

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use OPDIVO safely and effectively. See full prescribing information for OPDIVO.

**OPDIVO (nivolumab) injection, for intravenous use**  
Initial U.S. Approval: 2014

-----RECENT MAJOR CHANGES-----

Indications and Usage (1) 10/2015  
Dosage and Administration (2) 10/2015  
Warnings and Precautions (5) 10/2015

-----INDICATIONS AND USAGE-----

OPDIVO is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of:

- Unresectable or metastatic melanoma:
    - as a single agent in patients with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. (1.1)
    - in combination with ipilimumab in patients with BRAF V600 wild-type melanoma. (1.1)
- These indications are approved under accelerated approval based on tumor response rate and durability of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- Metastatic non-small cell lung cancer in patients 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. (1.2)

-----DOSAGE AND ADMINISTRATION-----

- Administer as an intravenous infusion over 60 minutes.
- Unresectable or metastatic melanoma
    - OPDIVO 3 mg/kg every 2 weeks. (2.1)
    - OPDIVO in combination with ipilimumab: OPDIVO 1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks. (2.1)
  - Metastatic non-small cell lung cancer
    - OPDIVO 3 mg/kg every 2 weeks. (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

Injection: 40 mg/4 mL and 100 mg/10 mL solution in a single-use vial. (3)

-----CONTRAINDICATIONS-----

None. (4)

-----WARNINGS AND PRECAUTIONS-----

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis:
  - OPDIVO as a single agent: Withhold for moderate or severe and permanently discontinue for life-threatening colitis. (5.2)
  - OPDIVO in combination with ipilimumab: Withhold for moderate and permanently discontinue for severe or life-threatening colitis. (5.2)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.3)
- Immune-mediated endocrinopathies: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis. Withhold for moderate and permanently discontinue for severe or life-threatening adrenal insufficiency. Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. (5.4)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation. (5.5)
- Immune-mediated rash: Withhold for severe and permanently discontinue for life-threatening rash. (5.6)
- Immune-mediated encephalitis: Monitor for changes in neurologic function. Withhold for new-onset moderate to severe neurological signs or symptoms and permanently discontinue for immune-mediated encephalitis. (5.7)
- Embryofetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.10, 8.1, 8.3)

-----ADVERSE REACTIONS-----

Most common adverse reactions (≥20%) in patients with melanoma were:

- OPDIVO as a single agent: rash. (6.1)
- OPDIVO in combination with ipilimumab: rash, pruritus, headache, vomiting, and colitis. (6.1)

Most common adverse reactions (≥20%) in patients with metastatic non-small cell lung cancer were fatigue, musculoskeletal pain, decreased appetite, cough, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

-----USE IN SPECIFIC POPULATIONS-----

Lactation: Discontinue breastfeeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Unresectable or Metastatic Melanoma

- OPDIVO<sup>®</sup> (nivolumab) as a single agent is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor [see *Clinical Studies (14.1)*].

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma [see *Clinical Studies (14.1)*].

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

#### 1.2 Metastatic Non-Small Cell Lung Cancer

OPDIVO<sup>®</sup> (nivolumab) is indicated for the treatment of 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 [see *Clinical Studies (14.2)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage for Melanoma

- The recommended dose of OPDIVO administered as a single agent is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
- The recommended dose of OPDIVO is 1 mg/kg administered as an intravenous infusion over 60 minutes, followed by ipilimumab on the same day, every 3 weeks for 4 doses [see *Clinical Studies (14.1)*]. The recommended subsequent dose of OPDIVO, as a single agent, is 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

Review the Full Prescribing Information for ipilimumab prior to initiation.

#### 2.2 Recommended Dosage for NSCLC

The recommended dose of OPDIVO is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

#### 2.3 Dose Modifications

Guidelines for treatment modifications are provided in Table 1.

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

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

**Table 1: Recommended Dose Modifications for OPDIVO**

Adverse Reaction	Severity	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose <sup>a</sup>
	Grade 3 diarrhea or colitis	
	<u>Single-agent OPDIVO</u>	Withhold dose <sup>a</sup>
	<u>OPDIVO, in combination with ipilimumab</u>	Permanently discontinue
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose <sup>a</sup>
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose <sup>a</sup>
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose <sup>a</sup>
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose <sup>a</sup>
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose <sup>a</sup>
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Rash	Grade 3 rash	Withhold dose <sup>a</sup>
	Grade 4 rash	Permanently discontinue
Encephalitis	New onset moderate or severe neurologic signs or symptoms	Withhold dose <sup>a</sup>
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction	
	First occurrence	Withhold dose <sup>a</sup>
	Recurrence of same Grade 3 adverse reactions	Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

<sup>a</sup> Resume treatment when adverse reaction returns to Grade 0 or 1.

When OPDIVO is administered in combination with ipilimumab, if OPDIVO is withheld, ipilimumab should also be withheld.

## 2.4 Preparation and Administration

Visually inspect drug product solution for particulate matter and discoloration prior to administration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

### Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.

### Storage of Infusion

The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

### Administration

Administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

When administered in combination with ipilimumab, infuse OPDIVO first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

## 3 DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) solution in a single-use vial.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with OPDIVO treatment. Across clinical trial experience with solid tumors receiving OPDIVO as a single agent, fatal immune-mediated pneumonitis occurred in 0.5% (5/978) of patients. All five fatal cases occurred in a dose-finding study with OPDIVO doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

Across the clinical trial experience in 188 patients with melanoma who received OPDIVO in combination with ipilimumab, in Trial 4 (n=94) and an additional dose-finding study (n=94), fatal immune-mediated pneumonitis occurred in 0.5% (1/188) of patients. In Trial 4, there were six additional patients who died without resolution of abnormal respiratory findings.

Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis [*see Dosage and Administration (2.3)*].

#### Melanoma

In Trial 1, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis occurred in 2.2% (6/268) of patients receiving OPDIVO: one with Grade 3 and five with Grade 2 pneumonitis. The median time to onset for the six cases was 2.2 months (range: 25 days to 3.5 months). In two patients, pneumonitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 pneumonitis led to interruption or permanent discontinuation of OPDIVO in the remaining four patients. All six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day); immune-mediated pneumonitis improved to Grade 0 or 1 with corticosteroids in all six patients. There were two patients with Grade 2 pneumonitis that completely resolved (defined as complete resolution of symptoms with completion of corticosteroids) and OPDIVO was restarted without recurrence of pneumonitis.

In Trial 4, pneumonitis, including interstitial lung disease, occurred in 10% (9/94) of patients receiving OPDIVO in combination with ipilimumab and 2.2% (1/46) of patients receiving ipilimumab. Immune-mediated pneumonitis occurred in 6% (6/94) of patients receiving OPDIVO in combination with ipilimumab: Grade 5 (n=1), Grade 3 (n=2) and Grade 2 (n=3) pneumonitis. The median time to onset for the six cases was 2.5 months (range: 1.3 to 4.6 months). In the patient with fatal pneumonitis, the event was diagnosed after discontinuation of OPDIVO in combination with ipilimumab for another immune-mediated adverse reaction; this patient died from pneumonitis more than 30 days after the last dose. The remaining five patients had dose interruption or permanent discontinuation of OPDIVO in combination with ipilimumab. All six patients received high-dose corticosteroids. Immune-mediated pneumonitis completely resolved in the five patients with Grade 2 or 3 pneumonitis. OPDIVO in combination with

ipilimumab was restarted for one patient with Grade 2 pneumonitis after complete resolution, and pneumonitis did not recur.

## NSCLC

In Trial 3, pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients receiving OPDIVO. Of these 10 patients, there were five patients with Grade 3, two patients with Grade 2, and three patients with Grade 1 immune-mediated pneumonitis. The median time to onset was 7.2 months (range: 2.7 to 13.1 months). All five patients with Grade 3 and one of two patients with Grade 2 pneumonitis received high-dose corticosteroids and permanently discontinued OPDIVO; two of these seven were documented radiographically to have complete resolution of pneumonitis. One patient with Grade 2 pneumonitis had OPDIVO temporarily withheld, received low-dose corticosteroids, experienced complete resolution and was retreated without recurrence of pneumonitis.

## 5.2 Immune-Mediated Colitis

Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for signs and symptoms of colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents.

When administered as a single agent, withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon restarting OPDIVO [*see Dosage and Administration (2.3)*].

When administered in combination with ipilimumab, withhold OPDIVO for moderate colitis (Grade 2). Permanently discontinue OPDIVO for severe or life-threatening (Grade 3 or 4) colitis or for recurrent colitis upon restarting OPDIVO [*see Dosage and Administration (2.3)*].

## Melanoma

In Trial 1, diarrhea or colitis occurred in 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis occurred in 2.2% (6/268) of patients receiving OPDIVO: five patients with Grade 3 and one patient with Grade 2 colitis. The median time to onset of immune-mediated colitis from initiation of OPDIVO was 2.5 months (range: 1 to 6 months). In three patients, colitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 or 3 colitis led to interruption or permanent discontinuation of OPDIVO in the remaining three patients. Five of these six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.4 months (range: 3 days to 2.4 months) preceding corticosteroid taper. The sixth patient continued on low-dose corticosteroids started for another immune-mediated adverse reaction. Immune-mediated colitis improved to Grade 0 with corticosteroids in five patients, including one

patient with Grade 3 colitis retreated after complete resolution (defined as improved to Grade 0 with completion of corticosteroids) without additional events of colitis. Grade 2 colitis was ongoing in one patient.

In Trial 4, diarrhea or colitis occurred in 57% (54/94) of patients receiving OPDIVO in combination with ipilimumab and 46% (21/46) of patients receiving ipilimumab. Immune-mediated colitis occurred in 33% (31/94) of patients receiving OPDIVO in combination with ipilimumab: one patient with Grade 4, 16 patients with Grade 3, nine patients with Grade 2, and five patients with Grade 1 colitis. The median time to onset was 1.4 months (range: 6.1 days to 5.3 months). Immune-mediated colitis led to permanent discontinuation of OPDIVO in combination with ipilimumab in 17 patients. Thirty of the 31 patients received high-dose corticosteroids for a median duration of 1.2 months (range: 1 day to 6 months) and 11 received infliximab. Immune-mediated colitis resolved following treatment with immunosuppressive medications in 30 patients. Four patients with Grade 2 immune-mediated colitis experienced complete resolution after restarting OPDIVO in combination with ipilimumab. In Trial 4, there were three patients who died without resolution of immune-mediated colitis.

## NSCLC

In Trial 3, diarrhea or colitis occurred in 17% (50/287) of patients receiving OPDIVO. Immune-mediated colitis occurred in 2.4% (7/287) of patients: three patients with Grade 3, two patients with Grade 2, and two patients with Grade 1. The median time to onset in these seven patients was 2.7 months (range: 4 weeks to 19 months). All seven patients received corticosteroids, six of these seven received high-dose corticosteroids for a median duration of 2.9 weeks (range: 1 week to 2.1 months). One patient with Grade 3 colitis permanently discontinued OPDIVO. All seven patients experienced complete resolution. Five of the seven patients were retreated after complete resolution without recurrence of diarrhea or colitis.

### 5.3 Immune-Mediated Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis [see *Dosage and Administration (2.3) and Adverse Reactions (6.1)*].

## Melanoma

In Trial 1, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs. 12%), alkaline phosphatase (22% vs. 13%), ALT (16% vs. 5%), and total bilirubin (9% vs. 0). Immune-mediated hepatitis occurred in 1.1% (3/268) of patients receiving OPDIVO: two patients with Grade 3 and one patient with Grade 2 hepatitis. The time to onset was 97, 113, and 86 days after initiation of OPDIVO. In one patient, hepatitis was diagnosed after discontinuation of OPDIVO for other reasons. In two patients, OPDIVO was withheld. All three patients received high-dose

corticosteroids (at least 40 mg prednisone equivalents). Liver tests improved to Grade 1 within 4 to 15 days of initiation of corticosteroids. Immune-mediated hepatitis resolved and did not recur with continuation of corticosteroids in two patients; the third patient died of disease progression with persistent hepatitis. The two patients with Grade 3 hepatitis that resolved restarted OPDIVO and, in one patient, Grade 3 immune-mediated hepatitis recurred resulting in permanent discontinuation of OPDIVO.

In Trial 4, immune-mediated hepatitis occurred in 15% (14/94) of patients receiving OPDIVO in combination with ipilimumab: three patients with Grade 4, nine patients with Grade 3, and two patients with Grade 2 hepatitis. The median time to onset was 2.8 months (range: 3 weeks to 5.7 months). Five patients discontinued OPDIVO in combination with ipilimumab due to hepatitis. Thirteen of the 14 patients received high-dose corticosteroids and three received mycophenolic acid. Complete resolution (defined as improved to Grade 0 with completion of corticosteroids) occurred in nine patients. Among four patients for whom OPDIVO in combination with ipilimumab was restarted, three had recurrence or worsening of hepatitis and one improved on corticosteroids.

## NSCLC

In Trial 3, one patient developed immune-mediated hepatitis (0.3%) after 7.8 months of OPDIVO exposure. The event resolved following temporary withholding of OPDIVO and high-dose corticosteroid therapy. Immune-mediated hepatitis recurred following resumption of OPDIVO, resulting in permanent discontinuation.

## 5.4 Immune-Mediated Endocrinopathies

### Hypophysitis

Hypophysitis can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis. Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) and permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis [see *Dosage and Administration* (2.3)].

In Trial 4, hypophysitis occurred in 13% (12/94) of patients receiving OPDIVO in combination with ipilimumab: two patients with Grade 3 and 10 patients with Grade 2 hypophysitis. The median time to onset was 2.9 months (range: 1.4 to 5.5 months). Ten patients received corticosteroids, including both patients with Grade 3 hypophysitis. OPDIVO in combination with ipilimumab was restarted for eight patients without resulting in worsening of hypophysitis. Four patients were continuing with corticosteroids.

### Adrenal Insufficiency

Adrenal insufficiency can occur with OPDIVO treatment. Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold OPDIVO for moderate (Grade 2) and permanently

discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency [see *Dosage and Administration (2.3)*].

In Trial 4, adrenal insufficiency occurred in 9% (8/94) of patients receiving OPDIVO in combination with ipilimumab: three patients with Grade 3, four patients with Grade 2, and one patient with Grade 1 adrenal insufficiency. The median time to onset was 3 months (range: 1.2 to 5.6 months). Grade 3 adrenal insufficiency led to discontinuation of OPDIVO in combination with ipilimumab in one patient. The remaining events each occurred after treatment discontinuation, except in two cases where OPDIVO in combination with ipilimumab was restarted and did not lead to recurrence. Three patients received high-dose corticosteroids. Six patients experienced resolution of adrenal insufficiency, three of whom remained on corticosteroids. In Trials 1 and 3 (n=555), 1% of OPDIVO-treated patients developed adrenal insufficiency.

### Hypothyroidism and Hyperthyroidism

Thyroid disorders can occur with OPDIVO treatment. Monitor thyroid function prior to and periodically during treatment. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of OPDIVO for hypothyroidism or hyperthyroidism.

#### *Melanoma*

In Trial 1, where patients were evaluated at baseline and during the trial for thyroid function, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. The median time to onset was 2.5 months (range: 24 days to 11.7 months). Seventeen of the 21 patients with hypothyroidism received levothyroxine. Fifteen of 17 patients received subsequent OPDIVO dosing while continuing to receive levothyroxine.

In Trial 1, Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients receiving OPDIVO and 1% (1/102) of patients receiving chemotherapy. The median time to onset in OPDIVO-treated patients was 1.6 months (range: 0 to 3.3 months). Four of five patients with Grade 1 hyperthyroidism and two of three patients with Grade 2 hyperthyroidism had documented resolution of hyperthyroidism; all three patients received medical management for Grade 2 hyperthyroidism.

In Trial 4, where patients were evaluated at baseline and during the trial for thyroid function, hypothyroidism occurred in 19% (18/94) of patients receiving OPDIVO in combination with ipilimumab. All were Grade 1 or 2 in severity except for one patient who experienced Grade 3 autoimmune thyroiditis. The median time to onset was 2.1 months (range: 1 day to 4.7 months). Two patients received high-dose corticosteroids. Sixteen of the 18 patients received replacement therapy with levothyroxine. Complete resolution of hypothyroidism occurred in one patient allowing discontinuation of levothyroxine. Thirteen of 16 patients received subsequent OPDIVO in combination with ipilimumab while continuing to receive levothyroxine.

In Trial 4, Grade 1 hyperthyroidism occurred in 2.1% (2/94) of patients receiving OPDIVO in combination with ipilimumab. The time to onset for both cases was 3 weeks. Both patients had a resolution of hyperthyroidism without requiring medical management and both subsequently developed hypothyroidism.

#### NSCLC

In Trial 3, Grade 1 or Grade 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) of patients receiving OPDIVO and 0% (0/268) of patients receiving docetaxel, while elevated TSH occurred in 17% of patients receiving OPDIVO and 5% of patients receiving docetaxel. The median time to onset of hypothyroidism/thyroiditis was 2.9 months (range: 1.4 to 11.8 months). All 20 patients received levothyroxine. Two patients received corticosteroids; one of whom received high-dose corticosteroids. Complete resolution of hypothyroidism occurred in one patient. OPDIVO was temporarily withheld due to hypothyroidism/thyroiditis in three patients; no patients discontinued OPDIVO due to hypothyroidism/thyroiditis.

Grade 1 or Grade 2 hyperthyroidism occurred in 1.4% (4/287) of patients. The median time to onset was 2 months (range: 4.1 weeks to 2.8 months). Two of four patients received methimazole and one patient also received treatment with high-dose corticosteroids. All four patients experienced complete resolution.

### 5.5 Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis, defined as renal dysfunction or  $\geq$  Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue OPDIVO. Permanently discontinue OPDIVO and administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine [see *Dosage and Administration* (2.3) and *Adverse Reactions* (6.1)].

#### Melanoma

In Trial 1, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs. 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction occurred in 0.7% (2/268) of patients at 3.5 and 6 months after OPDIVO initiation, respectively. OPDIVO was permanently discontinued in both patients; both received high-dose corticosteroids (at least 40 mg prednisone equivalents). Immune-mediated nephritis resolved and did not recur with continuation of corticosteroids in one patient. Renal dysfunction was ongoing in one patient.

In Trial 4, Grade 2 or higher immune-mediated nephritis or renal dysfunction occurred in 2.1% (2/94) of patients. Time to onset was 1.3 weeks and 6.7 months, respectively. In one of these patients, immune-mediated renal dysfunction resolved with corticosteroids and withholding of OPDIVO, whereas the second patient died with persistent renal dysfunction.

## NSCLC

In Trial 3, immune-mediated renal dysfunction (Grade 2) occurred in 0.3% (1/287) of patients. The time to onset in this patient was 1.5 months. The patient permanently discontinued OPDIVO, received high-dose corticosteroids, and experienced complete resolution.

### 5.6 Immune-Mediated Rash

Immune-mediated rash can occur with OPDIVO treatment. Monitor patients for rash. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash [*see Dosage and Administration (2.3)*].

In Trial 4, immune-mediated rash occurred in 37% (35/94) of patients receiving OPDIVO in combination with ipilimumab: six patients with Grade 3, 10 patients with Grade 2, and 19 patients with Grade 1 rash. The median time to onset was 2.4 weeks (range: 1 day to 6.5 months). Among the six patients with Grade 3 rash, four received systemic corticosteroids, four had OPDIVO in combination with ipilimumab withheld then restarted without resulting in recurrence of high-grade rash, and all had resolution to Grade 0 or 1 with no further requirement for systemic corticosteroids. Among the 29 patients with Grade 1 or 2 rash, six received systemic corticosteroids and two had OPDIVO in combination with ipilimumab withheld. None of the 35 patients discontinued treatment due to immune-mediated rash. In Trial 1 (n=268), the incidence of rash was 21%; the incidence of Grade 3 or 4 rash was 0.4%. In Trial 3, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO. Grade 3 rash developed in four patients (1.4%), of whom one discontinued treatment.

### 5.7 Immune-Mediated Encephalitis

Immune-mediated encephalitis can occur with OPDIVO treatment. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis [*see Dosage and Administration (2.3)*].

Across clinical studies of 8490 patients receiving OPDIVO as a single agent or in combination with ipilimumab, less than 1% of patients were identified as having encephalitis. In Trial 3, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO after 7.2 months of exposure. OPDIVO was discontinued; corticosteroids were administered.

## 5.8 Other Immune-Mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event [*see Dosage and Administration (2.3)*].

The following clinically significant, immune-mediated adverse reactions occurred in less than 2% of OPDIVO-treated patients in Trials 1 and 3 (n=555): uveitis, pancreatitis, abducens nerve paresis, demyelination, polymyalgia rheumatica, and autoimmune neuropathy. In Trial 4, the following additional immune-mediated adverse reactions occurred in 1% of patients treated with OPDIVO in combination with ipilimumab: Guillain-Barré syndrome and hypopituitarism.

Across clinical trials of OPDIVO as a single agent administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: facial nerve paralysis, motor dysfunction, vasculitis, diabetic ketoacidosis, and myasthenic syndrome.

Across clinical trials of OPDIVO in combination with ipilimumab, the following additional clinically significant, immune-mediated adverse reactions were identified: uveitis, sarcoidosis, duodenitis, pancreatitis, and gastritis.

## 5.9 Infusion Reactions

Severe infusion reactions have been reported in <1% of patients in clinical trials of OPDIVO as a single agent. In Trial 3, Grade 2 infusion reactions occurred in 1% (3/287) of patients receiving OPDIVO. In Trial 4, Grade 2 infusion reactions occurred in 3% (3/94) of patients receiving OPDIVO in combination with ipilimumab. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

## 5.10 Embryofetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO-containing regimen and for at least 5 months after the last dose of OPDIVO [*see Use in Specific Populations (8.1, 8.3)*].

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-Mediated Pneumonitis [*see Warnings and Precautions (5.1)*]
- Immune-Mediated Colitis [*see Warnings and Precautions (5.2)*]
- Immune-Mediated Hepatitis [*see Warnings and Precautions (5.3)*]
- Immune-Mediated Endocrinopathies [*see Warnings and Precautions (5.4)*]
- Immune-Mediated Nephritis and Renal Dysfunction [*see Warnings and Precautions (5.5)*]
- Immune-Mediated Rash [*see Warnings and Precautions (5.6)*]
- Immune-Mediated Encephalitis [*see Warnings and Precautions (5.7)*]
- Other Immune-Mediated Adverse Reactions [*see Warnings and Precautions (5.8)*]
- Infusion Reactions [*see Warnings and Precautions (5.9)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warning and Precautions section reflect exposure to OPDIVO, as a single agent, for clinically significant adverse reactions in 978 patients enrolled in Trials 1, 3, a single-arm trial in NSCLC, or an additional dose finding study (n=306) administering OPDIVO as a single agent at doses of 0.1 to 10 mg/kg every 2 weeks [*see Warnings and Precautions (5.1, 5.8)*]. In addition, clinically significant adverse reactions with OPDIVO, in combination with ipilimumab, were evaluated in 188 patients with melanoma enrolled in Trial 4 (n=94) or an additional dose-finding study (n=94) administering OPDIVO in combination with ipilimumab at doses of OPDIVO ranging from 0.3 to 3 mg/kg and doses of ipilimumab ranging from 1 to 3 mg/kg, supplemented by immune-mediated adverse reaction reports in ongoing clinical trials [*see Warnings and Precautions (5.1, 5.8)*].

The data described below reflect exposure to OPDIVO as a single agent in Trial 1 and to OPDIVO in combination with ipilimumab in Trial 4, which are randomized, active-controlled trials conducted in patients with unresectable or metastatic melanoma, and in Trial 3, which is a randomized trial in patients with metastatic non-squamous non-small cell lung cancer (NSCLC).

#### Unresectable or Metastatic Melanoma

##### *OPDIVO as a Single Agent*

The safety of OPDIVO as a single agent was evaluated in Trial 1, a randomized, open-label trial in which 370 patients with unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m<sup>2</sup> every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m<sup>2</sup> every 3 weeks [*see Clinical Studies (14.1)*]. The median duration of

exposure was 5.3 months (range: 1 day to 13.8+ months) with a median of eight doses (range: 1 to 31) in OPDIVO-treated patients and was 2 months (range: 1 day to 9.6+ months) in chemotherapy-treated patients. In this ongoing trial, 24% of patients received OPDIVO for greater than 6 months and 3% of patients received OPDIVO for greater than 1 year.

In Trial 1, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV.

The study population characteristics in the OPDIVO group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% white, baseline ECOG performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the OPDIVO group with elevated LDH at baseline (51% vs. 38%).

OPDIVO was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving OPDIVO had a drug delay for an adverse reaction. Serious adverse reactions occurred in 41% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in 2% to less than 5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase.

Table 2 summarizes the adverse reactions that occurred in at least 10% of OPDIVO-treated patients in Trial 1. The most common adverse reaction (reported in at least 20% of patients) was rash.

**Table 2: Selected Adverse Reactions Occurring in  $\geq 10\%$  of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]) (Trial 1)**

Adverse Reaction	OPDIVO (n=268)		Chemotherapy (n=102)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash <sup>a</sup>	21	0.4	7	0
Pruritus	19	0	3.9	0
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>				
Cough	17	0	6	0
<b>Infections and Infestations</b>				
Upper respiratory tract infection <sup>b</sup>	11	0	2.0	0
<b>General Disorders and Administration Site Conditions</b>				
Peripheral edema	10	0	5	0

<sup>a</sup> Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, and dermatitis acneiform.

<sup>b</sup> Upper respiratory tract infection is a composite term which includes rhinitis, pharyngitis, and nasopharyngitis.

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in Trial 1 were:

*Cardiac Disorders:* ventricular arrhythmia

*Eye Disorders:* iridocyclitis

*General Disorders and Administration Site Conditions:* infusion-related reactions

*Investigations:* increased amylase, increased lipase

*Nervous System Disorders:* dizziness, peripheral and sensory neuropathy

*Skin and Subcutaneous Tissue Disorders:* exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis

**Table 3: Selected Laboratory Abnormalities Worsening from Baseline Occurring in  $\geq 10\%$  of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]) (Trial 1)**

Test	Percentage of Patients with Worsening Laboratory Test from Baseline <sup>a</sup>			
	OPDIVO		Chemotherapy	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Increased AST	28	2.4	12	1.0
Increased alkaline phosphatase	22	2.4	13	1.1
Hyponatremia	25	5	18	1.1
Increased ALT	16	1.6	5	0
Hyperkalemia	15	2.0	6	0

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 252 to 256 patients) and chemotherapy group (range: 94 to 96 patients).

#### *OPDIVO in Combination with Ipilimumab*

The safety of OPDIVO, administered in combination with ipilimumab, was evaluated in Trial 4, a randomized, double-blind trial in which 140 previously untreated patients with unresectable or metastatic melanoma received OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for four cycles, followed by OPDIVO 3 mg/kg as a single agent every 2 weeks (n=94) or single-agent ipilimumab 3 mg/kg every 3 weeks for four cycles followed by placebo every 2 weeks (n=46) [see *Clinical Studies (14.1)*]. The median duration of exposure to OPDIVO was 2.2 months (range: 1 day to 10 months). Among patients who received OPDIVO in combination with ipilimumab, 29% were exposed to OPDIVO for at least 6 months.

Trial 4 enrolled patients who had not received systemic anticancer therapy for unresectable or metastatic melanoma and excluded patients with ocular melanoma, autoimmune disease, any condition requiring chronic systemic treatment with corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, or a history of HIV.

The study population characteristics were: 67% male, median age 65 years, 98% white, baseline ECOG performance status 0 (82%) or 1 (17%), 46% with M1c stage disease; 25% with elevated LDH at baseline, 3% with a history of brain metastasis, and 23% had BRAF V600 mutation-positive melanoma. There were more patients in the OPDIVO plus ipilimumab group who had cutaneous melanoma (84% vs. 62%), while a greater proportion of patients in the ipilimumab group had acral/mucosal melanoma (8% vs. 21%).

Serious adverse reactions (62% vs. 39%), adverse reactions leading to permanent discontinuation (43% vs. 11%) or dose delays (47% vs. 22%), and Grade 3 or 4 adverse reactions (69% vs. 43%) all occurred more frequently in patients receiving OPDIVO plus ipilimumab compared with those receiving single-agent ipilimumab. In the OPDIVO plus ipilimumab group, 27% (25/94) of patients did not complete all four cycles of OPDIVO in combination with ipilimumab. The first occurrence of a Grade 3 or 4 adverse reaction was during administration of OPDIVO in

combination with ipilimumab in 56 patients (59%) while 9 patients (10%) experienced first occurrence of a Grade 3 or 4 adverse reaction during administration of OPDIVO as a single agent.

The most common adverse reactions leading to discontinuation of OPDIVO, as compared to single-agent ipilimumab, were colitis (16% vs. 2%), diarrhea not treated with corticosteroids (4% vs. 4%), increased ALT levels (4% vs. 0), pneumonitis (3% vs. 0), and AST increase (3% vs. 0). The most frequent serious adverse events with OPDIVO in combination with ipilimumab, as compared to single-agent ipilimumab, were colitis (17% vs. 9%), diarrhea (9% vs. 7%), pyrexia (6% vs. 7%), and pneumonitis (5% vs. 0). The most common adverse reactions (reported in at least 20% of patients) in Trial 4 receiving OPDIVO in combination with ipilimumab were rash, pruritus, headache, vomiting, and colitis.

Table 4 summarizes the incidence of selected adverse reactions occurring in at least 10% of patients treated with OPDIVO, in combination with ipilimumab.

**Table 4: Selected Adverse Reactions Occurring in  $\geq 10\%$  of Patients Receiving OPDIVO in Combination with Ipilimumab and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]) (Trial 4)**

Adverse Reaction	OPDIVO plus Ipilimumab <sup>a</sup> (n=94)		Ipilimumab (n=46)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage (%) of Patients			
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash <sup>b</sup>	67	9	57	2.2
Pruritus	37	1.1	26	0
<b>Nervous System Disorders</b>				
Headache	24	2.1	20	0
<b>Gastrointestinal Disorders</b>				
Vomiting	23	2.1	15	0
Colitis	22	16	11	7
<b>Metabolism and Nutrition Disorders</b>				
Dehydration	17	3.2	7	2.2
<b>Endocrine Disorders</b>				
Hypothyroidism	14	0	9	0
Hypophysitis	13	2.1	7	4.3
<b>Eye Disorders</b>				
Blurred vision	12	0	0	0
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>				
Pneumonitis	10	2.1	2.2	0

<sup>a</sup> OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg as a single agent every 2 weeks until disease progression or unacceptable toxicity.

<sup>b</sup> Rash is a composite term which includes dermatitis, dermatitis acneiform, dermatitis bullous, erythema, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, and rash pruritic.

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in combination with ipilimumab were:

*Nervous system Disorders:* peripheral neuropathy

*Gastrointestinal Disorders:* stomatitis, colonic perforation

**Table 5: Selected Laboratory Abnormalities Worsening from Baseline Occurring in  $\geq 10\%$  of Patients Receiving OPDIVO in Combination with Ipilimumab and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]) (Trial 4)**

Test	Percentage of Patients with Worsening Laboratory Test from Baseline <sup>a</sup>			
	OPDIVO plus Ipilimumab <sup>b</sup>		Ipilimumab	
	All Grades	Grades 3-4	All Grades	Grades 3-4
<b>Chemistry</b>				
Increased ALT	45	13	20	0
Increased AST	43	10	22	0
Hyponatremia	38	9	20	2.2
Increased lipase	36	13	17	7
Increased alkaline phosphatase	30	0	17	0
Hypocalcemia	29	2.3	15	2.2
Increased creatinine	24	1.1	13	0
Increased amylase	23	6	9	0
Hypomagnesemia	15	0	9	0
Hypokalemia	15	3.4	7	0
<b>Hematology</b>				
Anemia	40	1.1	35	2.2
Lymphopenia	37	9	30	2.2
Neutropenia	11	1.1	2.2	0

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO in combination with ipilimumab group (range: 84 to 88 patients) and ipilimumab group (range: 45 to 46 patients).

<sup>b</sup> OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg as a single agent every 2 weeks until disease progression or unacceptable toxicity.

### Metastatic Non-Squamous Non-Small Cell Lung Cancer

The safety of OPDIVO was evaluated in Trial 3, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen [see *Clinical Studies (14.2)*]. Patients received 3 mg/kg of OPDIVO (n=287) administered intravenously over 60 minutes every 2 weeks or docetaxel (n=268) administered intravenously at 75 mg/m<sup>2</sup> every 3 weeks. The median duration of therapy was 2.6 months (range: 0 to 24.0+ months) in OPDIVO-treated patients and was 2.3 months (range: 0 to 15.9 months) in docetaxel-treated patients. In this trial, 30% of patients received

OPDIVO for greater than 6 months and 20% of patients received OPDIVO for greater than 1 year.

Trial 3 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease.

The median age of all randomized patients was 62 years (range: 21 to 85); 37% of patients in the OPDIVO group were ≥65 years of age and 47% of patients in the docetaxel group were ≥65 years of age, 55% were male, and 92% were white. Twelve percent of patients had brain metastases and ECOG performance status was 0 (31%) or 1 (69%).

OPDIVO was discontinued in 13% of patients, and was delayed in 29% of patients for an adverse reaction. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure. In the OPDIVO arm, seven deaths were due to infection including one case of pneumocystis jirovecii pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis.

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, cough, decreased appetite, and constipation. Table 6 summarizes selected adverse reactions occurring more frequently in at least 10% of OPDIVO-treated patients.

**Table 6: Selected Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 3)**

Adverse Reaction	OPDIVO (n=287)		Docetaxel (n=268)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>				
Cough	30	0.3	25	0
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite	29	1.7	22	1.5
<b>Gastrointestinal Disorders</b>				
Constipation	23	0.7	17	0.7
<b>Skin and Subcutaneous Tissue Disorders</b>				
Pruritus	11	0	1.9	0

Other clinically important adverse reactions observed in patients treated with OPDIVO and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (49% Grade 1-4, 6% Grade 3-4), musculoskeletal pain (36%), pleural effusion (5.6%), pulmonary embolism (4.2%), urticaria (1.4%), and polymyalgia rheumatica (0.3%).

**Table 7: Selected Laboratory Abnormalities Worsening from Baseline Occurring in  $\geq 10\%$  of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]) (Trial 3)**

Test	Percentage of Patients with Worsening Laboratory Test from Baseline <sup>a</sup>			
	OPDIVO		Docetaxel	
	All Grades	Grades 3-4	All Grades	Grades 3-4
<b>Chemistry</b>				
Hyponatremia	35	6	32	2.7
Increased AST	28	2.8	14	0.4
Increased alkaline phosphatase	27	1.1	18	0.4
Increased ALT	23	2.4	15	0.4
Increased creatinine	18	0	13	0.4
Increased TSH <sup>b</sup>	17	N/A	5	N/A

<sup>a</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 280 to 287 patients) and docetaxel group (range: 252 to 262 patients); TSH: OPDIVO group n=209 and docetaxel group n=207.

<sup>b</sup> Not graded per NCI CTCAE v4.0.

## 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Of 532 patients who were treated with OPDIVO 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 67 patients (12.6%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies against nivolumab were detected in five patients (0.9%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-nivolumab binding antibody development.

Of 105 patients who were treated with OPDIVO in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, 23 patients (21.9%) tested positive for treatment-emergent anti-nivolumab antibodies by an ECL assay. Neutralizing antibodies against nivolumab were detected in one patient (1%). There was no evidence of altered toxicity profile with anti-nivolumab antibody development.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to OPDIVO with the incidences of antibodies to other products may be misleading.

## 7 DRUG INTERACTIONS

No formal pharmacokinetic drug-drug interaction studies have been conducted with OPDIVO.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on its mechanism of action [*see Clinical Pharmacology (12.1)*] and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (12.1)*]. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death [*see Data*]. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

#### Data

##### *Animal Data*

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

## **8.2 Lactation**

### **Risk Summary**

It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment with OPDIVO.

## **8.3 Females and Males of Reproductive Potential**

### **Contraception**

Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO.

## **8.4 Pediatric Use**

The safety and effectiveness of OPDIVO have not been established in pediatric patients.

## **8.5 Geriatric Use**

Of the 272 patients randomized to OPDIVO in Trial 1, 35% of patients were 65 years or older and 15% were 75 years or older. Of the 292 patients randomized to OPDIVO in Trial 3, 37% of patients were 65 years or older and 7% were 75 years or older. In these trials, no overall differences in safety or efficacy were reported between elderly patients and younger patients. Trial 4, OPDIVO in combination with ipilimumab, did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

## **8.6 Renal Impairment**

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with renal impairment [see *Clinical Pharmacology (12.3)*].

## **8.7 Hepatic Impairment**

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild hepatic impairment. OPDIVO has not been studied in patients with moderate or severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

## **10 OVERDOSAGE**

There is no information on overdosage with OPDIVO.

## **11 DESCRIPTION**

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous infusion

is supplied in single-use vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.

### **12.3 Pharmacokinetics**

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent OPDIVO and OPDIVO in combination with ipilimumab.

*OPDIVO as a single agent:* The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO every 2 or 3 weeks. The geometric mean (% coefficient of variation [CV%]) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (V<sub>ss</sub>) is 8.0 L (30.4%), and geometric mean elimination half-life (t<sub>1/2</sub>) is 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

*OPDIVO in combination with ipilimumab:* The geometric mean (%CV) CL, V<sub>ss</sub>, and terminal half-life of nivolumab were 10.0 mL/h (50.3%), 7.92 L (30.1%), and 24.8 days (94.3%), respectively. When administered in combination, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab.

When administered in combination, the clearance of nivolumab increased by 42% in the presence of anti-nivolumab antibodies. There was no effect of anti-ipilimumab antibodies on the clearance of ipilimumab.

*Specific Populations:* Based on a population PK analysis, the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of

nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

*Renal Impairment:* The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m<sup>2</sup>; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m<sup>2</sup>; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m<sup>2</sup>; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function [see Use in Specific Populations (8.6)].

*Hepatic Impairment:* The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n=92). No clinically important differences in the clearance of nivolumab were found between patients with mild hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe hepatic impairment (TB greater than 3 times ULN and any AST) [see Use in Specific Populations (8.7)].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

### **13.2 Animal Toxicology and/or Pharmacology**

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *M. tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

## **14 CLINICAL STUDIES**

### **14.1 Unresectable or Metastatic Melanoma**

#### **OPDIVO as a Single Agent**

Trial 1 was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either OPDIVO administered intravenously at 3 mg/kg every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m<sup>2</sup> every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m<sup>2</sup> every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring systemic

immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in Trial 1 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed objective response rate (ORR) as measured by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response.

Among the 120 patients treated with OPDIVO, the median age was 58 years (range: 25 to 88), 65% of patients were male, 98% were white, and the Eastern Cooperative Oncology Group (ECOG) performance score was 0 (58%) or 1 (42%). Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), elevated LDH (56%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%).

The ORR was 32% (95% confidence interval: 23, 41), consisting of 4 complete responses and 34 partial responses in OPDIVO-treated patients. Of 38 patients with responses, 33 patients (87%) had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer.

There were objective responses in patients with and without BRAF V600 mutation positive-melanoma.

#### OPDIVO in Combination with Ipilimumab

Trial 4 was a multicenter, double-blind trial that randomized (2:1) patients with previously untreated, unresectable or metastatic melanoma to receive either OPDIVO in combination with ipilimumab or single-agent ipilimumab. Key eligibility criteria were no prior systemic therapy for metastatic disease; adjuvant treatment completed at least 6 weeks prior to the first dose was permitted. Patients with ocular melanoma, active brain metastasis, autoimmune disease, or medical condition requiring systemic immunosuppression were ineligible. Patients in the combination arm received OPDIVO 1 mg/kg and ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Patients in the ipilimumab arm received ipilimumab 3 mg/kg and OPDIVO-matched placebo intravenously every 3 weeks for 4 doses followed by placebo. At the time of disease progression, patients in the ipilimumab arm were offered OPDIVO 3 mg/kg every 2 weeks. Randomization was stratified by BRAF V600 mutation status based on an FDA-approved test. Tumor assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

The major efficacy outcome measure was confirmed ORR, as determined by investigator per RECIST v1.1, in patients with BRAF V600 wild-type melanoma. Additional efficacy outcome measures were investigator-assessed duration of response and progression-free survival (PFS) in patients with BRAF V600 wild-type melanoma.

Among the 109 randomized patients with BRAF V600 wild-type melanoma, the median age was 66 years (range: 27 to 87 years); 65% of patients were male; 97% were white; the ECOG performance score was 0 (84%) or 1 (15%). Forty-six percent of patients had M1c disease, 20% had elevated LDH at baseline, and 100% had no evidence of BRAF V600 mutation. Clinically important differences between arms in baseline characteristics were history of brain metastasis (6% in the combination arm and none in the ipilimumab arm), acral/mucosal melanoma (10% and 24%, respectively), and cutaneous melanoma (82% and 57%, respectively). Among patients randomized to OPDIVO in combination with ipilimumab, 59% received 4 doses of OPDIVO and ipilimumab over a median of 9.1 weeks (range: 9.0 weeks to 26.3 weeks).

The study demonstrated a statistically significant increase in the confirmed ORR for patients randomized to OPDIVO in combination with ipilimumab compared with those randomized to single-agent ipilimumab (see Table 8).

**Table 8: Efficacy Results in BRAF V600 Wild-Type Melanoma in Trial 4**

Endpoint	OPDIVO plus Ipilimumab <sup>a</sup> (n=72)	Ipilimumab (n=37)
<b>Objective Response Rate (95% CI)</b>	60% (48, 71)	11% (3, 25)
Difference in ORR (95% CI)	49 (31, 61)	
p-value	<0.001	
CR (%)	17%	0
PR (%)	43%	11%
<b>Progression-free Survival</b>		
Number of events	27	23
Median PFS (months) (95% CI)	8.9 (7.0, NA)	4.7 (2.8, 5.3)
Hazard ratio (95% CI)	0.40 (0.22, 0.71)	
p-value	<0.002	

<sup>a</sup> OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg as a single agent every 2 weeks until disease progression or unacceptable toxicity.

Of 43 patients randomized to OPDIVO in combination with ipilimumab, 9 patients (21%) with response duration ranging from 3 to 7 months have progressed after response, died, or received subsequent therapy. The remaining 34 patients (79%) had ongoing responses at the time of final analysis; in 14 patients the duration of ongoing responses is at least 6 months but less than 9 months and in 20 patients the duration of ongoing responses is at least 9 months.

## 14.2 Metastatic Non-Small Cell Lung Cancer

### Second-line Treatment of Metastatic Squamous NSCLC

Trial 2 was a randomized (1:1), open-label study enrolling 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received OPDIVO (n=135) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=137) administered intravenously at 75 mg/m<sup>2</sup> every 3 weeks. This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, symptomatic interstitial lung disease, or untreated

brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was overall survival (OS).

In Trial 2, the median age was 63 years (range: 39 to 85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were white (93%) and male (76%). Baseline ECOG performance status was 0 (24%) or 1 (76%).

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis) (Table 9 and Figure 1).

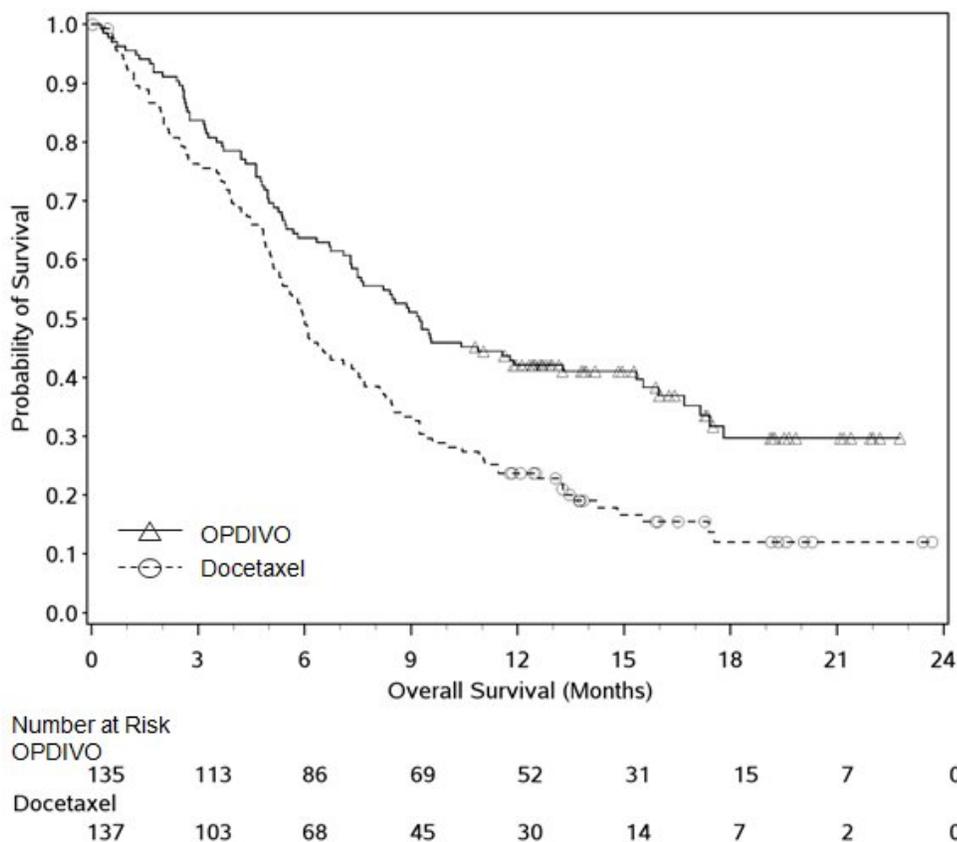
**Table 9: Overall Survival in Trial 2 (Intent-to-Treat Analysis)**

	<b>OPDIVO (n=135)</b>	<b>Docetaxel (n=137)</b>
<b>Prespecified Interim Analysis</b>		
Events (%)	86 (64%)	113 (82%)
Median survival in months (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
p-value <sup>a</sup>	0.00025	
Hazard ratio (95% CI) <sup>b</sup>	0.59 (0.44, 0.79)	

<sup>a</sup> P-value is derived from a log-rank test stratified by region and prior paclitaxel use; the corresponding O'Brien-Fleming efficacy boundary significance level is 0.0315.

<sup>b</sup> Derived from a stratified proportional hazards model.

**Figure 1: Overall Survival - Trial 2**



### Second-line Treatment of Metastatic Non-Squamous NSCLC

Trial 3 was a randomized (1:1), open-label study of 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. Patients received OPDIVO (n=292) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=290) administered intravenously at 75 mg/m<sup>2</sup> every 3 weeks. Randomization was stratified by prior maintenance therapy (yes vs. no) and number of prior therapies (1 vs. 2). The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures were investigator-assessed objective response rate (ORR) and progression-free survival (PFS). In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression.

In Trial 3, the median age was 62 years (range: 21 to 85) with 42% of patients  $\geq 65$  years and 7% of patients  $\geq 75$  years. The majority of patients were white (92%) and male (55%); the majority of patients were enrolled in Europe (46%) followed by the US/Canada (37%) and the rest of the world (17%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. Prior therapy included platinum-doublet regimen (100%) and 40% received maintenance therapy as part of the first-line regimen. Histologic subtypes included adenocarcinoma (93%), large cell (2.4%), and bronchoalveolar (0.9%).

Trial 3 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis) (Table 10 and Figure 2).

**Table 10: Efficacy Results in Trial 3**

	<b>OPDIVO (n=292)</b>	<b>Docetaxel (n=290)</b>
<b>Overall Survival</b>		
Deaths (%)	190 (65%)	223 (77%)
Median (months) (95% CI)	12.2 (9.7, 15.0)	9.4 (8.0, 10.7)
p-value <sup>a,b</sup> Hazard ratio (95% CI) <sup>c</sup>	0.0015 0.73 (0.60, 0.89)	
<b>Objective Response Rate</b>		
(95% CI)	56 (19%) (15, 24)	36 (12%) (9, 17)
p-value <sup>d</sup>	0.02	
Complete response	4 (1.4%)	1 (0.3%)
Partial response	52 (18%)	35 (12%)
Median duration of response (months)	17	6
<b>Progression-free Survival</b>		
Disease progression or death (%)	234 (80%)	245 (84%)
Median (months)	2.3	4.2
p-value <sup>a</sup> Hazard ratio (95% CI) <sup>c</sup>	0.39 0.92 (0.77, 1.11)	

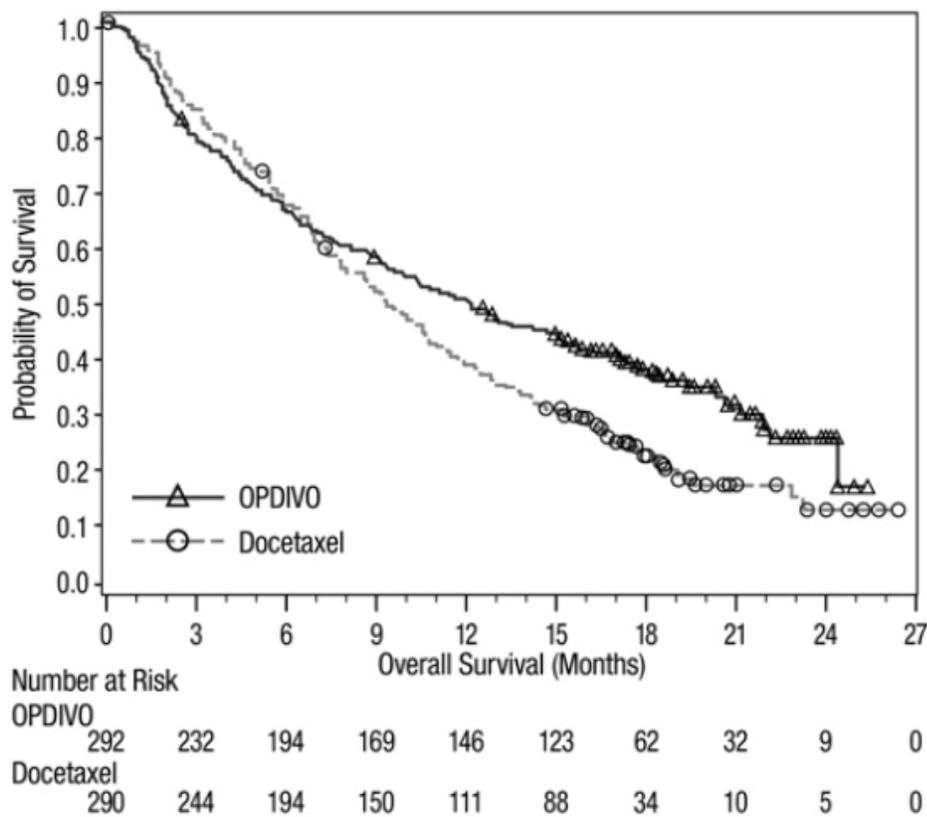
<sup>a</sup> Based on stratified log-rank test.

<sup>b</sup> p-value is compared with .0408 of the allocated alpha for this interim analysis.

<sup>c</sup> Based on a stratified proportional hazards model.

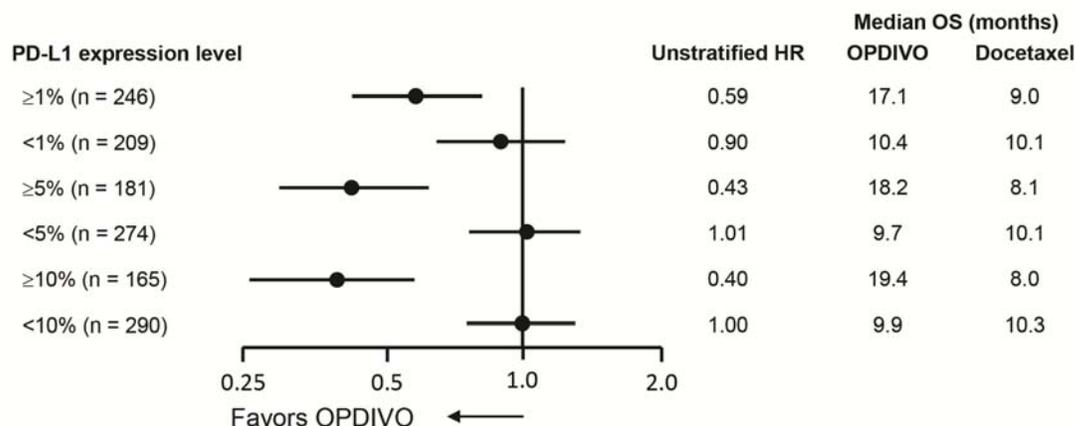
<sup>d</sup> Based on the stratified Cochran-Mantel-Haenszel test.

**Figure 2: Overall Survival - Trial 3**

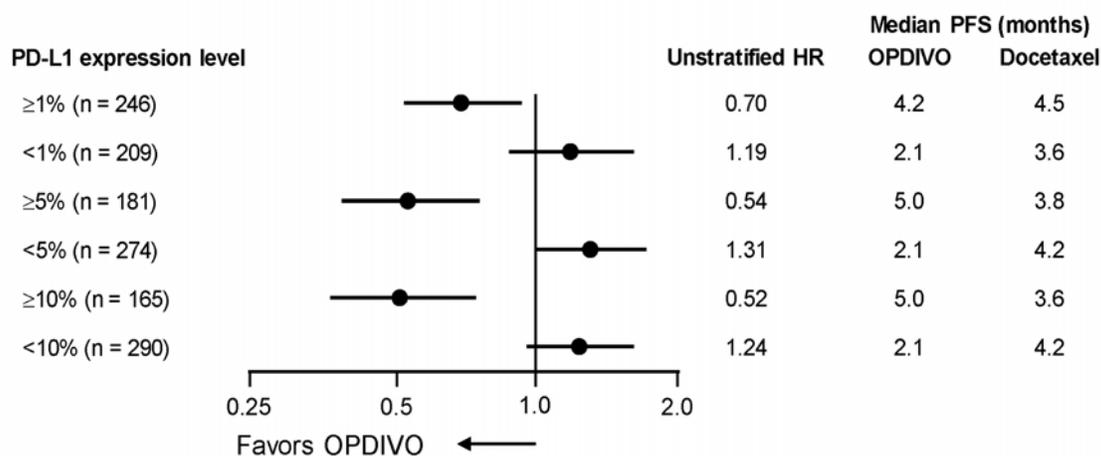


Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% (209/455) PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% (246/455) had PD-L1 expression, defined as  $\geq 1\%$  of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% (65/246) had  $\geq 1\%$ , but <5% tumor cells with positive staining, 7% (16/246) had  $\geq 5\%$  but <10% tumor cells with positive staining, and 67% (165/246) had greater than or equal to 10% tumor cells with positive staining. Figure 3 summarizes the results of prespecified analyses of survival in subgroups determined by percentage of tumor cells expressing PD-L1. Figure 4 summarizes the results of prespecified analyses of progression-free survival in subgroups determined by percentage of tumor cells expressing PD-L1.

**Figure 3: Forest Plot: OS Based on PD-L1 Expression - Trial 3**



**Figure 4: Forest Plot: PFS Based on PD-L1 Expression - Trial 3**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO<sup>®</sup> (nivolumab) is available as follows:

Carton Contents	NDC
40 mg/4 mL single-use vial	0003-3772-11
100 mg/10 mL single-use vial	0003-3774-12

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

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see *Warnings and Precautions (5.1)*].
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [see *Warnings and Precautions (5.2)*].
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see *Warnings and Precautions (5.3)*].
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, and hyperthyroidism [see *Warnings and Precautions (5.4)*].
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction [see *Warnings and Precautions (5.5)*].
- Rash: Advise patients to contact their healthcare provider immediately for rash [see *Warnings and Precautions (5.6)*].
- Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis [see *Warnings and Precautions (5.7)*].
- Infusion Reactions: Advise patients of the potential risk of infusion reaction [see *Warnings and Precautions (5.9)*].
- Females of Reproductive Potential: Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.10)*, *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO [see *Use in Specific Populations (8.3)*].
- Lactation: Advise women not to breastfeed while taking OPDIVO [see *Use in Specific Populations (8.2)*].

Manufactured by:

Bristol-Myers Squibb Company

Princeton, NJ 08543 USA

U.S. License No. 1713

**MEDICATION GUIDE**  
**OPDIVO® (op-DEE-voh)**  
**(nivolumab)**  
**injection**

Read this Medication Guide before you start receiving OPDIVO and before each infusion. There may be new information. If your healthcare provider prescribes OPDIVO in combination with ipilimumab (YERVOY®), also read the Medication Guide that comes with ipilimumab. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is the most important information I should know about OPDIVO?**

OPDIVO is a medicine that may treat your melanoma or lung cancer by working with your immune system. OPDIVO can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death. These problems may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when OPDIVO is used in combination with ipilimumab.

**Call or see your healthcare provider right away if you develop any symptoms of the following problems or these symptoms get worse:**

**Lung problems (pneumonitis).** Symptoms of pneumonitis may include:

- new or worsening cough
- chest pain
- shortness of breath

**Intestinal problems (colitis) that can lead to tears or holes in your intestine.** Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- severe stomach-area (abdomen) pain or tenderness

**Liver problems (hepatitis).** Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual

**Hormone gland problems (especially the thyroid, pituitary, and adrenal glands).**

Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- hair loss
- feeling cold
- constipation
- voice gets deeper

**Kidney problems, including nephritis and kidney failure.** Signs of kidney problems may include:

- decrease in the amount of urine
- blood in your urine
- swelling in your ankles
- loss of appetite

**Inflammation of the brain (encephalitis).** Signs and symptoms of encephalitis may include:

- headache
- fever
- tiredness or weakness
- confusion
- memory problems
- sleepiness
- seeing or hearing things that are not really there (hallucinations)
- seizures
- stiff neck

**Problems in other organs.** Signs of these problems may include:

- rash
- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness

**Getting medical treatment right away may keep these problems from becoming more serious.**

Your healthcare provider will check you for these problems during treatment with OPDIVO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with OPDIVO, if you have severe side effects.

### **What is OPDIVO?**

OPDIVO is a prescription medicine used to treat:

- **a type of skin cancer called melanoma.**

**OPDIVO may be used alone when your melanoma:**

- has spread or cannot be removed by surgery (advanced melanoma), **and**,
- after you have tried a medicine called ipilimumab and it did not work or is no longer working **and**,
- if your tumor has an abnormal "BRAF" gene, and you have also tried a different medicine called a BRAF inhibitor, and it did not work or is no longer working.

**OPDIVO may be used in combination with the medicine ipilimumab when your melanoma:**

- has spread or cannot be removed by surgery (advanced melanoma), **and**
- has a normal BRAF gene (wild-type)

- **a type of advanced stage lung cancer (called non-small cell lung cancer)**

**OPDIVO may be used when your lung cancer:**

- has spread or grown and,
- you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

If your tumor has an abnormal EGFR or ALK gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, **and** it did not work or is no longer working.

It is not known if OPDIVO is safe and effective in children less than 18 years of age.

**What should I tell my healthcare provider before receiving OPDIVO?**

**Before you receive OPDIVO, tell your healthcare provider if you:**

- have immune system problems such as Crohn’s disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. OPDIVO can harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during and for at least 5 months after the last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant during treatment with OPDIVO.
- are breastfeeding or plan to breastfeed. It is not known if OPDIVO passes into your breast milk. **Do not** breastfeed during treatment with OPDIVO.

**Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.**

Know the medicines you take. Keep a list of them to show your healthcare providers and pharmacist when you get a new medicine.

**How will I receive OPDIVO?**

- Your healthcare provider will give you OPDIVO into your vein through an intravenous (IV) line over 60 minutes.
- OPDIVO is usually given every 2 weeks.
- When used in combination with ipilimumab, OPDIVO is usually given every 3 weeks, for a total of 4 doses. After that, OPDIVO will be given alone every 2 weeks. Ipilimumab will be given through an IV line over 90 minutes.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments call your healthcare provider as soon as possible to reschedule your appointment.

**What are the possible side effects of OPDIVO?**

**OPDIVO can cause serious side effects, including:**

- **See “What is the most important information I should know about OPDIVO?”**
- **Severe infusion reactions.** Tell your doctor or nurse right away if you get these symptoms during an infusion of OPDIVO:
  - chills or shaking
  - itching or rash
  - flushing
  - difficulty breathing
  - dizziness
  - fever
  - feeling like passing out

**The most common side effect of OPDIVO when used alone in people with melanoma is rash.**

The most common side effects of OPDIVO when used in combination with ipilimumab include:

- rash
- itching
- inflammation of the intestines (colitis). **See “What is the most important information I should know about OPDIVO?”**
- headache
- vomiting

**The most common side effects of OPDIVO in people with non-small cell lung cancer include:**

- feeling tired
- pain in muscles, bones, and joints
- decreased appetite
- cough
- constipation

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OPDIVO. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of OPDIVO.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about OPDIVO, talk with your healthcare provider. You can ask your healthcare provider for information about OPDIVO that is written for health professionals. For more information, call 1-855-673-4861 or go to [www.OPDIVO.com](http://www.OPDIVO.com).

**What are the ingredients in OPDIVO?**

**Active ingredient:** nivolumab

**Inactive ingredients:** mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and Water for Injection. May contain hydrochloric acid and/or sodium hydroxide.

Manufactured by:  
Bristol-Myers Squibb Company  
Princeton, NJ 08543 USA

U.S. License No. 1713

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: October 2015