OPDIVO (nivolumab 10 mg/mL)

Concentrate for solution for infusion

FULL PRESCRIBING INFORMATION

The marketing of OPDIVO is subject to a risk management plan (RMP) including a patient safety information card and brochures providing important safety information.
Please ensure you are familiar with this important information and explain to the patient the need to review the card and brochures before starting treatment.

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

OPDIVO, as monotherapy or in combination with ipilimumab, is indicated for the treatment of advanced unresectable or metastatic melanoma in adults.

1.2 Adjuvant Treatment of Melanoma

OPDIVO is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

1.3 Metastatic Non-Small Cell Lung Cancer

- Opdivo, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
- OPDIVO is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

1.4 Small Cell Lung Cancer

OPDIVO is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy.

1.5 Renal Cell Carcinoma

- OPDIVO as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) in patients who have received prior anti-angiogenic therapy.
- OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma (RCC).

1.6 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.

1.7 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.

1.8 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.

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

OPDIVO, as a single agent or in combination with ipilimumab, 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.

1.10 Hepatocellular Carcinoma

OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) Child-Pugh A who have been previously treated withsorafenib.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosages of OPDIVO as a single agent are presented in Table 1.

Table 1: Recommended Dosages for OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (60-minute intravenous infusion)	Until disease progression or unacceptable toxicity
Advanced renal cell carcinoma		
Adjuvant treatment of melanoma	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (60-minute intravenous infusion)	Until disease recurrence or unacceptable toxicity for up to 1 year
Metastatic non-small cell lung cancer	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity
Classical Hodgkin lymphoma		
Squamous cell carcinoma of the head and neck		
Urothelial carcinoma		
Hepatocellular carcinoma		
Small cell lung cancer		

Table 1: Recommended Dosages for OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks (30-minute intravenous infusion)	

The recommended dosages of OPDIVO in combination with ipilimumab, or other therapeutic agents are presented in Table 2. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with OPDIVO for the recommended dosage information, as appropriate.

Table 2: Recommended Dosages of OPDIVO in Combination with Other Therapeutic Agents

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg intravenously over 90 minutes on the same day	In combination with ipilimumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier
	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (60-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
Metastatic or recurrent non-small cell lung cancer	360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) and histology-based platinum doublet chemotherapy every 3 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
		2 cycles of histology-based platinum-doublet chemotherapy
Advanced renal cell carcinoma	3 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg intravenously over 30 minutes on the same day	In combination with ipilimumab for 4 doses
	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (60-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	3 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg intravenously over 30 minutes on the same day	In combination with ipilimumab for 4 doses
	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks (30-minute intravenous infusion)	
Hepatocellular carcinoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg intravenously over 30 minutes on the same day	In combination with ipilimumab for 4 doses

	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity

2.2 Dose Modifications

Recommendations for OPDIVO modifications are provided in Table 3. When OPDIVO is administered in combination with ipilimumab, if OPDIVO is withheld, ipilimumab should also be withheld. Review the Prescribing Information for ipilimumab for recommended dose modifications.

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

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

Table 3: 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/non-HCC[b]	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose[a]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis/HCC[b]	• If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN • If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN • If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Withhold dose[c]
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue

Table 3: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
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 ULN	Withhold dose[a]
	Serum creatinine more than 6 times the ULN	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 improves to Grade 0 or 1.

[b] HCC: hepatocellular carcinoma.

[c] Resume treatment when AST/ALT returns to baseline.

2.3 Preparation and Administration

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

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. The total volume of infusion must not exceed 160 mL.
    - For adult and pediatric patients with body weight ≥40 kg, do not exceed a total volume of infusion of 160 mL.

- For adult and pediatric patients with body weight <40 kg, do not exceed a total volume of infusion of 4 mL/kg of body weight.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.
- The product does not contain a preservative.

- After preparation, store the diluted solution either:
  - at room temperature for no more than 8 hours from the time of preparation to end of the infusion. Discard diluted solution if not used within 8 hours from the time of preparation; or
  - under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to end of infusion. Discard diluted solution if not used within 24 hours from the time of preparation.
- Do not freeze.

Administration

- Administer the infusion over 30 minutes or 60 minutes depending on the dose (see Tables 1 and 2) 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).
- Administer OPDIVO in combination with other therapeutic agents as follows:
  - With ipilimumab: administer OPDIVO first followed by ipilimumab on the same day.
  - With platinum-doublet chemotherapy: administer OPDIVO first followed by platinum doublet chemotherapy on the same day
  - With ipilimumab and platinum-doublet chemotherapy: administer OPDIVO first followed by ipilimumab and then platinum-doublet chemotherapy on the same day.
- Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not co-administer other drugs through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL (10 mg/mL), and 100 mg/10 mL (10 mg/mL) clear to opalescent, colorless to pale-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

Hypersensitivity to Nivolumab or to any of the excipients listed in section 11 (Description).

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

OPDIVO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1

blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.1)]*. In general, if OPDIVO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis, which is defined as requiring use of steroids and no clear alternate etiology. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

OPDIVO as a Single Agent

Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%) adverse reactions. Pneumonitis led to permanent discontinuation of OPDIVO in 1.1% and withholding of OPDIVO in 0.8% of patients.

Systemic corticosteroids were required in 100% (61/61) of patients with pneumonitis. Pneumonitis resolved in 84% of the 61 patients. Of the 15 patients in whom OPDIVO was withheld for pneumonitis, 14 reinitiated OPDIVO after symptom improvement; of these, 4 (29%) had recurrence of pneumonitis.

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

OPDIVO as a Single Agent

Immune-mediated colitis occurred in 2.9% (58/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (1.7%) and Grade 2 (1%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.9% of patients.

Systemic corticosteroids were required in 100% (58/58) of patients with colitis. Four patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 86% of the 58 patients. Of the 18 patients in whom OPDIVO was withheld for colitis, 16 reinitiated OPDIVO after symptom improvement; of these, 12 (75%) had recurrence of colitis.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Immune-mediated colitis occurred in 25% (115/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (0.4%), Grade 3 (14%), and Grade 2 (8%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO with ipilimumab in 14% and withholding of OPDIVO with ipilimumab in 4.4% of patients.

Systemic corticosteroids were required in 100% (115/115) of patients with colitis. Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 93% of the 115 patients. Of the 20 patients in whom OPDIVO with ipilimumab was withheld for colitis, 16 reinitiated treatment after symptom improvement; of these, 9 (56%) had recurrence of colitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated colitis occurred in 9% (60/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (4.4%) and Grade 2 (3.7%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.2% and withholding of OPDIVO with ipilimumab in 2.7% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (60/60) of patients with colitis. Approximately 23% of patients with immune-mediated colitis required addition of infliximab to high-dose corticosteroids. Colitis resolved in 95% of the 60 patients. Of the 18 patients in whom OPDIVO with ipilimumab was withheld for colitis, 16 reinitiated treatment after symptom improvement; of these, 10 (63%) had recurrence of colitis.

Immune-Mediated Hepatitis

OPDIVO can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.

OPDIVO as a Single Agent

Immune-mediated hepatitis occurred in 1.8% (35/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%) adverse reactions. Hepatitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.6% of patients.

Systemic corticosteroids were required in 100% (35/35) of patients with hepatitis. Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 35 patients. Of the 12 patients in whom OPDIVO was withheld for hepatitis, 11 reinitiated OPDIVO after symptom improvement; of these, 9 (82%) had recurrence of hepatitis.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Immune-mediated hepatitis occurred in 15% (70/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 8% or withholding of OPDIVO with ipilimumab in 3.5% of patients.

Systemic corticosteroids were required in 100% (70/70) of patients with hepatitis. Approximately 9% of patients with immune-mediated hepatitis required the addition mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 70 patients. Of the 16 patients in whom OPDIVO with ipilimumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement; of these, 8 (57%) had recurrence of hepatitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated hepatitis occurred in 7% (48/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%) adverse reactions. Immune-mediated hepatitis led to permanent

discontinuation of OPDIVO with ipilimumab in 3.6% and withholding of OPDIVO with ipilimumab in 2.6% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (48/48) of patients with hepatitis. Approximately 19% of patients with immune-mediated hepatitis required addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 88% of the 48 patients. Of the 17 patients in whom OPDIVO with ipilimumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement; of these, 10 (71%) had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

OPDIVO can cause primary or secondary adrenal insufficiency. For grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.1)]*.

OPDIVO as a Single Agent

Adrenal insufficiency occurred in 1% (20/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.6%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.4% of patients.

Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 90% (18/20) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 35% of the 20 patients. Of the 8 patients in whom OPDIVO was withheld for adrenal insufficiency, 4 reinitiated OPDIVO after symptom improvement and all required hormone replacement therapy for their ongoing adrenal insufficiency.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Adrenal insufficiency occurred in 8% (35/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO with ipilimumab in 0.4% and withholding of OPDIVO with ipilimumab in 2.0% of patients.

Approximately 71% (25/35) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 37% of the 35 patients. Of the 9 patients in whom OPDIVO with ipilimumab was withheld for adrenal insufficiency, 7 reinitiated treatment after symptom improvement and all required hormone replacement therapy for their ongoing adrenal insufficiency.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Adrenal insufficiency occurred in 7% (48/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% and withholding of OPDIVO with ipilimumab in 2.1% of patients with RCC or CRC.

Approximately 94% (45/48) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 29% of the 48 patients. Of the 14 patients in whom OPDIVO with ipilimumab was withheld for adrenal insufficiency, 11 reinitiated treatment after symptom improvement; of these, all received hormone replacement therapy and 2 (18%) had recurrence of adrenal insufficiency.

Hypophysitis

OPDIVO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.1)]*.

OPDIVO as a Single Agent

Hypophysitis occurred in 0.6% (12/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.2%) and Grade 2 (0.3%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO in <0.1% and withholding of OPDIVO in 0.2% of patients.

Approximately 67% (8/12) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 42% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for hypophysitis, 2 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hypophysitis.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Hypophysitis occurred in 9% (42/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (2.4%) and Grade 2 (6%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO with ipilimumab in 0.9% and withholding of OPDIVO with ipilimumab in 4.2% of patients.

Approximately 86% of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 88% (37/42) of patients with hypophysitis. Hypophysitis resolved in 38% of the 42 patients. Of the 19 patients in whom OPDIVO with ipilimumab was withheld for hypophysitis, 9 reinitiated treatment after symptom improvement; of these, 1 (11%) had recurrence of hypophysitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Hypophysitis occurred in 4.4% (29/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% and withholding of OPDIVO with ipilimumab in 2.1% of patients with RCC or CRC.

Approximately 72% (21/29) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 59% of the 29 patients. Of the 14 patients in whom OPDIVO with ipilimumab was withheld for hypophysitis, 11 reinitiated treatment after symptom improvement; of these, 2 (18%) had recurrence of hypophysitis.

Thyroid Disorders

OPDIVO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.1)]*.

Thyroiditis

OPDIVO as a Single Agent

Thyroiditis occurred in 0.6% (12/1994) of patients receiving OPDIVO as a single agent, including Grade 2 (0.2%) adverse reactions. Thyroiditis led to permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.2% of patients.

Systemic corticosteroids were required in 17% (2/12) of patients with thyroiditis. Thyroiditis resolved in 58% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for thyroiditis, 1 reinitiated OPDIVO after symptom improvement without recurrence of thyroiditis.

Hyperthyroidism

OPDIVO as a Single Agent

Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (<0.1%) and Grade 2 (1.2%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.4% of patients.

Approximately 19% of patients with hyperthyroidism received methimazole, 7% received carbimazole, and 4% received propylthiouracil. Systemic corticosteroids were required in 9% (5/54) of patients. Hyperthyroidism resolved in 76% of the 54 patients. Of the 7 patients in whom OPDIVO was withheld for hyperthyroidism, 4 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hyperthyroidism.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Hyperthyroidism occurred in 9% (42/456) of patients with melanoma or HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (0.9%) and Grade 2 (4.2%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of OPDIVO with ipilimumab in no patients and withholding of OPDIVO with ipilimumab in 2.4% of patients.

Approximately 26% of patients with hyperthyroidism received methimazole and 21% received carbimazole. Systemic corticosteroids were required in 17% (7/42) of patients. Hyperthyroidism resolved in 91% of the 42 patients. Of the 11 patients in whom OPDIVO with ipilimumab was withheld for hyperthyroidism, 8 reinitiated treatment after symptom improvement; of these, 1 (13%) had recurrence of hyperthyroidism.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Hyperthyroidism occurred in 12% (80/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (0.6%) and Grade 2 (4.5%) adverse reactions. Hyperthyroidism led to permanent discontinuation of OPDIVO with ipilimumab in no patients and withholding of OPDIVO with ipilimumab in 2.3% of patients with RCC or CRC.

Of the 80 patients with RCC or CRC who developed hyperthyroidism, approximately 16% received methimazole and 3% received carbimazole. Systemic corticosteroids were required in 20% (16/80) of patients with hyperthyroidism. Hyperthyroidism resolved in 85% of the 80 patients. Of the 15 patients in whom OPDIVO with ipilimumab was withheld for hyperthyroidism, 11 reinitiated treatment after symptom improvement; of these, 3 (27%) had recurrence of hyperthyroidism.

Hypothyroidism

OPDIVO as a Single Agent

Hypothyroidism occurred in 8% (163/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.2%) and Grade 2 (4.8%) adverse reactions. Hypothyroidism led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.5% of patients.

Approximately 79% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 3.1% (5/163) of patients with hypothyroidism. Hypothyroidism resolved in 35% of the 163 patients. Of the 9 patients in whom OPDIVO was withheld for hypothyroidism, 3 reinitiated OPDIVO after symptom improvement; of these, 1 (33%) had recurrence of hypothyroidism.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Hypothyroidism occurred in 20% (91/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (0.4%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to the permanent discontinuation of OPDIVO with ipilimumab in 0.9% and withholding of OPDIVO with ipilimumab in 0.9% of patients.

Approximately 89% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 2.2% (2/91) of patients with hypothyroidism. Hypothyroidism resolved in 41% of the 91 patients. Of the 4 patients in whom OPDIVO with ipilimumab was withheld for hypothyroidism, 2 reinitiated treatment after symptom improvement; of these, none had recurrence of hypothyroidism.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Hypothyroidism occurred in 18% (122/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (0.6%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to permanent discontinuation of OPDIVO with ipilimumab in 0.2% and withholding of OPDIVO with ipilimumab in 1.4% of patients with RCC or CRC.

Of the 122 patients with RCC or CRC who developed hypothyroidism, approximately 82% received levothyroxine. Systemic corticosteroids were required in 7% (9/122) of patients with hypothyroidism. Hypothyroidism resolved in 27% of the 122 patients. Of the 9 patients in whom OPDIVO with ipilimumab was withheld for hypothyroidism, 5 reinitiated treatment after symptom improvement; of these, 1 (20%) had recurrence of hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.1)]*.

OPDIVO as a Single Agent

Diabetes occurred in 0.9% (17/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.3%) adverse reactions, and two cases of diabetic ketoacidosis. Diabetes led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.1% of patients.

No patients (0/17) with diabetes required systemic corticosteroids. Diabetes resolved in 29% of the 17 patients. Of the 2 patients in whom OPDIVO was withheld for diabetes, both reinitiated OPDIVO after symptom improvement; of these, neither had recurrence of diabetes.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear alternate etiology.

OPDIVO as a Single Agent

Immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.4% of patients.

Systemic corticosteroids were required in 100% (23/23) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 78% of the 23 patients. Of the 7 patients in whom OPDIVO was withheld for nephritis or renal dysfunction, 7 reinitiated OPDIVO after symptom improvement; of these, 1 (14%) had recurrence of nephritis or renal dysfunction.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis, defined as requiring the use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.1)]*.

OPDIVO as a Single Agent

Immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.5% of patients.

Systemic corticosteroids were required in 100% (171/171) of patients with immune-mediated rash. Rash resolved in 72% of the 171 patients. Of the 10 patients in whom OPDIVO was withheld for immune-mediated rash, 9 reinitiated OPDIVO after symptom improvement; of these, 3 (33%) had recurrence of immune-mediated rash.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Immune-mediated rash occurred in 28% (127/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (4.8%) and Grade 2 (10%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO with ipilimumab in 0.4% and withholding of OPDIVO with ipilimumab in 3.9% of patients.

Systemic corticosteroids were required in 100% (127/127) of patients with immune-mediated rash. Rash resolved in 84% of the 127 patients. Of the 18 patients in whom OPDIVO with ipilimumab was withheld for immune-mediated rash, 15 reinitiated treatment after symptom improvement; of these, 8 (53%) had recurrence of immune-mediated rash.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated rash occurred in 16% (108/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (3.5%) and Grade 2 (4.2%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO with ipilimumab in 0.5% of patients and withholding of OPDIVO with ipilimumab in 2.0% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (108/108) of patients with immune-mediated rash. Rash resolved in 75% of the 108 patients. Of the 13 patients in whom OPDIVO with ipilimumab was withheld for immune-mediated rash, 11 reinitiated treatment after symptom improvement; of these, 5 (46%) had recurrence of immune-mediated rash.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO or OPDIVO in combination with ipilimumab, or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in

combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatic

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

5.2 Infusion-Related Reactions

OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients.

In a trial assessing the pharmacokinetics and safety of a more rapid infusion, in which patients received OPDIVO as a 60-minute intravenous infusion or a 30-minute intravenous infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Infusion-related reactions occurred in 2.5% (10/407) of patients with melanoma and in 8% (4/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Infusion-related reactions occurred in 5.1% (28/547) of patients with RCC and 4.2% (5/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, respectively.

5.3 Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause) *[see Adverse Reactions (6.1)]*. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody prior to or after an allogeneic HSCT.

5.4 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 OPDIVO and for at least 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.5 Increased Mortality in Patients with Multiple Myeloma when OPDIVO Is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including OPDIVO, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.3)]*

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 WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO as a single agent in 1994 patients enrolled in CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 or a single-arm trial in NSCLC (n=117); OPDIVO 1 mg/kg with ipilimumab 3 mg/kg in patients enrolled in CHECKMATE-067 (n=313), CHECKMATE-040 (n=49), or another randomized trial (n=94); OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg (n=666) in patients enrolled in CHECKMATE-214 or CHECKMATE-142 and OPDIVO 360 mg with ipilimumab 1 mg/kg and 2 cycles of platinum-doublet chemotherapy in CHECKMATE-9LA (n=361).

<u>Unresectable or Metastatic Melanoma</u>

Previously Treated Metastatic Melanoma

The safety of OPDIVO was evaluated in CHECKMATE-037, a randomized, open-label trial in 370 patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. Patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102): dacarbazine 1000 mg/m^2 intravenously every 3 weeks or carboplatin AUC 6 mg/mL/min and paclitaxel 175 mg/m^2 intravenously every 3 weeks. 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 >6 months and 3% of patients received OPDIVO for >1 year.

The 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 lactate dehydrogenase (LDH) at baseline (51% vs. 38%).

Serious adverse reactions occurred in 41% of patients receiving OPDIVO. OPDIVO was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving OPDIVO had a dose interruption for an adverse reaction. 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 <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. The most common adverse reaction (reported in ≥20% of patients) was rash.

Tables 4 and 5 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-037.

Table 4: 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 (%)
Skin and Subcutaneous Tissue				
Rash[a]	21	0.4	7	0
Pruritus	19	0	3.9	0
Respiratory, Thoracic and Mediastinal				
Cough	17	0	6	0
Infections				
Upper respiratory tract infection[b]	11	0	2.0	0
General				
Peripheral edema	10	0	5	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, and acneiform dermatitis.

[b] Includes rhinitis, pharyngitis, and nasopharyngitis.

Clinically important adverse reactions in <10% of patients who received OPDIVO were:

Cardiac Disorders: ventricular arrhythmia

Eye Disorders: iridocyclitis

General Disorders and Administration Site Conditions: infusion-related reactions

Investigations: increased amylase, increased lipase

Nervous System Disorders: dizziness, peripheral and sensory neuropathy

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

Table 5: Laboratory Abnormalities Worsening from Baseline[a] 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	OPDIVO		Chemotherapy	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased AST	28	2.4	12	1.0
Hyponatremia	25	5	18	1.1
Increased alkaline phosphatase	22	2.4	13	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 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease and patients requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=206) or dacarbazine 1000 mg/m^2 intravenously every 3 weeks (n=205). 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 >6 months and 12% of patients received OPDIVO for >1 year.

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%).

Serious adverse reactions occurred in 36% of patients receiving OPDIVO. 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. Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO.

The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were increased gamma-glutamyltransferase (3.9%) and diarrhea (3.4%). The most common adverse reactions (reported in ≥20% of patients and at a higher incidence than in the dacarbazine arm) were fatigue, musculoskeletal pain, rash, and pruritus.

Tables 6 and 7 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-066.

Table 6: 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 (%)
General				
Fatigue	49	1.9	39	3.4
Edema[a]	12	1.5	4.9	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	32	2.9	25	2.4
Skin and Subcutaneous Tissue				
Rash[c]	28	1.5	12	0
Pruritus	23	0.5	12	0
Vitiligo	11	0	0.5	0
Erythema	10	0	2.9	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.

Clinically important adverse reactions in <10% of patients who received OPDIVO were:

Nervous System Disorders: peripheral neuropathy

Table 7: Laboratory Abnormalities Worsening from Baseline[a] 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	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, a randomized (1:1:1), double-blind trial in 937 patients with previously untreated, unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. The trial 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.

Patients were randomized to receive:

- OPDIVO 1 mg/kg over 60 minutes with ipilimumab 3 mg/kg by intravenous infusion every 3 weeks for 4 doses followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO and ipilimumab arm; n=313), or
- OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO arm; n=313), or
- Ipilimumab 3 mg/kg by intravenous infusion 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 36.4 months) for the OPDIVO and ipilimumab arm and 6.6 months (range: 1 day to 36.0 months) for the OPDIVO arm. In the OPDIVO and ipilimumab arm, 39% were exposed to OPDIVO for ≥6 months and 30% exposed for >1 year. In the OPDIVO arm, 53% were exposed for ≥6 months and 40% for >1 year.

The population characteristics were: 65% male, median age 61 years, 97% White, baseline ECOG performance status 0 (73%) or 1 (27%), 93% with American Joint Committee on Cancer (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.

Serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO and ipilimumab arm relative to the OPDIVO arm.

The most frequent (≥10%) serious adverse reactions in the OPDIVO and ipilimumab arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). The most frequent adverse reactions leading to discontinuation of both drugs in the OPDIVO and ipilimumab arm and of OPDIVO in the OPDIVO arm, respectively, were colitis (10% and 0.6%), diarrhea (8% and 2.2%), increased ALT (4.8% and 1.0%), increased AST (4.5% and 0.6%), and pneumonitis (1.9% and 0.3%).

The most common (≥20%) adverse reactions in the OPDIVO and ipilimumab arm were fatigue, diarrhea, rash, nausea, pyrexia, pruritus, musculoskeletal pain, vomiting, decreased appetite, cough, headache, dyspnea, upper respiratory tract infection, arthralgia, and increased transaminases. The most common (≥20%) adverse reactions in the OPDIVO arm were fatigue, rash, musculoskeletal pain, diarrhea, nausea, cough, pruritus, upper respiratory tract infection, decreased appetite, headache, constipation, arthralgia, and vomiting.

Tables 8 and 9 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-067.

Table 8: Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO and 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	OPDIVO and 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						
Fatigue[a]	62	7	59	1.6	51	4.2
Pyrexia	40	1.6	16	0	18	0.6
Gastrointestinal						
Diarrhea	54	11	36	5	47	7
Nausea	44	3.8	30	0.6	31	1.9
Vomiting	31	3.8	20	1.0	17	1.6
Skin and Subcutaneous Tissue						
Rash[b]	53	6	40	1.9	42	3.5
Vitiligo	9	0	10	0.3	5	0

Table 8: Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO and 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	OPDIVO and Ipilimumab (n=313)		OPDIVO (n=313)		Ipilimumab (n=311)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[c]	32	2.6	42	3.8	36	1.9
Arthralgia	21	0.3	21	1.0	16	0.3
Metabolism and Nutrition						
Decreased appetite	29	1.9	22	0	24	1.3
Respiratory, Thoracic and Mediastinal						
Cough/productive cough	27	0.3	28	0.6	22	0
Dyspnea/exertional dyspnea	24	2.9	18	1.3	17	0.6
Infections						
Upper respiratory tract infection[d]	23	0	22	0.3	17	0
Endocrine						
Hypothyroidism	19	0.6	11	0	5	0
Hyperthyroidism	11	1.3	6	0	1	0
Investigations						
Decreased weight	12	0	7	0	7	0.3
Vascular						
Hypertension[e]	7	2.2	11	5	9	2.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia and fatigue.

[b] Includes pustular rash, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, exfoliative dermatitis, psoriasiform dermatitis, drug eruption, exfoliative rash, erythematous rash, generalized rash, macular rash, maculopapular rash, morbilliform rash, papular rash, papulosquamous rash, and pruritic rash.

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

[d] Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis.

[e] Includes hypertension and blood pressure increased.

Clinically important adverse reactions in <10% of patients who received OPDIVO with ipilimumab or OPDIVO as a single agent were:

Gastrointestinal Disorders: stomatitis, intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

Musculoskeletal and Connective Tissue Disorders: myopathy, Sjogren's syndrome, spondyloarthropathy, myositis (including polymyositis)

Nervous System Disorders: neuritis, peroneal nerve palsy

Table 9: Laboratory Abnormalities Worsening from Baseline[a] 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	OPDIVO and Ipilimumab		OPDIVO		Ipilimumab	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry						
Increased ALT	55	16	25	3.0	29	2.7
Hyperglycemia	53	5.3	46	7	26	0
Increased AST	52	13	29	3.7	29	1.7
Hyponatremia	45	10	22	3.3	26	7
Increased lipase	43	22	32	12	24	7
Increased alkaline phosphatase	41	6	27	2.0	23	2.0
Hypocalcemia	31	1.1	15	0.7	20	0.7
Increased amylase	27	10	19	2.7	15	1.6
Increased creatinine	26	2.7	19	0.7	17	1.3
Hematology						
Anemia	52	2.7	41	2.6	41	6
Lymphopenia	39	5	41	4.9	29	4.0

[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 and ipilimumab (range: 75 to 297); OPDIVO (range: 81 to 306); ipilimumab (range: 61 to 301).

Adjuvant Treatment of Melanoma

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-238, a randomized (1:1), double-blind trial in 905 patients with completely resected Stage IIIB/C or Stage IV melanoma received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=452) or ipilimumab 10 mg/kg by intravenous infusion every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year (n=453) *[see Clinical Studies (14.2)]*. The median duration of exposure was 11.5 months in OPDIVO-treated patients and was 2.7 months in ipilimumab-treated patients. In this ongoing trial, 74% of patients received OPDIVO for >6 months.

Serious adverse reactions occurred in 18% of OPDIVO-treated patients. Study therapy was discontinued for adverse reactions in 9% of OPDIVO-treated patients and 42% of ipilimumab-treated patients. Twenty-eight percent of OPDIVO-treated patients had at least one omitted dose for an adverse reaction. Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients.

The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. The most common adverse reactions (at least 20%) were fatigue, diarrhea, rash, musculoskeletal pain, pruritus, headache, nausea, upper respiratory infection, and abdominal pain. The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%).

Tables 10 and 11 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-238.

Table 10: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238

Adverse Reaction	OPDIVO (n=452)		Ipilimumab 10 mg/kg (n=453)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	57	0.9	55	2.4
Gastrointestinal				
Diarrhea	37	2.4	55	11
Nausea	23	0.2	28	0
Abdominal pain[b]	21	0.2	23	0.9
Constipation	10	0	9	0
Skin and Subcutaneous Tissue				
Rash[c]	35	1.1	47	5.3
Pruritus	28	0	37	1.1
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	32	0.4	27	0.4
Arthralgia	19	0.4	13	0.4
Nervous System				
Headache	23	0.4	31	2.0
Dizziness[e]	11	0	8	0
Infections				
Upper respiratory tract infection[f]	22	0	15	0.2
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	19	0	19	0
Dyspnea/exertional dyspnea	10	0.4	10	0.2
Endocrine				
Hypothyroidism[g]	12	0.2	7.5	0.4

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.

[c] Includes dermatitis described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.

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

[e] Includes postural dizziness and vertigo.

[f] Includes upper respiratory tract infection including viral respiratory tract infection, lower respiratory tract infection, rhinitis, pharyngitis, and nasopharyngitis.

[g] Includes secondary hypothyroidism and autoimmune hypothyroidism.

Table 11: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238

Laboratory Abnormality	OPDIVO		Ipilimumab 10 mg/kg	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	27	0.4	12	0.9
Anemia	26	0	34	0.5
Leukopenia	14	0	2.7	0.2
Neutropenia	13	0	6	0.5
Chemistry				
Increased Lipase	25	7	23	9
Increased ALT	25	1.8	40	12
Increased AST	24	1.3	33	9
Increased Amylase	17	3.3	13	3.1
Hyponatremia	16	1.1	22	3.2
Hyperkalemia	12	0.2	9	0.5
Increased Creatinine	12	0	13	0
Hypocalcemia	10	0.7	16	0.5

[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: 400 to 447 patients) and ipilimumab 10 mg/kg group (range: 392 to 443 patients).

Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

The safety of OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.3)]*. Patients received either OPDIVO 360 mg administered every 3 weeks in combination with ipilimumab 1 mg/kg administered every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received OPDIVO and ipilimumab for >6 months and 13% of patients received OPDIVO and ipilimumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 12 and 13 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 12: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis

[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis

[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain

[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blenorrhagica, palmar-plantar erythrodysaesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria

[f] Includes pruritus and generalized pruritus

[g] Includes cough, productive cough, and upper-airway cough syndrome

[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea

[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine

[j] Includes dizziness, vertigo and positional vertigo

Table 13: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5
Chemistry				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.1

[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 and ipilimumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

Second-line Treatment of Metastatic NSCLC

The safety of OPDIVO 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 (14.3)]*. These trials excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received OPDIVO 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks or docetaxel 75 mg/m^2 intravenously 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 >6 months and 20% of patients received OPDIVO for >1 year.

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%).

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. Serious adverse reactions occurred in 46% of patients receiving OPDIVO. OPDIVO was discontinued in 11% of patients and was delayed in 28% of patients for an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. Across both trials,

the most common adverse reactions (≥20%) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

Tables 14 and 15 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-057.

Table 14: 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 (%)
Respiratory, Thoracic and Mediastinal				
Cough	31	0.7	24	0
Metabolism and Nutrition				
Decreased appetite	28	1.4	23	1.5
Skin and Subcutaneous Tissue				
Pruritus	10	0.2	2.0	0

Toxicity was graded per NCI CTCAE v4.

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

Table 15: Laboratory Abnormalities Worsening from Baseline[a] 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	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), except for TSH: OPDIVO group n=314 and docetaxel group n=297.

[b] Not graded per NCI CTCAE v4.

Small Cell Lung Cancer

The safety of OPDIVO was evaluated in CHECKMATE-032, a multicenter, multi-cohort, open-label, ongoing trial that enrolled 245 patients with SCLC with disease progression after platinum-based chemotherapy *[see Clinical Studies (14.4)]*. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks. The median duration of therapy in OPDIVO-treated patients was 1 month (range: 0 to 44.2+ months): 17% of patients received OPDIVO for >6 months and 9% of patients received OPDIVO for >1 year.

The population characteristics were: median age 63 years (range: 29 to 83), 92% White, and 60% male. Baseline ECOG performance status was 0 (30%) or 1 (70%), 94% were former/current smokers, 56% received one prior line of therapy, and 44% received two or more prior lines of therapy.

Serious adverse reactions occurred in 45% of patients. OPDIVO was discontinued for adverse reactions in 10% of patients and 25% of patients had at least one dose withheld for an adverse reaction.

The most frequent (≥2%) serious adverse reactions were pneumonia, dyspnea, pneumonitis, pleural effusion, and dehydration. The most common (≥20%) adverse reactions were fatigue, decreased appetite, musculoskeletal pain, dyspnea, nausea, diarrhea, constipation, and cough.

The toxicity profile observed in patients with metastatic SCLC was generally similar to that observed in patients with other solid tumors who received OPDIVO as a single agent.

Advanced Renal Cell Carcinoma

Previously Treated Renal Cell Carcinoma

The safety of OPDIVO was evaluated in CHECKMATE-025, a randomized open-label trial in 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimen received OPDIVO 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.5)]*. 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.

Rate of death on treatment or within 30 days of the last dose was 4.7% on the OPDIVO arm. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. Study therapy was discontinued for adverse reactions in 16% of OPDIVO patients. Forty-four percent (44%) of patients receiving OPDIVO had a dose interruption for an adverse reaction.

The most frequent serious adverse reactions in at least 2% of patients were: acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. The most common adverse reactions (≥20%) were fatigue, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia. 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, increased triglycerides, and hyperkalemia. In addition, among patients with TSH < ULN at baseline, a greater proportion of patients experienced a treatment-emergent elevation of TSH >ULN in the OPDIVO group compared to the everolimus group (26% and 14%, respectively).

Tables 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-025.

Table 16: Adverse Reactions in >15% of Patients Receiving OPDIVO - CHECKMATE-025

Adverse Reaction	OPDIVO (n=406)		Everolimus (n=397)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Adverse Reaction	98	56	96	62
General				
Fatigue[a]	56	6	57	7
Pyrexia	17	0.7	20	0.8
Respiratory, Thoracic and Mediastinal				
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				
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
Skin and Subcutaneous Tissue				

Table 16: Adverse Reactions in >15% of Patients Receiving OPDIVO - CHECKMATE-025

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

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia, decreased activity, fatigue, and malaise.

[b] Includes nasopharyngitis, pharyngitis, rhinitis, and viral upper respiratory infection (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

Table 17: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on OPDIVO - CHECKMATE-025

Laboratory Abnormality	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).

Previously Untreated Renal Cell Carcinoma

The safety of OPDIVO with ipilimumab was evaluated in CHECKMATE-214, a randomized open-label trial in 1082 patients with previously untreated advanced RCC received OPDIVO 3 mg/kg over 60 minutes with

ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (n=547) or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=535) *[see Clinical Studies (14.5)]*. The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in OPDIVO and ipilimumab-treated patients and 7.8 months (range: 1 day to 20.2+ months) in sunitinib-treated patients. In this trial, 57% of patients in the OPDIVO and ipilimumab arm were exposed to treatment for >6 months and 38% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 59% of patients receiving OPDIVO and ipilimumab. Study therapy was discontinued for adverse reactions in 31% of OPDIVO and ipilimumab patients. Fifty-four percent (54%) of patients receiving OPDIVO and ipilimumab had a dose interruption for an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO and ipilimumab were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea. The most common adverse reactions (reported in ≥20% of patients) were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, and decreased appetite. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of OPDIVO and ipilimumab-treated patients include increased lipase, anemia, increased creatinine, increased ALT, increased AST, hyponatremia, increased amylase, and lymphopenia.

Tables 18 and 19 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in >15% of OPDIVO and ipilimumab-treated patients in CHECKMATE-214.

Table 18: Adverse Reactions in >15% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-214

Adverse Reaction	OPDIVO and Ipilimumab (n=547)		Sunitinib (n=535)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Adverse Reaction	99	65	99	76
General				
Fatigue[a]	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema[b]	16	0.5	17	0.6
Skin and Subcutaneous Tissue				
Rash[c]	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Gastrointestinal				
Diarrhea	38	4.6	58	6
Nausea	30	2.0	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	37	4.0	40	2.6
Arthralgia	23	1.3	16	0
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Metabolism and Nutrition				
Decreased appetite	21	1.8	29	0.9
Nervous System				
Headache	19	0.9	23	0.9
Endocrine				
Hypothyroidism	18	0.4	27	0.2

Toxicity was graded per NCI CTCAE v4.
[a] Includes asthenia.
[b] Includes peripheral edema, peripheral swelling.
[c] Includes dermatitis described as acneiform, bullous, and exfoliative, drug eruption, rash described as exfoliative, erythematous, follicular, generalized, macular, maculopapular, papular, pruritic, and pustular, fixed-drug eruption.
[d] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

Table 19: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on OPDIVO and Ipilimumab - CHECKMATE-214

Laboratory Abnormality	OPDIVO and Ipilimumab		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased lipase	48	20	51	20
Increased creatinine	42	2.1	46	1.7
Increased ALT	41	7	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12	33	7
Hyponatremia	39	10	36	7
Increased alkaline phosphatase	29	2.0	32	1.0
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	21	0.4	35	0.6
Hypomagnesemia	16	0.4	26	1.6
Hematology				
Anemia	43	3.0	64	9
Lymphopenia	36	5	63	14

[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 and ipilimumab group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

In addition, among patients with TSH ≤ULN at baseline, a lower proportion of patients experienced a treatment-emergent elevation of TSH > ULN in the OPDIVO and ipilimumab group compared to the sunitinib group (31% and 61%, respectively).

Classical Hodgkin Lymphoma

The safety of OPDIVO was evaluated in 266 adult patients with cHL (243 patients in the CHECKMATE-205 and 23 patients in the CHECKMATE-039 trials) *[see Clinical Studies (14.6)]*. Patients received OPDIVO 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks 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).

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. Serious adverse reactions occurred in 26% of patients. Dose delay for an adverse reaction occurred in 34% of patients. OPDIVO was discontinued due to adverse reactions in 7% of patients.

The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. The most common adverse reactions (≥20%) among all patients were upper respiratory tract infection, fatigue, cough, diarrhea, pyrexia, musculoskeletal pain, rash, nausea, and pruritus.

Tables 20 and 21 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-205 and CHECKMATE-039.

Table 20: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

Adverse Reaction[a]	OPDIVO (n=266)	
	All Grades (%)	Grades 3-4 (%)
Infections		
Upper respiratory tract infection[b]	44	0.8
Pneumonia/bronchopneumonia[c]	13	3.8
Nasal congestion	11	0
General		
Fatigue[d]	39	1.9
Pyrexia	29	<1
Respiratory, Thoracic and Mediastinal		
Cough/productive cough	36	0
Dyspnea/exertional dyspnea	15	1.5
Gastrointestinal		
Diarrhea[e]	33	1.5
Nausea	20	0
Vomiting	19	<1
Abdominal pain[f]	16	<1
Constipation	14	0.4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[g]	26	1.1
Arthralgia	16	<1
Skin and Subcutaneous Tissue		
Rash[h]	24	1.5
Pruritus	20	0
Nervous System		
Headache	17	<1
Neuropathy peripheral[i]	12	<1
Injury, Poisoning and Procedural Complications		
Infusion-related reaction	14	<1
Endocrine		
Hypothyroidism/thyroiditis	12	0

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 nasopharyngitis, pharyngitis, rhinitis, and sinusitis.

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

[d] Includes asthenia.

[e] Includes colitis.

[f] Includes abdominal discomfort and upper abdominal pain.

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

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

[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: Treatment-emergent peripheral neuropathy was reported in 12% (31/266) of all patients receiving OPDIVO. Twenty-eight patients (11%) had new-onset peripheral neuropathy and 3 patients had worsening of neuropathy from baseline. The median time to onset was 50 (range: 1 to 309) days.

Complications of allogeneic HSCT after OPDIVO: Of 17 patients with cHL from the CHECKMATE-205 and CHECKMATE-039 trials who underwent allogeneic HSCT after treatment with OPDIVO, 6 patients (35%) died from transplant-related complications. Five deaths occurred in the setting of severe (Grade 3 to 4) or refractory GVHD. Hyperacute GVHD occurred in 2 patients (12%) and Grade 3 or higher GVHD was reported in 5 patients (29%). Hepatic VOD occurred in 1 patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure.

Table 21 summarizes laboratory abnormalities in patients with cHL. The most common (≥20%) treatment-emergent laboratory abnormalities included cytopenias, liver function abnormalities, and increased lipase. Other common findings (≥10%) included increased creatinine, electrolyte abnormalities, and increased amylase.

Table 21: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

Laboratory Abnormality	OPDIVO[a] (n=266)	
	All Grades (%)[b]	Grades 3-4 (%)[b]
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
Hyperkalemia	15	1.5
Hypomagnesemia	14	<1
Increased amylase	13	1.5
Increased bilirubin	11	1.5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement: range: 203 to 266 patients.

[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%).

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 (14.7)]*. The trial 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). Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=236) or investigator's choice of either cetuximab (400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly), or methotrexate (40 to 60 mg/m^2 intravenously weekly), or docetaxel (30 to 40 mg/m^2 intravenously 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 >6 months and 2.5% of patients received OPDIVO for >1 year.

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.

Serious adverse reactions occurred in 49% of patients receiving OPDIVO. OPDIVO was discontinued in 14% of patients and was delayed in 24% of patients for an adverse reaction. Adverse reactions and laboratory abnormalities occurring in patients with SCCHN were generally similar to those occurring in patients with melanoma and NSCLC.

The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. 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.

Urothelial Carcinoma

The safety of OPDIVO was evaluated in CHECKMATE-275, a single arm trial 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 *[see Clinical Studies (14.8)]*. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes 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 dose interruption 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. Serious adverse reactions occurred in 54% of patients. OPDIVO was discontinued for adverse reactions in 17% of patients.

The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, nausea, and decreased appetite.

Tables 22 and 23 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-275.

Table 22: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275

Adverse Reaction	**OPDIVO (n=270)**	
	All Grades (%)	**Grades 3-4 (%)**
Adverse Reaction	99	51
General		
Asthenia/fatigue/malaise	46	7
Pyrexia/tumor associated fever	17	0.4
Edema/peripheral edema/peripheral swelling	13	0.4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[a]	30	2.6
Arthralgia	10	0.7
Metabolism and Nutrition		
Decreased appetite	22	2.2
Gastrointestinal		
Nausea	22	0.7

Table 22: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275

Adverse Reaction	OPDIVO (n=270)	
	All Grades (%)	Grades 3-4 (%)
Diarrhea	17	2.6
Constipation	16	0.4
Abdominal pain[b]	13	1.5
Vomiting	12	1.9
Respiratory, Thoracic and Mediastinal		
Cough/productive cough	18	0
Dyspnea/exertional dyspnea	14	3.3
Infections		
Urinary tract infection/escherichia/fungal urinary tract infection	17	7
Skin and Subcutaneous Tissue		
Rash[c]	16	1.5
Pruritus	12	0
Endocrine		
Thyroid disorders[d]	15	0

Toxicity was graded per NCI CTCAE v4.

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

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

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

[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.

Table 23: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients - CHECKMATE-275

Laboratory Abnormality	OPDIVO[a]	
	All Grades (%)	Grades 3-4 (%)
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
Increased lipase	20	7
Hyperkalemia	19	1.2
Increased ALT	18	1.2
Increased amylase	18	4.4
Hypomagnesemia	16	0
Hematology		
Lymphopenia	42	9
Anemia	40	7
Thrombocytopenia	15	2.4
Leukopenia	11	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: range: 84 to 256 patients.

MSI-H or dMMR Metastatic Colorectal Cancer

The safety of OPDIVO administered as a single agent or in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-label trial *[see Clinical Studies (14.9)]*. In CHECKMATE-142, 74 patients with mCRC received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or until intolerable toxicity and 119 patients

with mCRC received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks until disease progression or until unacceptable toxicity.

In the OPDIVO with ipilimumab cohort, serious adverse reactions occurred in 47% of patients. Treatment was discontinued in 13% of patients and delayed in 45% of patients for an adverse reaction. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting.

Tables 24 and 25 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-142. Based on the design of CHECKMATE-142, the data below cannot be used to identify statistically significant differences between the two cohorts summarized below for any adverse reaction.

Table 24: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-142

Adverse Reaction	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	54	5	49	6
Pyrexia	24	0	36	0
Edema[b]	12	0	7	0
Gastrointestinal				
Diarrhea	43	2.7	45	3.4
Abdominal pain[c]	34	2.7	30	5
Nausea	34	1.4	26	0.8
Vomiting	28	4.1	20	1.7
Constipation	20	0	15	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	28	1.4	36	3.4
Arthralgia	19	0	14	0.8
Respiratory, Thoracic and Mediastinal				
Cough	26	0	19	0.8
Dyspnea	8	1	13	1.7
Skin and Subcutaneous Tissue				
Rash[e]	23	1.4	25	4.2
Pruritus	19	0	28	1.7
Dry Skin	7	0	11	0
Infections				
Upper respiratory tract infection[f]	20	0	9	0
Endocrine				
Hyperglycemia	19	2.7	6	1
Hypothyroidism	5	0	14	0.8
Hyperthyroidism	4	0	12	0
Nervous System				
Headache	16	0	17	1.7
Dizziness	14	0	11	0
Metabolism and Nutrition				
Decreased appetite	14	1.4	20	1.7
Psychiatric				
Insomnia	9	0	13	0.8
Investigations				
Weight decreased	8	0	10	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema and peripheral swelling.

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

[d] Includes back pain, pain in extremity, myalgia, neck pain, and bone pain.
[e] Includes dermatitis, dermatitis acneiform, and rash described as maculo-papular, erythematous, and generalized.
[f] Includes nasopharyngitis and rhinitis.

Clinically important adverse reactions reported in <10% of patients receiving OPDIVO with ipilimumab were encephalitis (0.8%), necrotizing myositis (0.8%), and uveitis (0.8%).

Table 25: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-142

Laboratory Abnormality	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	50	7	42	9
Lymphopenia	36	7	25	6
Neutropenia	20	4.3	18	0
Thrombocytopenia	16	1.4	26	0.9
Chemistry				
Increased alkaline phosphatase	37	2.8	28	5
Increased lipase	33	19	39	12
Increased ALT	32	2.8	33	12
Increased AST	31	1.4	40	12
Hyponatremia	27	4.3	26	5
Hypocalcemia	19	0	16	0
Hypomagnesemia	17	0	18	0
Increased amylase	16	4.8	36	3.4
Increased bilirubin	14	4.2	21	5
Hypokalemia	14	0	15	1.8
Increased creatinine	12	0	25	3.6
Hyperkalemia	11	0	23	0.9

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. Number of evaluable patients ranges from 62 to 71 for the OPDIVO cohort and from 87 to 114 for the OPDIVO and ipilimumab cohort.

Hepatocellular Carcinoma

The safety of OPDIVO 3 mg/kg every 2 weeks as a single agent was evaluated in a 154-patient subgroup of patients with HCC and Child-Pugh Class A cirrhosis who progressed on or were intolerant to sorafenib. These patients enrolled in Cohorts 1 and 2 of CHECKMATE-040, a multicenter, multiple cohort, open-label trial *[see Clinical Studies (14.10)]*. Patients were required to have an AST and ALT ≤5 x ULN and total bilirubin <3 mg/dL. The median duration of exposure to OPDIVO was 5 months (range: 0 to 22+ months). Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, pneumonia, and anemia.

The toxicity profile observed in these patients with advanced HCC was generally similar to that observed in patients with other cancers, with the exception of a higher incidence of elevations in transaminases and bilirubin levels. Treatment with OPDIVO resulted in treatment-emergent Grade 3 or 4 AST in 27 (18%) patients, Grade 3 or 4 ALT in 16 (11%) patients, and Grade 3 or 4 bilirubin in 11 (7%) patients. Immune-mediated hepatitis requiring systemic corticosteroids occurred in 8 (5%) patients.

The safety of OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg was evaluated in a subgroup comprising 49 patients with HCC and Child-Pugh Class A cirrhosis enrolled in Cohort 4 of the CHECKMATE-040 trial who progressed on or were intolerant to sorafenib. OPDIVO and ipilimumab were administered every 3 weeks for 4 doses, followed by single-agent OPDIVO 240 mg every 2 weeks until disease progression or unacceptable toxicity. During the OPDIVO and ipilimumab combination period, 33 of 49 (67%) patients received all 4 planned

doses of OPDIVO and ipilimumab. During the entire treatment period, the median duration of exposure to OPDIVO was 5.1 months (range: 0 to 35+ months) and to ipilimumab was 2.1 months (range: 0 to 4.5 months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

The most frequent serious adverse reactions (reported in ≥4% of patients) were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.

Tables 26 and 27 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-040. Based on the design of the study, the data below cannot be used to identify statistically significant differences between the cohorts summarized below for any adverse reaction.

Table 26: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 or OPDIVO in Cohorts 1 and 2 of CHECKMATE-040

Adverse Reaction	OPDIVO and Ipilimumab (n=49)		OPDIVO (n=154)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash	53	8	26	0.6
Pruritus	53	4	27	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain	41	2	36	1.9
Arthralgia	10	0	8	0.6
Gastrointestinal				
Diarrhea	39	4	27	1.3
Abdominal pain	22	6	34	3.9
Nausea	20	0	16	0
Ascites	14	6	9	2.6
Constipation	14	0	16	0
Dry mouth	12	0	9	0
Dyspepsia	12	2	8	0
Vomiting	12	2	14	0
Stomatitis	10	0	7	0
Abdominal distension	8	0	11	0
Respiratory, Thoracic and Mediastinal				
Cough	37	0	23	0
Dyspnea	14	0	13	1.9
Pneumonitis	10	2	1.3	0.6
Metabolism and Nutrition				
Decreased appetite	35	2	22	1.3
General				
Fatigue	27	2	38	3.2
Pyrexia	27	0	18	0.6
Malaise	18	2	6.5	0
Edema	16	2	12	0
Influenza-like illness	14	0	9	0
Chills	10	0	3.9	0
Nervous System				
Headache	22	0	11	0.6
Dizziness	20	0	9	0
Endocrine				
Hypothyroidism	20	0	4.5	0
Adrenal insufficiency	18	4	0.6	0
Investigations				
Weight decreased	20	0	7	0

Table 26: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 or OPDIVO in Cohorts 1 and 2 of CHECKMATE-040

Adverse Reaction	OPDIVO and Ipilimumab (n=49)		OPDIVO (n=154)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Psychiatric				
Insomnia	18	0	10	0
Blood and Lymphatic System				
Anemia	10	4	19	2.6
Infections				
Influenza	10	2	1.9	0
Upper Respiratory Tract Infection	6	0	12	0
Vascular				
Hypotension	10	0	0.6	0

Clinically important adverse reactions reported in <10% of patients who received OPDIVO with ipilimumab were hyperglycemia (8%), colitis (4%), and increased blood creatine phosphokinase (2%).

Table 27: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 or OPDIVO as a Single Agent in Cohorts 1 and 2 of CHECKMATE-040

Laboratory Abnormality	OPDIVO and Ipilimumab (n=47)		OPDIVO*	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	53	13	59	15
Anemia	43	4.3	49	4.6
Neutropenia	43	9	19	1.3
Leukopenia	40	2.1	26	3.3
Thrombocytopenia	34	4.3	36	7
Chemistry				
Increased AST	66	40	58	18
Increased ALT	66	21	48	11
Increased bilirubin	55	11	36	7
Increased lipase	51	26	37	14
Hyponatremia	49	32	40	11
Hypocalcemia	47	0	28	0
Increased alkaline phosphatase	40	4.3	44	7
Increased amylase	38	15	31	6
Hypokalemia	26	2.1	12	0.7
Hyperkalemia	23	4.3	20	2.6
Increased creatinine	21	0	17	1.3
Hypomagnesemia	11	0	13	0

* The denominator used to calculate the rate varied from 140 to 152 based on the number of patients with a baseline value and at least one post-treatment value.

In patients who received OPDIVO with ipilimumab, virologic breakthrough occurred in 4 of 28 (14%) patients and 2 of 4 (50%) patients with active HBV or HCV at baseline, respectively. In patients who received single-agent OPDIVO, virologic breakthrough occurred in 5 of 47 (11%) patients and 1 of 32 (3%) patients with active HBV or HCV at baseline, respectively. HBV virologic breakthrough was defined as at least a 1 log increase in HBV DNA for those patients with detectable HBV DNA at baseline. HCV virologic breakthrough was defined as a 1 log increase in HCV RNA from baseline.

6.2 Immunogenicity

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

Of the 2085 patients who were treated with OPDIVO as a single agent at dose of 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 11% tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 0.7% had neutralizing antibodies against nivolumab. There was no evidence of altered pharmacokinetic profile or increased incidence of infusion-related reactions with anti-nivolumab antibody development.

Of the patients with melanoma, advanced renal cell carcinoma, metastatic colorectal cancer, metastatic or recurrent non-small cell lung cancer who were treated with OPDIVO and ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26% (132/516) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks and 38% (149/394) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralizing antibodies against nivolumab was 0.8% (4/516) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks and 4.6% (18/394) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks.

Of the patients with hepatocellular carcinoma who were treated with OPDIVO and ipilimumab every 3 weeks for 4 doses followed by OPDIVO every 2 weeks and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 45% (20/44) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg and 56% (27/48) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg; the corresponding incidence of neutralizing antibodies against nivolumab was 14% (6/44) and 23% (11/48), respectively.

Of the patients with NSCLC who were treated with OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy, and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 34% (104/308); the incidence of neutralizing antibodies against nivolumab was 2.6% (8/308).

There was no evidence of increased incidence of infusion-related reactions with anti-nivolumab antibody development.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OPDIVO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye: Vogt-Koyanagi-Harada (VKH) syndrome

Complications of OPDIVO Treatment After Allogeneic HSCT: Treatment refractory, severe acute and chronic GVHD

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH) (including fatal cases), autoimmune hemolytic anemia (including fatal cases)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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 (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

8.2 Lactation

Risk Summary

There are no data on the presence of nivolumab in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment and for 5 months after the last dose of OPDIVO.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating OPDIVO *[see Use in Specific Populations (8.1)]*.

Contraception

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.

8.4 Pediatric Use

The safety and effectiveness of OPDIVO as a single agent and in combination with ipilimumab 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 *[see Dosage and Administration (2.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.9)]*.

The safety and effectiveness of OPDIVO have not been established (1) in pediatric patients <12 years old with MSI-H or dMMR mCRC or (2) in pediatric patients less than 18 years old for the other approved indications *[see Indications and Usage (1)]*.

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.

In CHECKMATE-238 (adjuvant treatment of melanoma), 26% of patients were 65 years or older and 3% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

CHECKMATE-037, CHECKMATE-205, CHECKMATE-039, CHECKMATE-141, CHECKMATE-142, CHECKMATE-040, and CHECKMATE-032 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.

Of the 550 patients randomized to OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg in CHECKMATE-214 (renal cell carcinoma), 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients. In elderly patients with intermediate or poor risk, no overall difference in effectiveness was reported.

Of the 49 patients who received OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in CHECKMATE-040 (hepatocellular carcinoma), 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of OPDIVO in combination with ipilimumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients.

Of the 361 patients randomized to OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of

13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

11 DESCRIPTION

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line.

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.3 Pharmacokinetics

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent OPDIVO and OPDIVO with ipilimumab. The PK of nivolumab was studied in patients over a dose range of 0.1 mg/kg to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO as a 60-minute intravenous infusion every 2 or 3 weeks. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion. Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold.

<u>Distribution</u>

The geometric mean volume of distribution at steady state (Vss) and coefficient of variation (CV%) is 6.8 L (27.3%).

<u>Elimination</u>

Nivolumab clearance (CL) decreases over time, with a mean maximal reduction from baseline values (CV%) of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population

clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state.

The geometric mean elimination half-life ($t_{1/2}$) is 25 days (77.5%).

Specific Populations

The following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), sex, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment (eGFR ≥ 15 mL/min/1.73 m^2), and mild (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). Nivolumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST).

Drug Interaction Studies

When OPDIVO 3 mg/kg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 3 weeks, the CL of nivolumab and ipilimumab were unchanged compared to nivolumab or ipilimumab administered alone.

When OPDIVO 1 mg/kg every 3 weeks was administered in combination with ipilimumab 3 mg/kg every 3 weeks, the CL of nivolumab was increased by 29% compared to OPDIVO administered alone and the CL of ipilimumab was unchanged compared to ipilimumab administered alone.

When OPDIVO 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy, the CL of nivolumab was unchanged compared to OPDIVO administered alone and the CL of ipilimumab increased by 22% compared to ipilimumab administered alone.

When administered in combination, the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies.

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 OPDIVO 3 mg/kg intravenously 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 intravenously every 3 weeks and paclitaxel 175 mg/m^2 intravenously every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring

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

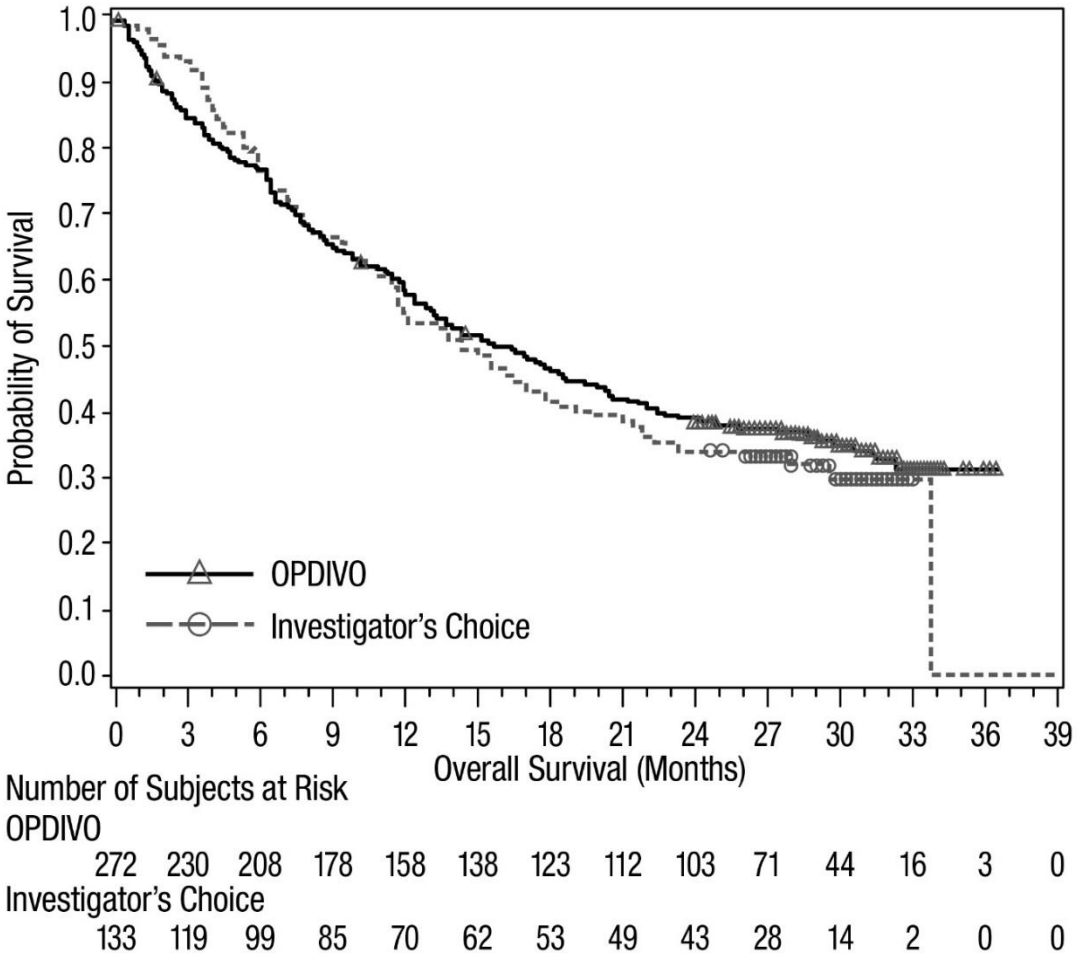
Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in CHECKMATE-037 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed overall response rate (ORR) 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, 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 responses in patients with and without BRAF V600 mutation-positive melanoma. A total of 405 patients were randomized and the median duration of OS was 15.7 months (95% CI: 12.9, 19.9) in OPDIVO-treated patients compared to 14.4 months (95% CI: 11.7, 18.2) (HR 0.95; 95.54% CI: 0.73, 1.24) in patients assigned to investigator's choice of treatment. Figure 1 summarizes the OS results.

Figure 1: Overall Survival - CHECKMATE-037*



* The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently

receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies, and differences in baseline factors.

Previously Untreated Metastatic Melanoma

CHECKMATE-066

CHECKMATE-066 (NCT01721772) was a multicenter, double-blind, randomized (1:1) trial in 418 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 intravenously every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (≥5% of tumor cell membrane staining by immunohistochemistry vs. <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 ORR per RECIST v1.1.

The trial population characteristics were: median age was 65 years (range: 18 to 87), 59% were male, and 99.5% were White. Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (11%), elevated LDH level (37%), PD-L1 ≥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%).

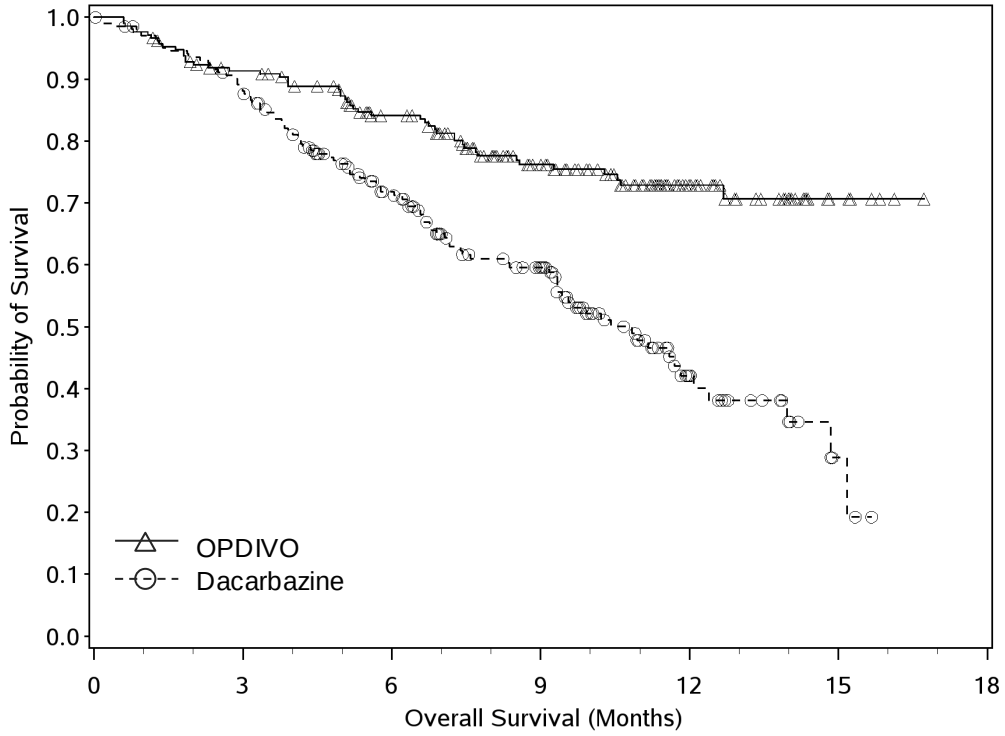
CHECKMATE-066 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. At the time of analysis, 88% (63/72) of OPDIVO-treated patients had ongoing responses, which included 43 patients with ongoing response of 6 months or longer. Efficacy results are shown in Table 28 and Figure 2.

Table 28: 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	
Overall 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.

Figure 2: **Overall Survival - CHECKMATE-066**



Number at Risk

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

CHECKMATE-067

CHECKMATE-067 (NCT01844505) was a multicenter, randomized (1:1:1), double-blind trial in 945 patients with previously untreated, unresectable or metastatic melanoma to one of the following arms: OPDIVO and 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 intravenously every 3 weeks for 4 doses, followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (OPDIVO and ipilimumab arm),
- OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (OPDIVO arm), or
- Ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by placebo every 2 weeks (ipilimumab arm).

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 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.

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%).

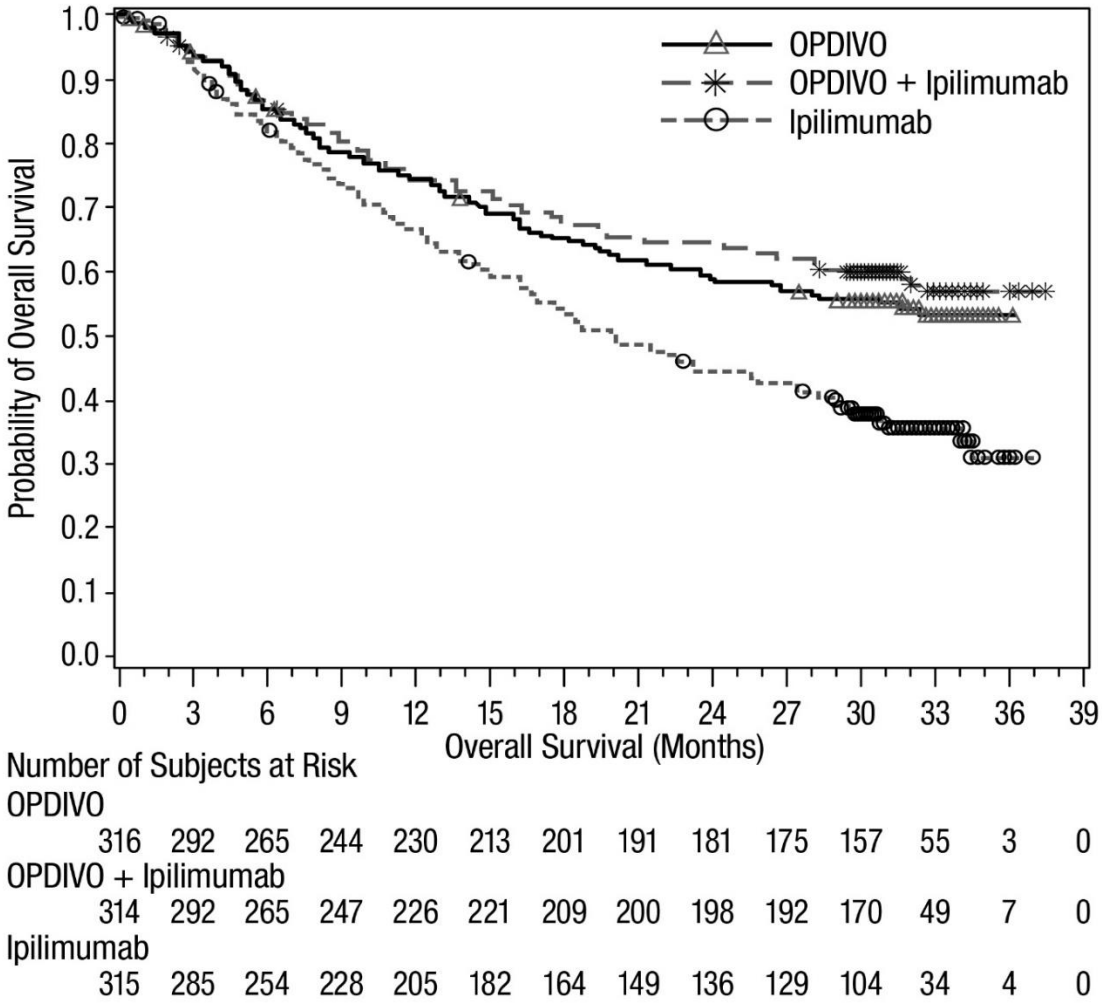
CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. The trial was not designed to assess whether adding ipilimumab to OPDIVO improves PFS or OS compared to OPDIVO as a single agent. Efficacy results are shown in Table 29 and Figure 3.

Table 29: Efficacy Results - CHECKMATE-067

	OPDIVO and Ipilimumab (n=314)	**OPDIVO (n=316)**	**Ipilimumab (n=315)**
Overall Survival[a]			
Deaths (%)	128 (41)	142 (45)	197 (63)
Hazard ratio[b] (vs. ipilimumab) (95% CI)	0.55 (0.44, 0.69)	0.63 (0.50, 0.78)	
p-value[c, d]	<0.0001	<0.0001	
Progression-free Survival[a]			
Disease progression or death	151 (48%)	174 (55%)	234 (74%)
Median (months) (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
Hazard ratio[b] (vs. ipilimumab) (95% CI)	0.42 (0.34, 0.51)	0.57 (0.47, 0.69)	
p-value[c, e]	<0.0001	<0.0001	
Confirmed Overall Response Rate[a]	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value[f]	<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] OS results are based on final OS analysis with 28 months of minimum follow-up; PFS (co-primary endpoint) and ORR (secondary endpoint) results were based on primary analysis with 9 months of minimum follow-up.
[b] Based on a stratified proportional hazards model.
[c] Based on stratified log-rank test.
[d] If the maximum of the two OS p-values is less than 0.04 (a significance level assigned by the Hochberg procedure), then both p-values are considered significant.
[e] p-value is compared with .005 of the allocated alpha for final PFS treatment comparisons.
[f] Based on the stratified Cochran-Mantel-Haenszel test.
+ Censored observation

Figure 3: Overall Survival - CHECKMATE-067



Based on a minimum follow-up of 48 months, the median OS was not reached (95% CI: 38.2, NR) in the OPDIVO and ipilimumab arm. The median OS was 36.9 months (95% CI: 28.3, NR) in the OPDIVO arm and 19.9 months (95% CI: 16.9, 24.6) in the ipilimumab arm.

Based on a minimum follow-up of 28 months, the median PFS was 11.7 months (95% CI: 8.9, 21.9) in the OPDIVO and ipilimumab arm, 6.9 months (95% CI: 4.3, 9.5) in the OPDIVO arm, and 2.9 months (95% CI: 2.8, 3.2) in the ipilimumab arm. Based on a minimum follow-up of 28 months, the proportion of responses lasting ≥ 24 months was 55% in the OPDIVO and ipilimumab arm, 56% in the OPDIVO arm, and 39% in the ipilimumab arm.

14.2 Adjuvant Treatment of Melanoma

CHECKMATE-238 (NCT02388906) was a randomized, double-blind trial in 906 patients with completely resected Stage IIIB/C or Stage IV melanoma. Patients were randomized (1:1) to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or ipilimumab 10 mg/kg intravenously every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. Enrollment required complete resection of melanoma with margins negative for disease within 12 weeks prior to randomization. The trial excluded patients with a history of ocular/uveal melanoma, autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization. Randomization was stratified by PD-L1 status (positive [based on 5% level] vs. negative/indeterminate) and AJCC stage (Stage IIIB/C vs. Stage IV M1a-M1b vs. Stage IV M1c). The major efficacy outcome measure was

recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurs first and as assessed by the investigator. Patients underwent imaging for tumor recurrence every 12 weeks for the first 2 years then every 6 months thereafter.

The trial population characteristics were: median age was 55 years (range: 18 to 86), 58% were male, 95% were White, and 90% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIB (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%).

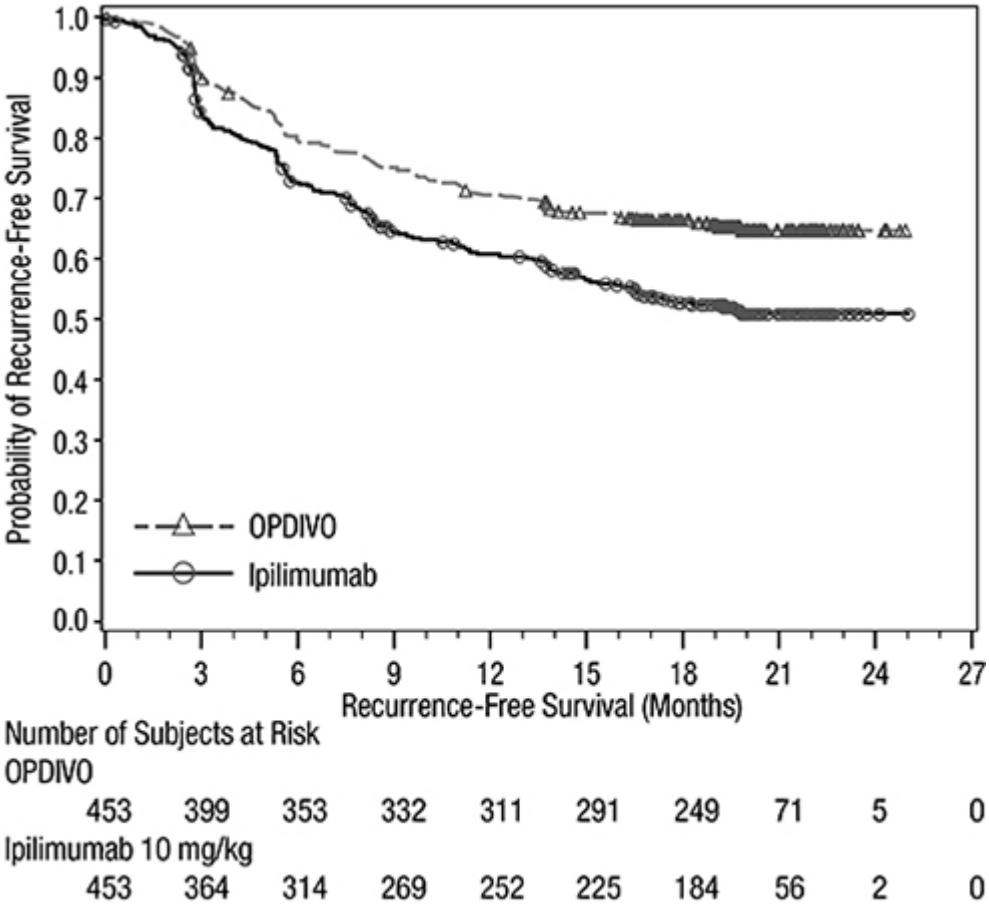
CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the ipilimumab 10 mg/kg arm. Efficacy results are shown in Table 30 and Figure 4.

Table 30: Efficacy Results - CHECKMATE-238

	OPDIVO N=453	**Ipilimumab 10 mg/kg N=453**
Recurrence-free Survival		
Number of events, n (%)	154 (34%)	206 (45%)
Median (months) (95% CI)	NR[a]	NR[a] (16.56, NR[a])
Hazard ratio[b] (95% CI) p-value[c,d]	0.65 (0.53, 0.80) p<0.0001	

[a] Not reached.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] p-value is compared with 0.0244 of the allocated alpha for this analysis.

Figure 4: Recurrence-free Survival -CHECKMATE-238



14.3 Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with stable brain metastases were eligible for enrollment.

Patients were randomized 1:1 to receive either:

- OPDIVO 360 mg administered intravenously over 30 minutes every 3 weeks, ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks, and platinum-doublet chemotherapy administered intravenously every 3 weeks for 2 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

Platinum-doublet chemotherapy consisted of either carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m^2, or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC. Patients with non-squamous NSCLC in the control arm could receive optional

pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent as part of the study. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

A total of 719 patients were randomized to receive either OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were White (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% had tumors with PD-L1 expression ≥1% and 37% had tumors with PD-L1 expression that was <1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 86% were former or current smokers.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR. Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) are presented in Table 31.

Table 31: Efficacy Results - CHECKMATE-9LA

	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=361)	**Platinum-Doublet Chemotherapy (n=358)**
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Progression-free Survival per BICR		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Median (months)[d] (95% CI)	6.8 (5.6, 7.7)	5.0 (4.3, 5.6)
Overall Response Rate per BICR (%)	38	25
(95% CI)[e]	(33, 43)	(21, 30)
Stratified CMH test p-value[f]	0.0003	
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

[a] Based on a stratified Cox proportional hazard model.

[b] p-value is compared with the allocated alpha of 0.033 for this interim analysis.

[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.

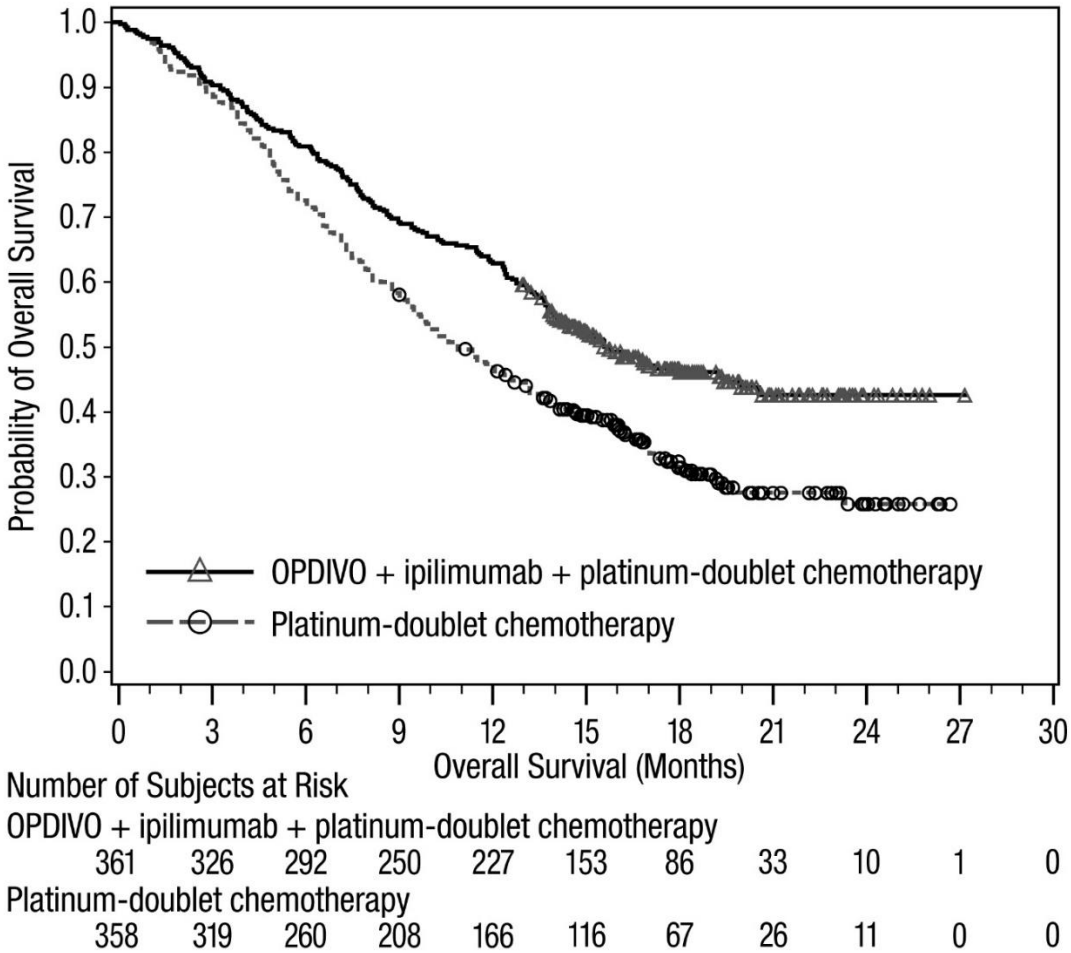
[d] Kaplan-Meier estimate.

[e] Confidence interval based on the Clopper and Pearson Method.

[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.

With an additional 4.6 months of follow-up, the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving OPDIVO and ipilimumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 5).

Figure 5: Overall Survival - CHECKMATE-9LA



Second-line Treatment of Metastatic Squamous NSCLC

CHECKMATE-017 (NCT01642004) was a randomized (1:1), open-label trial in 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=135) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=137). Randomization was stratified by prior paclitaxel vs. other prior treatment and region (US/Canada vs. Europe vs. Rest of World). This trial 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.

The trial population characteristics were: 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.

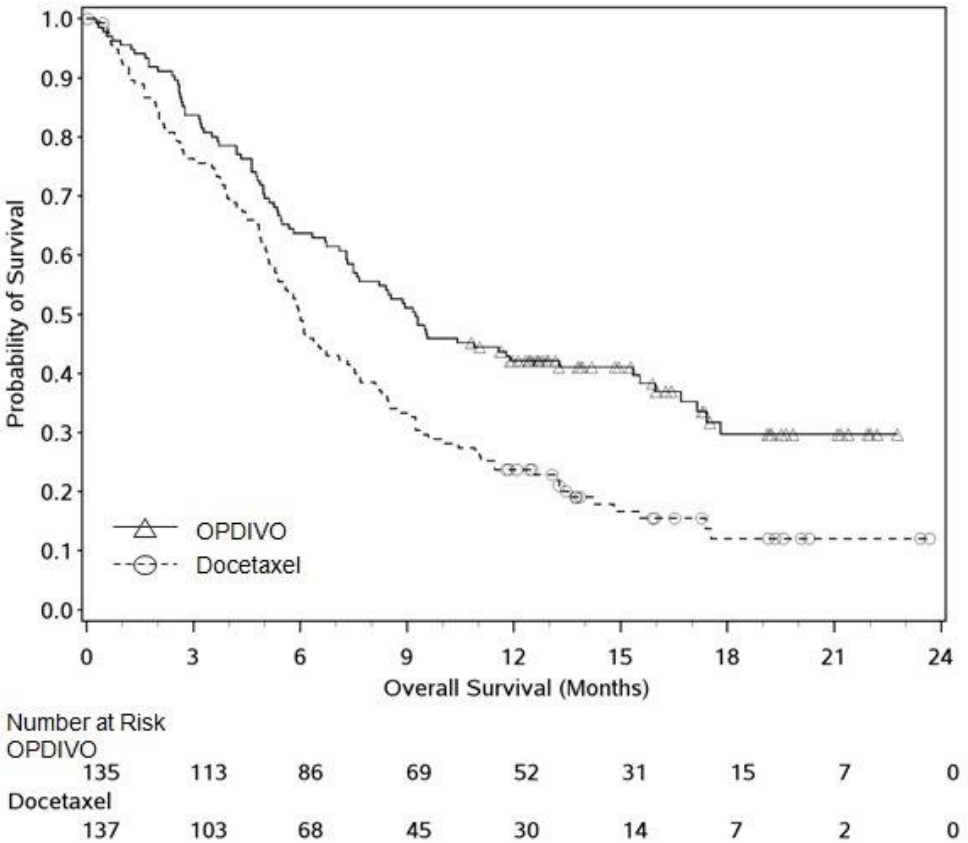
The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis). Efficacy results are shown in Table 32 and Figure 6.

Table 32: Efficacy Results - 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	
Overall 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.

Figure 6: Overall Survival - CHECKMATE-017



Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the trial population, 17% of 272 patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1 and 53% 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 subgroup.

Second-line Treatment of Metastatic Non-Squamous NSCLC

CHECKMATE-057 (NCT01673867) was a randomized (1:1), open-label trial in 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 3 mg/kg by intravenous infusion every 2 weeks (n=292) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=290). Randomization was stratified by prior maintenance therapy (yes vs. no) and number of prior therapies (1 vs. 2). The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression.

The trial population characteristics: 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%).

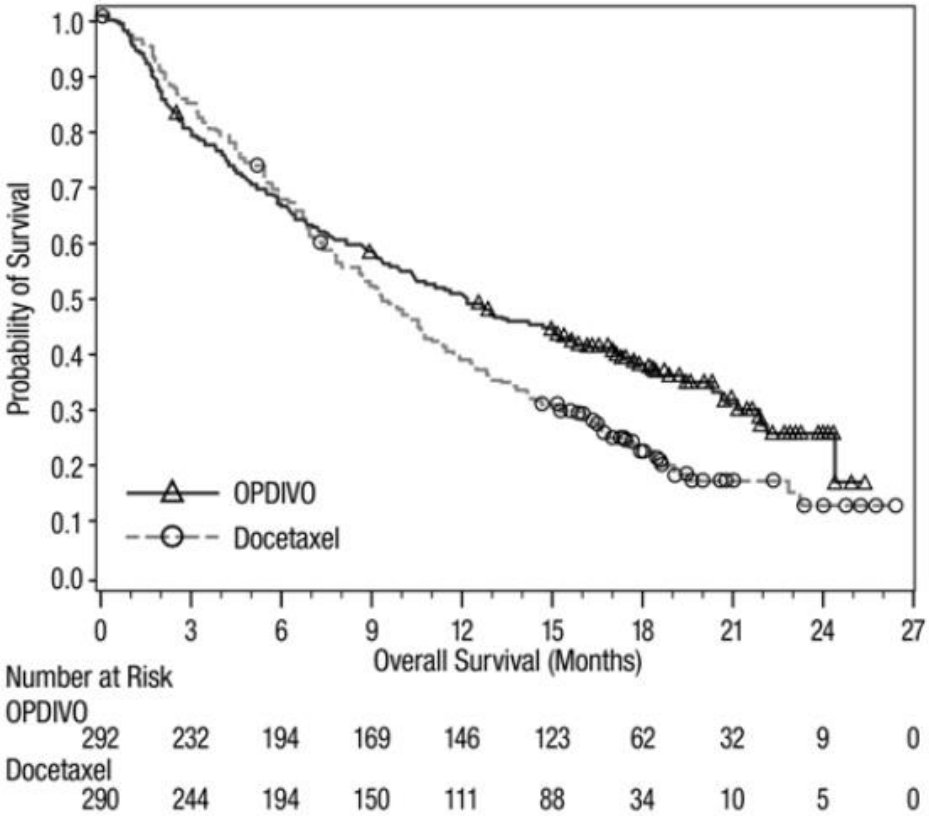
CHECKMATE-057 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 33 and Figure 7.

Table 33: Efficacy Results - 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	
Overall 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.

Figure 7: Overall Survival - CHECKMATE-057



Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the trial population, 22% of 582 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% PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% had PD-L1 expression, defined as ≥1% of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% had ≥1% but <5% tumor cells with positive staining, 7% had ≥5% but <10% tumor cells with positive staining, and 67% had ≥10% tumor cells with positive staining. Figures 8 and 9 summarize the results of prespecified analyses of OS and PFS in subgroups determined by percentage of tumor cells expressing PD-L1.

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

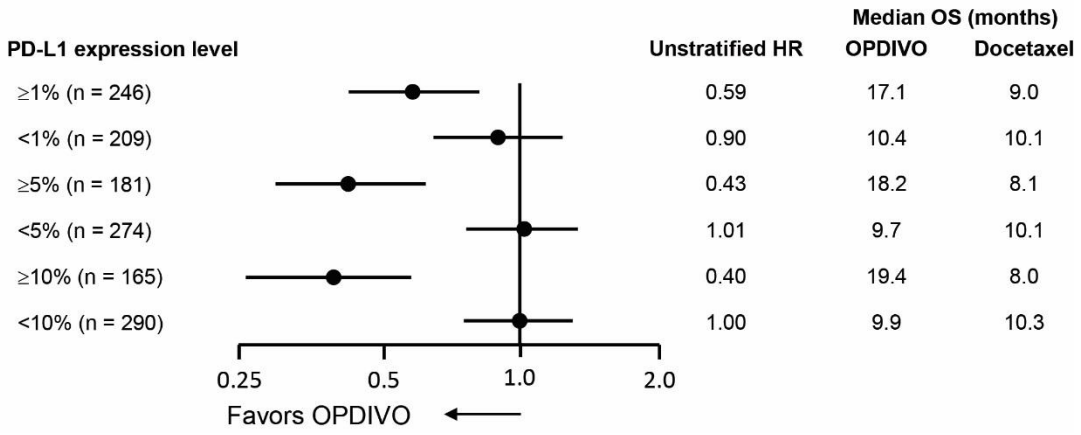
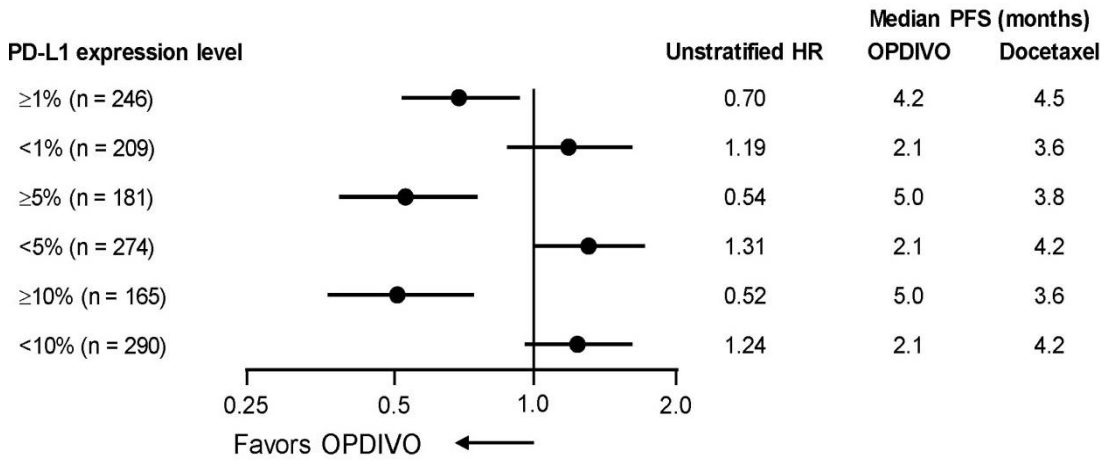


Figure 9: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



14.4 Small Cell Lung Cancer

CHECKMATE-032 (NCT01928394) was a multicenter, open-label, multi-cohort, ongoing trial evaluating nivolumab as a single agent or in combination with ipilimumab in patients with advanced or metastatic solid tumors. Several cohorts enrolled patients with metastatic small cell lung cancer (SCLC), regardless of PD-L1 tumor status, with disease progression after platinum-based chemotherapy to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks. 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. Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The major efficacy outcome measures were ORR and duration of response according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR).

A total of 109 patients with SCLC who progressed after platinum-based chemotherapy and at least one other prior line of therapy were enrolled. The trial population characteristics were: median age was 64 years (range: 45 to 81) with 45% of patients ≥65 years and 6% of patients ≥75 years. The majority (94%) of the patients were White, <1% were Asian, and 4% were Black; 56% were male. Baseline ECOG performance status was 0 (29%) or 1 (70%), 93% were former/current smokers, 7% had CNS metastases, 94% received two to three prior lines of therapy and 6% received four to five prior lines of therapy. Approximately 65% of patients had platinum-sensitive SCLC, defined as progression ≥90 days after the last dose of platinum-containing therapy.

Efficacy results are shown in Table 34.

Table 34: Efficacy Results - CHECKMATE-032

	OPDIVO (n=109)
Overall Response Rate	12%
(95% CI)	(6.5, 19.5)
Complete response	0.9%
Partial response	11%
Duration of Response	(n=13)
Range (months)	(3.0, 57.7+)
% with duration ≥12 months	69%
% with duration ≥18 months	54%

+ Indicates a censored value.

14.5 Advanced Renal Cell Carcinoma

Previously Treated Renal Cell Carcinoma

CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label trial 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. The trial excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by region, Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group and the number of prior anti-angiogenic therapies. Patients were randomized OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=410) or everolimus 10 mg orally daily (n=411). 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 population characteristics were: 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 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). OS benefit was observed regardless of PD-L1 expression level. Efficacy results are shown in Table 35 and Figure 10.

Table 35: Efficacy Results - CHECKMATE-025

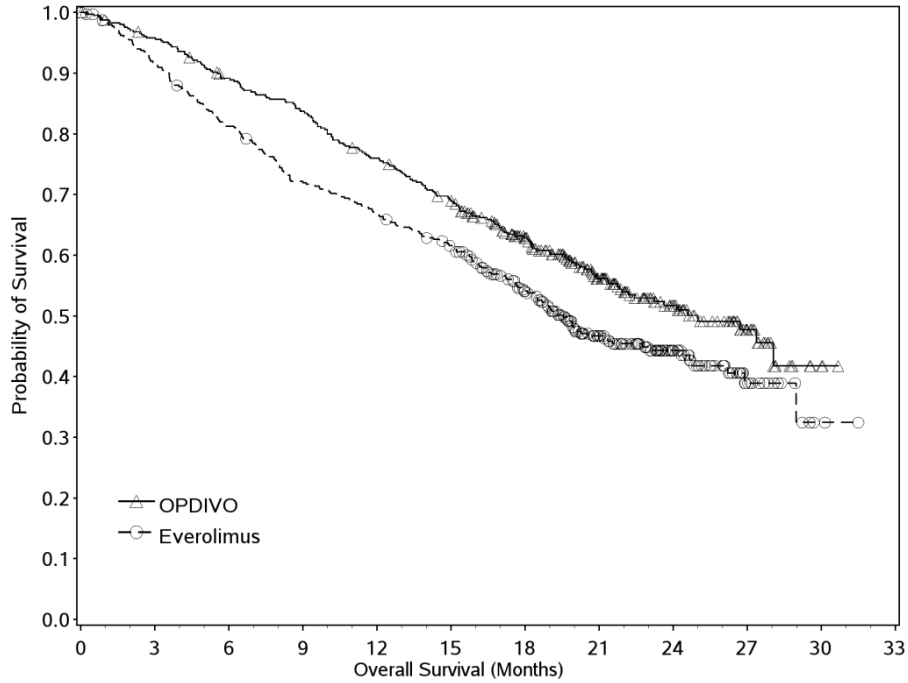
	OPDIVO (n=410)	**Everolimus (n=411)**
Overall Survival		
Deaths (%)	183 (45)	215 (52)
Median survival (months) (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0018	
Confirmed Overall Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median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

Figure 10: Overall Survival - CHECKMATE-025



Number at Risk

OPDIVO	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

Previously Untreated Renal Cell Carcinoma

CHECKMATE-214 (NCT02231749) was a randomized (1:1), open-label trial in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region.

Efficacy was evaluated in intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status <80%, hemoglobin less than the lower limit of normal, corrected calcium of >10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal).

Patients were randomized to OPDIVO 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by OPDIVO 3 mg/kg intravenously every two weeks (n=425), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=422). Treatment continued until disease progression or unacceptable toxicity.

The trial population characteristics were: median age was 61 years (range: 21 to 85) with 38% ≥65 years of age and 8% ≥75 years of age. The majority of patients were male (73%) and White (87%) and 26% and 74% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

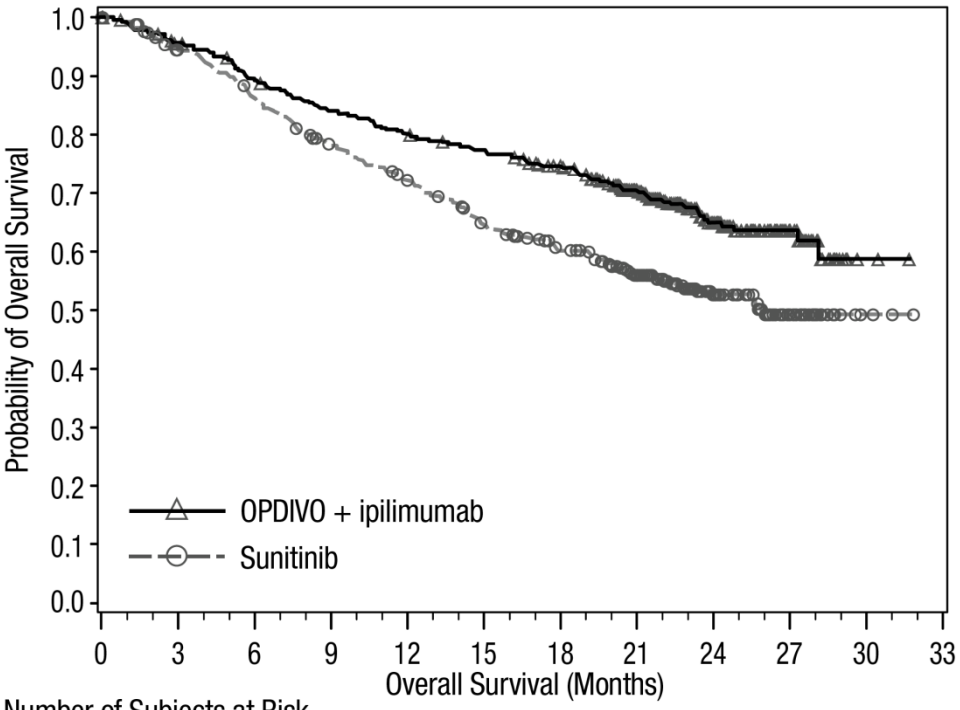
The major efficacy outcome measures were OS, PFS (independent radiographic review committee [IRRC]-assessed) and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to OPDIVO and ipilimumab as compared with sunitinib (Table 36 and Figure 11). OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS. Efficacy results are shown in Table 36 and Figure 11.

Table 36: Efficacy Results - CHECKMATE-214

	Intermediate/Poor-Risk	
	OPDIVO and Ipilimumab (n=425)	**Sunitinib (n=422)**
Overall Survival		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (months)	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	
Confirmed Overall Response Rate (95% CI)	41.6% (36.9, 46.5)	26.5% (22.4, 31.0)
p-value[d,e]	<0.0001	
Complete response (CR)	40 (9.4)	5 (1.2)
Partial response (PR)	137 (32.2)	107 (25.4)
Median duration of response (months) (95% CI)	NE (21.8, NE)	18.2 (14.8, NE)
Progression-free Survival		
Disease progression or death (%)	228 (53.6)	228 (54.0)
Median (months)	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[b]	NS[f]	

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[d] Based on the stratified DerSimonian-Laird test.
[e] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[f] Not Significant at alpha level of 0.009.

Figure 11: Overall Survival (Intermediate/Poor Risk Population) - CHECKMATE-214



Number of Subjects at Risk

OPDIVO + ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to OPDIVO and ipilimumab (n=125) or to sunitinib (n=124). These patients were not evaluated as part of the efficacy analysis population. OS in favorable risk patients receiving OPDIVO and ipilimumab compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of OPDIVO and ipilimumab in previously untreated renal cell carcinoma with favorable-risk disease has not been established.

14.6 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 trial in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation trial 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 <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 OPDIVO 3 mg/kg by intravenous infusion 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 ORR as determined by an IRRC. Additional outcome measures included duration of response (DOR).

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). Efficacy results are shown in Table 37.

Table 37: Efficacy in cHL after Autologous HSCT and Post-transplantation Brentuximab Vedotin

	CHECKMATE-205 and CHECKMATE-039 (n=95)
Overall Response Rate, n (%)[a] (95% CI)	63 (66%) (56, 76)
Complete remission rate (95% CI)	6 (6%) (2, 13)
Partial remission rate (95% CI)	57 (60%) (49, 70)
Duration of Response (months) Median[b] (95% CI) Range[c]	 13.1 (9.5, NE) 0+, 23.1+
Time to Response (months) Median Range	 2.0 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). Efficacy results are shown in Table 38.

Table 38: Efficacy in cHL after Autologous HSCT

	CHECKMATE-205 and CHECKMATE-039 (n=258)
Overall 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]	NE
(95% CI)	(12.0, NE)
Range	0+, 23.1+
Time to Response (months)	
Median	2.0
Range	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.

14.7 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

CHECKMATE-141 (NCT02105636) was a randomized (2:1), active-controlled, open-label trial 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 3 mg/kg by intravenous infusion every 2 weeks or investigator's choice of cetuximab (400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly), or methotrexate (40 to 60 mg/m^2 intravenously weekly), or docetaxel (30 to 40 mg/m^2 intravenously 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.

A total of 361 patients were randomized; 240 patients to the OPDIVO arm and 121 patients to the investigator's choice arm (docetaxel: 45%; methotrexate: 43%; and cetuximab: 12%). The trial population characteristics were: 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.

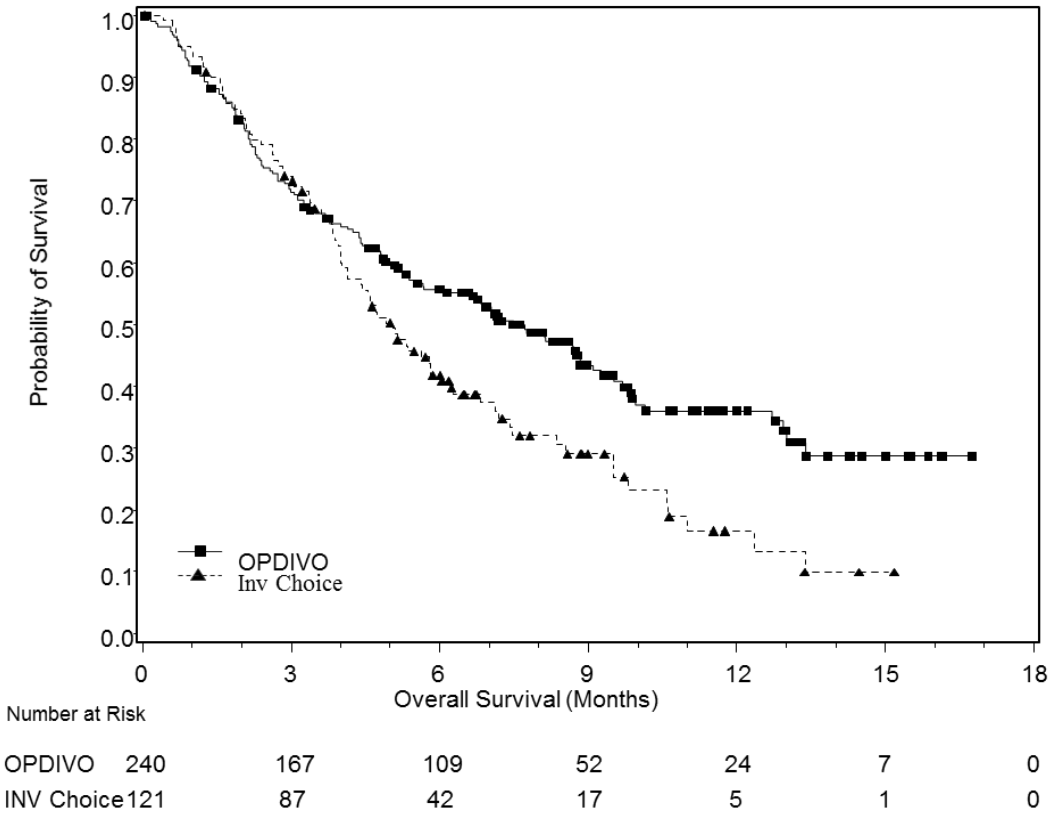
The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). There were no statistically significant differences between the two 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). Efficacy results are shown in Table 39 and Figure 12.

Table 39: Overall Survival - CHECKMATE-141

	OPDIVO (n=240)	Cetuximab, Methotrexate or Docetaxel (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.

Figure 12: 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 trial 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.

14.8 Urothelial Carcinoma

CHECKMATE-275 (NCT02387996) was a single-arm trial in 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. Patients were excluded for active brain or leptomeningeal metastases, active autoimmune

disease, medical conditions requiring systemic immunosuppression, and ECOG performance status >1. Patients received OPDIVO 3 mg/kg by intravenous infusion 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 ORR as assessed by IRRC using RECIST v1.1 and DOR.

The median age was 66 years (range: 38 to 90), 78% were male, 86% 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 shown in Table 40. Median time to response was 1.9 months (range: 1.6-7.2). 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 40: Efficacy Results - CHECKMATE-275

	All Patients N=270	**PD-L1 < 1% N=146**	**PD-L1 ≥ 1% N=124**
Confirmed Overall 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

14.9 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

CHECKMATE-142 (NCT02060188) was a multicenter, non-randomized, multiple parallel-cohort, open-label trial conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine- , oxaliplatin- , or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG performance status 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients enrolled in the single agent OPDIVO MSI-H mCRC cohort received OPDIVO 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the OPDIVO and ipilimumab MSI-H mCRC cohort received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses, followed by OPDIVO as a single agent at a dose of 3 mg/kg as intravenous infusion every 2 weeks. Treatment in both cohorts continued 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 ORR and DOR as assessed by BICR using RECIST v1.1.

A total of 74 patients were enrolled in the single-agent MSI-H mCRC OPDIVO cohort. 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; 7%, 30%, 28%, 19%, and 16% received 0, 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 42% of patients had received an anti-EGFR antibody.

A total of 119 patients were enrolled in the OPDIVO and ipilimumab MSI-H mCRC cohort. The median age was 58 years (range: 21 to 88), with 32% ≥65 years of age and 9% ≥75 years of age; 59% were male and 92% were White. Baseline ECOG performance status was 0 (45%) and 1 (55%), and 29% were reported to have Lynch Syndrome. Across the 119 patients, 69% had received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 10%, 40%, 24%, and 15% received 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 29% had received an anti-EGFR antibody.

Efficacy results for each of these single-arm cohorts are shown in Table 41.

Table 41: Efficacy Results - CHECKMATE-142

	OPDIVO[a] MSI-H/dMMR Cohort		**OPDIVO and Ipilimumab[b] MSI-H/dMMR Cohort**	
	All Patients (n=74)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)**	**All Patients (n=119)**	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
Overall Response Rate per BICR; n (%)	28 (38%)	17 (32%)	71 (60%)	46 (56%)
(95% CI)[c]	(27, 50)	(20, 46)	(50, 69)	(45, 67)
Complete Response (%)	8 (11%)	5 (9%)	17 (14%)	11 (13%)
Partial Response (%)	20 (27%)	12 (23%)	54 (45%)	35 (43%)
Duration of Response				
Proportion of responders with ≥6 months response duration	86%	94%	89%	87%
Proportion of responders with ≥12 months response duration	82%	88%	77%	74%

[a] Minimum follow-up 33.7 months for all patients treated with OPDIVO (n=74).

[b] Minimum follow-up 27.5 months for all patients treated with OPDIVO and ipilimumab (n=119).

[c] Estimated using the Clopper-Pearson method.

14.10 Hepatocellular Carcinoma

CHECKMATE-040 (NCT01658878), was a multicenter, multiple cohort, open-label trial that evaluated the efficacy of OPDIVO as a single agent and in combination with ipilimumab in patients with hepatocellular carcinoma (HCC) who progressed on or were intolerant to sorafenib. Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible.

Tumor assessments were conducted every 6 weeks for 48 weeks and then every 12 weeks thereafter. The major efficacy outcome measure was confirmed overall response rate, as assessed by BICR using RECIST v1.1 and modified RECIST (mRECIST) for HCC. Duration of response was also assessed.

The efficacy of OPDIVO as a single agent was evaluated in a pooled subgroup of 154 patients across Cohorts 1 and 2 who received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until disease progression or unacceptable toxicity. The median age was 63 years (range: 19 to 81), 77% were male, and 46% were White.

Baseline ECOG performance status was 0 (65%) or 1 (35%). Thirty-one percent (31%) of patients had active HBV infection, 21% had active HCV infection, and 49% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 18% and non-alcoholic fatty liver disease in 6.5% of patients. Child-Pugh class and score was A5 for 68%, A6 for 31%, and B7 for 1% of patients. Seventy-one percent (71%) of patients had extrahepatic spread, 29% had macrovascular invasion, and 37% had alfa-fetoprotein (AFP) levels ≥400 µg/L. Prior treatment history included surgical resection (66%), radiotherapy (24%), or locoregional treatment (58%). All patients had received prior sorafenib, of whom 36 (23%) were unable to tolerate sorafenib; 19% of patients had received 2 or more prior systemic therapies.

The efficacy of OPDIVO in combination with ipilimumab was evaluated in 49 patients (Cohort 4) who received OPDIVO 1 mg/kg and ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, followed by single-agent OPDIVO at 240 mg every 2 weeks until disease progression or unacceptable toxicity. The median age was 60 years (range: 18 to 80), 88% were male, 74% were Asian, and 25% were White. Baseline ECOG performance status was 0 (61%) or 1 (39%). Fifty-seven (57%) percent of patients had active HBV infection, 8% had active HCV infection, and 35% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 16% and non-alcoholic fatty liver disease in 6% of patients. Child-Pugh class and score was A5 for 82% and A6 for 18%; 80% of patients had extrahepatic spread; 35% had vascular invasion; and 51% had AFP levels ≥400 µg/L. Prior cancer treatment history included surgery (74%), radiotherapy (29%), or local treatment (59%). All patients had received prior sorafenib, of whom 10% were unable to tolerate sorafenib; 29% of patients had received 2 or more prior systemic therapies.

Efficacy results are shown in Table 42. Based on the design of this study, the data below cannot be used to identify statistically significant differences in efficacy between cohorts. The results for OPDIVO in Cohorts 1 and 2 are based on a minimum follow-up of approximately 27 months. The results for OPDIVO in combination with ipilimumab in Cohort 4 are based on a minimum follow-up of 28 months.

Table 42: Efficacy Results - Cohorts 1, 2, and 4 of CHECKMATE-040

	OPDIVO and Ipilimumab (Cohort 4) (n=49)	**OPDIVO (Cohorts 1 and 2) (n=154)**
Overall Response Rate per BICR,[a] n (%), RECIST v1.1	16 (33%)	22 (14%)
(95% CI)[b]	(20, 48)	(9, 21)
Complete response	4 (8%)	3 (2%)
Partial response	12 (24%)	19 (12%)
Duration of Response per BICR,[a] RECIST v1.1	n=16	n=22
Range (months)	4.6, 30.5+	3.2, 51.1+
Percent with duration ≥6 months	88%	91%
Percent with duration ≥12 months	56%	59%
Percent with duration ≥24 months	31%	32%
Overall Response Rate per BICR,[a] n (%), mRECIST	17 (35%)	28 (18%)
(95% CI)[b]	(22, 50)	(12, 25)
Complete response	6 (12%)	7 (5%)
Partial response	11 (22%)	21 (14%)

[a] Confirmed by BICR.

[b] Confidence interval is based on the Clopper and Pearson method.

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) Injection is available as follows:

Carton Contents
40 mg/4 mL single-dose vial
100 mg/10 mL single-dose vial

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

The expiry date of the product is indicated on the packaging materials.

Shelf life after opening:

From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately.

After preparation of infusion:

The administration of the OPDIVO infusion must be completed within 24 hours of preparation. If not used immediately, the solution may be stored under refrigeration conditions: 2°C to 8°C and protected from light for up to 24h (a maximum of 8h of the total 24h can be at room temperature 20°C to 25°C and room light – the maximum 8h period under room temperature and room light conditions should be inclusive of the product administration period).

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