Bristol Myers Squibb™

דצמבר 2023

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

רופא/ה ,רוקח/ת יקר/ה,

חברת בריסטול-מאיירס סקוויב (ישראל) מתכבדת להודיע על הרחבת התוויות ועדכון עלונים לרופא ולצרכן של התכשיר שבנדון.

להלן התוויות התכשיר כפי שמאושרות ע"י משרד הבריאות (העדכונים בהתוויות מסומנים בצבע אדום באשר תוספת טקסט מסומנת בקו תחתון, מחיקת טקסט ~~בקו חוצה~~):

Unresectable or Metastatic Melanoma

OPDIVO, as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults~~.~~ 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 ~~melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection~~ 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).

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

Hepatocellular Carcinoma

OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of 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.

העלונים לרופא ולצרכן עודכנו בהתאם להרחבות ההתוויות שאושרו.
השינויים העיקריים בעלון לרופא ובעלון לצרכן משוקפים בעמודים הבאים.

תוספת טקסט מסומנת בקו תחתון, מחיקת טקסט ~~בקו חוצה~~.

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

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

שינויים עיקריים בעלון לרופא:

OPDIVO (nivolumab 10 mg/mL)

Concentrate for solution for infusion

FULL PRESCRIBING INFORMATION

[...]

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 adults and pediatric patients 12 years and older.

1.2 Adjuvant Treatment of Melanoma

OPDIVO is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection completely resected Stage IIB, IIC, III, or IV melanoma.

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 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 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 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.

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

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

1.11 Hepatocellular Carcinoma

OPDIVO, as a single agent or 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 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.

1.13 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

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

2 DOSAGE AND ADMINISTRATION

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2.1 Recommended Dosage

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

Table 1: Recommended Dosages for OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
~~Unresectable or metastatic melanoma~~ Advanced renal cell carcinoma Esophageal squamous cell carcinoma	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)	Until disease progression or unacceptable toxicity
Unresectable or metastatic 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 (60-minute intravenous infusion)	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)	

Table 1: Recommended Dosages for 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 (~~60~~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	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
Classical Hodgkin lymphoma		
Squamous cell carcinoma of the head and neck		
Locally advanced or metastatic urothelial carcinoma		

Table 1: Recommended Dosages for OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Hepatocellular 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	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. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with OPDIVO for the recommended dosage information, as appropriate.

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

Indication	Recommended OPDIVO Dosage	Duration of Therapy
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
Metastatic or recurrent non-small cell lung cancer	360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) and histology-based platinum doublet chemotherapy every 3 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
		2 cycles of histology-based platinum-doublet chemotherapy

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

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

[...]

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

[...]

Adjuvant Treatment of Melanoma

CHECKMATE-76K

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-76K, a randomized (2:1), double-blind trial in 788 patients with completely resected Stage IIB/C melanoma who received OPDIVO 480 mg by intravenous infusion over 30 minutes every 4 weeks (n=524) or placebo by intravenous infusion over 30 minutes every 4 weeks (n=264) for up to 1 year *[see Clinical Studies (14.2)]*. The median duration of exposure was 11 months in patients treated with OPDIVO and 11 months in patients treated with placebo.

Serious adverse reactions occurred in 18% of patients treated with OPDIVO. A fatal adverse reaction occurred in 1 (0.2%) patient (heart failure and acute kidney injury). Permanent discontinuation of OPDIVO due to an adverse reaction occurred in 17% of patients. Adverse reactions which resulted in permanent discontinuation of OPDIVO in >1% of patients included diarrhea (1.1%), arthralgia (1.7%), and rash (1.7%).

Dosage interruptions of OPDIVO due to an adverse reaction occurred in 25% of patients. Adverse reactions which required dosage interruption in >1% of patients included COVID-19 infection, infusion related reaction, diarrhea, arthralgia, and increased ALT.

The most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, rash, diarrhea, and pruritus.

Tables 11 and 12 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-76K.

Table 11: Adverse Reactions Occurring in ≥10% of Patients Treated with OPDIVO - CHECKMATE-76K

Adverse Reaction	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	36	0.4	34	0.4
Musculoskeletal and connective tissue				
Musculoskeletal pain[b]	30	0.4	26	0.4
Skin and Subcutaneous Tissue				
Rash[c]	28	1.1	15	0.4
Pruritus	20	0.2	11	0
Gastrointestinal				
Diarrhea[d]	23	1.3	16	0
Nausea	14	0	11	0
Endocrine				
Hypothyroidism[e]	14	0	2.3	0
Nervous system				
Headache[f]	12	0.2	14	0.8

Toxicity was graded per NCI CTCAE v5.

[a] Includes asthenia.

[b] Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculosketal stiffness, myalgia, neck pain, non-cardiac chest pain, spinal pain, pain in extremity.

[c] Includes dermatitis, dermatitis acneiform, dyshidrotic eczema, eczema, eczema asteatotic, eyelid rash, genital rash, pemphigoid, penile rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, toxic skin eruption.

[d] Includes autoimmune colitis, colitis, diarrhea, enteritis, enterocolitis

[e] Includes autoimmune hypothyroidism, blood thyroid stimulating hormone increased.

[f] Includes cluster headache, migraine.

Table 12: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-76K

Laboratory Abnormality	OPDIVO (n=524)		Placebo (n=264)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				

Table 12: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-76K

Anemia	19	0	14	0
Lymphopenia	17	1.1	17	1.7
Neutropenia	10	0	10	0.4
Chemistry				
AST increased	25	2.2	16	0.4
Lipase increased	22	2.9	21	2.3
ALT increased	20	2.1	15	0.4
Amylase increased	17	0.4	9	0
Creatinine increased	15	0.4	13	0
Sodium decreased	13	0.6	11	0.4
Potassium increased	13	1.0	15	1.1

[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 group (range: 262 to 513 patients) and placebo group (range: 138 to 261 patients).

CHECKMATE-238

[...]

~~6.2 Immunogenicity~~

~~As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to OPDIVO with the incidences of antibodies to other products may be misleading.~~

~~Of the 2085 patients who were treated with OPDIVO as a single agent at dose of 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 11% tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 0.7% had neutralizing antibodies against nivolumab. There was no evidence of altered pharmacokinetic profile or increased incidence of infusion-related reactions with anti-nivolumab antibody development.~~

~~Of the patients with melanoma, advanced renal cell carcinoma, metastatic colorectal cancer, metastatic or recurrent non-small cell lung cancer, and malignant pleural mesothelioma who were treated with OPDIVO and ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26% (132/516) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks, 25.7% (69/269) with OPDIVO 3 mg/kg every 2 weeks and ipilimumab 1 mg every 6 weeks in malignant pleural mesothelioma patients, and 38% (149/394) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralizing antibodies against nivolumab was 0.8% (4/516) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks, 0.7% (2/269) with OPDIVO 3 mg/kg every 2 weeks and~~

~~ipilimumab 1 mg every 6 weeks in malignant pleural mesothelioma patients, and 4.6% (18/394) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks.~~

~~Of the patients with hepatocellular carcinoma who were treated with OPDIVO and ipilimumab every 3 weeks for 4 doses followed by OPDIVO every 2 weeks and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 45% (20/44) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg and 56% (27/48) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg; the corresponding incidence of neutralizing antibodies against nivolumab was 14% (6/44) and 23% (11/48), respectively.~~

~~Of the patients with NSCLC who were treated with OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy, and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 34% (104/308); the incidence of neutralizing antibodies against nivolumab was 2.6% (8/308).~~

~~There was no evidence of increased incidence of infusion related reactions with anti-nivolumab antibody development.~~

[...]

8.4 Pediatric Use

~~The safety and effectiveness of OPDIVO as a single agent and in combination with ipilimumab have been established in pediatric patients age 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for this indication is supported by evidence from adequate and well-controlled studies of OPDIVO in adults with MSI-H or dMMR mCRC with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady-state exposure of nivolumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MSI-H or dMMR mCRC is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.10)].*~~

~~The safety and effectiveness of OPDIVO have not been established (1) in pediatric patients <12 years old with MSI-H or dMMR mCRC or (2) in pediatric patients less than 18 years old for the other approved indications *[see Indications and Usage (1)].*~~

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 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)]*.

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.

[...]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

[...]

12.2 Pharmacodynamics

There are no clinically significant exposure-response relationships for efficacy or safety for nivolumab monotherapy, and in combination with ipilimumab and/or chemotherapy, over the approved dosing regimens, regardless of cancer type.

12.3 Pharmacokinetics

[...]

Specific Populations

The following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), sex, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment (eGFR $\geq$ 15 mL/min/1.73 m^2), and mild (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). Nivolumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST).

Pediatric Patients

The exposures of nivolumab in pediatric patients 12 years of age or older are comparable to those in adults at the recommended dosage. *[see Dosage and Administration (2.2).]*

Drug Interaction Studies

When OPDIVO 3 mg/kg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 3 weeks, the CL of nivolumab and ipilimumab were unchanged compared to nivolumab or ipilimumab administered alone.

When OPDIVO 1 mg/kg every 3 weeks was administered in combination with ipilimumab 3 mg/kg every 3 weeks, the CL of nivolumab was increased by 29% compared to OPDIVO administered alone and the CL of ipilimumab was unchanged compared to ipilimumab administered alone.

When OPDIVO 3 mg/kg every 2 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks, the CL of nivolumab was unchanged compared to OPDIVO administered alone and the CL of ipilimumab was increased by 30% compared to ipilimumab administered alone.

When OPDIVO 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy, the CL of nivolumab was unchanged compared to OPDIVO administered alone and the CL of ipilimumab increased by 22% compared to ipilimumab administered alone.

~~When administered in combination, the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies.~~

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of OPDIVO or of other nivolumab products.

Anti-drug antibody and neutralizing antibody responses were monitored throughout the treatment period where the benefit to risk ratio was assessed. Incidence of anti-drug antibodies and neutralizing antibodies are presented in Table 47.

Table 47: OPDIVO Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) Incidence

Treatment Regimen[a]	Indication(s)	ADA	NAb[b]
OPDIVO as a single agent	Multiple[c]	11% (229/2,085)	7% (15/229)
OPDIVO with ipilimumab for 4 doses followed by OPDIVO as a single agent	Melanoma	38% (149/394)	12% (18/149)
	HCC	56% (27/48)	41% (11/27)
	RCC and CRC	26% (132/516)	3% (4/132)
OPDIVO with ipilimumab	Malignant Pleural Mesothelioma	26% (69/269)	2.9% (2/69)
OPDIVO with ipilimumab and 2 cycles of platinum-doublet chemotherapy	NSCLC	34% (104/308)	8% (8/104)

[a] Details of each treatment regimen are described in Section 14 *[see Clinical Studies (14)]*.
[b] NAb incidence is reported among the subset of patients positive for ADA.
[c] Includes unresectable or metastatic melanoma, metastatic NSCLC, advanced RCC, cHL, recurrent or metastatic SCCHN, and UC indications.
ADA= treatment-emergent anti-nivolumab antibodies, NAb= neutralizing antibodies, HCC = hepatocellular carcinoma, RCC = renal cell carcinoma, CRC = colorectal cancer, NSCLC = non-small cell lung cancer.

Effects of Anti-Drug Antibodies

Presence of treatment-emergent anti-nivolumab antibodies increased nivolumab clearance by up to 20% after administration of nivolumab as monotherapy or in combination with ipilimumab. These anti-drug antibody-associated pharmacokinetic changes were not considered to be clinically significant. There was no identified clinically significant effect of anti-drug antibodies on incidence of infusion-related reactions. The effects of anti-drug antibodies on effectiveness have not been fully characterized.

14 CLINICAL STUDIES

[...]

14.2 Adjuvant Treatment of Melanoma

CHECKMATE-76K

CHECKMATE-76K (NCT04099251) was a randomized, double-blind trial in 790 patients with completely resected Stage IIB/C melanoma. Patients were randomized (2:1) to receive OPDIVO 480 mg or placebo by intravenous infusion every 4 weeks for up to 1 year or until disease recurrence or unacceptable toxicity. Enrollment required complete resection of the primary melanoma with negative margins and a negative sentinel lymph node within 12 weeks prior to randomization, and ECOG performance status of 0 or 1. The trial excluded patients with ocular/uveal or mucosal melanoma, autoimmune disease, any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery. Randomization was stratified by AJCC 8th staging system edition (T3b vs. T4a vs. T4b). The major efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurred first and as assessed by the investigator. Tumor assessments were conducted every 26 weeks during years 1-3 and every 52 weeks thereafter until year 5.

The trial population characteristics were: median age 62 years (range: 19 to 92), 61% were male, 98% were White, 0.4% Black or African American, 0.1% Asian, and 1.1% race unknown, 2.2% Hispanic or Latino, 58% Not Hispanic or Latino, 40% ethnicity unknown, and 94% had an ECOG performance status of 0. Sixty one percent had stage IIB and 39% had stage IIC melanoma.

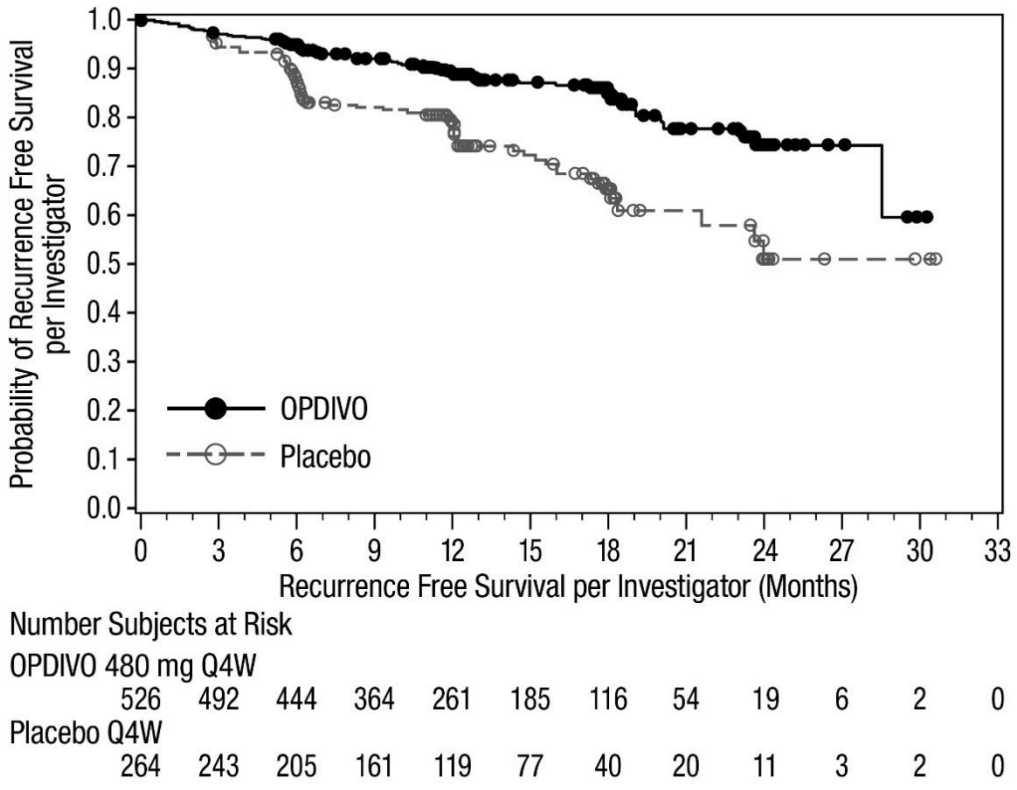
CHECKMATE-76K demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the placebo arm. Efficacy results are shown in Table 50 and Figure 4.

Table 50: Efficacy Results - CHECKMATE-76K

	OPDIVO N=526	Placebo N=264
Recurrence-free Survival		
Number of events, n (%)	66 (13%)	69 (26%)
Median (months) [b] (95% CI)	NR[a] (28.5, NR)	NR[a] (21.6, NR)
Hazard ratio[c] (95% CI) p-value[d]	0.42 (0.30, 0.59) p<0.0001	

[a] Not reached.
[b] Based on Kaplan-Meier estimates.
[c] Hazard Ratio is OPDIVO over placebo based on a stratified Cox proportional hazard model.
[d] Based on a 2-sided stratified log-rank test. Boundary for statistical significance: p-value <0.033.

Figure 4: Recurrence-free Survival -CHECKMATE-76K



CHECKMATE-238

[...]

שינויים עיקריים בעלון לצרכן:

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

אופדיבו
תמיסה מרוכזת להכנת תמיסה לעירוי תוך ורידי

...

מדריך כיס למטופל וכרטיס מידע בטיחותי למטופל
בנוסף לעלון, לתכשיר אופדיבו קיימים מדריך כיס למטופל וכרטיס מידע בטיחותי למטופל.
מדריך הכיס והכרטיס מכילים מידע בטיחותי חשוב, שעליך לדעת, לפני התחלת הטיפול ובמהלך הטיפול באופדיבו ולפעול על פיהם. יש לעיין במדריך הכיס למטופל, בכרטיס המידע הבטיחותי למטופל ובעלון לצרכן בטרם תחילת השימוש בתכשיר. יש לשמור את הכרטיס ומדריך הכיס לעיון נוסף במידת הצורך.

1. למה מיועדת התרופה?

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) ב~~מטופלים~~מבוגרים וילדים מגיל 12 ומעלה עם מלנומה בשלב IIB, IIC, III או IV ~~המערבת בלוטות לימפה או גרורתית,~~ לאחר ~~כריתה~~ הסרה מלאה.
- **סרטן ריאות מסוג תאים שאינם קטנים (non-small cell lung cancer)**
  - 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
  - אופדיבו, בשילוב עם איפילימומאב (ipilimumab) ושני מחזורי טיפול של משלב כימותרפי המכיל פלטינום (platinum-doublet chemotherapy), מיועדת כטיפול קו ראשון ב~~מטופלים~~מבוגרים עם סרטן ריאות גרורתי או חוזר מסוג תאים שאינם קטנים, וללא שינויים בגנים EGFR או ALK בגידול.
  - אופדיבו מיועדת לטיפול ב~~מטופלים~~מבוגרים 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 ב~~מטופלים~~מבוגרים עם סרטן תאי כליה מתקדם, בדרגת סיכון בינונית או גבוהה.
  - אופדיבו בשילוב עם קבוזנטיניב (cabozantinib) מיועדת לטיפול קו ראשון ב~~מטופלים~~מבוגרים עם סרטן תאי כליה מתקדם.
  - אופדיבו כטיפול יחיד מיועדת לטיפול ב~~מטופלים~~מבוגרים 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 ב~~מטופלים~~ מבוגרים 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) ב~~מטופלים~~ מבוגרים עם סרטן בדרכי השתן או שלפוחית השתן בסיכון גבוה להישנות המחלה לאחר הסרה רדיקלית של הגידול.
  - אופדיבו מיועדת לטיפול ב~~מטופלים~~ מבוגרים 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 כטיפול יחיד או בשילוב עם איפילימומאב (ipilimumab) מיועדת לטיפול ב~~מטופלים~~ מבוגרים וילדים מגיל 12 ומעלה עם סרטן גרורתי של המעי הגס או החלחולת המבטא dMMR (mismatch repair deficient) או MSI-H (microsatellite instability-high), שמחלתם התקדמה לאחר טיפול בפלואורופירימידין, אוקסליפלטין ואירינוטקאן.

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

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

קבוצה תרפויטית: אנטי-ניאופלסטי.

2. לפני השימוש בתרופה:

...

ילדים ומתבגרים:
לא קיים מידע לגבי יעילות ובטיחות אופדיבו:
- בילדים מתחת לגיל 12 עם מלנומה או סרטן גרורתי של המעי הגס או החלחולת המבטא dMMR או MSI-H, או
- בילדים ~~מתחת לגיל 18 לטיפול~~ ביתר סוגי הסרטן

...