Bristol Myers Squibb™

דצמבר 2025

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 רישום שלוש התוויות נוספות לתכשיר אופדיבו ועדכון עלונים לרופא ולצרכן של התכשיר בהתאם.

להלן התוויות התכשיר כפי שמאושרות ע"י משרד הבריאות (ההתוויות החדשות שנוספו 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 adult and pediatric patients 12 years and older.

Adjuvant Treatment of Melanoma

OPDIVO is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with completely resected Stage IIB, IIC, III, or IV melanoma.

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).

Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

OPDIVO, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) NSCLC with tumour cell PD-L1 expression ≥ 1% and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by single-agent OPDIVO as adjuvant treatment after surgery.

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 adult 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 adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).
- OPDIVO, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced RCC.
- OPDIVO as a single agent is indicated for the treatment of adult 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 adult 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 adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.
- OPDIVO, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.
- OPDIVO (Nivolumab) is indicated for the treatment of adult 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, in combination with ipilimumab, is indicated for the first-line treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).
- 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, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with Child-Pugh A unresectable or metastatic hepatocellular carcinoma (HCC).
- OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult 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 adult 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 adult 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 adult patients with unresectable advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

המרכיב הפעיל: Nivolumab 10mg/ml

העלונים לרופא ולצרכן עודכנו עם המידע הרלוונטי עבור ההתוויות החדשות.

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)

עדכונים בעלון לרופא:

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

OPDIVO, as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adult and pediatric patients 12 years and older.

1.2 Adjuvant Treatment of Melanoma

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1.3 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).

1.4 Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

OPDIVO, in combination with platinum-doublet chemotherapy, is indicated for the neoadjuvant treatment of adult patients with resectable (tumors ≥4 cm or node positive) NSCLC with tumour cell PD-L1 expression ≥ 1% and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, followed by single-agent OPDIVO as adjuvant treatment after surgery *[see Dosage and Administration (2.1)]*.

~~1.4~~1.5 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 adult patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

~~1.5~~1.6 Malignant Pleural Mesothelioma

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

~~1.6~~1.7 Advanced Renal Cell Carcinoma

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).
- OPDIVO, in combination with cabozantinib, is indicated for the first-line treatment of adult patients with advanced RCC.
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~~1.7~~1.8 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.

~~1.8~~1.9 Squamous Cell Carcinoma of the Head and Neck

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

~~1.9~~1.10 Urothelial Carcinoma

- OPDIVO is indicated for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.
- OPDIVO, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.
- OPDIVO (Nivolumab) is indicated for the treatment of adult 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.

~~1.10~~1.11 Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult and pediatric patients 12 years and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).
- 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.

~~1.11~~1.12 Hepatocellular Carcinoma

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with Child-Pugh A unresectable or metastatic hepatocellular carcinoma (HCC).
- OPDIVO, in combination with ipilimumab, is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) Child-Pugh A who have been previously treated with sorafenib.

~~1.12~~1.13 Esophageal Cancer

- OPDIVO is indicated for the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease in adult 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% *[see Dosage and Administration (2.1)]*.
- 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% *[see Dosage and Administration (2.1)]*~~.~~.
- OPDIVO is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

~~1.13~~1.14 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

Select patients with resectable (tumors ≥~~4~~ cm or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements for treatment with OPDIVO in combination with platinum-doublet chemotherapy based on PD-L1 expression *[see Clinical Studies (14.4)]*

Esophageal cancer

Select patients with ESCC for first-line treatment with OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy or OPDIVO in combination with ipilimumab based on PD-L1 expression *[see Clinical Studies (14.~~12~~13)]*.

2.2 Recommended Dosage

The recommended dosages of intravenous OPDIVO as a single agent are presented in Table 1.

Table 1: Recommended Dosages for Intravenous OPDIVO as a Single Agent

<table>
<tr><th>Indication</th><th>Recommended OPDIVO Dosage</th><th>Duration of Therapy</th></tr>
<tr><td>Advanced renal cell carcinoma</td><td rowspan="2">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)</td><td rowspan="2">Until disease progression or unacceptable toxicity</td></tr>
<tr><td>Esophageal squamous cell carcinoma</td></tr>
<tr><td rowspan="2">Unresectable or metastatic melanoma</td><td>Adult patients and pediatric patients age 12 years and older and weighing 50 kg or more:
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)</td><td rowspan="2">Until disease progression or unacceptable toxicity</td></tr>
<tr><td>Pediatric patients age 12 years and older and weighing less than 50 kg:
3 mg/kg every 2 weeks
(30-minute intravenous infusion)
or
6 mg/kg every 4 weeks
(30-minute intravenous infusion)</td></tr>
</table>

Table 1: Recommended Dosages for Intravenous OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Adjuvant treatment of melanoma	Adult patients and pediatric patients age 12 years and older and weighing 50 kg or more: 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 (30-minute intravenous infusion)	Until disease recurrence or unacceptable toxicity for up to 1 year
	Pediatric patients age 12 years and older and weighing less than 50 kg: 3 mg/kg every 2 weeks (30-minute intravenous infusion) or 6 mg/kg every 4 weeks (30-minute intravenous infusion)	
Metastatic non-small cell lung cancer Classical Hodgkin lymphoma Squamous cell carcinoma of the head and neck	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity

Table 1: Recommended Dosages for Intravenous OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Locally advanced or metastatic urothelial carcinoma		
Adjuvant treatment of urothelial carcinoma (UC)	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (60-minute intravenous infusion)	Until disease recurrence or unacceptable toxicity for up to 1 year
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following prior treatment for metastatic disease	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)	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)	
Adjuvant treatment of resected esophageal or gastroesophageal junction cancer	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity for a total treatment duration of 1 year

The recommended dosages of OPDIVO in combination with other therapeutic agents are presented in Table 2. Administer OPDIVO on the same day as other therapeutic agents.

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 Intravenous OPDIVO in Combination with Other Therapeutic Agents

Indication	Recommended OPDIVO Dosage	Duration of Therapy
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
	Adult patients and pediatric patients age 12 years and older and weighing 50 kg or more: 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
	Pediatric patients age 12 years and older and weighing less than 50 kg: 3 mg/kg every 2 weeks (30-minute intravenous infusion) or 6 mg/kg every 4 weeks (30-minute intravenous infusion)	
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
Neoadjuvant and adjuvant 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	Neoadjuvant: in combination with platinum-doublet chemotherapy until disease progression or unacceptable toxicity, for up to 4 cycles
	480 mg every 4 weeks (30-minute intravenous infusion)	Adjuvant: following neoadjuvant therapy and surgery, administer as a single agent until disease progression, recurrence, or unacceptable toxicity, for up to 13 cycles (approximately 1 year)
Metastatic or recurrent non-small cell lung cancer		In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression

	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	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
	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
	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~~

First-line unresectable or metastatic urothelial carcinoma	360 mg every 3 weeks (30-minute intravenous infusion) Administer OPDIVO in combination with cisplatin and gemcitabine on the same day every 3 weeks	In combination with cisplatin and gemcitabine for up to 6 cycles
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing up to 6 cycles of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years from first dose
First-line treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg 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 a maximum of 4 doses
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg intravenously over 30 minutes on the same day	
	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing a maximum of 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity, or up to 2 years
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks (30-minute intravenous infusion)	
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal	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

cancer that has progressed following prior treatment for metastatic disease	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 Child-Pugh A who have been previously treated with sorafenib.	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 a maximum of 4 doses
	3 mg/kg every 2 weeks (30-minute intravenous infusion) or 240 mg every 2 weeks (30-minute intravenous infusion	After completing a maximum of 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
Hepatocellular carcinoma Child-Pugh A First-line treatment	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg (30-minute intravenous infusion on the same day)	In combination with ipilimumab for a maximum of 4 doses
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing a maximum of 4 doses of combination therapy, administer as single agent until disease progression, unacceptable toxicity, or up to 2 years
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

2.3 Dosage Modifications

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2.4 Preparation and Administration

Visually inspect for particulate matter and discoloration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard if cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake.

Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.
  - For adult and pediatric patients with body weight 40 kg or greater, do not exceed a total volume of infusion of 160 mL.
  - For adult and pediatric patients with body weight less than 40 kg, do not exceed a total volume of infusion of 4 mL/kg of body weight.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.
- The product does not contain a preservative.

- After preparation, store the diluted solution either:

- at room temperature at 20°C to 25°C 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 7 days from the time of preparation to end of infusion. Discard diluted solution if not used within 7 days from the time of preparation.

- Do not freeze.

Administration

- Administer the infusion, after dilution, over 30 minutes or 60 minutes depending on the dose (see Tables 1 and 2) through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Administer OPDIVO in combination with other therapeutic agents as follows:

Combination Therapy	
Ipilimumab	Administer OPDIVO first, followed by the other therapeutic agent(s).
Platinum-Doublet Chemotherapy	
Ipilimumab and Platinum-Doublet Chemotherapy	
Fluoropyrimidine- and Platinum-Containing Chemotherapy	

  - ~~With ipilimumab: administer OPDIVO first followed by ipilimumab on the same day.~~
  - ~~With platinum-doublet chemotherapy: administer OPDIVO first followed by platinum-doublet chemotherapy on the same day.~~
  - ~~With ipilimumab and platinum-doublet chemotherapy: administer OPDIVO first followed by ipilimumab and then platinum-doublet chemotherapy on the same day.~~
  - ~~With fluoropyrimidine- and platinum-containing chemotherapy: administer OPDIVO first followed by fluoropyrimidine- and platinum-containing chemotherapy on the same day.~~

- Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not co-administer other drugs through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

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4 CONTRAINDICATIONS

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5 WARNINGS AND PRECAUTIONS

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5.7 Opdivo Contains Polysorbate 80

This medicinal product contains 0.94 mg of polysorbate 80 in each 4 mL vial and 2.14 mg of polysorbate 80 in each 10 mL vial. Polysorbates may cause allergic reactions.

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6 ADVERSE REACTIONS

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6.1 Clinical Trials Experience

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Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

The safety of OPDIVO in combination with neoadjuvant platinum-doublet chemotherapy followed by surgery and continued adjuvant treatment with OPDIVO as a single agent after surgery was evaluated in CHECKMATE-77T, a randomized, double-blind, multicenter trial in patients with previously untreated resectable Stage IIA (> 4 cm) to IIIB (T3N2 or T4N2) NSCLC (per the AJCC Cancer Staging Manual 8th Edition) *[see Clinical Studies (14.4)]*. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. The median duration of exposure to OPDIVO was 10.3 months (range: 1 day to 22.3 months).

The study population characteristics were: median age 66 years (range: 35 - 86); 71% male; 72% White, 25% Asian, 1.7% Black/African American, and 1.5% other race; and 6% Hispanic or Latino.

Adverse reactions occurring in patients with resectable NSCLC receiving OPDIVO in combination with platinum-doublet chemotherapy, given as neoadjuvant treatment and followed as a single agent adjuvant treatment after surgery, were generally similar to those occurring in patients in other clinical trials across tumor types receiving OPDIVO in combination with chemotherapy.

Neoadjuvant Phase of CHECKMATE-77T

A total of 228 patients received at least 1 dose of OPDIVO in combination with platinum-doublet chemotherapy as neoadjuvant treatment and 230 patients received at least 1 dose of placebo in combination with platinum-doublet chemotherapy as neoadjuvant treatment.

Serious adverse reactions occurred in 21% of patients who received OPDIVO in combination with platinum-doublet chemotherapy as neoadjuvant treatment; the most frequent (≥2%) serious adverse reactions was pneumonia. Fatal adverse reactions occurred in 2.2% of patients, due to cerebrovascular accident, COVID-19 infection, hemoptysis, pneumonia, and pneumonitis (0.4% each).

Permanent discontinuation of any study drug due to an adverse reaction occurred in 13% of patients who received OPDIVO in combination with platinum-doublet chemotherapy as neoadjuvant treatment; the most frequent (≥1%) adverse reaction that led to permanent discontinuation of any study drug was peripheral sensory neuropathy (2.2%).

Of the 228 OPDIVO-treated patients and 230 placebo-treated patients who received neoadjuvant treatment, 5.3% (n=12) and 3.5% (n=8), respectively, did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery in OPDIVO-treated patients were cerebrovascular accident, pneumonia, and colitis/diarrhea (2 patients each) and acute coronary syndrome, myocarditis, hemoptysis, pneumonitis, COVID-19, and myositis (1 patient each).

Of the 178 OPDIVO-treated patients who received surgery, 4.5% (n=8) experienced delay of surgery (surgery more than 6 weeks from last neoadjuvant treatment) due to adverse reactions. Of the 178 placebo-treated patients who received surgery, 3.9% (n=7) experienced delay of surgery due to adverse reactions.

Of the 178 OPDIVO-treated patients who received surgery, 7% (n=13) did not receive adjuvant treatment due to adverse reactions. Of the 178 placebo-treated patients who received surgery, 2.8% (n=5) did not receive adjuvant treatment due to adverse reactions.

Adjuvant Phase of CHECKMATE-77T

A total of 142 patients in the OPDIVO arm and 152 patients in the placebo arm received at least 1 dose of adjuvant treatment.

Of the patients who received single agent OPDIVO as adjuvant treatment, 22% experienced serious adverse reactions; the most frequent serious adverse reaction was pneumonitis/ILD (2.8%). One fatal adverse reaction due to COVID-19 occurred. Permanent discontinuation of adjuvant OPDIVO due to an adverse reaction occurred in 14% of patients; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of adjuvant OPDIVO were pneumonitis (4.2%) and diarrhea (1.4%).

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MSI-H or dMMR Metastatic Colorectal Cancer

Treatment of MSI-H or dMMR mCRC: In Combination with Ipilimumab

The safety of OPDIVO in combination with ipilimumab, or as a single agent, was evaluated in CHECKMATE-8HW, a randomized, open-label, three arm trial in immunotherapy naive patients

with MSI-H or dMMR mCRC *[see Clinical Studies (14.11)]*. Patients received one of the following:

- OPDIVO 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, then OPDIVO 480 mg every 4 weeks.
- OPDIVO 240 mg every 2 weeks for 6 doses, then OPDIVO 480 mg every 4 weeks.
- Investigator's choice chemotherapy: mFOLFOX or FOLFIRI *[see Clinical Studies (14.11)]*.

In the OPDIVO and ipilimumab arm, the median duration of exposure to OPDIVO was 20.5 months (range: 0 to 35.9 months), 70% of patients were exposed for >6 months and 63% were exposed for >1 year. In the OPDIVO arm, the median duration of exposure to OPDIVO was 16.4 months (range: 0 to 36 months), 64% of patients were exposed for >6 months and 54% were exposed for >1 year.

Serious adverse reactions occurred in 46% of patients receiving OPDIVO in combination with ipilimumab, and 39% of patients receiving OPDIVO alone. The most frequent serious adverse reactions reported in ≥1% of patients who received OPDIVO with ipilimumab were adrenal insufficiency (2.8%), hypophysitis (2.8%), diarrhea (2.0%), abdominal pain (2.0%), small intestinal obstruction (2.0%), pneumonia (1.7%), acute kidney injury (1.4%), immune mediated enterocolitis (1.4%), pneumonitis (1.4%), colitis (1.1%), large intestinal obstruction (1.1%), and urinary tract infection (1.1%). The most frequent serious adverse reactions reported in >1% of patients who received OPDIVO, as a single agent, were intestinal obstruction (2.3%), acute kidney injury (1.7%), COVID-19 (1.7%), abdominal pain (1.4%), diarrhea (1.4%), ileus (1.4%), subileus (1.4%), pulmonary embolism (1.4%), adrenal insufficiency (1.1%) and pneumonia (1.1%).

Fatal adverse reactions occurred in 2 (0.6%) patients who received OPDIVO in combination with ipilimumab; these included myocarditis, and pneumonitis (1 each). Fatal adverse reactions occurring in 3 (0.9%) patients who received OPDIVO as a single agent; these included pneumonitis (n=2) and myasthenia gravis.

OPDIVO and/or ipilimumab were permanently discontinued in 19% of patients receiving the combination. The most frequent adverse reactions (>1%) leading to permanent discontinuation were adrenal insufficiency (1.4%), immune mediated enterocolitis (1.1%), and pneumonitis (1.1%). OPDIVO was permanently discontinued in 13% of patients receiving single agent OPDIVO. Adverse reactions leading to the delay of OPDIVO and/or ipilimumab occurred in 48% of patients receiving the combination; single agent OPDIVO was delayed in 37% of patients due to adverse reactions.

The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with ipilimumab were fatigue, diarrhea, pruritus, abdominal pain, musculoskeletal pain, and nausea. The most common adverse reactions reported in ≥20% of patients treated with OPDIVO as a single agent, were fatigue, diarrhea, abdominal pain, pruritus, and musculoskeletal pain.

Tables 37 and 38 summarize selected adverse reactions and selected laboratory abnormalities for OPDIVO in combination with ipilimumab and the single agent OPDIVO arms respectively, in CHECKMATE-8HW.

Table 37: Adverse Reactions[a] in ≥10% in Patients with a Difference Between Arms of >5% for All Grades in CHECKMATE-8HW

Adverse Reaction	OPDIVO and ipilimumab (n=352)		OPDIVO (n=351)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or4 (%)
Gastrointestinal				
Diarrhea[a]	35	4.5	30	3.4
Skin and Subcutaneous Tissue				
Pruritus	30	0	23	0
Musculoskeletal and Connective Tissue				
Arthralgia	20	0.6	15	0.6
Endocrine				
Hypothyroidism	18	0.6	10	0
Hyperthyroidism	12	0	5	0

Toxicity was graded per NCI CTCAE v5.

[a] Includes colitis, diarrhea, enterocolitis, immune mediated enterocolitis

Table 38: Laboratory Values Worsening from Baseline[a] in ≥10% of Patients and a Difference Between Arms of >5% for All Grades - CHECKMATE-8HW

Laboratory Abnormality[a]	OPDIVO and Ipilimumab (n=352)		OPDIVO (n=351)	
	All Grades (%)	Grades 3-or 4 (%)	All Grades (%)	Grades 3 or -4 (%)
Hematology				
Lymphocytes decreased	30	5	37	4
Neutrophils decreased	21	1.7	12	0.6
Chemistry				
Lipase increased	44	10	32	11
Amylase increased	41	4.6	33	5
ALT increased	39	3.5	32	1.4
AST increased	38	3.2	29	1.4
Sodium decreased	36	3.2	30	2.3
Creatinine increased	32	2	25	1.4
Potassium increased	29	1.2	35	0.9
Glucose decreased	17	0	12	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 and ipilimumab group (range: 108 to 343 patients) or nivolumab group (range: 102 to 348 patients).

MSI-H or dMMR mCRC After Progression Following Treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan

The safety of OPDIVO administered as a single agent or in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-

label trial *[see Clinical Studies (14.~~10~~11)]*. In CHECKMATE-142, 74 patients with mCRC received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or until intolerable toxicity and 119 patients with mCRC received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks until disease progression or until unacceptable toxicity.

In the OPDIVO with ipilimumab cohort, serious adverse reactions occurred in 47% of patients. Treatment was discontinued in 13% of patients and delayed in 45% of patients for an adverse reaction. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting.

Tables ~~37~~ 39 and ~~38~~ 40 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-142. Based on the design of CHECKMATE-142, the data below cannot be used to identify statistically significant differences between the two cohorts summarized below for any adverse reaction.

Table ~~37~~39: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-142

Adverse Reaction	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	54	5	49	6
Pyrexia	24	0	36	0
Edema[b]	12	0	7	0
Gastrointestinal				
Diarrhea	43	2.7	45	3.4
Abdominal pain[c]	34	2.7	30	5
Nausea	34	1.4	26	0.8
Vomiting	28	4.1	20	1.7
Constipation	20	0	15	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	28	1.4	36	3.4
Arthralgia	19	0	14	0.8
Respiratory, Thoracic and Mediastinal				
Cough	26	0	19	0.8
Dyspnea	8	1	13	1.7
Skin and Subcutaneous Tissue				
Rash[e]	23	1.4	25	4.2
Pruritus	19	0	28	1.7
Dry Skin	7	0	11	0
Infections				
Upper respiratory tract infection[f]	20	0	9	0
Endocrine				
Hyperglycemia	19	2.7	6	1
Hypothyroidism	5	0	14	0.8
Hyperthyroidism	4	0	12	0
Nervous System				
Headache	16	0	17	1.7
Dizziness	14	0	11	0
Metabolism and Nutrition				
Decreased appetite	14	1.4	20	1.7
Psychiatric				
Insomnia	9	0	13	0.8
Investigations				
Weight decreased	8	0	10	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema and peripheral swelling.

[c] Includes upper abdominal pain, lower abdominal pain, and abdominal discomfort.

[d] Includes back pain, pain in extremity, myalgia, neck pain, and bone pain.

[e] Includes dermatitis, dermatitis acneiform, and rash described as maculo-papular, erythematous, and generalized.

[f] Includes nasopharyngitis and rhinitis.

Clinically important adverse reactions reported in <10% of patients receiving OPDIVO with ipilimumab were encephalitis (0.8%), necrotizing myositis (0.8%), and uveitis (0.8%).

Table ~~38~~40: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-142

Laboratory Abnormality	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	50	7	42	9
Lymphopenia	36	7	25	6
Neutropenia	20	4.3	18	0
Thrombocytopenia	16	1.4	26	0.9
Chemistry				
Increased alkaline phosphatase	37	2.8	28	5
Increased lipase	33	19	39	12
Increased ALT	32	2.8	33	12
Increased AST	31	1.4	40	12
Hyponatremia	27	4.3	26	5
Hypocalcemia	19	0	16	0
Hypomagnesemia	17	0	18	0
Increased amylase	16	4.8	36	3.4
Increased bilirubin	14	4.2	21	5
Hypokalemia	14	0	15	1.8
Increased creatinine	12	0	25	3.6
Hyperkalemia	11	0	23	0.9

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. Number of evaluable patients ranges from 62 to 71 for the OPDIVO cohort and from 87 to 114 for the OPDIVO and ipilimumab cohort.

Hepatocellular Carcinoma

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-9DW, a randomized, open-label trial in adult patients with unresectable or metastatic HCC *[see Clinical Studies (14.12)]*. Patients received OPDIVO in combination with ipilimumab (n=332) or investigator's choice of lenvatinib (n=275) or sorafenib (n=50) at the following dosage:

- OPDIVO 1 mg/kg administered intravenously over 30 minutes in combination with ipilimumab 3 mg/kg administered intravenously over 30 minutes every 3 weeks, for a maximum of 4 doses, followed by single-agent OPDIVO at 480 mg administered intravenously over 30 minutes every 4 weeks, or
- Investigator's choice:
  - Lenvatinib 8 mg orally daily (if body weight <60 kg) or 12 mg orally daily (if body weight ≥60 kg), or
  - Sorafenib 400 mg orally twice daily

In the OPDIVO and ipilimumab arm, the median duration of exposure to OPDIVO was 4.7 months (range: <0.1 to 24.4 months), 45% were exposed for >6 months and 30% were exposed for >1 year.

Serious adverse reactions occurred in 53% of patients treated with OPDIVO in combination with ipilimumab. The most frequent non-liver-related serious adverse reactions reported in ≥2% of patients who received OPDIVO in combination with ipilimumab were diarrhea/colitis (4.5%), gastrointestinal hemorrhage (3%), and rash (2.4%).

Liver-related serious adverse reactions occurred in 17% of patients treated with OPDIVO in combination with ipilimumab, including Grade 3-4 events in 16% of patients. The most frequently reported all grade liver-related serious adverse reactions occurring in ≥1% of patients who received OPDIVO in combination with ipilimumab were immune-mediated hepatitis (3%), increased AST/ALT (3%), hepatic failure (2.4%), ascites (2.4%), and hepatotoxicity (1.2%).

Fatal adverse reactions occurred in 12 (3.6%) patients who received OPDIVO in combination with ipilimumab; these included 4 (1.2%) patients who died due to immune-mediated or autoimmune hepatitis and 4 (1.2%) patients who died of hepatic failure.

Permanent discontinuations of OPDIVO due to an adverse reaction occurred in 27% of patients. Adverse reactions leading to permanent discontinuation of OPDIVO in >1% of patients included immune-mediated hepatitis (1.8%), diarrhea/colitis (1.8%), hepatic failure (1.2%).

Dosage interruptions of OPDIVO due to an adverse reaction occurred in 62% of patients. Adverse reactions which required dosage interruption in >5% of patients included increased AST (13%), increased ALT (11%), and diarrhea/colitis (8%).

The most common (>20%) adverse reactions were rash, pruritus, fatigue, and diarrhea.

Tables 41 and 42 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9DW.

Table 41: Adverse Reactions Occurring in ≥10% of OPDIVO in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	OPDIVO and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	36	3.6	15	1.2
Pruritus	34	1.5	7	0.3
General				
Fatigue[a]	33	2.4	39	4
Pyrexia[a]	15	0.6	9	1.5
Edema[a]	13	1.2	13	1.5
Gastrointestinal				
Diarrhea[a]	25	6	39	3.4
Abdominal pain[a]	14	1.2	27	2.5

Table 41: Adverse Reactions Occurring in ≥10% of OPDIVO in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	OPDIVO and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Nausea	10	0.3	16	0.9
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[a]	17	0.6	23	0.3
Arthralgia	12	0.3	13	0.6
Metabolism and Nutrition				
Decreased appetite	16	1.2	28	1.8
Endocrine				
Hypothyroidism[a]	14	0	27	0
Hyperthyroidism	11	0.6	1.5	0
Respiratory, Thoracic and Mediastinal				
Cough[a]	13	0	8	0

Toxicity was graded per NCI CTCAE v5

[a] Represents a composite of multiple related terms.

Clinically important adverse reactions reported in <10% of patients who received OPDIVO with ipilimumab were hyperglycemia (8%), adrenal insufficiency (4.2%), pneumonitis (2.7%), and pancreatitis (2.4%).

Table 42: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of OPDIVO in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	OPDIVO and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased AST	62	29	51	14
Increased ALT	61	17	46	9
Increased lipase	58	16	39	5
Decreased albumin	48	0.9	57	0.6
Hyponatremia	45	6	42	3.8
Hyperglycemia	44	15	32	2.1
Increased bilirubin	44	10	44	8

Table 42: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of OPDIVO in combination with Ipilimumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	OPDIVO and Ipilimumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Increased amylase	41	6	26	1
Increased alkaline phosphatase	36	1.2	38	5
Hypocalcemia	29	0.9	46	0
Increased creatinine	26	2.4	23	0.6
Hypokalemia	21	2.1	20	2.6
Hematology				
Anemia	44	5	40	3.8
Lymphopenia	40	6.1	40	8
Thrombocytopenia	27	4	44	4.8
Neutropenia	24	4	32	3.5

[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 ipilimumab group (range: 168 to 331 patients) and lenvatinib or sorafenib group (range: 145 to 315 patients).

Previously Treated Hepatocellular Carcinoma

The safety of OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg was evaluated in a subgroup comprising 49 patients with HCC and Child-Pugh Class A cirrhosis enrolled in Cohort 4 of CHECKMATE-040, a multicenter, multiple cohort, open-label trial *[see Clinical Studies (14.~~11~~12)]* who progressed on or were intolerant to sorafenib. OPDIVO and ipilimumab were administered every 3 weeks for 4 doses, followed by single-agent OPDIVO 240 mg every 2 weeks until disease progression or unacceptable toxicity. During the OPDIVO and ipilimumab combination period, 33 of 49 (67%) patients received all 4 planned doses of OPDIVO and ipilimumab. During the entire treatment period, the median duration of exposure to OPDIVO was 5.1 months (range: 0 to 35+ months) and to ipilimumab was 2.1 months (range: 0 to 4.5 months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

The most frequent serious adverse reactions (reported in ≥4% of patients) were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.

Tables ~~39~~ 43 and ~~40~~ 44 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-040.

Table ~~39~~43: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	OPDIVO and Ipilimumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue		
Rash	53	8
Pruritus	53	4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain	41	2
Arthralgia	10	0
Gastrointestinal		
Diarrhea	39	4
Abdominal pain	22	6
Nausea	20	0
Ascites	14	6
Constipation	14	0
Dry mouth	12	0
Dyspepsia	12	2
Vomiting	12	2
Stomatitis	10	0
Respiratory, Thoracic and Mediastinal		
Cough	37	0
Dyspnea	14	0
Pneumonitis	10	2
Metabolism and Nutrition		
Decreased appetite	35	2
General		
Fatigue	27	2
Pyrexia	27	0
Malaise	18	2
Edema	16	2
Influenza-like illness	14	0
Chills	10	0
Nervous System		
Headache	22	0
Dizziness	20	0
Endocrine		
Hypothyroidism	20	0
Adrenal insufficiency	18	4
Investigations		
Weight decreased	20	0
Psychiatric		
Insomnia	18	0
Blood and Lymphatic System		
Anemia	10	4
Infections		
Influenza	10	2
Vascular		
Hypotension	10	0

Clinically important adverse reactions reported in <10% of patients who received OPDIVO with ipilimumab were hyperglycemia (8%), colitis (4%), and increased blood creatine phosphokinase (2%).

Table ~~40~~44: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 of CHECKMATE-040

Laboratory Abnormality	OPDIVO and Ipilimumab (n=47)	
	All Grades (%)	Grades 3-4 (%)
Hematology		
Lymphopenia	53	13
Anemia	43	4.3
Neutropenia	43	9
Leukopenia	40	2.1
Thrombocytopenia	34	4.3
Chemistry		
Increased AST	66	40
Increased ALT	66	21
Increased bilirubin	55	11
Increased lipase	51	26
Hyponatremia	49	32
Hypocalcemia	47	0
Increased alkaline phosphatase	40	4.3
Increased amylase	38	15
Hypokalemia	26	2.1
Hyperkalemia	23	4.3
Increased creatinine	21	0
Hypomagnesemia	11	0

In patients who received OPDIVO with ipilimumab, virologic breakthrough occurred in 4 of 28 (14%) patients and 2 of 4 (50%) patients with active HBV or HCV at baseline, respectively. HBV virologic breakthrough was defined as at least a 1 log increase in HBV DNA for those patients with detectable HBV DNA at baseline. HCV virologic breakthrough was defined as a 1 log increase in HCV RNA from baseline.

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8 USE IN SPECIFIC POPULATIONS

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8.1 Pregnancy

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8.2 Lactation

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8.3 Females and Males of Reproductive Potential

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8.4 Pediatric Use

The safety and effectiveness of OPDIVO have been established in pediatric patients aged 12 years and older for the following indications: as a single agent and in combination with ipilimumab for the treatment of unresectable or metastatic melanoma, as a single agent for the adjuvant treatment of completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma, in combination with ipilimumab for the first line treatment of MSI-H or dMMR unresectable and metastatic CRC, and~~,~~ as a single agent or in combination with ipilimumab for the treatment of MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for these indications is supported by evidence from adequate and well-controlled studies in adults with melanoma or MSI-H or dMMR mCRC and additional pharmacokinetic data in pediatric patients. Nivolumab exposure in pediatric patients 12 years and older is comparable to that of adults and the courses of melanoma and MSI-H or dMMR mCRC are similar in pediatric patients aged 12 years and older to that of adults to allow extrapolation of safety and efficacy *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.1, 14.~~10~~11)]*.

The safety and effectiveness of OPDIVO have not been established for pediatric patients younger than 12 years old with melanoma or MSI-H or dMMR mCRC.

The safety and effectiveness of OPDIVO have not been established in pediatric patients with non-small cell lung cancer, malignant pleural mesothelioma, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, hepatocellular carcinoma, esophageal cancer, gastric cancer, gastroesophageal cancer and esophageal adenocarcinoma.

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.~~4~~5, 14.~~6~~7, 14.~~9~~10, 14.~~12~~13, 14.~~13~~14)]*.

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.~~7~~8, 14.~~8~~9, 14.~~10~~11)]*.

OPDIVO 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.~~5~~6)]*. 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.~~6~~7)]*.

Of the 354 patients with dMMR or MSI-H metastatic CRC (mCRC) who were randomized to OPDIVO in combination with ipilimumab, 44% were 65 years or older and 14% were 75 years or older. Of the 353 patients randomized to OPDIVO, as a single agent, 45% were 65 years or older and 13% were 75 years or older. There was a higher incidence of any Grade 3 or 4 adverse reactions (55%) in patients aged 65 years or older receiving OPDIVO in combination with ipilimumab compared to those younger than 65 receiving the combination (42%). There was also a higher incidence of any Grade 3 or 4 adverse reactions (55%) in patients aged 65 years or older receiving OPDIVO in combination with ipilimumab relative to patients aged 65 years or older receiving single-agent OPDIVO (41%). There was a similar incidence of any Grade 3 or 4 adverse reactions in patients receiving single-agent OPDIVO aged 65 years or older (41%) relative to patients younger than 65 years (45%). Patients 65 years or older who received OPDIVO with ipilimumab discontinued treatment due to adverse reaction at a higher rate (23%) relative to patients 65 years or older receiving nivolumab (15%). No overall differences in effectiveness were reported between elderly patients and younger patients receiving either OPDIVO in combination with ipilimumab or single-agent OPDIVO *[see Clinical Studies (14.11)]*.

Of the 335 patients with unresectable hepatocellular carcinoma who were randomized to OPDIVO in combination with ipilimumab, 52% were 65 years or older and 14% were 75 years or older. No overall difference in safety was reported between elderly 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 (67% and 35%, respectively) relative to all patients who received OPDIVO with ipilimumab (53% and 27%, respectively).

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.~~11~~12)]*.

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~~13)]*.

OPDIVO in Combination with Platinum-Containing 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)]*.

Of the 229 patients with NSCLC who were randomized to OPDIVO 360 mg in combination with platinum-doublet chemotherapy every 3 weeks for up to 4 cycles, followed by OPDIVO 480 mg every 4 weeks, 56% were 65 years old or older and 7% were 75 years old or older. No overall differences in safety or effectiveness were reported between patients older and younger than 65 years.

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~~13, 14.~~13~~14)]*.

Of the 304 patients with UC who were treated with OPDIVO in combination with gemcitabine and platinum-doublet chemotherapy, 40% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years of age and over and younger patients. Clinical studies of OPDIVO with platinum-doublet chemotherapy did not include sufficient numbers of patients aged 75 years and over to determine whether safety and effectiveness differs compared to younger patients. *[see Clinical Studies (14.~~9~~10)]*.

OPDIVO 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.~~4~~5)]*.

OPDIVO 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~~7)]*.

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12 CLINICAL PHARMACOLOGY

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13 NONCLINICAL TOXICOLOGY

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14 CLINICAL STUDIES

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14.4 Neoadjuvant and Adjuvant Treatment of Resectable Non-Small Cell Lung Cancer

The efficacy of OPDIVO, in combination with platinum-doublet chemotherapy, followed by surgery, and continued adjuvant treatment with OPDIVO as a single agent, was investigated in CHECKMATE-77T (NCT04025879), a randomized, double-blind trial in 461 patients with resectable NSCLC. The trial included patients with resectable, suspected or histologically confirmed Stage IIA (>4 cm) to IIIB (T3-T4 N2) NSCLC (per the 8th edition American Joint Committee on Cancer (AJCC) Staging Manual), and ECOG performance status 0 or 1. Patients with unresectable or metastatic NSCLC, EGFR mutations or known ALK translocations, brain metastasis, Grade 2 or greater peripheral neuropathy, interstitial lung disease or active, non-infectious pneumonitis (symptomatic and/or requiring treatment), active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Randomization was stratified by tumor PD-L1 expression level (≥1% versus <1% versus indeterminate/not evaluable), disease stage (Stage II versus Stage III), and tumor histology (squamous versus nonsquamous).

Patients were randomized (1:1) to receive either:

- Neoadjuvant OPDIVO 360 mg administered intravenously over 30 minutes in combination with one of the following platinum-doublet chemotherapy regimens every 3 weeks for four cycles:
    - 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 or carboplatin AUC 5 or AUC 6 (nonsquamous histology)
    - Cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 (squamous histology).

  Within 90 days after the surgery, OPDIVO 480 mg was administered intravenously over 30 minutes every 4 weeks.

or

- Neoadjuvant placebo administered intravenously over 30 minutes in combination with platinum-doublet chemotherapy *(see above)* every 3 weeks for four cycles. Within 90 days after the surgery, placebo was administered intravenously over 30 minutes every 4 weeks.

All study medications were administered via intravenous infusion. Treatment continued until disease progression, recurrence, or unacceptable toxicity for up to 13 cycles (1 year). Tumor assessments were performed every 12 weeks for 2 years, then every 24 weeks for up to 5 years or until disease recurrence or progression was confirmed by BICR.

The trial was not designed to isolate the effect of OPDIVO in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measure was event-free survival (EFS) based on BICR assessment. Additional efficacy outcome measures included overall survival (OS), pathologic complete response (pCR), and major pathologic response (MPR).

The median age was 66 years (range: 35 to 86); 71% were male; 72% were White, 25% were Asian, 1.7% were Black, and 1.5% were mixed race/ race unknown/ not reported; and 6% were Hispanic or Latino. Baseline ECOG performance status was 0 (62%) or 1 (38%); 56% had tumors with PD-L1 expression ≥1% and 40% had tumors with PD-L1 expression <1%; 35% had stage II and 64% had stage III disease; 23% had N1 disease and 39% had N2 disease; 51% had tumors with squamous histology and 49% had tumors with nonsquamous histology; and 90% were former/current smokers.

Seventy-eight percent of patients in the neoadjuvant OPDIVO in combination with platinum-doublet chemotherapy followed by adjuvant OPDIVO arm had definitive surgery compared to 77% of patients in the neoadjuvant placebo and platinum-doublet chemotherapy followed by placebo arm.

In a pre-specified interim analysis in all randomised patients with a median follow-up of 25.4 months (range: 15.7-44.2 months), the study demonstrated statistically significant improvement of EFS. Median EFS was not reached (95% CI: 28.94, NE) in the nivolumab in combination with chemotherapy/nivolumab arm and 18.43 months (95% CI: 13.63, 28.06) in the placebo with chemotherapy/placebo arm (HR = 0.58, 97.36% CI: 0.42, 0.81; stratified log-rank p-value 0.00025). In a pre-specified interim analysis in all randomised patients with a median follow-up

of 41 months (range: 31.3-59.8 months), median OS was not reached in both the nivolumab in combination with chemotherapy/nivolumab arm and in the placebo with chemotherapy/placebo arm (HR = 0.85, 97.63% CI: 0.58, 1.25).

Exploratory subgroup analysis by tumour PD-L1 expression

EFS for the subgroup of patients with tumour PD-L1 expression ≥ 1%, with a median follow-up of 41 months (range: 31.3-59.8 months), are presented in Table 60 and Figure 7.

Table 60: Efficacy results in patients with tumour PD-L1 ≥ 1% (CA20977T)

	nivolumab with chemotherapy/ nivolumab (n=128)	placebo with chemotherapy/ placebo (n=128)
Event-free survival (EFS) per BICR		
Events (%)	47 (37%)	70 (55%)
Median (months)[a] (95% CI)	46.55 (35.81, NE)	15.08 (9.33, 31.41)
Hazard Ratio[b] (95% CI)	0.53 (0.36, 0.76)	

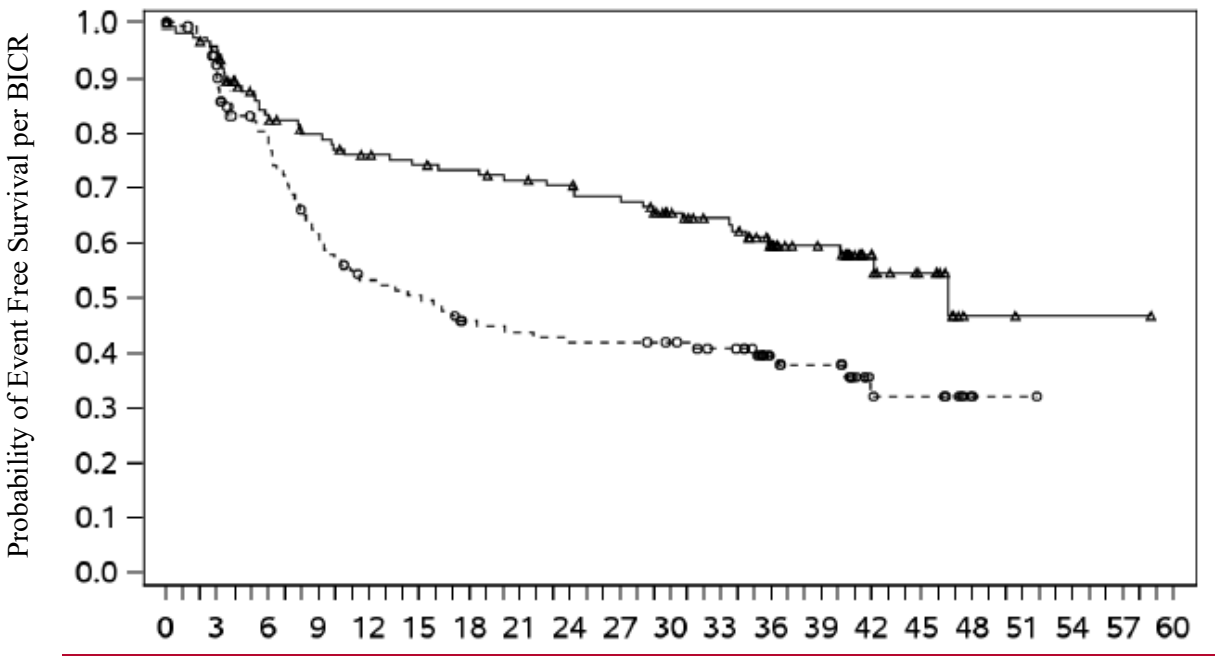
NE = non-estimable

Minimum follow-up for EFS was 31.3 months; data cut-off: 11-Nov-2024.

[a] Kaplan-Meier estimate.

[b] Based on an unstratified Cox proportional hazard model.

Figure 7: Kaplan-Meier curves of EFS in patients with tumour PD-L1 ≥1% (CA20977T)



Event Free Survival per BICR (Months)

Number of Subjects at Risk

Nivolumab + chemotherapy/Nivolumab	128	119	95	89	83	80	78	75	73	70	61	55	44	35	17	11	2	1	1	1	0
Placebo + chemotherapy/Placebo	128	110	87	68	57	54	46	44	42	42	40	36	23	20	9	8	2	1	0	0	0

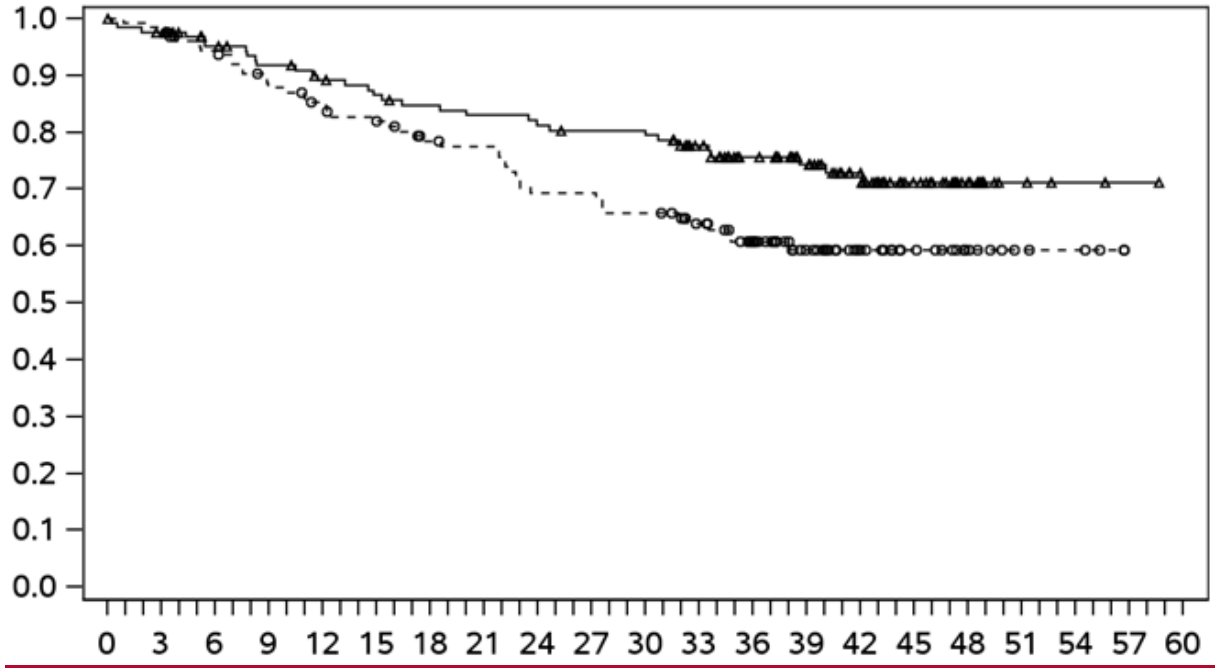
—△——Nivolumab + chemotherapy/Nivolumab (events: 47/128), median and 95% CI:46.55 (35.81, NE)

- - -❍- - -Placebo + Chemotherapy/Placebo (events: 70/128), median and 95% CI: 15.08 (9.33, 31.41)

Based on data cut-off 11-Nov-2024, minimum follow-up of 31.3 months

At the time of the updated EFS analysis, an interim analysis for OS was performed (minimum follow-up of 31.3 months). The exploratory, descriptive HR for OS in patients with tumour PD-L1 expression ≥ 1% was 0.61 (95% CI: 0.39, 0.97) for the nivolumab in combination with chemotherapy/nivolumab arm vs. the placebo with chemotherapy/placebo arm. The Kaplan-Meier curves for OS for the subgroup of patients with tumour PD-L1 expression ≥ 1% are shown in Figure 8.

Figure 8: Kaplan-Meier curves of OS in patients with tumour PD-L1 ≥ 1% (CA20977T)



Overall Survival (Months)

Number of Subjects at Risk

Nivolumab + chemotherapy/Nivolumab	128	123	114	108	103	99	96	94	92	90	90	80	67	55	42	26	15	4	2	1	0
Placebo + chemotherapy/Placebo	128	126	116	106	101	96	88	86	77	77	73	65	54	36	25	17	10	5	4	0	0

—△——Nivolumab + chemotherapy/Nivolumab (events: 31/128), median and 95% CI: NR

- - -❍- - -Placebo + Chemotherapy/Placebo (events: 46/128), median and 95% CI: NR (38.08, NE)

Based on data cut-off 11-Nov-2024, minimum follow-up of 31.3 months

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14.11 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

Treatment of MSI-H or dMMR mCRC In Combination with Ipilimumab

CHECKMATE-8HW (NCT03143153) was a randomized, 3-arm, open-label trial in immunotherapy-naive patients across all lines of therapy with unresectable or metastatic CRC with known tumor MSI-H or dMMR (MSI-H/dMMR) status as determined in accordance with local standard of practice using PCR, NGS, or IHC assays. Central assessment of MSI-H status using PCR (Idylla MSI) test and dMMR status using IHC (Omnis MMR) test was conducted retrospectively on patient tumor specimens used for local MSI-H/dMMR status determination. Patients with confirmed MSI-H/dMMR status by either central test comprised the primary study population.

The trial excluded patients with brain metastasis that were symptomatic, had active autoimmune disease, used systemic corticosteroids or immunosuppressants, or had been treated with checkpoint inhibitors.

Patients were randomized to receive one of the following treatments:

- OPDIVO 240 mg every 3 weeks and ipilimumab 1 mg/kg every 3 weeks for a maximum of 4 doses, then OPDIVO 480 mg every 4 weeks.
- OPDIVO 240 mg every 2 weeks for 6 doses, then OPDIVO 480 mg every 4 weeks.
- Investigator's choice chemotherapy
    - mFOLFOX6 (oxaliplatin, leucovorin, and FU) with or without either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus followed by FU 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg or cetuximab 500 mg/m^2 administered prior to mFOLFOX6 every 2 weeks.
    - FOLFIRI (irinotecan, leucovorin, and FU) with or without either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus and FU 2400 mg/m^2 over 46 hours every 2 weeks. Bevacizumab 5 mg/kg on or cetuximab 500 mg/m^2 administered prior to FOLFIRI every 2 weeks.

Randomization was stratified by tumor location (right vs left) and by prior lines of therapy (0, 1, 2L+). Patients randomized to the chemotherapy arm could receive OPDIVO in combination with ipilimumab upon progression assessed by BICR.

Study treatment was administered until disease progression, unacceptable toxicity, or for up to 2 years for patients who received OPDIVO plus ipilimumab or nivolumab monotherapy. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent. OPDIVO with or without ipilimumab could be administered beyond RECIST 1.1-assessed progressive disease if there was a clinical benefit as determined by investigator and therapy was tolerated. Tumor assessments per RECIST v1.1 were

conducted every 6 weeks for the first 24 weeks, then every 8 weeks thereafter up until week 96, then every 16 weeks thereafter up until week 144, and then every 24 weeks.

The evaluation of efficacy relied on the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomized to OPDIVO in combination with ipilimumab versus chemotherapy in the first-line (1L) setting and the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomized to OPDIVO plus ipilimumab vs nivolumab in all lines setting.

The major efficacy outcome measure was BICR-assessed PFS per RECIST 1.1. Additional efficacy outcome measures included ORR and duration of response assessed by BICR and OS.

The baseline characteristics of the total of 839 patients randomized were: the median age was 63 years (range: 20 to 87), with 46% ≥65 years of age and 14% ≥75 years of age; 50% were male and 87% were White, 9.3% were Asian, 1.5% Black or African American, and 2.3% other race; 9.2% were Hispanic or Latino, 50% Not Hispanic or Latino, 41% ethnicity unknown. Baseline ECOG performance status was 0 (52%) and 1 (48%); number of prior lines of therapy was 0 (56%), 1 (24%), and ≥2 (19%); and tumor location was right-sided or left-sided for 69% and 31% of patients. The baseline characteristics in patients with centrally confirmed MSI-H/dMMR is consistent with that of all randomized patients.

First Line OPDIVO in combination with ipilimumab

Among 303 patients in the first-line setting who were randomly assigned to OPDIVO in combination with ipilimumab (202) and to chemotherapy (101), 171 and 84 patients had centrally confirmed MSI-H/dMMR status in OPDIVO in combination with ipilimumab arm and chemotherapy arm, respectively.

In the 1L setting 200 of 202 patients assigned to receive OPDIVO combined with ipilimumab and 88 of 101 patients assigned to receive chemotherapy received at least 1 dose of study treatment. Among the 88 patients who received chemotherapy, 58% and 42% of patients received oxaliplatin-containing regimens and irinotecan-containing regimens, respectively, and 66 (75%) patients received a targeted agent, either bevacizumab (64%) or cetuximab (11%).

The BICR-assessed PFS efficacy results for patients with centrally confirmed MSI-H/dMMR randomized to the OPDIVO and ipilimumab arm compared with chemotherapy in the 1L setting are presented in Table 75 and Figure 23. The comparative results of ORR and OS between arms were not available at the time of the PFS analysis due to statistical testing strategy.

Table 75: Efficacy Results, First Line - CHECKMATE-8HW

	OPDIVO and Ipilimumab (n=171)	**Chemotherapy (n=84)**
Progression-free Survival		
Disease progression or death (%)	48 (28)	52 (62)
Median in months[b] (95% CI)	NR (38.4, NE)	5.8 (4.4, 7.8)
Hazard ratio[c] (95% CI)	0.21 (0.14, 0.32)	

p-value[a]	<0.0001

NR: Not Reached; NE: Not Estimable.

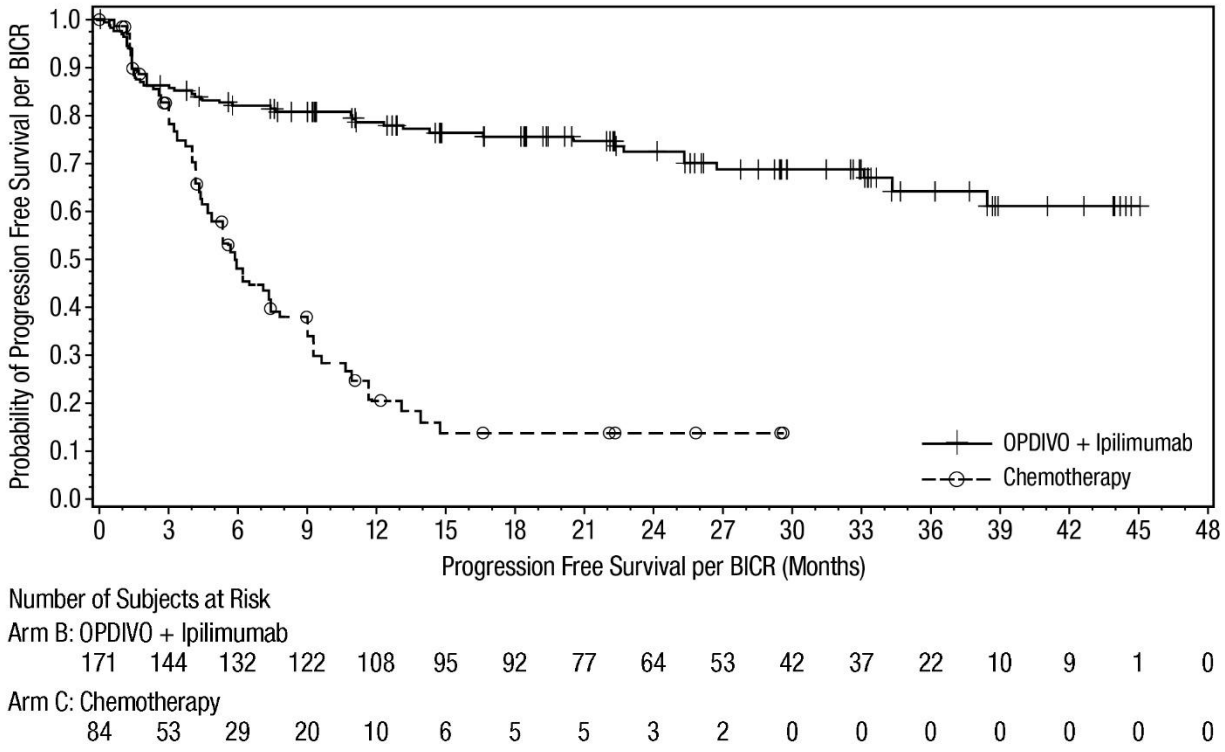
Minimum follow-up was 6.1 months at data cutoff date 12Oct2023.

[a] Based on log-rank test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.0209.

[b] Based on Kaplan-Meier estimates.

[c] HR from a Cox proportional hazards model stratified by tumor sidedness (left vs right) per IRT.

Figure 23: Progression-free Survival (First Line OPDIVO + Ipilimumab vs Chemotherapy) - CHECKMATE-8HW



All Lines OPDIVO in combination with ipilimumab

Among 707 patients across all treatment lines who were randomly assigned to OPDIVO in combination with ipilimumab (354) and to OPDIVO (353) single agent, 296 and 286 patients had centrally confirmed MSI-H/dMMR status in the OPDIVO in combination with ipilimumab arm and in the OPDIVO arm, respectively. Patients receiving at least 1 dose of study treatment included 352 of 354 patients randomized to OPDIVO in combination with ipilimumab, and 351 of 353 patients randomized to single agent OPDIVO.

The BICR-assessed PFS and ORR efficacy results for patients with centrally confirmed MSI-H/dMMR randomized to the OPDIVO in combination with ipilimumab compared with nivolumab single agent across all treatment lines setting are presented in Table 76 and Figure 24. The comparative results of OS between arms were not available at the time of the PFS analysis due to statistical testing strategy.

Table 76: Efficacy Results, All Lines - CHECKMATE-8HW

	OPDIVO and Ipilimumab (n=296)	OPDIVO (n=286)
Progression-free Survival		
Disease progression or death n (%)	101 (34)	136 (48)
Median (months)[b] (95% CI)	NR (53.8, NE)	39.3 (22.1, NE)
Hazard ratio[c] (95% CI)	0.62 (0.48, 0.81)	
p-value[a]	0.0003	
Objective Response Rate (ORR)		
Response Rate, n (%) (95% CI)	209 (71%) (65, 76)	165 (58%) (52, 63)
Complete Response Rate, n (%)	90 (30%)	80 (28%)
Partial Response Rate, n (%)	119 (40%)	85 (30%)
p-value[d]	0.0011	

NR: Not Reached; NE: Not Estimable.

Minimum follow-up was 16.7 months at data cutoff date 28Aug2024.

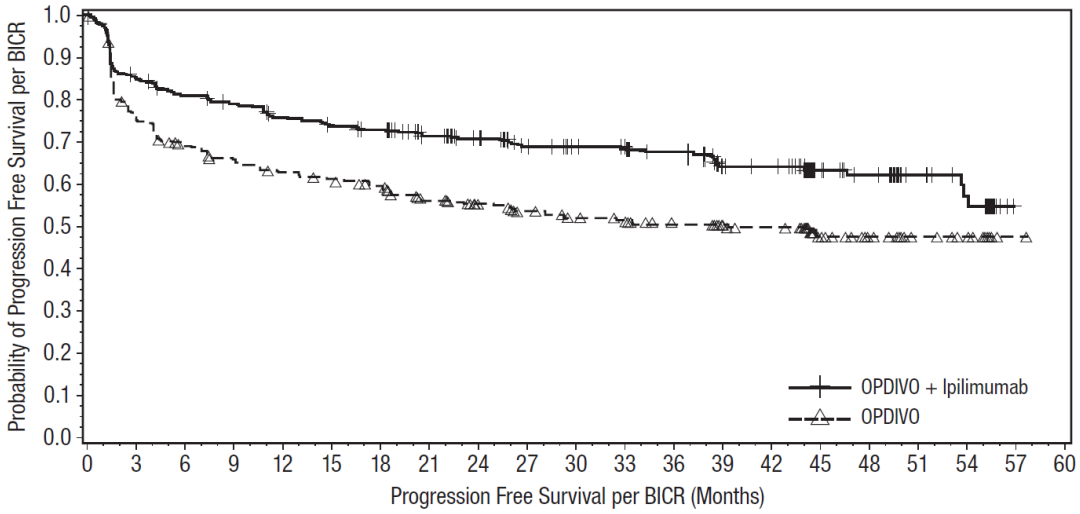
[a] Based on log-rank test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.0095.

[b] Based on Kaplan-Meier estimates.

[c] HR from a Cox proportional hazards model stratified by tumor sidedness (left vs right) and prior lines of therapy (0, 1, ≥2) per IRT.

[d] Based on Cochran-Mantel-Haenszel test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.006.

Figure 24: Progression-free Survival (All lines OPDIVO + Ipilimumab vs OPDIVO) - CHECKMATE-8HW



Number of Subjects at Risk

Arm A: OPDIVO	286	210	191	179	169	164	158	141	124	109	98	95	81	72	69	39	31	15	12	1	0
Arm B: OPDIVO + Ipilimumab	296	248	234	225	214	207	200	180	164	146	136	134	121	102	100	61	54	29	23	0	0

Treatment of MSI-H or dMMR mCRC after Progression Following Treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan

CHECKMATE-142 (NCT02060188) was a multicenter, non-randomized, multiple parallel-cohort, open-label trial conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine--, oxaliplatin--, or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG performance status 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients enrolled in the single agent OPDIVO MSI-H mCRC cohort received OPDIVO 3 mg/kg by intravenous infusion (IV) every 2 weeks. Patients enrolled in the OPDIVO and ipilimumab MSI-H mCRC cohort received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses, followed by OPDIVO as a single agent at a dose of 3 mg/kg as intravenous infusion every 2 weeks. Treatment in both cohorts continued until unacceptable toxicity or radiographic progression.

Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included ORR and DOR as assessed by BICR using RECIST v1.1.

A total of 74 patients were enrolled in the single-agent MSI-H mCRC OPDIVO cohort. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% ≥75 years of age, 59% were male and 88% were White. Baseline ECOG performance status was 0 (43%), 1 (55%), or 3 (1.4%) and 36% were reported to have Lynch Syndrome. Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 7%, 30%, 28%, 19%, and 16%

received 0, 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 42% of patients had received an anti-EGFR antibody.

A total of 119 patients were enrolled in the OPDIVO and ipilimumab MSI-H mCRC cohort. The median age was 58 years (range: 21 to 88), with 32% ≥65 years of age and 9% ≥75 years of age; 59% were male and 92% were White. Baseline ECOG performance status was 0 (45%) and 1 (55%), and 29% were reported to have Lynch Syndrome. Across the 119 patients, 69% had received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 10%, 40%, 24%, and 15% received 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 29% had received an anti-EGFR antibody.

Efficacy results for each of these single-arm cohorts are shown in Table ~~70~~77.

Table ~~70~~77: Efficacy Results - CHECKMATE-142

	OPDIVO[a] MSI-H/dMMR Cohort		OPDIVO and Ipilimumab[b] MSI-H/dMMR Cohort	
	All Patients (n=74)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)**	**All Patients (n=119)**	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
Overall Response Rate per BICR; n (%)	28 (38%)	17 (32%)	71 (60%)	46 (56%)
(95% CI)[c]	(27, 50)	(20, 46)	(50, 69)	(45, 67)
Complete Response (%)	8 (11%)	5 (9%)	17 (14%)	11 (13%)
Partial Response (%)	20 (27%)	12 (23%)	54 (45%)	35 (43%)
Duration of Response				
Proportion of responders with ≥6 months response duration	86%	94%	89%	87%
Proportion of responders with ≥12 months response duration	82%	88%	77%	74%

[a] Minimum follow-up 33.7 months for all patients treated with OPDIVO (n=74).

[b] Minimum follow-up 27.5 months for all patients treated with OPDIVO and ipilimumab (n=119).

[c] Estimated using the Clopper-Pearson method.

14.12 Hepatocellular Carcinoma

Treatment of Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

CHECKMATE-9DW (NCT04039607) was a randomized (1:1), open-label trial in adults (18 years of age or older) with unresectable or metastatic HCC. Patients had histologically confirmed HCC, Child Pugh Class A, ECOG performance status 0 or 1, and no prior systemic therapy for advanced disease. Esophagogastroduodenoscopy was not mandated prior to enrollment. The trial excluded patients with known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC, active autoimmune disease, brain or leptomeningeal metastases, a history of hepatic encephalopathy (within 12 months of randomization), a platelet count <60,000, clinically

significant ascites, medical conditions requiring systemic immunosuppression, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV).

Patients were randomized to receive either:

- OPDIVO 1 mg/kg administered intravenously over 30 minutes in combination with ipilimumab 3 mg/kg administered intravenously over 30 minutes every 3 weeks, for a maximum of 4 doses, followed by single agent OPDIVO at 480 mg administered intravenously over 30 minutes every 4 weeks, or
- Investigator's choice:
    - Lenvatinib 8 mg orally daily (if body weight <60 kg) or 12 mg orally daily (if body weight ≥60 kg), or
    - Sorafenib 400 mg orally twice daily

Randomization was stratified by etiology (HBV vs. HCV vs. non-viral), macrovascular invasion and/or extrahepatic spread (present or absent), and alpha-fetoprotein levels (≥400 or <400 ng/mL). Study treatment for OPDIVO in combination with ipilimumab continued until disease progression, unacceptable toxicity, or up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent. Treatment beyond RECIST 1.1 defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at week 9 and week 16, then every 8 weeks up to 48 weeks, and then every 12 weeks thereafter until disease progression, treatment discontinuation, or initiation of subsequent therapy. The primary efficacy outcome measure was OS in all randomized patients. Additional efficacy measures included BICR-assessed ORR and DOR based on RECIST 1.1 criteria.

A total of 668 patients were randomized to receive OPDIVO in combination with ipilimumab (n=335) or investigator's choice (n=333) of lenvatinib or sorafenib. In the investigator arm, 85% and 15% of treated patients received lenvatinib or sorafenib, respectively. The trial population characteristics were median age 66 years (range: 20 to 89), with 53% ≥65 years old; 82% male; 53% White, 44% Asian, 2.2% Black; 12% Hispanic or Latino, 48% Not Hispanic or Latino, 40% not reported. Baseline ECOG performance status was 0 (71%) or 1 (29%). Thirty-four percent (34%) of patients had HBV infection, 28% had HCV infection, and 36% had no evidence of HBV or HCV infection.

Nineteen percent (19%) of patients had alcoholic liver disease and 11% had non-alcoholic fatty liver disease. The majority of patients had BCLC stage C (73%) disease at baseline, 19% had stage B, and 6% had stage A. Patients with Child-Pugh scores of 5, 6, and 7 were 77%, 20%, and 3%, respectively; 1 patient with Child Pugh 8 was enrolled. A total of 54% of patients had extrahepatic spread; 25% had macrovascular invasion; and 33% had AFP levels ≥400 µg/L.

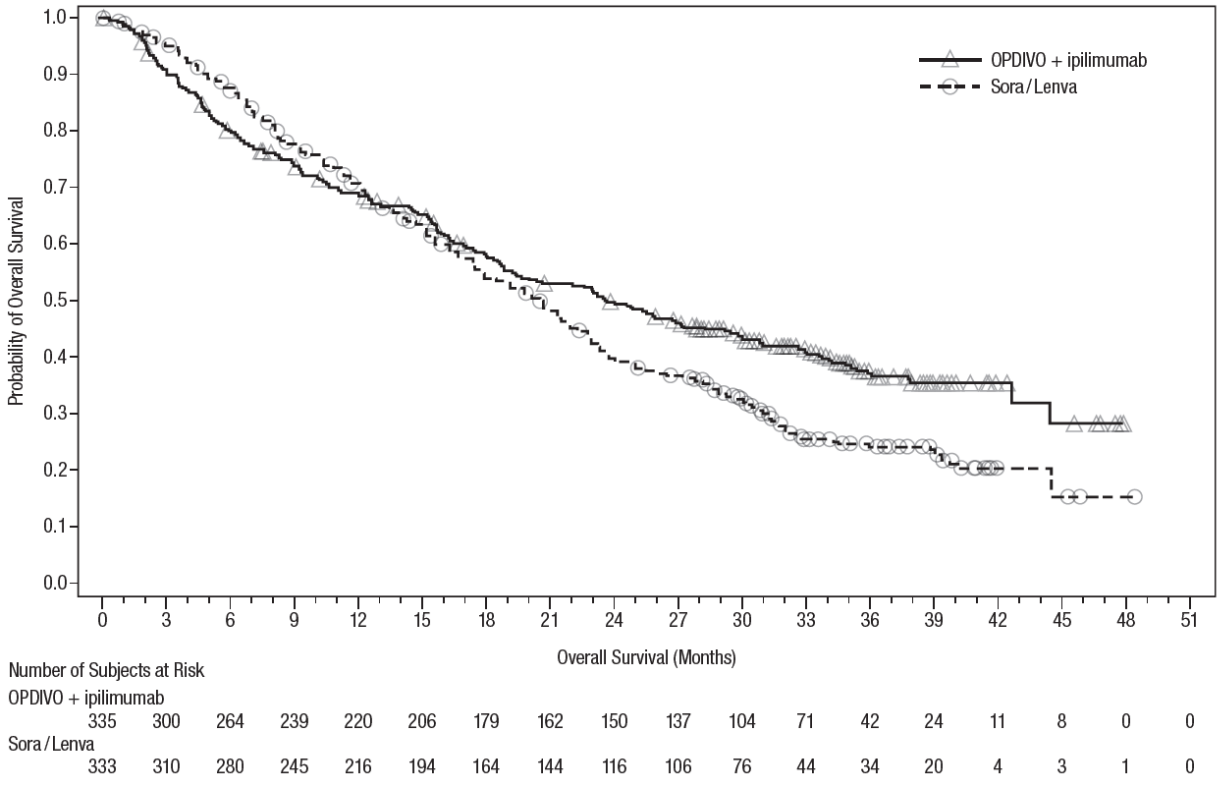
CHECKMATE-9DW demonstrated a statistically significant improvement in OS and ORR. The minimum follow-up was 26.8 months. Efficacy results are shown in Table 78 and Figure 25.

Table 78: Efficacy Results - CHECKMATE-9DW

	OPDIVO and Ipilimumab (n=335)	Lenvatinib or Sorafenib (n=333)
Overall Survival		
Deaths (%)	194 (58%)	228 (68%)
Median (months) (95% CI)	23.7 (18.8, 29.4)	20.6 (17.5, 22.5)
Hazard ratio (95% CI)[a]	0.79 (0.65, 0.96)	
p-value[b]	0.0180	
Overall Response Rate, n (%)[c]	121 (36.1)	44 (13.2)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
p-value[d]	<0.0001	
Complete response (%)	23 (6.9)	6 (1.8)
Partial response (%)	98 (29.3)	38 (11.4)
Duration of Response (months)[c]		
Median (95% CI)	30.4 (21.2, NR[e])	12.9 (10.2, 31.2)
Range	1.5+, 36.9+	2.1+, 32.5+

[a] Based on stratified Cox proportional hazard model.
[b] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value ≤0.0257.
[c] Assessed by BICR using RECIST 1.1.
[d] Based on a 2-sided stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: p-value ≤0.025.
[e] NR: Not Reached.
+ Censored observation.

Figure 25: Overall Survival - CHECKMATE-9DW



Previously Treated Hepatocellular Carcinoma

CHECKMATE-040 (NCT01658878) was a multicenter, multiple cohort, open-label trial that evaluated the efficacy of OPDIVO as a single agent and in combination with ipilimumab in patients with hepatocellular carcinoma (HCC) who progressed on or were intolerant to sorafenib. Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible.

Tumor assessments were conducted every 6 weeks for 48 weeks and then every 12 weeks thereafter. The major efficacy outcome measure was confirmed overall response rate, as assessed by BICR using RECIST v1.1 and modified RECIST (mRECIST) for HCC. Duration of response was also assessed.

The efficacy of OPDIVO in combination with ipilimumab was evaluated in 49 patients (Cohort 4) who received OPDIVO 1 mg/kg and ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, followed by single-agent OPDIVO at 240 mg every 2 weeks until disease progression or unacceptable toxicity. The median age was 60 years (range: 18 to 80), 88% were male, 74% were Asian, and 25% were White. Baseline ECOG performance status was 0 (61%) or 1 (39%). Fifty-seven (57%) percent of patients had active HBV infection, 8% had active HCV infection, and 35% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 16%

and non-alcoholic fatty liver disease in 6% of patients. Child-Pugh class and score was A5 for 82% and A6 for 18%; 80% of patients had extrahepatic spread; 35% had vascular invasion; and 51% had AFP levels ≥400 µg/L. Prior cancer treatment history included surgery (74%), radiotherapy (29%), or local treatment (59%). All patients had received prior sorafenib, of whom 10% were unable to tolerate sorafenib; 29% of patients had received 2 or more prior systemic therapies.

Efficacy results are shown in Table ~~71~~79. The results for OPDIVO in combination with ipilimumab in Cohort 4 are based on a minimum follow-up of 28 months.

Table ~~71~~79: Efficacy Results - Cohort 4 of CHECKMATE-040

	OPDIVO and Ipilimumab (Cohort 4) (n=49)
Overall Response Rate per BICR,[a] n (%), RECIST v1.1	16 (33%)
(95% CI)[b]	(20, 48)
Complete response	4 (8%)
Partial response	12 (24%)
Duration of Response per BICR,[a] RECIST v1.1	n=16
Range (months)	4.6, 30.5+
Percent with duration ≥6 months	88%
Percent with duration ≥12 months	56%
Percent with duration ≥24 months	31%
Overall Response Rate per BICR,[a] n (%), mRECIST	17 (35%)
(95% CI)[b]	(22, 50)
Complete response	6 (12%)
Partial response	11 (22%)

[a] Confirmed by BICR.

[b] Confidence interval is based on the Clopper and Pearson method.

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עדכונים בעלון לצרכן:

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1. <u>למה מיועדת התרופה?</u>

אופדיבו ניתנת לטיפול ב:

- **סרטן עור מסוג מלנומה**
  - אופדיבו כטיפול יחיד או בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול במבוגרים וילדים מגיל 12 ומעלה עם מלנומה מתקדמת (לא נתיחה או גרורתית).
  - אופדיבו מיועדת כטיפול משלים (adjuvant) במבוגרים וילדים מגיל 12 ומעלה עם מלנומה בשלב IIB , IIC, III או IV לאחר הסרה מלאה.
- **סרטן ריאות מסוג תאים שאינם קטנים (non-small cell lung cancer)**
  - <u>אופדיבו, בשילוב עם משלב כימותרפי המכיל פלטינום (platinum-doublet chemotherapy), מיועדת לטיפול קדם ניתוחי (neoadjuvant) במבוגרים עם סרטן ריאות נתיח (גידולים בגודל של 4 ס"מ ומעלה או מערבים בלוטות לימפה) מסוג תאים שאינם קטנים.</u>
  - <u>אופדיבו בשילוב עם משלב כימותרפי המכיל פלטינום (platinum-doublet chemotherapy) מיועדת לטיפול קדם ניתוחי (neoadjuvant) במבוגרים עם סרטן ריאות מסוג תאים שאינם קטנים (NSCLC), נתיח (גידולים בגודל של 4 ס"מ ומעלה או עם מעורבות של בלוטות לימפה), עם ביטוי של PD-L1 בתאי הגידול בשיעור של 1% ומעלה, וללא שינויים בגנים EGFR או ALK בגידול. לאחר הניתוח, אופדיבו כטיפול יחיד מיועדת לטיפול משלים (adjuvant).</u>
  - אופדיבו, בשילוב עם איפילימומאב (ipilimumab) ושני מחזורי טיפול של משלב כימותרפי המכיל פלטינום (platinum-doublet chemotherapy), מיועדת כטיפול קו ראשון במבוגרים עם סרטן ריאות גרורתי או חוזר מסוג תאים שאינם קטנים, וללא שינויים בגנים EGFR או ALK בגידול.
  - אופדיבו מיועדת לטיפול במבוגרים 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 במבוגרים עם סרטן תאי כליה מתקדם, בדרגת סיכון בינונית או גבוהה.
  - אופדיבו בשילוב עם קבוזנטיניב (cabozantinib) מיועדת לטיפול קו ראשון במבוגרים עם סרטן תאי כליה מתקדם.
  - אופדיבו כטיפול יחיד מיועדת לטיפול במבוגרים 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 במבוגרים עם הישנות או גרורות של סרטן תאי קשקש של הראש והצוואר שמחלתם התקדמה תוך כדי או לאחר טיפול כימותרפי המבוסס פלטינום.

- **קרצינומה של תאי האורותל (urothelial carcinoma) - סרטן בדרכי השתן או שלפוחית השתן**
  - אופדיבו מיועדת כטיפול משלים (adjuvant) במבוגרים עם סרטן בדרכי השתן או שלפוחית השתן בסיכון גבוה להישנות המחלה לאחר הסרה רדיקלית של הגידול.
  - אופדיבו בשילוב עם ציספלטין וגמציטאבין מיועדת לטיפול קו ראשון במבוגרים עם סרטן בדרכי השתן או שלפוחית השתן, שאינו נתיח או גרורתי.

- אופדיבו מיועדת לטיפול במבוגרים 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 (neoadjuvant) או כטיפול משלים (adjuvant) לאחר ניתוח.

- **סרטן גרורתי של המעי הגס או החלחולת**
  - אופדיבו בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול קו ראשון במבוגרים וילדים מגיל 12 ומעלה עם סרטן לא נתיח או גרורתי של המעי הגס או החלחולת המבטא dMMR (mismatch repair deficient) או MSI-H (microsatellite instability-high).
  - אופדיבו כטיפול יחיד או בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול במבוגרים 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 בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול במבוגרים עם סרטן כבד עם פגיעה כבדית קלה (Child-Pugh A) לאחר טיפול בסוראפניב (sorafenib).
  - אופדיבו בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול קו ראשון במבוגרים עם סרטן כבד לא נתיח או גרורתי, עם פגיעה כבדית קלה (Child-Pugh A).

- **סרטן ושט**
  - אופדיבו מיועדת כטיפול משלים (adjuvant) לאחר כריתה מלאה של סרטן ושט או סרטן צומת קיבה-ושט, עם שארית מחלה פתולוגית, במבוגרים 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 במבוגרים 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 במבוגרים עם סרטן לא נתיח, מתקדם או גרורתי של הקיבה, צומת קיבה ושט או אדנוקרצינומה של הוושט.

קבוצה תרפויטית: אנטי-ניאופלסטי.

2. לפני השימוש בתרופה:

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אופדיבו מכילה פוליסורבט 80 (Polysorbate 80)
התרופה מכילה 0.94 מ״ג פוליסורבט 80 בכל בקבוקון של 4 מ״ל ו- 2.14 מ״ג בכל בקבוקון של 10 מ״ל. פוליסורבטים עלולים לגרום לתגובות אלרגיות. יש ליידע את הרופא אם ידוע לך על אלרגיות כלשהן.

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 לוריד 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~~ במזותליומה ממאירה של הפלאורה (ראה בהמשך), אופדיבו תינתן בדרך כלל כל 3 שבועות, ~~לסה"כ~~ למשך עד 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 (כימותרפיה המכילה פלטינום ותרופה כימותרפית נוספת) כל 3 שבועות למשך 3 מחזורי טיפול. במקרים מסוימים אופדיבו בשילוב עם משלב כימותרפי ניתנת לפני הניתוח כל שלושה שבועות למשך עד 4 מחזורי טיפול, בהמשך לאחר הניתוח, אופדיבו ניתנת לבד כל 4 שבועות, עד שנה לכל היותר-.
- 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 טיפול במזותליומה ממאירה של הפלאורה, אופדיבו תינתן כל שבועיים או כל 3 שבועות ואיפילימומאב (ipilimumab) תינתן כל 6 שבועות למשך שנתיים לכל היותר.
- עבור טיפול בסרטן 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.
- עבור סרטן בדרכי השתן או שלפוחית השתן שאינו נתיח או גרורתי, כאשר אופדיבו ניתנת בשילוב עם התרופות הכימותרפיות ציספלטין וגמציטאבין, אופדיבו ניתנת כל 3 שבועות למשך 6 מחזורי טיפול לכל היותר. הכימותרפיה תינתן באותו היום. לאחר מכן אופדיבו תינתן כטיפול יחיד כל שבועיים או כל 4 שבועות כתלות במנה שאתה מקבל.
- 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 טיפול בסרטן קיבה, בסרטן צומת קיבה-ושט ובאדנוקרצינומה 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:

תופעות לוואי של אופדיבו כטיפול יחיד כוללות:

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

- קצב לב לא סדיר
- דלקת בקשתית העין והגוף הריריי (iridocyclitis)
- דלקת בעצבים המתבטאת בחוסר תחושה, חולשה, עקצוץ או כאב המלווה בתחושת שריפה (נוירופתיה תחושתית והיקפית)
- התנקבות במעי
- פצעים או כיבים בחלל בפה (סטומטיטיס)
- בעיית עור חמורה שגורמת להופעת נקודות אדומות שלעיתים מגרדות, בדומה לפריחה של חצבת, שמתחילות בגפיים ולפעמים על הפנים ושאר הגוף (erythema multiforme)
- דלקת חמורה בעור שמתבטאת באדמומיות וקילוף באזורים נרחבים (דרמטיטיס אקספוליאטיבי)
- ספחת (פסוריאזיס)

- הצטברות נוזל בחלל האדר העוטף את הריאות (תפליט פלאורלי) אשר עלולה לגרום לקוצר נשימה, ולעיתים גם לכאב בחזה ולחום
- תסחיף ריאתי (קריש דם בריאות)
- דלקת ברקמות הריאה (פנאומוניטיס) המאופיינת בנשימה המלווה בשיעול וקשיי נשימה, קוצר נשימה ושיעול
- מחלה בין רקמתית של הריאה (מחלת ריאות אינטרסטיציאלית) שמאופיינת בקוצר נשימה ושיעול יבש וגורמת להצטלקות בריאות
- אי ספיקה נשימתית (קשיי נשימה קיצוניים)
- פגיעה כלייתית חריפה
- אלח דם
- ירידה כללית במצב הבריאותי
- חסימת מעיים (כולל חסימה חלקית)~~(חסימה במעי הדק)~~
- דלקת של המעי הגס (קוליטיס)
- בעיות בכבד
- יובש בעור
- בטן נפוחה כתוצאה מהצטברות נוזלים (מיימת)
- דימום מדליות בוושט
- יובש בפה
- מחלה דמוית שפעת
- שפעת
- צמרמורת
- מוות כתוצאה מתופעות לוואי
- 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)
- זיהום בדרכי נשימה
- שרירים כואבים, חולשת שרירים שלא כתוצאה מאימון (מיופתיה)
- דלקת שרירים (מיוזיטיס)
- תסמונת שגרן (Sjogren's syndrome), מחלה שבה מערכת החיסון תוקפת בעיקר בלוטות דמעות ורוק
- דלקת מפרקים כרונית שבדרך כלל מערבת מפרקי עמוד השדרה (ספונדילוארתרופתיה)
- אי ספיקת בלוטות יותרת הכליה (אדרנל) (ירידה ברמת ההורמונים המופרשים על ידי בלוטות יותרת הכליה, שממוקמות מעל הכליות)
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תופעות לוואי שאינן שכיחות (uncommon), תופעות שמופיעות ב-1-10 משתמשים מתוך 1,000:

- לחץ דם נמוך
- ~~אי ספיקת בלוטות יותרת הכליה (אדרנל) (ירידה ברמת ההורמונים המופרשים על ידי בלוטות יותרת הכליה, שממוקמות מעל הכליות)~~
- מוות פתאומי
- דימום במערכת העיכול
- הלם זיהומי
- פיסטולה בוושט

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<u>תופעות הלוואי במתן משולב של אופדיבו עם איפילימומאב (ipilimumab) כוללות:</u>

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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)
- התייבשות
- פגיעה כלייתית חריפה
- אירוע כבדי
- תפקודי כבד לא תקינים
- אי ספיקת כבד
- רעילות כבדית
- 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 (ספונדילואארתרופתיה)
- חוסר תחושה, כאב, עקצוץ או צריבה בכפות ידיים או רגליים (נוירופתיה היקפית)
- תגובות הקשורות בעירוי
- חסימת מעיים (של המעי הדק או המעי הגס)
- זיהום בדרכי השתן
- דימום במערכת עיכול
- דלקת בלבלב (פנקריאטיטיס)

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)
- דלקת שריר הלב (מיוקרדיטיס)

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תופעות הלוואי במתן משולב של אופדיבו עם כימותרפיה המכילה פלטינום ותרופה כימותרפית נוספת כוללות:

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

- דלקת ריאות
- תגובה אלרגית קשה (תגובה אנפילקטית)
- פגיעה כלייתית חריפה
- אלח דם
- תסחיף ריאתי
- מוות כתוצאה מתופעות לוואי

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

- אירוע מוחי
- דלקת ברקמות הריאה (פנאומוניטיס) המאופיינת בנשימה המלווה בשיעול וקשיי נשימה, קוצר נשימה ושיעול
- דלקת של המעי הגס (קוליטיס)
- תסמונת כלילית חריפה
- שיעול דמי
- דלקת שריר הלב (מיוקרדיטיס)
- דלקת שרירים (מיוזיטיס)

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