Bristol Myers Squibb™

דצמבר 2025

YERVOY 5mg/ml
Concentrate for solution for infusion
יירבוי 5 מ"ג/מ"ל
תמיסה מרוכזת להכנת תמיסה לעירוי

רופא/ה ,רוקח/ת יקר/ה,

חברת בריסטול-מאיירס סקוויב (ישראל) מתכבדת להודיע על אישור שתי התוויות חדשות לתכשיר יירבוי ועדכון עלונים לרופא ולצרכן של התכשיר בהתאם.

להלן התוויות התכשיר כפי שמאושרות ע"י משרד הבריאות (ההתוויות החדשנות שנוספו מסומנות באדום):

Unresectable or Metastatic Melanoma

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

Advanced Renal Cell Carcinoma

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

Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer

- YERVOY, in combination with nivolumab, 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).
- YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age 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.

Metastatic Non-Small Cell Lung Cancer

YERVOY, in combination with nivolumab 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.

Hepatocellular Carcinoma

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

Malignant Pleural Mesothelioma
YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Esophageal cancer
Yervoy in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥1%

המרכיב הפעיל: Ipilimumab 5mg/ml

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:

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1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

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

1.2 Advanced Renal Cell Carcinoma

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

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

- YERVOY, in combination with nivolumab, 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).
- YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age 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.

1.4 Hepatocellular Carcinoma

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

1.5 Metastatic Non-Small Cell Lung Cancer

YERVOY, in combination with nivolumab 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.

1.6 Malignant Pleural Mesothelioma

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

1.7 Esophageal Cancer

YERVOY, in combination with nivolumab, 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%.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with ESCC for first-line treatment with YERVOY in combination with nivolumab based on PD-L1 expression *[see Clinical Studies (14.7)]*.

2.2 Recommended Dosage

The recommended dosage of YERVOY as a single agent is presented in Table 1.

Table 1: Recommended Dosages for YERVOY as a Single Agent

Indication	Recommended YERVOY Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 3 weeks (90-minute intravenous infusion)	Maximum of 4 doses

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

Refer to the respective Prescribing Information for each therapeutic agent administered in combination with YERVOY for recommended dosage information, as appropriate.

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

Indication	Recommended YERVOY Dosage	Duration of Therapy
Unresectable or metastatic melanoma	3 mg/kg every 3 weeks (90-minute intravenous infusion) with nivolumab 1 mg/kg (30-minute intravenous infusion on the same day)	In combination with nivolumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier. After completing 4 doses of combination therapy, administer nivolumab as a single agent until disease progression or unacceptable toxicity.†

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

Indication	Recommended YERVOY Dosage	Duration of Therapy
Advanced renal cell carcinoma	1 mg/kg every 3 weeks with nivolumab 3 mg/kg (30-minute intravenous infusion on the same day)	In combination with nivolumab for 4 doses. After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity†
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: 1 mg/kg every 3 weeks with nivolumab 240 mg (30-minute intravenous infusion on the same day) Pediatric patients age 12 years and older and weighing less than 40 kg: 1 mg/kg every 3 weeks with nivolumab 3 mg/kg (30-minute intravenous infusion on the same day)	In combination with nivolumab for a maximum of 4 doses. After completing 4 doses of combination therapy, administer nivolumab as single agent until disease progression, unacceptable toxicity, or up to 2 years. †
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following prior treatment for metastatic disease	1 mg/kg every 3 weeks with nivolumab 3 mg/kg (30-minute intravenous infusion on the same day)	In combination with nivolumab for a maximum of 4 doses. After completing a maximum of 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity†
Hepatocellular carcinoma	3 mg/kg every 3 weeks with nivolumab 1 mg/kg (30-minute intravenous infusion on the same day)	In combination with nivolumab for a maximum of 4 doses. After completing a maximum of 4 doses of combination therapy, administer nivolumab as single agent until disease progression or unacceptable toxicity†
Metastatic or recurrent non-small cell lung cancer	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks (30-minute intravenous infusion) and histology-based platinum-doublet	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression†

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

Indication	Recommended YERVOY Dosage	Duration of Therapy
	chemotherapy every 3 weeks	2 cycles of histology-based platinum-doublet chemotherapy
Malignant pleural mesothelioma	1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks (30-minute intravenous infusion) or 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks (30-minute intravenous infusion)	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression†
Esophageal squamous cell carcinoma	1 mg/kg every 6 weeks (30-minute intravenous infusion) with nivolumab 3 mg/kg every 2 weeks or 360 mg every 3 weeks (30-minute intravenous infusion)	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years

* Refer to the Prescribing Information for the agents administered in combination with YERVOY for recommended dosing information, as appropriate.

† Refer to the Prescribing Information for nivolumab for dosage information after completing use in combination with YERVOY.

2.3 Recommended Dosage Modifications for Adverse Reactions

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2.4 Preparation and Administration

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3 DOSAGE FORMS AND STRENGTHS

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4 CONTRAINDICATIONS

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5 WARNINGS AND PRECAUTIONS

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6 ADVERSE REACTIONS

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6.1 Clinical Trials Experience

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MSI-H or dMMR Metastatic Colorectal Cancer: In Combination with Nivolumab

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

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-8HW, a randomized, open-label, three arm trial in immunotherapy naïve patients with MSI-H or dMMR mCRC *[see Clinical Studies (14.4)]*. Patients received one of the following:

- YERVOY 1 mg/kg every 3 weeks and nivolumab 240 mg every 3 weeks for a maximum of 4 doses, then nivolumab 480 mg every 4 weeks
- Nivolumab 240 mg every 2 weeks for 6 doses, then nivolumab 480 mg every 4 weeks.
- Investigator's choice chemotherapy: mFOLFOX or FOLFIRI *[see Clinical Studies (14.3)]*.

In the YERVOY and nivolumab arm, the median duration of exposure to YERVOY was 2.1 months (range 1 day to 3.7 months); patients received a median of 4 doses (range 1-4). The median duration of treatment in the YERVOY and nivolumab arm was 20.5 months (range: 1 day to 35.9 months); 70% were exposed to treatment for >6 months, and 63% were exposed for >1 year. The median duration of treatment was 16.4 months (range: 1 day to 36 months) in the nivolumab-only arm; 64% were exposed to treatment for >6 months, and 54% were exposed for >1 year.

Serious adverse reactions occurred in 46% of patients receiving YERVOY in combination with nivolumab, and 39% of patients receiving nivolumab alone. The most frequent serious adverse reactions reported in ≥1% of patients who received YERVOY with nivolumab 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 YERVOY in combination with nivolumab; these included myocarditis, and pneumonitis (1 each).

YERVOY and/or nivolumab 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%). Nivolumab was permanently discontinued in 13% of patients receiving single agent

nivolumab. Adverse reactions leading to the delay of YERVOY and/or nivolumab occurred in 48% of patients receiving the combination; single agent nivolumab was delayed in 37% of patients due to adverse reactions.

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

Tables 9 and 10 summarize the adverse reactions and selected laboratory abnormalities, for YERVOY in combination with nivolumab and nivolumab arms respectively, in CHECKMATE-8HW.

Table 9: Adverse Reactions in ≥10% in Patient and a Difference Between Arms of >5% for All Grades in - CHECKMATE-8HW

Adverse Reaction	YERVOY and Nivolumab (n=352)		Nivolumab (n=351)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
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 10: 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]	YERVOY and Nivolumab (n=352)		Nivolumab (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

Table 10: 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]	YERVOY and Nivolumab (n=352)		Nivolumab (n=351)	
	All Grades (%)	Grades 3-or 4 (%)	All Grades (%)	Grades 3 or -4 (%)
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: YERVOY and nivolumab 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 YERVOY with nivolumab was evaluated in 119 patients with previously treated MSI-H or dMMR mCRC in a single-arm cohort of CHECKMATE-142 *[see Clinical Studies (14.3)]*. All patients had received prior fluorouracil-based chemotherapy for metastatic disease; 69% had received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan and 29% had received an anti-EGFR antibody. Patients received YERVOY 1 mg/kg and nivolumab 3 mg/kg on Day 1 of each 21-day cycle for 4 doses, then nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The median duration of exposure for YERVOY was 2.1 months.

Serious adverse reactions occurred in 47% of patients receiving YERVOY and nivolumab. 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 (≥20%) in the YERVOY and nivolumab cohort were fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting. Table ~~9~~ 11 summarizes adverse reactions in CHECKMATE-142.

Table ~~9~~11: Adverse Reactions Occurring in ≥10% of Patients (CHECKMATE-142)

Adverse Reaction	YERVOY and Nivolumab MSI-H/dMMR Cohort (n=119)	
	All Grades (%)	Grades 3-4 (%)
General and Administration Site Conditions		
Fatigue[a]	49	6
Pyrexia	36	0
Edema[b]	7	0
Gastrointestinal		

Table ~~9~~11: Adverse Reactions Occurring in ≥10% of Patients (CHECKMATE-142)

Adverse Reaction	YERVOY and Nivolumab MSI-H/dMMR Cohort (n=119)	
	All Grades (%)	Grades 3-4 (%)
Diarrhea	45	3.4
Abdominal pain[c]	30	5
Nausea	26	0.8
Vomiting	20	1.7
Constipation	15	0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[d]	36	3.4
Arthralgia	14	0.8
Skin and Subcutaneous Tissue		
Pruritus	28	1.7
Rash[e]	25	4.2
Dry Skin	11	0
Infections and Infestations		
Upper respiratory tract infection[f]	9	0
Metabolism and Nutrition		
Decreased appetite	20	1.7
Respiratory, Thoracic, and Mediastinal		
Cough	19	0.8
Dyspnea	13	1.7
Nervous System		
Headache	17	1.7
Dizziness	11	0
Endocrine		
Hyperglycemia	6	1
Hypothyroidism	14	0.8
Hyperthyroidism	12	0
Investigations		
Weight decreased	10	0
Psychiatric		
Insomnia	13	0.8

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.

Other clinically important adverse reactions reported in <10% of patients receiving YERVOY in CHECKMATE-142 were encephalitis (0.8%), necrotizing myositis (0.8%), and uveitis (0.8%).

Table ~~10~~ 12 summarizes laboratory abnormalities in CHECKMATE-142.

Table ~~10~~12: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients (CHECKMATE-142)

Laboratory Abnormality	YERVOY and Nivolumab MSI-H/dMMR Cohort (n=119)	
	All Grades (%)	Grades 3-4 (%)
Hematology		
Anemia	42	9
Thrombocytopenia	26	0.9
Lymphopenia	25	6
Neutropenia	18	0
Chemistry		
Increased AST	40	12
Increased lipase	39	12
Increased amylase	36	3.4
Increased ALT	33	12
Increased alkaline phosphatase	28	5
Hyponatremia	26	5
Increased creatinine	25	3.6
Hyperkalemia	23	0.9
Increased bilirubin	21	5
Hypomagnesemia	18	0
Hypocalcemia	16	0
Hypokalemia	15	1.8

[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 87 to 114 for nivolumab with YERVOY and from 62 to 71 for nivolumab.

Hepatocellular Carcinoma: In Combination with Nivolumab

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-9DW, a randomized, open-label trial in adult patients with unresectable or metastatic HCC *[see Clinical Studies (14.5)]*. Patients received YERVOY in combination with nivolumab (n=332) or investigator's choice of lenvatinib (n=275) or sorafenib (n=50) at the following dosage:

- YERVOY 3 mg/kg administered intravenously over 30 minutes in combination with nivolumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks, for a maximum of 4 doses, followed by single agent nivolumab 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 YERVOY and nivolumab arm, the median duration of exposure to nivolumab 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 YERVOY in combination with nivolumab. The most frequent non-liver-related serious adverse reactions reported in ≥2% were diarrhea/colitis (4.5%), gastrointestinal hemorrhage (3%), and rash (2.4%).

Liver-related serious adverse reactions occurred in 17% of patients treated with YERVOY in combination with nivolumab, 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 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 YERVOY in combination with nivolumab; 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 discontinuation due to an adverse reaction occurred in 27% of patients treated with YERVOY in combination with nivolumab. Adverse reactions leading to permanent discontinuation in >1% of patients included immune-mediated hepatitis (1.8%), diarrhea/colitis (1.8%), and hepatic failure (1.2%).

Dosage interruptions due to an adverse reaction occurred in 62% of patients treated with YERVOY in combination with nivolumab. 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 13 and 14 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9DW.

Table 13: Adverse Reactions Occurring in ≥10% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	YERVOY and Nivolumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				

Table 13: Adverse Reactions Occurring in ≥10% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Adverse Reaction	YERVOY and Nivolumab (n=332)		Lenvatinib or Sorafenib (n=325)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
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	25	6	39	3.4
Abdominal pain[a]	14	1.2	27	2.5
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 YERVOY with nivolumab were hyperglycemia (8%), adrenal insufficiency (4.2%), pneumonitis (2.7%), and pancreatitis (2.4%).

Table 1: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of YERVOY in combination with Nivolumab-Treated Patients - CHECKMATE-9DW

Laboratory Abnormality	YERVOY and Nivolumab (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
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: YERVOY and nivolumab group (range: 168 to 331 patients) and lenvatinib or sorafenib group (range: 145 to 315 patients).

Previously Treated Hepatocellular Carcinoma

The safety of YERVOY 3 mg/kg in combination with nivolumab 1 mg/kg was evaluated in a subgroup of 49 patients with HCC and Child-Pugh Class A cirrhosis who progressed on or were intolerant to sorafenib enrolled in Cohort 4 of CHECKMATE-040. YERVOY and nivolumab were administered every 3 weeks for four doses, followed by single-agent nivolumab 240 mg every 2 weeks until disease progression or unacceptable toxicity.

During the YERVOY and nivolumab combination period, 33 of 49 (67%) patients received all four planned doses of YERVOY and nivolumab. During the entire treatment period, the median duration of exposure to YERVOY was 2.1 months (range: 0 to 4.5 months) and to nivolumab was

5.1 months (range: 0 to 35+ 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.

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.

Table ~~11~~ 15 summarizes the adverse reactions and Table ~~12~~ 16 summarizes the laboratory abnormalities of YERVOY in combination with nivolumab in CHECKMATE-040.

Table ~~11~~15: Adverse Reactions Occurring in ≥10% of Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	YERVOY and Nivolumab (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

Table ~~11~~15: Adverse Reactions Occurring in ≥10% of Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	YERVOY and Nivolumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
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 receiving YERVOY with nivolumab were hyperglycemia (8%), colitis (4%), and increased blood creatine phosphokinase (2%).

Table ~~12~~16: Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Laboratory Abnormality	YERVOY and Nivolumab (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 YERVOY with nivolumab, 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

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 YERVOY have been established in pediatric patients aged 12 years and older for the following indications: in combination with nivolumab for unresectable or metastatic melanoma, ~~and,~~ in combination with nivolumab for the first-line treatment of MSI-H or dMMR unresectable and metastatic CRC, and in combination with nivolumab for MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of YERVOY 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. Ipilimumab exposures in pediatric patients 12 years and older are 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 (14.3)]*.

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

The safety and effectiveness of YERVOY have not been established in pediatric patients for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, metastatic non-small cell lung cancer, malignant pleural mesothelioma and esophageal cancer.

In a dose-finding trial (NCT01445379), 33 patients aged 2 to 21 years (median 13 years) with relapsed or refractory solid tumors were evaluated including unresectable stage IIIc or stage IV melanoma (12), progressive or refractory sarcomas (17), renal or bladder carcinoma (3), and neuroblastoma (1). No responses in the patients with non-melanoma solid tumors and no new safety signals were observed in pediatric patients in this study.

8.5 Geriatric Use

Single Agent

Of the 511 patients treated with YERVOY in Study MDX010-20 (unresectable or metastatic melanoma), 28% were 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients.

In Combination with Nivolumab

Of the 314 patients randomized to YERVOY administered with nivolumab in CHECKMATE-067, 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.

Of the 303 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-743 (malignant pleural mesothelioma), 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 rate due to adverse reactions in patients aged 75 years or older (68% and 35%, respectively) relative to all patients who received YERVOY with nivolumab (54% and 28%, respectively). For patients aged 75 years or older who received chemotherapy, the rate of serious adverse reactions was 34% and discontinuation 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 YERVOY in combination with nivolumab. 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 Yervoy in combination with nivolumab.

Of the 550 patients randomized to YERVOY 1 mg/kg with nivolumab in CHECKMATE-214 (renal cell carcinoma), 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was observed between these patients and younger patients. In geriatric patients with intermediate or poor risk, no overall difference in effectiveness was observed.

Of the 354 patients with dMMR or MSI-H metastatic CRC (mCRC) who were randomized to YERVOY in combination with nivolumab, 44% were 65 years or older and 14% were 75 years or older. Of the 353 patients randomized to nivolumab, 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 YERVOY in combination with nivolumab compared to those younger than 65 receiving the combination (42%). There was a higher incidence of adverse reactions leading to discontinuation in patients aged 65 years or older receiving YERVOY in combination with nivolumab (23%) compared to those younger than 65 receiving the combination (15%). No overall differences in effectiveness were reported between elderly patients and younger patients receiving YERVOY in combination with nivolumab *[see Clinical Studies (14.3)]*.

Of the 335 patients with unresectable hepatocellular carcinoma who were randomized to YERVOY in combination with nivolumab, 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.

Of the 49 patients who received YERVOY 3 mg/kg with nivolumab in Cohort 4 of CHECKMATE-040 (previously treated hepatocellular carcinoma), 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of YERVOY in combination with nivolumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients.

Of the 325 patients who received YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-648 (ESCC), 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 YERVOY with nivolumab (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.

CHECKMATE-142 (metastatic colorectal cancer) did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

In Combination with Nivolumab and Platinum-Doublet Chemotherapy

Of the 361 patients randomized to YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 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 YERVOY with nivolumab 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 YERVOY in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, 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.

11 DESCRIPTION

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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12.3 Pharmacokinetics

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12.6 Immunogenicity

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

Eleven (1.1%) of 1024 evaluable patients with unresectable or metastatic melanoma tested positive for treatment-emergent binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay had substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Seven (4.9%) of 144 patients receiving ipilimumab developed anti-ipilimumab antibodies and 7 (4.5%) of 156 patients receiving placebo for the adjuvant treatment of melanoma tested positive for anti-ipilimumab antibodies using an ECL assay with improved drug tolerance. No patients tested positive for neutralizing antibodies. No infusion-related reactions occurred in patients who tested positive for anti-ipilimumab antibodies.

Of the 499 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-214 and CHECKMATE-142, 27 (5.4%) were positive for anti-ipilimumab antibodies; there were no patients with neutralizing antibodies against ipilimumab. There was no evidence of increased incidence of infusion reactions to YERVOY in patients with anti-ipilimumab antibodies.

Of 305 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-9LA, 8% were positive for anti-ipilimumab antibodies and 1.6% were positive for anti-ipilimumab neutralizing antibodies. There was no evidence of increased incidence of infusion reactions to YERVOY in patients with anti-ipilimumab antibodies. Of 308 patients evaluable for anti-nivolumab antibodies in CHECKMATE-9LA, 34% were positive for anti-nivolumab antibodies and 2.6% had neutralizing antibodies against nivolumab.

Of 271 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-743, 13.7% were positive for anti-ipilimumab antibodies and 0.4% were positive for anti-ipilimumab neutralizing antibodies. Of 269 patients evaluable for anti-nivolumab antibodies in CHECKMATE-743, 25.7% were positive for anti-nivolumab antibodies and 0.7% had neutralizing antibodies against nivolumab.

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 23.

Table 23: YERVOY Anti-Drug Antibody (ADA) and Neutralizing Antibody (NAb) Incidence

Treatment Regimen[a]	Indication(s)	ADA	NAb[b]
YERVOY as a single agent	Melanoma	1.1% (11/1024)	0 (0/11)
	Adjuvant Melanoma	4.9 (7/144)	0 (0/7)
YERVOY with nivolumab for 4 doses followed by nivolumab as a single agent	Melanoma	8.4% (33/391)	3% (1/33)
	HCC	5.3% (13/244)	0 (0/13)
	RCC and CRC	5.4% (27/499)	0% (0/27)
YERVOY with nivolumab	Malignant Pleural Mesothelioma	13.7% (37/271)	2.7% (1/37)
	NSCLC	8.5% (41/483)	0 (0/41)
YERVOY with nivolumab and 2 cycles of platinum-doublet chemotherapy	NSCLC	7.5% (23/305)	21.7% (5/23)

[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.
ADA = treatment-emergent anti-ipilimumab 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-ipilimumab antibodies did not affect ipilimumab clearance after administration of ipilimumab as monotherapy or in combination with nivolumab. 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. In hepatocellular carcinoma, there was no identified clinically significant effect of anti-drug antibodies on efficacy for ipilimumab in combination with nivolumab. For other indications, the effects of anti-drug antibodies on effectiveness have not been fully characterized.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

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14.2 Advanced Renal Cell Carcinoma

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

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

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:

- YERVOY 1 mg/kg every 3 weeks and nivolumab 240 mg every 3 weeks for a maximum of 4 doses, then nivolumab 480 mg every 4 weeks
- Nivolumab 240 mg every 2 weeks for 6 doses, then nivolumab 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 YERVOY plus nivolumab combination upon progression assessed by BICR.

Study treatment was administered until disease progression, unacceptable toxicity, or for up to 2 years for patients who received YERVOY plus nivolumab or nivolumab monotherapy. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab as a single agent. Nivolumab with or without YERVOY 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 YERVOY in combination with nivolumab versus chemotherapy in the first-line (1L) setting and the comparison of patients with centrally confirmed MSI-H/dMMR mCRC randomized to YERVOY in combination with nivolumab vs nivolumab in all lines setting.

The major efficacy outcome measure was BICR-assessed PFS per RECIST 1.1. Additional efficacy 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 (48%); number of prior lines of therapy was 0 (56%) and 1 (24%), and ≥2 (19%); 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 all randomized patients.

First Line YERVOY in combination with nivolumab

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

In the 1L setting, 200 of 202 patients assigned to receive YERVOY in combination with nivolumab and 88 of 101 patients assigned to received 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 YERVOY and nivolumab arm compared with chemotherapy in the 1L setting are presented in Table 27 and Figure 4. 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 27: Efficacy Results - CHECKMATE-8HW

	YERVOY and Nivolumab (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	

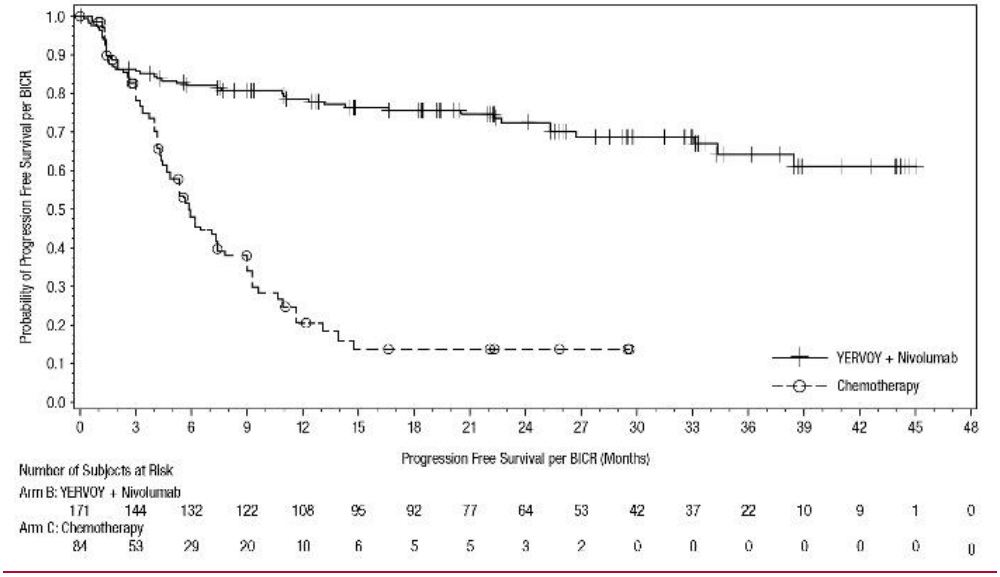
NR: Not Reached; NE: Not Estimable.
Minimum follow-up was 6.1 months at data cutoff date 12Oct2023.

[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 4: Progression-free Survival, (First line YERVOY + nivolumab vs Chemotherapy)- CHECKMATE-8HW



All Lines YERVOY in combination with nivolumab

Among 707 patients across all treatment lines who were randomly assigned to YERVOY in combination with nivolumab (354) and to nivolumab (353) single agent, 296 and 286 patients had centrally confirmed MSI-H/dMMR status in the YERVOY in combination with nivolumab arm and in the nivolumab 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 YERVOY in combination with nivolumab compared with nivolumab

single agent across all treatment lines setting are presented in Table 28 and Figure 5. At the time of PFS analysis OS between arms were not available due to statistical testing strategy.

Table 28: Efficacy Results All Lines - CHECKMATE-8HW

	YERVOY and Nivolumab (n=296)	Nivolumab (n=286)
Progression-free Survival		
Disease progression or death n (%)	101 (34)	136 (48)
Median (months)[b] (95% CI)	NR (53.82, 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, n (%)	119 (40%)	65 (30%)
p-value[d]	0.0011	

NR: Not Reached; NE: Not Estimable.
Minimum follow-up was 16.7 months at data cutoff date 28Aug2024.

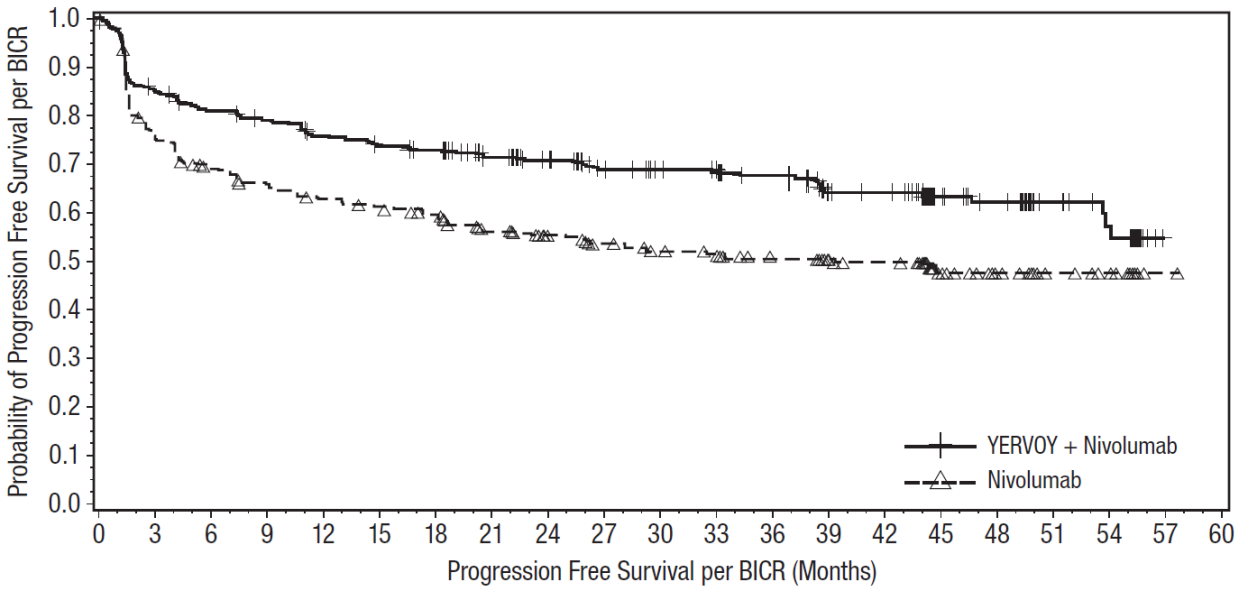
[a] Based on log-rank test stratified by the same factors as used in the Cox proportional hazards model. The p-value threshold for statistical significance was 0.0095.

[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 5: Progression-free Survival (All lines (YERVOY + Nivolumab vs Nivolumab)- CHECKMATE-8HW



Number of Subjects at Risk

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

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

The efficacy of YERVOY with nivolumab was evaluated in CHECKMATE-142 (NCT02060188), a multicenter, non-randomized, multiple parallel-cohort, open-label study conducted in patients with locally determined dMMR or MSI-H 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 PS 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients enrolled in the YERVOY and nivolumab MSI-H or dMMR mCRC cohort received YERVOY 1 mg/kg and nivolumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg intravenously as a single agent every 2 weeks. Efficacy outcome measures were overall response rate (ORR) as assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR). Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter.

A total of 119 patients were enrolled in the YERVOY and nivolumab 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 PS was 0 (45%) or 1 (55%), and 29% were reported to have

Lynch Syndrome. Across the cohort, 69% 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 are shown in Table ~~22~~29.

Table ~~22~~29: Efficacy Results in MSI-H/dMMR Cohort of CHECKMATE-142

	YERVOY and Nivolumab[a] MSI-H/dMMR Cohort	
	All Patients (n=119)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
Overall Response Rate per BICR; n (%)	71 (60%)	46 (56%)
(95% CI)[b]	(50, 69)	(45, 67)
Complete Response (%)	17 (14%)	11 (13%)
Partial Response (%)	54 (45%)	35 (43%)
Duration of Response		
Proportion of responders with ≥6 months response duration	89%	87%
Proportion of responders with ≥12 months response duration	77%	74%

[a] Minimum follow-up 27.5 months for all patients treated with YERVOY and nivolumab (n=119).

[b] Estimated using the Clopper-Pearson method.

14.4 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:

- YERVOY 3 mg/kg administered intravenously over 30 minutes in combination with nivolumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks, for a

maximum of 4 doses, followed by single agent nivolumab 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 YERVOY in combination with nivolumab continued until disease progression, unacceptable toxicity, or up to 2 years. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab 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 YERVOY in combination with nivolumab (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 was 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 30 and Figure 6.

Table 30: Efficacy Results - CHECKMATE-9DW

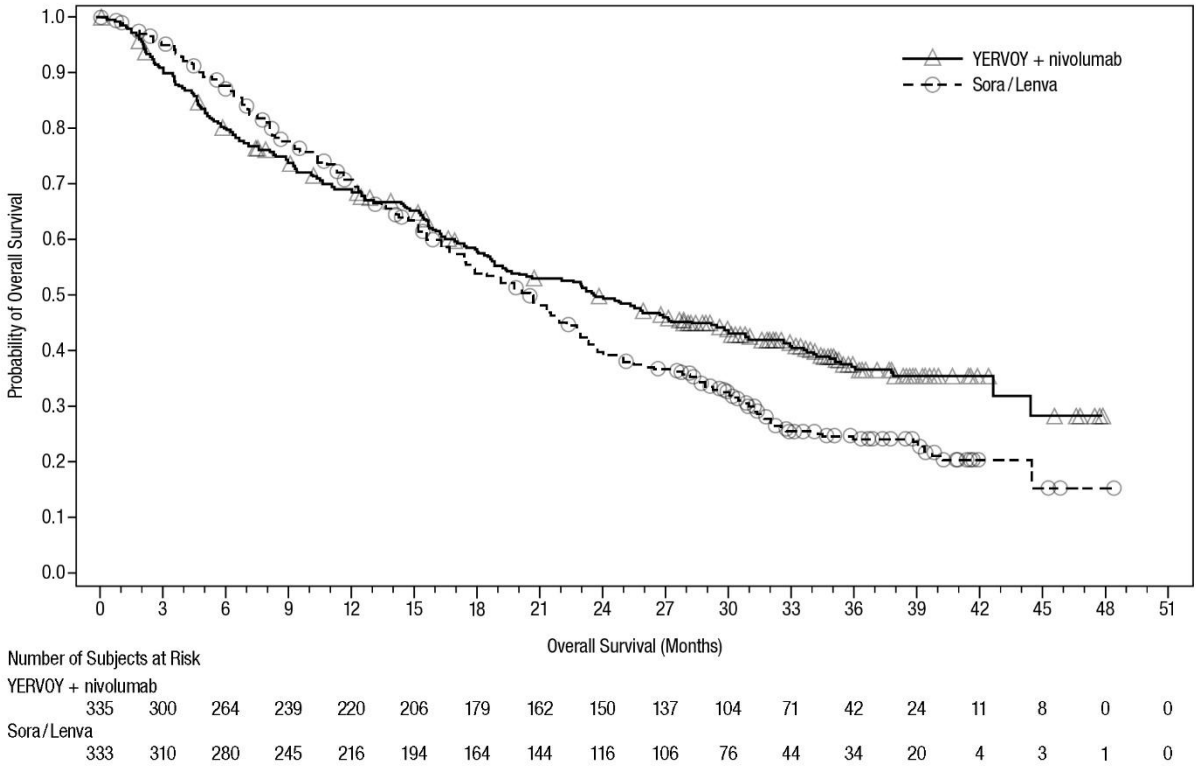
	YERVOY and Nivolumab (n=335)	**Lenvatinib or Sorafenib (n=333)**
Overall Survival		
Deaths (%)	194 (58%)	228 (68%)

Table 30: Efficacy Results - CHECKMATE-9DW

	YERVOY and Nivolumab (n=335)	Lenvatinib or Sorafenib (n=333)
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 6: Overall Survival - CHECKMATE-9DW



Previously Treated Hepatocellular Carcinoma

CHECKMATE-040 (NCT01658878) was a multicenter, multiple cohort, open-label trial conducted in patients with 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.

The efficacy of YERVOY 3 mg/kg in combination with nivolumab 1 mg/kg was evaluated in Cohort 4 of CHECKMATE-040. A total of 49 patients received the combination regimen, which was administered every 3 weeks for four doses, followed by single-agent nivolumab 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 percent (57%) 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 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 alfa-fetoprotein

(AFP) levels ≥400 µg/L. Prior 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 ~~23~~31.

Table ~~23~~31: Efficacy Results - Cohort 4 of CHECKMATE-040

	YERVOY and Nivolumab (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. למה מיועדת התרופה?

1. **סרטן עור מסוג מלנומה בלתי נתיחה או גרורתית**
יירבוי מיועדת לטיפול במבוגרים עם מלנומה מתקדמת (לא נתיחה או גרורתית).
יירבוי בשילוב עם ניבולומאב (nivolumab) מיועדת לטיפול במבוגרים וילדים מגיל 12 ומעלה עם מלנומה מתקדמת (לא נתיחה או גרורתית).

2. **סרטן תאי כליה מתקדם (advanced renal cell carcinoma)**
יירבוי בשילוב עם ניבולומאב (nivolumab) מיועדת לטיפול כקו ראשון במבוגרים עם סרטן תאי כליה מתקדם, בדרגת סיכון בינונית או גבוהה.

3. **סרטן גרורתי של המעי הגס או החלחולת**
- יירבוי בשילוב עם ניבולומאב (nivolumab) מיועדת לטיפול כקו 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).
- יירבוי בשילוב עם ניבולומאב (nivolumab) 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.

4. **סרטן ריאות גרורתי מסוג תאים שאינם קטנים (non-small cell lung cancer)**
יירבוי בשילוב עם ניבולומאב (nivolumab) 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 גנומיים ב- EGFR או ALK בגידול.

5. **סרטן כבד (hepatocellular carcinoma)**
- יירבוי בשילוב עם ניבולומאב (nivolumab) מיועדת לטיפול קו ראשון במבוגרים עם סרטן לא נתיח או גרורתי של הכבד עם פגיעה כבדית קלה (Child-Pugh A).
- יירבוי בשילוב עם ניבולומאב (nivolumab) מיועדת לטיפול בסרטן כבד עם פגיעה כבדית קלה (Child-Pugh A), במבוגרים אשר טופלו בעבר עם סוראפניב (sorafenib).

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

7. **סרטן ושט מסוג קרצינומה של תאי קשקש (esophageal squamous cell carcinoma)**
יירבוי בשילוב עם ניבולומאב (nivolumab) מיועדת לטיפול קו ראשון במבוגרים עם סרטן ושט מסוג קרצינומה של תאי קשקש שאינו נתיח, מתקדם, חוזר או גרורתי, עם ביטוי של PD-L1 ב- 1% ומעלה מתאי הגידול.

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3. כיצד תשתמש בתרופה?

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

אין לעבור על המנה המומלצת.

הטיפול ביירבוי ניתן על ידי צוות רפואי.
- כאשר יירבוי ניתנת כטיפול יחיד היא ניתנת ישירות לווריד באמצעות צינורית תוך ורידית במשך 90 דקות.

- כאשר יירבוי ניתנת בשילוב עם ניבולומאב (nivolumab) (למעט עבור טיפול במלנומה בלתי-נתיחה או גרורתית), ניבולומאב (nivolumab) ניתנת ישירות לווריד באמצעות צינורית תוך ורידית במשך 30 דקות. לאחר מכן ובאותו היום יירבוי ניתנת גם כן ישירות לווריד באמצעות צינורית תוך ורידית במשך 30 דקות.
- עבור טיפול במלנומה מתקדמת (בלתי-נתיחה או גרורתית), כאשר יירבוי ניתנת בשילוב עם ניבולומאב (nivolumab), ניבולומאב ניתנת ישירות לווריד באמצעות צינורית תוך ורידית במשך 30 דקות. לאחר מכן ובאותו היום יירבוי ניתנת גם כן ישירות לווריד באמצעות צינורית תוך ורידית במשך 90 דקות.
- יירבוי בשילוב עם ניבולומאב (nivolumab) ניתנת בדרך כלל כל 3 שבועות, ~~ובסה"כ~~ למשך עד ~~-~~4 מנות טיפול. לאחר מכן, ניבולומאב תינתן לבד בדרך כלל כל שבועיים או כל 4 שבועות.
  - עבור טיפול בסרטן ריאות גרורתי מסוג תאים שאינם קטנים (non-small cell lung cancer) שהתפשט לחלקים אחרים בגופך, יירבוי ניתנת כל 6 שבועות וניבולומאב (nivolumab) ניתנת כל 3 שבועות למשך שנתיים לכל היותר. תזדקק גם למתן של טיפול כימותרפי כל 3 שבועות למשך שני מחזורי טיפול.
  - עבור טיפול במזותליומה ממאירה של הפלאורה (Malignant Pleural Mesothelioma), שאינה ניתנת להסרה ע"י ניתוח, יירבוי ניתנת כל 6 שבועות וניבולומאב (nivolumab) ניתנת כל שבועיים או כל 3 שבועות, לפי החלטת הרופא המטפל. בכל מקרה, הטיפול ניתן למשך שנתיים לכל היותר.
  - כאשר יירבוי ניתנת בשילוב עם ניבולומאב (nivolumab) לטיפול בסרטן ושט מסוג קרצינומה של תאי קשקש (esophageal squamous cell carcinoma), יירבוי ניתנת כל 6 שבועות וניבולומאב (nivolumab) ניתנת כל שבועיים או כל 3 שבועות, למשך שנתיים לכל היותר.
- הרופא המטפל יחליט לכמה טיפולים הינך זקוק.
- הרופא המטפל יערוך בדיקות דם לפני התחלת הטיפול עם יירבוי, וכן במהלכו.
- אם אינך יכול להגיע לטיפול שנקבע לך, צור קשר עם הרופא המטפל בהקדם האפשרי על מנת לקבוע מועד חדש לטיפול.

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4. תופעות לוואי

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תופעות לוואי נוספות:

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תופעות לוואי בזמן טיפול משולב של יירבוי עם ניבולומאב (nivolumab)

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

- רמה גבוהה של סוכר בדם (היפרגליקמיה)
- דלקת בלוטת יותרת המוח (היפופיזיטיס)
- התייבשות
- פגיעה כלייתית חריפה
- אירוע כבדי
- תפקודי כבד לא תקינים
- אי ספיקת כבד
- רעילות כבדית
- דימום מדליות הוושט
- הצטברות נוזל בחלל האדר העוטף את הריאות (תפליט פלאורלי) אשר עלולה לגרום לקוצר נשימה, וכן לעיתים לכאב בחזה ולחום
- תסחיף ריאתי (קריש דם בריאות)
- ויטיליגו (בהקת) – מחלה שבה מופיעים כתמים בהירים על העור
- לחץ דם גבוה
- התנקבות במעי
- שרירים כואבים, חולשת שרירים שלא כתוצאה מאימון (מיופתיה)
- תסמונת שגרן (Sjogren's syndrome), מחלה שבה מערכת החיסון תוקפת בעיקר בלוטות דמעות ורוק
- דלקת מפרקים כרונית שבדרך כלל מערבת את מפרקי עמוד השדרה (ספונדילוארתרופתיה)

- 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)
- מוות כתוצאה מתופעות לוואי
- תגובות הקשורות לעירוי
- חסימת מעיים (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 בשריר הלב (מיוקרדיטיס)

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