



מאי 2017

Opdivo (nivolumab)
Concentrate for solution for infusion

רופא/ה, רוקח/ת יקר/ה,

חברת בריסטול-מאיירס סקוויב (ישראל) שמחה לבשר על אישור משרד הבריאות להרחבת ההתוויה של התכשיר **אופדיבו** (ניבולומב) בישראל.

ההתוויות אשר אושרו על ידי משרד הבריאות (טקסט שנוסף מסומן בצבע אדום ובקו תחתון) :

Opdivo (nivolumab) is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Opdivo, in combination with ipilimumab, is indicated for the treatment of patients with advanced (unresectable or metastatic) melanoma.

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.

Opdivo (nivolumab) is indicated for the treatment of patients with advanced clear cell renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

Opdivo (nivolumab) is indicated for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post transplantation brentuximab vedotin.

OPDIVO is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

בנוסף עודכנו העלון לרופא והעלון לצרכן.
בפירוט שלהלן כלולים העדכונים המהותיים בלבד (טקסט שנוסף מסומן בצבע אדום ובקו תחתון, טקסט שהוסר מסומן בצבע אדום ובקו אמצעי).
למידע מלא על התרופה יש לעיין בעלון לרופא ובעלון לצרכן כפי שאושרו על ידי משרד הבריאות.

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפס על ידי פנייה לבעל הרישום בריסטול-מאיירס סקוויב (ישראל) בע"מ, ת.ד. 3661, קרית אריה, פתח תקווה 4951448 או בטלפון 03-5231021.

בכבוד רב,
מיכל ניר ורדימון
מנהלת רגולציה

1 INDICATIONS AND USAGE

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1.5 Squamous Cell Carcinoma of the Head and Neck

OPDIVO is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy [see Clinical Studies (14.5)].

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2 DOSAGE AND ADMINISTRATION

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2.5 Recommended Dosage for SCCHN

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

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5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

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

Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis every 2 to 3 days for mild (Grade 1) and daily for moderate (Grade 2) Pneumonitis

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5.3 Immune-Mediated Hepatitis

OPDIVO can cause immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology. Monitor patients for abnormal liver tests prior to and periodically during treatment. Increase frequency monitoring to every 3 days for moderate (Grade 2) and to every 1 to 2 days for severe (Grade 3) or life threatening (Grade 4) transaminase elevations with or without concomitant elevation in total bilirubin.

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5.5 Immune-Mediated Nephritis and Renal Dysfunction

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

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5.7 Immune-Mediated Encephalitis

~~OPDIVO~~OPDIVO can cause immune-mediated encephalitis with no clear alternate etiology.

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6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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Also described below are single-agent OPDIVO data from Trials 2 and 3, which are randomized trials in patients with metastatic NSCLC, Trial 5, which is a randomized trial in patients with advanced RCC, Trials 7 and 8, which are open-label, multiple-cohort trials in patients with cHL₂, and Trial 9, a randomized trial in patients with recurrent or metastatic SCCHN.

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Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

The safety of OPDIVO was evaluated in Trial 9, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCHN with progression during or within 6 months of receiving prior platinum-based therapy [see Clinical Studies (14.5)]. Patients received 3 mg/kg of OPDIVO (n=236) administered intravenously (IV) over 60 minutes every 2 weeks or investigator's choice of either:

- cetuximab (n=13), 400 mg/m² loading dose IV followed by 250 mg/m² weekly
- or methotrexate (n=46) 40 to 60 mg/m² IV weekly, or
- docetaxel (n=52) 30 to 40 mg/m² IV weekly.

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

Trial 9 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma).

The median age of all randomized patients was 60 years (range: 28 to 83); 28% of patients in the OPDIVO group were ≥65 years of age and 37% in the comparator group were ≥65 years of age, 83% were male and 83% were White, 12% were Asian, and 4% were Black. Baseline ECOG performance status was 0 (20%) or 1 (78%), 45% of patients received only one prior line of systemic therapy, the remaining 55% of patients had two or more prior lines of therapy, and 90% had prior radiation therapy.

OPDIVO was discontinued in 14% of patients and was delayed in 24% of patients for an adverse reaction. Serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. Adverse reactions and laboratory abnormalities occurring in patients with SCCHN were generally similar to those occurring in patients with melanoma and NSCLC. The most common adverse reactions occurring in >10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were cough and dyspnea.

The most common laboratory abnormalities occurring in ≥10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were increased alkaline phosphatase, increased amylase, hypercalcemia, hyperkalemia, and increased TSH.

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14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

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Previously Untreated Metastatic Melanoma

Trial 4

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Table 14: Efficacy Results - Trial 4

	OPDIVO (n=210)	Dacarbazine (n=208)
Overall Survival		
Deaths (%)	50 (24)	96 (46)
Median, months (95% CI)	Not Reached	10.8 (9.3, 12.1)
Hazard ratio (95% CI) ^a	0.42 (0.30, 0.60)	
p-value ^{b,c}	<0. 0001 ^a <u>0001</u>	
Progression-Free Survival		
Disease progression or death (%)	108 (51)	163 (78)
Median, months (95% CI)	5.1 (3.5, 10.8)	2.2 (2.1, 2.4)
Hazard ratio (95% CI) ^a	0.43 (0.34, 0.56)	
p-value ^{b,c}	<0. 0001 ^a <u>0001</u>	
Objective Response Rate	34%	9%
(95% CI)	(28, 41)	(5, 13)
Complete response rate	4%	1%
Partial response rate	30%	8%

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14.2 Metastatic Non-Small Cell Lung Cancer (NSCLC)

Second-line Treatment of Metastatic Squamous NSCLC

Table 16: Efficacy Results in Trial 2

	OPDIVO (n=135)	Docetaxel (n=137)
Overall Survival		
Deaths (%)	86 (64%)	113 (82%)
Median (months) (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
Hazard ratio (95% CI) ^a	0.59 (0.44, 0.79)	
p-value ^{b,c}	0.0002	
Objective Response Rate	27 (20%)	12 (9%)
(95% CI)	(14, 28)	(5, 15)
p-value ^d	0.0083	
Complete response	1 (0.7%)	0
Median duration of response, months (95% CI)	NR (9.8, NR)	8.4 (3.6, 10.8)
Progression-free Survival		
Disease progression or death (%)	105 (78%)	122 (89%)
Median (months)	3.5	2.8
Hazard ratio (95% CI) ^{e,f}	0.62 (0.47, 0.81)	
p-value ^a <u>value</u> ^b	0.0004	

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14.5 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Trial 9 was a randomized (2:1), active-controlled, open-label study enrolling patients with metastatic or recurrent SCCHN who had experienced disease progression during or within 6 months of receiving platinum-based therapy administered in either the adjuvant, neo-adjuvant, primary (unresectable locally advanced) or metastatic setting. The trial excluded patients with autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. Patients were randomized to receive OPDIVO administered intravenously (IV) at 3 mg/kg every 2 weeks or investigator's choice of:

- cetuximab 400 mg/m² loading dose IV followed by 250 mg/m² weekly,
- methotrexate 40 to 60 mg/m² IV weekly, or
- docetaxel 30 to 40 mg/m² IV weekly.

Randomization was stratified by prior cetuximab treatment (yes/no). The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS and ORR.

In Trial 9, total of 361 patients were randomized; 240 patients to OPDIVO and 121 patients to investigator's choice (45% received docetaxel, 43% received methotrexate, and 12% received cetuximab). The median age was 60 years (range: 28 to 83) with 31% ≥65 years of age, 83% were White, 12% Asian, and 4% were Black, and 83% male. Baseline ECOG performance status was 0 (20%) or 1 (78%), 76% were former/current smokers, 90% had Stage IV disease, 45% of patients received only one prior line of systemic therapy, the remaining 55% received two or more prior lines of systemic therapy, and 25% had HPVp16-positive tumors, 24% had HPV p16-negative tumors, and 51% had unknown status.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). The survival results are displayed in Table 20 and Figure 11. There were no statistically significant differences between the two arms for PFS (HR=0.89; 95% CI: 0.70, 1.13) or ORR (13.3% [95% CI: 9.3, 18.3] vs 5.8% [95% CI: 2.4, 11.6] for nivolumab and investigator's choice, respectively).

Table 20: Overall Survival in Trial 9

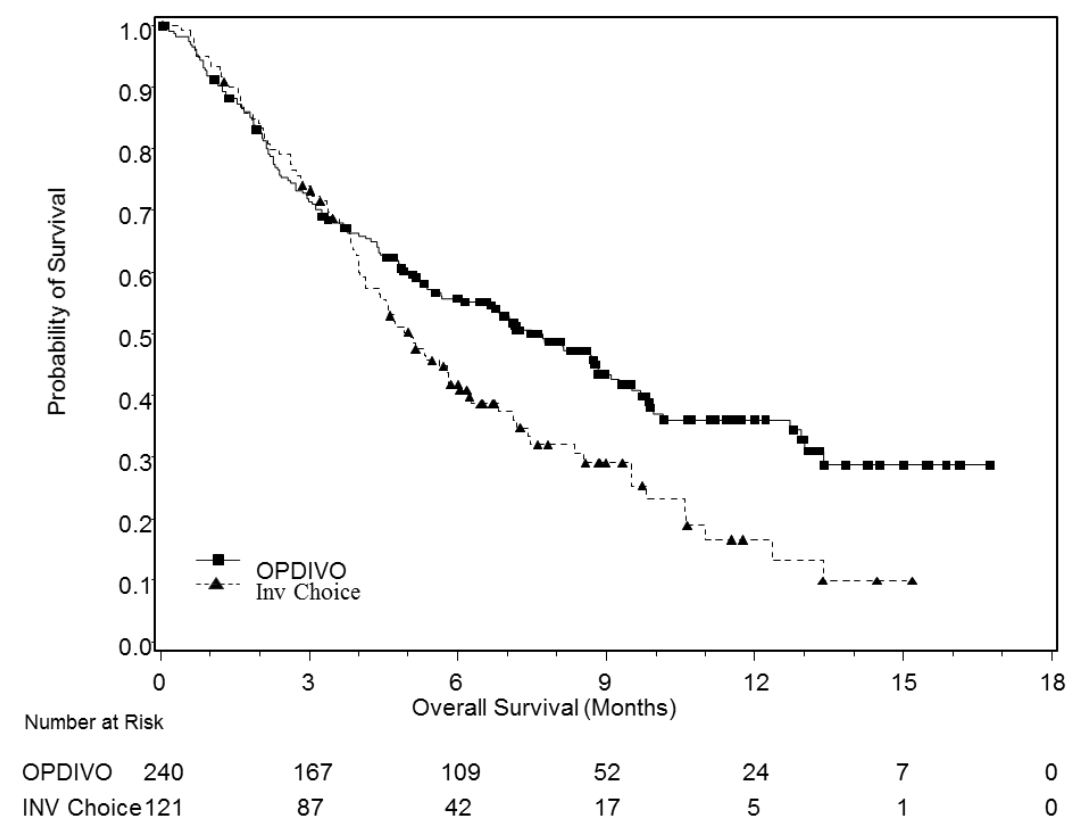
	<u>OPDIVO (n=240)</u>	<u>Investigator's Choice (n=121)</u>
<u>Overall Survival</u>		
<u>Deaths (%)</u>	<u>133 (55%)</u>	<u>85 (70%)</u>
<u>Median (months) (95% CI)</u>	<u>7.5 (5.5, 9.1)</u>	<u>5.1 (4.0, 6.0)</u>
<u>Hazard ratio (95% CI)^a</u>	<u>0.70 (0.53, 0.92)</u>	
<u>p-value^{b,c}</u>	<u>0.0101</u>	

^a Based on stratified proportional hazards model.

^b Based on stratified log-rank test.

^c p-value is compared with 0.0227 of the allocated alpha for this interim analysis.

Figure 11: Overall Survival - Trial 9



Archival tumor specimens were retrospectively evaluated for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx assay. Across the study population, 28% (101/361) of patients had non-quantifiable results. Among the 260 patients with quantifiable results, 43% (111/260) had PD-L1 negative SCCHN, defined as <1% of tumor cells expressing PD-L1, and 57% (149/260) had PD-L1 positive SCCHN, defined as $\geq 1\%$ of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratio for survival was 0.89 (95% CI: 0.54, 1.45) with median survivals of 5.7 and 5.8 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 negative subgroup. The HR for survival was 0.55 (95% CI: 0.36, 0.83) with median survivals of 8.7 and 4.6 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 positive SCCHN subgroup.

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עדכונים מהותיים בעלון לצרכן:

1. למה מיועדת התרופה?

אופדיבו ניתנת לטיפול ב:

- סרטן ראש וצוואר.

אופדיבו ניתנת לחולים שמחלתם חזרה או התפשטה לאחר טיפולים כימותרפיים המבוססים על פלטינום, או במהלכם.

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2. לפני שימוש בתרופה:

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

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1 הריון והנקה:

אופדיבו עלולה לפגוע בעוברך.

נשים היכולות להרות צריכות להשתמש באמצעי מניעה יעיל במהלך הטיפול ולמשך לפחות במשך 5 חודשים לאחר מתן המנה האחרונה של אופדיבו. היועצי ברופא המטפל שלך לגבי אמצעי המניעה בהם תוכלי להשתמש בתקופת הטיפול.

דווחי לרופא המטפל באופן מיידי אם נכנסת להריון במהלך הטיפול באופדיבו. אל תניקי במהלך הטיפול באופדיבו, לא ידוע אם אופדיבו יכולה לעבור לחלב האם שלך.

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4. תופעות לוואי:

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אופדיבו הינה תרופה המטפלת במלנומה, בסרטן ריאות, בסרטן תאי הכליה או בסרטן תאי הדם וסרטן ראש וצוואר על-ידי שפעול מערכת החיסון שלך. אופדיבו עלולה לגרום למערכת החיסון שלך לתקוף רקמות ואיברים בריאים במקומות רבים בגוף שלך ולהשפיע על אופן פעילותם. פעילות זו עלולה לגרום לתופעות לוואי חמורות או מסכנות חיים אף להביא להבאיא למוות.

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פנה מיד לרופא אם הנך חווה את התסמינים הבאים או אם ישנה החמרה בתסמינים הבאים:

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

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- נטייה לדימום או לחבורות יותר בקלות מהרגיל

...

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

- כאבי ראש שאינם חולפים או כאבי ראש לא אופייניים

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

- עייפות
- שלשול
- חום
- קוצר נשימה פריחה
- פריחה
- בחילה
- הקאה