EMPLICITI® (elotuzumab), OPDIVO® (nivolumab), OPDIVO® (nivolumab) + YERVOY® (ipilimumab), Opdualag™ (nivolumab and relatlimab–rmbw), & YERVOY® (ipilimumab)]**

**The BMS Co-Pay Assistance Program is designed to assist eligible commercially insured patients who have been prescribed select BMS medications with out-of-pocket deductibles, co-pays, or co-insurance requirements.**

### Patient Eligibility:

- Patients must have commercial insurance, but their coverage does not cover the full cost of their prescribed Bristol Myers Squibb (BMS) medication. Co-pay assistance is not valid where the entire cost of the medication is reimbursed by insurance.
- Patients are not eligible if they participate in any state or federal healthcare program including Medicaid, Medicare, Medigap, CHAMPVA, TriCare, Veterans Affairs (VA), or Department of Defense (DoD), or any state, patient, or pharmaceutical assistance program. Patients who move from commercial insurance to a state or federal healthcare program will no longer be eligible.
- Cash-paying patients are not eligible for co-pay assistance.
- Patients or their guardian must be 18 years of age or older.
- Patients must live in the United States or Puerto Rico.

### Program Benefits:

- For eligible commercially insured patients, the patient may pay as little as $0 per infusion.
- This Program will cover the co-pay for each dose of a BMS medication, up to a maximum of $25,000 per BMS medication during a calendar year.
- Patients are responsible for any costs that exceed the Program's maximum of $25,000 per BMS Medication.
- In order to receive the Program benefits, the patient or provider must submit an Explanation of Benefits (EOB) form or a Remittance Advice (RA). The submitted form must include the name of the insurer, plan information, and show that the BMS medication supported by this Program was the medication that was given. The form must be submitted within 180 days of the date the claim was processed.
- The Program may apply retroactively to out-of-pocket expenses that occurred within 180 days prior to the date of the enrollment. These benefits are subject to the 12-month Program maximum of $25,000 per medication.
- The Program benefits are limited to the co-pay costs for BMS medications covered by this Program that the patient receives as an outpatient. The Program will not cover and shall not be applied toward the cost of any dosing procedure, any other healthcare provider service, supply charges or other treatment costs, or any costs associated with a hospital stay.
- All Program payments are for the benefit of the patient only.

### Program Timing:

- January 1, 2024 – December 31, 2024
- The enrollment period is 1 calendar year.

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# BMS Access Support®

## BMS ACCESS SUPPORT CO-PAY ASSISTANCE PROGRAM TERMS & CONDITIONS (continued)

### Additional Terms and Conditions of Program:

- Patients, pharmacists, and healthcare providers must not seek reimbursement from health insurance or any third party for any part of the benefits received by the patient through this Program. Patients must not seek reimbursement from any health savings, flexible spending, or other healthcare reimbursement accounts for the amount of assistance received from the Program.
- Acceptance of this offer confirms that this offer is consistent with patient's insurance. Patients, pharmacists, and healthcare providers must report the receipt of co-pay assistance benefits as may be required by patient's insurance provider.
- The Program benefits are not transferable and is limited to one (1) per patient, per medication. This offer cannot be combined with any other offer, rebate, coupon or free trial.
- Only valid in the United States and Puerto Rico; this offer is void where prohibited by law, taxed, or restricted.
- The Program benefits are nontransferable.
- No membership fees.
- This Program is not conditioned on any past, present, or future purchase, including additional doses.
- **The Program is Not Insurance.**
- Bristol Myers Squibb reserves the right to rescind, revoke, or amend this offer at any time without notice







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# Important Safety Information

## IMPORTANT SAFETY INFORMATION FOR OPDIVO® (nivolumab) and YERVOY® (ipilimumab)

**Severe and Fatal Immune-Mediated Adverse Reactions**
Immune-mediated adverse reactions listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment, they can also occur after discontinuation of OPDIVO or YERVOY. Early identification and management are essential to ensure safe use of OPDIVO and YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and periodically during treatment with OPDIVO and before each dose of YERVOY. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if OPDIVO or YERVOY interruption or discontinuation is required, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO and YERVOY can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients receiving OPDIVO monotherapy, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 7% (31/456) of patients, including Grade 4 (0.2%), Grade 3 (2.0%), and Grade 2 (4.4%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated pneumonitis occurred in 3.9% (26/666) of patients, including Grade 3 (1.4%) and Grade 2 (2.6%). In NSCLC patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, immune-mediated pneumonitis occurred in 9% (50/576) of patients, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%). Four patients (0.7%) died due to pneumonitis.

In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO, including Grade 3 (n=1) and Grade 2 (n=12).

Immune-Mediated Colitis

OPDIVO and YERVOY can cause immune-mediated colitis, which may be fatal. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients, including Grade 3 (1.7%) and

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# Important Safety Information

## IMPORTANT SAFETY INFORMATION FOR OPDIVO® (nivolumab) and YERVOY® (ipilimumab) (cont.)

Grade 2 (1%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated colitis occurred in 25% (115/456) of patients, including Grade 4 (0.4%), Grade 3 (14%) and Grade 2 (8%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated colitis occurred in 9% (60/666) of patients, including Grade 3 (4.4%) and Grade 2 (3.7%).

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO and YERVOY can cause immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 15% (70/456) of patients, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated hepatitis occurred in 7% (48/666) of patients, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%).

OPDIVO in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to OPDIVO alone. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. In patients receiving OPDIVO and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% of patients.

Immune-Mediated Endocrinopathies

OPDIVO and YERVOY can cause primary or secondary adrenal insufficiency, immune-mediated hypophysitis, immune-mediated thyroid disorders, and Type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Withhold OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated.

In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994), including Grade 3 (0.4%) and Grade 2 (0.6%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, adrenal insufficiency occurred in 8% (35/456), including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, adrenal insufficiency occurred in 7% (48/666) of patients, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%). In patients receiving OPDIVO and cabozantinib, adrenal insufficiency occurred in 4.7% (15/320) of patients, including Grade 3 (2.2%) and Grade 2 (1.9%).

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients, including Grade 3 (0.2%) and Grade 2 (0.3%).

In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypophysitis occurred in 9% (42/456), including Grade 3 (2.4%) and Grade 2 (6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypophysitis occurred in 4.4% (29/666) of patients, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%).

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OPDIVO® (nivolumab)
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## IMPORTANT SAFETY INFORMATION FOR OPDIVO® (nivolumab) and YERVOY® (ipilimumab) (cont.)

In patients receiving OPDIVO monotherapy, thyroiditis occurred in 0.6% (12/1994) of patients, including Grade 2 (0.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, thyroiditis occurred in 2.7% (22/666) of patients, including Grade 3 (4.5%) and Grade 2 (2.2%).

In patients receiving OPDIVO monotherapy, hyperthyroidism occurred in 2.7% (54/1994) of patients, including Grade 3 (<0.1%) and Grade 2 (1.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hyperthyroidism occurred in 9% (42/456) of patients, including Grade 3 (0.9%) and Grade 2 (4.2%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hyperthyroidism occurred in 12% (80/666) of patients, including Grade 3 (0.6%) and Grade 2 (4.5%).

In patients receiving OPDIVO monotherapy, hypothyroidism occurred in 8% (163/1994) of patients, including Grade 3 (0.2%) and Grade 2 (4.8%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, hypothyroidism occurred in 20% (91/456) of patients, including Grade 3 (0.4%) and Grade 2 (11%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, hypothyroidism occurred in 18% (122/666) of patients, including Grade 3 (0.6%) and Grade 2 (11%).

In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients, including Grade 3 (0.4%) and Grade 2 (0.3%), and 2 cases of diabetic ketoacidosis. In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, diabetes occurred in 2.7% (15/666) of patients, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2 (0.9%).

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO and YERVOY can cause immune-mediated nephritis. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated nephritis with renal dysfunction occurred in 4.1% (27/666) of patients, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%).

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, SJS, TEN, and DRESS. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes.

Withhold or permanently discontinue OPDIVO and YERVOY depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%). In patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, immune-mediated rash occurred in 28% (127/456) of patients, including Grade 3 (4.8%) and Grade 2 (10%). In patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, immune-mediated rash occurred in 16% (108/666) of patients, including Grade 3 (3.5%) and Grade 2 (4.2%).

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## IMPORTANT SAFETY INFORMATION FOR OPDIVO® (nivolumab) and YERVOY® (ipilimumab) (cont.)

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO monotherapy or OPDIVO in combination with YERVOY or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *cardiac/vascular*: myocarditis, pericarditis, vasculitis; *nervous system*: meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *ocular*: uveitis, iritis, and other ocular inflammatory toxicities can occur; *gastrointestinal*: pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis; *musculoskeletal and connective tissue*: myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica; *endocrine*: hypoparathyroidism; *other (hematologic/immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

In addition to the immune-mediated adverse reactions listed above, across clinical trials of YERVOY monotherapy or in combination with OPDIVO, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified: *nervous system*: autoimmune neuropathy (2%), myasthenic syndrome/myasthenia gravis, motor dysfunction; *cardiovascular*: angiopathy, temporal arteritis; *ocular*: blepharitis, episcleritis, orbital myositis, scleritis; *gastrointestinal*: pancreatitis (1.3%); *other (hematologic/immune)*: conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, hypersensitivity vasculitis, neurosensory hypoacusis, psoriasis.

Some ocular IMAR cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, which has been observed in patients receiving OPDIVO and YERVOY, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

### Infusion-Related Reactions

OPDIVO and YERVOY can cause severe infusion-related reactions. Discontinue OPDIVO and YERVOY in patients with severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild (Grade 1) or moderate (Grade 2) infusion-related reactions. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In melanoma patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 2.5% (10/407) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg every 3 weeks, infusion-related reactions occurred in 8% (4/49) of patients. In RCC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3

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## IMPORTANT SAFETY INFORMATION FOR OPDIVO® (nivolumab) and YERVOY® (ipilimumab) (cont.)

weeks, infusion-related reactions occurred in 5.1% (28/547) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg every 3 weeks, infusion-related reactions occurred in 4.2% (5/119) of patients. In MPM patients receiving OPDIVO 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks, infusion-related reactions occurred in 12% (37/300) of patients.

**Complications of Allogeneic Hematopoietic Stem Cell Transplantation**

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with OPDIVO or YERVOY. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between OPDIVO or YERVOY and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with OPDIVO and YERVOY prior to or after an allogeneic HSCT.

**Embryo-Fetal Toxicity**

Based on its mechanism of action and findings from animal studies, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. The effects of YERVOY are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and YERVOY and for at least 5 months after the last dose.

**Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone**

In randomized clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**Lactation**

There are no data on the presence of OPDIVO or YERVOY in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 5 months after the last dose.

**Serious Adverse Reactions**

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In

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## IMPORTANT SAFETY INFORMATION FOR OPDIVO® (nivolumab) and YERVOY® (ipilimumab) (cont.)

Checkmate 067, serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent (≥10%) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). In Checkmate 238, serious adverse reactions occurred in 18% of patients receiving OPDIVO (n=452). Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients (n=452). The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. In Checkmate 816, serious adverse reactions occurred in 30% of patients (n=176) who were treated with OPDIVO in combination with platinum-doublet chemotherapy. Serious adverse reactions in >2% included pneumonia and vomiting. No fatal adverse reactions occurred in patients who received OPDIVO in combination with platinum-doublet chemotherapy. In Checkmate 77T, serious adverse reactions occurred in 21% of patients who received OPDIVO in combination with platinum-doublet chemotherapy as neoadjuvant treatment (n=228). The most frequent (≥2%) serious adverse reactions was pneumonia. Fatal adverse reactions occurred in 2.2% of patients, due to cerebrovascular accident, COVID-19 infection, hemoptysis, pneumonia, and pneumonitis (0.4% each). In the adjuvant phase of Checkmate 77T, 22% of patients experienced serious adverse reactions (n=142). The most frequent serious adverse reaction was pneumonitis/ILD (2.8%). One fatal adverse reaction due to COVID-19 occurred. In Checkmate 227, serious adverse reactions occurred in 58% of patients (n=576). The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. In Checkmate 9LA, serious adverse reactions occurred in 57% of patients (n=358). The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. In Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 057, fatal adverse reactions occurred; these included events of infection (7 patients, including one case of *Pneumocystis jirovecii* pneumonia), pulmonary embolism (4 patients), and limbic encephalitis (1 patient). In Checkmate 743, serious adverse reactions occurred in 54% of patients receiving OPDIVO plus YERVOY. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis, and encephalitis. In Checkmate 214, serious adverse reactions occurred in 59% of patients receiving OPDIVO plus YERVOY (n=547). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pyrexia, pneumonia, pneumonitis,

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## IMPORTANT SAFETY INFORMATION FOR OPDIVO® (nivolumab) and YERVOY® (ipilimumab) (cont.)

hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis. In Checkmate 9ER, serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib (n=320). The most frequent serious adverse reactions reported in ≥2% of patients were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT. In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO (n=236). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. In Checkmate 274, serious adverse reactions occurred in 30% of patients receiving OPDIVO (n=351). The most frequent serious adverse reaction reported in ≥2% of patients receiving OPDIVO was urinary tract infection. Fatal adverse reactions occurred in 1% of patients; these included events of pneumonitis (0.6%). In Checkmate 901, serious adverse reactions occurred in 48% of patients receiving OPDIVO in combination with chemotherapy. The most frequent serious adverse reactions reporting in ≥2% of patients who received OPDIVO with chemotherapy were urinary tract infection (4.9%), acute kidney injury (4.3%), anemia (3%), pulmonary embolism (2.6%), sepsis (2.3%), and platelet count decreased (2.3%). Fatal adverse reactions occurred in 3.6% of patients who received OPDIVO in combination with chemotherapy; these included sepsis (1%). OPDIVO and/or chemotherapy were discontinued in 30% of patients and were delayed in 67% of patients for an adverse reaction. In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=119), serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. In Checkmate 040, serious adverse reactions occurred in 59% of patients receiving OPDIVO with YERVOY (n=49). Serious adverse reactions reported in ≥4% of patients were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis. In Attraction-3, serious adverse reactions occurred in 38% of patients receiving OPDIVO (n=209). Serious adverse reactions reported in ≥2% of patients who received OPDIVO were pneumonia, esophageal fistula, interstitial lung disease, and pyrexia. The following fatal adverse reactions occurred in patients who received OPDIVO: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death

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## IMPORTANT SAFETY INFORMATION FOR OPDIVO® (nivolumab) and YERVOY® (ipilimumab) (cont.)

(0.5%). In Checkmate 577, serious adverse reactions occurred in 33% of patients receiving OPDIVO (n=532). A serious adverse reaction reported in ≥2% of patients who received OPDIVO was pneumonitis. A fatal reaction of myocardial infarction occurred in one patient who received OPDIVO. In Checkmate 648, serious adverse reactions occurred in 62% of patients receiving OPDIVO in combination with chemotherapy (n=310). The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were pneumonia (11%), dysphagia (7%), esophageal stenosis (2.9%), acute kidney injury (2.9%), and pyrexia (2.3%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with chemotherapy; these included pneumonitis, pneumatosis intestinalis, pneumonia, and acute kidney injury. In Checkmate 648, serious adverse reactions occurred in 69% of patients receiving OPDIVO in combination with YERVOY (n=322). The most frequent serious adverse reactions reported in ≥2% who received OPDIVO in combination with YERVOY were pneumonia (10%), pyrexia (4.3%), pneumonitis (4.0%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%). Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with YERVOY; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome. In Checkmate 649, serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy (n=782). The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated intravascular coagulation. In Checkmate 76K, serious adverse reactions occurred in 18% of patients receiving OPDIVO (n=524). Adverse reactions which resulted in permanent discontinuation of OPDIVO in >1% of patients included arthralgia (1.7%), rash (1.7%), and diarrhea (1.1%). A fatal adverse reaction occurred in 1 (0.2%) patient (heart failure and acute kidney injury). The most frequent Grade 3-4 lab abnormalities reported in ≥1% of OPDIVO-treated patients were increased lipase (2.9%), increased AST (2.2%), increased ALT (2.1%), lymphopenia (1.1%), and decreased potassium (1.0%).

### Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥20%) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (62%), diarrhea (54%), rash (53%), nausea (44%), pyrexia (40%), pruritus (39%), musculoskeletal pain (32%), vomiting (31%), decreased appetite (29%), cough (27%), headache (26%), dyspnea (24%), upper respiratory tract infection (23%), arthralgia (21%), and increased transaminases (25%). In Checkmate 067, the most common (≥20%) adverse reactions in the OPDIVO arm (n=313) were fatigue (59%), rash (40%), musculoskeletal pain (42%), diarrhea (36%), nausea

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(30%), cough (28%), pruritus (27%), upper respiratory tract infection (22%), decreased appetite (22%), headache (22%), constipation (21%), arthralgia (21%), and vomiting (20%). In Checkmate 238, the most common adverse reactions (≥20%) reported in OPDIVO-treated patients (n=452) vs ipilimumab-treated patients (n=453) were fatigue (57% vs 55%), diarrhea (37% vs 55%), rash (35% vs 47%), musculoskeletal pain (32% vs 27%), pruritus (28% vs 37%), headache (23% vs 31%), nausea (23% vs 28%), upper respiratory infection (22% vs 15%), and abdominal pain (21% vs 23%). The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%). In Checkmate 816, the most common (>20%) adverse reactions in the OPDIVO plus chemotherapy arm (n=176) were nausea (38%), constipation (34%), fatigue (26%), decreased appetite (20%), and rash (20%). In Checkmate 77T, the most common adverse reactions (reported in ≥20%) in patients receiving OPDIVO in combination with chemotherapy (n= 228) were anemia (39.5%), constipation (32.0%), nausea (28.9%), fatigue (28.1%), alopecia (25.9%), and cough (21.9%). In Checkmate 227, the most common (≥20%) adverse reactions were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). In Checkmate 9LA, the most common (>20%) adverse reactions were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%). In Checkmate 017 and 057, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 743, the most common adverse reactions (≥20%) in patients receiving OPDIVO plus YERVOY were fatigue (43%), musculoskeletal pain (38%), rash (34%), diarrhea (32%), dyspnea (27%), nausea (24%), decreased appetite (24%), cough (23%), and pruritus (21%). In Checkmate 214, the most common adverse reactions (≥20%) reported in patients treated with OPDIVO plus YERVOY (n=547) were fatigue (58%), rash (39%), diarrhea (38%), musculoskeletal pain (37%), pruritus (33%), nausea (30%), cough (28%), pyrexia (25%), arthralgia (23%), decreased appetite (21%), dyspnea (20%), and vomiting (20%). In Checkmate 9ER, the most common adverse reactions (≥20%) in patients receiving OPDIVO and cabozantinib (n=320) were diarrhea (64%), fatigue (51%), hepatotoxicity (44%), palmar-plantar erythrodysaesthesia syndrome (40%), stomatitis (37%), rash (36%), hypertension (36%), hypothyroidism (34%), musculoskeletal pain (33%), decreased appetite (28%), nausea (27%), dysgeusia (24%), abdominal pain (22%), cough (20%) and upper respiratory tract infection (20%). In Checkmate 025, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were fatigue (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 205 and 039, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO (n=236) were cough (14%) and dyspnea (14%) at a higher incidence than investigator's choice. In Checkmate 275, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%). In Checkmate

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# Important Safety Information

## IMPORTANT SAFETY INFORMATION FOR OPDIVO® (nivolumab) and YERVOY® (ipilimumab) (cont.)

274, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=351) were rash (36%), fatigue (36%), diarrhea (30%), pruritus (30%), musculoskeletal pain (28%), and urinary tract infection (22%).In Checkmate 901, the most common adverse reactions (≥20%) were nausea, fatigue, musculoskeletal pain, constipation, decreased appetite, rash, vomiting, and peripheral neuropathy. In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO as a single agent (n=74), the most common adverse reactions (≥20%) were fatigue (54%), diarrhea (43%), abdominal pain (34%), nausea (34%), vomiting (28%), musculoskeletal pain (28%), cough (26%), pyrexia (24%), rash (23%), constipation (20%), and upper respiratory tract infection (20%). In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY (n=119), the most common adverse reactions (≥20%) were fatigue (49%), diarrhea (45%), pyrexia (36%), musculoskeletal pain (36%), abdominal pain (30%), pruritus (28%), nausea (26%), rash (25%), decreased appetite (20%), and vomiting (20%). In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO with YERVOY (n=49), were rash (53%), pruritus (53%), musculoskeletal pain (41%), diarrhea (39%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (22%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decreased (20%). In Attraction-3, the most common adverse reactions (≥20%) in OPDIVO-treated patients (n=209) were rash (22%) and decreased appetite (21%). In Checkmate 577, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=532) were fatigue (34%), diarrhea (29%), nausea (23%), rash (21%), musculoskeletal pain (21%), and cough (20%). In Checkmate 648, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=310) were nausea (65%), decreased appetite (51%), fatigue (47%), constipation (44%), stomatitis (44%), diarrhea (29%), and vomiting (23%). In Checkmate 648, the most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with YERVOY were rash (31%), fatigue (28%), pyrexia (23%), nausea (22%), diarrhea (22%), and constipation (20%). In Checkmate 649, the most common adverse reactions (≥20%) in patients treated with OPDIVO in combination with chemotherapy (n=782) were peripheral neuropathy (53%), nausea (48%), fatigue (44%), diarrhea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), and musculoskeletal pain (20%). In Checkmate 76K, the most common adverse reactions (≥20%) reported with OPDIVO (n=524) were fatigue (36%), musculoskeletal pain (30%), rash (28%), diarrhea (23%) and pruritis (20%).

### Surgery Related Adverse Reactions

In Checkmate 77T, 5.3% (n=12) of the OPDIVO-treated patients who received neoadjuvant treatment, did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery in OPDIVO-treated patients were cerebrovascular accident, pneumonia, and colitis/diarrhea (2 patients each) and acute coronary syndrome, myocarditis, hemoptysis, pneumonitis, COVID-19, and myositis (1 patient each).

Please see US Full Prescribing Information for OPDIVO and YERVOY

### Clinical Trials and Patient Populations

Checkmate 227—previously untreated metastatic non-small cell lung cancer, in combination with YERVOY; Checkmate 9LA–previously untreated recurrent or metastatic non-small cell lung cancer in combination with YERVOY and 2 cycles of platinum-doublet chemotherapy by histology; Checkmate 649–previously untreated

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advanced or metastatic gastric cancer, gastroesophageal junction and esophageal adenocarcinoma; Checkmate 577–adjuvant treatment of esophageal or gastroesophageal junction cancer; Checkmate 238–adjuvant treatment of patients with completely resected Stage III or Stage IV melanoma; Checkmate 76K– adjuvant treatment of patients 12 years of age and older with completely resected Stage IIB or Stage IIC melanoma; Checkmate 274–adjuvant treatment of urothelial carcinoma; Checkmate 275–previously treated advanced or metastatic urothelial carcinoma; Checkmate 142–MSI-H or dMMR metastatic colorectal cancer, as a single agent or in combination with YERVOY; Checkmate 142–MSI-H or dMMR metastatic colorectal cancer, as a single agent or in combination with YERVOY; Attraction-3–esophageal squamous cell carcinoma; Checkmate 648—previously untreated, unresectable advanced recurrent or metastatic esophageal squamous cell carcinoma in combination with chemotherapy; Checkmate 648—previously untreated, unresectable advanced recurrent or metastatic esophageal squamous cell carcinoma combination with YERVOY; Checkmate 040–hepatocellular carcinoma, in combination with YERVOY; Checkmate 743–previously untreated unresectable malignant pleural mesothelioma, in combination with YERVOY; Checkmate 037–previously treated metastatic melanoma; Checkmate 066—previously untreated metastatic melanoma; Checkmate 067– previously untreated metastatic melanoma, as a single agent or in combination with YERVOY; Checkmate 017–second-line treatment of metastatic squamous non-small cell lung cancer; Checkmate 057–second-line treatment of metastatic non-squamous non-small cell lung cancer; Checkmate 816–neoadjuvant non-small cell lung cancer, in combination with platinum-doublet chemotherapy; Checkmate 77T–Neoadjuvant treatment with platinum-doublet chemotherapy for non-small cell lung cancer followed by single-agent OPDIVO as adjuvant treatment after surgery; Checkmate 901–Adult patients with unresectable or metastatic urothelial carcinoma; Checkmate 141–recurrent or metastatic squamous cell carcinoma of the head and neck; Checkmate 025–previously treated renal cell carcinoma; Checkmate 214–previously untreated renal cell carcinoma, in combination with YERVOY; Checkmate 9ER–previously untreated renal cell carcinoma, in combination with cabozantinib; Checkmate 205/039–classical Hodgkin lymphoma

**Please see Important Safety Information for OPDIVO and YERVOY® (ipilimumab), and US Full Prescribing Information for OPDIVO and YERVOY.**
**For reimbursement assistance, call BMS Access Support® at 1-800-861-0048, 8 AM to 8 PM ET, Monday-Friday, or visit www.BMSAccessSupport.com.**

Bristol Myers Squibb®





**Important Safety Information for OPDIVO® (nivolumab) and YERVOY® (ipilimumab)**

OPDIVO® (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL