

## 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)	05/2016
Dosage and Administration (2)	05/2016
Warnings and Precautions (5)	05/2016

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

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

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent. (1.1)
- BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- Unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- Metastatic non-small cell lung cancer and 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)
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.3)
- Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. 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. (1.4)

#### -----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 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)
- Advanced renal cell carcinoma
  - OPDIVO 3 mg/kg every 2 weeks. (2.3)
- Classical Hodgkin lymphoma
  - OPDIVO 3 mg/kg every 2 weeks. (2.4)

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

Injection: 40 mg/4 mL and 100 mg/10 mL solution in a single-dose 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: Withhold OPDIVO when given as a single agent for moderate or severe and permanently discontinue for life-threatening colitis. Withhold OPDIVO when given with ipilimumab 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. Monitor for hyperglycemia. Withhold for severe and permanently discontinue for life-threatening hyperglycemia. (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)
- Infusion reactions: Discontinue OPDIVO for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. (5.9)
- Complications of allogeneic HSCT after OPDIVO: Monitor for hyperacute graft-versus-host-disease (GVHD), grade 3-4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions. Transplant-related mortality has occurred. (5.10)
- Embryo-fetal 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: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, and nausea. (6.1)
- OPDIVO with ipilimumab: fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea. (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)

Most common adverse reactions (≥20%) in patients with advanced renal cell carcinoma were: asthenic conditions, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia. (6.1)

Most common adverse reactions (≥20%) in patients with classical Hodgkin lymphoma were: fatigue, upper respiratory tract infection, pyrexia, diarrhea, and cough. (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: 05/2016

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Unresectable or Metastatic Melanoma

- OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma [see *Clinical Studies (14.1)*].
- OPDIVO (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma [see *Clinical Studies (14.1)*].

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

OPDIVO (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)*].

#### 1.3 Renal Cell Carcinoma

OPDIVO (nivolumab) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy [see *Clinical Studies (14.3)*].

#### 1.4 Classical Hodgkin Lymphoma

OPDIVO (nivolumab) is indicated for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin [see *Clinical Studies (14.4)*]. 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 [see *Clinical Studies (14.4)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage for Melanoma

The recommended dose of OPDIVO 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 Recommended Dosage for RCC

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.

## 2.4 Recommended Dosage for cHL

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.

## 2.5 Dose Modifications

Recommendations for OPDIVO modifications are provided in Table 1. When OPDIVO is administered in combination with ipilimumab, if OPDIVO is withheld, ipilimumab should also be withheld.

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	Withhold dose <sup>a</sup> when administered as a single agent Permanently discontinue when administered with ipilimumab
	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

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

Adverse Reaction	Severity*	Dose Modification
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose <sup>a</sup>
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose <sup>a</sup>
	Grade 4 hyperglycemia	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

\* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4).

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

## 2.6 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-dose vial.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with OPDIVO treatment. Across clinical trial experience in patients receiving OPDIVO, fatal immune-mediated pneumonitis occurred in 0.2% (5/2166) 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 501 patients with melanoma who received OPDIVO with ipilimumab, in Trial 4 (n=94), Trial 7 (n=313), and an additional dose-finding study (n=94), fatal immune-mediated pneumonitis occurred in 0.2% (1/501) 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* (2.5)].

## **Melanoma**

### *OPDIVO as a Single Agent*

In Trials 1, 5, and 7, immune-mediated pneumonitis occurred in 1.8% (14/787) of patients receiving OPDIVO: two patients with Grade 3 and 12 patients with Grade 2 pneumonitis. The median time to onset of immune-mediated pneumonitis was 2.2 months (range: 25 days to 9.7 months). Grade 3 pneumonitis led to permanent discontinuation in one patient (0.1%), and Grade 2 pneumonitis led to withholding of OPDIVO in eight patients (1.0%). All 14 patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 18 days (range: 4 days to 1.2 months). Complete resolution (defined as complete resolution of symptoms with completion of corticosteroids) occurred in 11 patients. None of the seven patients who resumed OPDIVO after resolution had recurrence of pneumonitis.

### *OPDIVO with Ipilimumab*

In Trials 4 and 7, immune-mediated pneumonitis occurred in 6% (25/407) of patients receiving OPDIVO with ipilimumab: 1 fatal, 6 Grade 3, 17 Grade 2, and 1 Grade 1 pneumonitis. The median time to onset of immune-mediated pneumonitis was 1.6 months (range: 24 days to 10.1 months). Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO and of ipilimumab in nine patients (2.2%) and withholding of OPDIVO and of ipilimumab in 15 patients (3.7%). Twenty-one patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 30 days (range: 5 days to 11.8 months). One patient with Grade 2 pneumonitis required mycophenolic acid in addition to high-dose corticosteroids. Complete resolution occurred in 17 patients. Among the eight patients who resumed OPDIVO with ipilimumab, one had recurrence of immune-mediated pneumonitis.

## **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.

## **RCC**

In Trial 6, pneumonitis, including interstitial lung disease, occurred in 5% (21/406) of patients receiving OPDIVO and 18% (73/397) patients receiving everolimus. Immune-mediated pneumonitis occurred in 4.4% (18/406) of patients receiving OPDIVO (one with Grade 4, four with Grade 3, twelve with Grade 2, and one with Grade 1). In two of the patients, pneumonitis occurred after they had received OPDIVO followed by everolimus. One patient with ongoing pneumonitis died due to disease progression. The median time to onset was 3.82 months (range: 2 days to 22.3 months). The median duration was 1.3 months (range: 0.3 to 9.8 months).

OPDIVO was permanently discontinued in six patients. Dose delay occurred in nine patients. Seven patients had complete resolution. Among the six patients who resumed OPDIVO, three did not have recurrence of pneumonitis.

## **cHL**

In Trials 8 and 9, pneumonitis, including interstitial lung disease, occurred in 4.9% (13/263) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 3.4% (9/263) of patients receiving OPDIVO (one Grade 3 and eight Grade 2). The median time to onset was 2.2 months (range: 1 day to 10.1 months). All nine patients received systemic corticosteroids, with resolution in seven. One patient permanently discontinued OPDIVO due to Grade 2 pneumonitis. Dose delay occurred in three patients. Five patients resumed OPDIVO, of whom none had 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 (2.5)*].

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 (2.5)*].

## **Melanoma**

### *OPDIVO as a Single Agent*

In Trials 1, 5, and 7, diarrhea or colitis occurred in 31% (242/787) of patients. Immune-mediated colitis occurred in 4.1% (32/787) of patients: 20 patients with Grade 3, 10 patients with Grade 2, and two patients with Grade 1 colitis. The median time to onset of immune-mediated colitis was 5.6 months (range: 3 days to 13.1 months). Immune-mediated colitis led to permanent discontinuation of OPDIVO in seven patients (0.9%) and to withholding of OPDIVO in six patients (0.8%). Thirty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 4.2 months (range: 3 days to 9.3 months). Three patients with Grade 2 or 3 colitis required addition of infliximab to high-dose corticosteroids. Complete resolution (defined as improved to baseline with completion of corticosteroids) occurred in 17 patients. Among the nine patients who resumed OPDIVO after resolution, two had recurrence of immune-mediated colitis.



### *OPDIVO with Ipilimumab*

In Trials 4 and 7, diarrhea or colitis occurred in 56% (228/407) of patients. Immune-mediated colitis occurred in 26% (107/407) of patients: 2 patients with Grade 4, 60 patients with Grade 3, 32 patients with Grade 2, and 13 patients with Grade 1 colitis. The median time to onset of immune-mediated colitis was 1.6 months (range: 3 days to 15.2 months). Immune-mediated colitis led to permanent discontinuation of OPDIVO and of ipilimumab in 64 patients (16%) or to withholding of OPDIVO and of ipilimumab in 30 patients (7%). One hundred three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.1 month (range: 1 day to 11.7 months). Twenty-five patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 80 patients. Among the 29 patients who resumed OPDIVO with ipilimumab after resolution, eight had recurrence of immune-mediated colitis. 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.

### **RCC**

In Trial 6, diarrhea or colitis occurred in 25% (100/406) of patients receiving OPDIVO and 32% (126/397) of patients receiving everolimus. Immune-mediated diarrhea or colitis occurred in 3.2% (13/406) of patients receiving OPDIVO (five patients with Grade 3, seven with Grade 2, and one with Grade 1). The median time to onset was 4.8 months (range: 2 days to 15.6 months). The median duration was 1.3 months (range: 0.2 to 3.9 months). OPDIVO was permanently discontinued in four patients. Dose delay occurred in nine patients. Twelve patients had complete resolution. Among the nine patients who resumed OPDIVO after resolution, four had no recurrence of diarrhea or colitis.

### **cHL**

In Trials 8 and 9, diarrhea or colitis occurred in 30% (80/263) of patients receiving OPDIVO. Immune-mediated diarrhea (Grade 3) occurred in 1.1% (3/263) of patients.

## **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 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations, with or without

concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) 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 (2.5)*].

## **Melanoma**

### *OPDIVO as a Single Agent*

In Trials 1, 5, and 7, immune-mediated hepatitis occurred in 2.3% (18/787) of patients receiving OPDIVO: three patients with Grade 4, 11 patients with Grade 3, and four patients with Grade 2 hepatitis. The median time to onset was 3.7 months (range: 6 days to 9 months). Immune-mediated hepatitis led to permanent discontinuation of OPDIVO in five patients (0.6%) and withholding of OPDIVO in six patients (0.8%). All 18 patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 28 days (range: 5 days to 2 months). One patient with Grade 3 hepatitis required the addition of mycophenolic acid to high-dose corticosteroids. Complete resolution (defined as improved to baseline with completion of corticosteroids) occurred in 13 patients. Among the four patients who resumed OPDIVO after resolution, one had recurrence of immune-mediated hepatitis.

### *OPDIVO with Ipilimumab*

In Trials 4 and 7, immune-mediated hepatitis occurred in 13% (51/407) of patients receiving OPDIVO with ipilimumab: eight patients with Grade 4, 37 patients with Grade 3, five patients with Grade 2, and one patient with Grade 1 hepatitis. The median time to onset was 2.1 months (range: 15 days to 11 months). Immune-mediated hepatitis led to permanent discontinuation of OPDIVO and of ipilimumab in 26 patients (6%) and withholding of OPDIVO and of ipilimumab in 21 patients (5%). Forty-seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.1 month (range: 1 day to 13.2 months). One patient (Grade 3 hepatitis) required infliximab, and four patients (three patients with Grade 3 or 4 transaminase increases and one patient with Grade 3 autoimmune hepatitis) required mycophenolic acid in addition to high-dose corticosteroids. Complete resolution occurred in 38 patients. Among the nine patients who resumed OPDIVO with ipilimumab after resolution, one had recurrence of hepatitis.

## **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.

## **RCC**

In Trial 6, there was an increased incidence of liver test abnormalities compared to baseline with increases in AST (33% vs. 39%), alkaline phosphatase (32% vs. 32%), ALT (22% vs. 31%), and total bilirubin (9% vs. 3.5%) in the OPDIVO and everolimus arms, respectively. Immune-

mediated hepatitis requiring systemic immunosuppression occurred in 1.5% (6/406) of patients receiving OPDIVO (five with Grade 3 and one with Grade 2). None of the six patients had liver metastases. The median time to onset was 3.7 months (range: 14 days to 5.3 months). The median duration was 1.8 months (range: 0.9 to 16.3 months). OPDIVO was permanently discontinued in four patients. Dose delay occurred in all patients. Five patients had complete resolution. Among the three patients who resumed OPDIVO, two had no recurrence of liver test abnormalities. One patient with immune-mediated nephritis developed hepatic failure on the date of death.

## **cHL**

In Trials 8 and 9, hepatitis occurred in 11% (30/263) of patients receiving OPDIVO. Immune-mediated hepatitis occurred in 3.4% (9/263) of patients (seven with Grade 3 and two with Grade 2), with a median time to onset of 2.4 months (range 1.5 to 6 months). Three patients permanently discontinued OPDIVO, and five patients had dose delay. All nine patients received systemic corticosteroids and one patient also received mycophenolic acid, with resolution in seven patients. Among the six patients who resumed OPDIVO, one had recurrence of the event.

## **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* (2.5)].

### **Melanoma**

#### *OPDIVO as a Single Agent*

In Trials 1, 5, and 7, hypophysitis occurred in 0.9% (7/787) of patients: two patients with Grade 3, three patients with Grade 2, and two patients with Grade 1 hypophysitis. The median time to onset was 5.5 months (range: 1.6 to 11 months). Hypophysitis led to withholding of OPDIVO in one patient (0.1%). Three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 22 days (range: 5 to 26 days).

#### *OPDIVO with Ipilimumab*

In Trials 4 and 7, hypophysitis occurred in 9% (36/407) of patients: eight patients with Grade 3, 25 patients with Grade 2, and three patients with Grade 1 hypophysitis. The median time to onset was 2.7 months (range: 27 days to 5.5 months). Hypophysitis led to permanent discontinuation of OPDIVO and of ipilimumab in four patients (1.0%) and withholding of OPDIVO and of ipilimumab in 16 patients (3.9%). Twenty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 19 days (range: 1 day to 2.0 months).

## **RCC**

In Trial 6, hypophysitis occurred in 0.5% (2/406) of patients receiving OPDIVO. The time to onset for the Grade 3 event was 9.2 months and for the Grade 1 event was 3.2 months. Both patients received steroid replacement doses. The Grade 3 event resulted in permanent discontinuation and the other patient with the Grade 1 event discontinued due to progressive disease. Neither patient had complete resolution or resumed treatment with OPDIVO.

## **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* (2.5)].

## **Melanoma**

### *OPDIVO as a Single Agent*

In Trials 1, 5, and 7, adrenal insufficiency occurred in 1% (8/787) of patients: two patients with Grade 3, five patients with Grade 2, and one patient with Grade 1 adrenal insufficiency. The median time to onset was 3.6 months (range: 15 days to 5.0 months). Adrenal insufficiency led to withholding of OPDIVO in four patients (0.5%). One patient received high-dose corticosteroids (at least 40 mg prednisone equivalents) for 11 days.

### *OPDIVO with Ipilimumab*

In Trials 4 and 7, adrenal insufficiency occurred in 5% (21/407) of patients: one patient with Grade 4, seven patients with Grade 3, 11 patients with Grade 2, and two patients with Grade 1 adrenal insufficiency. The median time to onset was 3.0 months (range: 21 days to 9.4 months). Adrenal insufficiency led to permanent discontinuation of OPDIVO and of ipilimumab in two patients (0.5%) and withholding of OPDIVO and of ipilimumab in seven patients (1.7%). Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 9 days (range: 1 day to 2.7 months).

## **NSCLC**

In Trial 3, 0.3% (1/287) of OPDIVO-treated patients developed adrenal insufficiency.

## **RCC**

In Trial 6, adrenal insufficiency occurred in 2.0% (8/406) of patients receiving OPDIVO (three with Grade 3, four with Grade 2, and one with Grade 1). The median time to onset was 5.8 months (range: 22 days to 20.9 months). OPDIVO was permanently discontinued in one patient. Dose delay occurred in five patients.

## **cHL**

In Trials 8 and 9, adrenal insufficiency (Grade 2) occurred in 0.4% (1/263) of patients receiving OPDIVO.

## **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**

### *OPDIVO as a Single Agent*

In Trials 1, 5, and 7, hypothyroidism or thyroiditis occurred in 9% (73/787) of patients: one patient with Grade 3, 37 patients with Grade 2, and 35 patients with Grade 1 hypothyroidism. The median time to onset was 2.8 months (range: 15 days to 13.8 months). Resolution occurred in 26 patients. Management of hypothyroidism included levothyroxine in 56 patients.

Hyperthyroidism occurred in 4.4% (35/787) of patients receiving OPDIVO: one patient with Grade 3, 12 patients with Grade 2, and 22 patients with Grade 1 hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 13.4 months). Resolution occurred in 27 patients. Management of hyperthyroidism included methimazole (five patients), carbimazole (four patients), and propylthiouracil (two patients).

### *OPDIVO with Ipilimumab*

In Trials 4 and 7, hypothyroidism or thyroiditis occurred in 22% (89/407) of patients: six patients with Grade 3, 47 patients with Grade 2, and 36 patients with Grade 1 hypothyroidism. The median time to onset was 2.1 months (range: 1 day to 10.1 months). Resolution occurred in 40 patients. Management of hypothyroidism included levothyroxine (65 patients).

Hyperthyroidism occurred in 8% (34/407) of patients receiving OPDIVO with ipilimumab: four patients with Grade 3, 17 patients with Grade 2, and 13 patients with Grade 1 hyperthyroidism. The median time to onset was 23 days (range: 3 days to 3.7 months). Resolution occurred in 32 patients. Management of hyperthyroidism included methimazole (ten patients) and carbimazole (eight patients).

## **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 thyroid stimulating hormone (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.

## **RCC**

In Trial 6, thyroid disease occurred in 11% (43/406) of patients on OPDIVO, including one Grade 3 event, and in 12/397 (3.0%) patients on everolimus. Hypothyroidism/thyroiditis occurred in 8% (33/406) of patients receiving OPDIVO (two patients with Grade 3, 17 patients with Grade 2, and 14 patients with Grade 1). The median time to onset was 4.6 months (range: 15 days to 13.6 months). Twenty-eight of the 33 patients received levothyroxine. No events led to permanent discontinuation. Dose delay occurred in four patients. Four patients, including three patients that never required levothyroxine, had complete resolution and three of these four patients continued OPDIVO throughout the event.

Hyperthyroidism occurred in 2.5% (10/406) of patients receiving OPDIVO (five patients with Grade 2 and five patients with Grade 1). The median time to onset was 3 months (range: 24 days to 14.2 months). No events led to permanent discontinuation. Seven patients had complete resolution. Seven were treated through the event and two had a dose delay with no recurrence of hyperthyroidism when OPDIVO was resumed. Four patients developed hyperthyroidism followed by hypothyroidism.

## **cHL**

In Trials 8 and 9, hypothyroidism/thyroiditis occurred in 12% (32/263) of patients receiving OPDIVO (18 with Grade 2 and 14 with Grade 1). The median time to onset was 2.8 months (range: 1 day to 16.6 months). Twenty of the 32 patients received levothyroxine. Two patients had dose delay. No immunosuppressant therapy was required for hypothyroidism.

Hyperthyroidism occurred in 1.5% (4/263) of patients receiving OPDIVO (three Grade 2 and one Grade 1). The time to onset ranged from 1 to 2.5 months.

## **Type 1 Diabetes Mellitus**

Type 1 diabetes mellitus can occur with OPDIVO treatment. Monitor for hyperglycemia. Administer insulin for type 1 diabetes and withhold OPDIVO in cases of severe (Grade 3)

hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia.

### **Melanoma**

#### *OPDIVO as a Single Agent*

In Trials 1, 5, and 7, diabetes mellitus or diabetic ketoacidosis occurred in 0.8% (6/787) of patients: two patients with Grade 3, three patients with Grade 2, and one patient with Grade 1 events. The median time to onset was 3.6 months (range: 1.4 to 12 months). Four patients initiated insulin and four patients initiated oral hypoglycemic therapy.

#### *OPDIVO with Ipilimumab*

In Trials 4 and 7, diabetes mellitus or diabetic ketoacidosis occurred in 1.5% (6/407) of patients: three patients with Grade 4, one patient with Grade 3, one patient with Grade 2, and one patient with Grade 1 events. The median time to onset was 2.5 months (range: 1.3 to 4.4 months). Grade 4 diabetes led to permanent discontinuation of OPDIVO and of ipilimumab in one patient and Grade 3 diabetes led to withholding of OPDIVO and of ipilimumab in one patient. Six patients initiated insulin and four patients initiated oral hypoglycemic therapy.

### **RCC**

In Trial 6, hyperglycemic adverse events occurred in 9% (37/406) of patients. Diabetes mellitus or diabetic ketoacidosis occurred in 1.5% (6/406) of patients receiving OPDIVO (three patients with Grade 3, two patients with Grade 2, and one patient with Grade 1). The median time to onset was 7.8 months (range: 2.3 to 21.8 months). Four patients received insulin. One patient was on corticosteroids prior to the event. No events led to permanent discontinuation. Dose delay occurred in one patient. One patient had ongoing hyperglycemia when OPDIVO was resumed.

### **cHL**

In Trials 8 and 9, diabetes mellitus occurred in 0.8% (2/263) of patients receiving OPDIVO (one Grade 3 and one Grade 1).

## **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 (2.5) and Adverse Reactions (6.1)*].

## **Melanoma**

### *OPDIVO as a Single Agent*

In Trials 1, 5, and 7, nephritis and renal dysfunction of any grade occurred in 5% (40/787) of patients. Immune-mediated nephritis and renal dysfunction occurred in 0.8% (6/787) of patients: four patients with Grade 3 and two patients with Grade 2 cases. The median time to onset of immune-mediated nephritis and renal dysfunction was 4.8 months (range: 1 to 7.5 months). Immune-mediated nephritis and renal dysfunction led to withholding of OPDIVO in four patients (0.5%). Six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 16 days (range: 1 day to 9.9 months). Complete resolution (defined as improved to baseline with completion of corticosteroids) occurred in three patients. Three patients resumed OPDIVO after resolution without recurrence of nephritis or renal dysfunction.

### *OPDIVO with Ipilimumab*

In Trials 4 and 7, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients: four patients with Grade 4, three patients with Grade 3, and two patients with Grade 2 cases. The median time to onset was 2.7 months (range: 9 days to 7.9 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO and of ipilimumab in three patients (0.7%) and withholding of OPDIVO and of ipilimumab in two patients (0.5%). Six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 13.5 days (range: 1 day to 1.1 months). Complete resolution occurred in nine patients. Two patients resumed OPDIVO with ipilimumab after resolution without recurrence of nephritis or 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.

## **RCC**

In Trial 6, renal injury occurred in 7% (27/406) of patients on OPDIVO and 3.0% (12/397) of patients on everolimus, rather than laboratory creatinine. Immune-mediated nephritis and renal dysfunction occurred in 3.2% (13/406) of patients receiving OPDIVO (one with Grade 5, one with Grade 4, five with Grade 3, and six with Grade 2). The median time to onset was 5.4 months (range: 1.1 to 12.3 months). Median duration was 1.4 months (range: 0.1 to 18 months). OPDIVO was permanently discontinued in five patients. Dose delay occurred in eight patients. Five patients had complete resolution. Two patients resumed OPDIVO after complete resolution and had no recurrence of nephritis.

## **cHL**

In Trials 8 and 9, nephritis and renal dysfunction occurred in 4.9% (13/263) of patients treated with OPDIVO. This included one reported case (0.3%) of autoimmune nephritis (Grade 3).



## 5.6 Immune-Mediated Rash

Immune-mediated rash can occur with OPDIVO treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of OPDIVO. 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* (2.5)].

### Melanoma

#### *OPDIVO as a Single Agent*

In Trials 1, 5, and 7, immune-mediated rash occurred in 9% (72/787) of patients: seven patients with Grade 3, 15 patients with Grade 2, and 50 patients with Grade 1 rash. The median time to onset was 2.8 months (range: 3 days to 13.8 months). Immune-mediated rash led to permanent discontinuation of OPDIVO in one patient (0.1%) and withholding of OPDIVO in six patients (0.8%). Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 15 days (range: 4 days to 1.0 months). Complete resolution (defined as complete resolution of symptoms with completion of corticosteroids) occurred in 32 patients (44%). Among the 35 patients who resumed OPDIVO after resolution, one had recurrence.

#### *OPDIVO with Ipilimumab*

In Trials 4 and 7, immune-mediated rash occurred in 22.6% (92/407) of patients: 15 patients with Grade 3, 31 patients with Grade 2, and 46 patients with Grade 1 rash. The median time to onset was 18 days (range: 1 day to 9.7 months). Immune-mediated rash led to permanent discontinuation of OPDIVO and of ipilimumab in two patients (0.5%) and withholding of OPDIVO and of ipilimumab in 16 patients (3.9%). Sixteen patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 14 days (range: 2 days to 4.7 months). Complete resolution occurred in 43 patients. Among the 54 patients who resumed OPDIVO and ipilimumab after resolution, three had recurrence.

### NSCLC

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.

### RCC

In Trial 6, rash occurred in 28% (112/406) of patients on OPDIVO and 36% (143/397) of patients on everolimus. Immune-mediated rash, defined as a rash treated with systemic or topical corticosteroids, occurred in 7% (30/406) of patients receiving OPDIVO (four with Grade 3, seven with Grade 2, and nineteen with Grade 1). The median time to onset was 3.2 months (range: 2 days to 25.8 months). Median duration was 2.6 months (range: 0.3 to 9.4 months). Four patients received oral and 26 received topical corticosteroids. Two patients permanently discontinued and dose delay occurred in two patients. Seventeen patients had complete resolution. Thirteen patients who continued on OPDIVO or experienced a dose delay had no recurrence of rash.

## **cHL**

In Trials 8 and 9, rash occurred in 22% (58/263) of patients receiving OPDIVO. Immune-mediated rash occurred in 7% (18/263), with a median time to onset of 2.2 months (range: 1 day to 8.5 months). Of these 18 cases, four were Grade 3, three were Grade 2, and 11 were Grade 1. Nine patients received systemic corticosteroids with or without topical steroids, and the remaining nine patients received topical corticosteroids alone. Three patients had dose delay. No patients permanently discontinued OPDIVO due to rash.

### **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 (2.4)*].

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. In Trial 7, encephalitis was identified in one patient receiving OPDIVO with ipilimumab (0.2%) after 1.7 months of exposure. In Trials 8 and 9, encephalitis occurred in two patients (0.8%) after allogeneic HSCT after OPDIVO [*see Warnings and Precautions (5.10)*].

### **5.8 Other Immune-Mediated Adverse Reactions**

Other clinically significant immune-mediated adverse reactions can occur with OPDIVO. 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 (2.5)*].

In less than 1.0% of patients receiving OPDIVO as a single agent or in combination with ipilimumab in Trials 1, 3, 4, 5, 6, 7, 8, and 9 (n=2150), the following clinically significant, immune-mediated adverse reactions occurred: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, and sarcoidosis.

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: motor dysfunction, vasculitis, and myasthenic syndrome.

## 5.9 Infusion Reactions

Severe infusion reactions have been reported in less than 1.0% of patients in clinical trials of OPDIVO. 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.

### Melanoma

In Trials 1, 5, and 7, infusion-related reactions occurred in 2.7% (21/787) of patients receiving OPDIVO: two patients with Grade 3, eight patients with Grade 2, and 11 patients with Grade 1 infusion-related reactions. In Trials 4 and 7, infusion-related reactions occurred in 2.5% (10/407) of patients receiving OPDIVO with ipilimumab: six patients with Grade 2 and four patients with Grade 1 infusion-related reactions.

### NSCLC

In Trial 3, Grade 2 infusion reactions requiring corticosteroids occurred in 1.0% (3/287) of patients receiving OPDIVO.

### RCC

In Trial 6, hypersensitivity/infusion-related reactions occurred in 6% (25/406) of patients receiving OPDIVO and 1.0% (4/397) of patients receiving everolimus. The median time to onset in the OPDIVO group was 1.4 months (range: 1 day to 27.6 months). Seven patients received corticosteroids on the day of administration. Two patients discontinued OPDIVO, one for a Grade 4 reaction and one for a Grade 2 event. No events led to dose delay. Interruption of the infusion was required in ten patients.

### cHL

In Trials 8 and 9, hypersensitivity/infusion-related reactions occurred in 16% (42/263) of patients receiving OPDIVO: Two patients with Grade 3, 24 with Grade 2, and 16 with Grade 1 reactions. Ten patients received systemic corticosteroids. Infusion was interrupted in seven patients. Two patients had dose delay. No events led to permanent discontinuation of OPDIVO.

## 5.10 Complications of Allogeneic HSCT after OPDIVO

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from Trials 8 and 9 who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, two with myeloablative conditioning). The median age at HSCT was 33 (range: 18 to 56), and a median of 9 doses of OPDIVO had been administered (range: 4 to 16). Six of 17 patients (35%) died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 5/17 patients (29%). Hyperacute GVHD, defined as GVHD occurring within 14 days after stem cell infusion, was reported in 2 patients (20%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (35%) within the first 6 weeks post-transplantation, with five patients responding to steroids. Two cases of encephalitis were reported: one case of Grade 3 lymphocytic encephalitis without an identified infectious cause, which occurred and

resolved on steroids, and one case of Grade 3 suspected viral encephalitis which was resolved with antiviral treatment. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic SCT and died of GVHD and multi-organ failure.

Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported.

These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

### **5.11 Embryo-Fetal 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 an 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)]
- Complications of Allogeneic HSCT after OPDIVO [see *Warnings and Precautions* (5.10)]

## 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 Warnings and Precautions section reflect exposure to OPDIVO, as a single agent, for clinically significant adverse reactions in 2166 patients enrolled in Trials 1, 3, 5, 6, 7, 8, 9, a single-arm trial in NSCLC (n=117), 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 of OPDIVO with ipilimumab were evaluated in 501 patients with melanoma enrolled in Trial 4 (n=94), Trial 7 (n=313), or an additional dose-finding study (n=94) administering OPDIVO 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 Trials 1, 5, and 7, and to OPDIVO with ipilimumab in Trial 7, which are randomized, active-controlled trials conducted in patients with unresectable or metastatic melanoma. Also described below are single-agent OPDIVO data from Trial 3, which is a randomized trial in patients with metastatic non-squamous NSCLC, Trial 6, which is a randomized trial in patients with advanced RCC, and Trials 8 and 9, which are open-label, multiple-cohort trials in patients with cHL.

### Unresectable or Metastatic Melanoma

#### *Previously Treated Metastatic Melanoma*

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) 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 Eastern Cooperative Oncology Group (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

Toxicity was graded per NCI CTCAE v4.

<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).

### *Previously Untreated Metastatic Melanoma*

#### Trial 5

The safety of OPDIVO was also evaluated in Trial 5, a randomized, double-blind, active-controlled trial in which 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=206) or dacarbazine 1000 mg/m<sup>2</sup> every 3 weeks (n=205) [see *Clinical Studies (14.1)*]. The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. In this trial, 47% of patients received OPDIVO for greater than 6 months and 12% of patients received OPDIVO for greater than 1 year.

The trial excluded patients with autoimmune disease and patients requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications.

The study population characteristics in the OPDIVO group and dacarbazine group were generally similar: 59% male, median age 65 years, 99.5% white, 61% with M1c stage disease, 74% with cutaneous melanoma, 11% with mucosal melanoma, 4% with brain metastasis, and 37% with elevated LDH at baseline. There were more patients in the OPDIVO group with ECOG performance status 0 (71% vs. 59%).

Adverse reactions led to permanent discontinuation of OPDIVO in 7% of patients and dose interruption in 26% of patients; no single type of adverse reaction accounted for the majority of OPDIVO discontinuations. Serious adverse reactions occurred in 36% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%).

Table 4 summarizes selected adverse reactions that occurred in at least 10% of OPDIVO-treated patients. The most common adverse reactions (reported in at least 20% of patients and at a higher incidence than in the dacarbazine arm) were fatigue, musculoskeletal pain, rash, and pruritus.

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

Adverse Reaction	OPDIVO (n=206)		Dacarbazine (n=205)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
<b>General Disorders and Administration Site Conditions</b>				
Fatigue	49	1.9	39	3.4
Edema <sup>a</sup>	12	1.5	4.9	0
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Musculoskeletal pain <sup>b</sup>	32	2.9	25	2.4
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash <sup>c</sup>	28	1.5	12	0
Pruritus	23	0.5	12	0
Erythema	10	0	2.9	0
Vitiligo	11	0	0.5	0
<b>Infections and Infestations</b>				
Upper respiratory tract infection <sup>d</sup>	17	0	6	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes periorbital edema, face edema, generalized edema, gravitational edema, localized edema, peripheral edema, pulmonary edema, and lymphedema.

<sup>b</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, pain in jaw, and spinal pain.

<sup>c</sup> Includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, dermatitis, dermatitis allergic, dermatitis exfoliative, dermatitis acneiform, drug eruption, and skin reaction.

<sup>d</sup> Includes rhinitis, viral rhinitis, pharyngitis, and nasopharyngitis.

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in Trial 5 were:

*Nervous System Disorders:* peripheral neuropathy



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

Test	Percentage of Patients with Worsening Laboratory Test from Baseline <sup>a</sup>			
	OPDIVO		Dacarbazine	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Increased ALT	25	3.0	19	0.5
Increased AST	24	3.6	19	0.5
Increased alkaline phosphatase	21	2.6	14	1.6
Increased bilirubin	13	3.1	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: 194 to 197 patients) and dacarbazine group (range: 186 to 193 patients).

### Trial 7

The safety of OPDIVO, administered with ipilimumab or as a single agent, was evaluated in Trial 7 [see *Clinical Studies (14.1)*], a randomized (1:1:1), a double-blind trial in which 937 patients with previously untreated, unresectable or metastatic melanoma received:

- OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks (OPDIVO plus ipilimumab arm; n=313),
- OPDIVO 3 mg/kg every 2 weeks (OPDIVO arm; n=313), or
- Ipilimumab 3 mg/kg every 3 weeks for up to 4 doses (ipilimumab arm; n=311).

The median duration of exposure to OPDIVO was 2.8 months (range: 1 day to 18.8 months) for the OPDIVO plus ipilimumab arm and 6.6 months (range: 1 day to 17.3 months) for the OPDIVO arm. In the OPDIVO plus ipilimumab arm, 39% were exposed to OPDIVO for  $\geq 6$  months and 24% exposed for  $>1$  year. In the OPDIVO arm, 53% were exposed for  $\geq 6$  months and 32% for  $>1$  year.

Trial 7 excluded patients with autoimmune disease, a medical condition requiring systemic treatment with corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive medication within 14 days of the start of study therapy, a positive test result for hepatitis B or C, or a history of HIV.

The study population characteristics were: 65% male, median age 61 years, 97% White, baseline ECOG performance status 0 (73%) or 1 (27%), 93% with AJCC Stage IV disease, 58% with M1c stage disease; 36% with elevated LDH at baseline, 4% with a history of brain metastasis, and 22% had received adjuvant therapy.

In Trial 7, serious adverse reactions (73% and 37%), adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and Grade 3 or 4 adverse

reactions (72% and 44%) all occurred more frequently in the OPDIVO plus ipilimumab arm relative to the OPDIVO arm.

The most frequent ( $\geq 10\%$ ) serious adverse reactions in the OPDIVO plus ipilimumab arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). The most frequent adverse reactions leading to discontinuation of both drugs in the OPDIVO plus ipilimumab arm and of OPDIVO in the OPDIVO arm, respectively, were diarrhea (8% and 1.9%), colitis (8% and 0.6%), increased ALT (4.8% and 1.3%), increased AST (4.5% and 0.6%), and pneumonitis (1.9% and 0.3%). The most common ( $\geq 20\%$ ) adverse reactions in the OPDIVO plus ipilimumab arm were fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea. The most common ( $\geq 20\%$ ) adverse reactions in the OPDIVO arm were fatigue, rash, diarrhea, and nausea. Table 6 summarizes the incidence of adverse reactions occurring in at least 10% of patients in either OPDIVO-containing arm in Trial 7.

**Table 6: Selected Adverse Reactions Occurring in  $\geq 10\%$  of Patients on the OPDIVO plus Ipilimumab Arm or the OPDIVO Arm 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 7)**

System Organ Class/ Preferred Term	Percentage (%) of Patients					
	OPDIVO plus Ipilimumab (n=313)		OPDIVO (n=313)		Ipilimumab (n=311)	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
<b>General Disorders and Administration Site Conditions</b>						
Fatigue <sup>a</sup>	59	6	53	1.9	50	3.9
Pyrexia	37	1.6	14	0	17	0.6
<b>Skin and Subcutaneous Tissue Disorders</b>						
Rash <sup>b</sup>	53	5	40	1.6	42	3.9
<b>Gastrointestinal Disorders</b>						
Diarrhea	52	11	31	3.8	46	8
Nausea	40	3.5	28	0.6	29	1.9
Vomiting	28	3.5	17	1.0	16	1.6
<b>Respiratory, Thoracic and Mediastinal Disorders</b>						
Dyspnea	20	2.2	12	1.3	13	0.6

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Fatigue is a composite term which includes asthenia and fatigue.

<sup>b</sup> Rash is a composite term which includes rash pustular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption, erythema, exfoliative rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, and seborrheic dermatitis.

Other clinically important adverse reactions in less than 10% of patients treated with either OPDIVO with ipilimumab or single-agent OPDIVO in Trial 7 were:

*Gastrointestinal Disorders:* stomatitis, intestinal perforation

*Skin and Subcutaneous Tissue Disorders:* vitiligo

*Musculoskeletal and Connective Tissue Disorders:* myopathy, Sjogren's syndrome, spondyloarthritis

*Nervous System Disorders:* neuritis, peroneal nerve palsy

**Table 7: Selected Laboratory Abnormalities Worsening from Baseline Occurring in  $\geq 20\%$  of Patients Treated with OPDIVO with Ipilimumab or Single-Agent OPDIVO 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 7)**

Test	Percentage (%) of Patients <sup>a</sup>					
	OPDIVO plus Ipilimumab		OPDIVO		Ipilimumab	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
<b>Chemistry</b>						
Increased ALT	53	15	23	3.0	28	2.7
Increased AST	47	13	27	3.7	27	1.7
Hyponatremia	42	9	20	3.3	25	7
Increased lipase	41	20	29	9	23	7
Increased alkaline phosphatase	40	6	24	2.0	22	2.0
Hypocalcemia	29	1.1	13	0.7	21	0.7
Increased amylase	25	9.1	15	1.9	14	1.6
Increased creatinine	23	2.7	16	0.3	16	1.3
<b>Hematology</b>						
Anemia	50	2.7	39	2.6	40	6
Lymphopenia	35	4.8	39	4.3	27	3.4

<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 plus ipilimumab (range: 241 to 297); OPDIVO (range: 260 to 306); ipilimumab (range: 253 to 304).

### 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  $\geq 65$  years of age and 47% of patients in the docetaxel group were  $\geq 65$  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 8 summarizes selected adverse reactions occurring more frequently in at least 10% of OPDIVO-treated patients.

**Table 8: Selected Adverse Reactions Occurring in  $\geq 10\%$  of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [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

Toxicity was graded per NCI CTCAE v4.

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 9: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥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.

### Renal Cell Carcinoma

The safety of OPDIVO was evaluated in Trial 6, a randomized open-label trial in which 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimens received OPDIVO 3 mg/kg every 2 weeks (n=406) or everolimus 10 mg daily (n=397) [see *Clinical Studies (14.3)*]. The median duration of treatment was 5.5 months (range: 1 day to 29.6+ months) in OPDIVO-treated patients and 3.7 months (range: 6 days to 25.7+ months) in everolimus-treated patients.

Study therapy was discontinued for adverse reactions in 16% of OPDIVO patients and 19% of everolimus patients. Forty-four percent (44%) of patients receiving OPDIVO had a drug delay 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 were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia.

Rate of death on treatment or within 30 days of the last dose of study drug was 4.7% on the OPDIVO arm versus 8.6% on the everolimus arm.

The most common adverse reactions (reported in at least 20% of patients) were asthenic conditions, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia. Table 10 summarizes adverse reactions that occurred in greater than 15% of OPDIVO-treated patients.

**Table 10: Grade 1-4 Adverse Reactions in >15% of Patients Receiving OPDIVO (Trial 6)**

	OPDIVO (n=406)		Everolimus (n=397)	
	Percentage (%) of Patients			
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
<b>Any Adverse Reactions</b>	98	56	96	62
<b>General Disorders and Administration Site Conditions</b>				
Asthenic conditions <sup>a</sup>	56	6	57	7
Pyrexia	17	0.7	20	0.8
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough/productive cough	34	0	38	0.5
Dyspnea/exertional dyspnea	27	3.0	31	2.0
Upper respiratory infection <sup>b</sup>	18	0	11	0
<b>Gastrointestinal Disorders</b>				
Nausea	28	0.5	29	1
Diarrhea <sup>c</sup>	25	2.2	32	1.8
Constipation	23	0.5	18	0.5
Vomiting	16	0.5	16	0.5
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash <sup>d</sup>	28	1.5	36	1.0
Pruritus/generalized pruritus	19	0	14	0
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite	23	1.2	30	1.5
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Arthralgia	20	1.0	14	0.5
Back pain	21	3.4	16	2.8

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Asthenic conditions covering PTs asthenia, decreased activity, fatigue, and malaise.

<sup>b</sup> Includes nasopharyngitis, pharyngitis, rhinitis, and viral URI.

<sup>c</sup> Includes colitis, enterocolitis, and gastroenteritis.

<sup>d</sup> Includes dermatitis, dermatitis acneiform, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, erythema multiforme, and erythema.

Other clinically important adverse reactions in Trial 6 were:

*General Disorders and Administration Site Conditions:* peripheral edema/edema

*Gastrointestinal Disorders:* abdominal pain/discomfort

*Musculoskeletal and Connective Tissue Disorders:* extremity pain, musculoskeletal pain

*Nervous System Disorders:* headache/migraine, peripheral neuropathy

*Investigations:* weight decreased

*Skin Disorders:* Palmar-plantar erythrodysesthesia

The most common laboratory abnormalities which have worsened compared to baseline in  $\geq 30\%$  of patients include increased creatinine, lymphopenia, anemia, increased AST, increased alkaline phosphatase, hyponatremia, elevated triglycerides, and hyperkalemia. Table 11 summarizes the laboratory abnormalities that occurred in greater than 15% of OPDIVO-treated patients.

**Table 11: Grade 1-4 Laboratory Values Worsening from Baseline Occurring in >15% of Patients on OPDIVO (Trial 6)**

Test	Percentage of Patients with Worsening Laboratory Test from Baseline <sup>a</sup>			
	OPDIVO		Everolimus	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
<b>Hematology</b>				
Lymphopenia	42	6	53	11
Anemia	39	8	69	16
<b>Chemistry</b>				
Increased creatinine	42	2.0	45	1.6
Increased AST	33	2.8	39	1.6
Increased alkaline phosphatase	32	2.3	32	0.8
Hyponatremia	32	7	26	6
Hyperkalemia	30	4.0	20	2.1
Hypocalcemia	23	0.9	26	1.3
Increased ALT	22	3.2	31	0.8
Hypercalcemia	19	3.2	6	0.3
<b>Lipids</b>				
Increased triglycerides	32	1.5	67	11
Increased cholesterol	21	0.3	55	1.4

<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: 259 to 401 patients) and everolimus group (range: 257 to 376 patients).

In addition, among patients with TSH less than ULN at baseline, a greater proportion of patients experienced a treatment-emergent elevation of TSH greater than ULN in the OPDIVO group compared to the everolimus group (26% and 14%, respectively).

## Classical Hodgkin Lymphoma

The safety of OPDIVO 3 mg/kg every 2 weeks was evaluated in 263 adult patients with cHL (240 patients in Trial 8 and 23 patients in Trial 9). Treatment could continue until disease progression, maximal clinical benefit, or unacceptable toxicity.

The median age was 34 years (range 18 to 72), 98% of patients had received autologous HSCT, none had received allogeneic HSCT, and 74% had received brentuximab vedotin. The median number of prior systemic regimens was 4 (range: 1 to 15). Patients received a median of 10 doses (cycles) of OPDIVO (range: 1 to 48), with a median duration of therapy of 4.8 months (range: 0.3 to 24 months).

OPDIVO was discontinued due to adverse reactions in 4.2% of patients. Twenty-three percent (23%) of patients had a dose delay for an adverse reaction. Serious adverse reactions occurred in 21% of patients. The most frequent serious adverse reactions reported in at least 1% of patients were infusion-related reaction, pneumonia, pleural effusion, pyrexia, rash, and pneumonitis. Ten patients died from causes other than disease progression, including 6 who died from complications of allogeneic HSCT.

The most common adverse reactions (reported in at least 20%) among all patients (safety population), were fatigue, upper respiratory tract infection, pyrexia, diarrhea, and cough.

Among the subset of patients in the efficacy population, the most common adverse reactions also included rash, musculoskeletal pain, pruritus, nausea, arthralgia, and peripheral neuropathy. Serious adverse reactions occurred in 27% of these patients.

Table 12 summarizes both the adverse reactions that occurred in at least 10% of patients in the safety population (n=263) and the efficacy population (n=95). There is a greater incidence of adverse reactions in the subset of patients evaluated for efficacy; these patients received a median of 17 doses of OPDIVO and a median of 5 prior systemic regimens [see *Clinical Studies (14.4)*].



**Table 12: Selected Non-Hematologic Adverse Reactions Occurring in ≥10% of Patients with cHL (Trials 8 and 9)**

Adverse Reaction <sup>a</sup>	OPDIVO cHL Safety Population(n=263)		OPDIVO cHL Efficacy Population (n=95)	
	Percentage (%) of Patients			
	All Grades	Grades 3-4	All Grades	Grades 3-4
<b>General Disorders and Administration Site Conditions</b>				
Fatigue <sup>b</sup>	32	1.1	43	1.1
Pyrexia	24	0.8	35	1.1
<b>Gastrointestinal Disorders</b>				
Diarrhea	23	0.8	30	1.1
Nausea	17	0	23	0
Vomiting	15	0.8	16	1.1
Abdominal pain <sup>c</sup>	11	0.8	13	2.1
Constipation	9	0.4	14	0
<b>Infections and Infestations</b>				
Upper respiratory tract infection <sup>d</sup>	28	0.4	48	1.1
Pneumonia / bronchopneumonia <sup>e</sup>	9	3.0	19	5.3
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough/productive cough	22	0	35	0
Dyspnea/exertional dyspnea	10	0.8	16	2.1
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash <sup>f</sup>	19	1.5	31	3.2
Pruritus	17	0	25	0
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Musculoskeletal pain <sup>g</sup>	19	1.1	27	1.1
Arthralgia	11	0	21	0
<b>Endocrine Disorders</b>				
Hypothyroidism/thyroiditis	12	0	17	0
Hyperglycemia/Blood Glucose Increased	9	0.4	14	1.1
<b>Nervous System Disorders</b>				
Headache	12	0.4	12	1.1
Neuropathy peripheral <sup>h</sup>	11	0.4	21	0
<b>Injury, Poisoning and Procedural Complications</b>				
Infusion-related reaction	12	0.4	18	0

Toxicity was graded per NCI CTCAE v4.

<sup>a</sup> Includes events occurring up to 30 days after last nivolumab dose, regardless of causality. After an immune-mediated adverse reaction, reactions following nivolumab rechallenge were included if they occurred up to 30 days after completing the initial nivolumab course.

<sup>b</sup> Includes asthenia.

<sup>c</sup> Includes abdominal discomfort and upper abdominal pain.

<sup>d</sup> Includes nasopharyngitis, pharyngitis, rhinitis, and sinusitis.

<sup>e</sup> Includes pneumonia bacterial, pneumonia mycoplasmal, pneumocystis jirovecii pneumonia.

- <sup>f</sup> Includes dermatitis, dermatitis acneiform, dermatitis exfoliative, and rash described as macular, papular, maculopapular, pruritic, exfoliative, or acneiform.
- <sup>g</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, and pain in extremity.
- <sup>h</sup> Includes hyperesthesia, hypoesthesia, paresthesia, dysesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Additional information regarding clinically important adverse reactions:

*Peripheral neuropathy:* In Trials 8 and 9, peripheral neuropathy was observed in 11% (30/263) of all patients receiving OPDIVO. Twenty-two patients (8%) had new-onset peripheral neuropathy, and four patients had worsening from baseline. Four additional patients with peripheral neuropathy at baseline (three Grade 1 and one Grade 2) did not worsen. All events were Grade 1 or 2, except for 1 Grade 3 event (0.4%).

*Complications of allogeneic HSCT after OPDIVO:* [see Warnings and Precautions (5.10)].

**Table 13: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated cHL Patients (Trials 8 and 9)**

Test	OPDIVO cHL Safety Population <sup>a</sup>		OPDIVO cHL Efficacy Population <sup>b</sup>	
	Percentage (%) of Patients <sup>c</sup>			
	All Grades	Grades 3-4	All Grades	Grades 3-4
<b>Hematology</b>				
Neutropenia	29	3.6	37	6
Thrombocytopenia	28	2.4	33	3.2
Lymphopenia	24	8	32	7
Anemia	22	2.8	27	2.1
<b>Chemistry</b>				
Increased ALT	24	2.0	25	2.1
Increased AST	23	2.4	32	3.2
Increased alkaline phosphatase	17	1.6	21	2.1
Increased lipase	16	6.5	28	12
Hyponatremia	14	0.8	15	1.1
Hypokalemia	11	1.6	14	3.2
Hypocalcemia	11	0.4	14	1.1
Hypomagnesemia	10	0.4	15	1.3
Increased creatinine	10	0	15	0
Increased bilirubin	9	0.8	10	0

<sup>a</sup> Number of evaluable patients for the safety population ranges from 226 to 253.

<sup>b</sup> Number of evaluable patients for the efficacy population ranges from 80 to 85.

<sup>c</sup> Includes events occurring up to 30 days after last nivolumab dose. After an immune-mediate adverse reaction, reactions following nivolumab rechallenge were included if they occurred within 30 days of completing the initial nivolumab course.

## 6.2 Immunogenicity

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

Of 1586 patients who were treated with OPDIVO as a single agent 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 157 patients (9.9%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and nine patients (0.6%) had neutralizing antibodies against nivolumab. There was no evidence of altered pharmacokinetic profile or increased incidence of infusion reactions with anti-nivolumab antibody development.

Of 394 patients who were treated with OPDIVO with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, 149 patients (37.8%) tested positive for treatment-emergent anti-nivolumab antibodies by an ECL assay and 18 patients (4.6%) had neutralizing antibodies against nivolumab. Of the 391 patients evaluable for the presence of anti-ipilimumab antibodies, 33 patients (8.4%) tested positive for treatment-emergent anti-ipilimumab antibodies by an ECL assay and one patient (0.3%) had neutralizing antibodies against ipilimumab. There was no evidence of increased incidence of infusion reactions 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. 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% were 65 years or older and 15% were 75 years or older. Of the 292 patients randomized to OPDIVO in Trial 3, 37% were 65 years or older and 7% were 75 years or older. Of the 210 patients randomized to OPDIVO in Trial 5, 50% were 65 years or older and 13% were 75 years or older. Of the 406 patients treated with OPDIVO in Trial 6, 37% of patients were 65 years or older and 8% were 75 years or older. Of the 316 patients randomized to OPDIVO in Trial 7, 37% were 65 years or older and 12% were 75 years or older. No overall differences in safety or efficacy were reported between elderly patients and younger patients. In Trials 8 and 9, OPDIVO monotherapy for cHL did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

Of the 314 patients randomized to OPDIVO administered with ipilimumab in Trial 7, 41% were 65 years or older and 11% were 75 years or older. No overall differences in safety or efficacy were reported between elderly patients and 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-dose 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 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 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, solid 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**

#### **Previously Treated Metastatic Melanoma**

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 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 [CI]: 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.



## Previously Untreated Metastatic Melanoma

### Trial 5

Trial 5 was a multicenter, double-blind, randomized (1:1) trial conducted in patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m<sup>2</sup> by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (greater than or equal to 5% of tumor cell membrane staining by immunohistochemistry vs. less than 5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). Key eligibility criteria included histologically confirmed, unresectable or metastatic, cutaneous, mucosal, or acral melanoma; no prior therapy for metastatic disease; completion of prior adjuvant or neoadjuvant therapy at least 6 weeks prior to randomization; ECOG performance status 0 or 1; absence of autoimmune disease; and absence of active brain or leptomeningeal metastases. The trial excluded patients with ocular melanoma. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year and then every 12 weeks thereafter.

The major efficacy outcome measure was overall survival (OS). Additional outcome measures included investigator-assessed progression-free survival (PFS) and objective response rate (ORR) per RECIST v1.1.

A total of 418 patients were randomized to OPDIVO (n=210) or dacarbazine (n=208). The median age was 65 years (range: 18 to 87), 59% were men, and 99.5% were white. Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (11%), elevated LDH level (37%), PD-L1 greater than or equal to 5% tumor cell membrane expression (35%), and history of brain metastasis (4%). More patients in the OPDIVO arm had an ECOG performance status of 0 (71% vs. 58%).

Trial 5 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. Table 14 and Figure 1 summarize the efficacy results.

**Table 14: Efficacy Results - Trial 5**

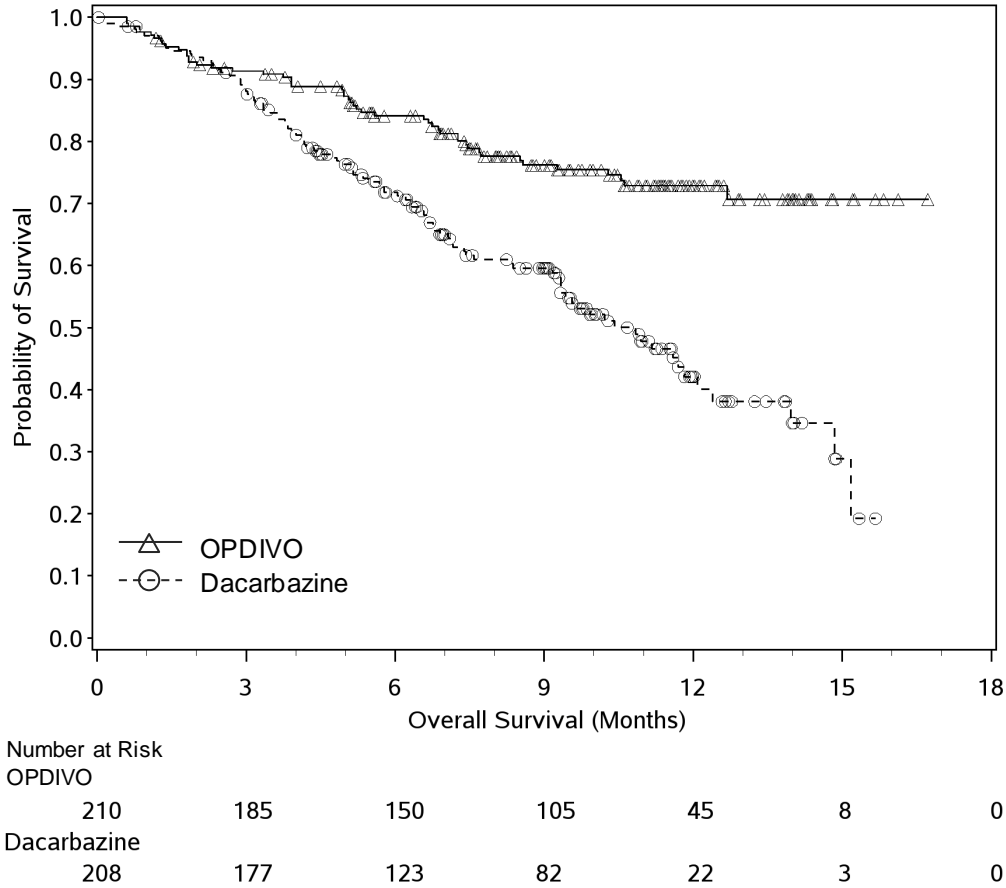
	<b>OPDIVO (n=210)</b>	<b>Dacarbazine (n=208)</b>
<b>Overall Survival</b>		
Events (%)	50 (24)	96 (46)
Median, months (95% CI)	Not Reached	10.8 (9.3, 12.1)
Hazard ratio (95% CI)	0.42 (0.30, 0.60)	
p-value	<0.0001 <sup>a</sup>	
<b>Progression-Free Survival</b>		
Events (%)	108 (51)	163 (78)
Median, months (95% CI)	5.1 (3.5, 10.8)	2.2 (2.1, 2.4)
Hazard ratio (95% CI)	0.43 (0.34, 0.56)	
p-value	<0.0001 <sup>a</sup>	

**Table 14: Efficacy Results - Trial 5**

<b>Objective Response Rate</b>	34%	9%
(95% CI)	(28, 41)	(5, 13)
Complete response rate	4%	1%
Partial response rate	30%	8%

<sup>a</sup> p-value is compared with the allocated alpha of 0.0021 for this interim analysis.

**Figure 1: Kaplan-Meier Curves of Overall Survival - Trial 5**



At the time of analysis, 88% (63/72) of OPDIVO-treated patients had ongoing responses, which included 43 patients with ongoing response of 6 months or longer.

**Trial 7**

Trial 7 was a multicenter, double-blind trial that randomized (1:1:1) patients with previously untreated, unresectable or metastatic melanoma to one of the following arms: OPDIVO plus ipilimumab, OPDIVO, or ipilimumab. Patients were required to have completed adjuvant or neoadjuvant treatment at least 6 weeks prior to randomization and have no prior treatment with anti-CTLA-4 antibody and no evidence of active brain metastasis, ocular melanoma, autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients were randomized to receive:

- OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg as a single agent every 2 weeks (OPDIVO plus ipilimumab arm),
- OPDIVO 3 mg/kg every 2 weeks (OPDIVO arm), or
- Ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by placebo every 2 weeks (ipilimumab arm).

Randomization was stratified by PD-L1 expression ( $\geq 5\%$  vs.  $< 5\%$  tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b vs. M1c). 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 measures were investigator-assessed PFS per RECIST v1.1 and OS. Additional efficacy outcome measures were confirmed ORR and duration of response.

A total of 945 patients were randomized, 314 patients to the OPDIVO plus ipilimumab arm, 316 to the OPDIVO arm, and 315 to the ipilimumab arm. The study population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1  $\geq 5\%$  tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%).

Trial 7 demonstrated statistically significant improvements in PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. Efficacy results are presented in Table 15 and Figure 2.

**Table 15: Efficacy Results in Trial 7**

	<b>OPDIVO plus Ipilimumab (n=314)</b>	<b>OPDIVO (n=316)</b>	<b>Ipilimumab (n=315)</b>
<b>Progression-free Survival</b>			
Number of events	151	174	234
Median in months (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
Hazard ratio <sup>a</sup> (vs. ipilimumab)	0.42	0.57	
(95% CI)	(0.34, 0.51)	(0.47, 0.69)	
p-value <sup>b,c</sup>	<0.0001	<0.0001	
<b>Confirmed Objective Response Rate</b>			
	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value <sup>d</sup>	<0.0001	<0.0001	
Complete response	8.9%	8.5%	1.9%
Partial response	41%	31%	12%
<b>Duration of Response</b>			
Proportion ≥6 months in duration	76%	74%	63%
Range (months)	1.2+ to 15.8+	1.3+ to 14.6+	1.0+ to 13.8+

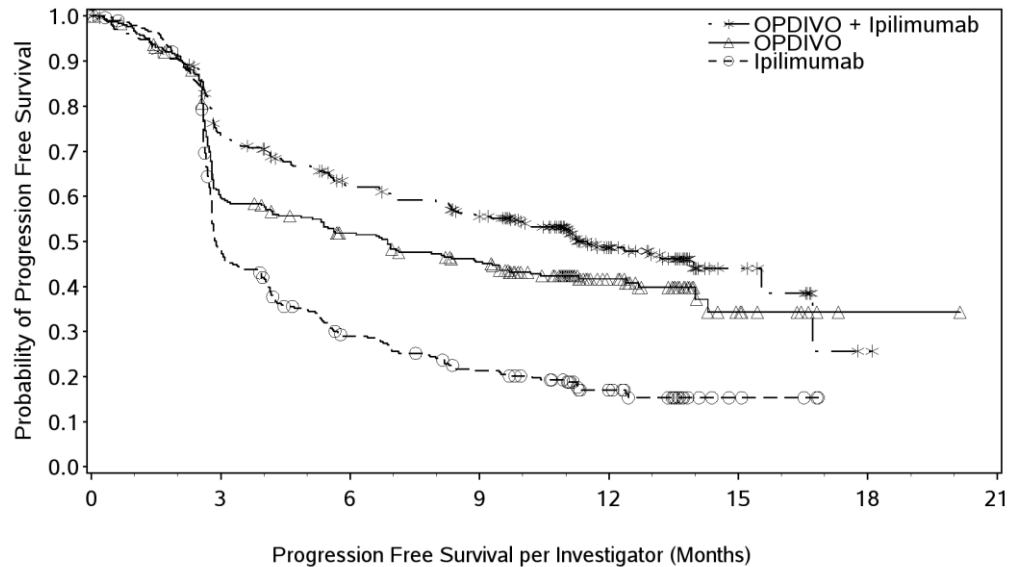
<sup>a</sup> Based on a stratified proportional hazards model.

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

<sup>c</sup> p-value is compared with .005 of the allocated alpha for final PFS treatment comparisons.

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

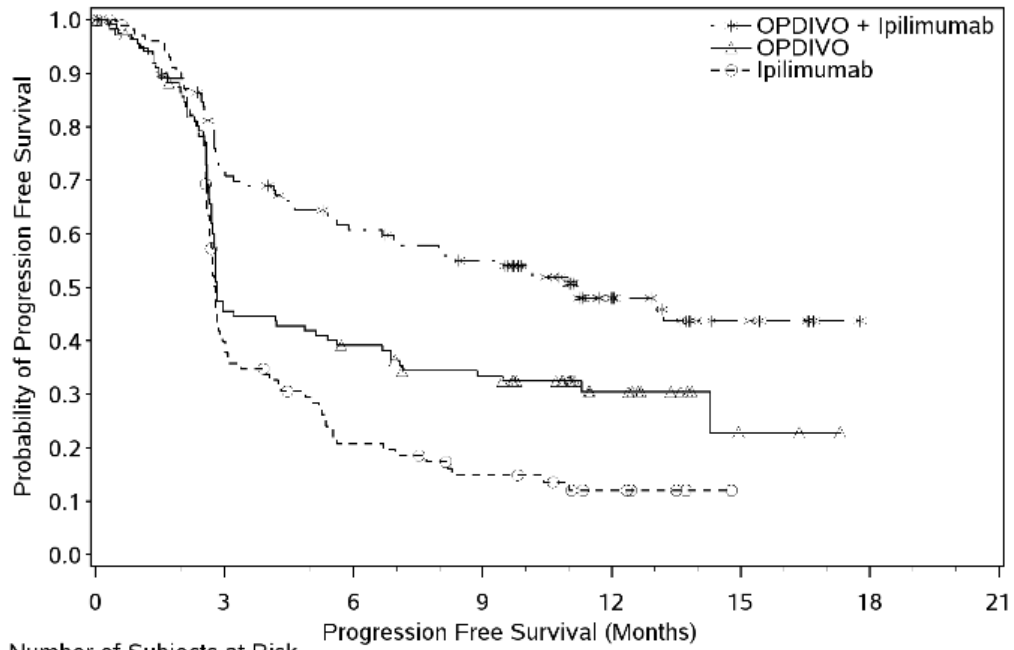
**Figure 2: Progression-free Survival: Unresectable or Metastatic Melanoma - Trial 7**



Number of Subjects at Risk								
OPDIVO + Ipilimumab	314	219	173	151	65	11	1	0
OPDIVO	316	177	147	124	50	9	1	0
Ipilimumab	315	137	77	54	24	4	0	0

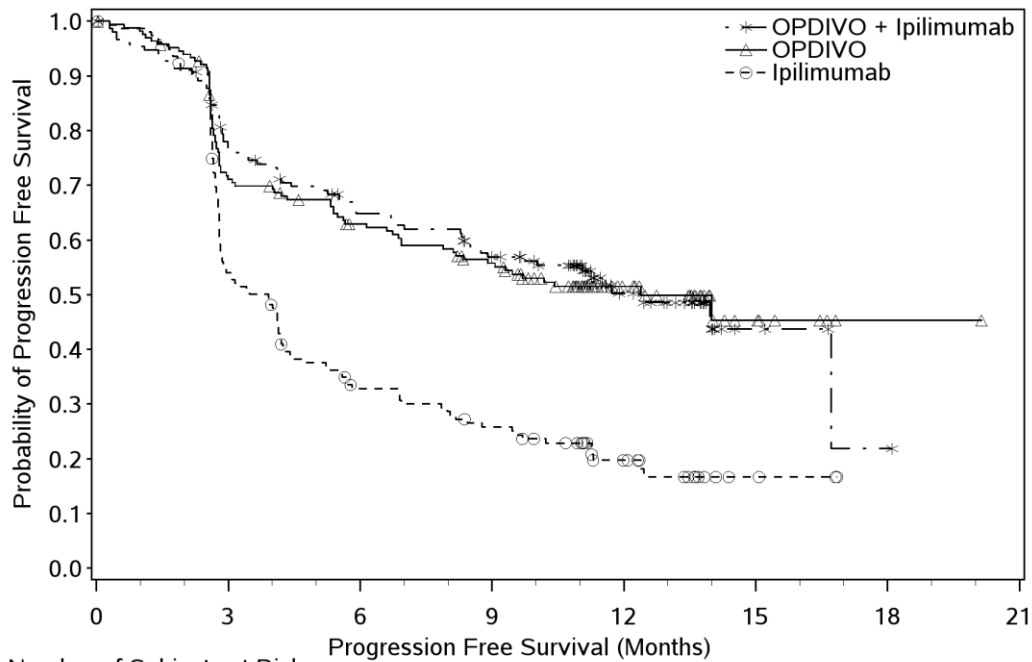
Figures 3 and 4 present exploratory efficacy subgroup analyses of PFS based on defined PD-L1 expression levels determined in archival tumor specimens using the PD-L1 IHC 28-8 pharmDx assay. Tumor samples were available for retrospective assessment for 97% of the study population; PD-L1 expression status was ascertained for 89% of the study population while in 6% of patients, melanin precluded evaluation of PD-L1 expression status. PD-L1 expression status was unknown for 5% of the study population due to consent withdrawal or missing samples.

**Figure 3: Progression-free Survival by PD-L1 Expression (<1%) - Trial 7**



Number of Subjects at Risk		Progression Free Survival (Months)						
		0	3	6	9	12	15	18
OPDIVO + Ipilimumab	123	82	65	57	26	6	0	0
OPDIVO	117	50	42	34	13	2	0	0
Ipilimumab	113	39	19	12	5	0	0	0

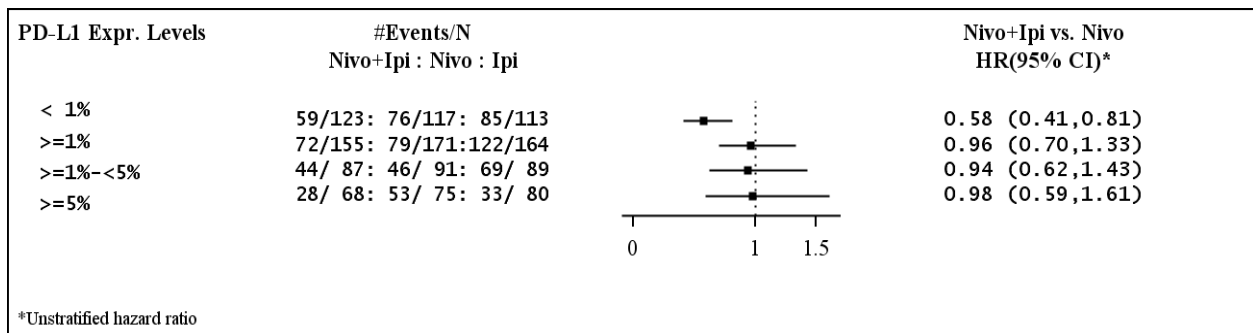
**Figure 4: Progression-free Survival by PD-L1 Expression ( $\geq 1\%$ ) - Trial 7**



Number of Subjects at Risk		Progression Free Survival (Months)							
		0	3	6	9	12	15	18	21
OPDIVO + Ipilimumab	155	113	91	78	32	4	1	0	
OPDIVO	171	115	97	83	34	7	1	0	
Ipilimumab	164	83	47	36	16	3	0	0	

The data presented in the figure below summarize the results of exploratory analyses comparing the two OPDIVO-containing arms in subgroups defined by PD-L1 tumor expression.

**Figure 5: Forest Plot: PFS Based on PD-L1 Expression Comparing OPDIVO-Containing Arms - Trial 7**



## 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 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 16 and Figure 6).

**Table 16: Overall Survival in Trial 2 (Intent-to-Treat Analysis)**

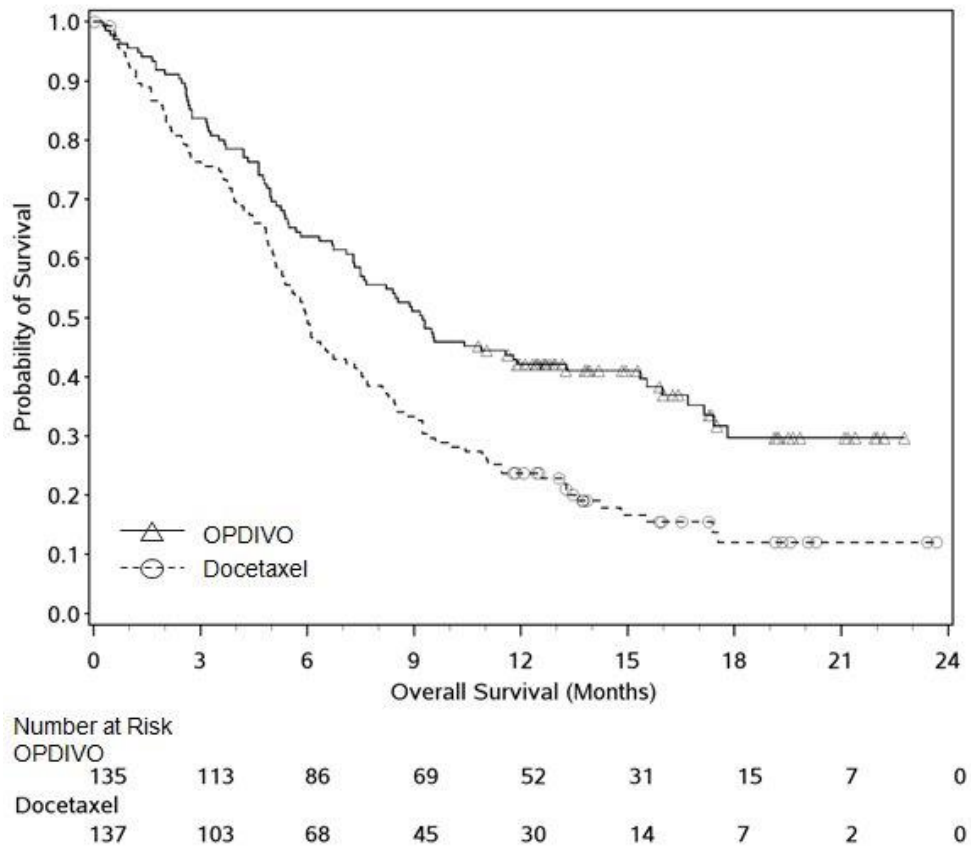
	<b>OPDIVO (n=135)</b>	<b>Docetaxel (n=137)</b>
<b>Prespecified Interim Analysis</b>		
Events (%)	86 (64%)	113 (82%)
Median survival in months (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
p-value <sup>a</sup>	0.00025	
Hazard ratio (95% CI) <sup>b</sup>	0.59 (0.44, 0.79)	

<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 6: 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 OS. Additional efficacy outcome measures were investigator-assessed ORR and 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 17 and Figure 7).

**Table 17: 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>	0.0015	
Hazard ratio (95% CI) <sup>c</sup>	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>	0.39	
Hazard ratio (95% CI) <sup>c</sup>	0.92 (0.77, 1.11)	

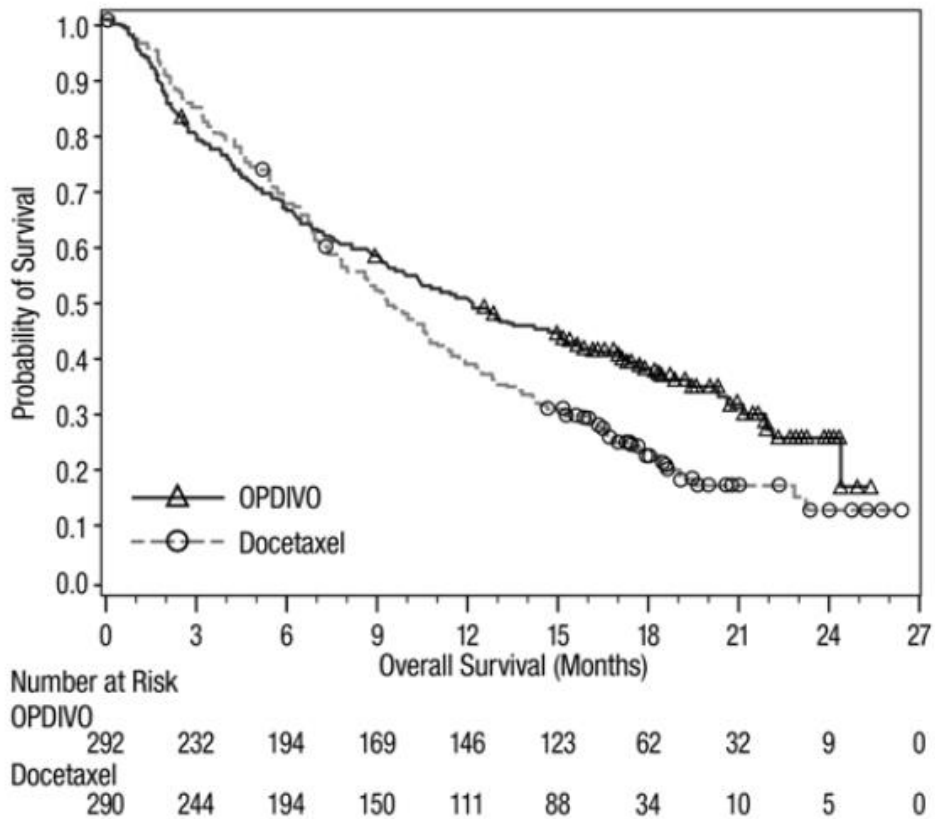
<sup>a</sup> Based on stratified log-rank test.

<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.

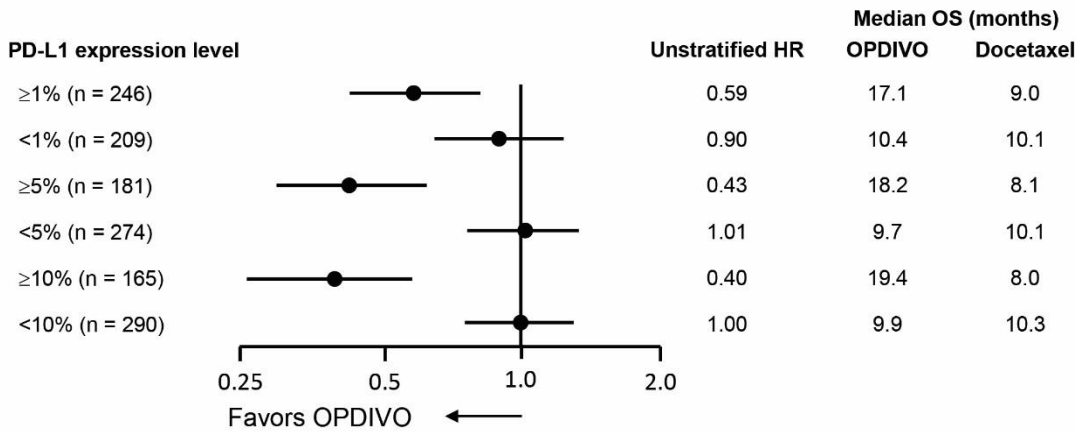
<sup>d</sup> Based on the stratified Cochran-Mantel-Haenszel test.

**Figure 7: Overall Survival - Trial 3**

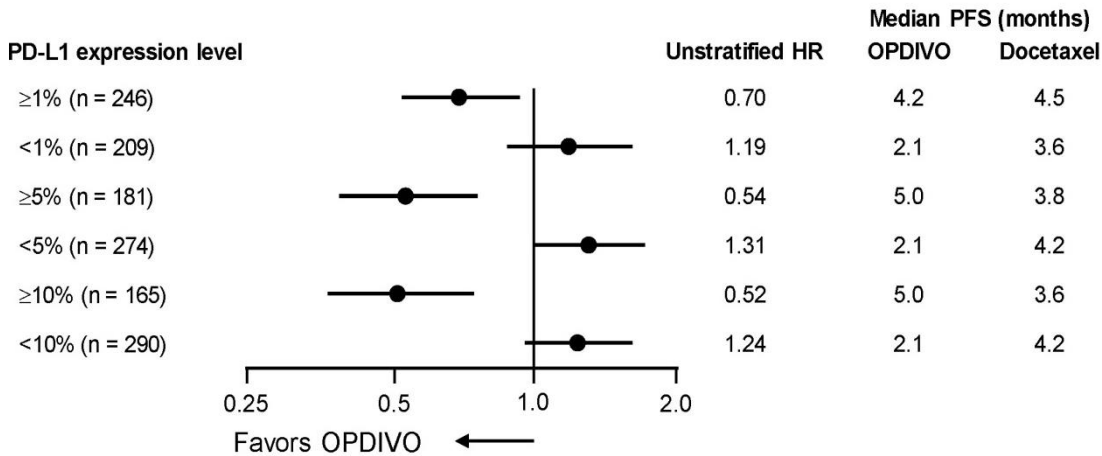


Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing 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 8 summarizes the results of prespecified analyses of survival in subgroups determined by percentage of tumor cells expressing PD-L1. Figure 9 summarizes the results of prespecified analyses of progression-free survival in subgroups determined by percentage of tumor cells expressing PD-L1.

**Figure 8: Forest Plot: OS Based on PD-L1 Expression - Trial 3**



**Figure 9: Forest Plot: PFS Based on PD-L1 Expression - Trial 3**



### 14.3 Renal Cell Carcinoma

Trial 6 was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after one or two prior anti-angiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. Trial 6 excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by region, Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group and the number of prior anti-angiogenic therapies.

Patients were randomized to OPDIVO (n=410) administered intravenously at 3 mg/kg every 2 weeks or everolimus (n=411) administered orally 10 mg daily. The median age was 62 years (range: 18 to 88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and white (88%) and 34% and 66% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. The majority of patients (77%) were treated with one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 34% favorable, 47% intermediate, and 19% poor.

The first tumor assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later.

The major efficacy outcome measure was overall survival (OS). The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 18 and Figure 10). OS benefit was observed regardless of PD-L1 expression level.

Other endpoints include confirmed objective response rates, which are also presented in Table 18.

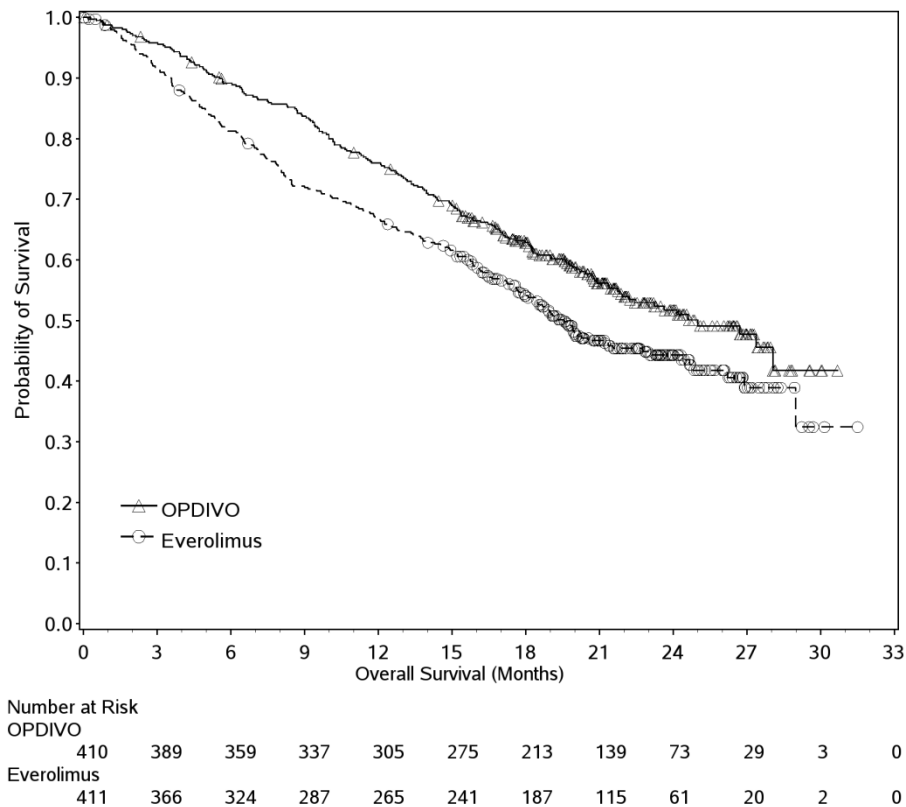
**Table 18: Efficacy Results - Trial 6**

	<b>OPDIVO (n=410)</b>	<b>Everolimus (n=411)</b>
<b>Overall Survival</b>		
Events (%)	183 (45)	215 (52)
Median survival in months (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (95% CI)	0.73 <sup>a</sup> (0.60, 0.89)	
p-value	0.0018 <sup>b</sup>	
<b>Confirmed Objective Response Rate (95% CI)</b>	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median duration of response in months (95% CI)	23.0 (12.0, NE)	13.7 (8.3, 21.9)
Median time to onset of confirmed response in months (min, max)	3.0 (1.4, 13.0)	3.7 (1.5, 11.2)

<sup>a</sup> Hazard ratio is obtained from a Cox proportional hazards model stratified by MSKCC risk group, number of prior anti-angiogenic therapies, and region with treatment as the sole covariate.

<sup>b</sup> p-value is obtained from a two-sided log-rank test stratified by MSKCC risk group, number of prior anti-angiogenic therapies, and region. The corresponding O'Brien-Fleming efficacy boundary significance level is 0.0148.

**Figure 10: Overall Survival - Trial 6**



#### 14.4 Classical Hodgkin Lymphoma

Two studies evaluated the efficacy of OPDIVO as a single agent in patients with cHL after failure of autologous HSCT and post-transplantation brentuximab vedotin.

Trial 8 was a single-arm, open-label, multicenter, multicohort study in cHL. Trial 9 was an open-label, multicenter, dose escalation study that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance less than 40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity.

Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity. A cycle consisted of one dose. Dose reduction was not permitted.

Efficacy was evaluated by objective response rate (ORR) as determined by an independent radiographic review committee (IRRC). Additional outcome measures included duration of response. Efficacy was evaluated in 95 patients in Trials 8 and 9 combined who had received brentuximab vedotin after failure of autologous HSCT. The median age was 37 years (range: 18

to 72). The majority were male (64%) and white (87%). Patients had received a median of 5 prior systemic regimens (range: 3 to 15).

Results are shown in Table 19. Patients received a median of 17 doses of OPDIVO (range 3 to 48), with a median duration of therapy of 8.3 months (range 1.9 to 24 months).

**Table 19: Efficacy in cHL after Autologous HSCT and Brentuximab Vedotin**

	<b>Trial 8 and Trial 9 (n=95)</b>
<b>Objective Response Rate, n (%)</b> <sup>a</sup> (95% CI)	62 (65%) (55, 75)
Complete Remission Rate (95% CI)	7 (7%) (3, 15)
Partial Remission Rate (95% CI)	55 (58%) (47, 68)
<b>Median Duration of Response (months)</b> (95% CI) Range	8.7 (6.8, NE) 0.0+, 23.1+
<b>Median Time to Response (months)</b> Range	2.1 0.7, 5.7

<sup>a</sup> Per 2007 revised International Working Group criteria.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

<b>Carton Contents</b>	<b>NDC</b>
40 mg/4 mL single-dose vial	0003-3772-11
100 mg/10 mL single-dose 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 withholding 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, hyperthyroidism, and diabetes mellitus [*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)*].
- Complications of allogeneic HSCT after OPDIVO: Advise patients of potential risk of post-transplant complications [*see Warnings and Precautions (5.10)*].
- 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 (5.11), 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)*].

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**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, lung cancer, kidney cancer, or blood 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, adrenal glands, and pancreas).** 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
- excessive thirst or lots of urine

**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

**Skin Problems.** Signs of these problems may include:

- rash
- itching
- skin blistering
- ulcers in mouth or other mucous membranes

**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:

- 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 that has spread or cannot be removed by surgery (advanced melanoma).** You may receive OPDIVO alone or in combination with ipilimumab.
- **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.
- **kidney cancer (renal cell carcinoma)**
  - OPDIVO may be used when your cancer has spread or grown after treatment with other cancer medications.
- **a type of blood cancer that affects white blood cells known as lymphocytes (called classical Hodgkin lymphoma)**  
**OPDIVO may be used if:**
  - your cancer has come back or spread after a type of stem cell transplant that uses your own stem cells (autologous), **and**
  - you used the drug brentuximab vedotin (Adcetris<sup>®</sup>) after your stem cell transplant.

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. Ipilimumab will be given on the same day. After that, OPDIVO will be given alone every 2 weeks.
- 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
- **Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO.** These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

**The most common side effects of OPDIVO when used alone in people with melanoma include:**

- feeling tired
- pain in muscles, bones, and joints
- diarrhea
- rash
- itchy skin
- nausea

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

- feeling tired
- diarrhea
- fever
- shortness of breath
- rash
- nausea
- 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

**The most common side effects of OPDIVO in people with renal cell carcinoma include:**

- feeling tired
- shortness of breath
- pain in muscles, bones, and joints
- decreased appetite
- cough
- nausea
- diarrhea
- constipation
- rash

**The most common side effects of OPDIVO in people with classical Hodgkin lymphoma include:**

- feeling tired
- upper respiratory tract infection
- fever
- diarrhea
- cough

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.

**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.

OPDIVO<sup>®</sup> and YERVOY<sup>®</sup> are trademarks of Bristol-Myers Squibb Company. Other brands listed are the trademarks of their respective owners.

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For more information, call 1-855-673-4861 or go to [www.OPDIVO.com](http://www.OPDIVO.com).

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

Revised: May 2016