

Product Fact Sheet for OPDIVO® (nivolumab)

For Previously Treated Metastatic Squamous Non-Small Cell Lung Cancer

Supplied and Marketed by	Bristol-Myers Squibb Internet: www.bms.com						
Product Name	OPDIVO®						
Established Name	Nivolumab						
Indication and Usage¹	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.						
Contraindication¹	None						
How Supplied¹	OPDIVO is supplied in two quantities (both in a 10 mL vial). Product Description: <ul style="list-style-type: none"> • 40 mg/4 mL (10 mg/mL) solution in a single-use vial • 100 mg/10 mL (10 mg/mL) solution in a single-use vial 						
Ordering Information	Determining Your Order for OPDIVO Step 1. Calculate total dosage in mg needed: (weight in kg x 3 mg = total dosage in mg). Step 2. Determine quantity of single-use vials needed based on total dosage.						
HCPCS Codes²⁻⁴	Physician Offices: <ul style="list-style-type: none"> • J9999 is the most commonly used NOC code for anticancer therapies^{2,3} • J3590 and J3490 may be used in rare cases^{2,4} HOPD: <ul style="list-style-type: none"> • C9399 can be used until a unique C-code is assigned. Temporary "C" HCPCS codes were established to permit payment for Medicare patients being treated at HOPD. Other payers may utilize "C" HCPCS codes. Please consult your payer for guidance on use of temporary "C" HCPCS codes 						
CPT Code⁵	96413—chemotherapy administration IV infusion technique; up to one hour, single or initial substance						
ICD-9-CM Codes	Please visit www.bmsaccesssupport.com for ICD-9-CM coding information.						
ICD-10-CM Codes	Please visit www.bmsaccesssupport.com for ICD-10-CM coding information.						
National Drug Codes (NDCs)¹	<table border="0"> <tr> <td>40 mg (10 mg/mL), single-use vial</td> <td>100 mg (10 mg/mL), single-use vial</td> </tr> <tr> <td>0003-3772-11</td> <td>0003-3774-12</td> </tr> <tr> <td>00003-3772-11</td> <td>00003-3774-12</td> </tr> </table>	40 mg (10 mg/mL), single-use vial	100 mg (10 mg/mL), single-use vial	0003-3772-11	0003-3774-12	00003-3772-11	00003-3774-12
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0003-3772-11	0003-3774-12						
00003-3772-11	00003-3774-12						
BMS Access Support Information	BMS Access Support®—your source for reimbursement information and support. For more information: <ul style="list-style-type: none"> • Contact your Area Reimbursement Manager for assistance and to schedule an office visit • Contact BMS Access Support at 1-800-861-0048, Monday-Friday, 8 AM to 8 PM ET • Visit www.bmsaccesssupport.com for resources to help your patients with access to Bristol-Myers Squibb Oncology products 						

HOPD=hospital outpatient department; NOC=not otherwise classified.

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

Select Important Safety Information

OPDIVO is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypothyroidism, hyperthyroidism, other adverse reactions; and embryofetal toxicity.

Please see additional Important Safety Information on page 2.



Important Safety Information for OPDIVO® (nivolumab)

Immune-Mediated Pneumonitis

- Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience in 691 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.7% (5/691) of patients receiving OPDIVO; no cases occurred in Trial 3. In Trial 3, immune-mediated pneumonitis occurred in 6% (7/117) of patients receiving OPDIVO including five Grade 3 and two Grade 2 cases. Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue OPDIVO for Grade 3 or 4 and withhold OPDIVO until resolution for Grade 2.

Immune-Mediated Colitis

- In Trial 3, diarrhea occurred in 21% (24/117) of patients receiving OPDIVO. Grade 3 immune-mediated colitis occurred in 0.9% (1/117) of patients. Monitor patients for immune-mediated colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO for Grade 2 or 3. Permanently discontinue OPDIVO for Grade 4 colitis or recurrent colitis upon restarting OPDIVO.

Immune-Mediated Hepatitis

- In Trial 3, the incidences of increased liver test values were AST (16%), alkaline phosphatase (14%), ALT (12%), and total bilirubin (2.7%). Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4 immune-mediated hepatitis.

Immune-Mediated Nephritis and Renal Dysfunction

- In Trial 3, the incidence of elevated creatinine was 22%. Immune-mediated renal dysfunction (Grade 2) occurred in 0.9% (1/117) of patients. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 serum creatinine elevation, withhold OPDIVO and administer corticosteroids; if worsening or no improvement occurs, permanently discontinue OPDIVO. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue OPDIVO.

Immune-Mediated Hypothyroidism and Hyperthyroidism

- In Trial 3, hypothyroidism occurred in 4.3% (5/117) of patients receiving OPDIVO. Hyperthyroidism occurred in 1.7% (2/117) of patients including one Grade 2 case. Monitor thyroid

function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism.

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred in <2% of OPDIVO-treated patients: adrenal insufficiency, uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction and vasculitis. Across clinical trials of OPDIVO administered at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome. Based on the severity of adverse reaction, withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy.

Embryofetal Toxicity

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

Lactation

- 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.

Serious Adverse Reactions

- In Trial 3, serious adverse reactions occurred in 59% of patients receiving OPDIVO. The most frequent serious adverse drug reactions reported in ≥2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain.

Common Adverse Reactions

- The most common adverse reactions (≥20%) reported with OPDIVO in Trial 3 were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%).

Please see accompanying Full Prescribing Information at the end of this document.

References:

- OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.
- Centers for Medicare and Medicaid Services. Medicare Claims Processing Manual, Chapter 17 – Drugs and Biologicals. Revision 3055, August 29, 2014. www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c17.pdf. Accessed January 7, 2015.
- Centers for Medicare and Medicaid Services. 2015 Table of Drugs. www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/Downloads/2015-Table-of-Drugs-.pdf. Accessed January 7, 2015.
- Medi-Cal. Injections: an overview. https://files.medi-cal.ca.gov/pubsdoco/publications/masters-mtp/part2/injectanover_m00o03o04o11p00.doc. Accessed January 7, 2015.
- American Medical Association. *Current Procedural Terminology 2015*. Professional ed. Chicago, IL: American Medical Association; 2014.



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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 (1.2) 3/2015
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6) 3/2015

INDICATIONS AND USAGE

OPDIVO is a programmed death receptor-1 (PD-1) blocking antibody 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. (1.1)
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 the confirmatory trials. (1.1, 14.1)
- metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy. (1.2)

DOSAGE AND ADMINISTRATION

Administer 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.1)

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 adverse reactions: Administer corticosteroids based on the severity of the reaction. (5.1, 5.2, 5.3, 5.4, 5.6)

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis: Withhold for moderate or severe and permanently discontinue for 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 nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation. (5.4)
- Immune-mediated hypothyroidism and hyperthyroidism: Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. (5.5)
- Embryofetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reaction ($\geq 20\%$) in patients with melanoma was rash. (6.1)

Most common adverse reactions ($\geq 20\%$) 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: 3/2015

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1 INDICATIONS AND USAGE**1.1 Unresectable or Metastatic Melanoma**

OPDIVO® (nivolumab) 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 the 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**

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.

2.2 Dose Modifications

There are no recommended dose modifications for hypothyroidism or hyperthyroidism. Withhold OPDIVO for any of the following:

- Grade 2 pneumonitis [see *Warnings and Precautions* (5.1)]
- Grade 2 or 3 colitis [see *Warnings and Precautions* (5.2)]
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN [see *Warnings and Precautions* (5.3)]
- Creatinine greater than 1.5 and up to 6 times ULN or greater than 1.5 times baseline [see *Warnings and Precautions* (5.4)]
- Any other severe or Grade 3 treatment-related adverse reactions [see *Warnings and Precautions* (5.6)]

Resume OPDIVO in patients whose adverse reactions recover to Grade 0 to 1.

Permanently discontinue OPDIVO for any of the following:

- Any life-threatening or Grade 4 adverse reaction
- Grade 3 or 4 pneumonitis [see *Warnings and Precautions* (5.1)]
- Grade 4 colitis [see *Warnings and Precautions* (5.2)]
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN [see *Warnings and Precautions* (5.3)]
- Creatinine greater than 6 times ULN [see *Warnings and Precautions* (5.4)]
- Any severe or Grade 3 treatment-related adverse reaction that recurs
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 treatment-related adverse reactions that do not recover to Grade 1 or resolve within 12 weeks after last dose of OPDIVO

2.3 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, is 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–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.

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**

Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience in 691 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.7% (5/691) of patients receiving OPDIVO. 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).

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, defined as requiring use of corticosteroids and no clear alternate etiology, 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 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).

Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for 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* (2.2)].

5.2 Immune-Mediated Colitis

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, defined as requiring use of corticosteroids with no clear alternate etiology, 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 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.

Monitor patients for immune-mediated 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. Withhold OPDIVO for Grade 2 or 3 immune-mediated colitis. Permanently discontinue OPDIVO for Grade 4 colitis or for recurrent colitis upon restarting OPDIVO [see *Dosage and Administration* (2.2)].

5.3 Immune-Mediated Hepatitis

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, defined as requirement for corticosteroids and no clear alternate etiology, 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 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.

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 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 (2.2) and Adverse Reactions (6.1)].

5.4 Immune-Mediated Nephritis and Renal Dysfunction

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 (defined as \geq Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology) 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 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.

Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) serum creatinine elevation and permanently discontinue OPDIVO. For severe (Grade 3) or moderate (Grade 2) serum creatinine elevation, withhold OPDIVO 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 [see Dosage and Administration (2.2) and Adverse Reactions (6.1)].

5.5 Immune-Mediated Hypothyroidism and Hyperthyroidism

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.

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 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. 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.

Hyperthyroidism occurred in 1.7% (2/117) of patients. 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.

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.

5.6 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.

The following clinically significant, immune-mediated adverse reactions occurred in less than 2% of OPDIVO-treated patients in Trials 1 and 3 (n=385): adrenal insufficiency, uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction, and vasculitis.

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

For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, 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 (2.2)].

5.7 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 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 Nephritis and Renal Dysfunction [see Warnings and Precautions (5.4)]
- Immune-Mediated Hypothyroidism and Hyperthyroidism [see Warnings and Precautions (5.5)]
- Other Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.6)]

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 clinical practice. The data described in the WARNINGS and PRECAUTIONS section and below reflect exposure to OPDIVO in Trial 1, a randomized trial in patients with unresectable or metastatic melanoma and in Trial 3, a single-arm trial in patients with metastatic squamous non-small cell lung cancer (NSCLC).

Clinically significant adverse reactions were evaluated in a total of 691 patients enrolled in Trials 1, 3, or an additional dose finding study (n=306) administering OPDIVO at doses of 0.1 to 10 mg/kg every 2 weeks [see Warnings and Precautions (5.1, 5.6)].

Unresectable or Metastatic Melanoma

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

Table 1: Selected Adverse Reactions Occurring in \geq 10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Based on 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 Disorders				
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.

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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 2: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥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).

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 3 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 3: 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

(Continued)

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

Adverse Reaction	OPDIVO (n=117)	
	All Grades	Grades 3-4
	Percentage (%) of Patients	
Metabolism and Nutrition Disorders		
Decreased appetite	35	2.6
Gastrointestinal Disorders		
Nausea	29	1.7
Constipation	24	0
Vomiting	19	0.9
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 4: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients for all NCI CTCAE Grades or ≥2% for Grades 3-4 (Trial 3)

Test	Percentage of Patients with Worsening Laboratory Test from Baseline ^a	
	All Grades	Grades 3-4
	Percentage (%) of Patients	
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-product antibodies, 24 patients (8.5%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in two patients (0.7%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-product binding antibody development based on the population pharmacokinetic and exposure-response analyses.

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 did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 272 patients randomized to OPDIVO in Trial 1, 35% of patients were 65 years or older and 15% were 75 years or older. Of the 117 patients treated with OPDIVO in Trial 3, 50% of patients were 65 years or older and 14% were 75 years or older.

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.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of 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. Based on a population pharmacokinetic (PK) analysis using data from 909 patients, 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.

Specific Populations: Based on a population PK analysis using data from 909 patients, 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

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 ECOG PS 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.

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%).

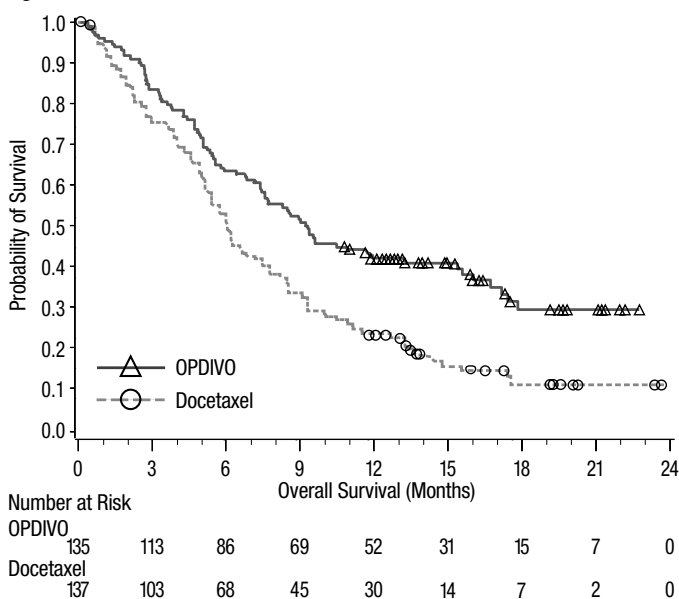
The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis) (Table 5 and Figure 1).

Table 5: 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 (DoR).

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 IIb (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)].
- **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* (5.4)].
- **Hypothyroidism and Hyperthyroidism:** Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism and hyperthyroidism [see *Warnings and Precautions* (5.5)].

Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests [see *Warnings and Precautions* (5.3, 5.4, 5.5, 5.6)].

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* (5.7), *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)].

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

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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. 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.

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 bruise more easily than normal
- feeling less hungry than usual

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

Hormone gland problems (especially the thyroid, pituitary, and 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
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- dizziness or fainting
- hair loss
- feeling cold
- constipation
- voice gets deeper

Problems in other organs. Signs of these problems 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 medicines and 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 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.
- **a type of advanced stage lung cancer (called squamous non-small cell lung cancer)**
 - OPDIVO may be used 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.
- 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. See “What is the most important information I should know about OPDIVO?”

The most common side effects of OPDIVO in people with melanoma include:

- Rash

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.

OPDIVO® (nivolumab)

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.

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

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