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)	7/2017
Dosage and Administration (2)	9/2017
Warnings and Precautions (5)	9/2017

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

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

- patients with BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent. (1.1)
- patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- patients with unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. (1.2)
- patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.3)
- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after:
  - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy that includes autologous HSCT.

  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.4)
- patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy. (1.5)
- patients with locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

  This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.6)
- adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

  This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.7)

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

Administer as an intravenous infusion over 60 minutes.

- Unresectable or metastatic melanoma
  - OPDIVO 240 mg every 2 weeks. (2.1)
  - OPDIVO with ipilimumab: OPDIVO 1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then OPDIVO 240 mg every 2 weeks. (2.1)
- Metastatic non-small cell lung cancer
  - OPDIVO 240 mg every 2 weeks. (2.2)
- Advanced renal cell carcinoma
  - OPDIVO 240 mg every 2 weeks. (2.3)
- Classical Hodgkin lymphoma
  - OPDIVO 3 mg/kg every 2 weeks. (2.4)
- Recurrent or metastatic squamous cell carcinoma of the head and neck
  - OPDIVO 3 mg/kg every 2 weeks. (2.5)
- Locally advanced or metastatic urothelial carcinoma
  - OPDIVO 240 mg every 2 weeks (2.6)
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
  - OPDIVO 240 mg every 2 weeks. (2.7)

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

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

----------CONTRAINDICATIONS----------

None. (4)

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

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis: Withhold OPDIVO when given as a single agent for moderate or severe and permanently discontinue for life-threatening colitis. Withhold OPDIVO when given with ipilimumab for moderate and permanently discontinue for severe or life-threatening colitis. (5.2)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.3)
- Immune-mediated endocrinopathies: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis. Withhold for moderate and permanently discontinue for severe or life-threatening adrenal insufficiency. Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. Monitor for hyperglycemia. Withhold for severe and permanently discontinue for life-threatening hyperglycemia. (5.4)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation. (5.5)
- Immune-mediated skin adverse reactions: Withhold for severe and permanently discontinue for life-threatening rash. (5.6)
- Immune-mediated encephalitis: Monitor for changes in neurologic function. Withhold for new-onset moderate to severe neurological signs or symptoms and permanently discontinue for immune-mediated encephalitis. (5.7)
- Infusion reactions: Discontinue OPDIVO for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. (5.9)
- Complications of allogeneic HSCT after OPDIVO: Monitor for hyperacute graft-versus-host-disease (GVHD), grade 3-4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions. Transplant-related mortality has occurred. (5.10)
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.11, 8.1, 8.3)

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

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

- OPDIVO as a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia. (6.1)
- OPDIVO with ipilimumab: fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea. (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.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

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

  This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*.

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

1.2 Metastatic Non-Small Cell Lung Cancer

OPDIVO is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO *[see Clinical Studies (14.2)]*.

1.3 Renal Cell Carcinoma

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

1.4 Classical Hodgkin Lymphoma

OPDIVO is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- 3 or more lines of systemic therapy that includes autologous HSCT.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials *[see Clinical Studies (14.4)]*.

1.5 Squamous Cell Carcinoma of the Head and Neck

OPDIVO is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy *[see Clinical Studies (14.5)]*.

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1.6 Urothelial Carcinoma

OPDIVO (nivolumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials *[see Clinical Studies (14.6)]*.

1.7 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

OPDIVO is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan *[see Clinical Studies (14.7)]*.

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Melanoma

The recommended dose of OPDIVO as a single agent is 240 mg 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 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Review the Full Prescribing Information for ipilimumab prior to initiation.

2.2 Recommended Dosage for NSCLC

The recommended dose of OPDIVO is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.3 Recommended Dosage for RCC

The recommended dose of OPDIVO is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

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2.4 Recommended Dosage for cHL

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

2.5 Recommended Dosage for SCCHN

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.

2.6 Recommended Dosage for Urothelial Carcinoma

The recommended dose of OPDIVO is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.7 Recommended Dosage for CRC

The recommended dose of OPDIVO is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.8 Dose Modifications

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

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

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

Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[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

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Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose[a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	 Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

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

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

2.9 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.

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Storage of Infusion

The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

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

Do not freeze.

Administration

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

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology. Fatal cases have been reported.

Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) 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 (2.8)]*.

Reference ID: 4149162

OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. The median time to onset of immune-mediated pneumonitis was 3.5 months (range: 1 day to 22.3 months). Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO in 1.1%, and withholding of OPDIVO in 1.3% of patients. Approximately 89% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 26 days (range: 1 day to 6 months). Complete resolution of symptoms following corticosteroid taper occurred in 67% of patients. Approximately 8% of patients had recurrence of pneumonitis after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, immune-mediated pneumonitis occurred in 6% (25/407) of patients. The median time to onset of immune-mediated pneumonitis was 1.6 months (range: 24 days to 10.1 months). Immune-mediated pneumonitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 2.2% and 3.7% of patients, respectively. Approximately 84% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 30 days (range: 5 days to 11.8 months). Complete resolution occurred in 68% of patients. Approximately 13% of patients had recurrence of pneumonitis after re-initiation of OPDIVO with ipilimumab.

5.2 Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology.

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.

Withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon re-initiation of OPDIVO *[see Dosage and Administration (2.8)]*.

When administered in combination with ipilimumab, withhold OPDIVO and ipilimumab for moderate colitis (Grade 2). Permanently discontinue OPDIVO and ipilimumab for severe or life-threatening (Grade 3 or 4) colitis or for recurrent colitis *[see Dosage and Administration (2.8)]*.

Reference ID: 4149162

OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, immune-mediated colitis occurred in 2.9% (58/1994) of patients; the median time to onset was 5.3 months (range: 2 days to 20.9 months). Immune-mediated colitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 1% of patients. Approximately 91% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 23 days (range: 1 day to 9.3 months). Four patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 16% of patients had recurrence of colitis after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases. The median time to onset of immune-mediated colitis was 1.6 months (range: 3 days to 15.2 months). Immune-mediated colitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 16% and 7% of patients, respectively. Approximately 96% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.1 month (range: 1 day to 12 months). Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 75% of patients. Approximately 28% of patients had recurrence of colitis after re-initiation of OPDIVO with ipilimumab.

5.3 Immune-Mediated Hepatitis

OPDIVO can cause immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology. 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 followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations. 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 (2.8)]*.

OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients; the median time to onset was 3.3 months (range: 6 days to 9 months). Immune-mediated hepatitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 1% of patients. All patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 23 days (range: 1 day to 2 months). Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 29% of patients had recurrence of hepatitis after re-initiation of OPDIVO.

Reference ID: 4149162

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, immune-mediated hepatitis occurred in 13% (51/407) of patients; the median time to onset was 2.1 months (range: 15 days to 11 months). Immune-mediated hepatitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 6% and 5% of patients, respectively. Approximately 92% of patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.1 month (range: 1 day to 13.2 months). Complete resolution occurred in 75% of patients. Approximately 11% of patients had recurrence of hepatitis after re-initiation of OPDIVO with ipilimumab.

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

OPDIVO can cause immune-mediated hypophysitis. Monitor patients for signs and symptoms of hypophysitis. Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3). Permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.8)]*.

In patients receiving OPDIVO as a single agent, hypophysitis occurred in 0.6% (12/1994) of patients; the median time to onset was 4.9 months (range: 1.4 to 11 months). Hypophysitis led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.2% of patients. Approximately 67% of patients with hypophysitis received hormone replacement therapy and 33% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 14 days (range: 5 to 26 days).

In patients receiving OPDIVO with ipilimumab, hypophysitis occurred in 9% (36/407) of patients; the median time to onset was 2.7 months (range: 27 days to 5.5 months). Hypophysitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 1.0% and 3.9% of patients, respectively. Approximately 75% of patients with hypophysitis received hormone replacement therapy and 56% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 19 days (range: 1 day to 2.0 months).

Adrenal Insufficiency

OPDIVO can cause immune-mediated adrenal insufficiency. Monitor patients for signs and symptoms of adrenal insufficiency. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper 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 (2.8)]*.

Reference ID: 4149162

In patients receiving OPDIVO as a single agent, adrenal insufficiency occurred in 1% (20/1994) of patients and the median time to onset was 4.3 months (range: 15 days to 21 months). Adrenal insufficiency led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.5% of patients. Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy and 25% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 11 days (range: 1 day to 1 month).

In patients receiving OPDIVO with ipilimumab, adrenal insufficiency occurred in 5% (21/407) of patients and the median time to onset was 3.0 months (range: 21 days to 9.4 months). Adrenal insufficiency led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.5% and 1.7% of patients, respectively. Approximately 57% of patients with adrenal insufficiency received hormone replacement therapy and 33% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 9 days (range: 1 day to 2.7 months).

Hypothyroidism and Hyperthyroidism

OPDIVO can cause autoimmune thyroid disorders. Monitor thyroid function prior to and periodically during OPDIVO 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.

In patients receiving OPDIVO as a single agent, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients; the median time to onset was 2.9 months (range: 1 day to 16.6 months). Approximately 79% of patients with hypothyroidism received levothyroxine and 4% also required corticosteroids. Resolution occurred in 35% of patients.

Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO as a single agent; the median time to onset was 1.5 months (range: 1 day to 14.2 months). Approximately 26% of patients with hyperthyroidism received methimazole, 9% received carbimazole, 4% received propylthiouracil, and 9% received corticosteroids. Resolution occurred in 76% of patients.

In patients receiving OPDIVO with ipilimumab, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients; the median time to onset was 2.1 months (range: 1 day to 10.1 months). Approximately 73% of patients with hypothyroidism or thyroiditis received levothyroxine. Resolution occurred in 45% of patients.

Hyperthyroidism occurred in 8% (34/407) of patients receiving OPDIVO with ipilimumab: the median time to onset was 23 days (range: 3 days to 3.7 months). Approximately 29% of patients with hyperthyroidism received methimazole and 24% received carbimazole. Resolution occurred in 94% of patients.

Type 1 Diabetes Mellitus

OPDIVO can cause Type 1 diabetes mellitus. Monitor for hyperglycemia. Withhold OPDIVO in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia *[see Dosage and Administration (2.8)]*.

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In patients receiving OPDIVO as a single agent, diabetes occurred in 0.9% (17/1994) of patients including two cases of diabetic ketoacidosis. The median time to onset was 4.4 months (range: 15 days to 22 months).

In patients receiving OPDIVO with ipilimumab, diabetes occurred in 1.5% (6/407) of patients; the median time to onset was 2.5 months (range: 1.3 to 4.4 months). OPDIVO with ipilimumab was withheld in a patient and permanently discontinued in a second patient who developed diabetes.

5.5 Immune-Mediated Nephritis and Renal Dysfunction

OPDIVO can cause immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology. 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) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents.

Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine. Permanently discontinue OPDIVO for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)]*.

OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients; the median time to onset was 4.6 months (range: 23 days to 12.3 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.8% of patients. All patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 21 days (range: 1 day to 15.4 months). Complete resolution occurred in 48% of patients. No patients had recurrence of nephritis or renal dysfunction after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients; the median time to onset was 2.7 months (range: 9 days to 7.9 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.7% and 0.5% of patients, respectively. Approximately 67% of patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 13.5 days (range: 1 day to 1.1 months). Complete resolution occurred in all patients. Two patients resumed OPDIVO with ipilimumab without recurrence of nephritis or renal dysfunction.

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5.6 Immune-Mediated Skin Adverse Reactions

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue OPDIVO *[see Dosage and Administration (2.8)]*.

For immune-mediated rash, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper 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.

OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, immune-mediated rash occurred in 9% (171/1994) of patients; the median time to onset was 2.8 months (range: <1 day to 25.8 months). Immune-mediated rash led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.8% of patients. Approximately 16% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 1 days to 8.9 months) and 85% received topical corticosteroids. Complete resolution occurred in 48% of patients. Recurrence of rash occurred in 1.4% of patients who resumed OPDIVO after resolution of rash.

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, immune-mediated rash occurred in 22.6% (92/407) of patients; the median time to onset was 18 days (range: 1 day to 9.7 months). Immune-mediated rash led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.5% and 3.9% of patients, respectively. Approximately 17% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 14 days (range: 2 days to 4.7 months). Complete resolution occurred in 47% of patients. Approximately 6% of patients who resumed OPDIVO and ipilimumab after resolution had recurrence of rash.

5.7 Immune-Mediated Encephalitis

OPDIVO can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis *[see Dosage and Administration (2.8)]*.

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OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, encephalitis occurred in 0.2% (3/1994). Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. In the other two patients encephalitis occurred post-allogeneic HSCT *[see Warnings and Precautions (5.10)]*.

OPDIVO with Ipilimumab

Encephalitis occurred in one patient receiving OPDIVO with ipilimumab (0.2%) after 1.7 months of exposure.

5.8 Other Immune-Mediated Adverse Reactions

OPDIVO can cause other clinically significant and potentially fatal immune-mediated adverse reactions. 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 (2.8)]*.

Across clinical trials of OPDIVO administered as a single agent or in combination with ipilimumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in less than 1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, and myasthenic syndrome.

5.9 Infusion Reactions

OPDIVO can cause severe infusion reactions, which have been reported in less than 1.0% of patients in clinical trials. 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 *[see Dosage and Administration (2.8)]*.

OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, infusion-related reactions occurred in 6.4% (127/1994) of patients.

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, infusion-related reactions occurred in 2.5% (10/407) of patients.

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5.10 Complications of Allogeneic HSCT after OPDIVO

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from the CHECKMATE-205 and CHECKMATE-039 trials who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, two with myeloablative conditioning). The median age at HSCT was 33 (range: 18 to 56), and a median of 9 doses of OPDIVO had been administered (range: 4 to 16). Six of 17 patients (35%) died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 5/17 patients (29%). Hyperacute GVHD, defined as GVHD occurring within 14 days after stem cell infusion, was reported in 2 patients (20%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (35%) within the first 6 weeks post-transplantation, with five patients responding to steroids. Two cases of encephalitis were reported: one case of Grade 3 lymphocytic encephalitis without an identified infectious cause, which occurred and resolved on steroids, and one case of Grade 3 suspected viral encephalitis which was resolved with antiviral treatment. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure.

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

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

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

5.11 Embryo-Fetal Toxicity

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

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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 Skin Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Immune-Mediated Encephalitis *[see Warnings and Precautions (5.7)]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.8)]*
- Infusion Reactions *[see Warnings and Precautions (5.9)]*
- Complications of Allogeneic HSCT after OPDIVO *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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

The data in the Warnings and Precautions section reflect exposure to OPDIVO, as a single agent, for clinically significant adverse reactions in 1994 patients enrolled in the CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 trials or a single-arm trial in NSCLC (n=117) administering OPDIVO as a single agent *[see Warnings and Precautions (5.1, 5.8)]*. In addition, clinically significant adverse reactions of OPDIVO administered with ipilimumab were evaluated in 407 patients with melanoma enrolled in CHECKMATE-067 (n=313) or a Phase 2 randomized study (n=94), administering OPDIVO with ipilimumab, supplemented by immune-mediated adverse reaction reports in ongoing clinical trials *[see Warnings and Precautions (5.1, 5.8)]*.

The data described below reflect exposure to OPDIVO as a single agent in CHECKMATE-037, CHECKMATE-066, and CHECKMATE-067, and to OPDIVO with ipilimumab in CHECKMATE-067, which are randomized, active-controlled trials conducted in patients with unresectable or metastatic melanoma. Also described below are single-agent OPDIVO data from CHECKMATE-017 and CHECKMATE-057, which are randomized trials in patients with metastatic NSCLC, CHECKMATE-025, which is a randomized trial in patients with advanced RCC, CHECKMATE-205 and CHECKMATE-039, which are open-label, multiple-cohort trials in patients with cHL, CHECKMATE-141, a randomized trial in patients with recurrent or metastatic SCCHN, and CHECKMATE-275, which is a single-arm trial in patients with urothelial carcinoma.

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Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-037, a randomized, open-label trial in which 370 patients with unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m^2 every 3 weeks *[see Clinical Studies (14.1)]*. The median duration of exposure was 5.3 months (range: 1 day to 13.8+ months) in OPDIVO-treated patients and was 2 months (range: 1 day to 9.6+ months) in chemotherapy-treated patients. In this ongoing trial, 24% of patients received OPDIVO for greater than 6 months and 3% of patients received OPDIVO for greater than 1 year.

In CHECKMATE-037, 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 trial population characteristics in the OPDIVO group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% white, baseline Eastern Cooperative Oncology Group (ECOG) performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the OPDIVO group with elevated LDH at baseline (51% vs. 38%).

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

Table 2 summarizes the adverse reactions that occurred in at least 10% of OPDIVO-treated patients in CHECKMATE-037. The most common adverse reaction (reported in at least 20% of patients) was rash.

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Table 2: Adverse Reactions 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]) (CHECKMATE-037)

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				
Upper respiratory tract infection[b]	11	0	2.0	0
General Disorders and Administration Site Conditions				
Peripheral edema	10	0	5	0

Toxicity was graded per NCI CTCAE v4.

[a] Rash is a composite term which includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, and acneiform dermatitis.

[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 CHECKMATE-037 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

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Table 3: 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]) (CHECKMATE-037)

Laboratory Abnormality	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).

Previously Untreated Metastatic Melanoma

CHECKMATE-066

The safety of OPDIVO was also evaluated in CHECKMATE-066, a randomized, double-blind, active-controlled trial in which 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=206) or dacarbazine 1000 mg/m^2 every 3 weeks (n=205) *[see Clinical Studies (14.1)]*. The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. In this trial, 47% of patients received OPDIVO for greater than 6 months and 12% of patients received OPDIVO for greater than 1 year.

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

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

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

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

Table 4: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (CHECKMATE-066)

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

Toxicity was graded per NCI CTCAE v4.

[a] Includes periorbital edema, face edema, generalized edema, gravitational edema, localized edema, peripheral edema, pulmonary edema, and lymphedema.

[b] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, pain in jaw, and spinal pain.

[c] Includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, dermatitis, allergic dermatitis, exfoliative dermatitis, acneiform dermatitis, drug eruption, and skin reaction.

[d] Includes rhinitis, viral rhinitis, pharyngitis, and nasopharyngitis.

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in CHECKMATE-066 were:

Nervous System Disorders: peripheral neuropathy

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Table 5: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (CHECKMATE-066)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO		Dacarbazine	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Increased ALT	25	3.0	19	0.5
Increased AST	24	3.6	19	0.5
Increased alkaline phosphatase	21	2.6	14	1.6
Increased bilirubin	13	3.1	6	0

[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: 194 to 197 patients) and dacarbazine group (range: 186 to 193 patients).

CHECKMATE-067

The safety of OPDIVO, administered with ipilimumab or as a single agent, was evaluated in CHECKMATE-067 *[see Clinical Studies (14.1)]*, a randomized (1:1:1), a double-blind trial in which 937 patients with previously untreated, unresectable or metastatic melanoma received:

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

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

CHECKMATE-067 excluded patients with autoimmune disease, a medical condition requiring systemic treatment with corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive medication within 14 days of the start of study therapy, a positive test result for hepatitis B or C, or a history of HIV.

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

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In CHECKMATE-067, serious adverse reactions (73% and 37%), adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and Grade 3 or 4 adverse reactions (72% and 44%) all occurred more frequently in the OPDIVO plus ipilimumab arm relative to the OPDIVO arm.

The most frequent (≥10%) serious adverse reactions in the OPDIVO plus ipilimumab arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). The most frequent adverse reactions leading to discontinuation of both drugs in the OPDIVO plus ipilimumab arm and of OPDIVO in the OPDIVO arm, respectively, were diarrhea (8% and 1.9%), colitis (8% and 0.6%), increased ALT (4.8% and 1.3%), increased AST (4.5% and 0.6%), and pneumonitis (1.9% and 0.3%). The most common (≥20%) adverse reactions in the OPDIVO plus ipilimumab arm were fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea. The most common (≥20%) adverse reactions in the OPDIVO arm were fatigue, rash, diarrhea, and nausea. Table 6 summarizes the incidence of adverse reactions occurring in at least 10% of patients in either OPDIVO-containing arm in CHECKMATE-067.

Table 6: Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO plus Ipilimumab Arm or the OPDIVO Arm and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (CHECKMATE-067)

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

Toxicity was graded per NCI CTCAE v4.

[a] Fatigue is a composite term which includes asthenia and fatigue.

[b] Rash is a composite term which includes pustular rash, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, exfoliative dermatitis, psoriasiform dermatitis, drug eruption, erythema, exfoliative

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rash, erythematous rash, generalized rash, macular rash, maculopapular rash, morbilliform rash, papular rash, papulosquamous rash, pruritic rash, and seborrheic dermatitis.

Other clinically important adverse reactions in less than 10% of patients treated with either OPDIVO with ipilimumab or single-agent OPDIVO in CHECKMATE-067 were:

Gastrointestinal Disorders: stomatitis, intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

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

Nervous System Disorders: neuritis, peroneal nerve palsy

Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Treated with OPDIVO with Ipilimumab or Single-Agent OPDIVO and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (CHECKMATE-067)

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

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

Reference ID: 4149162

Metastatic Non-Small Cell Lung Cancer

The safety of OPDIVO in metastatic NSCLC was evaluated in CHECKMATE-017, a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.2)]*. Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks or docetaxel administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy in OPDIVO-treated patients in CHECKMATE-017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1 year and in CHECKMATE-057, 30% of patients received OPDIVO for greater than 6 months and 20% of patients received OPDIVO for greater than 1 year.

CHECKMATE-017 and CHECKMATE-057 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease.

Across both trials, the median age of OPDIVO-treated patients was 61 years (range: 37 to 85); 38% were ≥65 years of age, 61% were male, and 91% were white. Ten percent of patients had brain metastases and ECOG performance status was 0 (26%) or 1 (74%).

OPDIVO was discontinued in 11% of patients, and was delayed in 28% of patients for an adverse reaction. Serious adverse reactions occurred in 46% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In CHECKMATE-057, in the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. Across both trials, the most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

Table 8 summarizes selected adverse reactions occurring more frequently in at least 10% of OPDIVO-treated patients.

Reference ID: 4149162

Table 8: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (CHECKMATE-017 and CHECKMATE-057)

Adverse Reaction	OPDIVO (n=418)		Docetaxel (n=397)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	31	0.7	24	0
Metabolism and Nutrition Disorders				
Decreased appetite	28	1.4	23	1.5
Skin and Subcutaneous Tissue Disorders				
Pruritus	10	0.2	2.0	0

Toxicity was graded per NCI CTCAE v4.

Other clinically important adverse reactions observed in patients treated with OPDIVO and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (48% Grade 1-4, 5% Grade 3-4), musculoskeletal pain (33%), pleural effusion (4.5%), pulmonary embolism (3.3%).

Table 9: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (CHECKMATE-017 and CHECKMATE-057)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO		Docetaxel	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Chemistry				
Hyponatremia	35	7	34	4.9
Increased AST	27	1.9	13	0.8
Increased alkaline phosphatase	26	0.7	18	0.8
Increased ALT	22	1.7	17	0.5
Increased creatinine	18	0	12	0.5
Increased TSH[b]	14	N/A	6	N/A

[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: 405 to 417 patients) and docetaxel group (range: 372 to 390 patients); TSH: OPDIVO group n=314 and docetaxel group n=297.

[b] Not graded per NCI CTCAE v4.

Reference ID: 4149162

Renal Cell Carcinoma

The safety of OPDIVO was evaluated in CHECKMATE-025, a randomized open-label trial in which 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimens received OPDIVO 3 mg/kg every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.3)]*. The median duration of treatment was 5.5 months (range: 1 day to 29.6+ months) in OPDIVO-treated patients and 3.7 months (range: 6 days to 25.7+ months) in everolimus-treated patients.

Study therapy was discontinued for adverse reactions in 16% of OPDIVO patients and 19% of everolimus patients. Forty-four percent (44%) of patients receiving OPDIVO had a drug delay for an adverse reaction. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia.

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

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

Table 10: Grade 1-4 Adverse Reactions in >15% of Patients Receiving OPDIVO (CHECKMATE-025)

	OPDIVO (n=406)		**Everolimus (n=397)**	
	Percentage (%) of Patients			
	Grades 1-4	**Grades 3-4**	**Grades 1-4**	**Grades 3-4**
Adverse Reaction	98	56	96	62
General Disorders and Administration Site Conditions				
Asthenic conditions[a]	56	6	57	7
Pyrexia	17	0.7	20	0.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough/productive cough	34	0	38	0.5
Dyspnea/exertional dyspnea	27	3.0	31	2.0
Upper respiratory infection[b]	18	0	11	0
Gastrointestinal Disorders				
Nausea	28	0.5	29	1
Diarrhea[c]	25	2.2	32	1.8
Constipation	23	0.5	18	0.5
Vomiting	16	0.5	16	0.5

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	OPDIVO (n=406)		Everolimus (n=397)	
	Percentage (%) of Patients			
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Skin and Subcutaneous Tissue Disorders				
Rash[d]	28	1.5	36	1.0
Pruritus/generalized pruritus	19	0	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	23	1.2	30	1.5
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	20	1.0	14	0.5
Back pain	21	3.4	16	2.8

Toxicity was graded per NCI CTCAE v4.

[a] Asthenic conditions covering PTs asthenia, decreased activity, fatigue, and malaise.

[b] Includes nasopharyngitis, pharyngitis, rhinitis, and viral URI.

[c] Includes colitis, enterocolitis, and gastroenteritis.

[d] Includes dermatitis, acneiform dermatitis, erythematous rash, generalized rash, macular rash, maculopapular rash, papular rash, pruritic rash, erythema multiforme, and erythema.

Other clinically important adverse reactions in CHECKMATE-025 were:

General Disorders and Administration Site Conditions: peripheral edema/edema

Gastrointestinal Disorders: abdominal pain/discomfort

Musculoskeletal and Connective Tissue Disorders: extremity pain, musculoskeletal pain

Nervous System Disorders: headache/migraine, peripheral neuropathy

Investigations: weight decreased

Skin Disorders: Palmar-plantar erythrodysesthesia

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

Reference ID: 4149162

Table 11: Grade 1-4 Laboratory Values Worsening from Baseline Occurring in >15% of Patients on OPDIVO (CHECKMATE-025)

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

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

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

Classical Hodgkin Lymphoma

The safety of OPDIVO 3 mg/kg every 2 weeks was evaluated in 266 adult patients with cHL (243 patients in the CHECKMATE-205 and 23 patients in the CHECKMATE-039 trials). Treatment could continue until disease progression, maximal clinical benefit, or unacceptable toxicity.

The median age was 34 years (range: 18 to 72), 98% of patients had received autologous HSCT, none had received allogeneic HSCT, and 74% had received brentuximab vedotin. The median number of prior systemic regimens was 4 (range: 2 to 15). Patients received a median of 23 doses (cycles) of OPDIVO (range: 1 to 48), with a median duration of therapy of 11 months (range: 0 to 23 months).

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OPDIVO was discontinued due to adverse reactions in 7% of patients. Dose delay for an adverse reaction occurred in 34% of patients. Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in at least 1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last nivolumab dose, 2 from infection 8 to 9 months after completing nivolumab, and 6 from complications of allogeneic HSCT.

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

Table 12 summarizes the adverse reactions, excluding laboratory terms that occurred in at least 10% of patients in the safety population.

Table 12: Non-Laboratory Adverse Reactions Occurring in ≥10% of Patients with cHL (CHECKMATE-205 and CHECKMATE-039)

	OPDIVO cHL Safety Population (n=266)	
	Percentage (%)	
Adverse Reaction[a]	**All Grades**	**Grades 3-4**
General Disorders and Administration Site Conditions		
Fatigue[b]	39	1.9
Pyrexia	29	<1
Gastrointestinal Disorders		
Diarrhea[c]	33	1.5
Nausea	20	0
Vomiting	19	<1
Abdominal pain[d]	16	<1
Constipation	14	0.4
Infections		
Upper respiratory tract infection[e]	44	0.8
Pneumonia/bronchopneumonia[f]	13	3.8
Nasal congestion	11	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough/productive cough	36	0
Dyspnea/exertional dyspnea	15	1.5
Skin and Subcutaneous Tissue Disorders		
Rash[g]	24	1.5
Pruritus	20	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[h]	26	1.1
Arthralgia	16	<1

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	OPDIVO cHL Safety Population (n=266)	
	Percentage (%)	
Adverse Reaction[a]	**All Grades**	**Grades 3-4**
Endocrine Disorders		
Hypothyroidism/thyroiditis	12	0
Nervous System Disorders		
Headache	17	<1
Neuropathy peripheral[i]	12	<1
Injury, Poisoning and Procedural Complications		
Infusion-related reaction	14	<1

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes asthenia.

[c] Includes colitis.

[d] Includes abdominal discomfort and upper abdominal pain.

[e] Includes nasopharyngitis, pharyngitis, rhinitis, and sinusitis.

[f] Includes pneumonia bacterial, pneumonia mycoplasmal, pneumocystis jirovecii pneumonia.

[g] Includes dermatitis, dermatitis acneiform, dermatitis exfoliative, and rash described as macular, papular, maculopapular, pruritic, exfoliative, or acneiform.

[h] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, and pain in extremity.

[i] Includes hyperesthesia, hypoesthesia, paresthesia, dysesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy. These numbers are specific to treatment-emergent events.

Additional information regarding clinically important adverse reactions:

Immune-mediated pneumonitis: In CHECKMATE-205 and CHECKMATE-039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO (one Grade 3 and 12 Grade 2). The median time to onset was 4.5 months (range: 5 days to 12 months). All 13 patients received systemic corticosteroids, with resolution in 12. Four patients permanently discontinued OPDIVO due to pneumonitis. Eight patients continued OPDIVO (three after dose delay), of whom two had recurrence of pneumonitis.

Peripheral neuropathy: In CHECKMATE-205 and CHECKMATE-039, treatment-emergent peripheral neuropathy was reported in 14% (31/266) of all patients receiving OPDIVO. Twenty-eight patients (11%) had new-onset peripheral neuropathy, and 3 of 40 patients had worsening of neuropathy from baseline. These adverse reactions were Grade 1 or 2, except for 1 Grade 3 event (<1%). The median time to onset was 50 (range: 1 to 309) days.

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

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Table 13 summarizes laboratory abnormalities that developed or worsened in at least 10% of patients with cHL. The most common (reported in at least 20%) treatment-emergent laboratory events included cytopenias, liver function abnormalities, and elevated lipase. Other common findings (reported in at least 10%) included elevated creatinine, electrolyte abnormalities, and elevated amylase.

Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients with cHL (CHECKMATE-205 and CHECKMATE-039)

	OPDIVO cHL Safety Population[a] (n=266)	
	Percentage (%)[b]	
Laboratory Abnormality	**All Grades**	**Grades 3-4**
Hematology		
Leukopenia	38	4.5
Neutropenia	37	5
Thrombocytopenia	37	3.0
Lymphopenia	32	11
Anemia	26	2.6
Chemistry[c]		
Increased AST	33	2.6
Increased ALT	31	3.4
Increased lipase	22	9
Increased alkaline phosphatase	20	1.5
Hyponatremia	20	1.1
Hypokalemia	16	1.9
Increased creatinine	16	<1
Hypocalcemia	15	<1
Hypomagnesemia	14	<1
Hyperkalemia	15	1.5
Increased amylase	13	1.5
Increased bilirubin	11	1.5

[a] Number of evaluable patients for the safety population ranges from 203 to 266.

[b] Includes events occurring up to 30 days after last nivolumab dose. After an immune-mediated adverse reaction, reactions following nivolumab rechallenge were included if they occurred within 30 days of completing the initial nivolumab course.

[c] In addition, in the safety population, fasting hyperglycemia (all grade 1-2) was reported in 27 of 69 (39%) evaluable patients and fasting hypoglycemia (all grade 1-2) in 11 of 69 (16%).

Reference ID: 4149162

Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

The safety of OPDIVO was evaluated in CHECKMATE-141, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCHN with progression during or within 6 months of receiving prior platinum-based therapy *[see Clinical Studies (14.5)]*. Patients received 3 mg/kg of OPDIVO (n=236) administered intravenously (IV) over 60 minutes every 2 weeks or investigator's choice of either:

- cetuximab (n=13), 400 mg/m^2 loading dose IV followed by 250 mg/m^2 weekly
- or methotrexate (n=46) 40 to 60 mg/m^2 IV weekly, or
- docetaxel (n=52) 30 to 40 mg/m^2 IV weekly.

The median duration of exposure to nivolumab was 1.9 months (range: 1 day to 16.1+ months) in OPDIVO-treated patients. In this trial, 18% of patients received OPDIVO for greater than 6 months and 2.5% of patients received OPDIVO for greater than 1 year.

CHECKMATE-141 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma).

The median age of all randomized patients was 60 years (range: 28 to 83); 28% of patients in the OPDIVO group were ≥65 years of age and 37% in the comparator group were ≥65 years of age, 83% were male and 83% were White, 12% were Asian, and 4% were Black. Baseline ECOG performance status was 0 (20%) or 1 (78%), 45% of patients received only one prior line of systemic therapy, the remaining 55% of patients had two or more prior lines of therapy, and 90% had prior radiation therapy.

OPDIVO was discontinued in 14% of patients and was delayed in 24% of patients for an adverse reaction. Serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. Adverse reactions and laboratory abnormalities occurring in patients with SCCHN were generally similar to those occurring in patients with melanoma and NSCLC. The most common adverse reactions occurring in ≥10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were cough and dyspnea.

The most common laboratory abnormalities occurring in ≥10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were increased alkaline phosphatase, increased amylase, hypercalcemia, hyperkalemia, and increased TSH.

Reference ID: 4149162

Urothelial Carcinoma

The safety of OPDIVO was evaluated in CHECKMATE-275, a single arm study in which 270 patients with locally advanced or metastatic urothelial carcinoma had disease progression during or following platinum-containing chemotherapy or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy received OPDIVO 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 3.3 months (range: 0 to 13.4+). Forty-six percent (46%) of patients had a drug delay for an adverse reaction.

Fourteen patients (5.2%) died from causes other than disease progression. This includes 4 patients (1.5%) who died from pneumonitis or cardiovascular failure which was attributed to treatment with OPDIVO. OPDIVO was discontinued for adverse reactions in 17% of patients. Serious adverse reactions occurred in 54% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration.

Twenty-five (9%) patients received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5)]*.

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, nausea, and decreased appetite.

Table 14 summarizes adverse reactions that occurred in greater than 10% of patients.

Table 14: Adverse Reactions Occurring in ≥10% of Patients (CHECKMATE-275)

	OPDIVO Urothelial Carcinoma	
	Percentage (%) of Patients	
	All Grades	**Grades 3-4**
Adverse Reaction	99	51
General Disorders and Administration Site Conditions		
Asthenia/fatigue/malaise	46	7
Pyrexia/tumor associated fever	17	0.4
Edema/peripheral edema/peripheral swelling	13	0.4
Infections and Infestations		
Urinary Tract Infection/escherichia/fungal urinary tract infection	17	7
Respiratory, Thoracic, and Mediastinal Disorders		
Cough/productive cough	18	0
Dyspnea/exertional dyspnea	14	3.3
Gastrointestinal Disorders		
Nausea	22	0.7
Diarrhea	17	2.6
Constipation	16	0.4
Abdominal pain[a]	13	1.5

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	OPDIVO Urothelial Carcinoma	
	Percentage (%) of Patients	
	All Grades	Grades 3-4
Vomiting	12	1.9
Skin and Subcutaneous Tissue Disorders		
Rash[b]	16	1.5
Pruritus	12	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[c]	30	2.6
Arthralgia	10	0.7
Metabolism and Nutrition Disorders		
Decreased appetite	22	2.2
Endocrine Disorders		
Thyroid disorders[d]	15	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes abdominal discomfort, lower and upper abdominal pain.

[b] Includes dermatitis, dermatitis acneiform, dermatitis bullous, and rash described as generalized, macular, maculopapular, or pruritic.

[c] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity and spinal pain.

[d] Includes autoimmune thyroiditis, blood TSH decrease, blood TSH increase, hyperthyroidism, hypothyroidism, thyroiditis, thyroxine decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine free increased, tri-iodothyronine increased.

Reference ID: 4149162

Table 15: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients (CHECKMATE-275)

Test	OPDIVO Urothelial Carcinoma[a]	
	Percentage (%) of Patients	
	All Grades	Grades 3-4
Hematology		
Lymphopenia	42	9
Anemia	40	7
Thrombocytopenia	15	2.4
Leucopenia	11	0
Chemistry		
Hyperglycemia	42	2.4
Hyponatremia	41	11
Increased creatinine	39	2.0
Increased alkaline phosphatase	33	5.5
Hypocalcemia	26	0.8
Increased AST	24	3.5
Hyperkalemia	19	1.2
Increased ALT	18	1.2
Hypomagnesemia	16	0
Increased lipase	20	7
Increased amylase	18	4.4

[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: 84 to 256 patients.

6.2 Immunogenicity

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

Of 2085 patients who were treated with OPDIVO as a single agent 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 233 patients (11.2%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 15 patients (0.7%) had neutralizing antibodies against nivolumab. There was no evidence of altered pharmacokinetic profile or increased incidence of infusion reactions with anti-nivolumab antibody development.

Of 394 patients who were treated with OPDIVO with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, 149 patients (37.8%) tested positive for treatment-emergent anti-nivolumab antibodies by an ECL assay and 18 patients (4.6%) had neutralizing antibodies against nivolumab. Of the 391 patients evaluable for the presence of anti-ipilimumab antibodies, 33 patients (8.4%) tested positive for treatment-emergent anti-ipilimumab antibodies by an ECL assay and one patient (0.3%) had neutralizing antibodies against ipilimumab. There was no evidence of increased incidence of infusion reactions with anti-nivolumab antibody development.

Reference ID: 4149162

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 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.

Reference ID: 4149162

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 been established in pediatric patients age 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for this indication is supported by evidence from adequate and well-controlled studies of OPDIVO in adults with MSI-H or dMMR mCRC with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of nivolumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MSI-H or dMMR mCRC is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater for this indication is the same as that in adults *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3), and Clinical Studies (14)]*. The safety and effectiveness of OPDIVO have not been established (1) in pediatric patients less than 12 years old with MSI-H or dMMR mCRC or (2) in pediatric patients for the other approved indications.

8.5 Geriatric Use

Of the 1359 patients randomized to single-agent OPDIVO in CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, and CHECKMATE-067, 39% were 65 years or older and 9% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

In CHECKMATE-275 (Urothelial Cancer), 55% of patients were 65 years or older and 14% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

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CHECKMATE-037, CHECKMATE-205, CHECKMATE-039, CHECKMATE-141, and CHECKMATE-142 did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

Of the 314 patients randomized to OPDIVO administered with ipilimumab in CHECKMATE-067, 41% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

There is no information on overdosage with OPDIVO.

11 DESCRIPTION

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

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous infusion is supplied in single-dose vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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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.

12.2 Pharmacodynamics

Based on dose/exposure efficacy and safety relationships, there are no clinically significant differences in safety and efficacy between a nivolumab dose of 240 mg or 3 mg/kg every 2 weeks in patients with melanoma, NSCLC, RCC, urothelial carcinoma, and MSI-H CRC.

12.3 Pharmacokinetics

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

OPDIVO as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life ($t_{1/2}$) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

OPDIVO with ipilimumab: The geometric mean (CV%) CL, Vss, 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: The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m^2; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m^2; 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)]*.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

CHECKMATE-037 (NCT01721746) was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either OPDIVO administered intravenously at 3 mg/kg every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m^2 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.

Reference ID: 4149162

Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in CHECKMATE-037 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed objective response rate (ORR) as measured by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response.

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

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

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

Previously Untreated Metastatic Melanoma

CHECKMATE-066

CHECKMATE-066 (NCT01721772) was a multicenter, double-blind, randomized (1:1) trial conducted in patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m^2 by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (greater than or equal to 5% of tumor cell membrane staining by immunohistochemistry vs. less than 5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). Key eligibility criteria included histologically confirmed, unresectable or metastatic, cutaneous, mucosal, or acral melanoma; no prior therapy for metastatic disease; completion of prior adjuvant or neoadjuvant therapy at least 6 weeks prior to randomization; ECOG performance status 0 or 1; absence of autoimmune disease; and absence of active brain or leptomeningeal metastases. The trial excluded patients with ocular melanoma. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year and then every 12 weeks thereafter.

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

Reference ID: 4149162

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

CHECKMATE-066 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. Table 16 and Figure 1 summarize the efficacy results.

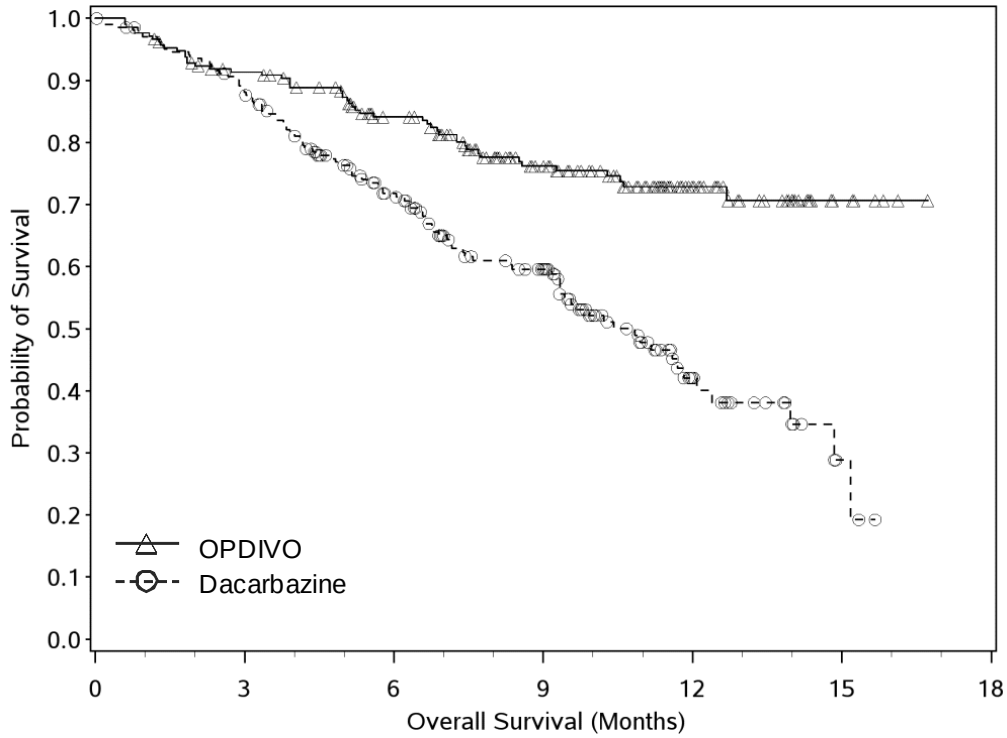
Table 16: Efficacy Results - CHECKMATE-066

	OPDIVO (n=210)	**Dacarbazine (n=208)**
Overall Survival		
Deaths (%)	50 (24)	96 (46)
Median, months (95% CI)	Not Reached	10.8 (9.3, 12.1)
Hazard ratio (95% CI)[a]	0.42 (0.30, 0.60)	
p-value[b,c]	<0.0001	
Progression-Free Survival		
Disease progression or death (%)	108 (51)	163 (78)
Median, months (95% CI)	5.1 (3.5, 10.8)	2.2 (2.1, 2.4)
Hazard ratio (95% CI)[a]	0.43 (0.34, 0.56)	
p-value[b,c]	<0.0001	
Objective Response Rate	34%	9%
(95% CI)	(28, 41)	(5, 13)
Complete response rate	4%	1%
Partial response rate	30%	8%

[a] Based on a stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with the allocated alpha of 0.0021 for this interim analysis.

Reference ID: 4149162

Figure 1: Kaplan-Meier Curves of Overall Survival - CHECKMATE-066



Number at Risk

OPDIVO	210	185	150	105	45	8	0
Dacarbazine	208	177	123	82	22	3	0

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

CHECKMATE-067

CHECKMATE-067 (NCT01844505) was a multicenter, double-blind trial that randomized (1:1:1) patients with previously untreated, unresectable or metastatic melanoma to one of the following arms: OPDIVO plus ipilimumab, OPDIVO, or ipilimumab. Patients were required to have completed adjuvant or neoadjuvant treatment at least 6 weeks prior to randomization and have no prior treatment with anti-CTLA-4 antibody and no evidence of active brain metastasis, ocular melanoma, autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients were randomized to receive:

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

Reference ID: 4149162

Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the American Joint Committee on Cancer (AJCC) staging system (M0, M1a, M1b vs. M1c). Tumor assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

The major efficacy outcome measures were investigator-assessed PFS per RECIST v1.1 and OS. Additional efficacy outcome measures were confirmed ORR and duration of response.

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

CHECKMATE-067 demonstrated statistically significant improvements in PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. Efficacy results are presented in Table 17 and Figure 2.

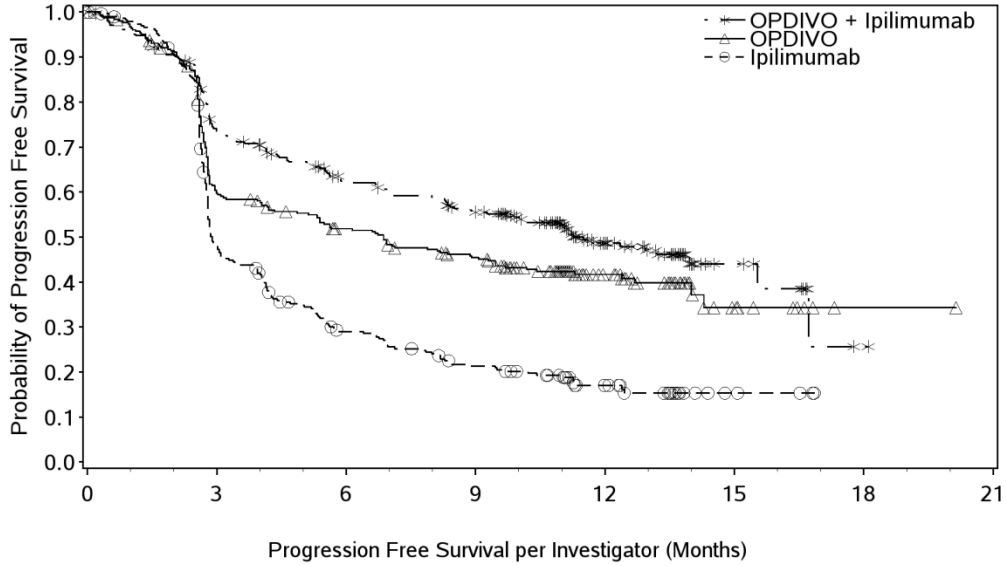
Table 17: Efficacy Results in CHECKMATE-067

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

[a] Based on a stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with .005 of the allocated alpha for final PFS treatment comparisons.
[d] Based on the stratified Cochran-Mantel-Haenszel test.

Reference ID: 4149162

Figure 2: Progression-free Survival: Unresectable or Metastatic Melanoma - CHECKMATE-067



Number of Subjects at Risk

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

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

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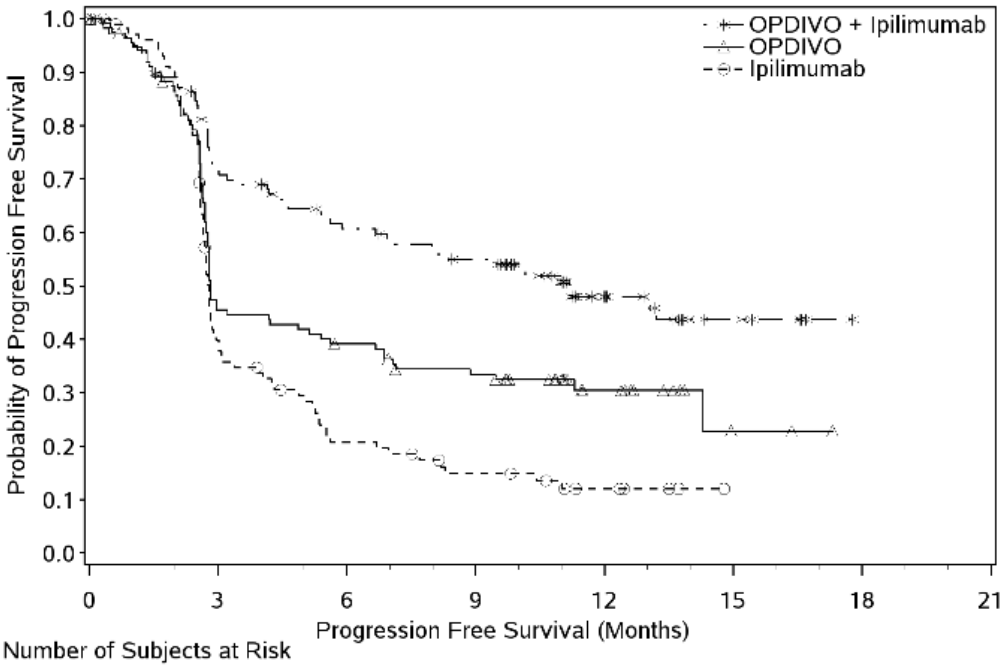
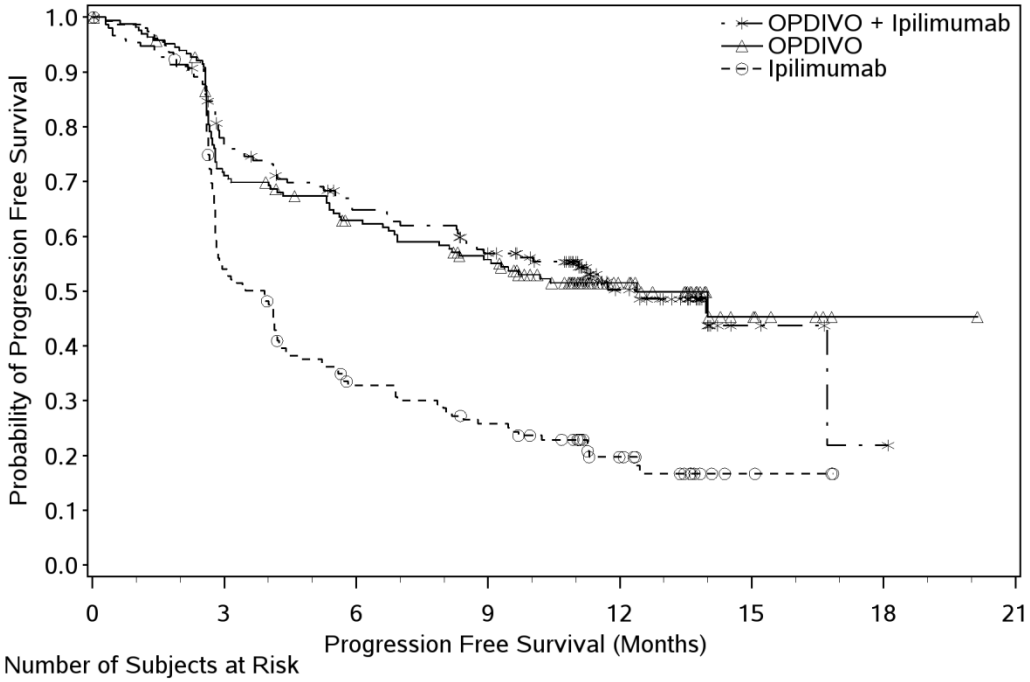
Figure 3: Progression-free Survival by PD-L1 Expression (<1%) - CHECKMATE-067



Number of Subjects at Risk

OPDIVO + Ipilimumab	123	82	65	57	26	6	0	0
OPDIVO	117	50	42	34	13	2	0	0
Ipilimumab	113	39	19	12	5	0	0	0

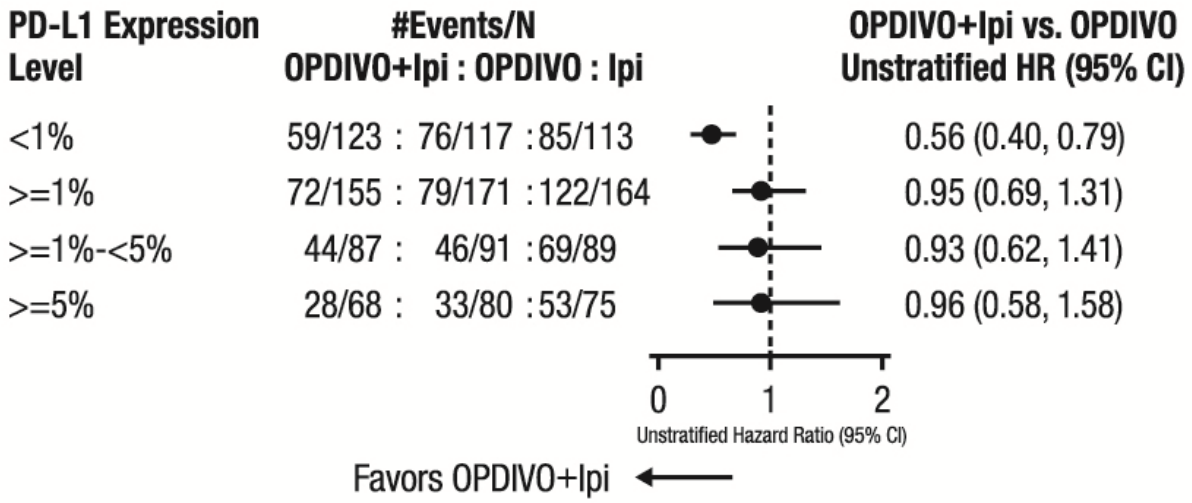
Figure 4: **Progression-free Survival by PD-L1 Expression (≥1%) - CHECKMATE-067**



Number of Subjects at Risk							
OPDIVO + Ipilimumab	155	113	91	78	32	4	1	0
OPDIVO	171	115	97	83	34	7	1	0
Ipilimumab	164	83	47	36	16	3	0	0

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

Figure 5: **Forest Plot: PFS Based on PD-L1 Expression Comparing OPDIVO-Containing Arms - CHECKMATE-067**



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14.2 Metastatic Non-Small Cell Lung Cancer (NSCLC)

Second-line Treatment of Metastatic Squamous NSCLC

CHECKMATE-017 (NCT01642004) was a randomized (1:1), open-label study enrolling 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received OPDIVO (n=135) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=137) administered intravenously at 75 mg/m^2 every 3 weeks. Randomization was stratified by prior paclitaxel vs. other prior treatment and region (US/Canada vs. Europe vs. Rest of World). This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS.

In CHECKMATE-017, 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%); the majority of patients were enrolled in Europe (57%) with the remainder in US/Canada (32%) and the rest of the world (11%). Baseline ECOG performance status was 0 (24%) or 1 (76%) and 92% were former/current smokers. Baseline disease characteristics of the population as reported by investigators were Stage IIIb (19%), Stage IV (80%), and brain metastases (6%). All patients received prior therapy with a platinum-doublet regimen and 99% of patients had tumors of squamous-cell histology.

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 18 and Figure 6).

Reference ID: 4149162

Table 18: Efficacy Results in CHECKMATE-017

	OPDIVO (n=135)	Docetaxel (n=137)
Overall Survival		
Deaths (%)	86 (64%)	113 (82%)
Median (months) (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
Hazard ratio (95% CI)[a]	0.59 (0.44, 0.79)	
p-value[b,c]	0.0002	
Objective Response Rate	27 (20%)	12 (9%)
(95% CI)	(14 , 28)	(5, 15)
p-value[d]	0.0083	
Complete response	1 (0.7%)	0
Median duration of response, months (95% CI)	NR (9.8, NR)	8.4 (3.6, 10.8)
Progression-free Survival		
Disease progression or death (%)	105 (78%)	122 (89%)
Median (months)	3.5	2.8
Hazard ratio (95% CI)[a]	0.62 (0.47, 0.81)	
p-value[b]	0.0004	

[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

[c] p-value is compared with .0315 of the allocated alpha for this interim analysis.

[d] Based on the stratified Cochran-Mantel-Haenszel test.

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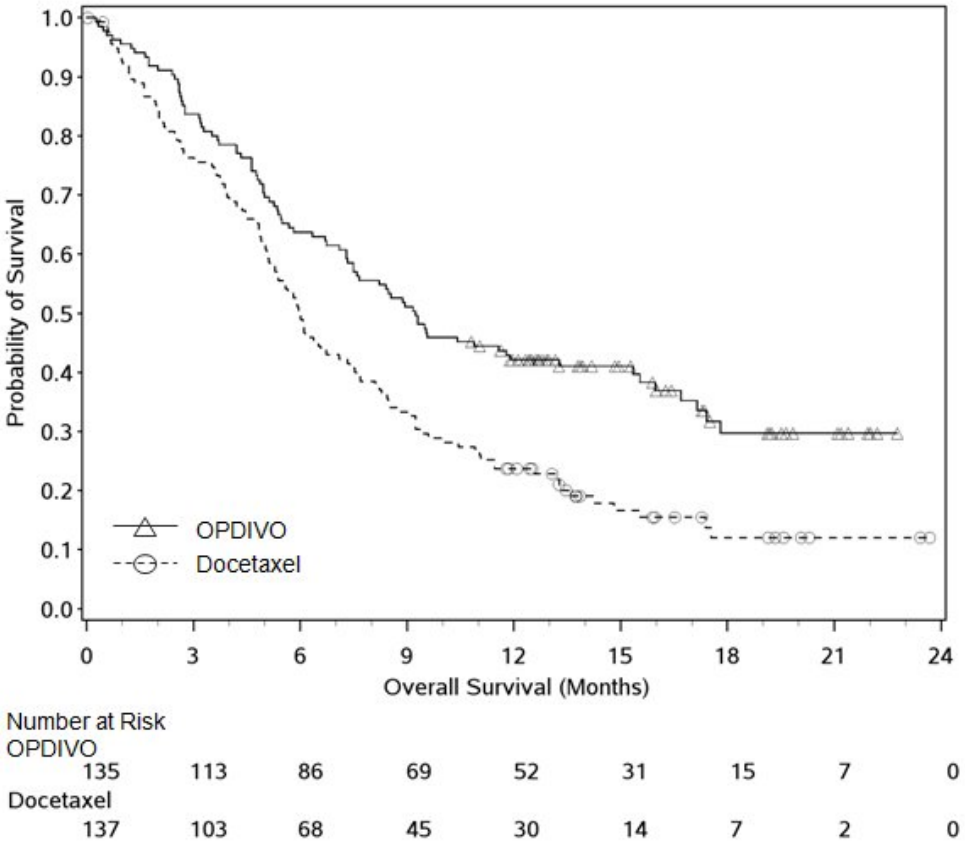
Figure 6: Overall Survival - CHECKMATE-017



Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the study population, 17% (47/272) of patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% (106/225) had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1, and 53% (119/225) had PD-L1 positive squamous NSCLC, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.58 (95% CI: 0.37, 0.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.45, 1.05) in the PD-L1 positive NSCLC subgroup.

Second-line Treatment of Metastatic Non-Squamous NSCLC

CHECKMATE-057 (NCT01673867) was a randomized (1:1), open-label study of 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. Patients received OPDIVO (n=292) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=290) administered intravenously at 75 mg/m^2 every 3 weeks. Randomization was stratified by prior maintenance therapy (yes vs. no) and number of prior therapies (1 vs. 2). The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. The first tumor assessments were conducted

Reference ID: 4149162

9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression.

In CHECKMATE-057, the median age was 62 years (range: 21 to 85) with 42% of patients ≥65 years and 7% of patients ≥75 years. The majority of patients were white (92%) and male (55%); the majority of patients were enrolled in Europe (46%) followed by the US/Canada (37%) and the rest of the world (17%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. Prior therapy included platinum-doublet regimen (100%) and 40% received maintenance therapy as part of the first-line regimen. Histologic subtypes included adenocarcinoma (93%), large cell (2.4%), and bronchoalveolar (0.9%).

CHECKMATE-057 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis) (Table 19 and Figure 7).

Table 19: Efficacy Results in CHECKMATE-057

	OPDIVO (n=292)	**Docetaxel (n=290)**
Overall Survival		
Deaths (%)	190 (65%)	223 (77%)
Median (months) (95% CI)	12.2 (9.7, 15.0)	9.4 (8.0, 10.7)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0015	
Objective Response Rate	56 (19%)	36 (12%)
(95% CI)	(15, 24)	(9, 17)
p-value[d]	0.02	
Complete response	4 (1.4%)	1 (0.3%)
Median duration of response (months) (95% CI)	17 (8.4, NR)	6 (4.4, 7.0)
Progression-free Survival		
Disease progression or death (%)	234 (80%)	245 (84%)
Median (months)	2.3	4.2
Hazard ratio (95% CI)[a]	0.92 (0.77, 1.11)	
p-value[b]	0.39	

[a] Based on a stratified proportional hazards model.

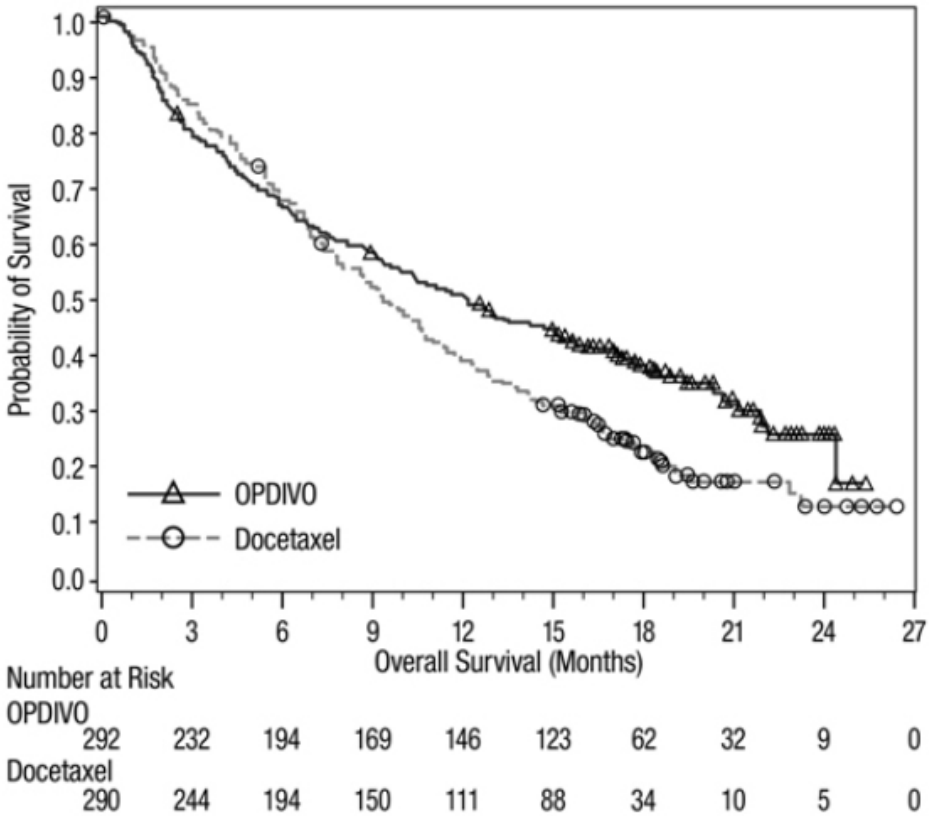
[b] Based on stratified log-rank test.

[c] p-value is compared with .0408 of the allocated alpha for this interim analysis.

[d] Based on the stratified Cochran-Mantel-Haenszel test.

Reference ID: 4149162

Figure 7: Overall Survival - CHECKMATE-057



Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% (209/455) PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% (246/455) had PD-L1 expression, defined as ≥1% of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% (65/246) had ≥1%, but <5% tumor cells with positive staining, 7% (16/246) had ≥5% but <10% tumor cells with positive staining, and 67% (165/246) had greater than or equal to 10% tumor cells with positive staining. Figure 8 summarizes the results of prespecified analyses of survival in subgroups determined by percentage of tumor cells expressing PD-L1. Figure 9 summarizes the results of prespecified analyses of progression-free survival in subgroups determined by percentage of tumor cells expressing PD-L1.

Reference ID: 4149162

Figure 8: Forest Plot: OS Based on PD-L1 Expression - CHECKMATE-057

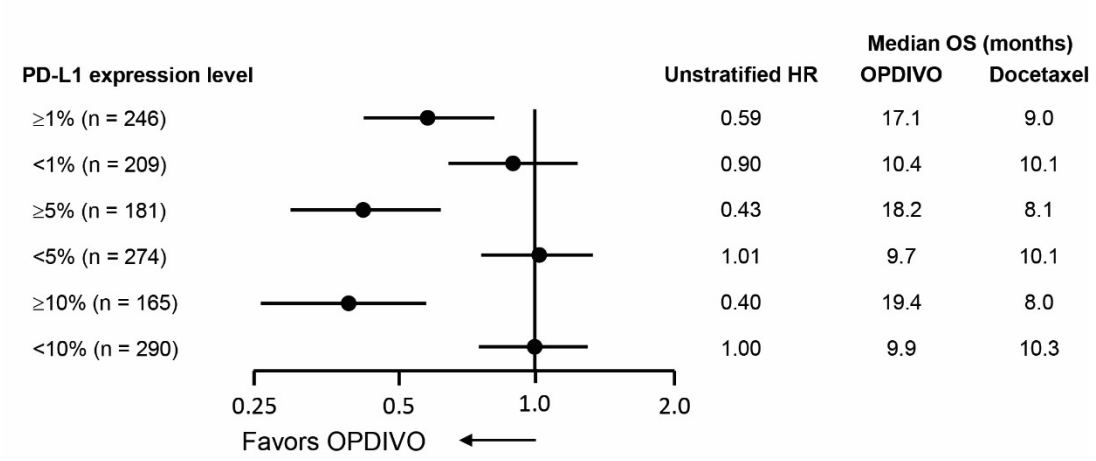
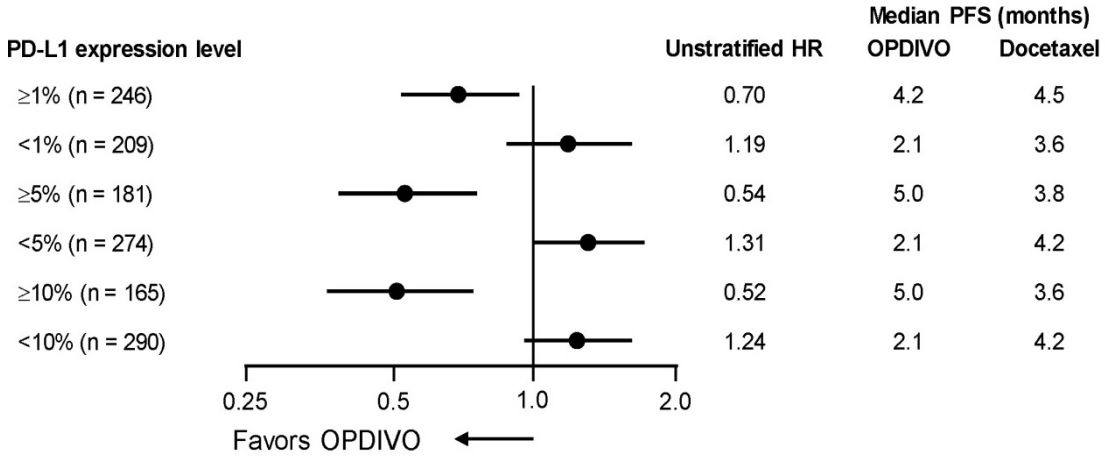


Figure 9: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



14.3 Renal Cell Carcinoma

CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label study in patients with advanced RCC who had experienced disease progression during or after one or two prior anti-angiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. CHECKMATE-025 excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by region, Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group and the number of prior anti-angiogenic therapies.

Reference ID: 4149162

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

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

The major efficacy outcome measure was overall survival (OS). The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 20 and Figure 10). OS benefit was observed regardless of PD-L1 expression level.

Other endpoints include confirmed objective response rates, which are also presented in Table 20.

Table 20: Efficacy Results - CHECKMATE-025

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

[a] Based on a stratified proportional hazards model.

[b] Based on a stratified log-rank test.

[c] p-value is compared with .0148 of the allocated alpha for this interim analysis.

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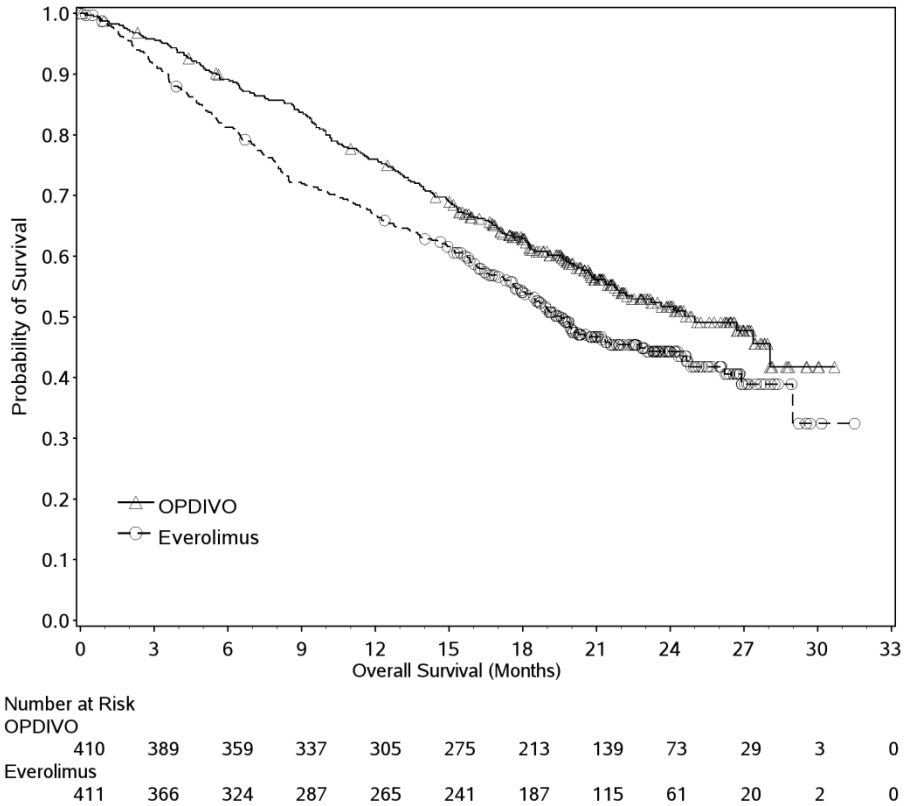
Figure 10: Overall Survival - CHECKMATE-025



14.4 Classical Hodgkin Lymphoma

Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with cHL after failure of autologous HSCT.

CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort study in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation study that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance less than 40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity.

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

Efficacy was evaluated by objective response rate (ORR) as determined by an independent radiographic review committee (IRRC). Additional outcome measures included duration of response (DOR).

Reference ID: 4149162

Efficacy was evaluated in 95 patients in CHECKMATE-205 and CHECKMATE-039 combined who had failure of autologous HSCT and post-transplantation brentuximab vedotin. The median age was 37 years (range: 18 to 72). The majority were male (64%) and white (87%). Patients had received a median of 5 prior systemic regimens (range: 2 to 15). They received a median of 27 doses of OPDIVO (range: 3 to 48), with a median duration of therapy of 14 months (range: 1 to 23 months). Results are shown in Table 21.

Table 21: Efficacy in cHL after Autologous HSCT and Post-transplantation Brentuximab Vedotin

	CHECKMATE-205 and CHECKMATE-039 (n=95)
Objective Response Rate, n (%)[a]	63 (66%)
(95% CI)	(56, 76)
Complete Remission Rate	6 (6%)
(95% CI)	(2, 13)
Partial Remission Rate	57 (60%)
(95% CI)	(49, 70)
Duration of Response (months)	
Median[b]	13.1
(95% CI)	(9.5, NE)
Range[c]	0+, 23.1+
Time to Response (months)	
Median	2.0
Range	0.7, 11.1

[a] Per 2007 revised International Working Group criteria.

[b] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 9.9 months.

[c] A + sign indicates a censored value.

Efficacy was also evaluated in 258 patients in CHECKMATE-205 and CHECKMATE-039 combined who had relapsed or progressive cHL after autologous HSCT. The analysis included the group described above. The median age was 34 years (range: 18 to 72). The majority were male (59%) and white (86%). Patients had a median of 4 prior systemic regimens (range: 2 to 15), with 85% having 3 or more prior systemic regimens and 76% having prior brentuximab vedotin. Of the 195 patients having prior brentuximab vedotin, 17% received it only before autologous HSCT, 78% received it only after HSCT, and 5% received it both before and after HSCT. Patients received a median of 21 doses of OPDIVO (range: 1 to 48), with a median duration of therapy of 10 months (range: 0 to 23 months). Results are shown in Table 22.

Reference ID: 4149162

Table 22: Efficacy in cHL after Autologous HSCT

	CHECKMATE-205 and CHECKMATE-039 (n=258)
Objective Response Rate, n (%) (95% CI)	179 (69%) (63, 75)
Complete Remission Rate (95% CI)	37 (14%) (10, 19)
Partial Remission Rate (95% CI)	142 (55%) (49, 61)
Duration of Response (months) Median[a,b] (95% CI) Range	 NE (12.0, NE) 0+, 23.1+
Time to Response (months) Median Range	 2.0 0.7, 11.1

[a] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 6.7 months.
[b] The estimated median duration of PR was 13.1 months (95% CI, 9.5, NE). The median duration of CR was not reached.

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

CHECKMATE-141 (NCT02105636) was a randomized (2:1), active-controlled, open-label study enrolling patients with metastatic or recurrent SCCHN who had experienced disease progression during or within 6 months of receiving platinum-based therapy administered in either the adjuvant, neo-adjuvant, primary (unresectable locally advanced) or metastatic setting. The trial excluded patients with autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. Patients were randomized to receive OPDIVO administered intravenously (IV) at 3 mg/kg every 2 weeks or investigator's choice of:

- cetuximab 400 mg/m^2 loading dose IV followed by 250 mg/m^2 weekly,
- methotrexate 40 to 60 mg/m^2 IV weekly, or
- docetaxel 30 to 40 mg/m^2 IV weekly.

Randomization was stratified by prior cetuximab treatment (yes/no). The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS and ORR.

Reference ID: 4149162

In CHECKMATE-141, total of 361 patients were randomized; 240 patients to OPDIVO and 121 patients to investigator's choice (45% received docetaxel, 43% received methotrexate, and 12% received cetuximab). The median age was 60 years (range: 28 to 83) with 31% ≥65 years of age, 83% were White, 12% Asian, and 4% were Black, and 83% male. Baseline ECOG performance status was 0 (20%) or 1 (78%), 76% were former/current smokers, 90% had Stage IV disease, 45% of patients received only one prior line of systemic therapy, the remaining 55% received two or more prior lines of systemic therapy, and 25% had HPVp16-positive tumors, 24% had HPV p16-negative tumors, and 51% had unknown status.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). The survival results are displayed in Table 23 and Figure 11. There were no statistically significant differences between the two arms for PFS (HR=0.89; 95% CI: 0.70, 1.13) or ORR (13.3% [95% CI: 9.3, 18.3] vs. 5.8% [95% CI: 2.4, 11.6] for nivolumab and investigator's choice, respectively).

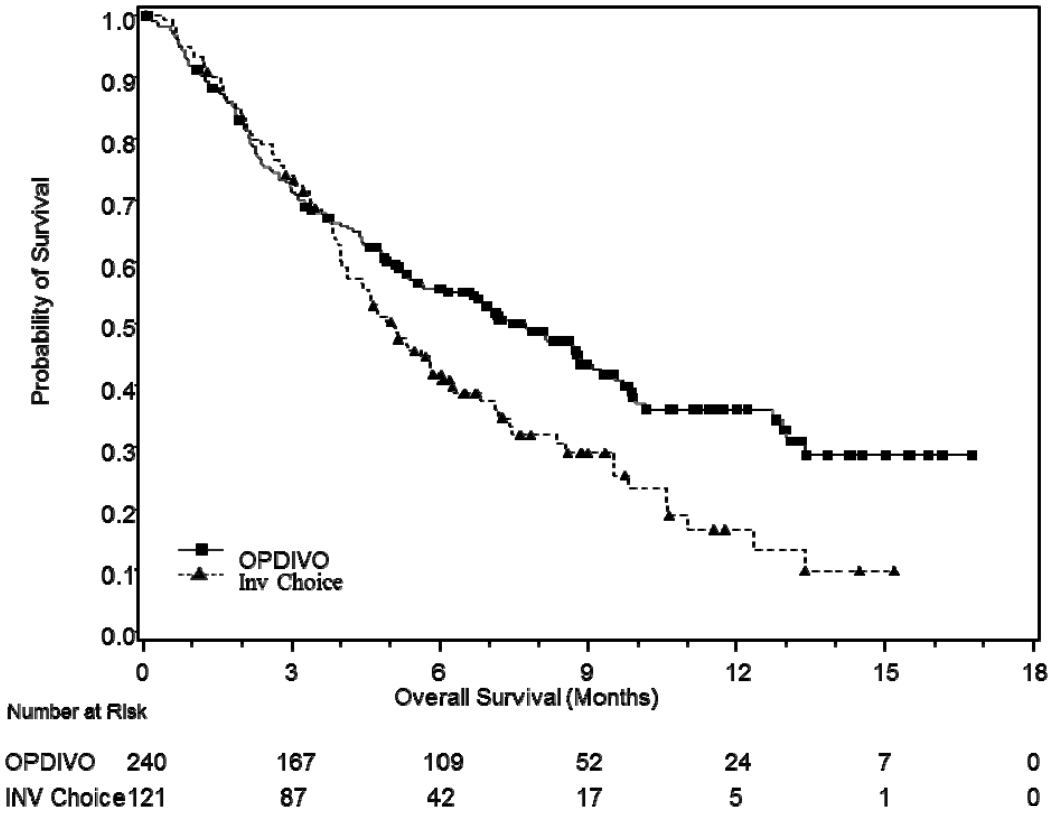
Table 23: Overall Survival in CHECKMATE-141

	OPDIVO (n=240)	**Investigator's Choice (n=121)**
Overall Survival		
Deaths (%)	133 (55%)	85 (70%)
Median (months) (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
Hazard ratio (95% CI)[a]	0.70 (0.53, 0.92)	
p-value[b,c]	0.0101	

[a] Based on stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with 0.0227 of the allocated alpha for this interim analysis.

Reference ID: 4149162

Figure 11: Overall Survival - CHECKMATE-141



Archival tumor specimens were retrospectively evaluated for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx assay. Across the study population, 28% (101/361) of patients had non-quantifiable results. Among the 260 patients with quantifiable results, 43% (111/260) had PD-L1 negative SCCHN, defined as <1% of tumor cells expressing PD-L1, and 57% (149/260) had PD-L1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratio for survival was 0.89 (95% CI: 0.54, 1.45) with median survivals of 5.7 and 5.8 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 negative subgroup. The HR for survival was 0.55 (95% CI: 0.36, 0.83) with median survivals of 8.7 and 4.6 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 positive SCCHN subgroup.

Reference ID: 4149162

14.6 Urothelial Carcinoma

In CHECKMATE-275 (NCT02387996), 270 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with OPDIVO. Patients were excluded for active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, and ECOG performance status >1. Patients received an intravenous infusion of 3 mg/kg of OPDIVO every 2 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 8 weeks for the first 48 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed objective response rate (ORR) as assessed by independent radiographic review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR).

The median age was 66 years (range: 38 to 90), 78% were male, 86% of patients were white. Twenty-seven percent had non-bladder urothelial carcinoma and 84% had visceral metastases. Thirty-four percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy. Twenty-nine percent of patients had received ≥2 prior systemic regimens in the metastatic setting. Thirty-six percent of patients received prior cisplatin only, 23% received prior carboplatin only, and 7% were treated with both cisplatin and carboplatin in the metastatic setting. Forty-six percent of patients had an ECOG performance status of 1. Eighteen percent of patients had a hemoglobin <10 g/dL, and twenty-eight percent of patients had liver metastases at baseline. Patients were included regardless of their PD-L1 status.

Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients, were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 24. Median time to response was 1.9 months (range: 1.6 to 7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%).

Table 24: Efficacy Results in CHECKMATE-275

	All Patients N=270	**PD-L1 <1% N=146**	**PD-L1 ≥1% N=124**
Confirmed Objective Response Rate, n (%) (95% CI)	53 (19.6%) (15.1, 24.9)	22 (15.1%) (9.7, 21.9)	31 (25.0%) (17.7, 33.6)
Complete Response Rate	7 (2.6%)	1 (0.7%)	6 (4.8%)
Partial Response Rate	46 (17.0%)	21 (14.4%)	25 (20.2%)
Median Duration of Response[a] (months) (range)	10.3 (1.9+, 12.0+)	7.6 (3.7, 12.0+)	NE (1.9+, 12.0+)

[a] Estimated from the Kaplan-Meier Curve

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14.7 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

CHECKMATE-142 (NCT02060188) was a multicenter, open-label, single arm study conducted in patients with locally determined dMMR or MSI-H metastatic CRC who had disease progression during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. All patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until unacceptable toxicity or radiographic progression. Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included objective response rate (ORR) as assessed by independent radiographic review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR).

A total of 74 patients were enrolled. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% ≥75 years of age, 59% were male and 88% were white. Baseline ECOG performance status was 0 (43%), 1 (55%), or 3 (1.4%) and 36% were reported to have Lynch Syndrome. Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 15%, 30%, 30%, and 24% received 1, 2, 3, or ≥4 prior lines of therapy, respectively, and 42% of patients had received an anti-EGFR antibody.

Efficacy results are shown in Table 25.

Table 25: Efficacy Results – CHECKMATE-142

	All Patients (n=74)	**Prior Treatment with Fluoropyrimidine, Oxaliplatin, and Irinotecan (n=53)**
IRC-Confirmed Objective Response Rate, n (%)	24 (32%)	15 (28%)
(95% CI)	(22, 44)	(17, 42)
Complete response (%)	2 (2.7%)	1 (1.9%)
Partial response (%)	22 (30%)	14 (26%)
Duration of Response		
Median in months (range)	NR (1.4+, 26.5+)	NR (2.8+, 22.1+)

NR=Not Reached

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16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) is available as follows:

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

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

17 PATIENT COUNSELING INFORMATION

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

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

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.4)]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.5)]*.
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions (5.6)]*.
- Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis *[see Warnings and Precautions (5.7)]*.
- Infusion Reactions: Advise patients of the potential risk of infusion reaction *[see Warnings and Precautions (5.9)]*.
- Complications of allogeneic HSCT after OPDIVO: Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.10)]*.

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- Females of Reproductive Potential: Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO *[see Use in Specific Populations (8.3)]*.
- Lactation: Advise women not to breastfeed while taking OPDIVO *[see Use in Specific Populations (8.2)]*.

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

U.S. License No. 1713

Reference ID: 4149162

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

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

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

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

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

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

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

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

Hormone gland problems (especially the thyroid, pituitary, adrenal glands, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:

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

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

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

Skin Problems. Signs of these problems may include:

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

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

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

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

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

Getting medical treatment right away may keep these problems from becoming more serious.
Your healthcare provider will check you for these problems during treatment with OPDIVO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with OPDIVO, if you have severe side effects.

What is OPDIVO?
OPDIVO is a prescription medicine used to treat:

- **people with a type of skin cancer called melanoma that has spread or cannot be removed by surgery (advanced melanoma).** You may receive OPDIVO alone or in combination with ipilimumab.
- **people with a type of advanced stage lung cancer (called non-small cell lung cancer).**
- **OPDIVO may be used when your lung cancer:**
  - has spread or grown, **and**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

  If your tumor has an abnormal EGFR or ALK gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, **and** it did not work or is no longer working.
- **people with kidney cancer (renal cell carcinoma).**
  - OPDIVO may be used when your cancer has spread or grown after treatment with other cancer medications.
- **adults with a type of blood cancer called classical Hodgkin lymphoma.**
- **OPDIVO may be used if:**
  - your cancer has come back or spread after a type of stem cell transplant that uses your own stem cells (autologous), **and**
  - you used the drug brentuximab vedotin (Adcetris®) before or after your stem cell transplant, **or**
  - you received at least 3 kinds of treatment including a stem cell transplant that uses your own stem cells (autologous).
- **people with head and neck cancer (squamous cell carcinoma)**
- **OPDIVO may be used when your head and neck cancer:**
  - has come back or spread, **and**
  - you have tried chemotherapy that contains platinum and it did not work or is no longer working.
- **people with bladder cancer (urothelial carcinoma).**
- **OPDIVO may be used when your bladder cancer:**
  - has spread or grown, **and**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- **adults and children 12 years of age and older with a type of colon or rectal cancer (colorectal cancer).**
- **OPDIVO may be used when your colon or rectal cancer**:
  - has spread to other parts of the body (metastatic),
  - has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, **and**
  - is mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H)

It is not known if OPDIVO is safe and effective in children less than 18 years of age for treatment of any cancer other than metastatic, MSI-H or dMMR, colorectal cancer.

What should I tell my healthcare provider before receiving OPDIVO?
Before you receive OPDIVO, tell your healthcare provider if you:

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

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them to show your healthcare providers and pharmacist when you get a new medicine.

How will I receive OPDIVO?

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

What are the possible side effects of OPDIVO?
OPDIVO can cause serious side effects, including:

- **See "What is the most important information I should know about OPDIVO?"**
- **Severe infusion reactions.** Tell your doctor or nurse right away if you get these symptoms during an infusion of OPDIVO:
  - chills or shaking
  - itching or rash
  - flushing
  - difficulty breathing
  - dizziness
  - fever
  - feeling like passing out
- **Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO.** These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

The most common side effects of OPDIVO when used alone include:

- feeling tired
- pain in muscles, bones, and joints
- diarrhea
- cough
- constipation
- back pain
- fever
- rash
- itchy skin
- nausea
- shortness of breath
- decreased appetite
- upper respiratory tract infection
- weakness

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

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

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

General information about the safe and effective use of OPDIVO.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about OPDIVO, talk with your healthcare provider. You can ask your healthcare provider for information about OPDIVO that is written for health professionals.

What are the ingredients in OPDIVO?
Active ingredient: nivolumab
Inactive ingredients: mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and Water for Injection. May contain hydrochloric acid and/or sodium hydroxide.

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For more information, call 1-855-673-4861 or go to www.OPDIVO.com.
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