יוני 2020

Opdivo (nivolumab)
10 MG/ML
Concentrate for solution for infusion

רופא/ה ,רוקח/ת יקר/ה,

חברת בריסטול-מאיירס סקוויב (ישראל) מבקשת להודיע על:

- הרחבת התוויות לתכשיר אופדיבו (ניבולומב)
- עדכון העלון לרופא של התכשיר
- עדכון העלון לצרכן של התכשיר

התוויות התכשיר כפי שאושרו ע"י משרד הבריאות (תוספת טקסט מסומנת בכחול עם קו תחתי, מחיקת טקסט מסומנת באדום עם קו אמצעי):

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.

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

Metastatic Non-Small Cell Lung Cancer:
Opdivo is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

Small Cell Lung Cancer (SCLC):
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.

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).

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 ~~post transplantation~~ brentuximab vedotin, or
* 3 or more lines of systemic therapy that includes autologous HSCT.

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.

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.

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.

Hepatocellular Carcinoma:
Opdivo is indicated for the treatment of patients with hepatocellular carcinoma Child-Pugh A after sorafenib therapy.

בפירוט שלהלן כלולים **העדכונים המהותיים בלבד** (טקסט שנוסף מסומן בכחול עם קו תחתי, טקסט שהוסר מסומן ~~באדום~~ עם קו אמצעי).
למידע מלא על התרופה יש לעיין בעלון לרופא ובעלון לצרכן כפי שאושרו על ידי משרד הבריאות.

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפס על ידי פנייה לבעל הרישום בריסטול-מאיירס סקוויב (ישראל) בע"מ.

בכבוד רב,
מיכל ניר ורדימון
מנהלת רגולציה

עדכונים מהותיים בעלון לרופא:

1 INDICATIONS AND USAGE

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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.

…

1.4 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

~~1.~~• OPDIVO ~~(nivolumab)~~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 ~~*[see Clinical Studies (14.3)]*~~.

• 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 ~~(nivolumab)~~ 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 ~~post-transplantation~~ brentuximab vedotin ~~*[see Clinical Studies (14.4)]*. This indication is approved based on overall response rate.~~, or
- 3 or more lines of systemic therapy that includes autologous HSCT.

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

~~OPDIVO~~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 ~~*[see Clinical Studies (14.7)]*~~.

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2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage ~~for Melanoma~~

The recommended ~~dose~~dosages of OPDIVO as a single agent ~~is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity~~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 ~~dose~~dosages of OPDIVO in combination with ipilimumab ~~is 1 mg/kg administered as an intravenous infusion over 60 minutes, followed by~~ are presented in Table 2. Refer to the ipilimumab ~~on the same day, every 3 weeks for 4 doses *[see Clinical Studies (14.1)]*. The recommended subsequent dose of OPDIVO, as a single agent, is 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Review the Full~~ Prescribing Information for recommended ipilimumab ~~prior to initiation~~dosage information.

~~2.2 Recommended Dosage for NSCLC~~

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

~~2.3 Recommended Dosage for RCC~~

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

~~2.4 Recommended Dosage for cHL~~

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

~~2.5 Recommended Dosage for SCCHN~~

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

~~2.6 Recommended Dosage for Urothelial Carcinoma~~

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

~~2.7 Recommended Dosage for CRC~~

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

~~2.8 Recommended Dosage for HCC~~

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

Table 2: Recommended Dosages of OPDIVO in Combination with Ipilimumab

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
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)	

~~2.9~~2.2 Dose Modifications

Recommendations for OPDIVO modifications are provided in Table ~~1~~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.

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~~2.10~~2.3 Preparation and Administration

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

Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. 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.

~~**Storage of Infusion**~~

- The product does not contain a preservative.
- After preparation, store the ~~OPDIVO infusion~~diluted solution either:
  - at room temperature for no more than ~~4~~8 hours from the time of preparation~~. This includes room temperature storage~~ to end of the infusion ~~in~~. Discard diluted solution if not used within 8 hours from the ~~IV container and~~ time ~~for administration~~ of ~~the infusion~~
    - 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 ~~infusion~~ 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).
- When administered with ipilimumab, administer OPDIVO first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not coadminister other drugs through the same intravenous line.
- ~~Flush the intravenous line at end of infusion.~~

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

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5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

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OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

~~In patients receiving OPDIVO with ipilimumab,~~ Immune-mediated pneumonitis occurred in 6% (25/407) of patients with melanoma who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. ~~The~~ Median time to onset ~~of immune-mediated pneumonitis~~ was 1.6 months (range: 24 days to 10.1 months). Immune-mediated pneumonitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 2.2% and 3.7% of patients, respectively. Approximately 84% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 30 days (range: 5 days to 11.8 months). Complete resolution occurred in 68% of patients. Approximately 13% of patients had recurrence of pneumonitis after re-initiation of OPDIVO with ipilimumab.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated pneumonitis occurred in 4.4% (24/547) of patients with RCC and 1.7% (2/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset of immune-mediated pneumonitis was 2.6 months (range: 8 days to 9.2 months) in patients with RCC and 1.9 months (range: 27 days to 3 months) in patients with CRC.

Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO with ipilimumab in 1.8% of patients with RCC or CRC (n=666) and withholding of OPDIVO with ipilimumab in 1.7%. All patients with pneumonitis required systemic corticosteroids, including 92% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 19 days (range: 4 days to 3.2 months). Approximately 8% required addition of infliximab to high-dose corticosteroids. Complete resolution of pneumonitis occurred in 81% of patients. Pneumonitis recurred after re-initiation of OPDIVO with ipilimumab in one patient with CRC.

5.2 Immune-Mediated Colitis

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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. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

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OPDIVO with Ipilimumab

~~In patients receiving~~ *OPDIVO 1 mg/kg with ~~ipilimumab, immune~~Ipilimumab 3 mg/kg*

Immune-mediated colitis occurred in 26% (107/407) of patients with melanoma who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including three fatal cases. ~~The median~~Median time to onset ~~of immune-mediated colitis~~ was 1.6 months (range: 3 days to 15.2 months). Immune-mediated colitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 16% and 7% of patients, respectively. Approximately 96% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.1 month (range: 1 day to 12 months). Approximately 23% of

patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 75% of patients. Approximately 28% of patients had recurrence of colitis after re-initiation of OPDIVO with ipilimumab.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated colitis occurred in 10% (52/547) of patients with RCC and 7% (8/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset of immune-mediated colitis was 1.7 months (range: 2 days to 19.2 months) in patients with RCC and 2.4 months (range: 22 days to 5.2 months) in patients with mCRC.

Immune-mediated colitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.2% of patients with RCC or CRC (n=666) and withholding of OPDIVO with ipilimumab in 3.9%. All patients with colitis required systemic corticosteroids, including 80% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 21 days (range: 1 day to 27 months). Approximately 23% of patients with immune-mediated colitis required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 88% of patients. Two patients with RCC had recurrence of colitis after re-initiation of OPDIVO with ipilimumab.

5.3 Immune-Mediated Hepatitis

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OPDIVO with Ipilimumab

~~***In patients receiving***~~ *OPDIVO 1 mg/kg with* ~~***ipilimumab, immune***~~*Ipilimumab 3 mg/kg*

Immune-mediated hepatitis occurred in 13% (51/407) of patients~~; the median~~ with melanoma receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 2.1 months (range: 15 days to 11 months). Immune-mediated hepatitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 6% and 5% of patients, respectively. Approximately 92% of patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.1 month (range: 1 day to 13.2 months). Complete resolution occurred in 75% of patients. Approximately 11% of patients had recurrence of hepatitis after re-initiation of OPDIVO with ipilimumab.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated hepatitis occurred in 7% (38/547) of patients with RCC and 8% (10/119) with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 2 months (range: 14 days to 26.8 months) in patients with RCC and 2.2 months (range: 22 days to 10.5 months) in patients with CRC.

Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.6% of patients with RCC or CRC (n=666) and withholding of OPDIVO and ipilimumab in 3.5%. All patients with hepatitis required systemic corticosteroids, including 94% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1 month (range: 1 day to 7 months). Approximately 19% of patients with immune-mediated hepatitis required addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 83% of patients. No patients had recurrence of hepatitis after re-initiation of OPDIVO with ipilimumab.

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

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~~In patients receiving~~ *OPDIVO with* ~~ipilimumab, hypophysitis~~*Ipilimumab*

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Hypophysitis occurred in 9% (36/407) of patients~~; the median~~ with melanoma receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 2.7 months (range: 27 days to 5.5 months). Hypophysitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 1.0% and 3.9% of patients, respectively. Approximately 75% of patients with hypophysitis received hormone replacement therapy and 56% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 19 days (range: 1 day to 2.0 months).

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Hypophysitis occurred in 4.6% (25/547) of patients with RCC and 3.4% (4/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 2.8 months (range: 1.3 months to 7.3 months) in patients with RCC and 3.7 months (range: 2.8 to 5.5 months) in patients with CRC.

Hypophysitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 1.2% and 2.6% of patients with RCC or CRC (n=666), respectively. Approximately 72% of patients with hypophysitis received hormone replacement therapy and 55% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 13 days (range: 1 day to 1.6 months).

Adrenal Insufficiency

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~~In patients receiving~~ *OPDIVO with* ~~ipilimumab, adrenal~~*Ipilimumab*

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Adrenal insufficiency occurred in 5% (21/407) of patients ~~and the median~~with melanoma receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 3.0 months (range: 21 days to 9.4 months). Adrenal insufficiency led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.5% and 1.7% of patients, respectively. Approximately 57% of patients with adrenal insufficiency received hormone replacement therapy and 33% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 9 days (range: 1 day to 2.7 months).

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Adrenal insufficiency occurred in 7% (41/547) of patients with RCC and 5.9% (7/119) patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 3.4 months (range: 2.0 months to 22.3 months) in RCC and 3.7 months (range: 2.5 to 13.4 months) in CRC.

Adrenal insufficiency led to permanent discontinuation of OPDIVO and ipilimumab in 1.2% of patients with RCC or CRC (n=666) and withholding of OPDIVO and ipilimumab in 2.6%. Approximately 94% of patients with adrenal insufficiency received hormone replacement therapy and 27% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 2 days to 5.6 months).

Hypothyroidism and Hyperthyroidism

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~~In patients receiving~~ *OPDIVO with* ~~ipilimumab, hypothyroidism~~*Ipilimumab*

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients~~; the median~~ with melanoma receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 2.1 months (range: 1– day to 10.1– months). Approximately 73% of patients with hypothyroidism or thyroiditis received levothyroxine. Resolution occurred in 45% of patients.

Hyperthyroidism occurred in 8% (34/407) of patients ~~receiving~~with melanoma who received OPDIVO with ipilimumab~~:~~; the median time to onset was 23 days (range: 3 days to 3.7 months). Approximately 29% of patients

with hyperthyroidism received methimazole and 24% received carbimazole. Resolution occurred in 94% of patients.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients with RCC and 15% (18/119) of patients with CRC who received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 2.2 months (range: 1 day to 21.4 months) in patients with RCC and 2.3 months (range: 22 days to 9.8 months) in patients with CRC. Of the 137 patients with RCC or CRC who developed hypothyroidism, approximately 81% of patients with RCC and 78% with CRC received levothyroxine.

Hyperthyroidism occurred in 12% (66/547) of patients with RCC and 12% (14/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 1.4 months (range: 6 days to 14.2 months) in RCC and 1.1 months (range: 21 days to 5.4 months) in CRC. Of the 80 patients with RCC or CRC who developed hyperthyroidism, approximately 15% received methimazole and 2% received carbimazole.

Type 1 Diabetes Mellitus

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~~In patients receiving~ *OPDIVO with* ~~ipilimumab, diabetes~~*Ipilimumab*

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Diabetes occurred in 1.5% (6/407) of patients~~; the median~~ with melanoma who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 2.5 months (range: 1.3 to 4.4 months). OPDIVO with ipilimumab was withheld in a patient and permanently discontinued in a second patient who developed diabetes.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Diabetes occurred in 2.7% (15/547) of patients with RCC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks; the median time to onset was 3.2 months (range: 19 days to 16.8 months). OPDIVO with ipilimumab was withheld in 33% of patients and permanently discontinued in 20% of patients who developed diabetes.

5.5 Immune-Mediated Nephritis and Renal Dysfunction

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OPDIVO with Ipilimumab

~~In patients receiving~ *OPDIVO 1 mg/kg with* ~~ipilimumab, immune~~*Ipilimumab 3 mg/kg*

Immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients~~; the median~~ with melanoma who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 2.7 months (range: 9 days to 7.9 months). Immune-~~-~~mediated nephritis and renal dysfunction led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.7% and 0.5% of patients, respectively. Approximately 67% of patients received high-dose corticosteroids (at least 40~~-~~ mg prednisone equivalents per day) for a median duration of 13.5 days (range: 1 day to 1.1 months). Complete resolution occurred in all patients. Two patients resumed OPDIVO with ipilimumab without recurrence of nephritis or renal dysfunction.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients with RCC and 1.7% (2/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 3 months (range: 1 day to 13.2 months) among these 27 patients.

Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% of patients with RCC or CRC (n=666) and withholding of OPDIVO and ipilimumab in 2.3%.

Approximately 78% of patients with immune-mediated nephritis and renal dysfunction received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 17 days (range: 1 day to 6 months). Complete resolution occurred in 63% of patients. One of 16 patients with RCC had recurrence of nephritis or renal dysfunction after re-initiation of OPDIVO with ipilimumab.

5.6 Immune-Mediated- Skin Adverse Reactions

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OPDIVO with Ipilimumab

~~In patients receiving~~ *OPDIVO 1 mg/kg with ~~ipilimumab, immune~~Ipilimumab 3 mg/kg*

Immune-mediated rash occurred in 22.6% (92/407) of patients~~; the median~~ with melanoma receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 18 days (range: 1 day to 9.7 months). Immune-mediated rash led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.5% and 3.9% of patients, respectively. Approximately 17% of patients with rash received high-dose corticosteroids (at least 40- mg prednisone equivalents per day) for a median duration of 14 days (range: 2- days to 4.7 months). Complete resolution occurred in 47% of patients. Approximately 6% of patients who resumed OPDIVO and ipilimumab after resolution had recurrence of rash.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated rash occurred in 16% (90/547) of patients with RCC and 14% (17/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 1.5 months (range: 1 day to 20.9 months) in RCC and 26 days (range: 5 days to 9.8 months) in CRC.

Immune-mediated rash led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.5% of patients with RCC or CRC (n=666) and withholding of OPDIVO with ipilimumab in 2.6% of patients. All patients with immune-mediated rash required systemic corticosteroids, including 19% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 22 days (range: 1 day to 23 months). Complete resolution occurred in 66% of patients. Immune-mediated rash recurred in approximately 3% (3/98) of patients who resumed OPDIVO and ipilimumab.

5.7 Immune-Mediated Encephalitis

…

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Encephalitis occurred in one patient ~~receiving~~(0.2%) with melanoma who received OPDIVO 1 mg/kg with ipilimumab ~~(0.2%)~~ 3 mg/kg every 3 weeks after 1.7- months of exposure.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Encephalitis occurred in one patient (0.2%) with RCC after approximately 4 months of exposure and one patient (0.8%) with CRC after 15 days of exposure. The patient with CRC required infliximab and high-dose corticosteroids (at least 40 mg prednisone equivalents per day).

…

5.9 Infusion-Related Reactions

…

OPDIVO as a Single Agent

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

~~OPDIVO with Ipilimumab~~

In a trial assessing the pharmacokinetics and safety of a more rapid infusion, in which patients ~~receiving OPDIVO with ipilimumab~~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 receiving 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.

…

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are ~~discussed~~described elsewhere in ~~greater detail in other sections of~~ the labeling.

- Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Colitis *[see Warnings and Precautions (5.2)]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions (5.3)]*
- Immune-Mediated Endocrinopathies *[see Warnings and Precautions (5.4)]*
- Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions (5.5)]*
- Immune-Mediated Skin Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Immune-Mediated Encephalitis *[see Warnings and Precautions (5.7)]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.8)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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

The data in ~~the Warnings and Precautions section~~WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO~~,~~ as a single agent~~, for clinically significant adverse reactions~~ in 1994 patients enrolled in ~~the~~ CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 ~~trials~~ or a single~~-~~-arm trial in NSCLC (n=117); ~~administering~~ OPDIVO ~~as a single agent *[see Warnings and Precautions (5.)]*. In addition, clinically significant adverse reactions of OPDIVO administered with ipilimumab were evaluated~~1 mg/kg with ipilimumab 3 mg/kg in ~~407~~ patients ~~with melanoma~~ enrolled in CHECKMATE-067 (n=313~~)~~), or ~~a Phase 2~~another randomized ~~study~~trial (n=94~~), administering~~); and OPDIVO 3 mg/kg administered with ipilimumab~~, supplemented by~~

~~immune-mediated adverse reaction reports~~ 1 mg/kg (n=666) in ~~ongoing clinical trials *[see Warnings and Precautions (5)]*~~ patients enrolled in CHECKMATE-214 or CHECKMATE-142.

~~The data described below reflect exposure to OPDIVO as a single agent in CHECKMATE-037, CHECKMATE-066 and CHECKMATE-067, and to OPDIVO with ipilimumab in CHECKMATE-067, which are randomized, active-controlled trials conducted in patients with unresectable or metastatic melanoma. Also described below are single-agent OPDIVO data from CHECKMATE-017 and CHECKMATE-057, which are randomized trials in patients with metastatic NSCLC, CHECKMATE-025, which is a randomized trial in patients with advanced RCC, CHECKMATE-205 and CHECKMATE-039, which are open-label, multiple-cohort trials in patients with cHL, CHECKMATE-141, a randomized trial in patients with recurrent or metastatic SCCHN, and CHECKMATE-275, which is a single-arm trial in patients with urothelial carcinoma and, CHECKMATE-040, which is an open-label, multiple-cohort trial in patients with HCC.~~

Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

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

~~In CHECKMATE-037, patients~~ had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV. 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 ~~trial~~ population characteristics in the OPDIVO group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% White, baseline Eastern Cooperative Oncology Group (ECOG) performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the OPDIVO group with elevated 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 ~~drug delay~~dose interruption for an adverse reaction. ~~Serious adverse reactions occurred in 41% of patients receiving OPDIVO.~~ Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in 2% to ~~less than~~ ≤5% of patients receiving OPDIVO were abdominal pain, hyponatremia,

increased aspartate aminotransferase, and increased lipase. The most common adverse reaction (reported in ≥20% of patients) was rash.

~~Table 2 summarizes~~Tables 4 and 5 summarize the adverse reactions ~~that occurred in at least 10% of OPDIVO-treated patients~~and laboratory abnormalities, respectively, in CHECKMATE-037. ~~The most common adverse reaction (reported in at least 20% of patients) was rash.~~

Table ~~2~~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 (%)
	~~Percentage (%) of Patients~~			
Skin and Subcutaneous Tissue ~~Disorders~~				
Rash[a]	21	0.4	7	0
Pruritus	19	0	3.9	0
Respiratory, Thoracic~~,~~ and Mediastinal ~~Disorders~~				
Cough	17	0	6	0
Infections				
Upper respiratory tract infection[b]	11	0	2.0	0
General ~~Disorders and Administration Site Conditions~~				
Peripheral edema	10	0	5	0

Toxicity was graded per NCI CTCAE v4.

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

[b] ~~Upper respiratory tract infection is a composite term which includes~~Includes rhinitis, pharyngitis, and nasopharyngitis.

~~Other clinically~~Clinically important adverse reactions in ~~less than~~ ≤10% of patients ~~treated with~~who received OPDIVO ~~in CHECKMATE-037~~ were:

Cardiac Disorders: ventricular arrhythmia

Eye Disorders: iridocyclitis

General Disorders and Administration Site Conditions: infusion-related reactions

Investigations: increased amylase, increased lipase

Nervous System Disorders: dizziness, peripheral and sensory neuropathy

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

Table ~~3~~5: Laboratory Abnormalities Worsening from ~~Baseline~~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~~Percentage of Patients with Worsening Laboratory Test from Baseline[a]~~		Chemotherapy	
	~~OPDIVO~~			
	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
~~Hyponatremia~~	~~25~~	~~5~~	~~18~~	~~1.1~~
Increased ALT	16	1.6	5	0
Hyperkalemia	15	2.0	6	0

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

Previously Untreated Metastatic Melanoma

CHECKMATE-066

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

The trial excluded patients with autoimmune disease and patients requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications. 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. ~~Serious adverse reactions occurred in 36% of patients receiving OPDIVO.~~ Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. ~~The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%).~~

~~Table~~The most frequent Grade 3 and 4 ~~summarizes selected~~ adverse reactions ~~that occurred~~reported in ~~at least 10~~≥2% of ~~OPDIVO-treated~~ patients. receiving OPDIVO were increased gamma-glutamyltransferase (3.9%) and diarrhea (3.4%). The most common adverse reactions (reported in ~~at least~~ ≥20% of patients and at a higher incidence than in the dacarbazine arm) were fatigue, musculoskeletal pain, rash, and pruritus.

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

Table 46: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3- 4]) () - CHECKMATE-066)

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

Other clinically

Clinically important adverse reactions in less than <10% of patients treated withwho received OPDIVO in CHECKMATE-066 were:

Nervous System Disorders: peripheral neuropathy

Table 57: Laboratory Abnormalities Worsening from BaselineBaseline[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	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased ALT	25	3.0	19	0.5
Increased AST	24	3.6	19	0.5
Increased alkaline phosphatase	21	2.6	14	1.6
Increased bilirubin	13	3.1	6	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 194 to 197 patients) and dacarbazine group (range: 186 to 193 patients).

CHECKMATE-067

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

~~8~~• OPDIVO 1 mg/kg over 60 minutes with ipilimumab 3 mg/kg by intravenous infusion every 3 weeks for 4 doses followed by OPDIVO ~~3 mg/kg~~ as a single agent at a dose of 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO ~~plus~~and ipilimumab arm; n=313), or

~~9~~• OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO arm; n=313), or

~~*10*~~• 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 ~~plus~~and ipilimumab arm and 6.6 months (range: 1 day to 36.0 months) for the OPDIVO arm. In the OPDIVO ~~plus~~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.

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

The~~ trial~~ population characteristics were: 65% male, median age 61 years, 97% White, baseline ECOG performance status 0 (73%) or 1 (27%), 93% with ~~AJCC~~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.

~~In CHECKMATE-067, serious~~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 ~~plus~~and ipilimumab arm relative to the OPDIVO arm.

The most frequent (≥10%) serious adverse reactions in the OPDIVO ~~plus~~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 ~~plus~~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 ~~plus~~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. ~~Table 6 summarizes the incidence of adverse reactions occurring in at least 10% of patients in either OPDIVO-containing arm in CHECKMATE-067.~~

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

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

Adverse Reaction	Percentage (%) of Patients					
	OPDIVO plus Ipilimumab (n=313)		OPDIVO (n=313)		Ipilimumab (n=311)	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
General Disorders and Administration Site Conditions						
Fatigue[a]	62	7	59	1.6	51	4.2
Pyrexia	40	1.6	16	0	18	0.6
Skin and Subcutaneous Tissue Disorders						
Rash[b]	53	6	40	1.9	42	3.5
Vitiligo	9	0	10	0.3	5	0
Gastrointestinal Disorders						
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
Respiratory, Thoracic, and Mediastinal Disorders						
Cough/productive cough	27	0.3	28	0.6	22	0
Dyspnea/exertional dyspnea	24	2.9	18	1.3	17	0.6
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal pain[c]	32	2.6	42	3.8	36	1.9
Arthralgia	21	0.3	21	1.0	16	0.3
Infections and Infestations						
Upper respiratory tract infection[d]	23	0	22	0.3	17	0
Metabolism and Nutrition Disorders						
Decreased appetite	29	1.9	22	0	24	1.3
Investigations						
Decreased weight	12	0	7	0	7	0.3
Vascular Disorders						
Hypertension[e]	7	2.2	11	5	9	2.3
Endocrine Disorders						
Hypothyroidism	19	0.6	11	0	5	0
Hyperthyroidism	11	1.3	6	0	1	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 (%)
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
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.

~~Other clinically~~Clinically important adverse reactions in ~~less than~~ ≤10% of patients ~~treated with either~~who received OPDIVO with ipilimumab or OPDIVO as a single- agent ~~OPDIVO in CHECKMATE-067~~ were:

Gastrointestinal Disorders: stomatitis, intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

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

Nervous System Disorders: neuritis, peroneal nerve palsy

Table ~~7~~9: Laboratory Abnormalities Worsening from ~~Baseline~~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~~	~~Percentage (%) of Patients[a]~~					
Laboratory Abnormality	**OPDIVO ~~plus~~and Ipilimumab**		**OPDIVO**		**Ipilimumab**	
	~~Any Grade~~All Grades (%)	**Grade 3-4 (%)**	**~~Any Grade~~All Grades (%)**	**Grade 3-4 (%)**	**~~Any Grade~~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 ~~plus~~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

~~-~~The safety of OPDIVO ~~in metastatic NSCLC~~ was evaluated in CHECKMATE-017, a randomized~~,~~ open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.~~2)]~~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 ~~of OPDIVO~~ over 60 minutes by intravenous infusion every 2 weeks or docetaxel ~~administered~~75 mg/m^2 intravenously ~~at 75 mg/m^2~~ every 3 weeks. The median duration of therapy in OPDIVO-treated patients in CHECKMATE-017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1- year and in CHECKMATE-057, 30% of patients received OPDIVO for ~~greater than~~ ≥6 months and 20% of patients received OPDIVO for ~~greater than~~ ≥1- year.

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

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

~~OPDIVO was discontinued in 11% of patients, and was delayed in 28% of patients for an adverse reaction. Serious adverse reactions occurred in 46% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure.~~ In CHECKMATE-057, in the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. 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 ~~(reported in at least~~ (≥20~~% of patients)~~%) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. ~~Table 8 summarizes~~

Tables 12 and 13 summarize selected adverse reactions ~~occurring more frequently~~and laboratory abnormalities, respectively, in ~~at least 10% of OPDIVO-treated patients~~CHECKMATE-057.

Table ~~8~~12: Adverse Reactions Occurring in ≥≥10% of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥≥5% ~~[~~All Grades~~]~~ or ≥≥2% ~~[~~Grades ~~3-4])~~ () - CHECKMATE-017 and CHECKMATE-057~~)~~

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

Toxicity was graded per NCI CTCAE v4.

~~Toxicity was graded per NCI CTCAE v4.~~

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

Table ~~9~~13: Laboratory Abnormalities Worsening from ~~Baseline~~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	~~Percentage of Patients with Worsening Laboratory Test from Baseline~~[a]OPDIVO		Docetaxel	
	~~OPDIVO~~			
	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 [b] ~~Not graded per NCI CTCAE v4.~~

Renal Cell Carcinoma

The safety of OPDIVO was evaluated in CHECKMATE-025, a randomized open-label trial in ~~which~~ 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimen received OPDIVO 3 mg/kg ~~of OPDIVO~~over 60 minutes by intravenous infusion every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.~~3~~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 ~~and 19% of everolimus patients.~~. Forty-four percent (44%) of patients receiving OPDIVO had a ~~drug delay~~dose interruption for an adverse reaction. ~~Serious adverse reactions occurred in 47% of patients receiving OPDIVO.~~

The most frequent serious adverse reactions ~~reported~~ in at least 2% of patients were: acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia.

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

The most common adverse reactions ~~(reported in at least~~ (≥20~~% of patients)~~%) were fatigue, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia. ~~Table 10 summarizes~~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 14 and 15 summarize adverse reactions ~~that occurred in greater than 15% of OPDIVO-treated patients~~and laboratory abnormalities, respectively, in CHECKMATE-025.

Table ~~10: Grade 1-4~~ 14: Adverse Reactions in >15% of Patients Receiving OPDIVO ~~(~~ CHECKMATE-025~~)~~

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

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes nasopharyngitis, pharyngitis, rhinitis, and viral ~~URI.~~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~~palmar-plantar erythrodysesthesia

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

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

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

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 259 to 401 patients) and everolimus group (range: 257 to 376 patients).

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 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in >15% of OPDIVO and ipilimumab-treated patients in CHECKMATE-214.

Table 16: 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 17: 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 ~~less than~~ ≤ULN at baseline, a ~~greater~~lower proportion of patients experienced a treatment-emergent elevation of TSH ~~greater than~~> ULN in the OPDIVO and ipilimumab group compared to the ~~everolimus~~sunitinib group (~~26~~31% and ~~14~~61%, respectively).

Classical Hodgkin Lymphoma

The safety of OPDIVO ~~3 mg/kg every 2 weeks~~ was evaluated in ~~263~~266 adult patients with cHL (~~240~~243 patients in the CHECKMATE-205 and 23 patients in the CHECKMATE-039~~). Treatment could continue~~ 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: ~~1~~2 to 15). Patients received a median of ~~10~~23 doses (cycles) of OPDIVO (range: 1 to 48), with a median duration of therapy of ~~4.8~~11 months (range: 0~~.3~~ to ~~24~~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 ~~4.2% of patients. Twenty-three percent (23%) of patients had a dose delay for an adverse reaction. Serious adverse reactions occurred in 21% of patients.~~ 7% of patients.

The most frequent serious adverse reactions reported in ~~at least~~ ≥1% of patients were pneumonia, infusion-related reaction, ~~pneumonia,~~ pyrexia, colitis or diarrhea, pleural effusion, ~~pyrexia, rash, and~~ pneumonitis~~. Ten patients died from causes other than disease progression, including 6 who died from complications of allogeneic HSCT.~~

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

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

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

Tables 18 and 19 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-205 and CHECKMATE-039.

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

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

[c] Includes abdominal discomfort and upper abdominal pain.

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

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

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

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

[h] Includes hyperesthesia, hypoesthesia, paresthesia, dysesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Table 18: 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 ~~4.9% (13/263~~6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in ~~3.~~4% (~~.9/263~~% (13/266) of patients receiving OPDIVO (one Grade 3 and ~~eight~~12 Grade 2). The median time to onset was ~~2.2~~4.5 months (range: ~~1 day~~5 days to ~~10.1~~ 12 months). All ~~nine~~13 patients received systemic corticosteroids, with resolution in ~~seven. One patient~~12. Four patients permanently discontinued OPDIVO due to ~~Grade 2~~ pneumonitis. ~~Dose delay occurred in three patients. Five~~Eight patients ~~resumed~~continued OPDIVO~~,~~ (three after dose delay), of whom ~~none~~two had recurrence of pneumonitis.

Peripheral neuropathy: In CHECKMATE-205 and CHECKMATE-039,Treatment-emergent peripheral neuropathy was observedreported in 11% (30/26312% (31/266) of all patients receiving OPDIVO. Twenty-twoeight patients (811%) had new-onset peripheral neuropathy, and four3 patients had worsening of neuropathy from baseline. Four additional patients with peripheral neuropathy at baseline (three Grade The median time to onset was 50 (range: 1 and one Grade 2) did not worsen. All events were Grade 1 or 2, except for 1 Grade 3 event (0.4%).to 309) days.

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

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 19 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 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients with cHL (CHECKMATE-205 and CHECKMATE-039)

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

[a] Number of evaluable patients for the safety population ranges from 226 to 253.

[b] Number of evaluable patients for the efficacy population ranges from 80 to 85.

[c] 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.

Table 19: 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 (14.5)]*. Patients received 3 mg/kg of OPDIVO (n=236) over 60 minutes by intravenous infusion every 2 weeks or investigator's choice of either:

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

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

CHECKMATE-141*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 (n=13), 400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly, or
- methotrexate (n=46) 40 to 60 mg/m^2 intravenously weekly, or
- docetaxel (n=52) 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. ~~Serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis.~~ Adverse reactions and laboratory abnormalities occurring in patients with SCCHN were generally similar to those occurring in patients with melanoma and NSCLC.

The most 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 ~~study~~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 ~~drug delay~~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. ~~Serious adverse reactions occurred in 54% of patients.~~

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

~~Twenty-five (9%) patients received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction *[see Warnings*~~Tables 20 and ~~*Precautions (5)]*.~~

The most common21 summarize adverse reactions (reportedand laboratory abnormalities, respectively, in CHECKMATE-275. at least 20% of patients) were fatigue, musculoskeletal pain, nausea, and decreased appetite.

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

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

	OPDIVO Urothelial Carcinoma	
	Percentage (%) of Patients	
	All Grades	Grades 3-4
Adverse Reaction	99	51
General Disorders and Administration Site Conditions		
Asthenia/fatigue/malaise	46	7
Pyrexia/tumor associated fever	17	0.4
Edema/peripheral edema/peripheral swelling	13	0.4
Infections and Infestations		
Urinary Tract Infection/escherichia/fungal urinary tract infection	17	7
Respiratory, Thoracic, and Mediastinal Disorders		
Cough/productive cough	18	0
Dyspnea/exertional dyspnea	14	3.3
Gastrointestinal Disorders		
Nausea	22	0.7
Diarrhea	17	2.6
Constipation	16	0.4
Abdominal pain[a]	13	1.5
Vomiting	12	1.9
Skin and Subcutaneous Tissue Disorders		
Rash[b]	16	1.5
Pruritus	12	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[c]	30	2.6
Arthralgia	10	0.7
Metabolism and Nutrition Disorders		
Decreased appetite	22	2.2
Endocrine Disorders		
Thyroid disorders[d]	15	0

Toxicity was graded per NCI CTCAE v4.

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

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

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

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

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

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

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

Table 20: 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
Diarrhea	17	2.6
Constipation	16	0.4
Abdominal pain[b]	13	1.5

Table 20: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275

Adverse Reaction	OPDIVO (n=270)	
	All Grades (%)	Grades 3-4 (%)
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 21: 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. OPDIVO 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 22 and 23 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 22: 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 23: 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 was evaluated in a 154-patient subgroup of patients with HCC and Child-Pugh A cirrhosis who progressed on or were intolerant to sorafenib enrolled in CHECKMATE-040, a multicenter, open-label trial~~.~~ *[see Clinical Studies (14.10)]*. Patients were required to have an AST and ALT ~~of no more than five times the upper limit of normal~~≤5 x ULN and total bilirubin ~~of less than~~ ≤3~~-~~ mg/dL. The median duration of exposure to OPDIVO was 6 months.

The toxicity profile observed in 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.

~~**10.11.1 Postmarketing Experience**~~

~~The following adverse reactions have been identified during post approval 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 disorders*: Vogt-Koyanagi-Harada (VKH) syndrome~~

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

~~6.3~~6.2 Immunogenicity

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

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

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

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 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.

There was no evidence of increased incidence of infusion-related reactions or effects on efficacy 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

Reporting of suspected adverse reactions

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

~~(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).~~

https://sideeffects.health.gov.il

~~7 DRUG INTERACTIONS~~

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

…

8.2 Lactation

Risk Summary

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

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

8.4 Pediatric Use

The safety and effectiveness of OPDIVO 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. ~~The recommended dose in pediatric patients 12 years of age or greater for this indication is the same as that in adults~~ *[see Dosage and Administration (2.~~7~~1), Adverse Reactions (6.1), Clinical Pharmacology (12.3), ~~and~~ Clinical Studies (14~~)]~~ .9)].*

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

8.5 Geriatric Use

…

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, ~~and~~ CHECKMATE-142, ~~and~~ 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.

~~8.6 Renal Impairment~~

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

~~8.7 Hepatic Impairment~~

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

~~10 OVERDOSAGE~~

~~There is no information on overdosage with OPDIVO.~~

….

16 HOW SUPPLIED/STORAGE AND HANDLING

…

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 ~~4h~~8h of the total 24h can be at room temperature 20°C to 25°C and room light – the maximum ~~4h~~8h period under room temperature and room light conditions should be inclusive of the product administration period).

…

עדכונים מהותיים בעלון לצרכן:

~~התכשיר מיועד לילדים מעל גיל 12 לטיפול בסרטן מעי גס גרורתי המבטא dMMR או MSI-H בלבד.~~ **~~לא הוכחה היעילות והבטיחות בילדים מתחת לגיל 18 ביתר ההתוויות המאושרות.~~**

1. למה מיועדת התרופה?

אופדיבו ניתנת לטיפול ב:

- **סרטן עור מסוג מלנומה**
  - אופדיבו ~~ניתנת~~כטיפול יחיד או בשילוב עם איפילימומאב (Ipilimumab) ניתנת למבוגרים במקרים בהם המלנומה מפושטת או מלנומה אשר לא ניתן להסירה באמצעות ניתוח (מלנומה מתקדמת).
  ~~אופדיבו בשילוב עם יירבוי Yervoy (Ipilimumab) ניתנת לטיפול בחולי מלנומה מפושטת או מלנומה אשר לא ניתן להסירה בניתוח (מלנומה מתקדמת).~~
  - אופדיבו ניתנת לטיפול במלנומה לאחר כריתה מלאה (טיפול Adjuvant)
- ....
- **סרטן ריאות גרורתי מסוג תאים קטנים** (small cell lung cancer) עבור חולים שמחלתם התקדמה לאחר טיפול בכימותרפיה המבוססת על פלטינום ולפחות קו טיפול אחר נוסף.
- **סרטן תאי הכליה** (הנקרא renal cell carcinoma)
  - אופדיבו כטיפול יחיד ניתנת לטיפול בחולי סרטן תאי כליה מתקדם שקיבלו טיפול אנטי-אנגיוגני קודם.
  - אופדיבו בשילוב עם איפילימומאב (Ipilimumab) ניתנת לטיפול בחולי סרטן כליה מתקדם, בעלי דרגת סיכון בינונית או גבוהה, שלא טופלו בעבר.
- **הודג'קין לימפומה מסוג קלאסי (סוג של סרטן הדם)**
אופדיבו ניתנת לטיפול במבוגרים במקרים של סרטן שחזר או התפשט לאחר:
- השתלת תאי גזע ממקור עצמוני (אוטולוגית), וקבלת תרופה בשם אדסטריס (brentuximab vedotin) ~~לאחר השתלת תאי גזע.~~ או
- לאחר קבלת 3 או יותר סוגי טיפולים כולל השתלת תאי גזע ממקור עצמוני (אוטולוגית).
- ....
- **סרטן המעי הגס או החלחולת הגרורתי במבוגרים וילדים מגיל 12 ומעלה**
אופדיבו ניתנת כטיפול יחיד או בשילוב עם איפילימומאב (Ipilimumab) לחולים שמחלתם התקדמה לאחר טיפול בפלואורופירימידין, אוקסליפלטין, ואירינוטקאן ושמחלתם מבטאת dMMR או MSI-H.

...

2. לפני השימוש בתרופה:

...

אזהרות מיוחדות הנוגעות לשימוש בתרופה~~:~~
לפני הטיפול באופדיבו, ספר לרופא אם:
- הינך סובל מבעיות הקשורות במערכת החיסון כגון מחלת קרוהן, דלקת כיבית של המעי הגס או זאבת (לופוס)

.....

ילדים ומתבגרים:
לא קיים מידע לגבי יעילות ובטיחות אופדיבו :
- בילדים מתחת לגיל 12 עם סרטן מעי גס וחלחולת גרורתי המבטא dMMR או MSI-H, **או**

- בילדים מתחת לגיל 18 לטיפול ביתר סוגי הסרטן

....

היריון והנקה:
אופדיבו עלולה לפגוע בעוברך.
נשים היכולות להרות ~~צריכות~~:
על הרופא המטפל לערוך בדיקת היריון לפני שאת מתחילה לקבל אופדיבו.

- עלייך להשתמש באמצעי מניעה יעיל במהלך הטיפול ולפחות במשך 5 חודשים לאחר מתן המנה האחרונה של אופדיבו. היוועצי ברופא המטפל שלך לגבי אמצעי המניעה בהם תוכלי להשתמש בתקופה זו.
- ....

...

3. כיצד תשתמש בתרופה?

...

- אופדיבו ניתנת ע"י הצוות הרפואי ישירות לווריד באמצעות צינורית תוך ורידית במשך 60 דקות או 30 דקות, בהתאם למינון ולתדירות שיקבע הרופא.
- אופדיבו בדרך כלל ניתנת כל שבועיים או כל 4 שבועות תלוי במנה שאתה מקבל.
- בטיפול משולב של אופדיבו עם יירבוי (Ipilimumab), התרופות תינתנה באותו היום, בדרך כלל כל 3 שבועות. סה"כ 4 מנות טיפול. לאחר מכן, אופדיבו תינתן לבד כל שבועיים או כל 4 שבועות תלוי במנה שאתה מקבל.
- ...

אין לעבור על המנה המומלצת

...

4. תופעות לוואי:

...
תופעות הלוואי השכיחות ביותר במתן משולב של אופדיבו עם יירבוי Yervoy (Ipilimumab) הן:
...

- כאב בטן

...

Information for Healthcare professionals:

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).
- When administered with ipilimumab, administer OPDIVO first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not coadminister other drugs through the same intravenous line.