הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

תאריך 2.6.2016

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

שם בעל הרישום BRISTOL-MYERS SQUIBB (ISRAEL)

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות נובעות עקב הוספת מידע בעקבות הרחבת התוויה

ההחמרות המבוקשות		
פרק בעלון	טקסט נוכחי	טקסט חדש

.... **Unresectable or Metastatic Melanoma** • OPDIVO (nivolumab) as a single agent is indicated for the treatment of patients with advanced (unresectable or metastatic) melanoma in adults *[see Clinical Studies (14.1)]*. • 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)]*.	..... **Unresectable or Metastatic Melanoma** • OPDIVO (nivolumab) as a single agent is indicated for the treatment of patients with advanced (unresectable or metastatic) melanoma in adults *[see Clinical Studies (14.1)]*. • 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)]*.	**INDICATIONS AND USAGE**
Immune-Mediated Pneumonitis **Melanoma** *OPDIVO as a Single Agent* In Trials 1, 5, and 7, immune-mediated pneumonitis~~, including interstitial lung disease,~~ occurred in ~~3.4% (9/268~~1.8% (14/787) of patients receiving OPDIVO~~ and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis, occurred in 2.2% (6/268) of patients receiving OPDIVO: one~~ : two patients with Grade 3 and ~~five~~12 patients with Grade 2 pneumonitis. The median time to onset ~~for the six cases of immune-mediated pneumonitis~~ was 2.2 months (range: 25 days to ~~3.5~~9.7 months). ~~In two patients,~~Grade 3 pneumonitis ~~was diagnosed after~~led to permanent discontinuation ~~of OPDIVO for other reasons,~~in one patient (0.1%), and Grade 2 pneumonitis led to ~~interruption or permanent discontinuation~~ withholding of OPDIVO in ~~the remaining four~~eight patients~~.~~ (1.0%). All ~~six~~14 patients received high-dose corticosteroids (at	**Immune-Mediated Pneumonitis** **Melanoma** *OPDIVO as a Single Agent* 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, 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 Grade 2 pneumonitis that completely resolved (defined as complete resolution of	**WARNINGS AND PRECAUTIONS**

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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 Grade 2 pneumonitis that completely resolved~~) for a median duration of 18 days (range: 4 days to 1.2 months). Complete resolution (defined as complete resolution of symptoms with completion of corticosteroids) ~~and OPDIVO was restarted without~~ occurred in 11 patients. None of the seven patients who resumed OPDIVO after resolution had recurrence of pneumonitis. *OPDIVO as a Single Agent* In Trials 1, 5, and 7, immune-mediated pneumonitis occurred in 1.8% (14/787) of patients receiving OPDIVO: two patients with Grade 3 and 12 patients with Grade 2 pneumonitis. The median time to onset of immune-mediated pneumonitis was 2.2 months (range: 25 days to 9.7 months). Grade 3 pneumonitis led to permanent discontinuation in one patient (0.1%), and Grade 2 pneumonitis led to withholding of OPDIVO in eight patients (1.0%). All 14 patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 18 days (range: 4 days to 1.2 months). Complete resolution (defined as complete resolution of symptoms with completion of corticosteroids) occurred in 11 patients. None of the seven patients who resumed OPDIVO after resolution had recurrence of pneumonitis. *OPDIVO ~~in Combination~~ with Ipilimumab* In Trials 4 and 7, immune-mediated pneumonitis occurred in 6% (25/407) of patients receiving OPDIVO with ipilimumab: 1 fatal, 6 Grade 3, 17 Grade 2, and 1 Grade 1 pneumonitis. The median time to onset of immune-mediated pneumonitis was 1.6 months (range: 24 days to 10.1 months). Immune-mediated pneumonitis	symptoms with completion of corticosteroids) and OPDIVO was restarted without recurrence of pneumonitis. 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*	

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led to permanent discontinuation of OPDIVO and of ipilimumab in nine patients (2.2%) and withholding of OPDIVO and of ipilimumab in 15 patients (3.7%). Twenty-one patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 30 days (range: 5 days to 11.8 months). One patient with Grade 2 pneumonitis required mycophenolic acid in addition to high-dose corticosteroids. Complete resolution occurred in 17 patients. Among the eight patients who resumed OPDIVO with ipilimumab, one had recurrence of immune-mediated pneumonitis.

Immune-Mediated Colitis

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Melanoma

OPDIVO as a Single Agent

In ~~Trial~~Trials 1, 5, and 7, diarrhea or colitis occurred in ~~21% (57/268~~31% (242/787) of patients~~ receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy.~~ Immune-mediated colitis occurred in ~~2.2% (6/268~~4.1% (32/787) of patients~~ receiving OPDIVO: five~~ ; 20 patients with Grade 3, 10 patients with Grade 2, and ~~one patient~~two patients with Grade ~~2~~1 colitis. The median time to onset of immune-mediated colitis ~~from initiation of OPDIVO~~ was ~~2.~~5.6 months (range: ~~1~~3 days to ~~6~~13.1 months). ~~In three patients, colitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 or 3 colitis~~ Immune-mediated colitis led to ~~interruption or~~ permanent discontinuation of OPDIVO in ~~the remaining three~~seven patients~~. Five~~ (0.9%) and to withholding of ~~these~~OPDIVO in six patients (0.8%). Thirty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of ~~1.~~4.2 months (range: 3 days to

Immune-Mediated Colitis

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Melanoma

OPDIVO as a Single Agent

In Trial 1, diarrhea or colitis occurred in 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis 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

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~~2.4~~ 9.3 months~~) preceding corticosteroid taper. The sixth patient continued on low~~). Three patients with Grade 2 or 3 colitis required addition of infliximab to high-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~~. Complete resolution (defined as improved to ~~Grade 0~~baseline with completion of corticosteroids) ~~without additional events of colitis. Grade 2 colitis was ongoing in one patient~~occurred in 17 patients. Among the nine patients who resumed OPDIVO after resolution, two had recurrence of immune-mediated colitis. *OPDIVO with Ipilimumab* In ~~Trial 5~~Trials 4 and 7, diarrhea or colitis occurred in ~~28% (58/206~~56% (228/407) 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~~26% (107/407) of patients: 2 patients with Grade 4, 60 patients with Grade 3, 32 patients with Grade 2, and 13 patients with Grade ~~3 and five with Grade 2.~~1 colitis. The median time to onset of immune-mediated colitis was ~~5.~~1.6 months (range: 3 days to ~~12.5~~15.2 months). Immune-mediated colitis led to permanent discontinuation of OPDIVO ~~in combination with~~and of ipilimumab in ~~17~~64 patients~~. Thirty of the 31~~ (16%) or to withholding of OPDIVO and of ipilimumab in 30 patients (7%). One hundred three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.~~2 months~~1 month (range: 1 day to ~~6 months) and 11 received~~7 months). Twenty-five patients required addition of infliximab~~, Immune~~ to high-dose corticosteroids. Complete resolution occurred in 80 patients. Among the 29	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 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 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	

patients who resumed OPDIVO with ipilimumab after resolution, eight had recurrence of 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. ..... **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~~0.5 to ~~2~~1 mg/kg/day prednisone equivalents for moderate (Grade 2) ~~or greater~~ transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) 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** *OPDIVO as a Single Agent* In Trials 1, 5, and 7, immune-mediated hepatitis occurred in 2.3% (18/787) of patients receiving OPDIVO:	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. ..... **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** *OPDIVO as a Single Agent* 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 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	

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three patients with Grade 4, 11 patients with Grade 3, and four patients with Grade 2 hepatitis. The median time to onset was 3.7 months (range: 6 days to 9 months). Immune-mediated hepatitis led to permanent discontinuation of OPDIVO in five patients (0.6%) and withholding of OPDIVO in six patients (0.8%). All 18 patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 28 days (range: 5 days to 2 months). One patient with Grade 3 hepatitis required the addition of mycophenolic acid to high-dose corticosteroids. Complete resolution (defined as improved to baseline with completion of corticosteroids) occurred in 13 patients. Among the four patients who resumed OPDIVO after resolution, one had recurrence of immune-mediated hepatitis. *OPDIVO ~~in Combination~~ with Ipilimumab* In Trials 4 and 7, immune-mediated hepatitis occurred in 13% (51/407) of patients receiving OPDIVO with ipilimumab: eight patients with Grade 4, 37 patients with Grade 3, five patients with Grade 2, and one patient with Grade 1 hepatitis. The median time to onset was 2.1 months (range: 15 days to 11 months). Immune-mediated hepatitis led to permanent discontinuation of OPDIVO and of ipilimumab in 26 patients (6%) and withholding of OPDIVO and of ipilimumab in 21 patients (5%). Forty-seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.1 month (range: 1 day to 13.2 months). One patient (Grade 3 hepatitis) required infliximab, and four patients (three patients with Grade 3 or 4 transaminase increases and one patient with Grade 3 autoimmune hepatitis) required mycophenolic acid in addition to high-dose corticosteroids. Complete resolution occurred in 38 patients. Among the nine patients who resumed OPDIVO with ipilimumab after resolution, one had recurrence of hepatitis.	days of initiation of corticosteroids. Immune-mediated hepatitis resolved and did not recur with continuation of corticosteroids 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 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%), 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. ..... **Immune-Mediated Endocrinopathies** **Hypophysitis**	

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מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', לא מודגש, לא נטוי, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), 10 נק'

מעוצב:H gnidaeH SMB 4

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', נטוי, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

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.....	***Melanoma***	
Immune-Mediated Endocrinopathies	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.	
Hypophysitis		
....	.....	
Melanoma		
OPDIVO as a Single Agent		
In ~~Trial 4~~Trials 1, 5, and 7, hypophysitis occurred in ~~13% (12/94~~0.9% (7/787) of patients ~~receiving OPDIVO in combination with ipilimumab~~; two patients with Grade ~~3 and 10~~, three patients with Grade 2, and two patients with Grade 1 hypophysitis. The ~~median~~ time to onset was ~~2.9~~5.5 months (range: 1.~~4~~6 to ~~5.5~~11 months). ~~Ten~~Hypophysitis led to withholding of OPDIVO in one patient (0.1%). Three patients received high-dose corticosteroids~~, including both patients~~ (at least 40 mg prednisone equivalents) for a median duration of 22 days (range: 5 to 26 days).		
.....		
OPDIVO with Ipilimumab		
In Trials 4 and 7, hypophysitis occurred in 9% (36/407) of patients: eight patients with Grade 3, 25 patients with Grade 2, and three patients with Grade 1 hypophysitis. The median time to onset was 2.7 months (range: 27 days to 5.5 months). Hypophysitis led to permanent discontinuation of OPDIVO and of ipilimumab in four patients (1.0%) and withholding of OPDIVO and of ipilimumab in 16 patients (3.9%). Twenty patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 19 days (range: 1 day to 2.0 months).		
.....	.....	
	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	

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~~*** *OPDIVO as a Single Agent* In ~~Trial 4~~Trials 1, 5, and 7, adrenal insufficiency occurred in ~~9~~1% (8/~~94~~787) of patients~~ receiving OPDIVO in combination with ipilimumab: three~~ : two patients with Grade 3, ~~four~~five patients with Grade 2, and one patient with Grade 1 adrenal insufficiency. The median time to onset was 3.6 months (range: ~~1.2~~15 days to 5.~~6~~0 months). ~~Grade 3 adrenal~~Adrenal insufficiency led to ~~discontinuation~~withholding 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~~four patients (0.5%). One patient received high-dose corticosteroids~~. Six~~ (at least 40 mg prednisone equivalents) for 11 days. *OPDIVO with Ipilimumab* In Trials 4 and 7, adrenal insufficiency occurred in 5% (21/407) of patients: one patient with Grade 4, seven patients with Grade 3, 11 patients with Grade 2, and two patients with Grade 1 adrenal insufficiency. The median time to onset was 3.0 months (range: 21 days to 9.4	(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.	

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מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', לא מודגש, לא נטוי, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), 10 נק'

מעוצב:SMB Heading 4

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', נטוי, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

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months). Adrenal insufficiency led to permanent discontinuation of OPDIVO and of ipilimumab in two patients (0.5%) and withholding of OPDIVO and of ipilimumab in seven patients (1.7%). Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 9 days (range: 1 day to 2.7 months). ... **Hypothyroidism and Hyperthyroidism** ..... ***Melanoma*** *OPDIVO as a Single Agent* In Trials 1, 5, and 7, hypothyroidism or thyroiditis occurred in 9% (73/787) of patients: one patient with Grade 3, 37 patients with Grade 2, and 35 patients with Grade 1 hypothyroidism. The median time to onset was 2.8 months (range: 15 days to 13.8 months). Resolution occurred in 26 patients. Management of hypothyroidism included levothyroxine in 56 patients. Hyperthyroidism occurred in 4.4% (35/787) of patients receiving OPDIVO: one patient with Grade 3, 12 patients with Grade 2, and 22 patients with Grade 1 hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 13.4 months). Resolution occurred in 27 patients. Management of hyperthyroidism included methimazole (five patients), carbimazole (four patients), and propylthiouracil (two patients). *OPDIVO with Ipilimumab* In Trials 4 and 7, hypothyroidism or thyroiditis occurred in 22% (89/407) of patients: six patients with Grade 3, 47	**Hypothyroidism and Hyperthyroidism** ..... ***Melanoma*** *OPDIVO as a Single Agent* In Trial 1, 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. In Trial 1, Grade 1 or 2 hyperthyroidism occurred in 3.0% (8/268) of patients receiving OPDIVO and 1.0% (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 resolution of hyperthyroidism; all three patients received medical management for Grade 2 hyperthyroidism. 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	

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מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), סמן

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', נטוי, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), סמן

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', נטוי, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), סמן

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), 10 נק', סמן

patients with Grade 2, and 36 patients with Grade 1 hypothyroidism. The median time to onset was 2.1 months (range: 1 day to 10.1 months). Resolution occurred in 40 patients. Management of hypothyroidism included levothyroxine (65 patients). Hyperthyroidism occurred in 8% (34/407) of patients receiving OPDIVO with ipilimumab: four patients with Grade 3, 17 patients with Grade 2, and 13 patients with Grade 1 hyperthyroidism. The median time to onset was 23 days (range: 3 days to 3.7 months). Resolution occurred in 32 patients. Management of hyperthyroidism included methimazole (ten patients) and carbimazole (eight patients). .... **Type 1 Diabetes Mellitus**	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 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. .... **Type 1 Diabetes Mellitus** ..... ***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 diabetic ketoacidosis	

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', מודגש, נטוי, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

מעוצב:גופן ברירת המחדל של פיסקה, גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', מודגש, צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA)

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), 10 נק'

מעוצב:4 gnidaeH SMB, כניסה: לפני: 0 ס"מ, תלויה: 30.2 ס"מ, רווח לפני: 0 נק', אל תשמור עם הבא

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..... ***Melanoma*** ***OPDIVO as a Single Agent*** In ~~Trial~~Trials 1, 5, and 7, diabetes mellitus or diabetic ketoacidosis occurred in ~~1.~~0~~% (2/206~~.8% (6/787) of patients ~~receiving OPDIVO and none of the 205 receiving dacarbazine. One patient had~~ : two patients with Grade 3, three patients with Grade 2, and one patient with Grade 1 events. The median time to onset was 3.6 months (range: 1.4 to 12 months). Four patients initiated insulin and four patients initiated oral hypoglycemic therapy. *OPDIVO with Ipilimumab* In Trials 4 and 7, diabetes mellitus or, diabetic ketoacidosis ~~and one patient had Grade 2 diabetes mellitus. Neither~~occurred in 1.5% (6/407) of patients: three patients with Grade 4, one patient with Grade 3, one patient ~~had a prior history of diabetes. Time~~with Grade 2, and one patient with Grade 1 events. The median 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 diabetic ketoacidosis resolved, and 5~~ months (range: 1.3 to 4.4 months). Grade 4 diabetes led to permanent discontinuation of OPDIVO ~~was resumed.~~and of ipilimumab in one patient and Grade ~~2~~3 diabetes ~~mellitus, which began while the patient was receiving corticosteroids for management of another adverse reaction, remained ongoing with continuation~~led to withholding of OPDIVO~~.~~ and of ipilimumab in one patient. Six patients initiated insulin and four patients initiated oral hypoglycemic therapy. .... 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. .... **Immune-Mediated Nephritis and Renal Dysfunction** ..... **Melanoma** *OPDIVO as a Single Agent* 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 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	

Immune-Mediated Nephritis and Renal Dysfunction ..... **Melanoma** *OPDIVO as a Single Agent* In ~~Trial~~Trials 1, ~~there was an increased incidence~~ 5, and 7, nephritis and renal dysfunction of ~~elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs. 9%).~~ any grade occurred in 5% (40/787) of patients. Immune-mediated nephritis and renal dysfunction occurred in 0.8% (6/787) of patients: four patients with Grade 3 and two patients with Grade 2 ~~or 3~~ cases. The median time to onset of immune-mediated nephritis ~~or~~and renal dysfunction ~~occurred in 0.7% (2/268) of patients at 3.5 and 6~~ was 4.8 months ~~after OPDIVO initiation, respectively. OPDIVO was permanently discontinued~~(range: 1 to 7.5 months). Immune-mediated nephritis and renal dysfunction led to withholding of OPDIVO in ~~both~~four patients~~; both~~ (0.5%). Six patients 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 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~~) for a median duration of ~~high-dose corticosteroids were followed by complete~~16 days (range: 1 day to 9.9 months). Complete resolution (defined as improved to ~~Grade 0~~baseline with completion of corticosteroids~~). OPDIVO was restarted with~~) occurred in three patients.	continuation of corticosteroids in one patient. Renal dysfunction was ongoing in one patient. 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. *OPDIVO in Combination with Ipilimumab* 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: (ברירת מחדל) +גוף עברי (lairA), 10 נק', גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), סמן

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), סמן

מעוצב:אל תשמור עם הבא, אל תשמור שורות יחד

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), סמן

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מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', צבע גופן: שחור, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), סמן

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', נטוי, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), סמן

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', נטוי, גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), סמן

מעוצב:גופן: (ברירת מחדל) +גוף עברי (lairA), 10 נק', גופן עבור עברית ושפות אחרות: +גוף עברי (lairA), 10 נק', סמן

מעוצב:אל תשמור עם הבא, אל תשמור שורות יחד

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Three patients resumed OPDIVO after resolution without recurrence of nephritis or renal dysfunction~~ and again resolved with corticosteroids~~.

OPDIVO ~~in Combination~~ with Ipilimumab

In ~~Trial~~Trials 4~~, Grade 2 or higher~~ and 7, immune-mediated nephritis ~~or~~and renal dysfunction occurred in 2.~~1% (2/94~~% (9/407) of patients~~. Time~~: four patients with Grade 4, three patients with Grade 3, and two patients with Grade 2 cases. The median time to onset was ~~1.3 weeks and 6~~2.7 months~~, respectively. In one of these patients, immune-~~ (range: 9 days to 7.9 months). Immune-mediated nephritis and renal dysfunction ~~resolved with corticosteroids~~ led to permanent discontinuation of OPDIVO and of ipilimumab in three patients (0.7%) and withholding of OPDIVO~~, whereas the second patient died with persistent~~ and of ipilimumab in two patients (0.5%). Six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 13.5 days (range: 1 day to 1.1 months). Complete resolution occurred in nine patients. Two patients resumed OPDIVO with ipilimumab after resolution without recurrence of nephritis or renal dysfunction.

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Immune-Mediated Rash

.....

Melanoma ~~(OPDIVO in Combination with Ipilimumab) and NSCLC~~

OPDIVO as a Single Agent

In ~~Trial 4~~Trials 1, 5, and 7, immune-mediated rash occurred in ~~37% (35/94~~9% (72/787) of patients~~ receiving OPDIVO in combination with ipilimumab: six~~: seven patients with Grade 3, ~~10~~15 patients with Grade 2, and

Immune-Mediated Rash

.....

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. .....

~~19~~ 50 patients with Grade 1 rash. The median time to onset was 2.~~4 weeks (range: 1 day to 6.5 months).~~8 months (range: 3 days to 13.8 months). Immune-mediated rash led to permanent discontinuation of OPDIVO in one patient (0.1%) and withholding of OPDIVO in six patients (0.8%). Seven patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 15 days (range: 4 days to 1.0 months). Complete resolution (defined as complete resolution of symptoms with completion of corticosteroids) occurred in 32 patients (44%). Among the ~~six~~35 patients who resumed OPDIVO after resolution, one had recurrence. *OPDIVO with Ipilimumab* In Trials 4 and 7, immune-mediated rash occurred in 22.6% (92/407) of patients: 15 patients with Grade 3 ~~rash, four received systemic corticosteroids, four had OPDIVO in combination with~~, 31 patients with Grade 2, and 46 patients with Grade 1 rash. The median time to onset was 18 days (range: 1 day to 9.7 months). Immune-mediated rash led to permanent discontinuation of OPDIVO and of ipilimumab in two patients (0.5%) and withholding of OPDIVO and of 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~~in 16 patients (3.9%). Sixteen patients received ~~systemic~~high-dose corticosteroids ~~and two had OPDIVO in combination with~~(at least 40 mg prednisone equivalents) for a median duration of 14 days (range: 2 days to 4.7 months). Complete resolution occurred in 43 patients. Among the 54 patients who resumed OPDIVO and ipilimumab ~~withheld. None of the 35 patients discontinued treatment due to immune-mediated rash.~~ after resolution, three had recurrence.	**Immune-Mediated Encephalitis** ..... 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** ..... 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): uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica,autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, and systemic inflammatory response syndrome	

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.....	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, 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.		
Immune-Mediated 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. In Trial 7, encephalitis was identified in one patient receiving OPDIVO with ipilimumab (0.2%) after 1.7 months of exposure. **Other Immune-Mediated Adverse Reactions** ..... ~~The following clinically significant, immune-mediated adverse reactions occurred in~~In less than 1.0% of patients receiving OPDIVO as a single agent or in combination with ipilimumab in Trials 1, 3, 4, 5, 6, and ~~6~~7 (n=~~1261):~~ 1887), the following clinically significant, immune-mediated adverse reactions occurred: uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, ~~and~~ systemic inflammatory response syndrome~~—~~, gastritis, duodenitis, and sarcoidosis. 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, 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~~motor dysfunction, vasculitis, and myasthenic syndrome.	**Infusion Reactions** ..... **Melanoma and NSCLC** 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.	

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Infusion Reactions ..... **Melanoma ~~and~~ ~~NSCLC~~** In Trials ~~3 and~~1, 5, ~~Grade 2~~and 7, infusion-related reactions occurred in ~~1.0% (5/493~~2.7% (21/787) of patients receiving OPDIVO~~. In Trial 4,~~: two patients with Grade 3, eight patients with Grade 2, and 11 patients with Grade 1 infusion-related reactions. In Trials 4 and 7, infusion-related reactions occurred in ~~3.~~2~~% (3/94~~.5% (10/407) of patients receiving OPDIVO ~~in combination~~ with ipilimumab~~.~~: six patients with Grade 2 and four patients with Grade 1 infusion-related reactions. **NSCLC** In Trial 3, Grade 2 infusion reactions requiring corticosteroids occurred in 1.0% (3/287) of patients receiving OPDIVO.		

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מעוצב:גופן: גופן עבור עברית ושפות אחרות: 10 נק'

Unresectable or Metastatic Melanoma ..... ~~*OPDIVO in Combination with Ipilimumab*~~ Trial 7 The safety of OPDIVO, administered ~~in combination~~ with ipilimumab or as a single agent, was evaluated in Trial ~~4,~~7 *[see Clinical Studies (14.1)]*, a randomized, (1:1:1), a double-blind trial in which ~~140~~ 937 patients with 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,~~4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks (~~n=94) or single-agent~~OPDIVO plus ipilimumab arm; n=313), • OPDIVO 3 mg/kg every 2 weeks (OPDIVO arm; n=313), or • Ipilimumab 3 ~~weeks for four cycles followed by placebo~~ mg/kg every ~~2~~3 weeks ~~(n=46) *[see Clinical Studies (14.1)]*.~~ for up to 4 doses (ipilimumab arm; n=311). The median duration of exposure to OPDIVO was 2.~~2~~8 months (range: 1 day to ~~10~~18.8 months~~). Among patients who received OPDIVO in combination with ipilimumab, 29~~) for the OPDIVO plus ipilimumab arm and 6.6 months (range: 1 day to 17.3 months) for the OPDIVO arm. In the OPDIVO plus ipilimumab arm, 39% were exposed to OPDIVO for ~~at least 6 months~~≥6 months and 24% exposed for >1 year. In the OPDIVO arm, 53% were exposed for ≥6 months and 32% for >1 year. ~~Trial 4 enrolled patients who had not received systemic anticancer therapy for unresectable or metastatic melanoma and~~ Trial 7 excluded patients with ~~ocular melanoma,~~ autoimmune disease, ~~any~~a medical condition requiring ~~chronic~~ systemic treatment with corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive ~~medications~~medication within 14 days of the start of study therapy, a positive test result for hepatitis B or C, or a history of HIV. The study population characteristics were: ~~67~~65% male, median age ~~65~~61 years, ~~98% white~~97% White, baseline ECOG performance status 0 (~~82~~73%) or 1	**Unresectable or Metastatic Melanoma** ..... *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 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.	**Clinical** **Experienc**

(~~17%), 46~~27%), 93% with AJCC Stage IV disease, 58% with M1c stage disease; ~~25~~36% with elevated LDH at baseline, ~~3~~4% with a history of brain metastasis, and ~~23~~22% 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%).~~received adjuvant therapy. ~~Serious~~In Trial 7, serious adverse reactions (~~62% vs. 39~~73% and 37%), adverse reactions leading to permanent discontinuation (43% ~~vs. 11~~and 14%) or ~~dose~~to dosing delays (~~47% vs. 22~~55% and 28%), and Grade 3 or 4 adverse reactions (~~69% vs. 43~~72% and 44%) all occurred more frequently in ~~patients receiving~~ the OPDIVO plus ipilimumab arm relative to the OPDIVO arm. The most frequent (≥10%) serious adverse reactions in the OPDIVO plus ipilimumab ~~compared with those receiving single-agent ipilimumab. In~~ arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). The most frequent adverse reactions leading to discontinuation of both drugs in the OPDIVO plus ipilimumab ~~group, 27% (25/94) of patients did not complete all four cycles~~arm and 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.~~ ~~The most common adverse reactions leading to discontinuation of~~ the OPDIVO~~, as compared to single-agent ipilimumab~~ arm, respectively, were ~~colitis (16% vs. 2%), diarrhea not treated with corticosteroids (4% vs. 4~~diarrhea (8% and 1.9%), colitis (8% and 0.6%), increased ALT ~~levels (4% vs. 0),~~(4.8% and 1.3%), increased AST (4.5% and 0.6%), and pneumonitis (~~3% vs. 0),~~1.9% and ~~AST increase (3% vs. 0).~~0.3%). The most ~~frequent serious~~common (≥20%) adverse ~~events with~~reactions in the OPDIVO ~~in combination with~~plus ipilimumab~~, as compared to single-agent ipilimumab,~~ arm were ~~colitis (17% vs. 9%),~~fatigue, rash, diarrhea ~~(9% vs. 7%),~~, nausea, pyrexia ~~(6% vs. 7%),~~, vomiting, and ~~pneumonitis (5% vs. 0).~~dyspnea. The most common (≥20%) adverse reactions ~~(reported~~ in ~~at least 20% of patients) in Trial 4 receiving~~the OPDIVO ~~in combination with ipilimumab~~arm were fatigue, rash, ~~pruritus, headache, vomiting~~diarrhea, and ~~colitis.~~	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%). 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	

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nausea. Table 6 summarizes the incidence of ~~selected~~ adverse reactions occurring in at least 10% of patients ~~treated with~~in either OPDIVO~~-~~-containing arm in ~~combination with ipilimumab~~Trial 7.

Table 6: Selected Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO plus Ipilimumab Arm or the OPDIVO Arm and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 7)

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

3 or 4 adverse reaction during administration of OPDIVO as a single agent.

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 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.

Disorders						
Dyspnea	20	2.2	12	1.3	13	0.6

Toxicity was graded per NCI CTCAE v4.

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

[b] Rash is a composite term which includes rash pustular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption, erythema, exfoliative rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash morbilliform, rash papular, ~~and~~ rash papulosquamous, rash pruritic, and seborrheic dermatitis.

Other clinically important adverse reactions in less than 10% of patients treated with either OPDIVO ~~in combination~~ with ipilimumab or single-agent OPDIVO in Trial 7 were:

~~*Nervous System Disorders:* peripheral neuropathy~~

Gastrointestinal Disorders: stomatitis, ~~colonic~~intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

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

Nervous System Disorders: neuritis, peroneal nerve palsy

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

Test	Percentage (%) of Patients[a]			
	OPDIVO plus Ipilimumab		OPDIVO	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Chemistry				
Increased ALT	53	15	23	3.0
Increased AST	47	13	27	3.7

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)

	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	28	2.7		
	27	1.7		

Hyponatremia	42	9	20	3.3
Increased lipase	41	20	29	9
Increased alkaline phosphatase	40	6	24	2.0
Hypocalcemia	29	1.1	13	0.7
Increased amylase	25	9.1	15	1.9
Increased creatinine	23	2.7	16	0.3
Hematology				
Anemia	50	2.7	39	2.6
Lymphopenia	35	4.8	39	4.3

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO plus ipilimumab (range: 241 to 297); OPDIVO (range: 260 to 306); ipilimumab (range: 253 to 304).

....

Disorders	25	7		
Headache	23	7	24	2.1	20	0
Gastrointestinal Disorders	22	2.0				
	21	0.7				
	14	1.6				
Vomiting	23		2.1	15	0
	16	1.3				
Colitis	22		16	11	7
Metabolism and Nutrition Disorders	40	6				
	27	3.4				
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

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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

Table 7: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥□0% 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	
	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: OPDIVO in combination with ipilimumab group (range: 84 to 88 patients) and ipilimumab group (range: 45 to 46 patients).

[b] 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.

Geriatric Use

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 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~~Of the 316 patients randomized to OPDIVO in Trial 7, 37% were 65 years or older and 12% were 75 years or older. 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.~~

Of the 314 patients randomized to OPDIVO administered with ipilimumab in Trial 7, 41% were 65 years or older and 11% were 75 years or older. No overall differences in safety or efficacy were reported between elderly patients and

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 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

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מעוצב:מנע הפרדת פיסקאות, מנע הפרדת שורות, עצירות טאב: לא ב 0 ס"מ + 72.1 ס"מ

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	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.	younger patients.

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מעוצב:gnidaeH SMB 2, מיושר לשני הצדדים, כניסה: לפני: 0 ס"מ, תלויה: 30.2 ס"מ

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.
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הועבר בדואר אלקטרוני בתאריך...2.6.2016.

- ✓ כל השינויים עולים בקנה אחד עם תנאי הרישום (תעודת הרישום, תעודת האיכות וטופס פרטי התכשיר העדכני).
- ✓ כל הכתוב בהצעת העלון, תואם את תנאי הרישום.
- ✓ קיים עלון לרופא והוא מעודכן בהתאם (הוגש).
- ✓ אסמכתא לבקשה:USPI, Jan 2016 - **האסמכתא מצ"ב.**
- ✓ השינוי הנ"ל אושר על ידי רשויות הבריאות בארה"ב
- ✓ אני, הרוקח הממונה של חברת בריסטול- מאיירס סקוויב מצהיר בזה כי אין שינויים נוספים, מלבד אלה שסומנו בהצעת העלון.
- ✓ אני מצהיר כי השינויים אינם יוצרים סתירה פנימית במידע בעלון.
- ✓ **ע**לון זה לא מטופל במקביל במסגרת אחרת (כגון: עדכון עלון במסגרת בקשה לתוספת התוויה, החמרה וכו') . במידה וקיים טיפול מקביל במסגרת אחרת- יש לציין זאת. **העלון מוגש במסגרת בקשה לתוספת התוויה**

חתימת הרוקח הממונה (שם וחתימה) **טליה בן דוד**

- **הודעה על החמרה (מידע בטיחות) בעלון לצרכן**
- **(מעודכן 05.2013)**

תאריך 2.6.2016

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

שם בעל הרישום Bristol-Myers Squibb Israel Ltd.

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
4. תופעות לוואי:	..	...
	תופעות הלוואי השכיחות ביותר במתן של אופדיבו לבד 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 • כאב ראש • הקאה	תופעות הלוואי השכיחות ביותר במתן של אופדיבו לבד באנשים בעלי מלנומה הינן: • עייפות • כאב בשרירים, בעצמות ובמפרקים • שלשול • פריחה • גירוד בעור • בחילה תופעות הלוואי השכיחות ביותר במתן משולב של אופדיבו עם יירבוי Yervoy (Ipilimumab) הן: • ~~פריחה~~ • ~~גרד~~ • ~~דלקת של המעי (קוליטיס) -ראה מטה בעיות במעיים~~ • ~~כאב ראש~~
	...	...

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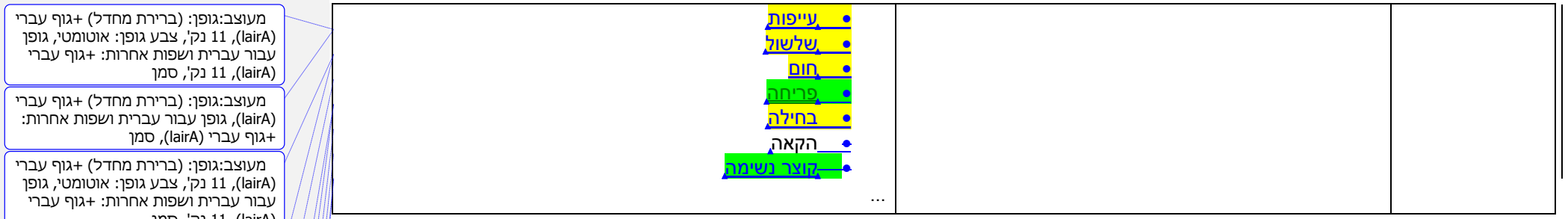

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