יוני 2023

OPDIVO
Concentrate for solution for infusion
אופדיבו
תמיסה מרוכזת להכנת תמיסה לעירוי

רופא/ה ,רוקח/ת יקר/ה,

חברת בריסטול-מאיירס סקוויב (ישראל) מתכבדת להודיע על עדכון העלונים לרופא ולצרכן של התכשיר שבנדון.

התוויות התכשיר כפי שמאושרות ע"י משרד-הבריאות:

Unresectable or Metastatic Melanoma

OPDIVO, as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Adjuvant Treatment of Melanoma

OPDIVO is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Neoadjuvant Treatment of Resectable Non-Small Cell Lung Cancer

OPDIVO, in combination with platinum-doublet chemotherapy, is indicated as neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) non-small cell lung cancer (NSCLC).

Metastatic Non-Small Cell Lung Cancer

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

Malignant Pleural Mesothelioma

OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Advanced Renal Cell Carcinoma

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of patients with intermediate or poor risk advanced renal cell carcinoma (RCC).
- OPDIVO, in combination with cabozantinib, is indicated for the first-line treatment of patients with advanced RCC.
- OPDIVO as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

Classical Hodgkin Lymphoma

OPDIVO is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- 3 or more lines of systemic therapy that includes autologous HSCT.

Squamous Cell Carcinoma of the Head and Neck

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

Urothelial Carcinoma

- OPDIVO is indicated for the adjuvant treatment of patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.
- OPDIVO (Nivolumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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

OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Hepatocellular Carcinoma

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

Esophageal Cancer

- OPDIVO is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in patients who have received neoadjuvant chemoradiotherapy (CRT).
- OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) with tumor cell PD-L1 expression ≥ 1%.
- OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) with tumor cell PD-L1 expression ≥ 1%.
- OPDIVO is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

Gastric Cancer, Gastroesophageal Junction Cancer, and EsophagealAdenocarcinoma

OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with unresectable advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

המרכיב הפעיל: Nivolumab 10mg/ml

מהות העדכון בעלונים לרופא ולצרכן מתייחסת להארכת in-use time של התכשיר לאחר ההכנה, מ-24 שעות ל-7 ימים, וכוללת גם עדכון לפרק הזמן הנדרש לשימוש באמצעי-מניעה לאחר סיום הטיפול בתכשיר.

לעלון לרופא נוספו גם נתוני-המשך של Overall Survival במחקר CHECKMATE-9ER
(1L advanced Renal Cell Carcinoma combination treatment - nivolumab and cabozantinib)
כמפורט מטה.

השינויים העיקריים בעלון לרופא ובעלון לצרכן משוקפים בעמודים הבאים.
תוספת טקסט מסומנת בקו תחתון, מחיקת טקסט ~~בקו חוצה~~.

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

בברכה,
לנה גיטלין
מנהלת רגולציה ורוקחת ממונה
בריסטול-מאיירס סקוויב (ישראל)

שינויים עיקריים בעלון לרופא:

OPDIVO (nivolumab 10 mg/mL)

Concentrate for solution for infusion

FULL PRESCRIBING INFORMATION

[...]

2 DOSAGE AND ADMINISTRATION

[...]

2.4 Preparation and Administration

[...]

Preparation

[...]

- After preparation, store the diluted solution either:
  - at room temperature and room light for no more than 8 hours from the time of preparation to end of the infusion. Discard diluted solution if not used within 8 hours from the time of preparation; or
  - under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light for no more than ~~24 hours~~ 7 days from the time of preparation to end of infusion. Discard diluted solution if not used within ~~24 hours~~ 7 days from the time of preparation.

[...]

5 WARNINGS AND PRECAUTIONS

[...]

5.4 Embryo-Fetal Toxicity

[...]

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for ~~at least~~ 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

[...]

8 USE IN SPECIFIC POPULATIONS

[...]

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating OPDIVO *[see Use in Specific Populations (8.1)]*.

Contraception

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

[...]

14 CLINICAL STUDIES

[...]

14.6 Advanced Renal Cell Carcinoma

First line Renal Cell Carcinoma

[...]

CHECKMATE-9ER

[...]

An updated OS analysis was conducted when 271 deaths were observed based on the pre-specified number of deaths for the pre-planned final analysis of OS. Efficacy results are shown in Table 56 and Figures 13 and 14.

Table 56: Efficacy Results - CHECKMATE-9ER

	OPDIVO and Cabozantinib (n=323)	**Sunitinib (n=328)**
Progression-free Survival		
Disease progression or death (%)	144 (45)	191 (58)
Median PFS (months)[a] (95% CI)	16.6 (12.5, 24.9)	8.3 (7.0, 9.7)
Hazard ratio (95% CI)[b]	0.51 (0.41, 0.64)	
p-value[c,d]	<0.0001	
Overall Survival		
Deaths (%)	67 (21)	99 (30)
Median OS (months)[a] (95% CI)	NR[e]	NR (22.6, NR[e])
Hazard ratio (98.89% CI)[b]	0.60 (0.40, 0.89)	
p-value[c,d,f]	0.0010	
Updated Overall Survival		
Deaths (%)	121 (37)	150 (46)
Median OS (months)[a] (95% CI)	37.7 (35.5, NR)	34.3 (29.0, NR)
Hazard ratio (95% CI)b	0.70 (0.55, 0.90)	
Confirmed Objective Response Rate (95% CI)[g]	55.7% (50.1, 61.2)	27.1% (22.4, 32.3)
p-value[h]	<0.0001	
Complete Response	26 (8%)	15 (4.6%)
Partial Response	154 (48%)	74 (23%)

Table 56: Efficacy Results - CHECKMATE-9ER

	OPDIVO and Cabozantinib (n=323)	Sunitinib (n=328)
Median duration of response in months (95% CI)[a]	20.2 (17.3, NR[e])	11.5 (8.3, 18.4)

[a] Based on Kaplan-Meier estimates.
[b] Stratified Cox proportional hazards model.
[c] Based on stratified log-rank test
[d] 2-sided p-values from stratified log-rank test.
[e] Not Reached
[f] p-value is compared with the allocated alpha of 0.0111 for this interim analysis
[g] CI based on the Clopper-Pearson method.
[h] 2-sided p-value from Cochran-Mantel-Haenszel test.

Figure 13: Progression-free Survival - CHECKMATE-9ER

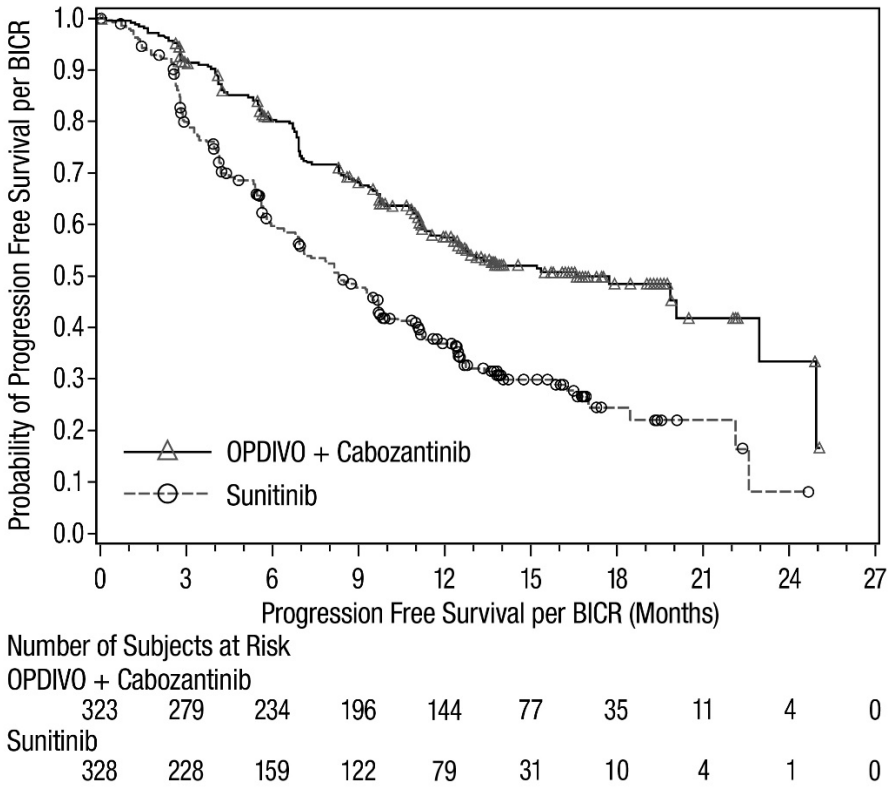
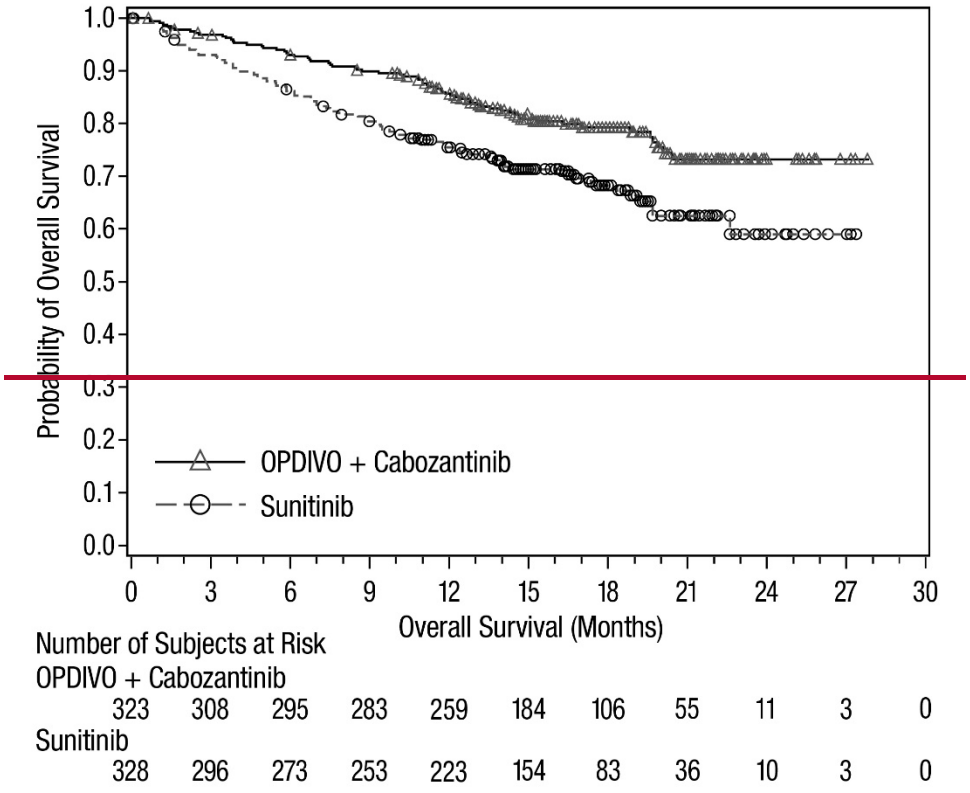
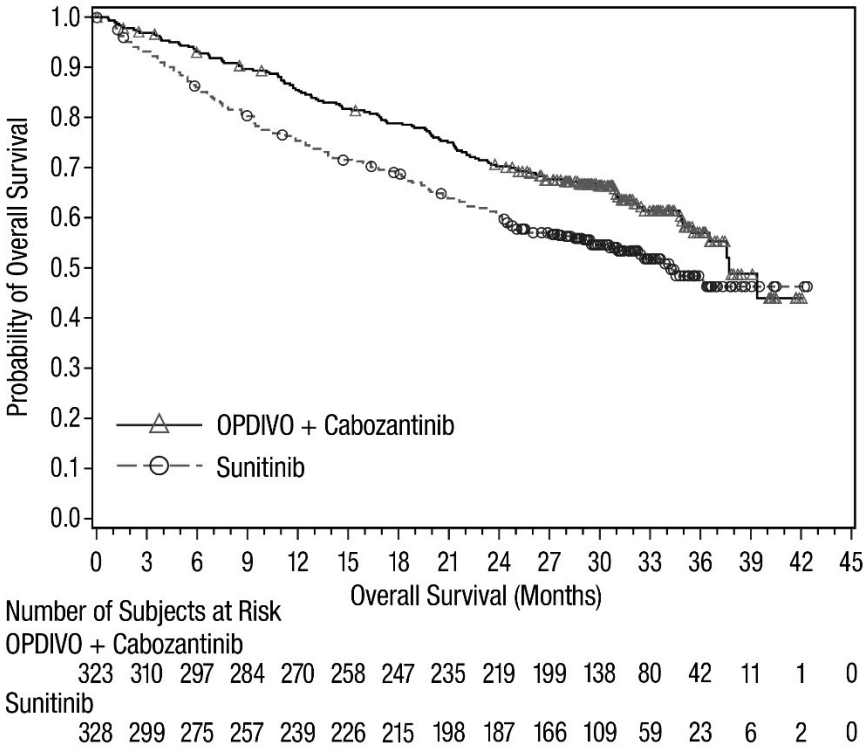


Figure 14: Updated Overall Survival - CHECKMATE-9ER





In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR (95% CI) of 1.03 (0.55, 1.92), 0.74 (0.54, 1.01), 0.65 (0.50, 0.85), and 0.49 (0.31, 0.79), respectively.

[...]

16 HOW SUPPLIED/STORAGE AND HANDLING

[...]

After preparation of infusion:

The administration of the OPDIVO infusion (undiluted or diluted with 0.9% Sodium Chloride Injection (NS) or 5% Dextrose Injection (D5W)) must be completed within ~~24 hours~~7 days of preparation. If not used immediately, the solution may be stored under refrigeration conditions: 2°C to 8°C and protected from light for up to ~~24h~~ 7 days (a maximum of 8h of the total ~~24h~~ 7 days can be at room temperature 20°C to 25°C and room light – the maximum 8h period under room temperature and room light conditions should be inclusive of the product administration period).

[...]

שינויים עיקריים בעלון לצרכן:

עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו – 1986
התרופה משווקת על פי מרשם רופא בלבד

אופדיבו
תמיסה מרוכזת להכנת תמיסה לעירוי תוך ורידי

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2. לפני השימוש בתרופה:

...

היריון והנקה

...

נשים היכולות להרות:

- על הרופא המטפל לערוך בדיקת היריון לפני שאת מתחילה לקבל אופדיבו.
- עלייך להשתמש באמצעי מניעה יעיל במהלך הטיפול ו~~לפחות~~במשך 5 חודשים לאחר מתן המנה האחרונה של אופדיבו. היוועצי ברופא המטפל לגבי אמצעי המניעה שבהם תוכלי להשתמש בתקופה זו.
- דווחי לרופא המטפל באופן מיידי אם נכנסת להיריון במהלך הטיפול עם אופדיבו.

...

5. איך לאחסן את התרופה?

...

- אחרי ההכנה של העירוי: יש להשלים את מתן העירוי תוך ~~24 שעות~~7 ימים מרגע ההכנה. אם העירוי לא ניתן מיידית, ניתן לאחסן אופדיבו לאחר הכנה:
  - בטמפרטורת חדר (20°C-25°C) ותאורת חדר לפרק זמן של לא יותר מ-8 שעות (מתוך ~~24 השעות~~7 הימים) מזמן ההכנה ועד סיום מתן העירוי.

  או
  - בקירור בטמפרטורה של 2°C-8°C ומוגן מאור לפרק זמן של עד ~~24 שעות~~ 7 ימים מרגע ההכנה ועד לסיום המתן.

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מידע לצוות הרפואי
معلومات للطاقم الطبي
Information for Healthcare professionals

Preparation and Administration

...

Preparation

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- After preparation, store the diluted solution either:
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