פברואר 2021

Yervoy (Ipilimumab) 5 mg/ml

Concentrate for solution for infusion

רופא/ה ,רוקח/ת יקר/ה, חברת בריסטול-מאיירס סקוויב (ישראל) מבקשת להודיע על:

- הרחבת התוויות לתכשיר יירבוי (איפילימומאב)
- עדכון העלון לרופא של התכשיר

התוויות התכשיר כפי שאושרו ע"י משרד הבריאות (תוספת טקסט מסומנת באדום):

Unresectable or Metastatic Melanoma

Yervoy (ipilimumab) is indicated for the treatment of advanced (unresectable or metastatic) melanoma.

Yervoy in combination with Opdivo (nivolumab) is indicated for the treatment of patient with advanced (unresectable or metastatic) melanoma.

Advanced Renal Cell Carcinoma

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

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

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 treatment of patients with hepatocellular carcinoma (HCC) Child-Pugh A who have been previously treated with sorafenib.

בפירוט שלהלן כלולים העדכונים המהותיים בלבד (טקסט שנוסף מסומן באדום עם קו תחתי ,טקסט שהוסר מסומן ~~בכחול~~עם קו אמצעי).

למידע מלא על התרופה יש לעיין בעלון לרופא כפי שאושר על ידי משרד הבריאות.
העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל הרישום בריסטול- מאיירס סקוויב (ישראל) בע"מ.

בכבוד רב,
שירן קלאורה
רוקחת ממונה

עדכונים מהותיים בעלון לרופא:

Patient safety information Card and Brochure

The marketing of Yervoy is subject to a risk management plan (RMP) including a 'patient safety information card'. The 'patient safety information card' emphasizes important safety information that the patient should be aware of before and during treatment. Please advise the patient the need to review the card before starting treatment.

For patients receiving Yervoy in combination with Opdivo, please provide the patient with the 'Patient safety information card' and 'patient brochure' available for Opdivo in combination with Yervoy, and advise the patient to review it before starting treatment.

~~**WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**~~

~~**YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.**~~

~~**Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.** ***[See Dosage and Administration (2.2).]***~~

~~**Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.** ***[See Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5).]***~~

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

- YERVOY (ipilimumab) is indicated for the treatment of advanced (unresectable or metastatic) melanoma.
- YERVOY (ipilimumab), in combination with nivolumab, is indicated for the treatment of patients with advanced (unresectable or metastatic) melanoma.

1.2 Advanced Renal Cell Carcinoma

YERVOY, in combination with nivolumab, is indicated for the treatment of patients with intermediate or poor risk, previously untreated 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 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 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.

1.5 Hepatocellular Carcinoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended ~~Dosing~~ Dosage

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The recommended dosages of YERVOY in combination with other therapeutic agents are presented in Table 1. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with YERVOY for recommended dosage information, as appropriate.

Table 1: Recommended Dosages of YERVOY in Combination with Other Therapeutic Agents

Indication	Recommended YERVOY Dosage	Duration of Therapy

Table 1: 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.
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	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
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 4 doses. After completing 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 chemotherapy every 3 weeks	In combination with nivolumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression **2 cycles of histology-based platinum-doublet chemotherapy**

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2.2 Preparation and Administration

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Preparation of Solution

- Allow the vial(s) to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of YERVOY and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to ~~prepare a diluted solution with~~ a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.

- After preparation, Sstore the diluted solution for no more than 24 hours under refrigeration at (2°C to 8°C). for no more than 24 hours from the time of preparation to the time of infusion.
- Discard partially used vials or empty vials of YERVOY.

Administration Instructions

- Do not mix YERVOY with, or co- administer as an infusion with, other medicinal products drugs through the same intravenous line.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 30 minutes or 90 minutes depending on the dose, through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.
- When administered in combination with nivolumab, infuse nivolumab first followed by YERVOY on the same day. When administered with nivolumab and platinum-doublet chemotherapy, infuse nivolumab first followed by YERVOY and then platinum-doublet chemotherapy on the same day. Use separate infusion bags and filters for each infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/10 mL (5 mg/mL) or
Injection: 200 mg/40 mL (5 mg/mL) as a clear to slightly opalescent, colorless to pale-yellow liquid that may contain light (few) particulates, in a single dose vial.

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5 WARNINGS AND PRECAUTIONS

YERVOY can result in severe and fatal immune-mediated reactions. *[See Boxed Warning.]*

5.1 Immune-Mediated Enterocolitis/Colitis

Immune-mediated enterocolitis, including fatal cases, can occur with YERVOY.

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

YERVOY is a fully human monoclonal antibody that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, thereby removing inhibition of the immune response with the potential for induction of immune-mediated adverse reactions. Immune-mediated adverse reactions listed herein may not be inclusive of all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting

YERVOY. While immune-mediated adverse reactions usually manifest during treatment, immune-mediated adverse reactions can also manifest after discontinuation of YERVOY.

Early identification and management are essential to ensure safe use of YERVOY. Monitor for signs and symptoms that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration]*. In general, if YERVOY requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Immune-Mediated Colitis

YERVOY can cause immune-mediated colitis, which may be fatal. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating ~~an~~ infectious workup to exclude alternative etiologies. ~~Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.~~

~~Permanently discontinue YERVOY in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients. Consider adding anti-TNF or other immunosuppressant agents for management of immune-mediated enterocolitis unresponsive to systemic corticosteroids within 3 to 5 days or recurring after symptom improvement, if other causes are excluded.~~

~~Withhold YERVOY dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for more than 1 week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent *[see Dosage and Administration (2.24)]*.~~

~~*YERVOY as a Single Agent*~~

~~Metastatic Melanoma~~

~~In patients receiving YERVOY 3 mg/kg in MDX010-20 (NCT00094653), , severe, life-threatening, or fatal (diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3 to 5) immune-mediated enterocolitis occurred in 34 YERVOY-treated patients (7%), and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 YERVOY-treated patients (5%). Across all YERVOY-treated patients (n=511), 5 patients (1%) developed intestinal perforation, 4 patients~~

~~(0.8%) died as a result of complications, and 26 patients (5%) were hospitalized for severe enterocolitis.~~

~~The median time to onset of Grade 3 to 5 enterocolitis was 1.7 months (range: 11 days to 3.1 months) and for Grade 2 enterocolitis was 1.4 months (range: 2 days to 4.3 months).~~

~~Twenty-nine patients (85%) with Grade 3 to 5 enterocolitis were treated with high-dose (≥40 mg prednisone equivalent per day) corticosteroids, with a median dose of 80 mg/day of prednisone or equivalent; the median duration of treatment was 16 days (ranging up to 3.2 months) followed by corticosteroid taper. Of the 28 patients with moderate enterocolitis, 46% were not treated with systemic corticosteroids, 29% were treated with <40 mg prednisone or equivalent per day for a median duration of 1.2 months, and 25% were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Infliximab was administered to 5 (8%) of the 62 patients with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.~~

~~Of the 34 patients with Grade 3 to 5 enterocolitis, 74% experienced complete resolution, 3% experienced improvement to Grade 2 severity, and 24% did not improve. Among the 28 patients with Grade 2 enterocolitis, 79% experienced complete resolution, 11% improved, and 11% did not improve.~~

YERVOY 3 mg/kg as a Single Agent

Immune-mediated colitis occurred in 12% (62/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (7%) and Grade 2 (5%). Colitis led to permanent discontinuation of YERVOY in 4.3% and withholding of at least one dose of YERVOY in 0.2% of patients.

Systemic corticosteroids were required in 74% (46/62) of patients with immune-mediated colitis. Five patients required coadministration of another immunosuppressant with corticosteroids. Colitis resolved in 76% of the 62 patients. One patient was withheld one or more doses of YERVOY for colitis, and no patient received additional treatment after symptom improvement.

YERVOY 1 mg/kg with Nivolumab

Immune-mediated colitis occurred in 9% (60/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (4.4%), and Grade 2 (3.7%). Colitis led to permanent discontinuation of YERVOY and nivolumab in 3.2% and withholding of YERVOY and nivolumab in 2.7% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated colitis. Systemic corticosteroids were therefore required in 100% (60/60) of patients with immune-mediated colitis. Approximately 23% of patients required coadministration of another immunosuppressant with corticosteroids. Colitis resolved in 95% of the 60 patients. Of the 18 patients in whom

YERVOY or nivolumab was withheld for colitis, 16 received additional treatment after symptom improvement; of these, 10 had recurrence of colitis.

YERVOY 3 mg/kg with Nivolumab

Immune-mediated colitis occurred in 10% (5/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Median time to onset was 2 months (range: 1.1 to 19 months). Immune-mediated colitis led to permanent discontinuation or withholding of treatment in 4.1% and 4.1% of patients, respectively. Sixty percent (60%) of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 15 days (range: 9 days to 1.1 months). Complete resolution occurred in 80% of patients. Of the 2 patients in whom YERVOY or nivolumab was withheld for colitis, 2 received additional treatment after symptom improvement, and 2 had recurrence of colitis.

Immune-Mediated Hepatitis

~~Immune-mediated hepatitis, including fatal cases, can occur with YERVOY.~~

~~Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.~~

~~Permanently discontinue YERVOY in patients with Grade 3 to 4 hepatotoxicity and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids. Withhold YERVOY in patients with Grade 2 hepatotoxicity *[see Dosage and Administration (2.2~~4~~)].~~

YERVOY 3 mg/kg as a Single Agent

~~Metastatic Melanoma~~
~~In patients receiving YERVOY 3 mg/kg in MDX010-20 ,, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations of more than 5 times the upper limit of normal or total bilirubin elevations more than 3 times the upper limit of normal; Grade 3 to 5) occurred in 8 YERVOY-treated patients (2%), with fatal hepatic failure in 0.2% and hospitalization in 0.4% of YERVOY-treated patients. An additional 13 patients (2.5%) experienced moderate hepatotoxicity manifested by liver function test abnormalities (AST or ALT elevations of more than 2.5 times but not more than 5 times the upper limit of normal or total bilirubin elevation of more than 1.5 times but not more than 3 times the upper limit of normal; Grade 2). The underlying pathology was not ascertained in all patients but in some instances included immune-mediated hepatitis. There were insufficient numbers of patients with biopsy-proven hepatitis to characterize the clinical course of this event.~~

Immune-mediated hepatitis occurred in 4.1% (21/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (1.6%) and Grade 2 (2.5%). Hepatitis led to permanent discontinuation of YERVOY in 0.4% of patients and withholding of at least one dose of YERVOY in none of the patients.

Systemic corticosteroids were required in 29% (6/21) of patients with immune-mediated hepatitis. No patients required the coadministration of another immunosuppressant with corticosteroids. Hepatitis resolved in 86% of the 21 patients.

YERVOY 3 mg/kg ~~Concurrent Administration~~ with Vemurafenib

The safety and effectiveness of YERVOY in combination with vemurafenib have not been established *[see Indications and Usage (1)]*. In a dose-finding trial, Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent YERVOY (3 mg/kg) and vemurafenib (960 mg ~~BID~~ or 720 mg ~~BID~~ twice daily).

YERVOY 1 mg/kg with Nivolumab

Immune-mediated hepatitis occurred in 7% (48/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%). Hepatitis led to permanent discontinuation of YERVOY and nivolumab in 3.6% and withholding of YERVOY and nivolumab in 2.6% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated hepatitis. Systemic corticosteroids were therefore required in 100% (48/48) of patients with immune-mediated hepatitis. Approximately 19% of patients required coadministration of another immunosuppressant with corticosteroids. Hepatitis resolved in 88% of the 48 patients. Of the 17 patients in whom YERVOY or nivolumab was withheld for hepatitis, 14 received additional treatment after symptom improvement; of these, 10 had recurrence of hepatitis.

YERVOY 3 mg/kg with Nivolumab

Immune-mediated hepatitis occurred in 20% (10/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Median time to onset was 1.3 months (range: 22 days to 4.1 months). Immune-mediated hepatitis led to permanent discontinuation or withholding of treatment in 6.1% and 12% of patients, respectively. Seventy percent (70%) of patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 14 days (range: 3 days to 34 months). Complete resolution occurred in 70% of patients. Of the 6 patients in whom YERVOY or nivolumab was withheld for hepatitis, 4 received additional treatment after symptom improvement, and 3 had recurrence of hepatitis.

Immune-Mediated ~~Dermatitis/Skin~~ Dermatologic Adverse Reactions

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms). Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration]*.

~~Immune-mediated dermatitis, including fatal cases, can occur with YERVOY.~~

~~Monitor patients for signs and symptoms of dermatitis, such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.~~

~~Permanently discontinue YERVOY in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms *[see Dosage and Administration (2.24)]*.~~

~~For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.~~

YERVOY 3 mg/kg as a Single Agent

~~YERVOY as a Single Agent~~

~~Metastatic Melanoma~~

~~In patients receiving YERVOY 3 mg/kg in MDX010-20, severe, life-threatening, or fatal immune-mediated dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3 to 5) occurred in 13 YERVOY-treated patients (2.5%). One patient (0.2%) died as a result of toxic epidermal necrolysis and one additional patient required hospitalization for severe dermatitis. There were 63 patients (12%) with moderate (Grade 2) dermatitis.~~

~~The median time to onset of moderate, severe, or life-threatening immune-mediated dermatitis was 22 days and ranged up to 4.0 months from the initiation of YERVOY.~~

~~Seven YERVOY-treated patients (54%) with severe dermatitis received high-dose corticosteroids (median dose 60 mg prednisone/day or equivalent) for up to 3.4 months followed by corticosteroid taper. Of these 7 patients, 6 had complete resolution; time to resolution ranged up to 3.6 months.~~

~~Of the 63 patients with moderate dermatitis, 25 (40%) were treated with systemic corticosteroids (median of 60 mg/day of prednisone or equivalent) for a median of 15 days, 7 (11%) were~~

~~treated with only topical corticosteroids, and 31 (49%) did not receive systemic or topical corticosteroids. Forty four patients (70%) with moderate dermatitis were reported to have complete resolution, 7 (11%) improved to mild (Grade 1) severity, and 12 (19%) had no reported improvement.~~

Immune-mediated rash occurred in 15% (76/511) of patients who received YERVOY 3 mg/kg as a single agent, including Grade 3-5 (2.5%) and Grade 2 (12%). Rash led to permanent discontinuation of YERVOY in 0.2% and withholding of at least one dose of YERVOY in 1.4% of patients.

Systemic corticosteroids were required in 43% (33/76) of patients with immune-mediated rash. Rash resolved in 71% of the 76 patients. Of the 7 patients in whom YERVOY was withheld for rash, 3 received additional treatment after symptom improvement; of these, 1 had recurrence of rash.

YERVOY 1 mg/kg with Nivolumab

Immune-mediated rash occurred in 16% (108/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (3.5%) and Grade 2 (4.2%). Rash led to permanent discontinuation of YERVOY and nivolumab in 0.5% of patients and withholding of YERVOY and nivolumab in 2.0% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated rash. Systemic corticosteroids were therefore required in 100% (108/108) of patients. Rash resolved in 75% of 108 patients. Of the 13 patients in whom YERVOY or nivolumab was withheld for rash, 11 received additional treatment after symptom improvement; of these, 5 had recurrence of rash.

YERVOY 3 mg/kg with Nivolumab

Immune-mediated rash occurred in 35% (17/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Median time to onset was 15 days (range: 6 days to 3.1 months). Immune-mediated rash led to withholding of treatment in 6% of patients. Twelve percent (12%) of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 8 days (range: 1 to 15 days). Complete resolution occurred in 65% of patients. Of the 3 patients in whom YERVOY or nivolumab was withheld for rash, 2 received additional treatment after symptom improvement, and none had recurrence of rash.

~~5.2 Immune-Mediated Neuropathies~~

~~Immune-mediated neuropathies, including fatal cases, can occur with YERVOY.~~

~~Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe~~

neuropathies. Withhold YERVOY dosing in patients with moderate neuropathy (not interfering with daily activities) [*see Dosage and Administration (2.24)*].

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported. Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.

Immune-Mediated Endocrinopathies

Immune-mediated endocrinopathies, including life-threatening cases, can occur with YERVOY.

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

Withhold YERVOY dosing in symptomatic patients and consider referral to an endocrinologist. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy. *[See Dosage and Administration (2.24).]*

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3 to 4) occurred in 9 YERVOY-treated patients (1.8%).

YERVOY 3 mg/kg as a Single Agent

Grade 2-5 immune-mediated endocrinopathies occurred in 4% (21/511) of patients who received YERVOY 3 mg/kg as a single agent.

Severe to life-threatening (Grade 3-4) endocrinopathies occurred in 9 patients (1.8%). All 9 of these patients had hypopituitarism and with some had patients having additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring

~~hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome.~~

~~The median time to onset of moderate to severe immune-mediated endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of YERVOY.~~

Moderate (Grade 2) endocrinopathy occurred in 12 patients (2.3%), including hypothyroidism, adrenal insufficiency, hypopituitarism, hyperthyroidism and Cushing's syndrome.

Of the 21 patients with moderate to life-threatening endocrinopathy, 17 ~~patients~~ required long-term hormone replacement therapy including, ~~most commonly,~~ adrenal hormones (n=10) and thyroid hormones (n=13).

YERVOY 1 mg/kg with Nivolumab

Hypophysitis:

YERVOY can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue YERVOY depending on severity *[see Dosage and Administration]*.

Hypophysitis occurred in 4.4% (29/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%). Hypophysitis led to permanent discontinuation of YERVOY and nivolumab in 1.2% and withholding of YERVOY with nivolumab in 2.1% of patients. Approximately 72% of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 72% (21/29) of patients with immune-mediated hypophysitis. Hypophysitis resolved in 59% of the 29 patients. Of the 14 patients in whom YERVOY or nivolumab was withheld for hypophysitis, 11 received additional treatment after symptom improvement; of these, 2 had recurrence of hypophysitis.

Adrenal Insufficiency:

Adrenal insufficiency occurred in 7% (48/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%). Adrenal insufficiency led to permanent discontinuation of YERVOY with nivolumab in 1.2% and withholding of YERVOY with nivolumab in 2.1% of patients. Approximately 94% of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 94% (45/48) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 29% of the 48 patients. Of the 14 patients in whom YERVOY or nivolumab was withheld for adrenal insufficiency, 11 received additional treatment after symptom improvement; of these, 2 had recurrence of adrenal insufficiency.

Hyperthyroidism:

Hyperthyroidism occurred in 12% (80/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (0.6%) and Grade 2 (4.5%). No patients discontinued YERVOY for hyperthyroidism. Hyperthyroidism led to withholding of YERVOY with nivolumab in 2.3% of patients. Approximately 19% received a thyroid synthesis inhibitor. Systemic corticosteroids were required in 20% (16/80) of patients with hyperthyroidism. Hyperthyroidism resolved in 85% of the 80 patients. Of the 15 patients in whom YERVOY or nivolumab was withheld for hyperthyroidism, 11 received additional treatment after symptom improvement; of these, 3 had recurrence of hyperthyroidism.

Hypothyroidism:

Hypothyroidism occurred in 18% (122/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (0.6%) and Grade 2 (11%). Hypothyroidism led to permanent discontinuation of YERVOY with nivolumab in 0.2% and withholding of YERVOY with nivolumab in 1.4% of patients. Approximately 82% received thyroid hormone replacement. Systemic corticosteroids were required in 7% (9/122) of patients with hypothyroidism. Hypothyroidism resolved in 27% of the 122 patients. Of the 9 patients in whom YERVOY or nivolumab was withheld for hypothyroidism, 5 received additional treatment after symptom improvement; of these, one patient had recurrence of hypothyroidism.

Thyroiditis:

Thyroiditis occurred in 2.7% (22/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (4.5%) and Grade 2 (2.2%). Thyroiditis led to permanent discontinuation of YERVOY with nivolumab in 0.2% and withholding of YERVOY with nivolumab in 0.8% of patients. Systemic corticosteroids were required in 18% (4/22) of patients with thyroiditis. Thyroiditis resolved in 64% of the 22 patients. Of the 5 patients in whom YERVOY or nivolumab was withheld for thyroiditis, 5 received additional treatment after symptom improvement; of these, no patients had recurrence of thyroiditis.

Type 1 Diabetes Mellitus

Diabetes occurred in 2.7% (15/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.6%), Grade 3 (0.3%), and Grade 2 (0.9%). Diabetes led to the permanent discontinuation of YERVOY with nivolumab in 0.5% and withholding of YERVOY with nivolumab in 0.5% of patients. Systemic corticosteroids were required in 7% (1/15) of patients with diabetes. Diabetes resolved in 27% of the 15 patients. Of the 3 patients in whom YERVOY or nivolumab was withheld for diabetes, 2 received additional treatment after symptom improvement; of these, none had recurrence of diabetes.

YERVOY 3 mg/kg with Nivolumab

Hypophysitis:

Hypophysitis occurred in 4% (2/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Median time to onset was 3.7 months (range: 3 to 4.3 months).

Hypophysitis led to withholding of treatment in 2% of patients. One patient with hypophysitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for 6 days.

Adrenal Insufficiency:

Adrenal insufficiency occurred in 18% (9/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Median time to onset was 2.8 months (range: 1.4 to 8 months). Adrenal insufficiency led to withholding of treatment in 4.1% of patients. One patient with adrenal insufficiency received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for 1.2 months. Complete resolution occurred in 22% of patients.

Hypothyroidism:

Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (11/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Median time to onset was 3.3 months (range: 1.4 to 16.2 months). Complete resolution occurred in 46% of patients.

Hyperthyroidism:

Hyperthyroidism occurred in 10% (5/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Median time to onset was 1.4 months (range: 1.4 to 2.8 months). Complete resolution occurred in 80% of patients.

Immune-Mediated Pneumonitis

~~Immune-mediated pneumonitis, including fatal cases, can occur with nivolumab with YERVOY. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY for life-threatening (Grade 4) pneumonitis *[see Dosage and Administration (2.24)]*.~~

YERVOY 1 mg/kg with Nivolumab

Immune-mediated pneumonitis occurred in 3.9% (26/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 3 (1.4%) and Grade 2 (2.6%). Pneumonitis led to permanent discontinuation of YERVOY and nivolumab in 1.8% and withholding of YERVOY and nivolumab in 1.5% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated pneumonitis. Systemic corticosteroids were therefore required in 100% (26/26) of patients with immune-mediated pneumonitis. Approximately 8% required coadministration of another immunosuppressant with corticosteroids. Pneumonitis resolved in 92% of the 26 patients. Of the 10 patients in whom

YERVOY or nivolumab was withheld for pneumonitis, 10 received additional treatment after symptom improvement; of these, 4 had recurrence of pneumonitis.

YERVOY 3 mg/kg with Nivolumab

Immune-mediated pneumonitis occurred in 10% (5/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC. Median time to onset was 8.3 months (range: 1.2 to 17.5 months). Immune-mediated pneumonitis led to permanent discontinuation or withholding of treatment in 6.1% and 4.1% of patients, respectively. All patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 23 days (range: 12 days to 1.4 months). Complete resolution occurred in 60% of patients. Of the 2 patients in whom YERVOY or nivolumab was withheld for pneumonitis, 2 received additional treatment after symptom improvement, and 1 had recurrence of pneumonitis.

Immune-Mediated Nephritis ~~and~~ with Renal Dysfunction

~~Immune-mediated nephritis can occur with nivolumab with YERVOY. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.24)]*.~~

YERVOY 1 mg/kg with Nivolumab

Immune-mediated nephritis with renal dysfunction occurred in 4.1% (27/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or mCRC, including Grade 4 (0.6%), Grade 3 (1.1%), and Grade 2 (2.2%). Nephritis with renal dysfunction led to permanent discontinuation of YERVOY and nivolumab in 1.2% and withholding of nivolumab and YERVOY in 1.8% of patients.

In patients who received YERVOY 1 mg/kg with nivolumab, use of systemic corticosteroids was one of the diagnostic criteria required to identify immune-mediated nephritis with renal dysfunction. Systemic corticosteroids were therefore required in 100% (27/27) of patients with immune-mediated nephritis with renal dysfunction. Nephritis with renal dysfunction resolved in 67% of the 27 patients. Of the 12 patients in whom YERVOY or nivolumab was withheld for nephritis, 10 received additional treatment after symptom improvement; of these, 4 had recurrence of nephritis.

~~5.3 Immune-Mediated Encephalitis~~

~~Immune-mediated encephalitis can occur with YERVOY. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.~~

~~Withhold YERVOY in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue YERVOY for immune-mediated encephalitis *[see Dosage and Administration (2.24)]*.~~

Other Immune-Mediated Adverse Reactions

Across clinical trials of YERVOY administered as a single agent or in combination with nivolumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1% of patients unless otherwise specified, as shown below:

Nervous System: Autoimmune neuropathy (2%), meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, motor dysfunction

Cardiovascular: Angiopathy, myocarditis, pericarditis, temporal arteritis, vasculitis

Ocular: Blepharitis, episcleritis, iritis, orbital myositis, scleritis, uveitis. Some cases can be associated with retinal detachment. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Gastrointestinal: Duodenitis, gastritis, pancreatitis (1.3%)

Musculoskeletal and Connective Tissue: Arthritis, myositis, polymyalgia rheumatica, polymyositis, rhabdomyolysis

Other (hematologic/immune): Aplastic anemia, conjunctivitis, cytopenias (2.5%), eosinophilia (2.1%), erythema multiforme, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), hypersensitivity vasculitis, meningitis, neurosensory hypoacusis, psoriasis, sarcoidosis, systemic inflammatory response syndrome, and solid organ transplant rejection

~~5.4~~5.2 Infusion Related Reactions

Severe infusion-related reactions can occur with ~~nivolumab with~~ YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions *[see Dosage and Administration (~~2.2~~)]*.

Infusion-related reactions occurred in 2.9% (28/982) of patients who received single-agent YERVOY 3 mg/kg for the treatment of melanoma. Infusion-related reactions occurred in 5%

(33/666) of patients who received YERVOY 1 mg/kg with nivolumab for the treatment of RCC or CRC. Infusion-related reactions occurred in 8% (4/49) of patients who received YERVOY 3 mg/kg with nivolumab for the treatment of HCC.

5.5 Other Immune-Mediated Adverse Reactions

YERVOY as a Single Agent

Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Monitor patients for signs or symptoms of ocular toxicity, which may include blurred vision and reduced visual acuity. Immune-mediated ocular toxicity may be associated with retinal detachment or permanent vision loss. Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. *[See Dosage and Administration (2.34).]* If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

5.3 Complications of Allogeneic Hematopoietic Stem Cell Transplant after YERVOY

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive a CTLA-4 receptor blocking antibody YERVOY either before or after allogeneic hematopoietic stem cell transplantation (HSCT). These complications may occur despite intervening therapy between CTLA-4 receptor blocking antibody and allogeneic HSCT. Follow patients closely for evidence of GVHD and intervene promptly. *[See Adverse Reactions (6.23).]* Consider the benefit versus risks of treatment with a CTLA-4 receptor blocking antibody YERVOY after allogeneic HSCT.

Metastatic Melanoma

In MDX010-20, the following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients: cytopenias, nephritis, pneumonitis, meningitis, pericarditis, uveitis, and iritis.

Other Clinical Experience

Across 21 dose-ranging trials administering YERVOY at doses of 0.1 to 20 mg/kg (n=2478), the following likely immune-mediated adverse reactions were also reported with less than 1% incidence unless specified: angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypoacusis, autoimmune

central neuropathy (encephalitis), myositis, polymyositis, ocular myositis, cytopenias (2.5%), and nephritis. Also observed pancreatitis, sarcoidosis and fatal myocarditis.

…

5.5 Risks Associated When Administered in Combination with Nivolumab

When YERVOY is indicated for use administered in combination with nivolumab for patients with advanced RCC, MSI-H or dMMR mCRC, HCC, and NSCLC. , Rrefer to the nivolumab Full Pprescribing Iinformation for additional risk information that applies to the combination use treatment.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere discussed in greater detail in other sections of the labeling:.

- Immune-mediated enterocolitis/colitis *[see Warnings and Precautions (5.1)]*.
- Immune-mediated hepatitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated dermatitis/skin adverse reactions *[see Warnings and Precautions (5.3)]*.
- Immune-mediated neuropathies *[see Warnings and Precautions (5.4)]*.
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.5)]*.
- *Immune-mediated pneumonitis [see Warnings and Precautions (5.6)]*.
- *Immune-mediated nephritis and renal dysfunction [see Warnings and Precautions (5.7)]*.
- *Immune-mediated encephalitis [see Warnings and Precautions (5.8)]*.
- *Infusion reactions [see Warnings and Precautions (5.9)]*.
- Severe and fatal Other immune-mediated adverse reactions *[see Warnings and Precautions (5.10)]*.
- Embryo-fetal toxicity *[see Warnings and Precautions (5.11)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.2)]*.

In patients receiving YERVOY 3 mg/kg for unresectable or metastatic melanoma in MDX010-20 , 15% of patients receiving monotherapy and 12% of patients treated in combination with gp100 peptide vaccine experienced Grade 3 to 5 immune-mediated reactions.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in other clinical trials or experience with therapeutics in the same class clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described ~~below~~ in the Warnings and Precautions section reflect exposure to YERVOY 3 mg/kg as a single agent (or in combination with an investigational gp100 peptide vaccine) in 511 patients in Study MDX010-20;~~- 20, a randomized trial in patients with unresectable or metastatic melanoma;~~ YERVOY 1 mg/kg administered with nivolumab 3 mg/kg in 486 patients in CHECKMATE-214, and CHECKMATE-142;

YERVOY 3 mg/kg administered with nivolumab 1 mg/kg in 49 patients in CHECKMATE-040; and to YERVOY 1 mg/kg, administered in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, an open-label, multicenter, randomized trial in adult patients with previously untreated metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

~~Clinically significant adverse reactions were evaluated in a total of 982 patients treated in MDX010-20 and CA184-029 and in 21 dose-ranging trials (n=2478) administering YERVOY at doses of 0.1 to 20 mg/kg [see *Warnings and Precautions (5.6)]*.~~

Unresectable or Metastatic Melanoma

The safety of YERVOY was evaluated in ~~MDX010-20, a randomized, double-blind clinical trial in which~~ 643 previously treated patients with unresectable or metastatic melanoma ~~received YERVOY 3 mg/kg for 4 doses given by intravenous infusion as a single agent (n=131), YERVOY with an investigational gp100 peptide vaccine (gp100) (n=380), or gp100 peptide vaccine as a single agent (n=132)~~ in Study MDX010-20 *[see Clinical Studies (14.1)]*. ~~Patients in the trial received a median of 4 doses (range: 1 to 4 doses).~~

Study MDX010-20 excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Patients received YERVOY 3 mg/kg by intravenous infusion for 4 doses as a single agent (n=131), YERVOY with an investigational gp100 peptide vaccine (n=380), or gp100 peptide vaccine as a single agent (n=132). Patients in the trial received a median of 4 doses (range: 1 to 4 doses).

The trial population characteristics were: median age 57 years (range: 19 to 90), 59% male, 94% ~~white~~White, and baseline ECOG performance status 0 (56%).

YERVOY was discontinued for adverse reactions in 10% of patients. Table ~~2~~ 3 presents ~~selected~~ adverse reactions from Study MDX010-20~~, which occurred in at least 5% of patients in the YERVOY-containing arms and with at least 5% increased incidence over the control gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3 to 5 events.~~

~~**Table 2: Selected Adverse Reactions in MDX010-20**~~

~~System Organ Class/ Preferred Term~~	~~Percentage (%) of Patients[a]~~					
	~~YERVOY 3 mg/kg n=131~~		~~YERVOY 3 mg/kg+gp100 n=380~~		~~gp100 n=132~~	
	~~Any Grade~~	~~Grade 3to 5~~	~~Any Grade~~	~~Grade 3to 5~~	~~Any Grade~~	~~Grade 3to 5~~
~~**General Disorders and Administration Site Conditions**~~						
~~Fatigue~~	~~41~~	~~7~~	~~34~~	~~5~~	~~31~~	~~3~~
~~**Gastrointestinal Disorders**~~						
~~Diarrhea~~	~~32~~	~~5~~	~~37~~	~~4~~	~~20~~	~~1~~
~~Colitis~~	~~8~~	~~5~~	~~5~~	~~3~~	~~2~~	~~0~~
~~**Skin and Subcutaneous Tissue Disorders**~~						
~~Pruritus~~	~~31~~	~~0~~	~~21~~	~~<1~~	~~11~~	~~0~~
~~Rash~~	~~29~~	~~2~~	~~25~~	~~2~~	~~8~~	~~0~~

Table 3: Selected Adverse Reactions (≥ 5%) in Patients Receiving YERVOY with a Difference Between Arms of >5% for All Grades and >1% for Grades 3 to 5 Compared to gp100 Peptide Vaccine in Study MDX010-20

Adverse Reactions	YERVOY 3 mg/kg n=131		YERVOY 3 mg/kg and gp100 n=380		gp100 n=132	
	All Grades (%)	Grade 3 to 5 (%)	All Grades (%)	Grade 3 to 5 (%)	All Grades (%)	Grade 3 to 5 (%)
General and Administration-Site Conditions						
Fatigue	41	7	34	5	31	3
Gastrointestinal						
Diarrhea	32	5	37	4	20	1
Colitis	8	5	5	3	2	0
Dermatologic						
Pruritus	31	0	21	<1	11	0
Rash	29	2	25	2	8	0

[a] ~~Incidences presented in this table are based on reports of adverse events regardless of causality.~~

~~Table 3 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from MDX010-20~~.

Table 3: Severe to Fatal Immune-Mediated Adverse Reactions in MDX010-20

	Percentage (%) of Patients	
	YERVOY 3 mg/kg n=131	YERVOY 3 mg/kg+gp100 n=380
Any Immune-Mediated Adverse Reaction	15	12
Enterocolitis[a,b]	7	7
Hepatotoxicity[a]	1	2
Dermatitis[a]	2	3
Neuropathy[a]	1	<1
Endocrinopathy	4	1
Hypopituitarism	4	1
Adrenal insufficiency	0	1
Other		
Pneumonitis	0	<1
Meningitis	0	<1
Nephritis	1	0
Eosinophilia[c]	1	0
Pericarditis[a,c]	0	<1

[a] Including fatal outcome.
[b] Including intestinal perforation.
[c] Underlying etiology not established.

…

Advanced Renal Cell Carcinoma

The safety of YERVOY in combination with nivolumab was evaluated in 1082 patients with previously untreated advanced RCC in CHECKMATE-214 *[see Clinical Studies (14.3)]*. Patients received YERVOY 1 mg/kg with nivolumab 3 mg/kg intravenously every 3 weeks for 4 doses followed by nivolumab as a single agent at a dose of 3 mg/kg every 2 weeks (n=547) or sunitinib 50 mg orally daily for first 4 weeks of each 6-week cycle (n=535). The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in YERVOY and nivolumab arm. In this trial, 57% of patients in the YERVOY and nivolumab arm were exposed to treatment for greater than 6 months and 38% of patients were exposed to treatment for greater than 1 year.

Serious adverse reactions occurred in 59% of patients receiving YERVOY with nivolumab. The most frequent serious adverse reactions reported in ≥2% of patients treated with YERVOY and nivolumab were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis.

In patients who received YERVOY with nivolumab, study therapy was discontinued for adverse reactions in 31% and delayed for adverse reactions in 54%.

The most common adverse reactions (≥20%) in the YERVOY and nivolumab arm were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, vomiting, dyspnea, and decreased appetite. Table 4 summarizes adverse reactions in CHECKMATE-214.

Table 4: Adverse Reactions (>15%) in Patients Receiving YERVOY and Nivolumab in CHECKMATE-214

Adverse Reaction	YERVOY 1 mg/kg and Nivolumab n=547		Sunitinib n=535	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General and Administration Site Conditions				
Fatigue[a]	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema[b]	16	0.5	17	0.6
Skin and Subcutaneous Tissue				
Rash[c]	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Gastrointestinal				
Diarrhea	38	4.6	58	6
Nausea	30	2.0	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	37	4.0	40	2.6
Arthralgia	23	1.3	16	0
Respiratory, Thoracic, and Mediastinal				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Metabolism and Nutrition				
Decreased appetite	21	1.8	29	0.9
Nervous System				
Headache	19	0.9	23	0.9
Endocrine				
Hypothyroidism	18	0.4	27	0.2

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema, peripheral swelling.

[c] Includes dermatitis described as acneiform, bullous, and exfoliative, drug eruption, rash described as exfoliative, erythematous, follicular, generalized, macular, maculopapular, papular, pruritic, and pustular, fixed-drug eruption.

[d] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

Table 5 summarizes the laboratory abnormalities in CHECKMATE-214.

Table 5: Laboratory Abnormalities (>15%) Worsening from Baseline in Patients Receiving YERVOY and Nivolumab in CHECKMATE-214

Laboratory Abnormality	YERVOY 1 mg/kg and Nivolumab[a]	Sunitinib[a]

	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased lipase	48	20	51	20
Increased creatinine	42	2.1	46	1.7
Increased ALT	41	7	44	2.7
Increased AST	40	4.8	60	2.1
Increased amylase	39	12	33	7
Hyponatremia	39	10	36	7
Increased alkaline phosphatase	29	2.0	32	1.0
Hyperkalemia	29	2.4	28	2.9
Hypocalcemia	21	0.4	35	0.6
Hypomagnesemia	16	0.4	26	1.6
Hematology				
Anemia	43	3.0	64	9
Lymphopenia	36	5	63	14

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: nivolumab and YERVOY group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

In addition, among patients with TSH ≤ ULN at baseline, a lower proportion of patients experienced a treatment-emergent elevation of TSH > ULN in the YERVOY with nivolumab group compared to the sunitinib group (31% and 61%, respectively).

MSI-H or dMMR Metastatic Colorectal Cancer

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 (14.4)]*. 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 6 summarizes adverse reactions in CHECKMATE-142.

Table 6: 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		
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 7 summarizes laboratory abnormalities in CHECKMATE-142.

Table 7: 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

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 8 summarizes the adverse reactions and Table 9 summarizes the laboratory abnormalities of YERVOY in combination with nivolumab in CHECKMATE-040.

Table 8: 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

Table 8: 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 (%)
General		
Fatigue	27	2
Pyrexia	27	0
Malaise	18	2
Edema	16	2
Influenza-like illness	14	0
Chills	10	0
Nervous System		
Headache	22	0
Dizziness	20	0
Endocrine		
Hypothyroidism	20	0
Adrenal insufficiency	18	4
Investigations		
Weight decreased	20	0
Psychiatric		
Insomnia	18	0
Blood and Lymphatic System		
Anemia	10	4
Infections		
Influenza	10	2
Vascular		
Hypotension	10	0

Clinically important adverse reactions reported in <10% of patients receiving YERVOY with nivolumab were hyperglycemia (8%), colitis (4%), and increased blood creatine phosphokinase (2%).

Table 9: 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.

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy

The safety of YERVOY in combination with nivolumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.6)]*. Patients received either YERVOY 1 mg/kg administered every 6 weeks in combination with nivolumab 360 mg administered every 3 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in YERVOY in combination with nivolumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received YERVOY and nivolumab for >6 months and 13% of patients received YERVOY and nivolumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with YERVOY in combination with nivolumab and platinum-doublet chemotherapy. The most frequent (>2%) serious adverse reactions were pneumonia, diarrhea, febrile neutropenia, anemia, acute kidney injury, musculoskeletal pain, dyspnea, pneumonitis, and respiratory failure. Fatal adverse reactions occurred in 7 (2%) patients, and included hepatic toxicity, acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia.

Study therapy with YERVOY in combination with nivolumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 10 and 11 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 10: Adverse Reactions in >10% of Patients Receiving YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis

[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis

[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain

[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis, eczema, keratoderma blenorrhagica, palmar-plantar erythrodysaesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria

[f] Includes pruritus and generalized pruritus

[g] Includes cough, productive cough, and upper-airway cough syndrome

[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea

[i] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine

[j] Includes dizziness, vertigo and positional vertigo

Table 11: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on YERVOY and Nivolumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9
Thrombocytopenia	23	4.3	24	5
Chemistry				
Hyperglycemia	45	7	42	2.6
Hyponatremia	37	10	27	7
Increased ALT	34	4.3	24	1.2
Increased lipase	31	12	10	2.2
Increased alkaline phosphatase	31	1.2	26	0.3
Increased amylase	30	7	19	1.3
Increased AST	30	3.5	22	0.3
Hypomagnesemia	29	1.2	33	0.6
Hypocalcemia	26	1.4	22	1.8
Increased creatinine	26	1.2	23	0.6
Hyperkalemia	22	1.7	21	2.1

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

~~6.2 Postmarketing Experience~~

~~The following adverse reactions have been identified during post approval use of YERVOY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.~~

~~*Immune system disorders:* graft-versus-host disease~~

~~*Skin and Subcutaneous Tissue Disorders:* Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)~~

~~6.3~~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 the incidence of antibodies ~~to ipilimumab~~ in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Eleven (1.1%) of 1024 evaluable patients with unresectable or metastatic melanoma tested positive for treatment-emergent binding antibodies against ipilimumab ~~(TE-ADAs)~~ 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 tested positive for TE-ADAs 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 ~~TE-ADAs~~ 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.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of YERVOY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH)

Immune System: graft-versus-host disease, solid organ transplant rejection

Skin and Subcutaneous Tissue: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

Reporting of suspected adverse reactions

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Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

~~http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il~~

7 DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with YERVOY.

8 USE IN SPECIFIC POPULATIONS

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8.2 Lactation

Risk Summary

It is not known whether There are no data on the presence of YERVOY is present in human milk or its effects on the breastfed child or milk production. In monkeys, ipilimumab was present in milk (see Data). There are no data to assess the effects of YERVOY on milk production. Advise Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed to discontinue breastfeeding during treatment with YERVOY and for 3 months following the final last dose.

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8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Based on its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months following the last dose of YERVOY.

8.4 Pediatric Use

Safety and effectiveness of YERVOY have not been established in pediatric patients.

The safety and effectiveness of YERVOY have been established in pediatric patients 12 years and older for the treatment of MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of YERVOY in this age group is supported by evidence from adequate and well-controlled studies of YERVOY in adults and population pharmacokinetic data demonstrating that the exposure at doses of 1 mg/kg in the pediatric and adult populations are comparable. In addition, the tumor biology and course of MSI-H or dMMR mCRC are sufficiently similar in adults and pediatric patients 12 years and older to allow extrapolation of data from adults to pediatric patients.

The safety and effectiveness for pediatric patients 12 years and older have not been established for the treatment of melanoma or for the treatment of renal cell carcinoma. In addition, the safety

and effectiveness have not been established with YERVOY for any indication in pediatric patients less than 12 years of age.

8.5 Geriatric Use

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 ~~efficacy~~ effectiveness were ~~reported~~ observed between these ~~the elderly~~ patients ~~(65 years and over)~~ and younger patients ~~(less than 65 years).~~

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.

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 49 patients who received YERVOY 3 mg/kg with nivolumab in Cohort 4 of CHECKMATE-040 (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 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.

8.6 Renal Impairment

No dose adjustment is needed for patients with renal impairment. *[See Clinical Pharmacology (12.3).]*

8.7 Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment (total bilirubin [TB] >1.0 to 1.5 times the upper limit of normal [ULN] or AST >ULN). YERVOY has not been studied in patients with moderate (TB >1.5 × to 3.0 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment. *[See Clinical Pharmacology (12.3).]*

10 OVERDOSAGE

There is no information on overdosage with YERVOY.

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12.3 Pharmacokinetics

The pharmacokinetics (PK) of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every 3 weeks for 4 doses.

The PK of ipilimumab is linear in the dose range of 0.3 mg/kg to 10 mg/kg. Following administration of YERVOY every 3 weeks, the systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean minimum concentration (Cmin) at steady-state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks. The mean value (percent coefficient of variation) based on population PK analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for clearance (CL) was 16.8 mL/h (38%).

Elimination

The mean (percent coefficient of variation) terminal half-life ($t_{1/2}$) was 15.4 days (34%) and then mean (percent coefficient of variation) clearance (CL) was 16.8 mL/h (38%).

The CL of ipilimumab was unchanged in presence of anti-ipilimumab antibodies.

Specific Populations

The CL of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23 to 88 years), sex, performance status, renal impairment (glomerular filtration rate ≥15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin [TB] >1 to 1.5 times the upper limit of normal [ULN] or AST > ULN), previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-White racial groups. YERVOY has not been studied in patients with

moderate (TB > 1.5 to 3 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment.

Pediatric Patients: Based on a population PK analysis using available pooled data from 565 patients from four adult studies (n=521) and two pediatric studies (n=44), body weight normalized clearance of ipilimumab is comparable between adult and pediatric patients. In pediatric patients with a dosing regimen of 3 mg/kg every 3 weeks, the model simulated geometric mean (CV%) steady-state serum peak and trough concentrations of ipilimumab were 65.8 (17.6%) and 20.7 (33.1%) mcg/mL (for 2 to 6 years old), 70.1 (19.6%) and 19.6 (42.9%) mcg/mL (for 6 to <12 years old), and 73.3 (20.6%) and 17.8 (50.8%) mcg/mL (for 12 years and older), which are comparable to those in adult patients.

Drug Interaction Studies

Ipilimumab with Nivolumab

When YERVOY 1 mg/kg was administered with nivolumab 3 mg/kg every 3 weeks, the CL of ipilimumab was unchanged compared to when YERVOY was administered alone.

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

~~*Specific Populations:*~~

~~The effects of various covariates on the PK of ipilimumab were assessed in population PK analyses. The CL of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23 to 88 years), sex, performance status, renal impairment, mild hepatic impairment, previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-Caucasian ethnic groups.~~

~~*Renal Impairment:* The effect of renal impairment on the CL of ipilimumab was evaluated in patients with mild (GFR <90 and ≥60 mL/min/1.73 m^2; n=349), moderate (GFR <60 and ≥30 mL/min/1.73 m^2; n=82), or severe (GFR <30 and ≥15 mL/min/1.73 m^2; n=4) renal impairment compared to patients with normal renal function (GFR ≥90 mL/min/1.73 m^2; n=350) in population PK analyses. No clinically important differences in the CL of ipilimumab were found between patients with renal impairment and patients with normal renal function. *[See Use in Specific Populations (8.6).]*~~

~~*Hepatic Impairment:* The effect of hepatic impairment on the CL of ipilimumab was evaluated in patients with mild hepatic impairment (n=76) compared to patients with normal hepatic function (n=708) in the population PK analyses, and no clinically important differences in the CL of ipilimumab were found. YERVOY has not been studied in patients with moderate or severe hepatic impairment. *[See Use in Specific Populations (8.7).]*~~

…

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

The ~~safety and~~ efficacy of YERVOY were investigated in a Study MDX010-20, a randomized (3:1:1), double-blind, double-dummy ~~(~~trial (~~MDX010-20,~~ NCT00094653) that included ~~676 randomized~~ patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. ~~Of these 676 patients, 403 were randomized to receive YERVOY at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100), 137 were randomized to receive YERVOY at 3 mg/kg, and 136 were randomized to receive gp100 as a single agent.~~ The trial enrolled only patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. Patients were randomized to YERVOY~~/placebo was~~ administered at a dose of 3 mg/kg as an intravenous infusion every 3 weeks for 4 doses with an investigational peptide vaccine with incomplete Freund's adjuvant – gp100~~. Gp100/placebo was~~ administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for 4 doses~~.~~; gp100 administered at a dose of 2 mg by deep subcutaneous injection every 3 weeks for 4 doses as a single agent with a placebo; or YERVOY administered at a dose of 3 mg/kg by intravenous infusion every 3 weeks for 4 doses with a placebo. ~~Assessment of tumor response was conducted at weeks 12 and 24, and every 3 months thereafter. Patients with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.~~

The major efficacy outcome measure was overall survival (OS) in the YERVOY ~~plus~~ and gp100 arm compared to that in the single agent gp100 arm. Secondary efficacy outcome measures were OS in the YERVOY and ~~plus~~ gp100 arm compared to the YERVOY arm, OS in the YERVOY arm compared to the gp100 arm, best overall response rate (BORR) as assessed by the investigator at week 24 between each of the trial arms, and duration of response. Assessment of tumor response was conducted at weeks 12 and 24, and every 3 months thereafter. Patients with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

A total of 676 patients were randomized, 403 to YERVOY and gp100 arm, 137 to YERVOY single agent arm and 136 to gp100 single agent arm. Of the randomized patients, 61%, 59%, and 54% in the YERVOY ~~plus~~ and gp100, YERVOY, and gp100 arms, respectively, were ~~men~~male. Twenty-nine percent were ≥65 years of age, the median age was 57 years, 71% had M1c stage, 12% had a history of previously treated brain metastasis, 98% had ECOG performance status of 0 and 1, 23% had received aldesleukin, and 38% had elevated LDH level. Sixty-one percent of patients randomized to either YERVOY-containing arm received all 4 planned doses. The median duration of follow-up was 8.9 months.

The ~~OS~~ efficacy results are shown in Table ~~4~~ 12 and Figure 1.

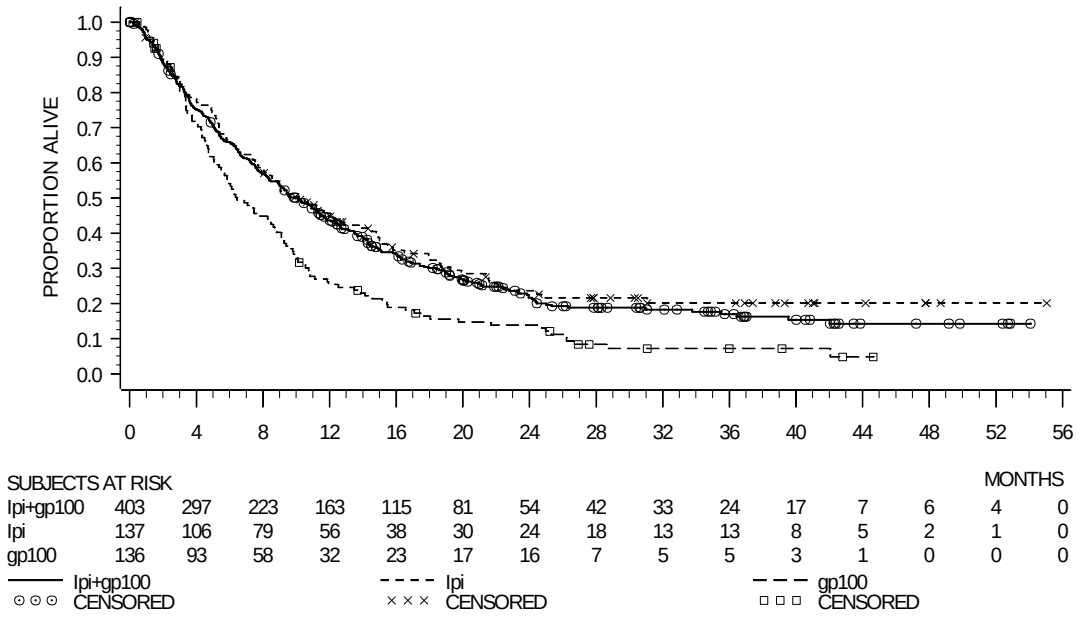
Table 412: Overall Survival Efficacy Results for Study MDX010-20

	YERVOY 3 mg/kg n=137	YERVOY 3 mg/kg + and gp 100 n=403	gp100 n=136
Overall Survival			
Median in months (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)
Hazard Rratio (vs. gp100) (95% CI) p-value	0.66 (0.51, 0.87) p=0.0026[a]	0.68 (0.55, 0.85) p=0.0004	
Hazard Ratio ratio (vs. YERVOY) (95% CI)		1.04 (0.83, 1.30)	
Median (months) **Best Overall Response Rate (BORR)** (95% CI)	10.9% (6.3%, 17.4%)10 (8.0, 13.8)	5.7% (3.7%, 8.4%)10 (8.5, 11.5)	1.5% (0.2%, 5.2%)6 (5.5, 8.7)
Median duration of response in months	NR[b]	11.5	NR[b]

[a] Not adjusted for multiple comparisons.

[b] Not reached

Figure 1: Kaplan Meier Curves for Overall Survival in Study MDX010-20



~~The best overall response rate (BORR) as assessed by the investigator was 5.7% (95% CI: 3.7%, 8.4%) in the YERVOY plus gp100 arm, 10.9% (95% CI: 6.3%, 17.4%) in the YERVOY arm, and 1.5% (95% CI: 0.2%, 5.2%) in the gp100 arm. The median duration of response was~~

~~11.5 months in the YERVOY plus gp100 arm and has not been reached in the YERVOY or gp100 arm.~~

14.2 Advanced Renal Cell Carcinoma

The efficacy of YERVOY with nivolumab was evaluated in CHECKMATE-214 (NCT02231749), a randomized (1:1), open-label study in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were randomized to nivolumab 3 mg/kg and YERVOY 1 mg/kg administered intravenously every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every two weeks or to sunitinib administered orally 50 mg daily for the first 4 weeks of each 6-week cycle. Treatment continued until disease progression or unacceptable toxicity. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region. The major efficacy outcome measures were OS, PFS (IRRC-assessed), and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. Intermediate/poor risk patients had at least 1 or more of 6 prognostic risk factors as per the IMDC criteria: less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status (KPS) <80%, hemoglobin less than the lower limit of normal, corrected calcium >10 mg/dL, platelet count > ULN, and absolute neutrophil count > ULN.

A total of 847 patients were randomized, 425 to YERVOY with nivolumab and 422 to sunitinib. The median age was 61 years (range: 21 to 85) with 38% ≥65 years of age and 8% ≥75 years of age. The majority of patients were male (73%) and White (87%) and 26% and 74% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

Efficacy results from CHECKMATE-214 are presented in Table 13 and Figure 2. In intermediate/poor risk patients, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to YERVOY and nivolumab arm as compared with sunitinib arm. OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS.

Table 13: Efficacy Results for CHECKMATE-214

Efficacy Parameter	**Intermediate/Poor-Risk**	
	YERVOY 1 mg/kg and Nivolumab n=425	**Sunitinib n=422**
Overall Survival		
Number of deaths	140 (32.9%)	188 (44.5%)
Median in months	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	
Confirmed Objective Response Rate (95% CI)	41.6% (36.9%, 46.5%)	26.5% (22.4%, 31.0%)
Complete Response	40 (9.4%)	5 (1.2%)
Partial Response	137 (32.2%)	107 (25.4%)
Median duration of response in months (95% CI)	NE (21.8, NE)	18.2 (14.8, NE)

Table 13: Efficacy Results for CHECKMATE-214

Efficacy Parameter	Intermediate/Poor-Risk	
	YERVOY 1 mg/kg and Nivolumab n=425	Sunitinib n=422
p-value[d,e]	<0.0001	
Progression-free Survival		
Number of events (progression or death)	228 (53.6%)	228 (54.0%)
Median in months	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[b]	NS[f]	

[a] Based on a stratified proportional hazards model.

[b] Based on a stratified log-rank test.

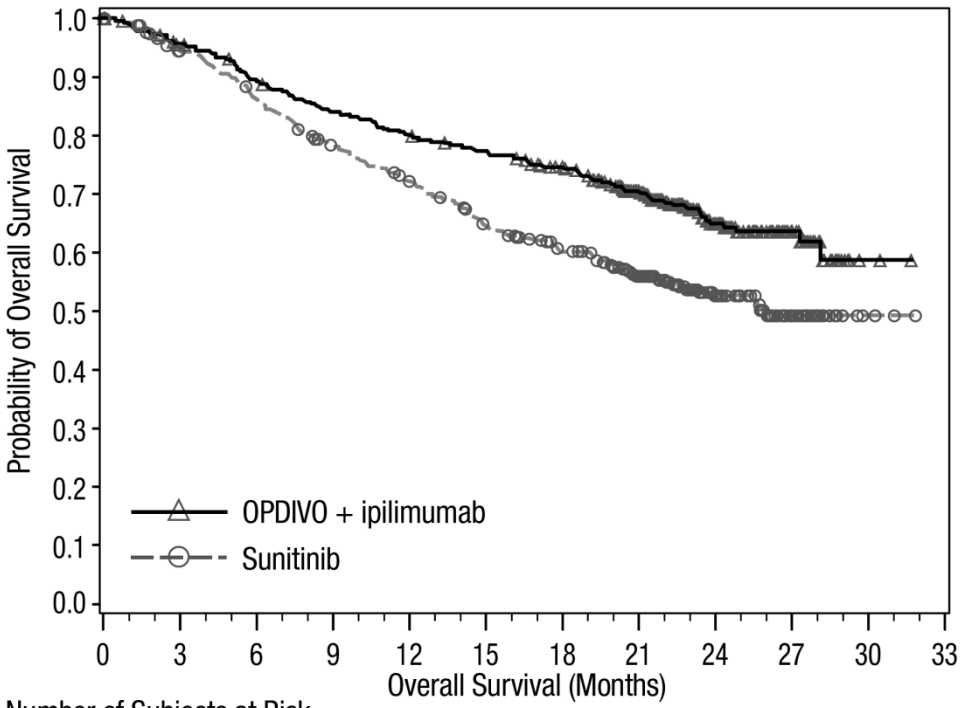
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.

[d] Based on the stratified DerSimonian-Laird test.

[e] p-value is compared to alpha 0.001 in order to achieve statistical significance.

[f] Not Significant at alpha level of 0.009

Figure 2: Kaplan-Meier Curves for Overall Survival (Intermediate/Poor Risk Population) in CHECKMATE-214



Number of Subjects at Risk

OPDIVO + ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to nivolumab and YERVOY (n=125) or to sunitinib (n=124). These patients were not evaluated as part of the efficacy analysis population. OS in favorable risk patients receiving nivolumab and YERVOY compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of nivolumab and YERVOY in previously untreated renal cell carcinoma with favorable risk disease has not been established.

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

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 14.

Table 14: 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

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 15.

Table 15: 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.

14.5 Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic or Recurrent NSCLC: In Combination with Nivolumab and Platinum-Doublet Chemotherapy

CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with stable brain metastases were eligible for enrollment.

Patients were randomized 1:1 to receive either:

- YERVOY 1 mg/kg administered intravenously over 30 minutes every 6 weeks, nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks, and

platinum-doublet chemotherapy administered intravenously every 3 weeks for 2 cycles, or

- platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

Platinum-doublet chemotherapy consisted of either carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m^2, or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m^2 for squamous NSCLC. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy. Stratification factors for randomization were tumor PD-L1 expression level (≥1% versus <1% or non-quantifiable), histology (squamous versus non-squamous), and sex (male versus female). Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse reaction attributed to YERVOY were permitted to continue nivolumab as a single agent as part of the study. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

A total of 719 patients were randomized to receive either YERVOY in combination with nivolumab and platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy (n=358). The median age was 65 years (range: 26 to 86) with 51% of patients ≥65 years and 10% of patients ≥75 years. The majority of patients were White (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% had tumors with PD-L1 expression ≥1% and 37% had tumors with PD-L1 expression that was <1%, 32% had tumors with squamous histology and 68% had tumors with non-squamous histology, 17% had CNS metastases, and 86% were former or current smokers.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR. Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) are presented in Table 16.

Table 16: Efficacy Results - CHECKMATE-9LA

	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy (n=361)	**Platinum-Doublet Chemotherapy (n=358)**
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)

Table 16: Efficacy Results - CHECKMATE-9LA

	YERVOY and Nivolumab and Platinum-Doublet Chemotherapy (n=361)	Platinum-Doublet Chemotherapy (n=358)
Median (months) (95% CI)	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Progression-free Survival per BICR		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Median (months)[d] (95% CI)	6.8 (5.6, 7.7)	5.0 (4.3, 5.6)
Overall Response Rate per BICR (%)	38	25
(95% CI)[e]	(33, 43)	(21, 30)
Stratified CMH test p-value[f]	0.0003	
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

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

[b] p-value is compared with the allocated alpha of 0.033 for this interim analysis.

[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.

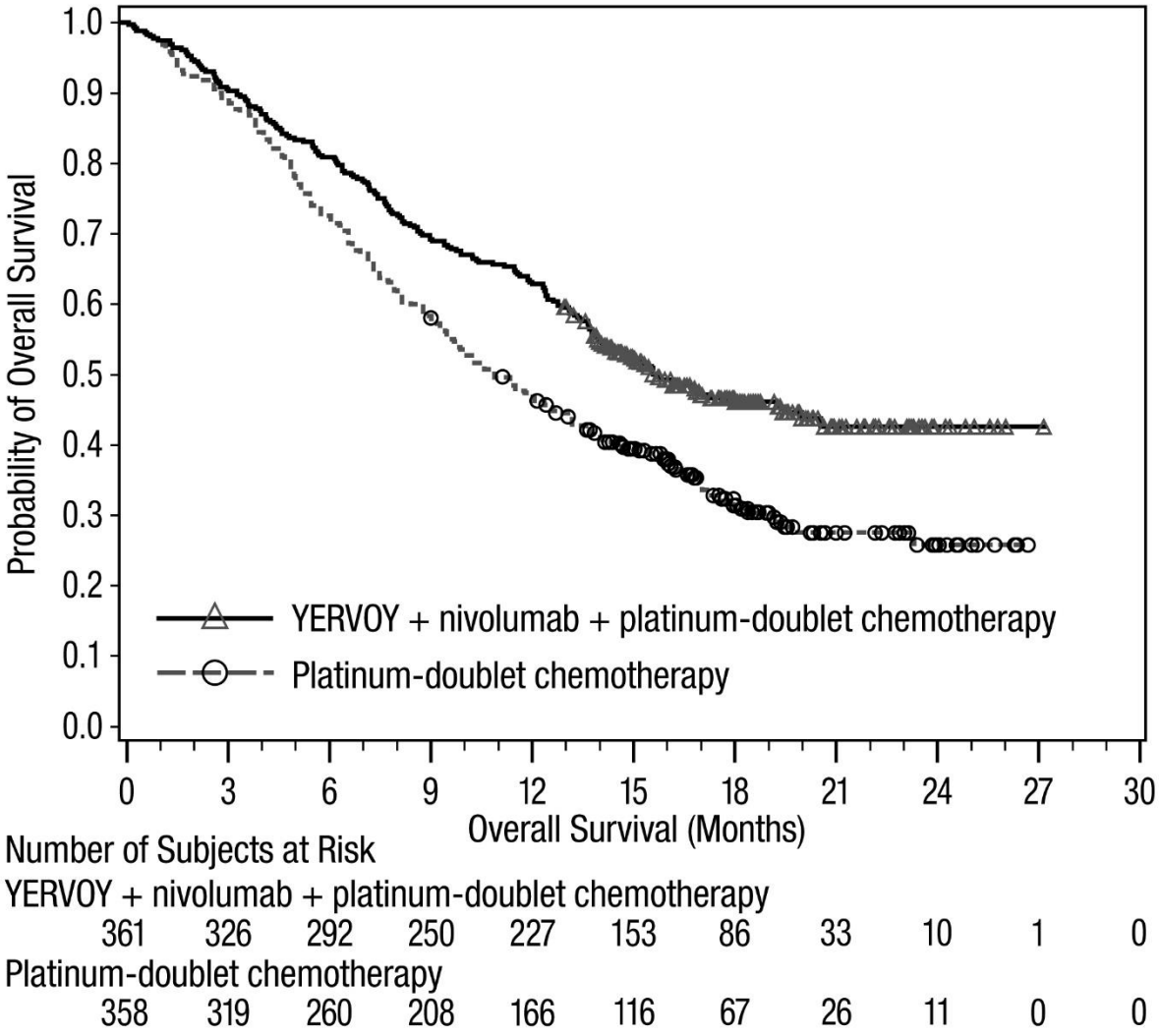
[d] Kaplan-Meier estimate.

[e] Confidence interval based on the Clopper and Pearson Method.

[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.

With an additional 4.6 months of follow-up the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving YERVOY and nivolumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 3).

Figure 3: Overall Survival - CHECKMATE-9LA



16 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY (ipilimumab) i~~I~~njection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow liquid that may contain light (few) particulates. YERVOY is available as follows:

Carton Contents
One 50 mg vial (5 mg/mL), single-~~use~~ dose vial
One 200 mg vial (5 mg/mL), single-~~use~~ dose vial

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