Bristol Myers Squibb™

דצמבר 2022

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

רופא/ה ,רוקח/ת יקר/ה,

חברת בריסטול-מאיירס סקוויב (ישראל) שמחה להודיע על רישום התוויות חדשות לתכשיר שבנדון ועדכון עלונים לרופא ולצרכן.

להלן התוויות התכשיר כפי שמאושרות ע"י משרד הבריאות (ההתוויות החדשות מסומנות בצבע אדום):

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 Esophageal Adenocarcinoma

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

העלונים לרופא ולצרכן עודכנו בהתאם לתוספת ההתוויות החדשות.

השינויים העיקריים בעלון לרופא ובעלון לצרכן משוקפים בעמודים הבאים.

תוספת טקסט מסומנת בקו תחתון, מחיקת טקסט ~~בקו חוצה~~. החמרות בעלון לצרכן מודגשות בצהוב.

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

[...]

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

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1.2 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.

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- 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.
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~~1.4~~1.5 Malignant Pleural Mesothelioma

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

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- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of patients with intermediate or poor risk advanced renal cell carcinoma (RCC).
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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.

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~~1.8~~1.9 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
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~~1.9~~1.10 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

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- 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.

~~1.12~~1.13 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with ESCC for fist-line treatment with OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy or OPDIVO in combination with ipilimumab based on PD-L1 expression *[see Clinical Studies (14.12)]*.

~~2.1~~2.2 Recommended Dosage

[...]

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

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

Indication	Recommended OPDIVO Dosage	Duration of Therapy
~~Malignant pleural mesothelioma~~	~~3 mg/kg every 2 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) or 360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion)~~	~~In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression~~
Unresectable or metastatic melanoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg intravenously over 90 minutes on the same day	In combination with ipilimumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier
	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (60-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
Neoadjuvant treatment of resectable non-small cell lung cancer	360 mg every 3 weeks (30-minute intravenous infusion) with platinum-doublet chemotherapy on the same day every 3 weeks	In combination with platinum-doublet chemotherapy for 3 cycles
Metastatic or recurrent non-small cell lung cancer	360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) and histology-based platinum doublet chemotherapy every 3 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
		2 cycles of histology-based platinum-doublet chemotherapy

Malignant pleural mesothelioma	3 mg/kg every 2 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) or 360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion)	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
Advanced renal cell carcinoma	3 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg intravenously over 30 minutes on the same day	In combination with ipilimumab for 4 doses
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (60-minute intravenous infusion) Administer OPDIVO in combination with cabozantinib 40 mg orally once daily without food	OPDIVO: Until disease progression, unacceptable toxicity, or up to 2 years
		Cabozantinib: Until disease progression or unacceptable toxicity
	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (60-minute intravenous infusion)	After completing 4 doses of combination therapy with ipilimumab, administer as single agent until disease progression or unacceptable toxicity
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	3 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg intravenously over 30 minutes on the same day	In combination with ipilimumab for 4 doses
	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks (30-minute intravenous infusion)	

Hepatocellular carcinoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg intravenously over 30 minutes on the same day	In combination with ipilimumab for 4 doses
	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
Esophageal squamous cell carcinoma	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion) Administer OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy	OPDIVO: Until disease progression, unacceptable toxicity, or up to 2 years
		Chemotherapy: Until disease progression or unacceptable toxicity
	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion)	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years
Gastric cancer, Gastroesophageal junction cancer, and Esophageal adenocarcinoma	240 mg every 2 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks or 360 mg every 3 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapyevery 3 weeks	Until disease progression, unacceptable toxicity, or up to 2 years

[...]

6 ADVERSE REACTIONS

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

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

The data in WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO as a single agent in 1994 patients enrolled in CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 or a single-arm trial in NSCLC (n=117); OPDIVO 1 mg/kg with ipilimumab 3 mg/kg in patients enrolled in CHECKMATE-067 (n=313), CHECKMATE-040 (n=49), or another randomized trial (n=94); OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg (n=666) in patients enrolled in CHECKMATE-214 or CHECKMATE-142; OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in patients enrolled in CHECKMATE-743 (n=300); OPDIVO 360 mg with ipilimumab 1 mg/kg and 2 cycles of platinum-doublet chemotherapy in CHECKMATE-9LA (n=361); and OPDIVO 240 mg with cabozantinib 40 mg in patients enrolled in CHECKMATE-9ER (n=320).

[...]

Neoadjuvant Treatment of Resectable (Tumors ≥4 cm or Node Positive) Non-Small Cell Lung Cancer

The safety of OPDIVO in combination with platinum-doublet chemotherapy was evaluated in CHECKMATE-816, a randomized, open-label, multicenter trial in patients with resectable NSCLC *[see Clinical Studies (14.3)]*. Patients received either OPDIVO 360 mg administered in combination with platinum-doublet chemotherapy administered every 3 weeks for 3 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 3 cycles.

The median age of patients who received OPDIVO in combination with platinum-doublet chemotherapy or platinum-doublet chemotherapy was 65 years (range: 34 – 84); 72% male; 47% White, 50% Asian, and 2% Black/African-American.

Serious adverse reactions occurred in 30% of patients who were treated with OPDIVO in combination with platinum-doublet chemotherapy. Serious adverse reactions in >2% included pneumonia and vomiting. No fatal adverse reactions occurred in patients who received OPDIVO in combination with platinum-doublet chemotherapy.

Study therapy with OPDIVO in combination with platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 10% of patients and 30% had at least one treatment withheld for an adverse reaction. The most common adverse reactions (≥1%) resulting

in permanent discontinuation of OPDIVO in combination with platinum-doublet chemotherapy were anaphylactic reaction (1.7%), acute kidney injury (1.1%), rash (1.1%), and fatigue (1.1%).

The most common (>20%) adverse reactions were nausea, constipation, fatigue, decreased appetite, and rash. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were neutropenia, hyperglycemia, leukopenia, lymphopenia, increased amylase, anemia, thrombocytopenia, and hyponatremia.

Tables 13 and 14 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-816.

Table 13: Adverse Reactions in >10% of Patients with Early Stage NSCLC Receiving Neoadjuvant OPDIVO and Platinum-Doublet Chemotherapy in CHECKMATE-816

Adverse Reaction	OPDIVO and Platinum-Doublet Chemotherapy (n=176)		Platinum-Doublet Chemotherapy (n=176)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal				
Nausea	38	0.6	45	1.1
Constipation	34	0	32	1.1
Vomiting	11	1.1	13	0.6
General				
Fatigue[a]	26	2.3	23	1.1
Malaise	15	0.6	14	0.6
Metabolism and Nutrition				
Decreased appetite	20	1.1	23	2.3
Skin and Subcutaneous Tissue				
Rash[b]	20	2.3	7	0
Alopecia	11	0	15	0
Nervous System				
Peripheral neuropathy[c]	13	0	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

[b] Includes rash, dermatitis, acneiform dermatitis, atopic dermatitis, bullous dermatitis, drug eruption, maculopapular rash, and pruritic rash.

[c] Includes peripheral neuropathy, dysesthesia, hypoesthesia, peripheral motor neuropathy, peripheral sensory neuropathy.

Table 14: Select Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients with Early Stage NSCLC Receiving Neoadjuvant OPDIVO and Platinum-Doublet Chemotherapy in CHECKMATE-816

Laboratory Abnormality	OPDIVO and Platinum-Doublet Chemotherapy[a]		Platinum-Doublet Chemotherapy[a]	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Hematology				
Anemia	63	3.5	70	6
Neutropenia	58	22	58	27
Leukopenia	53	5	51	11
Lymphopenia	38	4.7	31	1.8
Thrombocytopenia	24	2.9	22	3.0
Chemistry				
Hyperglycemia	37	6	35	2.9
Hypomagnesemia	25	1.2	29	1.2
Hyponatremia	25	2.4	28	1.8
Increased amylase	23	3.6	13	1.8
Increased ALT	23	0	20	1.2

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and platinum-doublet chemotherapy group (range: 73 to 171 patients) and platinum-doublet chemotherapy group (range: 68 to 171 patients).

[...]

First-line Treatment of Unresectable Advanced or Metastatic ESCC

The safety of OPDIVO in combination with chemotherapy or in combination with ipilimumab was evaluated in CHECKMATE-648, a randomized, active-controlled, multicenter, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC *[see Clinical Studies (14.12)]*. Patients received one of the following treatments:

- OPDIVO 240 mg on days 1 and 15, 5-FU (fluorouracil) 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).
- OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.
- 5-FU (fluorouracil) 800 mg/m^2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m^2 intravenously on day 1 (of a 4-week cycle).

Among patients who received OPDIVO with chemotherapy, the median duration of exposure was 5.7 months (range: 0.1 to 30.6 months). Among patients who received OPDIVO and ipilimumab, the median duration of exposure was 2.8 months (range: 0 to 24 months).

Serious adverse reactions occurred in 62% of patients receiving OPDIVO in combination with chemotherapy and in 69% of patients receiving OPDIVO in combination with ipilimumab. The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with chemotherapy were pneumonia (11%), dysphagia (7%), esophageal stenosis (2.9%), acute kidney

injury (2.9%), and pyrexia (2.3%). The most frequent serious adverse reactions reported in ≥2% of patients who received OPDIVO with ipilimumab were pneumonia (10%), pyrexia (4.3%), pneumonitis (4%), aspiration pneumonia (3.7%), dysphagia (3.7%), hepatic function abnormal (2.8%), decreased appetite (2.8%), adrenal insufficiency (2.5%), and dehydration (2.5%).

Fatal adverse reactions occurred in 5 (1.6%) patients who received OPDIVO in combination with chemotherapy; these included pneumonitis, pneumatosis intestinalis, pneumonia, and acute kidney injury and in 5 (1.6%) patients who received OPDIVO in combination with ipilimumab; these included pneumonitis, interstitial lung disease, pulmonary embolism, and acute respiratory distress syndrome.

OPDIVO and/or chemotherapy were discontinued in 39% of patients and were delayed in 71% of patients for an adverse reaction. OPDIVO and/or ipilimumab were discontinued in 23% of patients and were delayed in 46% of patients for an adverse reaction.

The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with chemotherapy were nausea, decreased appetite, fatigue, constipation, stomatitis, diarrhea, and vomiting. The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with ipilimumab were rash, fatigue, pyrexia, nausea, diarrhea, and constipation.

Tables 39 and 40 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-648.

Table 39: Adverse Reactions in ≥10% of Patients - CHECKMATE-648

Adverse Reaction	OPDIVO with Cisplatin and 5-FU (n=310)		OPDIVO and Ipilimumab (n=322)		Cisplatin and 5-FU (n=304)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal						
Nausea	65	4.2	22	0.6	56	2.6
Constipation	44	1.0	20	0.3	43	1.0
Stomatitis [a]	44	9	11	0.6	35	3.0
Diarrhea	29	2.9	22	1.9	20	2.0
Vomiting	23	2.3	15	1.6	19	3.0
Dysphagia	14	7	12	5	12	4.9
Abdominal pain [b]	13	1.9	10	0.9	11	0.7
Metabolism and Nutrition						
Decreased appetite	51	7	17	4.0	50	6
General						
Fatigue [c]	47	3.5	28	2.5	41	4.9
Pyrexia [d]	19	0.3	23	0.9	12	0.3
Edema [e]	16	0	7	0	13	0
Nervous System						
Peripheral neuropathy [f]	18	1.3	2.8	0	13	1.0
Psychiatric						
Insomnia	16	0	8	0	10	0.3

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Adverse Reaction	OPDIVO with Cisplatin and 5-FU (n=310)		OPDIVO and Ipilimumab (n=322)		Cisplatin and 5-FU (n=304)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue						
Rash[g]	16	0.6	31	3.1	7	0
Pruritus	11	0	17	0.9	3.6	0
Alopecia	10	0			11	0
Respiratory, Thoracic and Mediastinal						
Cough[h]	16	0.3	13	0.3	13	0.3
Infections and Infestations						
Pneumonia[i]	13	5	14	8	10	2.6
Endocrine						
Hypothyroidism	7	0	14	0	0.3	0
Investigations						
Weight decreased	12	0.6	12	1.9	11	1.0
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[j]	11	0.3	14	0.6	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes aphthous ulcer, mouth ulceration, and mucosal inflammation.
[b] Includes abdominal discomfort, abdominal pain lower, and abdominal pain upper.
[c] Includes asthenia and malaise.
[d] Includes tumor associated fever.
[e] Includes swelling, generalized edema, edema peripheral, and peripheral swelling.
[f] Includes hyperaesthesia, hypoaesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.
[g] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, and rash pruritic.
[h] Includes productive cough.
[i] Includes organizing pneumonia, pneumonia bacterial, and pneumonia pseudomonal.
[j] Includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, and spinal pain.

Table 40: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-648

Laboratory Abnormality	OPDIVO with Cisplatin and 5-FU (n=310)		OPDIVO and Ipilimumab (n=322)		Cisplatin and 5-FU (n=304)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology						
Anemia	81	21	52	7	66	14
Lymphopenia	67	23	50	13	44	8
Neutropenia	61	18	13	1.3	48	13
Leukopenia	53	11			39	5
Thrombocytopenia	43	3.3	12	1.0	29	2.8

Table 40: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-648

Laboratory Abnormality	OPDIVO with Cisplatin and 5-FU (n=310)		OPDIVO and Ipilimumab (n=322)		Cisplatin and 5-FU (n=304)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry						
Hyponatremia	52	15	45	11	40	8
Hypocalcemia	43	3.0	32	0	23	0.7
Increased creatinine	41	2.3	15	0.7	31	0.7
Hypomagnesemia	35	1.7	15	0	25	1.8
Hyperglycemia	34	0	43	4.3	36	0.8
Hyperkalemia	33	2.3	23	1.6	24	0.7
Hypokalemia	29	9	19	5	17	6
Increased alkaline phosphatase	26	1.3	31	3.3	15	0
Increased AST	23	3.3	39	6	11	1.4
Increased ALT	23	2.3	33	6	8	0.7
Hypoglycemia	18	0.4	15	1.2	7	0
Hypercalcemia	11	2.6	15	2.0	8	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 with cisplatin and 5-FU group (range: 60 to 305 patients), OPDIVO and ipilimumab group (range: 59 to 307 patients) or cisplatin and 5-FU group (range: 56 to 283 patients).

Previously Treated Unresectable Advanced, Recurrent or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

[...]

8 USE IN SPECIFIC POPULATIONS

[...]

8.5 Geriatric Use

Single Agent

Of 3569 patients with melanoma, NSCLC, renal cell carcinoma, urothelial carcinoma, ESCC, and esophageal or gastroesophageal junction cancer who were randomized to single agent OPDIVO in clinical studies, 41% were 65 years and over and 10% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients *[see Clinical Studies (14.1, 14.2, 14.~~3~~4, 14.~~5~~6, 14.~~8~~9, 14.~~11~~12,)]*.

In patients with cHL, recurrent head and neck SCC, or dMMR or MSI-H metastatic CRC (mCRC) who were treated with single agent OPDIVO in clinical studies did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients *[see Clinical Studies (14.~~6~~7, 14.~~7~~8, 14.~~9~~10)]*.

In Combination with Ipilimumab

Of the 314 patients with melanoma who were randomized to OPDIVO in combination with ipilimumab, 41% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients *[see Clinical Studies (14.1)]*.

Of the 303 patients with malignant pleural mesothelioma who were randomized to OPDIVO in combination with ipilimumab, 77% were 65 years old or older and 26% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (68% and 35%, respectively) relative to all patients who received OPDIVO with ipilimumab (54% and 28%, respectively). For patients aged 75 years or older who received chemotherapy, the rate of serious adverse reactions was 34% and the discontinuation rate due to adverse reactions was 26% relative to 28% and 19% respectively for all patients. The hazard ratio for overall survival was 0.76 (95% CI: 0.52, 1.11) in the 71 patients younger than 65 years compared to 0.74 (95% CI: 0.59, 0.93) in the 232 patients 65 years or older randomized to OPDIVO in combination with ipilimumab *[see Clinical Studies (14.~~4~~5)]*. The hazard ratio for overall survival was 0.67 (95% CI: 0.54, 0.84) in the patients younger than 75 years compared to 1.01 (95% CI: 0.70, 1.47) in the patients 75 years or older randomized to OPDIVO in combination with ipilimumab.

Of the 550 patients with renal cell carcinoma who were randomized to OPDIVO in combination with ipilimumab, 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients. In elderly patients with intermediate or poor risk, no overall difference in effectiveness was reported *[see Clinical Studies (14.~~5~~6)]*.

Of the 49 patients with hepatocellular carcinoma who were treated with OPDIVO in combination with ipilimumab, 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of OPDIVO in combination with ipilimumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients *[see Clinical Studies (14.~~10~~11)]*.

Of the 325 patients with ESCC who were randomized to OPDIVO in combination with ipilimumab, 43% were 65 years old or older and 7% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (38%) relative to all patients who received OPDIVO with ipilimumab (23%). For patients aged 75 years or older who received chemotherapy, the discontinuation rate due to adverse reactions was 33% relative to 23% for all patients *[see Clinical Studies (14.12)]*.

In Combination with Platinum-Doublet Chemotherapy

Of the 179 patients with NSCLC who were randomized to OPDIVO in combination with platinum-doublet chemotherapy, 48% were 65 years old or older and 6% were 75 years old or older. No overall differences in safety or effectiveness were reported between patients older and younger than 65 years *[see Clinical Studies (14.3)]*.

In Combination with Ipilimumab and Platinum-Doublet Chemotherapy

Of the 361 patients with NSCLC who were randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy , 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older *[see Clinical Studies (14.~~3~~4)]*.

In Combination with Cabozantinib

Of the 320 patients with renal cell carcinoma who were treated with OPDIVO in combination with cabozantinib, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients *[see Clinical Studies (14.6)]*.

In Combination with Fluoropyrimidine- and Platinum-Containing Chemotherapy

Of the 1,110 patients with ESCC, GC, GEJC, or EAC who were randomized to OPDIVO in combination with fluoropyrimidine- and platinum-containing chemotherapy), 42% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients *[see Clinical Studies (14.12, 14.13)]*.

~~Of the 789 patients randomized to OPDIVO 240 mg every 2 weeks or 360 mg every 3 weeks administered in combination with fluoropyrimidine- and platinum-containing chemotherapy in CHECKMATE-649 (GC, GEJC, or EAC), 40% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients *[see Clinical Studies (14.12)]*.~~

[...]

14 CLINICAL STUDIES

[...]

14.3 Neoadjuvant Treatment of Resectable (Tumors ≥4 cm or Node Positive) Non-Small Cell Lung Cancer

CHECKMATE-816 (NCT02998528) was a randomized, open label trial in patients with resectable NSCLC. The trial included patients with resectable, histologically confirmed Stage IB (≥4 cm), II, or IIIA NSCLC (per the 7th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging criteria), ECOG performance status 0 or 1, and measurable disease (per RECIST version 1.1). Patients with unresectable or metastatic NSCLC, **known EGFR mutations or ALK translocations**, Grade 2 or greater peripheral neuropathy, active autoimmune disease, or medical conditions requiring systemic immunosuppression **were excluded from the study.**

Patients were randomized to receive either:

- OPDIVO 360 mg administered intravenously over 30 minutes and platinum-doublet chemotherapy administered intravenously every 3 weeks for up to 3 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for up to 3 cycles.

Platinum-doublet chemotherapy consisted of paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 5 or AUC 6 (any histology); pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 (non-squamous histology); or gemcitabine 1000 mg/m^2 or 1250 mg/m^2 and cisplatin 75 mg/m^2 (squamous histology). In the platinum-doublet chemotherapy arm, two additional treatment regimen options included vinorelbine 25 mg/m^2 or 30 mg/m^2 and cisplatin 75 mg/m^2; or docetaxel 60 mg/m^2 or 75 mg/m^2 and cisplatin 75 mg/m^2 (any histology).

Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), disease stage (IB/II versus IIIA), and sex (male versus female). Tumor assessments were performed at baseline, within 14 days of surgery, every 12 weeks after surgery for 2 years, then every 6 months for 3 years, and every year for 5 years until disease recurrence or progression. The major efficacy outcome measures were event-free survival (EFS) based on BICR assessment and pathologic complete response (pCR) as evaluated by blinded independent pathology review (BIPR). Additional efficacy outcome measures included OS.

A total of 358 patients were randomized to receive either OPDIVO in combination with platinum-doublet chemotherapy (n=179) or platinum-doublet chemotherapy (n=179). The median age was 65 years (range: 34 to 84) with 51% of patients ≥65 years and 7% of patients ≥75 years, 50% were Asian, 47% were White, 2% were Black, and 71% were male. Baseline ECOG performance status was 0 (67%) or 1 (33%); 50% had tumors with PD-L1 expression ≥1%; 35% had stage IB/II and 64% had stage IIIA disease; 51% had tumors with squamous histology and 49% had tumors with non-squamous histology; and 89% were former/current smokers.

Eighty-three percent of patients in the OPDIVO in combination with platinum-doublet chemotherapy arm had definitive surgery compared to 75% of patients in the platinum-doublet chemotherapy arm.

The study demonstrated statistically significant improvements in EFS and pCR. Efficacy results are presented in Table 48 and Figure 5. Efficacy results by PD-L1 expression are presented in Table 49.

Table 48: Efficacy Results - CHECKMATE-816

	OPDIVO and Platinum-Doublet Chemotherapy (n=179)	**Platinum-Doublet Chemotherapy (n=179)**
Event-free Survival (EFS) per BICR		
Events (%)	64 (35.8)	87 (48.6)
Median (months)[a] (95% CI)	31.6 (30.2, NR)	20.8 (14.0, 26.7)

Table 48: Efficacy Results - CHECKMATE-816

	OPDIVO and Platinum-Doublet Chemotherapy (n=179)	Platinum-Doublet Chemotherapy (n=179)
Hazard Ratio[b] (95% CI)	0.63 (0.45, 0.87)	
Stratified log-rank p-value[c]	0.0052	
Pathologic Complete Response (pCR) per BIPR		
Number of patients with pCR	43	4
pCR Rate (%), (95% CI)[d]	24.0 (18.0, 31.0)	2.2 (0.6, 5.6)
Estimated treatment difference (95% CI)[e]	21.6 (15.1, 28.2)	
p-value[f]	<0.0001	

Minimum follow-up for EFS was 21 months.

[a] Kaplan-Meier estimate.

[b] Based on a stratified Cox proportional hazard model.

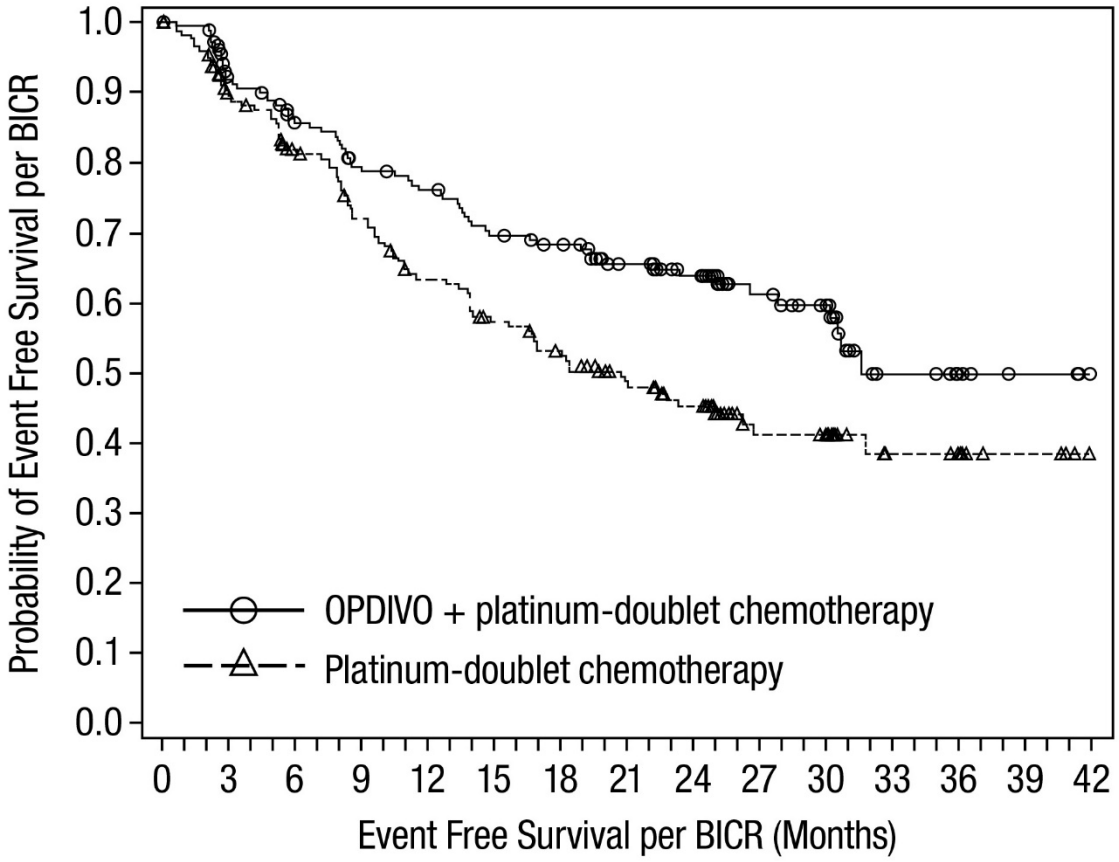
[c] Based on a stratified log-rank test. Boundary for statistical significance: p-value <0.0262.

[d] Based on Clopper and Pearson method.

[e] Strata-adjusted difference based on Cochran-Mantel-Haenszel method of weighting.

[f] From stratified CMH test.

Figure 5: Event-Free Survival - CHECKMATE-816



Number of Subjects at Risk

OPDIVO + platinum-doublet chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Platinum-doublet chemotherapy	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

At the time of the EFS analysis, 26% of the patients had died. A prespecified interim analysis for OS resulted in a HR of 0.57 (95% CI: 0.38, 0.87), which did not cross the boundary for statistical significance.

Table 49: Efficacy results by PD-L1 Expression - CHECKMATE-816

	PD-L1 < 1%		PD-L1 ≥ 1%	
	Nivo+Chemo N = 78	Chemo N = 77	Nivo+Chemo N = 89	Chemo N = 89
EFS per BICR (Primary Definition)				
Events, n	37	41	21	41
Median, mo.	25.10	18.40	Not reached	21.06
(95% CI)	(14.62, NA)	(13.86, 26.22)	(NA, NA)	(11.47, NA)
HR (95% CI)[a]	0.85 (0.54, 1.32)		0.41 (0.24, 0.70)	
pCR per BIPR				
Responses, n	13	2	29	2
pCR, %	16.7	2.6	32.6	2.2
(95% CI)	(9.2, 26.8)	(0.3, 9.1)	(23.0, 43.3)	(0.3, 7.9)
Difference (95% CI)[b]	14.1 (4.8, 24.0)		30.3 (19.9, 40.7)	

[a] Statistical model for hazard ratio: Unstratified Cox proportional hazard model.

[b] Two-sided 95% confidence interval for un-weighted difference was calculated using Newcombe method.

Database locks: 16-Sep-2020 for pCR and 20-Oct-2021 for EFS and OS.

[...]

14.12 Esophageal Cancer

[...]

First-line Treatment of Unresectable Advanced or Metastatic ESCC

CHECKMATE-648 (NCT03143153) was a randomized, active-controlled, open-label trial in patients with previously untreated unresectable advanced, recurrent or metastatic ESCC (squamous or adenosquamous histology). The trial enrolled patients whose tumor was evaluable for tumor cell (TC) PD-L1 expression [also called PD-L1 tumor proportion score (TPS)], which was evaluated using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. A retrospective scoring of a patient's tumor PD-L1 status using Combined Positive Score (CPS), was also conducted using the PD-L1-stained tumor specimens used for randomization. Patients were not amenable to chemoradiation or surgery with curative intent. Prior treatment with curative intent was allowed if completed more than six months prior to trial enrollment. The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or patients at high risk of bleeding or fistula due to apparent invasion of tumor to organs adjacent to the esophageal tumor. Patients were randomized to receive one of the following treatments:

- OPDIVO 240 mg on days 1 and 15, fluorouracil 800 mg/m2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m2 intravenously on day 1 (of a 4-week cycle).
- OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks.
- Fluorouracil 800 mg/m2/day intravenously on days 1 through 5 (for 5 days), and cisplatin 80 mg/m2 intravenously on day 1 (of a 4-week cycle).

Patients received OPDIVO until disease progression, unacceptable toxicity, or up to 2 years. In patients who received OPDIVO in combination with chemotherapy and in whom either fluorouracil and/or cisplatin were discontinued, other components of the treatment regimen were allowed to be continued. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent.

Randomization was stratified by TC PD-L1 expression (≥1% vs. <1% or indeterminate), region (East Asia vs. Rest of Asia vs. Rest of World), ECOG performance status (0 vs. 1), and number of organs with metastases (≤1 vs. ≥2). The major efficacy outcome measures were OS and BICR-assessed PFS in patients with TC PD-L1 expression ≥ 1%. Additional efficacy measures included OS in all randomized patients, BICR-assessed PFS in all randomized patients, and ORR assessed by BICR in TC PD-L1 expression ≥ 1% and in all randomized patients. The tumor assessments per RECIST v1.1 were conducted every 6 weeks up to and including week 48, then every 12 weeks thereafter.

A total of 970 patients were randomized in CHECKMATE-648 study among whom 965 and 906 patients had quantifiable TC PD-L1 expression and CPS at baseline, respectively. The trial population characteristics for all randomized patients were median age 64 years (range: 26 to 90), 47% were ≥65 years of age, 82.% were male, 71% were Asian, 26% were White, and 1.1% were Black. Patients had histological confirmation of squamous cell carcinoma (98%) or adenosquamous cell carcinoma (1.9%) in the esophagus. Baseline ECOG performance status was 0 (47.0%) or 1 (53%).

Efficacy results are shown in Table 66 and Figures 19 and 20.

Table 66: Efficacy Results - CHECKMATE-648

	OPDIVO with Cisplatin and Fluorouracil (n=321)	OPDIVO and Ipilimumab (n=325)	Cisplatin and Fluorouracil (n=324)	OPDIVO with Cisplatin and Fluorouracil (n=158)	OPDIVO and Ipilimumab (n=158)	Cisplatin and Fluorouracil (n=157)
	All Patients			TC PD-L1 expression ≥ 1%		
Overall Survival						
Deaths (%)	209 (65)	216 (66)	232 (72)	98 (62)	106 (67)	121 (77)
Median (months) (95% CI)	13.2 (11.1, 15.7)	12.8 (11.3, 15.5)	10.7 (9.4, 11.9)	15.4 (11.9, 19.5)	13.7 (11.2, 17.0)	9.1 (7.7, 10)
Hazard ratio (95% CI)[b]	0.74 (0.61, 0.90)	0.78 (0.65, 0.95)	-	0.54 (0.41, 0.71)	0.64 (0.49, 0.84)	-
p-value[c]	0.0021[S1]	0.0110[S2]	-	< 0.0001[S3]	0.0010[S4]	-
Progression-free Survival[a]						
Disease progression or death (%)	235 (73)	258 (79)	210 (65)	117 (74)	123 (78)	100 (64)

Median (months) (95% CI)	5.8 (5.6, 7.0)	2.9 (2.7, 4.2)	5.6 (4.3, 5.9)	6.9 (5.7, 8.3)	4.0 (2.4, 4.9)	4.4 (2.9, 5.8)
Hazard ratio (95% CI)[b]	0.81 (0.67, 0.99)	1.26 (1.04, 1.52)	-	0.65 (0.49, 0.86)	1.02 (0.78, 1.34)	-
p-value[c]	NS	NT	-	0.0023[S5]	NS	-
Overall Response Rate, n (%)[a, NT]	152 (47.4)	90 (27.7)	87 (26.9)	84 (53.2)	56 (35.4)	31 (19.7)
(95% CI)	(41.8, 53.0)	(22.9, 32.9)	(22.1, 32.0)	(45.1, 61.1)	(28.0, 43.4)	(13.8, 26.8)
Complete response (%)	43 (13.4)	36 (11.1)	20 (6.2)	26 (16.5)	28 (17.7)	8 (5.1)
Partial response (%)	109 (34.0)	54 (16.6)	67 (20.7)	58 (36.7)	28 (17.7)	23 (14.6)
Duration of Response (months)[a]						
Median (95% CI)	8.2 (6.9, 9.7)	11.1 (8.3, 14.0)	7.1 (5.7, 8.2)	8.4 (6.9, 12.4)	11.8 (7.1, 27.4)	5.7 (4.4, 8.7)
Range	1.4+, 35.9+	1.4+, 34.5+	1.4+, 31.8+	1.4+, 34.6	1.4+, 34.5+	1.4+, 31.8+

[a] Assessed by BICR.

[b] Based on stratified Cox proportional hazard model. Hazard ratios are reported for each OPDIVO containing arm compared to chemotherapy within each analysis population.

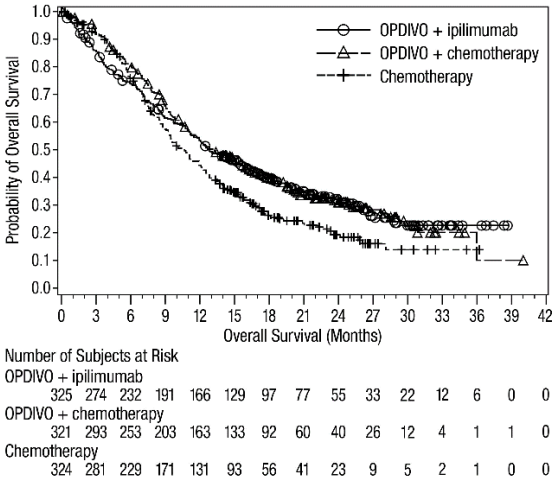
[c] Based on a stratified 2-sided log-rank test.

[S1, S2, S3, S4, S5] Significant p-value compared to stopping boundary of 0.009, 0.018, 0.005, 0.014, and 0.015 respectively.

NS: Not Statistically significant, NT: Not evaluated for statistical significance as per pre-specified hierarchical testing procedure

Figure 19: Overall Survival – CHECKMATE-648

(A) OS in All Randomized Patients



(B) OS in TC PD-L1 ≥1%

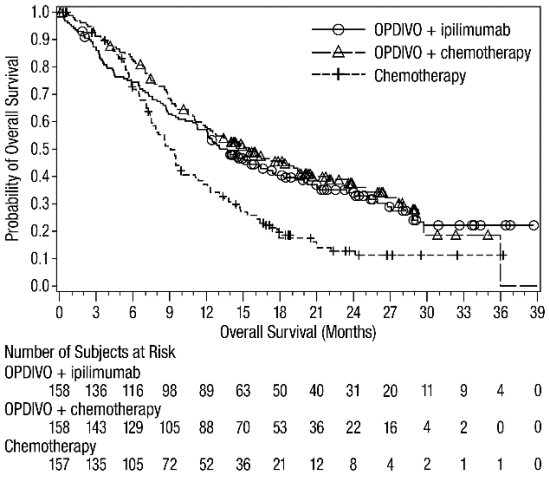
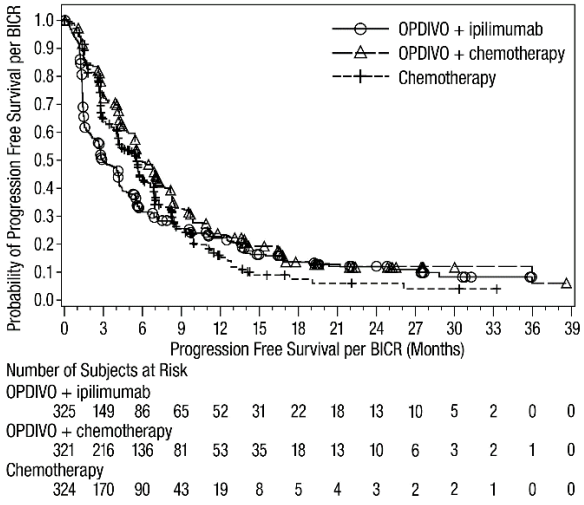
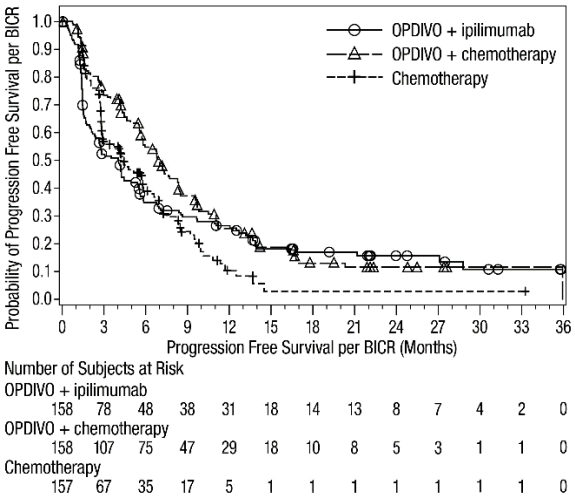


Figure 20: Progression Survival – CHECKMATE-648

(A) PFS in All Randomized Patients



(B) PFS in TC PD-L1 ≥1%



Exploratory subgroup analyses of patients with TC PD-L1 expression<1% (n=492) were conducted. OS results for each OPDIVO containing arm compared to chemotherapy were:

- OPDIVO with Chemotherapy (n=163) vs. Chemotherapy (n=165): unstratified OS HR was 0.99 (95% CI: 0.76, 1.29) with median OS of 12 months (95% CI: 9.9, 15.5) on the OPDIVO with Chemotherapy arm and 12.2 months (95% CI: 10.7, 14) on the Chemotherapy arm
- OPDIVO with Ipilimumab (n=164) vs. Chemotherapy (n=165): unstratified OS HR was 0.97 (95% CI: 0.74, 1.26) with median OS of 12 months (95% CI: 10.1, 16.0) on the OPDIVO with Ipilimumab arm and 12.2 months (95% CI: 10.7, 14) on the Chemotherapy arm

Exploratory subgroup analyses were also conducted by PD-L1 status per CPS (≥1 and <1) for each OPDIVO containing arm compared to chemotherapy. Among the 906 patients with quantifiable PD-L1 CPS at baseline, 278 in the OPDIVO with chemotherapy arm, 266 in the OPDIVO with Ipilimumab arm, and 280 in the chemotherapy arm had PD-L1 CPS≥1. A total of, 27 patients in the OPDIVO with chemotherapy arm, 31 patients in the OPDIVO with Ipilimumab arm, and 24 patients in the chemotherapy arm had PD-L1 CPS<1.

OS results for each comparison by PD-L1 CPS status were:

- OPDIVO with Chemotherapy vs. Chemotherapy: unstratified OS HR was 0.69 (95% CI: 0.56, 0.84) for PD-L1 CPS≥1 subgroup and 0.98 (95% CI: 0.50, 1.95) for PD-L1 CPS<1 subgroup.
- OPDIVO with Ipilimumab vs. Chemotherapy: unstratified OS HR was 0.76 (95% CI: 0.62, 0.93) for PD-L1 CPS≥1 subgroup and 1.0 (95% CI: 0.52, 1.94) for PD-L1 CPS<1 subgroup.

Previously Treated Unresectable Advanced, Recurrent or Metastatic Esophageal Squamous Cell ~~Cancer~~Carcinoma (ESCC)

[...]

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

.....

1. למה מיועדת התרופה?

אופדיבו ניתנת לטיפול ב:

- **סרטן עור מסוג מלנומה**
  - אופדיבו כטיפול יחיד או בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול במבוגרים עם מלנומה מתקדמת (לא נתיחה או גרורתית).
  - אופדיבו מיועדת כטיפול משלים (adjuvant) במטופלים עם מלנומה המערבת בלוטות לימפה או גרורתית, לאחר כריתה מלאה.

- **סרטן ריאות ~~גרורתי~~ מסוג תאים שאינם קטנים (non-small cell lung cancer)**
  - אופדיבו, בשילוב עם משלב כימותרפי המכיל פלטינום (platinum-doublet chemotherapy), מיועדת לטיפול קדם ניתוחי (neo-adjuvant) במבוגרים עם סרטן ריאות נתיח (גידולים בגודל של 4 ס"מ ומעלה או מערבים בלוטות לימפה) מסוג תאים שאינם קטנים
  - אופדיבו, בשילוב עם איפילימומאב (ipilimumab) ושני מחזורי טיפול של משלב כימותרפי המכיל פלטינום (platinum-doublet chemotherapy), מיועדת כטיפול קו ראשון במטופלים מבוגרים עם סרטן ריאות גרורתי או חוזר מסוג תאים שאינם קטנים, וללא שינויים בגנים EGFR או ALK בגידול.
  - אופדיבו מיועדת לטיפול במטופלים עם סרטן ריאות גרורתי מסוג תאים שאינם קטנים שמחלתם התקדמה תוך כדי טיפול או לאחר טיפול בכימותרפיה מבוססת פלטינום.

- **מזותליומה ממאירה של הפלאורה (malignant pleural mesothelioma) - סרטן של תאי מזותל המרכיבים את קרום האדר (מעטפת הריאה)**
  אופדיבו בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול קו ראשון במבוגרים עם מזותליומה ממאירה לא נתיחה של הפלאורה.

- **סרטן תאי הכליה מתקדם (advanced renal cell carcinoma)**
  - אופדיבו בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול קו ראשון במטופלים עם סרטן תאי כליה מתקדם, בדרגת סיכון בינונית או גבוהה.
  - אופדיבו בשילוב עם קבוזנטיניב (cabozantinib) מיועדת לטיפול קו ראשון במטופלים עם סרטן תאי כליה מתקדם.
  - אופדיבו כטיפול יחיד מיועדת לטיפול במטופלים עם סרטן תאי כליה מתקדם שקיבלו טיפול אנטי-אנגיוגני קודם.

- **הודג'קין לימפומה מסוג קלאסי (סוג של סרטן הדם)**
  אופדיבו מיועדת לטיפול במבוגרים עם הודג'קין לימפומה מסוג קלאסי שחזרה או התקדמה לאחר:
  - השתלת תאי גזע ממקור עצמוני (אוטולוגית) וטיפול בתרופה brentuximab vedotin או
  - 3 או יותר קווי טיפול סיסטמיים כולל השתלת תאי הגזע ממקור עצמוני (אוטולוגית).

- **סרטן תאי קשקש של הראש והצוואר (squamous cell carcinoma)**
  אופדיבו מיועדת לטיפול במטופלים עם הישנות או גרורות של סרטן תאי קשקש של הראש והצוואר שמחלתם התקדמה תוך כדי או לאחר טיפול כימותרפי ~~ה~~ המבוסס~~ת~~ פלטינום.

- **קרצינומה של תאי האורותל (urothelial carcinoma) - סרטן בדרכי השתן או שלפוחית השתן**
  - אופדיבו מיועדת כטיפול משלים (adjuvant) במטופלים עם סרטן בדרכי השתן או שלפוחית השתן בסיכון גבוה להישנות המחלה לאחר הסרה רדיקלית של הגידול.
  - אופדיבו מיועדת לטיפול במטופלים עם סרטן מתקדם מקומית או גרורתי בדרכי השתן או שלפוחית השתן:
    - לאחר שמחלתם התקדמה במהלך או לאחר טיפול כימותרפיה מבוססת פלטינום

- לאחר שמחלתם התקדמה במהלך 12 חודשים מטיפול כימותרפיה מבוססת פלטינום, שניתן לפני ניתוח להסרת הגידול (neo-adjuvant) או כטיפול משלים (adjuvant) לאחר ניתוח.

- **סרטן גרורתי של המעי הגס או החלחולת**
אופדיבו כטיפול יחיד או בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול במטופלים מבוגרים וילדים מגיל 12 ומעלה עם סרטן גרורתי של המעי הגס או החלחולת המבטא dMMR (mismatch repair deficient) או MSI-H (microsatellite instability-high), שמחלתם התקדמה לאחר טיפול בפלואורופירימידין, אוקסליפלטין ואירינוטקאן.

- **סרטן כבד (hepatocellular carcinoma)**
אופדיבו, כטיפול יחיד או בשילוב עם איפילימומאב (ipilimumab), מיועדת למטופלים עם סרטן כבד עם פגיעה כבדית קלה (Child-Pugh A) לאחר טיפול בסוראפניב (sorafenib).

- **סרטן ושט**
  - אופדיבו מיועדת כטיפול משלים (adjuvant) לאחר כריתה מלאה של סרטן ושט או סרטן צומת קיבה ושט, עם שארית מחלה פתולוגית, במטופלים שטופלו בטיפול כימו-קרינתי לפני הכריתה.
  - אופדיבו בשילוב עם משלב כימותרפי המבוסס פלואורופירימידין ופלטינום מיועדת לטיפול קו ראשון במבוגרים עם סרטן ושט מסוג קרצינומה של תאי קשקש (esophageal squamous cell carcinoma), שאינו נתיח מתקדם, חוזר או גרורתי, עם ביטוי של PD-L1 ב- 1% ומעלה מתאי הגידול.
  - אופדיבו בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול קו ראשון במבוגרים עם סרטן ושט מסוג קרצינומה של תאי קשקש (esophageal squamous cell carcinoma) שאינו נתיח מתקדם, חוזר או גרורתי, עם ביטוי של PD-L1 ב- 1% ומעלה מתאי הגידול.
  - אופדיבו מיועדת לטיפול במטופלים עם סרטן ושט מסוג קרצינומה של תאי קשקש (esophageal squamous cell carcinoma), שאינו נתיח, מתקדם, חוזר או גרורתי, לאחר טיפול קודם בכימותרפיה מבוססת פלואורופירימידין ופלטינום.

- **סרטן קיבה, סרטן צומת קיבה ושט ואדנוקרצינומה של הוושט**
אופדיבו בשילוב עם כימותרפיה המכילה פלואורופירימידין ופלטינום מיועדת לטיפול במטופלים עם סרטן לא נתיח, מתקדם או גרורתי של הקיבה, צומת קיבה ושט או אדנוקרצינומה של הוושט.

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3. כיצד תשתמש בתרופה?

יש להשתמש בתכשיר תמיד בהתאם להוראות הרופא.
עליך לבדוק עם הרופא או הרוקח אם אינך בטוח בנוגע למינון ואופן הטיפול בתכשיר.
המינון ואופן הטיפול ייקבעו על ידי הרופא בלבד.

- אופדיבו ניתנת על-ידי הצוות הרפואי ישירות לווריד באמצעות צינורית תוך ורידית במשך 60 דקות או 30 דקות, בהתאם למינון ולתדירות שיקבע הרופא.
- כאשר אופדיבו ניתנת לבד, היא ניתנת בדרך כלל כל שבועיים או כל 4 שבועות כתלות במנה שאתה מקבל.
- כאשר אופדיבו ניתנת בטיפול משולב עם איפילימומאב (ipilimumab), למעט עבור טיפול בסרטן ריאות גרורתי מסוג תאים שאינם קטנים (non-small cell lung cancer) ועבור טיפול בחלק מהמקרים של מזותליומה ממאירה של הפלאורה (ראה בהמשך), אופדיבו תינתן בדרך כלל כל 3 שבועות, לסה"כ 4 מנות טיפול. איפילימומאב (ipilimumab) תינתן באותו היום. לאחר מכן, אופדיבו תינתן לבד כל שבועיים או כל 4 שבועות כתלות במנה שאתה מקבל.
- עבור טיפול בסרטן ריאות מסוג תאים שאינם קטנים (non-small cell lung cancer) לפני הניתוח, אופדיבו ניתנת בשילוב עם משלב כימותרפי כל 3 שבועות למשך 3 מחזורי טיפול.
- עבור טיפול בסרטן ריאות גרורתי מסוג תאים שאינם קטנים (non-small cell lung cancer) אשר התפשט לאזורים נוספים בגוף, כשאופדיבו ניתנת בטיפול משולב עם איפילימומאב (ipilimumab), אופדיבו תינתן כל 3 שבועות, ואיפילימומאב (ipilimumab) תינתן כל 6 שבועות למשך שנתיים לכל היותר. תזדקק גם למתן של טיפול כימותרפי כל 3 שבועות למשך שני מחזורי טיפול.
- עבור מזותליומה ממאירה של הפלאורה אופדיבו תינתן כל שבועיים או כל 3 שבועות ואיפילימומאב (ipilimumab) תינתן כל 6 שבועות למשך שנתיים לכל היותר.
- עבור סרטן תאי כליה מתקדם כאשר אופדיבו ניתנת בטיפול משולב עם קבוזנטיניב, אופדיבו תינתן בדרך כלל כל שבועיים או כל 4 שבועות כתלות במנה שאתה מקבל. קבוזנטיניב תינתן פעם ביום דרך הפה.

- כאשר אופדיבו ניתנת בשילוב עם משלב כימותרפי המבוסס פלואורופירימידין ופלטינום לטיפול בסרטן ושט מסוג קרצינומה של תאי קשקש (esophageal squamous cell carcinoma), אופדיבו ניתנת כל שבועיים או כל 4 שבועות, למשך שנתיים לכל היותר.
- כאשר אופדיבו ניתנת בשילוב עם איפילימומאב (ipilimumab) לטיפול בסרטן ושט מסוג קרצינומה של תאי קשקש (esophageal squamous cell carcinoma), אופדיבו ניתנת כל שבועיים או כל 3 שבועות ואיפילימומאב (ipilimumab) ניתנת כל 6 שבועות, למשך שנתיים לכל היותר.
- עבור סרטן קיבה, סרטן צומת קיבה ושט ואדנוקרצינומה של הוושט, כאשר אופדיבו ניתנת בטיפול משולב עם כימותרפיה המכילה פלואורופירימידין ופלטינום, אופדיבו תינתן כל שבועיים או כל שלושה שבועות, כתלות במנה שאתה מקבל למשך שנתיים לכל היותר. הכימותרפיה תינתן באותו היום.
- הרופא המטפל יחליט לכמה טיפולים הינך זקוק.
- אם אינך יכול להגיע לטיפול שנקבע לך או אם שכחת להגיע לטיפול, צור קשר עם הרופא המטפל בהקדם האפשרי על מנת לקבוע מועד חדש לטיפול.

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4. תופעות לוואי

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תופעות לוואי נוספות:

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תופעות הלוואי במתן משולב של אופדיבו עם איפילימומאב (ipilimumab) כוללות:

תופעות לוואי שכיחות מאוד (very common), תופעות שמופיעות ביותר ממשתמש אחד מעשרה:

- תחושת עייפות
- חום
- נפיחות (בצקת)
- פריחה
- גרד, גרד מפושט
- יובש בעור
- שלשול
- בחילה
- הקאה
- כאב בטן
- עצירות
- בטן נפוחה כתוצאה מהצטברות נוזלים (מיימת)
- יובש בפה
- קשיי עיכול
- קושי בבליעה
- פצעים או כיבים בחלל בפה (סטומטיטיס)
- דלקת של המעי הגס (קוליטיס)
- כאב בשרירים, בעצמות ובמפרקים
- שיעול, שיעול עם ליחה
- קוצר נשימה, קוצר נשימה במאמץ
- דלקת ריאות
- זיהום בדרכי הנשימה העליונות
- דלקת ברקמות הריאה (פנאומוניטיס) המאופיינת בנשימה המלווה בשיעול וקשיי נשימה, קוצר נשימה ושיעול
- ירידה בתיאבון
- כאב ראש
- סחרחורת
- שפעת
- מחלה דמויית-שפעת

- חולשה, הרגשה כללית לא טובה
- צמרמורת
- לחץ דם נמוך
- רמות נמוכות של הורמון התירואיד [היפותירואידיזם (תת-פעילות בלוטת התריס)] שיכולות לגרום לעייפות ולעלייה במשקל
- רמות גבוהות של הורמון התירואיד [היפרתירואידיזם (פעילות יתר של בלוטת התריס)] שיכולות לגרום לקצב לב מהיר, להזעה ולאיבוד משקל
- אי ספיקת בלוטות יותרת הכליה (אדרנל) (ירידה ברמת ההורמונים המופרשים על ידי בלוטות יותרת הכליה, שממוקמות מעל הכליות)
- ירידה במשקל
- נדודי שינה
- תוצאות לא תקינות של בדיקות מעבדה

תופעות לוואי שכיחות (common), תופעות שמופיעות ב-1-10 משתמשים מתוך 100:

- ויטיליגו (בהקת), מחלה שבה מופיעים כתמים בהירים על העור
- לחץ דם גבוה
- רמה גבוהה של סוכר בדם (היפרגליקמיה)
- התנקבות במעי
- הצטברות נוזל בחלל האדר העוטף את הריאות (תפליט פלאורלי) אשר עלולה לגרום לקוצר נשימה, וכן לעיתים לכאב בחזה ולחום
- תסחיף ריאתי (קריש דם בריאות)
- דלקת בלוטת יותרת המוח (היפופיזיטיס)
- נפיחות בטנית
- התייבשות
- פגיעה כלייתית חריפה
- אירוע כבדי
- תפקודי כבד לא תקינים
- דימום מדליות בוושט
- מוות כתוצאה מתופעות לוואי
- שרירים כואבים, חולשת שרירים שלא כתוצאה מאימון (מיופתיה)
- דלקת שרירים (מיוזיטיס)
- דלקת עצבית (neuritis)
- שיתוק בעצב הפיבולארי ברגל המאופיין בכאבים בשוק, ירידה בתחושה או חוסר תחושה, חולשת שרירים, ובמקרים חמורים כף רגל שמוטה או צליעה אופיינית (peroneal nerve palsy)
- תסמונת שגרן (Sjogren's syndrome), מחלה שבה מערכת החיסון תוקפת בעיקר בלוטות דמעות ורוק
- דלקת מפרקים כרונית שבדרך כלל מערבת את מפרקי עמוד השדרה (ספונדילוארתרופתיה)
- חוסר תחושה, כאב, עקצוץ או צריבה בכפות ידיים או רגליים (נוירופתיה היקפית)
- תגובות הקשורות בעירוי

תופעות לוואי שאינן שכיחות (uncommon), תופעות שמופיעות ב-1-10 משתמשים מתוך 1,000:

- דלקת של המוח (אנצפליטיס)
- דלקת של שריר הגורמת לנמק
- כאב ואדמומיות בעין - דלקת הענביה (אובאיטיס)

תופעות הלוואי במתן משולב של אופדיבו עם כימותרפיה כוללות:

תופעות לוואי שכיחות מאוד (very common), תופעות שמופיעות ביותר ממשתמש אחד מעשרה:

- תחושת עייפות
- הרגשה כללית לא טובה
- בחילה
- עצירות
- הקאה
- ירידה בתאבון
- פריחה
- נשירת שיער

- חוסר תחושה, כאב, עקצוץ או צריבה בכפות ידיים או רגליים (נוירופתיה היקפית)
- תוצאות לא תקינות של בדיקות מעבדה

תופעות לוואי שכיחות (common), תופעות שמופיעות ב-1-10 משתמשים מתוך 100:
- דלקת ריאות
- תגובה אלרגית קשה (תגובה אנפילקטית)
- פגיעה כלייתית חריפה

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תופעות הלוואי במתן משולב של אופדיבו עם כימותרפיה המכילה פלואורופירימידין ופלטינום כוללות:

תופעות לוואי שכיחות מאוד (very common), תופעות שמופיעות ביותר ממשתמש אחד מעשרה:

- חוסר תחושה, כאב, עקצוץ או צריבה בכפות ידיים או רגליים (נוירופתיה היקפית)
- כאב ראש
- בחילה
- שלשול
- הקאה
- קושי בבליעה
- כאב בטן
- עצירות
- כיבים או פצעים בחלל הפה (סטומטיטיס)
- הרגשת עייפות
- חום
- נפיחות (בצקת)
- ירידה בתיאבון
- ירידה במשקל
- כאבי שרירים, עצמות ומפרקים
- פריחה
- גרד
- נשירת שיער
- פריחה, אדמומיות, כאב, נפיחות או הופעת שלפוחיות בכפות הידיים או הרגליים
- שיעול, שיעול עם ליחה
- זיהום בדרכי נשימה עליונות
- דלקת ריאות
- נדודי שינה
- תוצאות לא תקינות של בדיקות מעבדה

תופעות לוואי שכיחות (common), תופעות שמופיעות ב-1-10 משתמשים מתוך 100:
- ~~דלקת ריאות~~
- חום כתוצאה מרמה נמוכה של תאי דם לבנים מסוג נויטרופילים (חום נויטרופני)
- דלקת ברקמות הריאה (פנאומוניטיס) המאופיינת בנשימה המלווה בשיעול וקשיי נשימה, קוצר נשימה ושיעול
- רמות נמוכות של הורמון התירואיד [היפותירואידיזם (תת-פעילות בלוטת התריס)] שיכולות לגרום לעייפות ולעלייה במשקל
- היצרות בושט
- פגיעה כלייתית חריפה
- מוות כתוצאה מתופעות לוואי

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