פברואר 2021

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 באדום, מחיקת טקסט מסומנת בכחול):

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

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

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.

בפירוט שלהלן כלולים **העדכונים המהותיים בלבד** (טקסט שנוסף מסומן באדום עם קו תחתי, טקסט שהוסר מסומן ~~בכחול~~ עם קו אמצעי).

למידע מלא על התרופה יש לעיין בעלון לרופא ובעלון לצרכן כפי שאושרו על ידי משרד הבריאות.

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

בכבוד רב,
שירן קלאורה
רוקחת ממונה

עדכונים מהותיים בעלון לרופא:

1 INDICATIONS AND USAGE

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1.3 Metastatic Non-Small Cell Lung Cancer

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

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1.10 Hepatocellular Carcinoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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

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

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

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

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

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2.3 PREPARATION AND ADMINISTRATION

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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~~ Administer OPDIVO in combination with other therapeutic agents as follows:
  - With ipilimumab~~, :~~ administer OPDIVO first followed by ipilimumab on the same day.
  - With platinum-doublet chemotherapy: administer OPDIVO first followed by platinum doublet chemotherapy on the same day
  - With ipilimumab and platinum-doublet chemotherapy: administer OPDIVO first followed by ipilimumab and then platinum-doublet chemotherapy on the same day.
- Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not co-administer other drugs through the same intravenous line.

5 WARNINGS AND PRECAUTIONS

~~5.1 Immune-Mediated Pneumonitis~~

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

~~Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis every 2 to 3 days for mild (Grade 1) and daily for moderate (Grade 2) pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.2)]*.~~

~~OPDIVO as a Single Agent~~

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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. Median time to onset 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

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

Monitor patients for signs and symptoms of colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents.

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.

Withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon re-initiation of OPDIVO *[see Dosage and Administration (2.2)]*.

When administered in combination with ipilimumab, withhold OPDIVO and ipilimumab for moderate colitis (Grade 2). Permanently discontinue OPDIVO and ipilimumab for severe or life-threatening (Grade 3 or 4) colitis or for recurrent colitis *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

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

high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 16% of patients had recurrence of colitis after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with 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. Median time to onset 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

OPDIVO can cause immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology. Monitor patients for abnormal liver tests prior to and periodically during treatment. Increase frequency monitoring to every 3 days for moderate (Grade 2) and to every 1 to 2 days for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations.

For patients without hepatocellular carcinoma (HCC): withhold OPDIVO for moderate (Grade 2) immune-mediated hepatitis and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.2)]*.

For patients with HCC, permanently discontinue, withhold, or continue OPDIVO based on severity of immune-mediated hepatitis and baseline AST and ALT levels as described in Table 3 *[see Dosage and Administration (2.2)]*. In addition, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper when OPDIVO is withheld or discontinued due to immune-mediated hepatitis.

OPDIVO as a Single Agent

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

corticosteroids. Complete resolution occurred in 74% of patients. Approximately 29% of patients had recurrence of hepatitis after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Immune-mediated hepatitis occurred in 13% (51/407) of patients 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

OPDIVO can cause immune-mediated hypophysitis. Monitor patients for signs and symptoms of hypophysitis. Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3). Permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Hypophysitis occurred in 9% (36/407) of patients 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

OPDIVO can cause immune-mediated adrenal insufficiency. Monitor patients for signs and symptoms of adrenal insufficiency. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Adrenal insufficiency occurred in 5% (21/407) of patients 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

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients 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 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

OPDIVO can cause Type 1 diabetes mellitus. Monitor for hyperglycemia. Withhold OPDIVO in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Diabetes occurred in 1.5% (6/407) of patients 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

OPDIVO can cause immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology. Monitor patients for elevated serum creatinine prior to and periodically during treatment.

Monitor creatinine weekly for mild (Grade 1), every 2-3 days for moderate (Grade 2) or severe (Grade 3) and daily for life-threatening (Grade 4) increased serum creatinine.

Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents.

Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine. Permanently discontinue OPDIVO for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients 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

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue OPDIVO *[see Dosage and Administration (2.2)]*.

For immune-mediated rash, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Immune-mediated rash occurred in 22.6% (92/407) of patients 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 can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis *[see Dosage and Administration (2.2)]*.

~~OPDIVO as a Single Agent~~

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

~~OPDIVO with Ipilimumab~~

~~*OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg*~~

~~Encephalitis occurred in one patient (0.2%) with melanoma who received OPDIVO 1 mg/kg with ipilimumab 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).~~

~~5.8 Other Immune-Mediated Adverse Reactions~~

~~OPDIVO can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.2)]*.~~

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

~~If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients who received OPDIVO or OPDIVO in combination with ipilimumab and may require treatment with systemic steroids to reduce the risk of permanent vision loss.~~

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

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

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

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical

manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

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

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

Immune-Mediated Pneumonitis

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

OPDIVO as a Single Agent

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

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

Immune-Mediated Colitis

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

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

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

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

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

Immune-Mediated Hepatitis

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

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

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated hepatitis occurred in 7% (48/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.6% and withholding of OPDIVO with ipilimumab in 2.6% of patients with RCC or CRC.

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

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

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

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

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

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

Hypophysitis

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

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

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

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

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

Thyroid Disorders

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

Thyroiditis

OPDIVO as a Single Agent

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

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

Hyperthyroidism

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

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

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

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

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

Hypothyroidism

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

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

Approximately 89% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 2.2% (2/91) of patients with hypothyroidism. Hypothyroidism resolved in 41% of the 91 patients. Of

the 4 patients in whom OPDIVO with ipilimumab was withheld for hypothyroidism, 2 reinitiated treatment after symptom improvement; of these, none had recurrence of hypothyroidism.

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

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

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

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

OPDIVO as a Single Agent

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

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

Immune-Mediated Nephritis with Renal Dysfunction

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

OPDIVO as a Single Agent

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

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

Immune-Mediated Dermatologic Adverse Reactions

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

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

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

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

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

Other Immune-Mediated Adverse Reactions

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

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

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

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss

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

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

Endocrine: Hypoparathyroidism

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

5.2~~9~~ Infusion-Related Reactions

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

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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~~ and in 8% (4/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks.

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6 Adverse Reactions

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

- Severe and Fatal Immune-Mediated ~~Pneumonitis~~ Adverse Reactions *[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~~2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.~~10~~3)]*

6.1 Clinical Trials Experience

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

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

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Metastatic Non-Small Cell Lung Cancer

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

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

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

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

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

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

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

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

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

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

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

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

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

[f] Includes pruritus and generalized pruritus

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

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

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

[j] Includes dizziness, vertigo and positional vertigo

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

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

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

Second-line Treatment of Metastatic NSCLC

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Squamous Cell Carcinoma of the Head and Neck

The safety of OPDIVO was evaluated in CHECKMATE-141, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCHN with progression during or within 6 months of receiving prior platinum-based therapy *[see Clinical Studies (14.7)]*. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma). Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=236) or investigator's choice of either~~:~~

- cetuximab (~~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).

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Hepatocellular Carcinoma

The safety of OPDIVO 3 mg/kg every 2 weeks as a single agent was evaluated in a 154-patient subgroup of patients with HCC and Child-Pugh Class A cirrhosis who progressed on or were intolerant to sorafenib. These patients enrolled in Cohorts 1 and 2 of CHECKMATE-040, a multicenter, multiple cohort, open-label trial *[see Clinical Studies (14.10)]*. Patients were required to have an AST and ALT ≤5 x ULN and total bilirubin <3 mg/dL. The median duration of exposure to OPDIVO was ~~6~~ 5 months (range: 0 to 22+ months). Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, pneumonia, and anemia.

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

The safety of OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg was evaluated in a subgroup comprising 49 patients with HCC and Child-Pugh Class A cirrhosis enrolled in Cohort 4 of the CHECKMATE-040 trial who progressed on or were intolerant to sorafenib. OPDIVO and ipilimumab were administered every 3 weeks for 4 doses, followed by single-agent OPDIVO 240 mg every 2 weeks until disease progression or unacceptable toxicity. During the OPDIVO and ipilimumab combination period, 33 of 49 (67%) patients received all 4 planned doses of OPDIVO and ipilimumab. During the entire treatment period, the median duration of exposure to OPDIVO was 5.1 months (range: 0 to 35+ months) and to ipilimumab was 2.1 months (range: 0 to 4.5 months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

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

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

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

Adverse Reaction	OPDIVO and Ipilimumab (n=49)		OPDIVO (n=154)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash	53	8	26	0.6
Pruritus	53	4	27	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain	41	2	36	1.9
Arthralgia	10	0	8	0.6
Gastrointestinal				
Diarrhea	39	4	27	1.3
Abdominal pain	22	6	34	3.9
Nausea	20	0	16	0
Ascites	14	6	9	2.6
Constipation	14	0	16	0
Dry mouth	12	0	9	0
Dyspepsia	12	2	8	0
Vomiting	12	2	14	0
Stomatitis	10	0	7	0
Abdominal distension	8	0	11	0
Respiratory, Thoracic and Mediastinal				
Cough	37	0	23	0
Dyspnea	14	0	13	1.9
Pneumonitis	10	2	1.3	0.6
Metabolism and Nutrition				
Decreased appetite	35	2	22	1.3
General				
Fatigue	27	2	38	3.2
Pyrexia	27	0	18	0.6
Malaise	18	2	6.5	0
Edema	16	2	12	0
Influenza-like illness	14	0	9	0
Chills	10	0	3.9	0
Nervous System				
Headache	22	0	11	0.6
Dizziness	20	0	9	0
Endocrine				
Hypothyroidism	20	0	4.5	0
Adrenal insufficiency	18	4	0.6	0
Investigations				
Weight decreased	20	0	7	0
Psychiatric				
Insomnia	18	0	10	0
Blood and Lymphatic System				
Anemia	10	4	19	2.6
Infections				
Influenza	10	2	1.9	0
Upper Respiratory Tract Infection	6	0	12	0
Vascular				
Hypotension	10	0	0.6	0

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

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

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

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

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

6.2 Immunogenicity

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

Of the patients with hepatocellular carcinoma who were treated with OPDIVO and ipilimumab every 3 weeks for 4 doses followed by OPDIVO every 2 weeks and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 45% (20/44) with OPDIVO 3 mg/kg followed by ipilimumab 1

mg/kg and 56% (27/48) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg; the corresponding incidence of neutralizing antibodies against nivolumab was 14% (6/44) and 23% (11/48), respectively.

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

There was no evidence of increased incidence of infusion-related reactions ~~or effects on efficacy~~ with anti-nivolumab antibody development.

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8.5 Geriatric Use

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

Of the 361 patients randomized to OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

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12.3 PHARMACOKINETICS

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Drug Interaction Studies

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

~~When OPDIVO 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab and ipilimumab were unchanged.~~

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

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

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

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

14 CLINICAL STUDIES

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14.3 Metastatic Non-Small Cell Lung Cancer

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

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

Patients were randomized 1:1 to receive either:

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

Platinum-doublet chemotherapy consisted of either carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m^2, or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent as part of the study. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

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

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

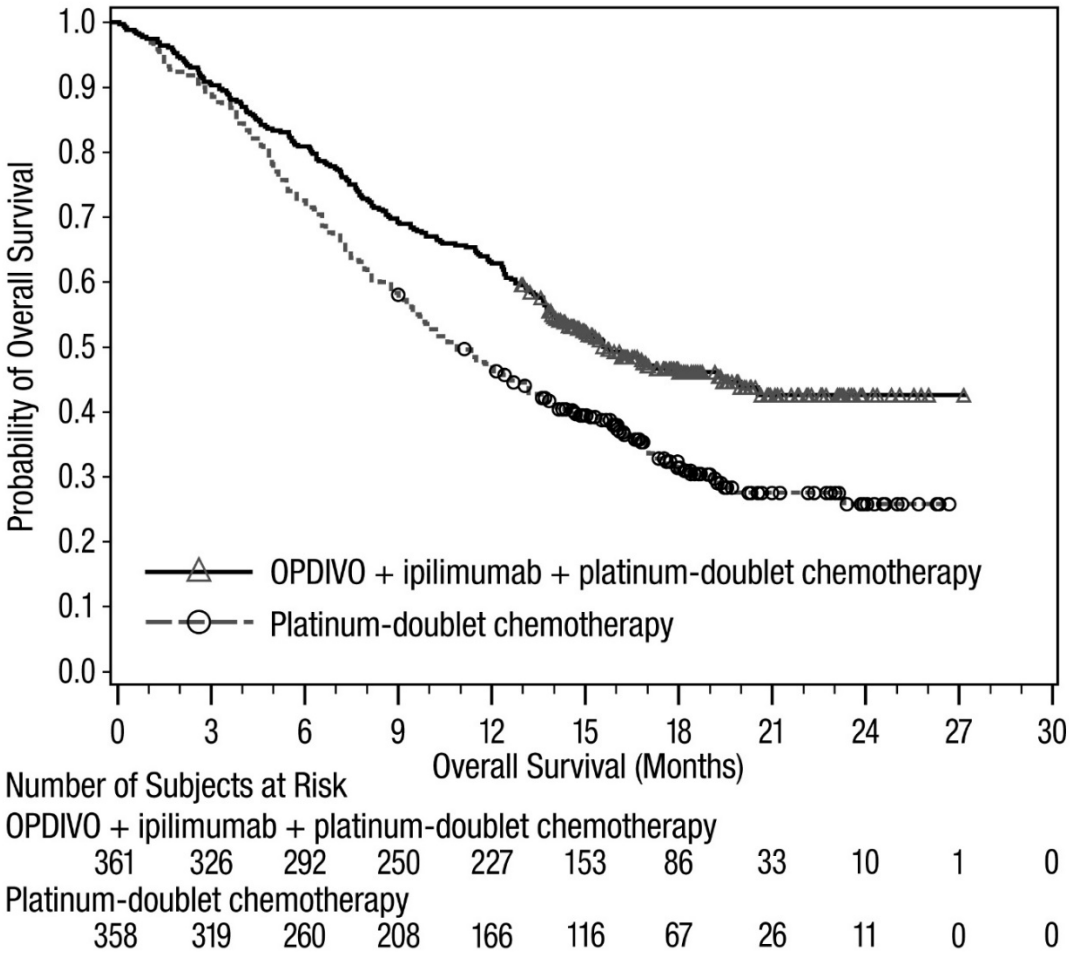
Table 31: Efficacy Results - CHECKMATE-9LA

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

[a] Based on a stratified Cox proportional hazard model.
[b] p-value is compared with the allocated alpha of 0.033 for this interim analysis.
[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.
[d] Kaplan-Meier estimate.
[e] Confidence interval based on the Clopper and Pearson Method.
[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.

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

Figure 5: Overall Survival - CHECKMATE-9LA



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14.10 Hepatocellular Carcinoma

~~The efficacy of OPDIVO was evaluated in a 154-patient subgroup of~~ CHECKMATE-040 (NCT01658878), was a multicenter, multiple cohort, open-label trial ~~conducted~~ that evaluated the efficacy of OPDIVO as a single agent and in combination with ipilimumab in patients with hepatocellular carcinoma (HCC) who progressed on or were intolerant to sorafenib. Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible. ~~Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks.~~

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

The ~~trial population characteristics were:~~ efficacy of OPDIVO as a single agent was evaluated in a pooled subgroup of 154 patients across Cohorts 1 and 2 who received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until disease progression or unacceptable toxicity. The median age was 63 years (range: 19 to 81), 77% were male, and 46% were White. ~~Across the population,~~ Baseline ECOG performance status was 0 (65%) or 1 (35%). Thirty-one percent (31%) of patients had active HBV infection, 21% had active HCV infection, and 49%

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

Efficacy results are shown in Table 37.

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

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

Table 37: Efficacy Results - CHECKMATE-040

		OPDIVO (n = 154)
Overall Response Rate[a], n (%), RECIST v1.1		22 (14.3%)
(95% CI)[b]		(9.2, 20.8)
Complete response	3 (1.9%)	
Partial response		19 (12.3%)
Duration of Response, RECIST v1.1		(n=22)
Range (months)		(3.2, 38.2+)
% with duration ≥6 months		91%
% with duration ≥12 months		55%
Overall Response Rate[a], n (%), mRECIST		28 (18.2%)
(95% CI)[b]		(12.4, 25.2)
Complete response		5 (3.2%)
Partial response		23 (14.9%)

[a] Overall response rate confirmed by BICR.

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

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

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

[a] Confirmed by BICR.

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

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עדכונים מהותיים בעלון לצרכן:

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1. למה מיועדת התרופה?

...

- **סרטן ריאות גרורתי מסוג תאים שאינם קטנים** (non-small cell lung cancer)
  - אופדיבו, בשילוב עם איפילימומאב (Ipilimumab) ושני מחזורי טיפול של כימותרפיה המכילה פלטינום ותרופת כימותרפיה נוספת, ניתנת כקו טיפול ראשון לחולים מבוגרים עם סרטן ריאות מפושט או חוזר מסוג תאים שאינם קטנים, וללא שינויים בגנים EGFR או ALK בגידול.
  - אופדיבו ניתנת לטיפול ~~עבור~~ בחולים שמחלתם התקדמה תוך כדי טיפול או לאחר טיפול בכימותרפיה המבוססת על פלטינום.

...

- **סרטן כבד (hepatocellular carcinoma)**

אופדיבו, ~~ניתנת~~ כטיפול יחיד או בשילוב עם איפילימומאב (Ipilimumab), ניתנת לחולים עם פגיעה כבדית קלה (child-pugh A) לאחר טיפול ב-סוראפניב (sorafenib).

...

2. לפני השימוש בתרופה:

...

אזהרות מיוחדות הנוגעות לשימוש בתרופה
לפני הטיפול באופדיבו, ספר לרופא על כל מצבך הרפואי, כולל אם:

- הינך סובל מבעיות הקשורות במערכת החיסון כגון מחלת קרוהן, דלקת כיבית של המעי הגס או זאבת (לופוס)
- עברת השתלת איברים
- ~~הינך סובל מבעיות נשימה או בעיות בריאות~~
- ~~הינך סובל מבעיות בכבד~~
- ~~הינך סובל מבעיה רפואית אחרת כלשהי~~
- עברת או שאתה עומד לעבור השתלת תאי גזע, כאשר ההשתלה היא מתורם (אלוגנאית)
- עברת בעבר טיפול קרינתי לאזור בית החזה וקיבלת תרופות אחרות הדומות לאופדיבו
- הינך סובל ממצב המשפיע על מערכת העצבים שלך כגון חולשת שרירים חמורה (מיאסתניה גרביס) או תסמונת בשם Guillain-barre
- הינך בהיריון או מתכנן להיכנס להיריון (ראי סעיף "היריון והנקה")
- את מיניקה או בכוונתך להניק (ראי סעיף "היריון והנקה")

ילדים ומתבגרים:
לא קיים מידע לגבי יעילות ובטיחות אופדיבו:

- בילדים מתחת לגיל 12 עם סרטן מעי גס וחלחולת גרורתי המבטא dMMR (Mismatch Repair Deficient) או MSI-H (Microsatellite Instability-High), **או**
- בילדים מתחת לגיל 18 לטיפול ביתר סוגי הסרטן

...

אינטראקציות/תגובות בין תרופתיות:
אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.
~~דע את התרופות שהינך נוטל. שמור רשימה של התרופות שלך והראה לרופא המטפל והרוקח עם קבלת תרופה חדשה.~~

...

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.
- כאשר אופדיבו ~~בדרך כלל~~ ניתנת לבד, היא ניתנת בדרך כלל כל שבועיים או כל 4 שבועות תלוי במנה שאתה מקבל.
- כאשר אופדיבו ניתנת בטיפול משולב ~~של אופדיבו~~ עם יירבוי (Ipilimumab), למעט עבור טיפול בסרטן ריאות גרורתי מסוג תאים שאינם קטנים (non-small cell lung cancer)

- ~~התרופות תינתנה באותו היום,~~אופדיבו תינתן בדרך כלל כל 3 שבועות~~.~~ , לסה"כ 4 מנות טיפול. יירבוי (Ipilimumab) תינתן באותו היום. לאחר מכן, אופדיבו תינתן לבד כל שבועיים או כל 4 שבועות ~~תלוי~~ כתלות במנה שאתה מקבל.
- עבור טיפול בסרטן ריאות גרורתי מסוג תאים שאינם קטנים (non-small cell lung cancer) אשר התפשט לאזורים נוספים בגוף, כשאופדיבו ניתנת בטיפול משולב עם יירבוי (ipilimumab), אופדיבו תינתן כל 3 שבועות, ויירבוי (ipilimumab) תינתן כל 6 שבועות למשך שנתיים לכל היותר. תזדקק גם למתן של טיפול כימותרפי כל 3 שבועות למשך שני מחזורי טיפול.

...

4. תופעות לוואי:

...

תופעות לוואי חמורות ~~של~~ בזמן מתן העירוי
דווח לרופא המטפל או לאחות מיידית, אם אתה חש אחד מהתסמינים המופיעים מטה בזמן קבלת עירוי של אופדיבו:

- צמרמורות או רעד
- גרד או פריחה
- הסמקה
- ~~קשיי נשימה~~קוצר נשימה או צפצופים בעת הנשימה
- סחרחורת
- תחושת ~~התעלפות~~עילפון
- חום
- ~~תחושת התעלפות~~
- ~~כאב בגב או בצוואר~~

אופדיבו הינה תרופה המטפלת בסוגי סרטן מסוימים על-ידי שפעול מערכת החיסון שלך. אופדיבו עלולה לגרום למערכת החיסון שלך לתקוף רקמות ואיברים בריאים בכל איזור בגוף שלך ולהשפיע על אופן פעילותם. פעילות זו עלולה לגרום לתופעות לוואי חמורות או ~~מסכנות חיים~~ להביא למוות. תופעות לוואי אלה עלולות להופיע בכל שלב בזמן הטיפול או אף לאחר סיום הטיפול. ייתכן ותחווה יותר מתופעת לוואי אחת באותו הזמן.
חלק מתופעות הלוואי הללו עלולות להתרחש בתדירות גבוהה יותר כשאופדיבו ניתנת בשילוב עם יירבוי Yervoy (Ipilimumab).

פנה מיד לרופא המטפל אם הינך חווה סימנים או תסמינים חדשים כלשהם או אם יש החמרה בסימנים או בתסמינים, כולל: ~~תסמין כלשהו מהתסמינים הבאים או אם ישנה החמרה בתסמינים הבאים:~~

בעיות בריאה. ~~(פנאומוניטיס - דלקת ברקמת הריאה).~~ ~~תסמינים של דלקת ברקמת הריאה (פנאומוניטיס) יכולים לכלול:~~

- שיעול חדש או החמרה בשיעול
- ~~כאב בחזה~~
- קוצר נשימה
- כאבים בחזה

בעיות במעיים. ~~(קוליטיס - דלקת במעי הגס) העלולות לגרום להופעת קרעים או חירור המעי שלך.~~ ~~סימנים ותסמינים של דלקת במעי הגס (קוליטיס) יכולים לכלול:~~

- שלשול (צואה רכה) או מספר פעולות מעיים ~~רב~~שכיח יותר מהרגיל
- ~~דם בצואה או~~ צואה שחורה הדומה לזפת, דביקה, ~~בצבע כהה, הדומה לזפת~~ או צואה עם דם או ריר
- כאב חמור או רגישות חמורה באזור הבטן

בעיות בכבד. ~~(דלקת הכבד/צהבת).~~ ~~סימנים ותסמינים של דלקת הכבד יכולים לכלול:~~

- הצהבה של העור שלך או של לובן העין שלך
- בחילה או הקאה חמורה
- כאב בצד ימין של ה~~אזור הקיבה (ב~~בטן~~)~~
- ~~שתנניות~~
- שתן ~~בצבע~~כהה (גוון של תה)
- נטייה לדימום או לחבורות ~~יותר בקלות מהרגיל~~ביתר קלות
- ~~ירידה בתחושת הרעב~~
- ~~אנרגיה ירודה~~

בעיות בבלוטות שמייצרות הורמונים. ~~**(במיוחד בבלוטת התריס, בלוטת יותרת המוח, בלוטות יותרת הכליה ובלבלב).** סימנים ותסמינים של תפקוד לא תקין של הבלוטות המייצרות הורמונים יכולים לכלול:~~

- כאבי ראש שאינם חולפים או כאבי ראש לא אופייניים
- רגישות בעיניים לאור
- בעיות עיניים
- קצב לב מהיר
- הזעה מוגברת
- עייפות קיצונית
- עלייה במשקל או איבוד משקל
- ~~סחרחורת או עילפון~~
- הרגשת צמאון או רעב מוגברת מהרגיל
- ~~שינויים במצב הרוח או שינויי התנהגות, כגון ירידה בחשק המיני, עצבנות או שכחה~~
- מתן שתן בתדירות גבוהה מהרגיל
- נשירת שיער
- תחושת קור
- עצירות
- שינוי בקול לקול עמוק ונמוך
- סחרחורת או עילפון
- ~~צימאון יתר או ריבוי שתן~~
- שינויים במצב הרוח או שינויי התנהגות, כגון ירידה בחשק המיני, עצבנות או שכחה

בעיות בכליה. ~~**כולל נפריטיס (דלקת הכליות) וכשל כלייתי.** סימנים של בעיות בכליה יכולים לכלול:~~

- ירידה בכמות השתן שלך
- הופעת דם בשתן שלך
- נפיחות בקרסוליים שלך
- איבוד תיאבון

בעיות בעור. ~~סימנים לכך עלולים להיות:~~

- פריחה
- גרד
- הופעת שלפוחיות בעור או קילופים בעור
- פצעים או כיבים כואבים בחלל הפה או ב~~רקמות ריריות אחרות~~אף, גרון או באזור איברי המין.

בעיות עלולות גם להופיע באיברים ורקמות אחרים. אלו לא כל הסימנים והתסמינים של בעיות במערכת החיסון העלולות להופיע בשימוש עם אופדיבו. פנה מיד לרופא המטפל עבור סימנים או תסמינים חדשים כלשהם או אם יש החמרה בסימנים או בתסמינים, היכולים לכלול:

- כאבים בחזה, קצב לב לא סדיר, קוצר נשימה או נפיחות בקרסוליים
- בלבול, ישנוניות, בעיות זיכרון, שינויים במצב הרוח או שינויי התנהגות, צוואר נוקשה, בעיות בשיווי המשקל, עקצוץ או חוסר תחושה בזרועות או ברגליים.
- ראייה כפולה, ראייה מטושטשת, רגישות לאור, כאב עיניים, שינויים בראייה
- כאבי שרירים או חולשה מתמשכים או חמורים, התכווציות שרירים
- ספירה נמוכה של תאי דם אדומים, נטייה לחבורות

~~**דלקת של רקמת המוח (אנצפליטיס).** סימנים ותסמינים של דלקת של רקמת המוח יכולים לכלול:~~

- ~~כאב ראש~~
- ~~חום~~
- ~~עייפות או חולשה~~
- ~~בלבול~~
- ~~בעיות זיכרון~~
- ~~ישנוניות~~
- ~~שמיעה או ראיית דברים שאינם קיימים (הזיות)~~
- ~~פרכוסים~~
- ~~צוואר נוקשה~~

~~**בעיות באיברים נוספים.** סימנים לכך יכולים להיות:~~

- ~~שינויים בראייה~~

- ~~כאבי שרירים או מפרקים מתמשכים או חמורים~~
- ~~חולשת שרירים חמורה~~
- ~~כאב בחזה~~

...

תופעות לוואי חמורות נוספות:
סיבוכי השתלת תאי גזע כאשר ההשתלה היא מתורם (אלוגנאית).
הסיבוכים הללו עלולים להיות חמורים ולהביא למוות. הסיבוכים עלולים להופיע אם ההשתלה נעשתה לפני או אחרי הטיפול באופדיבו. הרופא המטפל שלך יבצע מעקב לסימנים של סיבוכים אם תעבור השתלת תאי גזע מתורם.

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תופעות הלוואי השכיחות ביותר במתן משולב של אופדיבו עם יירבוי (Ipilimumab) Yervoy ~~הן~~כוללות:
- עייפות
- ~~פריחה~~
- שלשול
- פריחה
- גרד
- בחילה
- ~~חום~~
- כאב בשרירים, בעצמות ובמפרקים
- חום
- ~~זיהומים בדרכי הנשימה העליונות~~
- ~~גרד~~
- ~~כאב בטן~~
- ~~הקאה~~
- שיעול
- ירידה בתאבון
- הקאות~~ה~~
- כאב בטן
- קוצר נשימה
- זיהומים בדרכי הנשימה העליונות
- כאב ראש
- רמות נמוכות של הורמון התירואיד (היפותירואידיזם)
- ירידה במשקל
- סחרחורת

תופעות הלוואי השכיחות ביותר במתן משולב של אופדיבו עם יירבוי (Ipilimumab) Yervoy וכימותרפיה כוללות:
- עייפות
- כאב בשרירים, בעצמות ובמפרקים
- בחילה
- שלשול
- פריחה
- ירידה בתאבון
- עצירות
- גרד

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Preparation and Administration

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Administration

- Administer the infusion over 30 minutes or 60 minutes depending on the dose 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~~ Administer OPDIVO in combination with other therapeutic agents as follows:
    - With ipilimumab~~,~~ : administer OPDIVO first followed by ipilimumab on the same day.
    - With platinum-doublet chemotherapy: administer OPDIVO first followed by platinum doublet chemotherapy on the same day
    - With ipilimumab and platinum-doublet chemotherapy: administer OPDIVO first followed by ipilimumab and then platinum-doublet chemotherapy on the same day.

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