הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

ר _____29.11.2015_____

כשיר באנגלית ומספר הרישום __00-153-55-34333 Opdivo # _____

על הרישום BRISTOL-MYERS SQUIBB (ISRAEL)

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות נובעות עקב הוספת מידע בעקבות הרחבת התוויה

ההחמרות המבוקשות		
טקסט נוכחי	**טקסט חדש**	**ק בעלון**
Unresectable or Metastatic Melanoma • OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with (unresectable or metastatic) melanoma *[see Clinical Studies (14.1)]*. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in ~~the~~ confirmatory trials. • OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with BRAF V600 wild-type, advanced (unresectable or metastatic) melanoma *[see Clinical Studies (14.1)]*. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification	**Unresectable or Metastatic Melanoma** • OPDIVO® (nivolumab) is indicated for the treatment of patients with (unresectable or metastatic) melanoma *[see Clinical Studies (14.1)]*. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. **Metastatic Non-Small Cell Lung Cancer** OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy *[see Clinical Studies (14.2)]*.	Indication Usage

מעוצב:צבע גופן: שחור
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מעוצב:צבע גופן: שחור
מעוצב:גופן: (ברירת מחדל) lairA, 12 נק', מודגש, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: weN semiT namoR, 10 נק'
מעוצב:גופן: צבע גופן: שחור, גופן עבור עברית ושפות אחרות: weN semiT namoR, 10 נק'
מעוצב:גופן: (ברירת מחדל) semiT namoR weN, 12 נק', גופן עבור עברית ושפות אחרות: semiT namoR weN semiT, 10 נק'
מעוצב:גופן: (ברירת מחדל) semiT namoR weN, 12 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן)
מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן)
מעוצב:גופן: (ברירת מחדל) semiT namoR weN, 12 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן)
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מעוצב:צבע גופן: אוטומטי, סמן
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מעוצב:צבע גופן: שחור, סמן
מעוצב:צבע גופן: אוטומטי, סמן
מעוצב:צבע גופן: שחור, סמן
מעוצב:סמן
מעוצב:צבע גופן: שחור, סמן
מעוצב:סמן

מועצב:גופן: (ברירת מחדל) lairA, מודגש, צבע גופן: שחור

מועצב:גופן: צבע גופן: שחור, גופן עבור עברית ושפות אחרות: weN semiT namoR, 10 נק'

מועצב:גופן: נטוי, צבע גופן: אוטומטי

מועצב:צבע גופן: שחור

מועצב:צבע גופן: שחור, לא כתב עילי/כתב תחתי

מועצב:צבע גופן: שחור

מועצב:צבע גופן: שחור

מועצב:גופן: (ברירת מחדל) semiT namoR weN, נטוי, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: weN semiT namoR, 10 נק', (אסיאתי) סינית (טיוואן)

מועצב:צבע גופן: אוטומטי

מועצב:לא סמן

מועצב:גופן: (ברירת מחדל) lairA, מודגש, צבע גופן: שחור, רישיות בלבד

מועצב:גופן: (ברירת מחדל) semiT namoR weN, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: weN semiT namoR, 10 נק'

מועצב:צבע גופן: אוטומטי

מועצב:צבע גופן: שחור

מועצב:גופן: (ברירת מחדל) lairA, מודגש, צבע גופן: שחור

מועצב:גופן: צבע גופן: שחור, גופן עבור עברית ושפות אחרות: weN semiT namoR, 10 נק'

מועצב:גופן: 10 נק', מודגש, צבע גופן: אוטומטי, סמן

מועצב:גופן: 10 נק', מודגש, צבע גופן: אוטומטי, סמן

מועצב:גופן: מודגש, צבע גופן: אוטומטי, סמן

מועצב:סמן

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and description of clinical benefit in confirmatory trials.

Metastatic Non-Small Cell Lung Cancer

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy *[see Clinical Studies (14.2)]*.

Renal Cell Carcinoma

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

DOSAGE AND ADMINISTRATION

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

Dose Modifications

Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	

DOSAGE AND ADMINISTRATION

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Dose Modifications

Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity	Dose Modification
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Colitis	Grade 2 or 3 diarrhea or colitis	Withhold dose[a]
	Grade 4 diarrhea or colitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to	Withhold dose[a]

	Single-agent OPDIVO	Withhold dose[a]
	OPDIVO, in combination with ipilimumab	Permanently discontinue
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
~~Colitis~~	~~Grade 2 or 3 diarrhea or colitis~~	~~Withhold dose[a]~~
	~~Grade 4 diarrhea or colitis~~	~~Permanently discontinue~~
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose[a]
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4	Permanently discontinue
	5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose[a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Rash	Grade 3 rash	Withhold dose[a]
	Grade 4 rash	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction	
	First occurrence	Withhold dose[a]

	adrenal insufficiency	
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose[a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Rash	Grade 3 rash	Withhold dose[a]
	Grade 4 rash	Permanently discontinue
Encephalitis	New- onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction	
	First occurrence	Withhold dose[a]
	Recurrence of same Grade 3 adverse reactions	Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse	Permanently discontinue

	Recurrence of same Grade 3 adverse reactions	Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

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

מעוצב:גופן: צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: Calibri, 11 נק', סמן
מעוצב:סמן
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מעוצב:גופן: צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: Calibri, 11 נק', סמן
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מעוצב:סמן

	reactions lasting 12 weeks or longer	

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

~~1~~ WARNINGS AND PRECAUTIONS

~~1.1~~ Immune-Mediated Pneumonitis

Immune-mediated~~Severe~~ pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with OPDIVO treatment. Across ~~the~~ clinical trial experience ~~in 691 patients~~ with solid tumors receiving OPDIVO as a single agent, fatal immune-mediated pneumonitis occurred in 0.3% (5/1590) ~~0.7% (5/691)~~ of patients ~~receiving OPDIVO. No cases of fatal pneumonitis occurred in Trial 1 or Trial 3~~

All ~~five~~ fatal cases occurred in a dose-finding study with OPDIVO doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

Across the clinical trial experience in 188 patients with melanoma who received OPDIVO in combination with ipilimumab, in Trial 4 (n=94) and an additional dose-finding study (n=94), fatal immune-mediated pneumonitis occurred in 0.5% (1/188) of patients. In Trial 4, there were six additional patients who died without resolution of abnormal respiratory findings.

Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis

Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experiencein 691 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.7% (5/691) of patients receiving OPDIVO.No cases of fatal pneumonitis occurred in Trial 1 or Trial 3

All five fatal cases occurred in a dose-finding study with OPDIVO doses of 1 mg/kg (two patients), 3mg/kg (two patients), and 10 mg/kg (one patient).

In Trial 1, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology, occurred in 2.2% (6/268) of patients receiving OPDIVO: one with Grade 3 and five with Grade 2 pneumonitis. The median time to onset for the six cases was 2.2 months (range: 25 days to 3.5 months). In two patients, pneumonitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 pneumonitis led to interruption or permanent discontinuation of OPDIVO in the remaining four patients. All six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day); immune-mediated pneumonitis improved to Grade 0 or 1 with corticosteroids in all six patients. There were two patients with

Warnings
Precautio

מעוצב:כניסה: לפני: 36.0 ס"מ, ללא תבליטים או מספור, עצירות טאב: לא ב 72.1 ס"מ, מיקום: אופקי: מרכז, ביחס ל: שוליים, אנכי: -39.0 ס"מ, ביחס ל: פיסקה, אופקי: 23.0 ס"מ, גלישה סביב

מעוצב:צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: 10 נק'

מעוצב:צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: 10 נק'

מעוצב ...

מעוצב:גופן: namoR weN semiT, לא מודגש, צבע גופן: אוטומטי

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מעוצב:גופן: namoR weN semiT, לא מודגש, צבע גופן: אוטומטי, סמן

מעוצב ...

מעוצב:גופן: namoR weN semiT, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

(Grade 2) pneumonitis *[see Dosage and Administration (2.4)]*. **Melanoma** *OPDIVO as a Single Agent* In Trial 5, pneumonitis occurred in 1.4% (3/206) of patients receiving OPDIVO and in none of the 205 patients receiving dacarbazine. All cases were immune-mediated and Grade 2 in severity. The median time to onset was 2.8 months (range: 2 to 5.1 months). Pneumonitis led to interruption of OPDIVO in all three patients, all received high-dose corticosteroids, and pneumonitis completely resolved. OPDIVO was restarted in two of these patients without recurrence of pneumonitis. *OPDIVO in Combination with Ipilimumab* In Trial 4, pneumonitis, including interstitial lung disease, occurred in 10% (9/94) of patients receiving OPDIVO in combination with ipilimumab and 2.2% (1/46) of patients receiving ipilimumab. Immune-mediated pneumonitis occurred in 6% (6/94) of patients receiving OPDIVO in combination with ipilimumab: Grade 5 (n=1), Grade 3 (n=2), and Grade 2 (n=3) pneumonitis. The median time to onset for the six cases was 2.5 months (range: 1.3 to 4.6 months). In the patient with fatal pneumonitis, the event was diagnosed after discontinuation of OPDIVO in combination with ipilimumab for another immune-mediated adverse reaction; this patient died from pneumonitis more than 30 days after the last dose. The remaining five patients had dose interruption or permanent discontinuation of OPDIVO in combination with ipilimumab. All six patients received high-dose corticosteroids. Immune-mediated pneumonitis completely resolved in the five patients with Grade 2 or 3 pneumonitis. OPDIVO in combination with ipilimumab was restarted for one patient with Grade 2 pneumonitis after complete resolution, and pneumonitis did not recur. **NSCLC**	Grade 2 pneumonitis that completely resolved (defined as complete resolution of symptoms with completion of corticosteroids) and OPDIVO was restarted without recurrence of pneumonitis.In Trial 3, pneumonitis occurred in 6% (7/117) of patients receiving OPDIVO, including five Grade 3 and two Grade 2 cases, all immune-mediated. The median time to onset was 3.3 months (range: 1.4 to 13.5 months). All seven patients discontinued OPDIVO for pneumonitis or another event and all seven patients experienced complete resolution of pneumonitis following receipt of high-dose corticosteroids (at least 40 mg prednisone equivalents per day). Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.2)]*.	

מעוצב:גופן: namoR weN semiT, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: namoR weN semiT, לא מודגש, צבע גופן: שחור, (אסיאתי) סינית (טיוואן)

מעוצב:סמן

מעוצב:גופן: namoR weN semiT, לא מודגש, סמן

מעוצב:גופן: namoR weN semiT, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: נטוי, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', סמן

מעוצב:גופן: namoR weN semiT, לא מודגש, סמן

מעוצב:גופן: namoR weN semiT, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: gnidaeH SMB:2, מיושר לשני הצדדים, כניסה: לפני: 30.2 ס"מ, מרווח בין שורות: מרובה 1.1 שו, מיקום: אופקי: מרכז, ביחס ל: שוליים, אנכי: 39.0- ס"מ, ביחס ל: פיסקה, אופקי: 23.0 ס"מ, גלישה סביב

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:סמן

מעוצב:גופן: לא מודגש, סמן

מעוצב:גופן: לא מודגש, סמן (אסיאתי) סינית (טיוואן), סמן namoR weN semiT

In Trial 3, pneumonitis, including interstitial lung disease, occurred in 3.4% (10/287) of patients receiving OPDIVO. Of these 10 patients, there were five patients with Grade 3, two patients with Grade 2, and three patients with Grade 1 immune-mediated pneumonitis. The median time to onset was 7.2 months (range: 2.7 to 13.1 months). All five patients with Grade 3 and one of two patients with Grade 2 pneumonitis received high-dose corticosteroids and permanently discontinued OPDIVO; two of these seven were documented radiographically to have complete resolution of pneumonitis. One patient with Grade 2 pneumonitis had OPDIVO temporarily withheld, received low-dose corticosteroids, experienced complete resolution, and was retreated without recurrence of pneumonitis.

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

RCC

מעוצב:סמן

מעוצב:גופן: לא מודגש, סמן namoR weN semiT

מעוצב:גופן: לא מודגש, סמן (אסיאתי) סינית (טיוואן), סמן namoR weN semiT

In Trial 6, pneumonitis, including interstitial lung disease, occurred in 5% (21/406) of patients receiving OPDIVO and 18% (73/397) patients receiving everolimus. Immune-mediated pneumonitis occurred in 4.4% (18/406) of patients receiving OPDIVO (one with Grade 4, four with Grade 3, twelve with Grade 2, and one with Grade 1). In two of the patients, pneumonitis occurred after they had received OPDIVO followed by everolimus. One patient with ongoing pneumonitis died due to disease progression. The median time to onset was 3.82 months (range: 2 days to 22.3 months). The median duration was 1.3 months (range: 0.3 to 9.8 months). OPDIVO was permanently discontinued in six patients. Dose delay occurred in nine patients. Seven patients had complete resolution. Among the six patients who resumed OPDIVO, three did not have recurrence of pneumonitis.

מעוצב:גופן: 2 gnidaeH SMB, מיושר לשני הצדדים, מרווח בין שורות: מרובה 1.1 שו, מדורג ממוספר + רמה: 2 + סגנון מספור: 1, 2, 3, ... + התחל מ: 1 + יישור: לימין + מיושר ב: 0 ס"מ + טאב אחרי: 30.2 ס"מ + כניסה ב: 30.2 ס"מ, מיקום: אופקי: מרכז, ביחס ל: שוליים, אנכי: -39.0 ס"מ, ביחס ל: פיסקה, אופקי: 23.0 ס"מ, גלישה סביב

Immune-Mediated Colitis

מעוצב:סמן

Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, can occur with OPDIVO treatment.

Immune-Mediated Colitis

In Trial 1, diarrhea or colitis occurred in 21% (57/268) of

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. When administered as a single agent, withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon restarting OPDIVO *[see Dosage and Administration (2.4)]*. When administered in combination with ipilimumab, withhold OPDIVO for moderate colitis (Grade 2). Permanently discontinue OPDIVO for severe or life-threatening (Grade 3 or 4) colitis or for recurrent colitis upon restarting OPDIVO *[see Dosage and Administration (2.4)]*. **Melanoma** In Trial 5, diarrhea or colitis occurred in 28% (58/206) of patients receiving OPDIVO and 25% (52/205) of patients receiving dacarbazine. Immune-mediated colitis occurred in 4.9% (10/206) of patients receiving OPDIVO: five patients with Grade 3 and five with Grade 2. The median time to onset was 5.1 months (range: 3 days to 12.5 months). In six of ten patients, colitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 or 3 colitis was followed by interruption or permanent discontinuation of OPDIVO in the remaining four patients. Nine of these ten patients received high-dose corticosteroids for a median duration of 1 month (range: 3 days to 7.4 months) preceding corticosteroid taper. Colitis improved to Grade 0 with corticosteroids in nine patients, with complete resolution occurring in six of these patients. Two patients	patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, occurred in 2.2% (6/268) of patients receiving OPDIVO: five patients with Grade 3 and one patient with Grade 2 colitis. The median time to onset of immune-mediated colitis from initiation of OPDIVO was 2.5 months (range: 1 to 6 months). In three patients, colitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 or 3 colitis led to interruption or permanent discontinuation of OPDIVO in the remaining three patients. Five of these six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.4 months (range: 3 days to 2.4 months) preceding corticosteroid taper. The sixth patient continued on low-dose corticosteroids started for another immune-mediated adverse reaction. Immune-mediated colitis improved to Grade 0 with corticosteroids in five patients, including one patient with Grade 3 colitis retreated after complete resolution (defined as improved to Grade 0 with completion of corticosteroids) without additional events of colitis. Grade 2 colitis was ongoing in one patient. In Trial 3, diarrhea occurred in 21% (24/117) of patients. Immune-mediated colitis (Grade 3) occurred in 0.9% (1/117) of patients. The time to onset in this patient was 6.7 months. The patient received high-dose corticosteroids and was permanently discontinued from OPDIVO. Complete resolution occurred. Monitor patients for immune-mediated colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or	

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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA מודגש, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן

	who restarted OPDIVO after complete resolution had recurrence of colitis which again completely resolved with additional corticosteroids. In one patient, Grade 3 colitis was ongoing with corticosteroids continuing. *OPDIVO in Combination with Ipilimumab* In Trial 4, diarrhea or colitis occurred in 57% (54/94) of patients receiving OPDIVO in combination with ipilimumab and 46% (21/46) of patients receiving ipilimumab. Immune-mediated colitis occurred in 33% (31/94) of patients receiving OPDIVO in combination with ipilimumab: one patient with Grade 4, 16 patients with Grade 3, nine patients with Grade 2, and five patients with Grade 1 colitis. The median time to onset was 1.4 months (range: 6.1 days to 5.3 months). Immune-mediated colitis led to permanent discontinuation of OPDIVO in combination with ipilimumab in 17 patients. Thirty of the 31 patients received high-dose corticosteroids for a median duration of 1.2 months (range: 1 day to 6 months) and 11 received infliximab. Immune-mediated colitis resolved following treatment with immunosuppressive medications in 30 patients. Four patients with Grade 2 immune-mediated colitis experienced complete resolution after restarting OPDIVO in combination with ipilimumab. In Trial 4, there were three patients who died without resolution of immune-mediated colitis. **NSCLC** In Trial 3, diarrhea or colitis occurred in 17% (50/287) of patients receiving OPDIVO. Immune-mediated colitis occurred in 2.4% (7/287) of patients: three patients with Grade 3, two patients with Grade 2, and two patients with Grade 1. The median time to onset in these seven patients was 2.7 months (range: 4 weeks to 19 months). All seven patients received corticosteroids; six of these seven received high-dose corticosteroids for a median duration of 2.9 weeks (range: 1 week to 2.1 months). One patient with Grade 3 colitis permanently discontinued OPDIVO. All seven patients	no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Withhold OPDIVO for Grade 2 or 3 immune-mediated colitis. Permanently discontinue OPDIVO for Grade 4 colitis or for recurrent colitis upon restarting OPDIVO *[see Dosage and Administration (2.2)]*.	

מועצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מועצב:גופן: (ברירת מחדל) lairA, נטוי, סמן

מועצב:גופן: (ברירת מחדל) lairA, נטוי, סמן

מועצב:גופן: גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', סמן

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מועצב:גופן: (ברירת מחדל) lairA, מודגש, סמן

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experienced complete resolution. Five of the seven patients were retreated after complete resolution without recurrence of diarrhea or colitis.

RCC

In Trial 6, diarrhea or colitis occurred in 25% (100/406) of patients receiving OPDIVO and 32% (126/397) of patients receiving everolimus. Immune-mediated diarrhea or colitis occurred in 3.2% (13/406) of patients receiving OPDIVO (five patients with Grade 3, seven with Grade 2, and one with Grade 1). The median time to onset was 4.8 months (range: 2 days to 15.6 months). The median duration was 1.3 months (range: 0.2 to 3.9 months). OPDIVO was permanently discontinued in four patients. Dose delay occurred in nine patients. Twelve patients had complete resolution. Among the nine patients who resumed OPDIVO after resolution, four had no recurrence of diarrhea or colitis.

Immune-Mediated Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.4) and Adverse Reactions (6.1)]*.

Melanoma

In Trial 5, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the dacarbazine-treated group, with increases in ALT (25% vs. 19%),

Immune-Mediated Hepatitis

In Trial 1, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs. 12%), alkaline phosphatase (22% vs. 13%), ALT (16% vs. 5%), and total bilirubin (9% vs. 0). Immune-mediated hepatitis, defined as requirement for corticosteroids and no clear alternate etiology, occurred in 1.1% (3/268) of patients receiving OPDIVO: two patients with Grade 3 and one patient with Grade 2 hepatitis. The time to onset was 97, 113, and 86 days after initiation of OPDIVO. In one patient, hepatitis was diagnosed after discontinuation of OPDIVO for other reasons. In two patients, OPDIVO was withheld. All three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Liver tests improved to Grade 1 within 4 to 15 days of initiation of corticosteroids. Immune-mediated hepatitis resolved and did not recur with continuation of corticosteroids

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן

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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן

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AST (24% vs. 19%), alkaline phosphatase (21% vs. 14%), and total bilirubin (13% vs. 6%). Immune-mediated hepatitis occurred in 0.9% (2/206) of patients receiving OPDIVO: one patient with Grade 2 and one patient with Grade 3. The time to onset was 4.1 and 4.4 months after initiation of OPDIVO. In both patients, hepatitis was diagnosed after discontinuation of OPDIVO for other reasons. Both patients received high-dose corticosteroids; one also received mycophenolic acid. Hepatitis resolved in both patients, with corticosteroids continuing in one.

OPDIVO in Combination with Ipilimumab

In Trial 4, immune-mediated hepatitis occurred in 15% (14/94) of patients receiving OPDIVO in combination with ipilimumab: three patients with Grade 4, nine patients with Grade 3, and two patients with Grade 2 hepatitis. The median time to onset was 2.8 months (range: 3 weeks to 5.7 months). Five patients discontinued OPDIVO in combination with ipilimumab due to hepatitis. Thirteen of the 14 patients received high-dose corticosteroids and three received mycophenolic acid. Complete resolution (defined as improved to Grade 0 with completion of corticosteroids) occurred in nine patients. Among four patients for whom OPDIVO in combination with ipilimumab was restarted, three had recurrence or worsening of hepatitis and one improved on corticosteroids.

NSCLC

In Trial 3, one patient developed immune-mediated hepatitis (0.3%) after 7.8 months of OPDIVO exposure. The event resolved following temporary withholding of OPDIVO and high-dose corticosteroid therapy. Immune-mediated hepatitis recurred following resumption of OPDIVO, resulting in permanent discontinuation.

RCC

In Trial 6, there was an increased incidence of liver test

in two patients; the third patient died of disease progression with persistent hepatitis. The two patients with Grade 3 hepatitis that resolved restarted OPDIVO and, in one patient, Grade 3 immune-mediated hepatitis recurred resulting in permanent discontinuation of OPDIVO.

In Trial 3, the incidences of increased liver test values were AST (16%), alkaline phosphatase (14%), ALT (12%), and total bilirubin (2.7%). No cases of immune-mediated hepatitis occurred in this trial.

Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, נטוי, סמן

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מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן

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abnormalities compared to baseline with increases in AST (33% vs. 39%), alkaline phosphatase (32% vs. 32%), ALT (22% vs. 31%), and total bilirubin (9% vs. 3.5%) in the OPDIVO and everolimus arms, respectively. Immune-mediated hepatitis requiring systemic immunosuppression occurred in 1.5% (6/406) of patients receiving OPDIVO (five with Grade 3 and one with Grade 2). None of the six patients had liver metastases. The median time to onset was 3.7 months (range: 14 days to 5.3 months). The median duration was 1.8 months (range: 0.9 to 16.3 months). OPDIVO was permanently discontinued in four patients. Dose delay occurred in all patients. Five patients had complete resolution. Among the three patients who resumed OPDIVO, two had no recurrence of liver test abnormalities. One patient with immune-mediated nephritis developed hepatic failure on the date of death.

1.1 Immune-Mediated Endocrinopathies

Hypophysitis

Hypophysitis can occur with OPDIVO treatment. Monitor patients for signs and symptoms of hypophysitis. Administer corticosteroids at a dose of 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) and permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.4)]*.

Melanoma

In Trial 4, hypophysitis occurred in 13% (12/94) of patients receiving OPDIVO in combination with ipilimumab: two patients with Grade 3 and 10 patients with Grade 2 hypophysitis. The median time to onset was 2.9 months (range: 1.4 to 5.5 months). Ten patients received corticosteroids, including both patients with Grade 3 hypophysitis. OPDIVO in combination with ipilimumab was restarted for eight patients without resulting in worsening of hypophysitis. Four patients were continuing with corticosteroids.

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

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מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן

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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

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RCC

In Trial 6, hypophysitis occurred in 0.5% (2/406) of patients receiving OPDIVO. The time to onset for the Grade 3 event was 9.2 months and for the Grade 1 event was 3.2 months. Both patients received steroid replacement doses. The Grade 3 event resulted in permanent discontinuation and the other patient with the Grade 1 event discontinued due to progressive disease. Neither patient had complete resolution or resumed treatment with OPDIVO.

Adrenal Insufficiency

Adrenal insufficiency can occur with OPDIVO treatment. Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents 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 (2.4)]*.

Melanoma and NSCLC

In Trial 4, adrenal insufficiency occurred in 9% (8/94) of patients receiving OPDIVO in combination with ipilimumab: three patients with Grade 3, four patients with Grade 2, and one patient with Grade 1 adrenal insufficiency. The median time to onset was 3 months (range: 1.2 to 5.6 months). Grade 3 adrenal insufficiency led to discontinuation of OPDIVO in combination with ipilimumab in one patient. The remaining events each occurred after treatment discontinuation, except in two cases where OPDIVO in combination with ipilimumab was restarted and did not lead to recurrence. Three patients received high-dose corticosteroids. Six patients experienced resolution of adrenal insufficiency, three of whom remained on corticosteroids. In Trials 1, 3, and 5 (n=761), less than 1.0% of OPDIVO-treated patients developed adrenal insufficiency.

	RCC In Trial 6, adrenal insufficiency occurred in 2.0% (8/406) of patients receiving OPDIVO (three with Grade 3, four with Grade 2, and one with Grade 1). The median time to onset was 5.8 months (range: 22 days to 20.9 months). OPDIVO was permanently discontinued in one patient. Dose delay occurred in five patients. In Trial 5, hypothyroidism occurred in 7% (14/206) of patients receiving OPDIVO (one patient with Grade 3) and 0.9% (2/205) of patients receiving dacarbazine. The median time to onset in OPDIVO patients was 4.5 months (range: 1.4 to 13.8 months). Twelve of the 14 patients received levothyroxine. In two patients, hypothyroidism was diagnosed after treatment discontinuation; ten patients received subsequent OPDIVO dosing while continuing to receive levothyroxine. In Trial 5, hyperthyroidism occurred in 4.4% (9/206) of patients receiving OPDIVO (one patient with Grade 3) and 0.9% (2/205) of patients receiving dacarbazine. The median time to onset in OPDIVO-treated patients was 1.9 months (range: 1.1 to 8.3 months). The one patient with Grade 3 hyperthyroidism received high-dose corticosteroids (at least 40 mg prednisone equivalents) and medical management, with complete resolution (defined as improved to Grade 0 with completion of corticosteroids and medical management). Six of eight patients with Grade 1 or 2 hyperthyroidism had documented resolution; four of these eight received medical management and two developed subsequent hypothyroidism. ***OPDIVO in Combination with Ipilimumab*** In Trial 4, hypothyroidism occurred in 19% (18/94) of patients receiving OPDIVO in combination with ipilimumab. All were Grade 1 or 2 in severity except for one patient who experienced Grade 3 autoimmune thyroiditis. The median time to onset was 2.1 months (range: 1 day to 4.7 months). Two patients received high-dose		

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מעוצב:גופן: (ברירת מחדל) lairA, נטוי, סמן
מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן
מעוצב:סמן
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corticosteroids. Sixteen of the 18 patients received replacement therapy with levothyroxine. Complete resolution of hypothyroidism occurred in one patient allowing discontinuation of levothyroxine. Thirteen of 16 patients received subsequent OPDIVO in combination with ipilimumab while continuing to receive levothyroxine.

In Trial 4, Grade 1 hyperthyroidism occurred in 2.1% (2/94) of patients receiving OPDIVO in combination with ipilimumab. The time to onset for both cases was 3 weeks. Both patients had a resolution of hyperthyroidism without requiring medical management and both subsequently developed hypothyroidism.

NSCLC

In Trial 3, Grade 1 or Grade 2 hypothyroidism, including thyroiditis, occurred in 7% (20/287) of patients receiving OPDIVO and 0% (0/268) of patients receiving docetaxel, while elevated TSH occurred in 17% of patients receiving OPDIVO and 5% of patients receiving docetaxel. The median time to onset of hypothyroidism/thyroiditis was 2.9 months (range: 1.4 to 11.8 months). All 20 patients received levothyroxine. Two patients received corticosteroids; one of whom received high-dose corticosteroids. Complete resolution of hypothyroidism occurred in one patient. OPDIVO was temporarily withheld due to hypothyroidism/thyroiditis in three patients; no patients discontinued OPDIVO due to hypothyroidism/thyroiditis.

Grade 1 or Grade 2 hyperthyroidism occurred in 1.4% (4/287) of patients. The median time to onset was 2 months (range: 4.1 weeks to 2.8 months). Two of four patients received methimazole and one patient also received treatment with high-dose corticosteroids. All four patients experienced complete resolution.

RCC

In Trial 6, thyroid disease occurred in 11% (43/406) of patients on

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

מעוצב:סמן

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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, נטוי, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן

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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

מעוצב:סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, נטוי, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן

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OPDIVO, including one Grade 3 event, and in 12/397 (3.0%) patients on everolimus. Hypothyroidism/thyroiditis occurred in 8% (33/406) of patients receiving OPDIVO (two patients with Grade 3, 17 patients with Grade 2, and 14 patients with Grade 1). The median time to onset was 4.6 months (range: 15 days to 13.6 months). Twenty-eight of the 33 patients received levothyroxine. No events led to permanent discontinuation. Dose delay occurred in four patients. Four patients, including three patients that never required levothyroxine, had complete resolution and three of these four patients continued OPDIVO throughout the event.

Hyperthyroidism occurred in 2.5% (10/406) of patients receiving OPDIVO (five patients with Grade 2 and five patients with Grade 1). The median time to onset was 3 months (range: 24 days to 14.2 months). No events led to permanent discontinuation. Seven patients had complete resolution. Seven were treated through the event and two had a dose delay with no recurrence of hyperthyroidism when OPDIVO was resumed. Four patients developed hyperthyroidism followed by hypothyroidism.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus can occur with OPDIVO treatment. Monitor for hyperglycemia. Administer insulin for type 1 diabetes and withhold OPDIVO in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia.

Melanoma

In Trial 5, diabetes mellitus or diabetic ketoacidosis occurred in 1.0% (2/206) of patients receiving OPDIVO and none of the 205 receiving dacarbazine. One patient had Grade 3 diabetic ketoacidosis and one patient had Grade 2 diabetes mellitus. Neither patient had a prior history of diabetes. Time to onset was 2.1 and 2.8 months, respectively. In both patients, OPDIVO was withheld and management with insulin was initiated and continuing. Grade 3

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, נטוי, סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן

מעוצב:גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, נטוי, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן

מעוצב:סמן

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diabetic ketoacidosis resolved, and OPDIVO was resumed. Grade 2 diabetes mellitus, which began while the patient was receiving corticosteroids for management of another adverse reaction, remained ongoing with continuation of OPDIVO.

RCC

In Trial 6, hyperglycemic adverse events occurred in 9% (37/406) of patients. Diabetes mellitus or diabetic ketoacidosis occurred in 1.5% (6/406) of patients receiving OPDIVO (three patients with Grade 3, two patients with Grade 2, and one patient with Grade 1). The median time to onset was 7.8 months (range: 2.3 to 21.8 months). Four patients received insulin. One patient was on corticosteroids prior to the event. No events led to permanent discontinuation. Dose delay occurred in one patient. One patient had ongoing hyperglycemia when OPDIVO was resumed.

Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis, defined as renal dysfunction or ≥ Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology, can occur with OPDIVO treatment. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue OPDIVO. Permanently discontinue OPDIVO and 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 *[see Dosage and Administration (2.4) and Adverse Reactions (6.1)]*.

Immune-Mediated Nephritis and Renal Dysfunction

In Trial 1, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs. 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction (defined as ≥ Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology) occurred in 0.7% (2/268) of patients at 3.5 and 6 months after OPDIVO initiation, respectively. OPDIVO was permanently discontinued in both patients; both received high-dose corticosteroids (at least 40 mg prednisone equivalents). Immune-mediated nephritis resolved and did not recur with continuation of corticosteroids in one patient. Renal dysfunction was ongoing in one patient.

In Trial 3, the incidence of elevated creatinine was 22%. Immune-mediated renal dysfunction (Grade 2) occurred in 0.9% (1/117) of patients. The time to onset in this patient was 0.8 months. The patient received high-dose corticosteroids.

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, נטוי, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', סמן

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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן

מעוצב:גופן: גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', סמן

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Melanoma

In Trial 5, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the dacarbazine-treated group (11% vs. 10%). Grade 3 immune-mediated renal dysfunction occurred in 0.5% (1/206) of patients at 5.5 months after OPDIVO initiation. In this patient, dose interruption and initiation of high-dose corticosteroids were followed by complete resolution (defined as improved to Grade 0 with completion of corticosteroids). OPDIVO was restarted with recurrence of renal dysfunction and again resolved with corticosteroids.

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

OPDIVO in Combination with Ipilimumab

מעוצב:גופן: (ברירת מחדל) lairA, נטוי, סמן

In Trial 4, Grade 2 or higher immune-mediated nephritis or renal dysfunction occurred in 2.1% (2/94) of patients. Time to onset was 1.3 weeks and 6.7 months, respectively. In one of these patients, immune-mediated renal dysfunction resolved with corticosteroids and withholding of OPDIVO, whereas the second patient died with persistent renal dysfunction.

מעוצב:גופן: גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', סמן

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מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

NSCLC

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן

In Trial 3, immune-mediated renal dysfunction (Grade 2) occurred in 0.3% (1/287) of patients. The time to onset in this patient was 1.5 months. The patient permanently discontinued OPDIVO, received high-dose corticosteroids, and experienced complete resolution.

מעוצב:גופן: גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', סמן

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RCC

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סיניות (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן

In Trial 6, renal injury occurred in 7% (27/406) of patients on OPDIVO and 3.0% (12/397) of patients on everolimus, rather than laboratory creatinine. Immune-mediated nephritis and renal dysfunction occurred in 3.2% (13/406) of patients receiving OPDIVO (one with Grade 5, one with Grade 4, five with Grade 3, and six with Grade 2). The median time to onset was 5.4 months (range: 1.1 to 12.3 months). Median duration was 1.4 months

מעוצב:גופן: גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', סמן

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OPDIVO was withheld, and the patient discontinued due to disease progression prior to receiving additional OPDIVO. Immune-mediated renal dysfunction was ongoing.

Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) serum creatinine elevation and permanently discontinue OPDIVO. For severe (Grade 3) or moderate (Grade 2) serum creatinine elevation, withhold OPDIVO and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper; if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue OPDIVO *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Immune-Mediated Hypothyroidism and Hyperthyroidism

In Trial 1, where patients were evaluated at baseline and during the trial for thyroid function, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. The median time to onset was 2.5 months (range: 24 days to 11.7 months). Seventeen of the 21 patients with hypothyroidism received levothyroxine. Fifteen of 17 patients received subsequent OPDIVO dosing while continuing to receive levothyroxine.

Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients receiving OPDIVO and 1% (1/102) of patients receiving chemotherapy. The median time to onset in OPDIVO-treated patients was 1.6 months (range: 0 to 3.3 months). Four of five patients with Grade 1 hyperthyroidism and two of three patients with Grade 2 hyperthyroidism had documented

(range: 0.1 to 18 months). OPDIVO was permanently discontinued in five patients. Dose delay occurred in eight patients. Five patients had complete resolution. Two patients resumed OPDIVO after complete resolution and had no recurrence of nephritis.

1.2 Immune-Mediated Rash

Immune-mediated rash can occur with OPDIVO treatment. Severe rash (including rare cases of fatal toxic epidermal necrolysis) occurred in the clinical program of OPDIVO. Monitor patients for rash. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents 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 *[see Dosage and Administration (2.4)]*.

Melanoma (OPDIVO in Combination with Ipilimumab) and NSCLC

In Trial 4, immune-mediated rash occurred in 37% (35/94) of patients receiving OPDIVO in combination with ipilimumab: six patients with Grade 3, 10 patients with Grade 2, and 19 patients with Grade 1 rash. The median time to onset was 2.4 weeks (range: 1 day to 6.5 months). Among the six patients with Grade 3 rash, four received systemic corticosteroids, four had OPDIVO in combination with ipilimumab withheld then restarted without resulting in recurrence of high-grade rash, and all had resolution to Grade 0 or 1 with no further requirement for systemic corticosteroids. Among the 29 patients with Grade 1 or 2 rash, six received systemic corticosteroids and two had OPDIVO in combination with ipilimumab withheld. None of the 35 patients discontinued treatment due to immune-mediated rash. In Trial 3, immune-mediated rash occurred in 6% (17/287) of patients receiving OPDIVO. Grade 3 rash developed in four patients (1.4%), of whom one discontinued treatment.

RCC

resolution of hyperthyroidism; all three patients received medical management for Grade 2 hyperthyroidism.

In Trial 3, patients were evaluated for thyroid function at baseline, first day of treatment, and every 6 weeks. Hypothyroidism occurred in 4.3% (5/117) of patients. The median time to onset for these five cases was 4.1 months (range: 1.4 to 4.6 months). All five patients with hypothyroidism received levothyroxine. Complete resolution of hypothyroidism occurred in one patient allowing discontinuation of levothyroxine. Interruption of OPDIVO did not occur in these five patients.

Hyperthyroidism occurred in 1.7% (2/117) of patients. One patient experienced Grade 2 hyperthyroidism 5.2 months after the first dose of OPDIVO, requiring treatment with high-dose corticosteroids and methimazole. Thyroid laboratory tests returned to normal 4.7 months later.

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

מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן
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מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן
מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT weN namoR, 10 נק', סמן
מעוצב:גופן: (ברירת מחדל) semiT (ברירת מחדל) weN namoR, גופן עבור עברית ושפות אחרות: semiT weN namoR, 10 נק', (אסיאתי) סיניות (טיוואן), סמן
מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן
מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן
מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT weN namoR, 10 נק', סמן

In Trial 6, rash occurred in 28% (112/406) of patients on OPDIVO and 36% (143/397) of patients on everolimus. Immune-mediated rash, defined as a rash treated with systemic or topical corticosteroids, occurred in 7% (30/406) of patients receiving OPDIVO (four with Grade 3, seven with Grade 2, and nineteen with Grade 1). The median time to onset was 3.2 months (range: 2 days to 25.8 months). Median duration was 2.6 months (range: 0.3 to 9.4 months). Four patients received oral and 26 received topical corticosteroids. Two patients permanently discontinued and dose delay occurred in two patients. Seventeen patients had complete resolution. Thirteen patients who continued on OPDIVO or experienced a dose delay had no recurrence of rash.		
1.3 Immune-Mediated Encephalitis Immune-mediated encephalitis can occur with OPDIVO treatment. 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. Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. 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 (2.4)]*. Across clinical studies of 8490 patients receiving OPDIVO as a single agent or in combination with ipilimumab, less than 1.0% of patients were identified as having encephalitis. In Trial 3, fatal limbic encephalitis occurred in one patient (0.3%) receiving OPDIVO after 7.2 months of exposure. OPDIVO was discontinued; corticosteroids were administered.		
Other Immune-Mediated Adverse Reactions	**Other Immune-Mediated Adverse Reactions** Other clinically significant immune-mediated adverse reactions	

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מעוצב:גופן: (ברירת מחדל) lairA, מודגש, סמן
מעוצב:גופן: גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', סמן
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מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן
מעוצב:סמן

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. The following clinically significant, immune-mediated adverse reactions occurred in less than 1.0% of patients receiving OPDIVO as a single agent or in combination with ipilimumab in Trials 1, 3, 4, 5, and 6 (n=1261):~~2% of OPDIVO-treated patients in Trials 1 and 3 (n=385):~~ ~~adrenal insufficiency,~~ uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica,autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, and systemic inflammatory response syndrome ~~motor dysfunction, and vasculitis.~~ Across clinical trials of OPDIVO as a single agent administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: motor dysfunction, vasculitis, ~~hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome,~~ and myasthenic syndrome. Across clinical trials of OPDIVO in combination with ipilimumab, the following additional clinically significant, immune-mediated adverse reactions were identified: sarcoidosis, duodenitis, and gastritis. **1.4 Infusion Reactions** Severe infusion reactions have been reported in less than 1.0% of patients in clinical trials of OPDIVO as a single agent. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. **Melanoma and NSCLC**	can occur. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. The following clinically significant, immune-mediated adverse reactions occurred in less than 2% of OPDIVO-treated patients in Trials 1 and 3 (n=385): adrenal insufficiency, uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction, and vasculitis. Across clinical trials of OPDIVO administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.2)]*.	

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מעוצב:SMB ydoB Text, ללא תבליטים או מספור, מיקום: אופקי: מרכז, ביחס ל: שוליים, אנכי: -39.0 ס"מ, ביחס ל: פיסקה, אופקי: 23.0 ס"מ, גלישה סביב

מעוצב:סמן

מעוצב:גופן: Semi Normal, לא מודגש, סמן

מעוצב:גופן: Semi Normal, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) Semi Normal, גופן עבור עברית ושפות אחרות: Semi Normal, 10 נק', (אסיאתי) סינית (טיוואן), סמן

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מעוצב:גופן: semiT namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

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מעוצב:גופן: semiT namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

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In Trials 3 and 5, Grade 2 infusion reactions occurred in 1.0% (5/493) of patients receiving OPDIVO. In Trial 4, Grade 2 infusion reactions occurred in 3.2% (3/94) of patients receiving OPDIVO in combination with ipilimumab. **RCC** In Trial 6, hypersensitivity/infusion-related reactions occurred in 6% (25/406) of patients receiving OPDIVO and 1.0 % (4/397) of patients receiving everolimus. The median time to onset in the OPDIVO group was 1.4 months (range: 1 day to 27.6 months). Seven patients received corticosteroids on the day of administration. Two patients discontinued OPDIVO, one for a Grade 4 reaction and one for a Grade 2 event. No events led to dose delay. Interruption of the infusion was required in ten patients.		
~~2~~ **ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the labeling. • Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]* • Immune-Mediated Colitis *[see Warnings and Precautions (5.2)]* • Immune-Mediated Hepatitis *[see Warnings and Precautions (5.3)]* • Immune-Mediated Endocrinopathies *[see Warnings and Precautions (5.4)]* • Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions (5.~~4~~5)]* • ~~Immune-Mediated Hypothyroidism and Hyperthyroidism *[see Warnings and Precautions (5.5)]*~~ • Immune-Mediated Rash *[see Warnings and Precautions*	~~3~~ **ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the labeling. • Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]* • Immune-Mediated Colitis *[see Warnings and Precautions (5.2)]* • Immune-Mediated Hepatitis *[see Warnings and Precautions (5.3)]* • Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions (5.*Immune-Mediated Hypothyroidism and Hyperthyroidism *[see Warnings and Precautions (5.5)]* Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.8)]*	Adverse Reactions

מעוצב:רווח אחרי: 3 נק', ללא תבליטים או מספור, מיקום: אופקי: מרכז, ביחס ל: שוליים, אנכי: -39.0 ס"מ, ביחס ל: פיסקה, אופקי: 23.0 ס"מ, גלישה סביב

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: semiT weN namoR, 10 נק', (אסיאתי) סינית (טיוואן), (עברית ושפות אחרות) עברית

מעוצב:צבע גופן: שחור

מעוצב:צבע גופן: אוטומטי

מעוצב:צבע גופן: שחור

מעוצב:כניסה: לפני: 67.0 ס"מ, עצירות טאב: 25.1 ס"מ, כרטיסיית רשימה + לא ב 89.2 ס"מ, מיקום: אופקי: מרכז, ביחס ל: שוליים, אנכי: -39.0 ס"מ, ביחס ל: פיסקה, אופקי: 23.0 ס"מ, גלישה סביב

מעוצב:צבע גופן: שחור

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: semiT weN namoR, 10 נק', (אסיאתי) סינית (טיוואן)

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(5.6)] • Immune-Mediated Encephalitis *[see Warnings and Precautions (5.7)]* • Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.~~6~~)]* • Infusion Reactions [see Warnings and Precautions (5.9)] **~~2.1~~ Clinical Trials Experience** The data in the Warning and Precautions section reflect exposure to OPDIVO, as a single agent, for clinically significant adverse reactions in 1590 patients enrolled in Trials 1, 3, 5, 6, a single-arm trial in NSCLC (n=117), or an additional dose-finding study (n=306) administering OPDIVO as a single agent at doses of 0.1 to 10 mg/kg every 2 weeks *[see Warnings and Precautions (5.1, 5.8)]*. In addition, clinically significant adverse reactions with OPDIVO, in combination with ipilimumab, were evaluated in 188 patients with melanoma enrolled in Trial 4 (n=94) or an additional dose-finding study (n=94) administering OPDIVO in combination with ipilimumab at doses of OPDIVO ranging from 0.3 to 3 mg/kg and doses of ipilimumab ranging from 1 to 3 mg/kg, supplemented by immune-mediated adverse reaction reports in ongoing clinical trials *[see Warnings and Precautions (5.1, 5.8)]*. The data described below reflect exposure to OPDIVO as a single agent in Trials 1 and 5 and to OPDIVO in combination with ipilimumab in Trial 4, which are randomized, active-controlled trials conducted in patients with unresectable or metastatic melanoma. Also described below are single-agent OPDIVO data from Trial 3, which is a randomized trial in patients with metastatic non-squamous NSCLC, and Trial 6, which is a randomized trial in patients with advanced RCC.	Reporting of suspected adverse reactions • .... **~~3.1~~ Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The data described in the WARNINGS and PRECAUTIONS section and below reflect exposure to OPDIVO in Trial 1, a randomized trial in patients with unresectable or metastatic melanoma and in Trial 3, a single-arm trial in patients with metastatic squamous non-small cell lung cancer (NSCLC). Clinically significant adverse reactions were evaluated in a total of 691 patients enrolled in Trials 1, 3, or an additional dose finding study (n=306) administering OPDIVO at doses of 0.1 to 10 mg/kg every 2 weeks *[see Warnings and Precautions (5.1, 5.6)]*. **Unresectable or Metastatic Melanoma** The safety of OPDIVO was evaluated in Trial 1, a randomized, open-label trial in which 370patients with unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102),	

The safety of OPDIVO was also evaluated in Trial 5, a randomized, double-blind, active-controlled trial in which 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=206) or dacarbazine 1000 mg/m^2 every 3 weeks (n=205) *[see Clinical Studies (14.1)]*. The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. In this trial, 47% of patients received OPDIVO for greater than 6 months and 12% of patients received OPDIVO for greater than 1 year. The trial excluded patients with autoimmune disease and patients requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications. The study population characteristics in the OPDIVO group and dacarbazine group were generally similar: 59% male, median age 65 years, 99.5% white, 61% with M1c stage disease, 74% with cutaneous melanoma, 11% with mucosal melanoma, 4% with brain metastasis, and 37% with elevated LDH at baseline. There were more patients in the OPDIVO group with ECOG performance status 0 (71% vs. 59%). Adverse reactions led to permanent discontinuation of OPDIVO in 7% of patients and dose interruption in 26% of patients; no single type of adverse reaction accounted for the majority of OPDIVO discontinuations. Serious adverse reactions occurred in 36% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). Table 4 summarizes selected adverse reactions that occurred in at least 10% of OPDIVO-treated patients. The most common adverse	either dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m^2 every 3 weeks *[see Clinical Studies (14.1)]*. The median duration of exposure was 5.3 months (range: 1 day to 13.8+ months) with a median of eight doses (range: 1 to 31) in OPDIVO-treated patients and was 2 months (range: 1 day to 9.6+ months) in chemotherapytreated patients. In this ongoing trial, 24% of patients received OPDIVO for greater than 6 months and 3% of patients received OPDIVO for greater than 1 year. In Trial 1, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV. The study population characteristics in the OPDIVO group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% white, baseline ECOG performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the OPDIVO group with elevated LDH at baseline (51% vs. 38%). OPDIVO was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving OPDIVO had	

מעוצב:גופן: TimeS weN semiT, לא מודגש, (אסיאתי) סינית (טיוואן), סמן
מעוצב:גופן: TimeS weN semiT, לא מודגש, לא נטוי, צבע גופן: שחור, (אסיאתי) סינית (טיוואן)
מעוצב:גופן: TimeS weN semiT, לא מודגש, צבע גופן: אוטומטי, (אסיאתי) סינית (טיוואן)
מעוצב:גופן: TimeS weN semiT, לא מודגש, צבע גופן: שחור, (אסיאתי) סינית (טיוואן)
מעוצב:גופן: TimeS weN semiT, לא מודגש, צבע גופן: אוטומטי, (אסיאתי) סינית (טיוואן)
מעוצב:גופן: TimeS weN semiT, לא מודגש, לא נטוי, צבע גופן: שחור, (אסיאתי) סינית (טיוואן)
מעוצב:גופן: TimeS weN semiT, לא מודגש, לא נטוי, צבע גופן: שחור, (אסיאתי) סינית (טיוואן)
מעוצב:גופן: TimeS weN semiT, לא מודגש, לא נטוי, צבע גופן: שחור, (אסיאתי) סינית (טיוואן)
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reactions (reported in at least 20% of patients and at a higher incidence than in the dacarbazine arm) were fatigue, musculoskeletal pain, rash, and pruritus.

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

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

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

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

Table 1:Selected Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 1)

Adverse Reaction	OPDIVO (n=268)		Chemotherapy (n=102)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
Skin and Subcutaneous Tissue Disorders				
Rash[a]	21	0.4	7	0
Pruritus	19	0	3.9	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	17	0	6	0
Infections and Infestations				

Upper respiratory tract infection[d]	17	0	6	0

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

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

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

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

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

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

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in Trial 1 were:

Cardiac Disorders: ventricular arrhythmia

Eye Disorders: iridocyclitis

General Disorders and Administration Site Conditions: infusion-related reactions

Investigations: increased amylase, increased lipase

Nervous System Disorders: dizziness, peripheral and sensory neuropathy

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

Table 2: **Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 1)**

Percentage of Patients with Worsening Laboratory Test from Baseline[a]

מעוצב:אל תשמור שורות יחד, מיקום: אופקי: מרכז, ביחס ל: שוליים, אנכי: -39.0 ס"מ, ביחס ל: פיסקה, אופקי: 23.0 ס"מ, גלישה סביב

מעוצב:שמאל, אל תשמור שורות יחד, מיקום: אופקי: מרכז, ביחס ל: שוליים, אנכי: -39.0 ס"מ, ביחס ל: פיסקה, אופקי: 23.0 ס"מ, גלישה סביב

מעוצב:אל תשמור שורות יחד, מיקום: אופקי: מרכז, ביחס ל: שוליים, אנכי: -39.0 ס"מ, ביחס ל: פיסקה, אופקי: 23.0 ס"מ, גלישה סביב

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

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in Trial 5 were:

Nervous System Disorders: peripheral neuropathy

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

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

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

OPDIVO in Combination with Ipilimumab

The safety of OPDIVO, administered in combination with ipilimumab, was evaluated in Trial 4, a randomized, double-blind trial in which 140 previously untreated patients with unresectable or metastatic melanoma received OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for four cycles, followed by OPDIVO 3 mg/kg as a single agent every 2 weeks (n=94) or single-agent ipilimumab 3 mg/kg every 3 weeks for four cycles followed by placebo every 2 weeks (n=46) *[see Clinical Studies (14.1)]*. The median duration of exposure to OPDIVO was 2.2 months (range: 1 day to 10 months). Among patients who received OPDIVO in combination with ipilimumab, 29% were exposed to OPDIVO for at

Test	OPDIVO		Chemotherapy	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Increased AST	28	2.4	12	1.0
Increased alkaline phosphatase	22	2.4	13	1.1
Hyponatremia	25	5	18	1.1
Increased ALT	16	1.6	5	0
Hyperkalemia	15	2.0	6	0

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

The safety of OPDIVO was evaluated in Trial 3, a single-arm multinational, multicenter trial in 117 patients with metastatic squamous NSCLC and progression on both a prior platinum-based therapy and at least one additional systemic therapy *[see Clinical Studies (14.2)]*. Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks. The median duration of therapy was 2.3 months (range: 1 day to 16.1+ months). Patients received a median of 6 doses (range: 1 to 34).

Trial 3 excluded patients with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis. The median age of patients was 65 years (range: 37 to 87) with 50% ≥65 years of age and 14% ≥75 years of age. The majority of patients were male (73%) and white (85%). All patients received two or more prior systemic treatments. Baseline disease characteristics of the population were recurrent Stage IIIb (6%), Stage IV (94%), and brain metastases (1.7%). Baseline ECOG performance status was 0 (22%) or 1 (78%).

OPDIVO was discontinued due to adverse reactions in 27% of patients. Twenty-nine percent of patients receiving OPDIVO

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

least 6 months.

Trial 4 enrolled patients who had not received systemic anticancer therapy for unresectable or metastatic melanoma and excluded patients with ocular melanoma, autoimmune disease, any condition requiring chronic systemic treatment with corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, or a history of HIV.

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

The study population characteristics were: 67% male, median age 65 years, 98% white, baseline ECOG performance status 0 (82%) or 1 (17%), 46% with M1c stage disease; 25% with elevated LDH at baseline, 3% with a history of brain metastasis, and 23% had BRAF V600 mutation-positive melanoma. There were more patients in the OPDIVO plus ipilimumab group who had cutaneous melanoma (84% vs. 62%), while a greater proportion of patients in the ipilimumab group had acral/mucosal melanoma (8% vs. 21%).

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

Serious adverse reactions (62% vs. 39%), adverse reactions leading to permanent discontinuation (43% vs. 11%) or dose delays (47% vs. 22%), and Grade 3 or 4 adverse reactions (69% vs. 43%) all occurred more frequently in patients receiving OPDIVO plus ipilimumab compared with those receiving single-agent ipilimumab. In the OPDIVO plus ipilimumab group, 27% (25/94) of patients did not complete all four cycles of OPDIVO in combination with ipilimumab. The first occurrence of a Grade 3 or 4 adverse reaction was during administration of OPDIVO in combination with ipilimumab in 56 patients (59%) while 9 patients (10%) experienced first occurrence of a Grade 3 or 4 adverse reaction during administration of OPDIVO as a single agent.

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT, namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

The most common adverse reactions leading to discontinuation of OPDIVO, as compared to single-agent ipilimumab, were colitis (16% vs. 2%), diarrhea not treated with corticosteroids (4% vs. 4%), increased ALT levels (4% vs. 0), pneumonitis (3% vs. 0), and AST increase (3% vs. 0). The most frequent serious adverse events with had a drug delay for an adverse reaction. Serious adverse reactions occurred in 59% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain.

Table 3 summarizes adverse reactions that occurred in at least 10% of patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation.

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

Adverse Reaction	OPDIVO (n=117)	
	All Grades	Grades 3-4
	Percentage (%) of Patients	
General Disorders and Administration Site Conditions		
Fatigue	50	7
Asthenia	19	1.7
Edema[a]	17	1.7
Pyrexia	17	0
Chest pain[b]	13	0
Pain	10	2.6
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	38	9
Cough	32	1.7
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[c]	36	6
Arthralgia[d]	13	0

OPDIVO in combination with ipilimumab, as compared to single-agent ipilimumab, were colitis (17% vs. 9%), diarrhea (9% vs. 7%), pyrexia (6% vs. 7%), and pneumonitis (5% vs. 0). The most common adverse reactions (reported in at least 20% of patients) in Trial 4 receiving OPDIVO in combination with ipilimumab were rash, pruritus, headache, vomiting, and colitis.

Table 6 summarizes the incidence of selected adverse reactions occurring in at least 10% of patients treated with OPDIVO, in combination with ipilimumab.

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

Adverse Reaction	OPDIVO plus Ipilimumab[a] (n=94)		Ipilimumab (n=46)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
Skin and Subcutaneous Tissue Disorders				
Rash[b]	67	9	57	2.2
Pruritus	37	1.1	26	0
Nervous System Disorders				
Headache	24	2.1	20	0
Gastrointestinal Disorders				
Vomiting	23	2.1	15	0
Colitis	22	16	11	7
Metabolism and Nutrition Disorders				
Decreased appetite	35	2.6		
Gastrointestinal Disorders				
Nausea	29	1.7		
Constipation	24	0		
Vomiting	19	0.9		
Diarrhea	18	2.6		
Abdominal pain[e]	16	1.7		
Skin and Subcutaneous Tissue Disorders				
Rash[f]	16	0.9		
Pruritus	11	0.9		
Investigations				
Decreased weight	13	0.9		
Infections and Infestations				
Pneumonia[g]	10	5		

* National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

[a] Includes face edema, peripheral edema, local swelling, localized edema, lymphoedema.

[b] Includes chest discomfort and noncardiac chest pain.

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

[d] Includes arthritis and osteoarthritis.

[e] Includes abdominal pain lower, abdominal pain upper, gastrointestinal pain.

[f] Includes maculopapular rash, rash erythematous, erythema, dermatitis, dermatitis exfoliative, and dermatitis acneiform.

[g] Includes lung infection and pneumonia aspiration.

Other clinically important adverse reactions in less than 10% of patients in Trial 3 were:

General Disorders and Administration Site Conditions:

Dehydration	17	3.2	7	2.2
Endocrine Disorders				
Hypothyroidism	14	0	9	0
Hypophysitis	13	2.1	7	4.3
Eye Disorders				
Blurred vision	12	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Pneumonitis	10	2.1	2.2	0

[a] OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg as a single agent every 2 weeks until disease progression or unacceptable toxicity.

[b] Rash is a composite term which includes dermatitis, dermatitis acneiform, dermatitis bullous, erythema, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, and rash pruritic.

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in combination with ipilimumab were:

Nervous System Disorders: peripheral neuropathy

Gastrointestinal Disorders: stomatitis, colonic perforation

able 7: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 4)

Test	Percentage of Patients with Worsening Laboratory Test from Baseline[a]	
	OPDIVO plus Ipilimumab[b]	Ipilimumab

stomatitis

Nervous System Disorders: peripheral neuropathy

Infections and Infestations: bronchitis, upper respiratory tract infection

Table 4: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients for all NCI CTCAE Grades or ≥2% for Grades 3-4 (Trial 3)

	Percentage of Patients with Worsening Laboratory Test from Baseline[a]	
Test	**All Grades**	**Grades 3-4**
Chemistry		
Hyponatremia	38	10
Increased creatinine	22	0
Hypercalcemia	20	2.6
Hypokalemia	20	2.6
Hypomagnesemia	20	0
Hypocalcemia	18	1.8
Hyperkalemia	18	4.4
Increased AST	16	0.9
Increased alkaline phosphatase	14	0
Increased ALT	12	0
Hematology		
Lymphopenia	47	16
Anemia	28	2.6
Thrombocytopenia	14	0

	All Grades	Grades 3-4	All Grades	Grades 3-4
Chemistry				
Increased ALT	45	13	20	0
Increased AST	43	10	22	0
Hyponatremia	38	9	20	2.2
Increased lipase	36	13	17	7
Increased alkaline phosphatase	30	0	17	0
Hypocalcemia	29	2.3	15	2.2
Increased creatinine	24	1.1	13	0
Increased amylase	23	6	9	0
Hypomagnesemia	15	0	9	0
Hypokalemia	15	3.4	7	0
Hematology				
Anemia	40	1.1	35	2.2
Lymphopenia	37	9	30	2.2
Neutropenia	11	1.1	2.2	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range 111 to 114 patients).

[b] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO in combination with ipilimumab group (range: 84 to 88 patients) and ipilimumab group (range: 45 to 46 patients).

[c] OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg as a single agent every 2 weeks until disease progression or unacceptable toxicity.

Metastatic Non-Squamous Non-Small Cell Lung Cancer

The safety of OPDIVO was evaluated in Trial 3, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.2)]*. Patients received 3 mg/kg of OPDIVO (n=287) administered intravenously over 60 minutes every 2 weeks or docetaxel (n=268) administered intravenously at 75 mg/m^2 every 3 weeks. The median

duration of therapy was 2.6 months (range: 0 to 24.0+ months) in OPDIVO-treated patients and was 2.3 months (range: 0 to 15.9 months) in docetaxel-treated patients. In this trial, 30% of patients received OPDIVO for greater than 6 months and 20% of patients received OPDIVO for greater than 1 year.

Trial 3 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease.

The median age of all randomized patients was 62 years (range: 21 to 85); 37% of patients in the OPDIVO group were ≥65 years of age and 47% of patients in the docetaxel group were ≥65 years of age, 55% were male, and 92% were white. Twelve percent of patients had brain metastases and ECOG performance status was 0 (31%) or 1 (69%).

OPDIVO was discontinued in 13% of patients, and was delayed in 29% of patients for an adverse reaction. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure. In the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis.

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, cough, decreased appetite, and constipation. Table 8 summarizes selected adverse reactions occurring more frequently in at least 10% of OPDIVO-treated patients.

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: semiT namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: semiT namoR weN, 12 נק', לא מודגש, (אסיאתי) סינית (טיוואן), לא כתב עילי/ כתב תחתי, סמן

מעוצב:גופן: לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: semiT namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: semiT namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: סמן

מעוצב:גופן: semiT namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: semiT namoR weN, לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: semiT namoR weN, 10 נק', (אסיאתי) סינית (טיוואן), סמן

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

Adverse Reaction	OPDIVO (n=287)		Docetaxel (n=268)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	30	0.3	25	0
Metabolism and Nutrition Disorders				
Decreased appetite	29	1.7	22	1.5
Gastrointestinal Disorders				
Constipation	23	0.7	17	0.7
Skin and Subcutaneous Tissue Disorders				
Pruritus	11	0	1.9	0

Other clinically important adverse reactions observed in patients treated with OPDIVO and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (49% Grade 1-4, 6% Grade 3-4), musculoskeletal pain (36%), pleural effusion (5.6%), pulmonary embolism (4.2%), urticaria (1.4%), and polymyalgia rheumatica

(0.3%).

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

Test	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO		Docetaxel	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Chemistry				
Hyponatremia	35	6	32	2.7
Increased AST	28	2.8	14	0.4
Increased alkaline phosphatase	27	1.1	18	0.4
Increased ALT	23	2.4	15	0.4
Increased creatinine	18	0	13	0.4
Increased TSH[b]	17	N/A	5	N/A

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 280 to 287 patients) and docetaxel group (range: 252 to 262 patients); TSH: OPDIVO group n=209 and docetaxel group n=207.

[b] Not graded per NCI CTCAE v4.0.

Renal Cell Carcinoma

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

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

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

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

Table 10: Grade 1-4 Adverse Reactions in >15% of Patients Receiving OPDIVO (Trial 6)

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

Constipation	23	0.5	18	0.5
Vomiting	16	0.5	16	0.5
Skin and Subcutaneous Tissue Disorders				
Rash[d]	28	1.5	36	1.0
Pruritus/generalized pruritus	19	0	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	23	1.2	30	1.5
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	20	1.0	14	0.5
Back pain	21	3.4	16	2.8

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

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

[c] Includes colitis, enterocolitis, and gastroenteritis.

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

Other clinically important adverse reactions in Trial 6 were:

General Disorders and Administration Site Conditions: peripheral edema/edema

Gastrointestinal Disorders: abdominal pain/discomfort

Musculoskeletal and Connective Tissue Disorders: extremity pain, musculoskeletal pain

Nervous System Disorders: headache/migraine, peripheral neuropathy

*Investigations:*weight decreased

Skin Disorders: Palmar-plantar erythrodysesthesia

The most common laboratory abnormalities which have worsened compared to baseline in >30% of patients include increased

creatinine, lymphopenia, anemia, increased AST, increased alkaline phosphatase, hyponatremia, elevated triglycerides, and hyperkalemia. Table 11 summarizes the laboratory abnormalities that occurred in greater than 15% of OPDIVO-treated patients.

Table 11: Grade 1-4 Laboratory Values Worsening from Baseline Occurring in >15% of Patients on OPDIVO (Trial 6)

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

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

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

מעוצב:סמן מעוצב:צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: 10 נק' מעוצב:גופן: namoR weN semiT, צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: 10 נק', (אסיאתי) סינית (טיוואן)	Of the 272 patients randomized to OPDIVO in Trial 1, 35% of patients were 65 years or older and 15% were 75 years or older. Of the 292 patients randomized to OPDIVO in Trial 3, 37% of patients were 65 years or older and 7% were 75 years or older. Of the 210 patients randomized to OPDIVO in Trial 5, 50% of patients were 65	Clinical studies of OPDIVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 272 patients randomized to OPDIVO in Trial 1, 35% of patients were 65 years or older and 15% were 75 years or older. Of the 117	Geriatri

	years or older and 13% were 75 years or older. Of the 406 patients treated with OPDIVO in Trial 6, 37% of patients were 65 years or older and 8% were 75 years or older. In these trials, no overall differences in safety or efficacy were reported between elderly patients and younger patients. Trial 4, OPDIVO in combination with ipilimumab, did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.	patients treated with OPDIVO in Trial 3, 50% of patients were 65 years or older and 14% were 75 years or older.	
	• Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.4)]*. • Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.54)]*. • ~~Hypothyroidism and Hyperthyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism and hyperthyroidism *[see Warnings and Precautions (5.5)]*.~~ • Rash: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions (5.6)]*. • Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis *[see Warnings and Precautions (5.7)]*. • Infusion Reactions: Advise patients of the potential risk of infusion reaction *[see Warnings and Precautions (5.9)]*.	..... • Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.4)]*. • Hypothyroidism and Hyperthyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism and hyperthyroidism *[see Warnings and Precautions (5.5)]*.	Patient Counselin Informatio

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: weN semiT namoR, 10 נק', (אסיאתי) סינית (טיוואן)

מעוצב:סמן

מעוצב:צבע גופן: אוטומטי

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:צבע גופן: שחור

מעוצב:צבע גופן: אוטומטי

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מעוצב:סמן

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מעוצב:סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

מעוצב:סמן

מעוצב:גופן: (ברירת מחדל) semiT namoR weN, גופן עבור עברית ושפות אחרות: namoR weN semiT, 10 נק', (אסיאתי) סינית (טיוואן), סמן

הודעה על החמרה (מידע בטיחות) בעלון לצרכן

(מעודכן 05.2013)

ריך 29.11.2015

תכשיר באנגלית ומספר הרישום Opdivo # 153-55-34333-00

בעל הרישום Bristol-Myers Squibb Israel Ltd.

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ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
מה מיועדת התרופה?	אופדיבו ניתנת לטיפול ב: סרטן עור מסוג מלנומה. אופדיבו ניתנת במקרים בהם המלנומה מפושטת ולא ניתן להסירה באמצעות ניתוח (מלנומה מתקדמת). סרטן ריאות גרורתי מסוג תאים שאינם קטנים (non-small cell lung cancer) עבור חולים שמחלתם התקדמה תוך כדי טיפול או לאחר טיפול בכימותרפיה המבוססת על פלטינום.	אופדיבו ניתנת לטיפול ב: • סרטן עור מסוג מלנומה: אופדיבו ניתנת במקרים בהם המלנומה מפושטת או מלנומה אשר לא ניתן להסירה באמצעות ניתוח (מלנומה מתקדמת). אופדיבו בשילוב עם יירבוי Yervoy (Ipilimumab) ניתנת לטיפול בחולי מלנומה מפושטת אן מלנומה אשר לא ניתן להסירה בניתוח (מלנומה מתקדמת) עם גן BRAF V 600 ללא מוטציה (wild type). • סרטן ריאות גרורתי מסוג תאים שאינם קטנים (non-small cell lung cancer) עבור חולים שמחלתם התקדמה תוך כדי טיפול או לאחר טיפול בכימותרפיה המבוססת על פלטינום. סרטן תאי הכליה (הנקרא renal cell carcinoma) מסוג תאים בהירים (clear cell) אופדיבו ניתנת לטיפול בחולי סרטן תאי כליה מתקדם שקיבלו טיפול אנטי- אנגיוגני קודם.

4. תופעות לוואי:	תופעת הלוואי השכיחה ביותר באנשים בעלי מלנומה הינה פריחה. תופעות הלוואי השכיחות ביותר בחולי סרטן ריאות מסוג תאים שאינם קטנים (non-small cell): • עייפות • קוצר נשימה • כאב בשרירים, בעצמות ובמפרקים • ירידה בתיאבון • שיעול • בחילה • עצירות אופדיבו מטפלת במלנומה ובסרטן ריאות על-ידי שפעול מערכת החיסון. אופדיבו עלולה לגרום למערכת החיסון לתקוף רקמות ואיברים רגילים במקומות רבים בגוף ולהשפיע על אופן פעילותם. פעילות זו עלולה לגרום לתופעות לוואי חמורות ואף מסכנות חיים. תופעות לוואי אלה עלולות להופיע בזמן הטיפול ואף לאחר סיום הטיפול. פנה מיד לרופא אם הנך חווה את הסימנים והתסמינים הבאים או אם ישנה החמרה בתסמינים הבאים: בעיות בריאה (פנאומוניטיס). תסמינים של פנאומוניטיס יכולים לכלול: • שיעול חדש או החמרה בשיעול • כאב בחזה • קוצר נשימה בעיות במעיים (דלקת במעי) העלולות לגרום להופעת קרעים או חירור המעי שלך. סימנים ותסמינים של דלקת במעי (קוליטיס) יכולים לכלול: • שלשול (צואה רכה) או מספר פעולות מעיים רב מהרגיל • דם בצואה או צואה בצבע כהה, דביקה הדומה לזפת • כאב חריף או רגישות חריפה באזור הבטן בעיות בכבד (דלקת הכבד/ צהבת). סימנים ותסמינים של דלקת הכבד יכולים לכלול: • הצהבה של העור או העיניים (לובן העיין) שלך • בחילה או הקאה חמורה	.... תופעות לוואי חמורות בזמן מתן האינפוזיה, דווח לרופא המטפל או לאחות מיידית, אם אתה חש אחד מהסימפטומים המופעים מטה בזמן קבלת אינפוזיה של אופדיבו: • צמרמורות או רעד • גרד או פריחה • הסמקה • קשיי נשימה • סחרחורות • חום • תחושת התעלפות תופעות הלוואי השכיחות ביותר במתן של אופדיבו בלבד באנשים בעלי מלנומה הינן: • עייפות • כאב בשרירים, בעצמות ובמפרקים • פריחה • גירוד בעור תופעות הלוואי השכיחות ביותר במתן משולב של אופדיבו עם יירבוי Yervoy (Ipilimumab) הן: • פריחה • גרד • דלקת של המעי (קוליטיס) -ראה מטה בעיות במעיים • כאבי ראש • בחילה • .... תופעות הלוואי השכיחות ביותר בחולי סרטן תאי הכליה (RCC) הן: • עייפות • קוצר נשימה • כאב בשרירים, בעצמות ובמפרקים • ירידה בתיאבון • שיעול • בחילה • שלשול

מעוצב:גופן: 11 נק', צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: 11 נק', סמן
מעוצב:סמן
מעוצב:גופן: 11 נק', צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: 11 נק', סמן
מעוצב:סמן
מעוצב:גופן: 11 נק', צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: 11 נק', סמן
מעוצב:סמן
מעוצב:גופן: 11 נק', צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: 11 נק', סמן
מעוצב:סמן
מעוצב:גופן: 11 נק', צבע גופן: אוטומטי, גופן עבור עברית ושפות אחרות: 11 נק', סמן
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	• כאב בצד ימין של איזור הקיבה (בבטן) • ישנוניות • שתן בצבע כהה (גוון של תה) • נטייה לדימום או לחבורות יותר מהרגיל • ירידה בתחושת הרעב בעיות בכליה, כולל נפריטיס (דלקת הכליות) או כשל כלייתי. סימנים של בעיות בכליה יכולות לכלול: • ירידה בכמות שתן • הופעת דם בשתן • נפיחות בקרסוליים • איבוד תיאבון בעיות בבלוטות שמייצרות הורמונים (במיוחד בבלוטת התריס,בלוטת יותרת המוח ובבלוטות נוספות). סימנים ותסמינים המעידים על תפקוד לא תקין של הבלוטות המייצרות הורמונים יכולים לכלול: • כאבי ראש שאינם חולפים או לא אופייניים • עייפות קיצונית • עליה במשקל או איבוד משקל • שינויים במצב הרוח או שינויי התנהגות, כגון ירידה בחשק המיני, עצבנות, או שכחה • סחרחורת או עילפונשירת שיער • תחושת קור • עצירות • שינוי בקול לקול עמוק ונמוך בעיות באיברים נוספים. סימנים לכך יכולים להיות: • פריחה • שינוי בראייה • כאבי שרירים או מפרקים מתמשכים או חריפים חולשת שרירים חריפה	• עצירות • פריחה אופדיבו עלולה גם לגרום לתגובות אלרגיות חמורות (מופיעות בפחות ממטופל 1 מתוך 100). ספר לרופא המטפל או חפש עזרה רפואית מידית במידה ואתה חש אחד מהסימפטומים המופיעים מטה במהלך הטיפול באופדיבו או במשך 24 שעות לאחר הטיפול באופדיבו- • סרפדת (כתמים אדומים, תפוחים ומגרדים),פריחה, גרד או נפיחות של השפתיים, לשון, גרון או פנים • קוצר נשימה או צפצופים או שיעול פתאומי • סחרחורת או תחושת התעלפות או פלפיטציות (תחושת קצב לב מהיר או "מפרפר") ~~10~~ ... חלק מתופעות הלוואי הללו עלולות להתרחש בתדירות גבוהה יותר כשאופדיבו ניתנת בשילוב עם יירבוי Yervoy (Ipilimumab). • .... • ... • צימאון יתר או ריבוי שתן • ... דלקת של רקמת המוח (אנצפליטיס), סימנים של דלקת -של רקמת המוח יכולים לכלול: • כאבי ראש • חום • עייפות או חולשה • בלבול • בעיות זיכרון • ישנוניות יתר • שמיעה או ראיית דברים שאינם קיימים (הזיות) • פרכוסים

מועצב:מימין לשמאל, כניסה: לפני: 4.1 ס"מ, ללא תבליטים או מספור
מועצב:צבע גופן: אוטומטי, סמן
מועצב:רגיל, מימין לשמאל, כניסה: לפני: 20.0 ס"מ
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מועצב:גופן: (ברירת מחדל) lairA, גופן עבור עברית ושפות אחרות: lairA
מועצב:רגיל, מימין לשמאל, ללא תבליטים או מספור
מועצב:סמן
מועצב:גופן: (אסיאתי) סינית (טיוואן)
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• צוואר נוקשה בעיות בעור.סימנים לכך עלולים להיות: • פריחה • גרד • הופעת שלפוחיות בעור • כיבים בחלל הפה או ברקמות ריריות נוספות		

מעוצב:גופן: 11 נק', גופן עבור עברית ושפות אחרות: 11 נק', סמן

מעוצב:סמן

מעוצב:גופן: (ברירת מחדל) Arial, מודגש, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: Arial, סמן

מעוצב:גופן: מודגש, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: לא מודגש, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: צבע גופן: שחור, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: צבע גופן: שחור, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: צבע גופן: שחור, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: צבע גופן: שחור, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: צבע גופן: שחור, (אסיאתי) סינית (טיוואן), סמן

מעוצב:גופן: צבע גופן: שחור, (אסיאתי) סינית (טיוואן), לא קו חוצה, סמן

מעוצב:גופן: צבע גופן: שחור, (אסיאתי) סינית (טיוואן), סמן