

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) 9/2015
Dosage and Administration (2) 9/2015
Warnings and Precautions (5) 9/2015

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

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

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

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

Administer as an intravenous infusion over 60 minutes.

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

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

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

-----CONTRAINDICATIONS-----

None. (4)

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

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis:
 - OPDIVO as a single agent: Withhold for moderate or severe and permanently discontinue for life-threatening colitis. (5.2)
 - OPDIVO in combination with ipilimumab: Withhold for moderate and permanently discontinue for severe or life-threatening colitis. (5.2)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.3)
- Immune-mediated endocrinopathies: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis. Withhold for moderate and permanently discontinue for severe or life-threatening adrenal insufficiency. Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. (5.4)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation. (5.5)
- Immune-mediated rash: Withhold for severe and permanently discontinue for life-threatening rash. (5.6)
- Embryofetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.9, 8.1, 8.3)

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

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

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

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

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

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

Lactation: Discontinue breastfeeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2015

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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 unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor [*see Clinical Studies (14.1)*].

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

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

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

1.2 Metastatic Squamous Non-Small Cell Lung Cancer

OPDIVO[®] (nivolumab) is indicated for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy [*see Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Melanoma

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

Review the Full Prescribing Information for ipilimumab prior to initiation.

2.2 Recommended Dosage for Squamous NSCLC

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

2.3 Dose Modifications

Guidelines for treatment modifications are provided in Table 1.

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

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

Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose ^a
	Grade 3 diarrhea or colitis	
	<u>Single-agent OPDIVO</u>	Withhold dose ^a
	<u>OPDIVO, in combination with ipilimumab</u>	Permanently discontinue
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose ^a
	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 ^a
	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 ^a
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose ^a
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose ^a
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Rash	Grade 3 rash	Withhold dose ^a
	Grade 4 rash	Permanently discontinue
Other	Other Grade 3 adverse reaction	
	First occurrence	Withhold dose ^a
	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

^a Resume treatment when adverse reaction returns to Grade 0 or 1.

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

2.4 Preparation and Administration

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

Preparation

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

Storage of Infusion

The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

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

Do not freeze.

Administration

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

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with OPDIVO treatment. Across clinical trial experience with solid tumors receiving OPDIVO as a single agent, fatal immune-mediated pneumonitis occurred in 0.7% (5/691) of patients. No cases of fatal pneumonitis occurred in Trial 1 or Trial 3; all five fatal cases occurred in a dose-finding study with OPDIVO doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

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

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

Melanoma

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

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

resolved in the five patients with Grade 2 or 3 pneumonitis. OPDIVO in combination with ipilimumab was restarted for one patient with Grade 2 pneumonitis after complete resolution, and pneumonitis did not recur.

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In Trial 3, pneumonitis occurred in 6% (7/117) of patients receiving OPDIVO, including five Grade 3 and two Grade 2 cases, all immune-mediated. The median time to onset was 3.3 months (range: 1.4 to 13.5 months). All seven patients discontinued OPDIVO for pneumonitis or another event and all seven patients experienced complete resolution of pneumonitis following receipt of high-dose corticosteroids (at least 40 mg prednisone equivalents per day).

5.2 Immune-Mediated Colitis

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

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

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

Melanoma

In Trial 1, diarrhea or colitis occurred in 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis occurred in 2.2% (6/268) of patients receiving OPDIVO: five patients with Grade 3 and one patient with Grade 2 colitis. The median time to onset of immune-mediated colitis from initiation of OPDIVO was 2.5 months (range: 1 to 6 months). In three patients, colitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 or 3 colitis led to interruption or permanent discontinuation of OPDIVO in the remaining three patients. Five of these six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.4 months (range: 3 days to 2.4 months) preceding corticosteroid taper. The sixth patient continued on low-dose corticosteroids started for another immune-mediated adverse reaction. Immune-mediated colitis improved to Grade 0 with corticosteroids in five patients, including one patient with Grade 3 colitis retreated after complete resolution (defined as improved to Grade 0 with completion of corticosteroids) without additional events of colitis. Grade 2 colitis was ongoing in one patient.

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

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In Trial 3, diarrhea occurred in 21% (24/117) of patients. Immune-mediated colitis (Grade 3) occurred in 0.9% (1/117) of patients. The time to onset in this patient was 6.7 months. The patient received high-dose corticosteroids and was permanently discontinued from OPDIVO. Complete resolution occurred.

5.3 Immune-Mediated Hepatitis

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

Melanoma

In Trial 1, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs. 12%), alkaline phosphatase (22% vs. 13%), ALT (16% vs. 5%), and total bilirubin (9% vs. 0). Immune-mediated hepatitis occurred in 1.1% (3/268) of patients receiving OPDIVO: two patients with Grade 3 and one patient with Grade 2 hepatitis. The time to onset was 97, 113, and 86 days after initiation of OPDIVO. In one patient, hepatitis was diagnosed after discontinuation of OPDIVO for other reasons. In two patients, OPDIVO was withheld. All three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Liver tests improved to Grade 1 within 4 to 15 days of initiation of corticosteroids. Immune-mediated hepatitis resolved and did not recur with continuation of corticosteroids in two patients; the third patient died of disease progression with persistent hepatitis. The two patients with Grade 3 hepatitis that resolved restarted OPDIVO and, in one patient, Grade 3 immune-mediated hepatitis recurred resulting in permanent discontinuation of OPDIVO.

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

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In Trial 3, the incidences of increased liver test values were AST (16%), alkaline phosphatase (14%), ALT (12%), and total bilirubin (2.7%). No cases of immune-mediated hepatitis occurred in this trial.

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

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

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

Adrenal Insufficiency

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

In Trial 4, adrenal insufficiency occurred in 9% (8/94) of patients receiving OPDIVO in combination with ipilimumab: three patients with Grade 3, four patients with Grade 2, and one patient with Grade 1 adrenal insufficiency. The median time to onset was 3 months (range: 1.2 to 5.6 months). Grade 3 adrenal insufficiency led to discontinuation of OPDIVO in combination with ipilimumab in one patient. The remaining events each occurred after treatment discontinuation, except in two cases where OPDIVO in combination with ipilimumab was

restarted and did not lead to recurrence. Three patients received high-dose corticosteroids. Six patients experienced resolution of adrenal insufficiency, three of whom remained on corticosteroids. In Trials 1 and 3 (n=385), 2% of OPDIVO-treated patients developed adrenal insufficiency.

Hypothyroidism and Hyperthyroidism

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

Melanoma

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

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

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

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

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In Trial 3, patients were evaluated for thyroid function at baseline, first day of treatment, and every 6 weeks. Hypothyroidism occurred in 4.3% (5/117) of patients receiving OPDIVO. The median time to onset for these five cases was 4.1 months (range: 1.4 to 4.6 months). All five patients with hypothyroidism received levothyroxine. Complete resolution of hypothyroidism occurred in one patient allowing discontinuation of levothyroxine. Interruption of OPDIVO did not occur in these five patients.

In Trial 3, hyperthyroidism was identified in 1.7% (2/117) of patients receiving OPDIVO. One patient experienced Grade 2 hyperthyroidism 5.2 months after the first dose of OPDIVO, requiring treatment with high-dose corticosteroids and methimazole. Thyroid laboratory tests returned to normal 4.7 months later.

5.5 Immune-Mediated Nephritis and Renal Dysfunction

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

Melanoma

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

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

NSCLC

In Trial 3, the incidence of elevated creatinine was 22%. Immune-mediated renal dysfunction (Grade 2) occurred in 0.9% (1/117) of patients. The time to onset in this patient was 0.8 months. The patient received high-dose corticosteroids. OPDIVO was withheld, and the patient discontinued due to disease progression prior to receiving additional OPDIVO. Immune-mediated renal dysfunction was ongoing.

5.6 Immune-Mediated Rash

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

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

5.7 Other Immune-Mediated Adverse Reactions

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

The following clinically significant, immune-mediated adverse reactions occurred in less than 2% of OPDIVO-treated patients in Trials 1 and 3 (n=385): uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction, and vasculitis. In Trial 4, the following additional immune-mediated adverse reactions occurred in 1% of patients treated with OPDIVO in combination with ipilimumab: Guillain-Barré syndrome and hypopituitarism.

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

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

5.8 Infusion Reactions

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

5.9 Embryofetal Toxicity

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The data in the Warning and Precautions section reflect exposure to OPDIVO, as a single agent, for clinically significant adverse reactions in 691 patients enrolled in Trials 1, 3, 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, 5.7)*]. In addition, clinically significant adverse reactions with OPDIVO, in combination with ipilimumab, were evaluated in 188 patients with melanoma enrolled in Trial 4 (n=94) or an additional dose-finding study (n=94) administering OPDIVO in combination with ipilimumab at doses of OPDIVO ranging

from 0.3 to 3 mg/kg and doses of ipilimumab ranging from 1 to 3 mg/kg, supplemented by immune-mediated adverse reaction reports in ongoing clinical trials [see *Warnings and Precautions* (5.1, 5.7)].

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

Unresectable or Metastatic Melanoma

OPDIVO as a Single Agent

The safety of OPDIVO as a single agent was evaluated in Trial 1, a randomized, open-label trial in which 370 patients with unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m² every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m² every 3 weeks [see *Clinical Studies* (14.1)]. The median duration of exposure was 5.3 months (range: 1 day to 13.8+ months) with a median of eight doses (range: 1 to 31) in OPDIVO-treated patients and was 2 months (range: 1 day to 9.6+ months) in chemotherapy treated patients. In this ongoing trial, 24% of patients received OPDIVO for greater than 6 months and 3% of patients received OPDIVO for greater than 1 year.

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

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

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

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

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

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

^a 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.

^b 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 ^a			
	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

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

OPDIVO in Combination with Ipilimumab

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

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

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

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

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

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

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

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

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

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

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

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

Nervous system disorders: peripheral neuropathy

Gastrointestinal disorders: stomatitis, colonic perforation

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

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

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

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

Metastatic Squamous Non-Small Cell Lung Cancer

The safety of OPDIVO was evaluated in Trial 3, a single-arm multinational, multicenter trial in 117 patients with metastatic squamous NSCLC and progression on both a prior platinum-based therapy and at least one additional systemic therapy [see *Clinical Studies (14.2)*]. Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks. The

median duration of therapy was 2.3 months (range: 1 day to 16.1+ months). Patients received a median of 6 doses (range: 1 to 34).

Trial 3 excluded patients with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis. The median age of patients was 65 years (range: 37 to 87) with 50% ≥65 years of age and 14% ≥75 years of age. The majority of patients were male (73%) and white (85%). All patients received two or more prior systemic treatments. Baseline disease characteristics of the population were recurrent Stage IIIb (6%), Stage IV (94%), and brain metastases (1.7%). Baseline ECOG performance status was 0 (22%) or 1 (78%).

OPDIVO was discontinued due to adverse reactions in 27% of patients. Twenty-nine percent of patients receiving OPDIVO had a drug delay for an adverse reaction. Serious adverse reactions occurred in 59% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain.

Table 6 summarizes adverse reactions that occurred in at least 10% of patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation.

Table 6: Adverse Reactions Occurring in ≥10% of Patients for All NCI CTCAE* Grades or ≥5% for Grades 3-4 (Trial 3)

Adverse Reaction	OPDIVO (n=117)	
	All Grades	Grades 3-4
	Percentage (%) of Patients	
General Disorders and Administration Site Conditions		
Fatigue	50	7
Asthenia	19	1.7
Edema ^a	17	1.7
Pyrexia	17	0
Chest pain ^b	13	0
Pain	10	2.6
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	38	9
Cough	32	1.7
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain ^c	36	6
Arthralgia ^d	13	0
Metabolism and Nutrition Disorders		
Decreased appetite	35	2.6
Gastrointestinal Disorders		
Nausea	29	1.7
Constipation	24	0
Vomiting	19	0.9

Table 6: Adverse Reactions Occurring in ≥10% of Patients for All NCI CTCAE* Grades or ≥5% for Grades 3-4 (Trial 3)

Adverse Reaction	OPDIVO (n=117)	
	All Grades	Grades 3-4
	Percentage (%) of Patients	
Diarrhea	18	2.6
Abdominal pain ^e	16	1.7
Skin and Subcutaneous Tissue Disorders		
Rash ^f	16	0.9
Pruritus	11	0.9
Investigations		
Decreased weight	13	0.9
Infections and Infestations		
Pneumonia ^g	10	5

* National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

^a Includes face edema, peripheral edema, local swelling, localized edema, lymphoedema.

^b Includes chest discomfort and noncardiac chest pain.

^c Includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, spinal pain.

^d Includes arthritis and osteoarthritis.

^e Includes abdominal pain lower, abdominal pain upper, gastrointestinal pain.

^f Includes maculopapular rash, rash erythematous, erythema, dermatitis, dermatitis exfoliative, and dermatitis acneiform.

^g Includes lung infection and pneumonia aspiration.

Other clinically important adverse reactions in less than 10% of patients in Trial 3 were:

General Disorders and Administration Site Conditions: stomatitis

Nervous System Disorders: peripheral neuropathy

Infections and Infestations: bronchitis, upper respiratory tract infection

Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in $\geq 10\%$ of Patients for all NCI CTCAE Grades or $\geq 2\%$ for Grades 3-4 (Trial 3)

Test	Percentage of Patients with Worsening Laboratory Test from Baseline ^a	
	All Grades	Grades 3-4
Chemistry		
Hyponatremia	38	10
Increased creatinine	22	0
Hypercalcemia	20	2.6
Hypokalemia	20	2.6
Hypomagnesemia	20	0
Hypocalcemia	18	1.8
Hyperkalemia	18	4.4
Increased AST	16	0.9
Increased alkaline phosphatase	14	0
Increased ALT	12	0
Hematology		
Lymphopenia	47	16
Anemia	28	2.6
Thrombocytopenia	14	0

^a Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range: 111 to 114 patients).

6.2 Immunogenicity

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

Of 281 patients who were treated with OPDIVO 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 24 patients (8.5%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies against nivolumab were detected in two patients (0.7%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-nivolumab binding antibody development.

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

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For

these reasons, comparison of incidence of antibodies to OPDIVO with the incidences of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of OPDIVO, administered as a single agent in Trials 1 and 3 or in combination with ipilimumab in Trial 4 did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

There is no information on overdosage with OPDIVO.

11 DESCRIPTION

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

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous infusion is supplied in single-use vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg),

sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.3 Pharmacokinetics

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

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

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

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

Specific Populations: Based on a population PK analysis, the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m²; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m²; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m²; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function [see Use in Specific Populations (8.6)].

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

OPDIVO as a Single Agent

Trial 1 was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either OPDIVO administered intravenously at 3 mg/kg every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m² every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m² every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-

related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

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

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

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

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

OPDIVO in Combination with Ipilimumab

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

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

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

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

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

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

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

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

14.2 Metastatic Squamous Non-Small Cell Lung Cancer

Metastatic Squamous NSCLC Randomized Trial

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/m² every 3 weeks. This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, symptomatic interstitial lung disease, or untreated

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

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

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

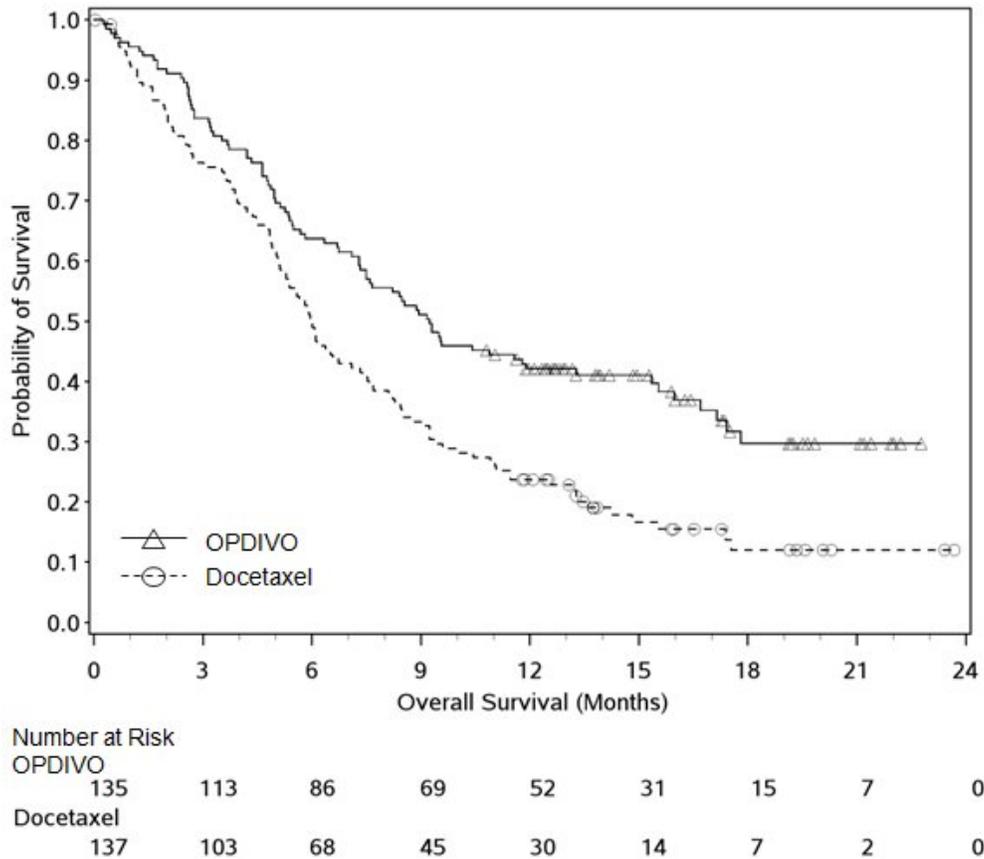
Table 9: Overall Survival in Trial 2 (Intent-to-Treat Analysis)

	OPDIVO (n=135)	Docetaxel (n=137)
Prespecified Interim Analysis		
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 ^a	0.00025	
Hazard ratio (95% CI) ^b	0.59 (0.44, 0.79)	

^a 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.

^b Derived from a stratified proportional hazards model.

Figure 1: Overall Survival - Trial 2



Metastatic Squamous NSCLC Single-Arm Trial

Trial 3 was a single-arm, multinational, multicenter trial in patients with metastatic squamous NSCLC. All patients had progressed after receiving a platinum-based therapy and at least one additional systemic treatment regimen. This study included patients regardless of their PD-L1 status. Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks. 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 8 weeks after the start of treatment and continued every 6 weeks thereafter.

The major efficacy outcome measure was confirmed objective response rate (ORR) as measured by independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Additional outcome measures included duration of response.

A total of 117 patients received treatment with OPDIVO. The median age was 65 years (range: 37 to 87) with 50% of patients ≥65 years of age and 14% of patients ≥75 years of age. The majority were male (73%) and white (85%). All patients received two or more prior systemic

treatments: 35% received two, 44% received three, and 21% received four or more. Baseline disease characteristics of the population were recurrent Stage IIIb (6%), Stage IV (94%), and brain metastases (1.7%). Baseline ECOG performance status was 0 (22%) or 1 (78%).

Based on IRC review and with a minimum follow-up of at least 10 months on all patients, confirmed ORR was 15% (17/117) (95% CI: 9, 22), of which all were partial responses. The median time to onset of response was 3.3 months (range: 1.7 to 8.8 months) after the start of OPDIVO treatment. Thirteen of the 17 patients (76%) with a confirmed response had ongoing responses with duration ranging from 1.9+ to 11.5+ months; 10 of these 17 (59%) patients had durable responses of 6 months or longer.

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) is available as follows:

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

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

17 PATIENT COUNSELING INFORMATION

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

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

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [*see Warnings and Precautions (5.1)*].
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain [*see Warnings and Precautions (5.2)*].
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [*see Warnings and Precautions (5.3)*].
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, and hyperthyroidism [*see Warnings and Precautions (5.4)*].
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction [*see Warnings and Precautions (5.5)*].
- Rash: Advise patients to contact their healthcare provider immediately for rash [*see Warnings and Precautions (5.6)*].

- Infusion Reactions: Advise patients of the potential risk of infusion reaction [*see Warnings and Precautions (5.8)*].
- 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 (5.9), Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO [*see Use in Specific Populations (8.3)*].
- Lactation: Advise women not to breastfeed while taking OPDIVO [*see Use in Specific Populations (8.2)*].

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

What is OPDIVO?

OPDIVO is a prescription medicine used to treat:

- **a type of skin cancer called melanoma.**
OPDIVO may be used alone when your melanoma:
 - has spread or cannot be removed by surgery (advanced melanoma), **and**,
 - after you have tried a medicine called ipilimumab and it did not work or is no longer working **and**,
 - if your tumor has an abnormal “BRAF” gene, and you have also tried a different medicine called a BRAF inhibitor, and it did not work or is no longer working.**OPDIVO may be used in combination with the medicine ipilimumab when your melanoma:**
 - has spread or cannot be removed by surgery (advanced melanoma), **and**
 - has a normal BRAF gene (wild-type)
- **a type of advanced stage lung cancer (called squamous non-small cell lung cancer)**
 - OPDIVO may be used alone when your cancer has spread or grown after treatment with platinum-based chemotherapy

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

What should I tell my healthcare provider before receiving OPDIVO?

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

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

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

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

How will I receive OPDIVO?

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

What are the possible side effects of OPDIVO?

OPDIVO can cause serious side effects, including:

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

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

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

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

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

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

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

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

General information about the safe and effective use of OPDIVO.

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

What are the ingredients in OPDIVO?

Active ingredient: nivolumab

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

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

U.S. License No. 1713

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

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