CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125377Orig1s106

Trade Name: **YERVOY**

Generic or Proper Name: ipilimumab

Sponsor: ***Bristol-Myers Squibb Company***

Approval Date: 06/29/2020

Indication:

YERVOY is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for:

Melanoma

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older.
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

Renal Cell Carcinoma (RCC)

- Treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab.

Colorectal Cancer

- Treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Hepatocellular Carcinoma

- Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Non-Small Cell Lung Cancer (NSCLC)

- Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab.
- Treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy.

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APPROVAL LETTER

U.S. FOOD & DRUG ADMINISTRATION

BLA 125377/S-106

BLA APPROVAL

Bristol-Myers Squibb Company
Attention: Noemi Guma, Ph.D.
Director, Global Regulatory and Safety Sciences
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Dr. Guma:

Please refer to your supplemental biologics license application (sBLA), dated and received May 2, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Yervoy (ipilimumab) injection, for intravenous use.

We also refer to our approval letter dated June 29, 2020 which contained the following error:

- formatting errors and inconsistencies including outline numbering and text bolding in the Medication Guide.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain June 29, 2020, the date of the original approval letter.

This Prior Approval supplemental biologics application provides for the following changes to the Prescribing Information (PI):

- Removal of the boxed warning for immune-mediated adverse reactions (IMARs);
- Updates to Section 2.5 Recommended Dose Modifications for Adverse Reactions;
- Major reorganization of Section 5 WARNINGS AND PRECAUTIONS to consolidate all the IMARs into one warning;
- Revisions to Efficacy tables in Section 14 CLINICAL STUDIES were consolidated to include all efficacy results for a specific study;
- Additional changes to language in the package insert for consistency and to update based on current regulations, recommendations and labeling practices.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Norma Griffin, Lead Regulatory Health Project Manager, at 301-796-4255.

Sincerely,

{See appended electronic signature page}

Jeffrey Summers, MD
Associate Director for Translational Sciences
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JEFFERY L SUMMERS
06/29/2020 12:00:00 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YERVOY safely and effectively. See full prescribing information for YERVOY.

YERVOY® (ipilimumab) injection, for intravenous use
Initial U.S. Approval: 2011

----------RECENT MAJOR CHANGES----------

Boxed Warning, Removed	6/2020
Indications and Usage (1)	5/2020
Dosage and Administration (2)	6/2020
Warnings and Precautions (5)	6/2020

----------INDICATIONS AND USAGE----------

YERVOY is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for:

Melanoma

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older. (1.1)
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy. (1.2)

Renal Cell Carcinoma (RCC)

- Treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab. (1.3)

Colorectal Cancer

- Treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.4)

Hepatocellular Carcinoma

- Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.5)

Non-Small Cell Lung Cancer (NSCLC)

- Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab. (1.6)
- Treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy. (1.6)

----------DOSAGE AND ADMINISTRATION----------

- Administer by intravenous infusion based upon recommended infusion rate for each indication. (2)
- Unresectable or Metastatic Melanoma: YERVOY 3 mg/kg every 3 weeks for a maximum of 4 doses. (2.1)
- Adjuvant Treatment of Melanoma: YERVOY 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years. (2.2)
- Advanced Renal Cell Carcinoma: YERVOY 1 mg/kg immediately following nivolumab 3 mg/kg on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.3)
- Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer: YERVOY 1 mg/kg intravenously over 30 minutes immediately following nivolumab 3 mg/kg intravenously over 30 minutes on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.4)
- Hepatocellular Carcinoma: YERVOY 3 mg/kg intravenously over 30 minutes immediately following nivolumab 1 mg/kg intravenously over 30 minutes on the same day, every 3 weeks for 4 doses. After completion 4 doses of the combination, administer nivolumab as a single agent as recommended in Full Prescribing Information for nivolumab. (2.5)
- Metastatic non-small cell lung cancer:
  - Nivolumab 3 mg/kg every 2 weeks with YERVOY 1 mg/kg every 6 weeks. (2.7)
  - Nivolumab 360 mg every 3 weeks with YERVOY 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy. (2.7)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Severe and Fatal Immune-Mediated Adverse Reactions: Immune-mediated adverse reactions (IMAR) can occur in any organ system or tissue, including the following: immune-mediated colitis, immune-mediated hepatitis, immune-mediated dermatologic adverse reactions, immune-mediated endocrinopathies, immune-mediated pneumonitis, and immune-mediated nephritis with renal dysfunction, and can occur at any time during treatment or after discontinuation. Monitor for symptoms and signs that may be clinical manifestations of IMAR. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function at baseline and before each dose. In general, withhold YERVOY for severe (grade 3) and permanently discontinue for life-threatening (grade 4) immune-mediated adverse reactions. See Full Prescribing Information for additional dosage modifications. (2.5, 5.1)
- Infusion-Related Reactions: Discontinue for severe and life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. (2.5, 5.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥5%) with YERVOY as a single agent are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia. (6.1)

Most common adverse reactions (≥20%) with YERVOY in combination with nivolumab are fatigue, rash, pruritus, diarrhea, musculoskeletal pain, cough, pyrexia, decreased appetite, nausea, abdominal pain, arthralgia, headache, vomiting, dyspnea, dizziness, hypothyroidism, and decreased weight. (6.1)

Most common adverse reactions (≥20%) with YERVOY in combination with nivolumab and platinum-doublet chemotherapy are fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2020

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- 1.2 Adjuvant Treatment of Melanoma
- 1.3 Advanced Renal Cell Carcinoma
- 1.4 Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer
- 1.5 Hepatocellular Carcinoma
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- 2.3 Recommended Dosage for Adjuvant Treatment of Melanoma
- 2.4 Recommended Dosage for Advanced Renal Cell Carcinoma

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* Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

YERVOY is indicated for the treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older.

1.2 Adjuvant Treatment of Melanoma

YERVOY is indicated for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

1.3 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).

1.4 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 and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.4)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.5 Hepatocellular Carcinoma

YERVOY, in combination with nivolumab, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.5)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.6 Metastatic Non-Small Cell Lung Cancer

YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with no EGFR or ALK genomic tumor aberrations.

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 NSCLC, with no EGFR or ALK genomic tumor aberrations.

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2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with metastatic NSCLC for treatment with YERVOY in combination with nivolumab based on PD-L1 expression *[see Clinical Studies (14.6)]*.

Information on FDA-approved tests for the determination of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage for Unresectable or Metastatic Melanoma

The recommended dosage of YERVOY is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a maximum of 4 doses.

2.3 Recommended Dosage for Adjuvant Treatment of Melanoma

The recommended dosage of YERVOY is 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses followed by 10 mg/kg every 12 weeks for up to 3 years.

2.4 Recommended Dosage for Advanced Renal Cell Carcinoma

The recommended dosage of YERVOY is 1 mg/kg administered intravenously over 30 minutes, immediately following nivolumab 3 mg/kg administered intravenously over 30 minutes on the same day, every 3 weeks for up to 4 doses or until intolerable toxicity or disease progression. After completing 4 doses of the combination, administer nivolumab as a single agent. Review the Prescribing Information for nivolumab for dosage information.

2.5 Recommended Dosage for MSI-H or dMMR Metastatic Colorectal Cancer

The recommended dosage of YERVOY is 1 mg/kg administered intravenously over 30 minutes, immediately following nivolumab 3 mg/kg administered intravenously over 30 minutes on the same day, every 3 weeks for up to 4 doses or until intolerable toxicity or disease progression. After completing 4 doses of the combination, administer nivolumab as a single agent. Review the Prescribing Information for nivolumab for dosage information.

2.6 Recommended Dosage for Hepatocellular Carcinoma

The recommended dosage of YERVOY is 3 mg/kg administered intravenously over 30 minutes, immediately following nivolumab 1 mg/kg administered intravenously over 30 minutes on the same day, every 3 weeks for up to 4 doses or until intolerable toxicity or disease progression. After completing 4 doses of the combination, administer nivolumab as a single agent. Review the Prescribing Information for nivolumab for dosage information.

2.7 Recommended Dosing for Metastatic NSCLC

The recommended dose of YERVOY in combination with nivolumab is nivolumab 3 mg/kg administered as an intravenous infusion over 30 minutes every 2 weeks and YERVOY 1 mg/kg administered as an intravenous infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression *[see Clinical*

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Studies (14.6)]. Review the Prescribing Information for nivolumab for recommended dosing information.

The recommended dose of YERVOY in combination with nivolumab and platinum-doublet chemotherapy is nivolumab 360 mg administered as an intravenous infusion over 30 minutes every 3 weeks and YERVOY 1 mg/kg administered as an intravenous infusion over 30 minutes every 6 weeks and **histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles** until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression *[see Clinical Studies (14.6)]*. Review the Prescribing Information for nivolumab and platinum-based chemotherapy for recommended dosing information.

2.8 Recommended Dosage Modifications for Adverse Reactions

No dose reduction for YERVOY is recommended. In general, withhold YERVOY for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue YERVOY for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, persistent moderate (Grade 2) or severe (Grade 3) reactions lasting 12 weeks or longer after last YERVOY dose (excluding endocrinopathy), or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids. Dosage modifications for YERVOY for adverse reactions that require management different from these general guidelines are summarized in Table 1.

When YERVOY is administered in combination with nivolumab, withhold or permanently discontinue both YERVOY and nivolumab for toxicity.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity***	**YERVOY Dosage Modifications**
Immune-Mediated Adverse Reactions *[See Warnings and Precautions (5.1)]*		
Colitis/diarrhea	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Hepatitis[b]	AST or ALT more than 3 times and up to 5 times the ULN or Total bilirubin more than 1.5 times and up to 3 times the ULN	Withhold[a]
	AST or ALT more than 5 times the ULN or Total bilirubin more than 3 times the ULN	Permanently discontinue
Exfoliative or Bullous Dermatologic	Grade 2	Withhold until specialist

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Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	YERVOY Dosage Modifications
Conditions		assessment
	Grade 3 or 4	Permanently discontinue
Endocrinopathies	Grades 2, 3, or 4	Withhold if not clinically stable
Hypophysitis[d]	Grade 2, 3, or 4	Withhold[e]
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Neurological Toxicities[c]	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Myocarditis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Ophthalmologic	Grade 2, 3, or 4 that does not improve to Grade 1 within 2 weeks while receiving topical therapy or that requires systemic treatment	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

* Graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4).

[a] Resume in patients with complete or partial resolution (Grade 0 or 1) after corticosteroid taper.

[b] Resume YERVOY when AST/ALT returns to baseline.

[c] Permanently discontinue YERVOY if signs of encephalitis or respiratory insufficiency due to neurological toxicity regardless of grade.

[d] Signs of mass effect, including headache, photophobia, or visual field cuts.

[e] Resume YERVOY when acute symptoms have resolved.

2.9 Preparation and Administration

- Do not shake product.
- Visually inspect for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

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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 a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- After preparation, store the diluted solution either refrigerated at 2°C to 8°C (36°F to 46°F) or at room temperature of 20°C to 25°C (68°F to 77°F) for no more than 24 hours from the time of preparation to the time of infusion.
- Discard partially used or empty vials of YERVOY.

Administration

- Do not co-administer other 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 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 200 mg/40 mL (5 mg/mL) as a clear to slightly opalescent, colorless to pale-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

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.

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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 (2.6)]*. 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 reaction is not controlled with corticosteroid therapy. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-Mediated Diarrhea or Colitis

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

YERVOY 3 mg/kg as a Single Agent

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

YERVOY 10 mg/kg as a Single Agent

Immune-mediated diarrhea/colitis occurred in 31% (144/471) of patients who received YERVOY 10 mg/kg as a single agent, including fatal (0.2%), Grade 4 (1.5%), Grade 3 (14%), and Grade 2 (14%). Diarrhea/colitis led to permanent discontinuation of YERVOY in 61% of patients and 3.8% of patients missed at least one dose of YERVOY due to diarrhea/colitis.

Systemic corticosteroids were required in 85% (123/144) of patients with immune-mediated diarrhea/colitis. Approximately 26% of the 144 patients required coadministration of another immunosuppressant with corticosteroids. Diarrhea/colitis resolved in 90% of the 144 patients. Of the 18 patients who missed one or more doses of YERVOY for diarrhea/colitis, 17 received additional treatment after symptom improvement; of these, 14 had recurrence of diarrhea/colitis.

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YERVOY 1 mg/kg with Nivolumab

Immune-mediated diarrhea/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%). Diarrhea/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 diarrhea/colitis. Systemic corticosteroids were therefore required in 100% (60/60) of patients with immune-mediated diarrhea/colitis. Approximately 23% of patients required coadministration of another immunosuppressant with corticosteroids. Diarrhea/colitis resolved in 95% of the 60 patients. Of the 18 patients in whom YERVOY or nivolumab was withheld for diarrhea/colitis, 16 received additional treatment after symptom improvement; of these, 10 had recurrence of diarrhea/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.

<u>Immune-Mediated Hepatitis</u>

YERVOY 3 mg/kg as a Single Agent

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 10 mg/kg as a Single Agent

Immune-mediated hepatitis occurred in 15% (73/471) of patients who received YERVOY 10 mg/kg as a single agent, including Grade 4 (2.8%), Grade 3 (8%), and Grade 2 (5%). Hepatitis led to permanent discontinuation of YERVOY in 56% of patients and 1.1% of patients missed at least one dose of YERVOY due to hepatitis.

Systemic corticosteroids were required in 85% (62/73) of patients with immune-mediated hepatitis. Approximately 15% of the 73 patients required the coadministration of another immunosuppressant with corticosteroids. Hepatitis resolved in 93% of 73 patients. Of the 5

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patients who missed one or more doses of YERVOY for hepatitis, 5 received additional treatment after symptom improvement; of these, 1 had recurrence of hepatitis.

YERVOY 3 mg/kg 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 or 720 mg 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.

<u>Immune-Mediated Dermatologic Adverse Reactions</u>

YERVOY can cause immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson Syndrome and toxic epidermal necrolysis (TEN). 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 (2.6)]*.

YERVOY 3 mg/kg as a Single Agent

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

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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 10 mg/kg as a Single Agent

Immune-mediated rash occurred in 25% (118/471) of patients who received YERVOY 10 mg/kg as a single agent, including Grade 3 (4%) and Grade 2 (21%). Rash led to permanent discontinuation in 8% of patients and 1.5% of patients missed at least one dose of YERVOY due to rash.

Systemic corticosteroids were required in 70% (83/118) of patients with immune-mediated rash. Rash resolved in 81% of 118 patients. Of the 7 patients who missed one or more doses of YERVOY for rash, 5 received additional treatment after symptom improvement; of these, 3 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.

<u>Immune-Mediated Endocrinopathies</u>

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.

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

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 required long-term hormone replacement therapy, including adrenal hormones (n=10) and thyroid hormones (n=13).

YERVOY 10 mg/kg as a Single Agent

Immune-mediated endocrinopathies occurred in 28% of patients (132/471), including Grade 4 (0.6%), Grade 3 (8%) and Grade 2 (20%).

Of the 39 patients with Grade 3 to 4 endocrinopathies, 35 patients had hypopituitarism (associated with one or more secondary endocrinopathies, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism), 3 patients had hyperthyroidism, and 1 had primary hypothyroidism. Twenty-seven of the 39 patients (69%) were hospitalized for endocrinopathies. Of the 39 patients, 10% were reported to have resolution.

Of the 93 patients with Grade 2 endocrinopathy, 74 had primary hypopituitarism associated with one or more secondary endocrinopathy, e.g., adrenal insufficiency, hypogonadism, and hypothyroidism, 9 had primary hypothyroidism, 3 had hyperthyroidism, 3 had thyroiditis with hypo- or hyperthyroidism, 2 had hypogonadism, 1 had both hyperthyroidism and hypopituitarism, and 1 subject developed Graves' ophthalmopathy. Of the 93 patients, 20% were reported to have resolution.

One hundred twenty-four patients received systemic corticosteroids as immunosuppression and/or adrenal hormone replacement for Grade 2 to 4 endocrinopathy. Of these, 42 (34%) were able to discontinue corticosteroids. Seventy-three patients received thyroid hormones for treatment of Grade 2 to 4 hypothyroidism. Of these, 14 patients (19%) were able to discontinue thyroid replacement therapy.

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 (2.6)]*.

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

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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.

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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.

<u>Immune-Mediated Pneumonitis</u>

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.

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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.

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks, including Grade 4 (0.5%), Grade 3 (3.5%), and Grade 2 (4.0%) immune-mediated pneumonitis. Four patients (0.7%) died due to pneumonitis. The median duration was 1.5 months (range: 5 days to 25+ months). Immune-mediated pneumonitis led to permanent discontinuation of YERVOY with nivolumab in 5% of patients and withholding of YERVOY with nivolumab in 3.6% of patients.

Systemic corticosteroids were required in 100% of patients with pneumonitis followed by a corticosteroid taper. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after re-initiation of YERVOY with nivolumab.

The incidence and severity of immune-mediated pneumonitis in patients with NSCLC treated with YERVOY 1 mg/kg every 6 weeks in combination with nivolumab 360 mg every 3 weeks and 2 cycles of platinum-doublet chemotherapy were comparable to treatment with YERVOY in combination with nivolumab only.

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.

<u>Immune-Mediated Nephritis with Renal Dysfunction</u>

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

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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.

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

5.2 Infusion-Related Reactions

Severe infusion-related reactions can occur 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 (2.6)]*. Infusion-related reactions occurred in 2.9% (28/982) of patients who received single-agent YERVOY 3 mg/kg or 10 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.

5.3 Complications of Allogenic Hematopoietic Stem Cell Transplant after YERVOY

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive YERVOY either before or after allogeneic hematopoietic stem cell transplantation (HSCT). These

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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 (6.2)]*. Consider the benefit versus risks of treatment with YERVOY after allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, YERVOY can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight) and higher incidences of infant mortality in a dose-related manner. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.5 Risks Associated When Administered in Combination with Nivolumab

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

6 ADVERSE REACTIONS

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

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

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

The data described 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; YERVOY 10 mg/kg as a single agent in 471 patients in Study CA184-029; YERVOY 1 mg/kg administered with nivolumab 3 mg/kg in 1,062 patients in CHECKMATE-214, CHECKMATE-142, and CHECKMATE-227; 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.

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Unresectable or Metastatic Melanoma

The safety of YERVOY was evaluated in 643 previously treated patients with unresectable or metastatic melanoma in Study MDX010-20 *[see Clinical Studies (14.1)]*. 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, and baseline ECOG performance status 0 (56%).

YERVOY was discontinued for adverse reactions in 10% of patients. Table 2 presents adverse reactions from Study MDX010-20.

Table 2: 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

Adjuvant Treatment of Melanoma

The safety of YERVOY was evaluated in 945 patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma in Study CA184-029 *[see Clinical Studies (14.2)]*. Study CA184-029 excluded patients with prior systemic therapy for melanoma, autoimmune disease, a condition requiring systemic immunosuppression, or a positive test for hepatitis B, hepatitis C, or HIV. Patients received YERVOY 10 mg/kg (n=471) or placebo (n=474) administered as an intravenous infusion for 4 doses every 3 weeks followed by 10 mg/kg every 12 weeks beginning at Week 24 up to a maximum of 3 years. In this trial, 36% of patients received YERVOY for longer than 6 months and 26% of patients received YERVOY for longer than 1 year. YERVOY-treated patients in the trial received a median of 4 doses (range: 1 to 16).

The trial population characteristics were: median age 51 years (range: 18 to 84 years), 62% male, 99% White, and baseline ECOG performance status 0 (94%).

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YERVOY was discontinued for adverse reactions in 52% of patients. Table 3 presents selected adverse reactions from Study CA184-029.

Table 3: Adverse Reactions (≥ 5%) in Patients Receiving YERVOY with a Difference Between Arms >5% Compared to Placebo in Study CA184-029

Adverse Reaction	YERVOY 10 mg/kg n=471		Placebo n=474	
	All Grades (%)	Grade 3 to 5 (%)	All Grades (%)	Grade 3 to 5 (%)
Dermatologic				
Rash	50	2.1	20	0
Pruritus	45	2.3	15	0
Gastrointestinal				
Diarrhea	49	10	30	2.1
Nausea	25	0.2	18	0
Colitis	16	8	1.5	0.4
Vomiting	13	0.4	6	0.2
General and Administration-Site Conditions				
Fatigue	46	2.3	38	1.5
Weight Decreased	32	0.2	9	0.4
Pyrexia	18	1.1	4.9	0.2
Nervous System				
Headache	33	0.8	18	0.2
Metabolism and Nutrition				
Decreased Appetite	14	0.2	3.4	0.2
Psychiatric				
Insomnia	10	0	4.4	0

Table 4 presents selected laboratory abnormalities from Study CA184-029.

Table 4: Laboratory Abnormalities (>5%) Worsening from Baseline in Patients Receiving YERVOY with a Difference Between Arms of >5% Compared to Placebo in CA184-029[a]

Laboratory Abnormality	YERVOY 10 mg/kg[a]		Placebo[a]	
	All Grades (%)	Grade 3 to 4 (%)	All Grades (%)	Grade 3 to 4 (%)
Chemistry				
Increased ALT	46	10	16	0
Increased AST	38	9	14	0.2
Increased lipase	26	9	17	4.5
Increased amylase	17	2.0	7	0.6
Increased alkaline phosphatase	17	0.6	6	0.2
Increased bilirubin	11	1.5	9	0
Increased creatinine	10	0.2	6	0
Hematology				
Decreased hemoglobin	25	0.2	14	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. Excluding lipase and amylase, YERVOY group (range: 466 to 470 patients) and placebo group (range: 472 to 474 patients). For lipase and amylase, YERVOY group (range: 447 to 448 patients) and placebo group (range: 462 to 464 patients).

Reference ID: 4633244

Other Clinical Experience

Across clinical studies in which patients received YERVOY as a single agent at doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were also reported (incidence <1% unless otherwise noted): urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

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%) of in the YERVOY and nivolumab arm were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, vomiting, dyspnea, and decreased appetite. Table 5 summarizes adverse reactions in CHECKMATE-214.

Table 5: Adverse Reactions (>15%) in Patients Receiving YERVOY with Nivolumab in CHECKMATE-214

Adverse Reaction	YERVOY 1 mg/kg with 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

Reference ID: 4633244

Table 5: Adverse Reactions (>15%) in Patients Receiving YERVOY with Nivolumab in CHECKMATE-214

Adverse Reaction	YERVOY 1 mg/kg with Nivolumab n=547		Sunitinib n=535	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
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 6 summarizes the laboratory abnormalities in CHECKMATE-214.

Table 6: Laboratory Abnormalities (>15%) Worsening from Baseline in Patients Receiving YERVOY with Nivolumab in CHECKMATE-214

Laboratory Abnormality	YERVOY 1 mg/kg with 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

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Table 6: Laboratory Abnormalities (>15%) Worsening from Baseline in Patients Receiving YERVOY with Nivolumab in CHECKMATE-214

Laboratory Abnormality	YERVOY 1 mg/kg with Nivolumab[a]		Sunitinib[a]	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
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 7 summarizes adverse reactions in CHECKMATE-142.

Table 7: Adverse Reactions Occurring in ≥10% of Patients (CHECKMATE-142)

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

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Table 7: Adverse Reactions Occurring in ≥10% of Patients (CHECKMATE-142)

	YERVOY plus Nivolumab MSI-H/dMMR Cohort (n=119)	
	Percentage (%) of Patients	
Adverse Reaction	**All Grades**	**Grades 3-4**
Diarrhea	45	3.4
Abdominal pain[c]	30	5
Nausea	26	0.8
Vomiting	20	1.7
Constipation	15	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	36	3.4
Arthralgia	14	0.8
Skin and Subcutaneous Tissue Disorders		
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 Disorders		
Decreased appetite	20	1.7
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	19	0.8
Dyspnea	13	1.7
Nervous System Disorders		
Headache	17	1.7
Dizziness	11	0
Endocrine Disorders		
Hyperglycemia	6	1
Hypothyroidism	14	0.8
Hyperthyroidism	12	0

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Table 7: Adverse Reactions Occurring in ≥10% of Patients (CHECKMATE-142)

	YERVOY plus Nivolumab MSI-H/dMMR Cohort (n=119)	
	Percentage (%) of Patients	
Adverse Reaction	**All Grades**	**Grades 3-4**
Investigations		
Weight decreased	10	0
Psychiatric Disorders		
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 8 summarizes laboratory abnormalities in CHECKMATE-142.

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Table 8: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients (CHECKMATE-142)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]	
	YERVOY plus 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

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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 9 summarizes the adverse reactions and Table 10 summarizes the laboratory abnormalities of YERVOY in combination with nivolumab in CHECKMATE-040.

Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

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

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Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving YERVOY in Combination with Nivolumab in Cohort 4 of CHECKMATE-040

Adverse Reaction	YERVOY and Nivolumab (n=49)	
	All Grades (%)	Grades 3-4 (%)
Investigations		
Weight decreased	20	0
Psychiatric		
Insomnia	18	0
Blood and Lymphatic System		
Anemia	10	4
Infections		
Influenza	10	2
Vascular		
Hypotension	10	0

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

Table 10: 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

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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 NSCLC: In Combination with Nivolumab

The safety of YERVOY in combination with nivolumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.6)]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received YERVOY 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks and nivolumab 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in YERVOY and nivolumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received YERVOY and nivolumab for >6 months and 23% of patients received YERVOY and nivolumab for >1 year. The population characteristics were: median age 64 years (range: 26 to 87); 48% were ≥65 years of age, 76% White, and 67% male. Baseline ECOG performance status was 0 (35%) or 1 (65%), 85% were former/current smokers, 11% had brain metastases, 28% had squamous histology and 72% had non-squamous histology.

Serious adverse reactions occurred in 58% of patients. YERVOY and nivolumab were discontinued for adverse reactions in 24% of patients and 53% had at least one dose withheld for an adverse reaction.

The most frequent (≥2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Fatal adverse reactions occurred in 1.7% of patients; these included events of pneumonitis (4 patients), myocarditis, acute kidney injury, shock, hyperglycemia, multi-system organ failure, and renal failure. The most common (≥20%) adverse reactions were fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, hepatitis, nausea, and pruritus.

Tables 11 and 12 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 11: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-227

Adverse Reaction	YERVOY and Nivolumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema[b]	14	0.2	12	0.5

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Table 11: Adverse Reactions in ≥10% of Patients Receiving YERVOY and Nivolumab - CHECKMATE-227

Adverse Reaction	YERVOY and Nivolumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[c]	34	4.7	10	0.4
Pruritus[d]	21	0.5	3.3	0
Metabolism and Nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[e]	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis[f]	26	3.6	16	0.9
Nausea	21	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	18	2.3
Abdominal pain[g]	10	0.2	9	0.7
Respiratory, Thoracic, and Mediastinal				
Dyspnea[h]	26	4.3	16	2.1
Cough[i]	23	0.2	13	0
Hepatobiliary				
Hepatitis[j]	21	9	10	1.2
Endocrine				
Hypothyroidism[k]	16	0.5	1.2	0
Hyperthyroidism[l]	10	0	0.5	0
Infections and Infestations				
Pneumonia[m]	13	7	8	4.0
Nervous System				
Headache	11	0.5	6	0

[a] Includes fatigue and asthenia.

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[b] Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.
[c] Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.
[d] Includes pruritus and pruritus generalized.
[e] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.
[f] Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.
[g] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.
[h] Includes dyspnea and dyspnea exertional.
[i] Includes cough and productive cough.
[j] Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased.
[k] Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.
[l] Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.
[m] Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, organizing pneumonia.

Other clinically important adverse reactions in CHECKMATE-227 were:

Skin and Subcutaneous Tissue: urticaria, alopecia, erythema multiforme, vitiligo

Gastrointestinal: stomatitis, pancreatitis, gastritis

Musculoskeletal and Connective Tissue: arthritis, polymyalgia rheumatica, rhabdomyolysis

Nervous System: peripheral neuropathy, autoimmune encephalitis

Blood and Lymphatic System: eosinophilia

Eye Disorders: blurred vision, uveitis

Cardiac: atrial fibrillation, myocarditis

Table 12: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on YERVOY and Nivolumab - CHECKMATE-227

Laboratory Abnormality	YERVOY and Nivolumab		Platinum-doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	46	3.6	78	14
Lymphopenia	46	5	60	15
Chemistry				

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Table 12: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on YERVOY and Nivolumab - CHECKMATE-227

Laboratory Abnormality	YERVOY and Nivolumab		Platinum-doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hyponatremia	41	12	26	4.9
Increased AST	39	5	26	0.4
Increased ALT	36	7	27	0.7
Increased lipase	35	14	14	3.4
Increased alkaline phosphatase	34	3.8	20	0.2
Increased amylase	28	9	18	1.9
Hypocalcemia	28	1.7	17	1.3
Hyperkalemia	27	3.4	22	0.4
Increased creatinine	22	0.9	17	0.2

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: YERVOY and nivolumab group (range: 494 to 556 patients) and chemotherapy group (range: 469 to 542 patients).

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.

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Tables 13 and 14 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 13: 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

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

[j] Includes dizziness, vertigo and positional vertigo

Table 14: 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 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 in the studies described below with the incidences of antibodies to 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 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 developed anti-ipilimumab antibodies and 7 (4.5%) of 156 patients receiving placebo for the adjuvant treatment of melanoma

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tested positive for anti-ipilimumab antibodies using an ECL assay with improved drug tolerance. No patients tested positive for neutralizing antibodies. No infusion-related reactions occurred in patients who tested positive for anti-ipilimumab antibodies.

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

Of 483 patients evaluable for anti-ipilimumab antibodies in CHECKMATE-227 Part 1, 8.5% were positive for treatment-emergent anti-ipilimumab antibodies. No patients had neutralizing antibodies against ipilimumab. In Part 1 of the same study, of 491 patients evaluable for anti-nivolumab antibodies, 36.7% were positive for anti-nivolumab antibodies and 1.4% had neutralizing antibodies against nivolumab.

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.

Immune System: graft-versus-host disease

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, YERVOY can cause fetal harm when administered to a pregnant woman. There is insufficient human data for YERVOY exposure in pregnant women. In animal reproduction studies, administration of ipilimumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner *(see Data)*. The effects of ipilimumab are likely to be greater during the second and third trimesters of pregnancy. Human IgG1 is known to cross the placental barrier and ipilimumab is an

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IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus. Report pregnancies to Bristol-Myers Squibb at 1-844-593-7869.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a combined study of embryo-fetal and peri-postnatal development, pregnant cynomolgus monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through parturition. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, administration of ipilimumab at doses resulting in exposures approximately 2.6 to 7.2 times the human exposure at a dose of 3 mg/kg resulted in dose-related increases in abortion, stillbirth, premature delivery (with corresponding lower birth weight), and an increased incidence of infant mortality. In addition, developmental abnormalities were identified in the urogenital system of 2 infant monkeys exposed in utero to 30 mg/kg of ipilimumab (7.2 times the humans exposure based on area under the curve at a dose of 3 mg/kg). One female infant monkey had unilateral renal agenesis of the left kidney and ureter, and 1 male infant monkey had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema.

Genetically engineered mice heterozygous for CTLA-4 (CTLA-4+/−), the target for ipilimumab, appeared healthy and gave birth to healthy CTLA-4+/− heterozygous offspring. Mated CTLA-4+/− heterozygous mice also produced offspring deficient in CTLA-4 (homozygous negative, CTLA-4−/−). The CTLA-4−/− homozygous negative offspring appeared healthy at birth, exhibited signs of multiorgan lymphoproliferative disease by 2 weeks of age, and all died by 3 to 4 weeks of age with massive lymphoproliferation and multiorgan tissue destruction.

8.2 Lactation

Risk Summary

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

Data

In monkeys treated at dose levels resulting in exposures 2.6 and 7.2 times higher than those in humans at a 3 mg/kg dose, ipilimumab was present in milk at concentrations of 0.1 mcg/mL and 0.4 mcg/mL, representing a ratio of up to 0.3% of the steady-state serum concentration of the drug.

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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

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.

8.4 Pediatric Use

The safety and effectiveness of YERVOY have been established in pediatric patients 12 years and older for the treatment of unresectable or metastatic melanoma or 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 3 mg/kg and 1 mg/kg in the pediatric and adult populations are comparable. In addition, the tumor biology and course of advanced melanoma and 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 adjuvant 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.

YERVOY was evaluated in a total of 45 pediatric patients across two clinical trials. In a dose-finding trial (NCT01445379), 33 pediatric patients with relapsed or refractory solid tumors were evaluated. The median age was 13 years (range 2 to 21 years) and 20 patients were ≥12 years old. YERVOY was also evaluated in an open-label, single-arm trial (NCT01696045) in 12 pediatric patients ≥12 years old (range 12 to 16 years) with previously treated or untreated, unresectable Stage 3 or 4 malignant melanoma. Of the 17 patients ≥12 years of age with melanoma treated with YERVOY across both studies, 2 patients experienced objective responses including one partial response that was sustained for 16 months. There were no responses in patients with non-melanoma solid tumors. No new safety signals were observed in pediatric patients in these two studies.

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 effectiveness were observed between these patients and younger patients.

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Study CA184-029 (adjuvant treatment of melanoma) and 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 576 patients randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks in CHECKMATE-227 (NSCLC), 48% 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 (29%) relative to all patients who received YERVOY with nivolumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to YERVOY 1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks with in CHECKMATE-227, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older *[see Clinical Studies (14.6)]*.

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.

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11 DESCRIPTION

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. Ipilimumab is a recombinant IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

YERVOY (ipilimumab) injection, for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-dose vials of 50 mg/10 mL or 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

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 (C_{min}) at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks.

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

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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 3 mg/kg every 2 weeks, the CL of ipilimumab increased by 30% compared to YERVOY administered alone and the CL of nivolumab was unchanged compared to nivolumab 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of ipilimumab has not been evaluated in long-term animal studies, and the genotoxic potential of ipilimumab has not been evaluated.

Fertility studies have not been performed with ipilimumab.

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

The efficacy of YERVOY were investigated in a Study MDX010-20, a randomized (3:1:1), double-blind, double-dummy trial (NCT00094653) that included patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. 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 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

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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. The major efficacy outcome measure was overall survival (OS) in the YERVOY and gp100 arm compared to that in the single-agent gp100 arm. Secondary efficacy outcome measures were OS in the YERVOY and 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 and gp100, YERVOY, and gp100 arms, respectively, were 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 efficacy results are shown in Table 15 and Figure 1.

Table 15: Efficacy Results for Study MDX010-20

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

[a] Not adjusted for multiple comparisons
[b] Not reached

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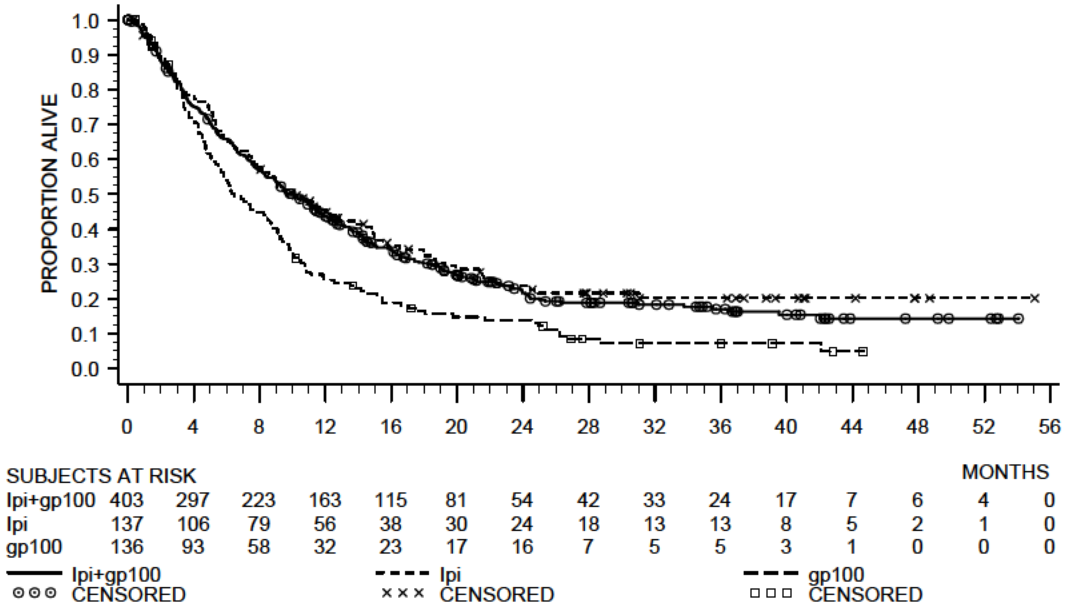
Figure 1: Kaplan Meier Curves for Overall Survival in Study MDX010-20



14.2 Adjuvant Treatment of Melanoma

The efficacy of YERVOY for the adjuvant treatment of melanoma was evaluated in Study CA184-029 (NCT00636168), a randomized (1:1), double-blind, placebo-controlled trial in patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) histologically confirmed cutaneous melanoma. Enrollment required complete resection of melanoma with full lymphadenectomy within 12 weeks prior to randomization. Patients with prior therapy for melanoma, autoimmune disease, and prior or concomitant use of immunosuppressive agents were ineligible. Patients were randomized to receive YERVOY 10 mg/kg or placebo as an intravenous infusion every 3 weeks for 4 doses, followed by YERVOY 10 mg/kg or placebo every 12 weeks from Week 24 to Week 156 (3 years) or until documented disease recurrence or unacceptable toxicity. Randomization was stratified by stage according to American Joint Committee on Cancer (AJCC) 2002 classification (Stage IIIA >1 mm nodal involvement, Stage IIIB, Stage IIIC with 1 to 3 involved lymph nodes, and Stage IIIC with ≥4 involved lymph nodes) and by region (North America, Europe, and Australia). The major efficacy outcome measures were independent review committee (IRC)-assessed recurrence-free survival (RFS), defined as the time between the date of randomization and the earliest date of first recurrence (local, regional, or distant metastasis) or death, and overall survival. Tumor assessment was conducted every 12 weeks for the first 3 years then every 24 weeks until distant recurrence.

Among 951 patients enrolled, 475 were randomized to receive YERVOY and 476 to placebo. Median age was 51 years (range: 18 to 84), 62% were male, 99% were White, 94% had ECOG performance status of 0. With regard to disease stage, 20% had Stage IIIA with lymph nodes

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>1 mm, 44% had Stage IIIB, and 36% had Stage IIIC (with no in-transit metastases). Other disease characteristics of the trial population were: clinically palpable lymph nodes (58%), 2 or more positive lymph nodes (54%), and ulcerated primary lesions (42%).

The efficacy results are in Table 16 and Figure 2.

Table 16: Efficacy Results for Study CA184-029

	YERVOY 10 mg/kg n=475	**Placebo n76**
Recurrence-Free Survival		
Number of events	234 (49%)	294 (62%)
Recurrence	220	289
Death	14	5
Median in months (95% CI)	26 (19, 39)	17 (13, 22)
Hazard ratio (95% CI)	0.75 (0.64, 0.90)	
p-value (stratified log-rank[a])	p<0.002	
Overall Survival		
Number of deaths	162 (34%)	214 (45%)
Hazard ratio (95% CI)	0.72 (0.58, 0.88)	
p-value (stratified log-rank[a])	p<0.002	

[a] Stratified by disease stage.

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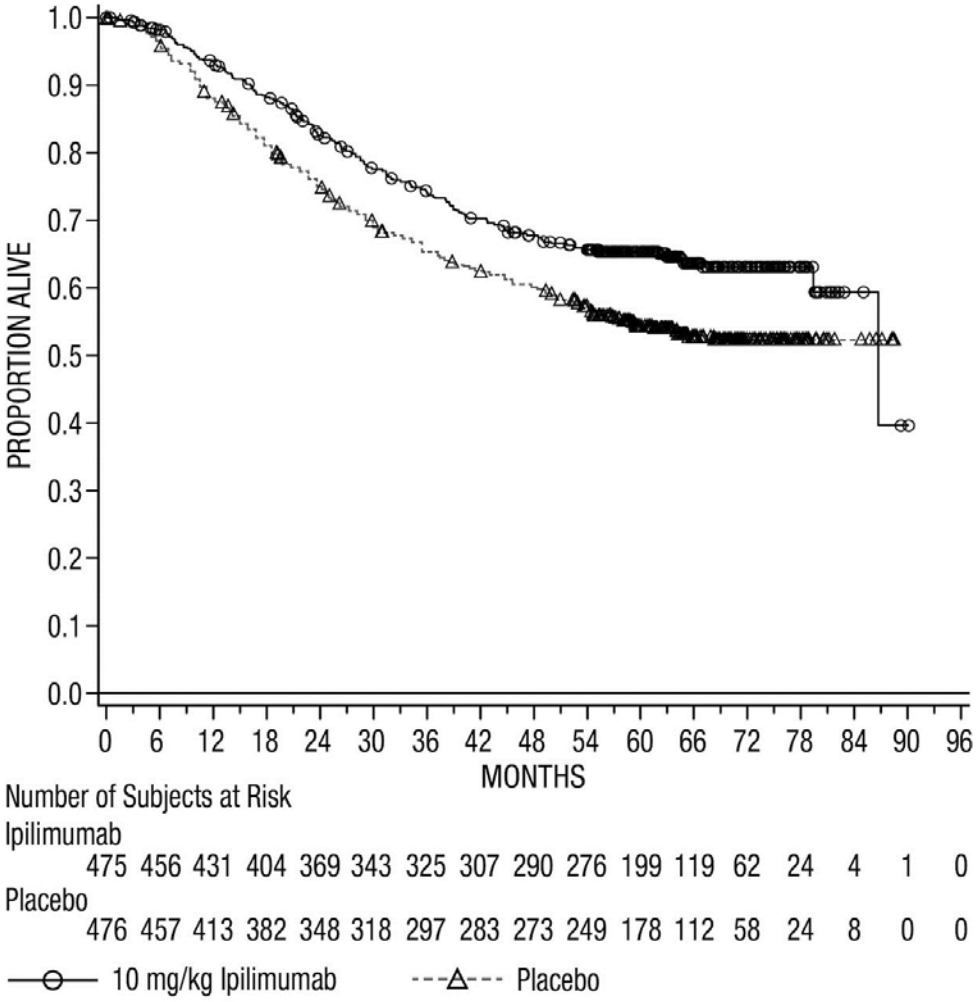
Figure 2: Kaplan-Meier Curves for Overall Survival in Study CA184-029



14.3 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)

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<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 17 and Figure 3. 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 17: Efficacy Results for CHECKMATE-214

Efficacy Parameter	**Intermediate/Poor-Risk**	
	YERVOY 1 mg/kg with 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)
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

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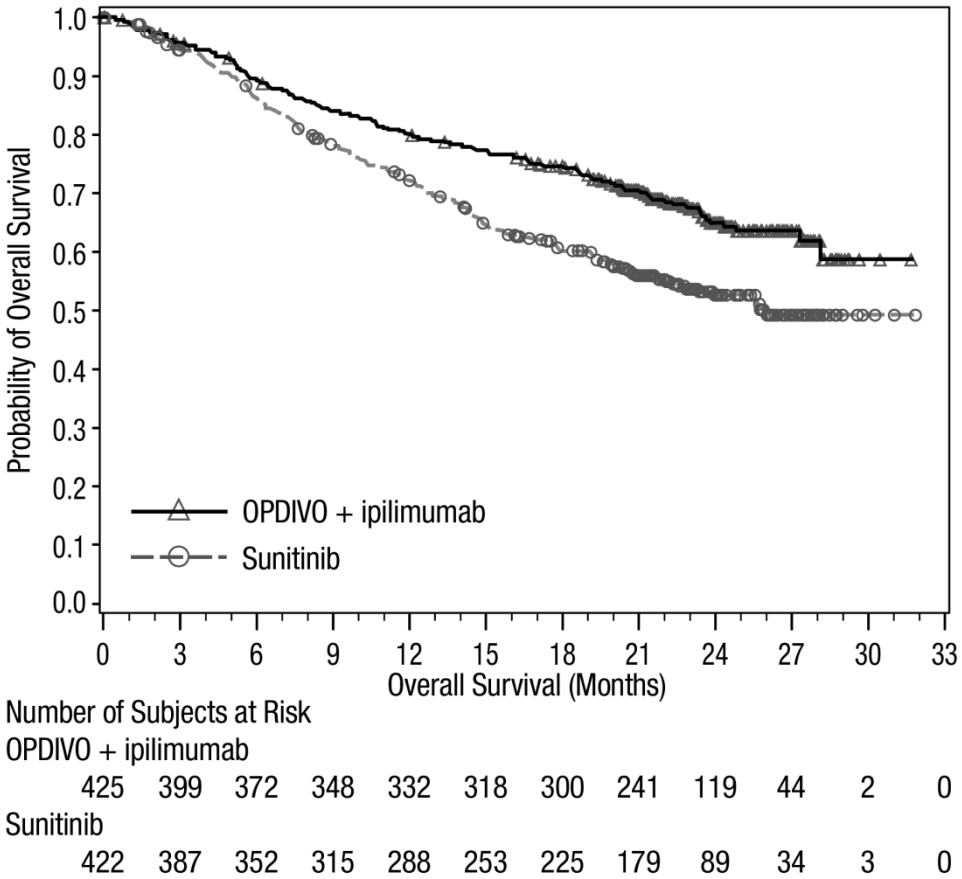
Figure 3: **Kaplan-Meier Curves for Overall Survival (Intermediate/Poor Risk Population) in CHECKMATE-214**



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.

14.4 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

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agent every 2 weeks. Efficacy outcome measures were overall response rate (ORR) as assessed by independent radiographic review committee (IRRC) 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 18.

Table 18: Efficacy Results in MSI-H/dMMR Cohort of CHECKMATE-142

	YERVOY plus Nivolumab MSI-H/dMMR Cohort	
	All Patients (n=119)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
IRRC Overall Response Rate; n (%)	58 (49%)	38 (46%)
(95% CI)[a]	(39, 58)	(35, 58)
Complete Response (%)	5 (4.2%)	3 (3.7%)
Partial Response (%)	53 (45%)	35 (43%)
Duration of Response		
Proportion with ≥6 months response duration	83%	89%
Proportion with ≥12[b] months response duration	19%	21%

[a] Estimated using the Clopper-Pearson method.

[b] In the monotherapy cohort, 55% of the 20 patients with ongoing responses were followed for less than 12 months from the date of onset of response. In the combination cohort, 78% of the 51 patients with ongoing responses were followed for less than 12 months from the date of onset of response.

14.5 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

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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 19.

Table 19: 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.

14.6 Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) Expressing PD-L1 (≥1%): In Combination with Nivolumab

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study 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 [ASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. 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

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conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Randomization was stratified by tumor histology (non-squamous versus squamous). The evaluation of efficacy relied on the comparison between:

- YERVOY 1 mg/kg administered intravenously over 30 minutes every 6 weeks in combination with nivolumab 3 mg/kg administered intravenously over 30 minutes every 2 weeks; or
- Platinum-doublet chemotherapy

Chemotherapy regimens consisted of pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) or pemetrexed (500 mg/m^2) and carboplatin (AUC 5 or 6) for non-squamous NSCLC or gemcitabine (1000 or 1250 mg/m^2) and cisplatin (75 mg/m^2) or gemcitabine (1000 mg/m^2) and carboplatin (AUC 5) (gemcitabine was administered on Days 1 and 8 of each cycle) for squamous NSCLC.

Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment continued 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 event attributed to YERVOY were permitted to continue nivolumab as a single agent. 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.

In Part 1a, a total of 793 patients were randomized to receive either YERVOY in combination with nivolumab (n=396) or platinum-doublet chemotherapy (n=397). The median age was 64 years (range: 26 to 87) with 49% of patients ≥65 years and 10% of patients ≥75 years, 76% White, and 65% male. Baseline ECOG performance status was 0 (34%) or 1 (65%), 50% with PD-L1 ≥50%, 29% with squamous and 71% with non-squamous histology, 10% had brain metastases, and 85% were former/current smokers.

The study demonstrated a statistically significant improvement in OS for PD-L1 ≥1% patients randomized to the YERVOY and nivolumab arm compared to platinum-doublet chemotherapy arm. The OS results are presented in Table 20 and Figure 4.

Table 20: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	YERVOY and Nivolumab (n=396)	**Platinum-Doublet Chemotherapy (n=397)**
Overall Survival		
Events (%)	258 (65%)	298 (75%)

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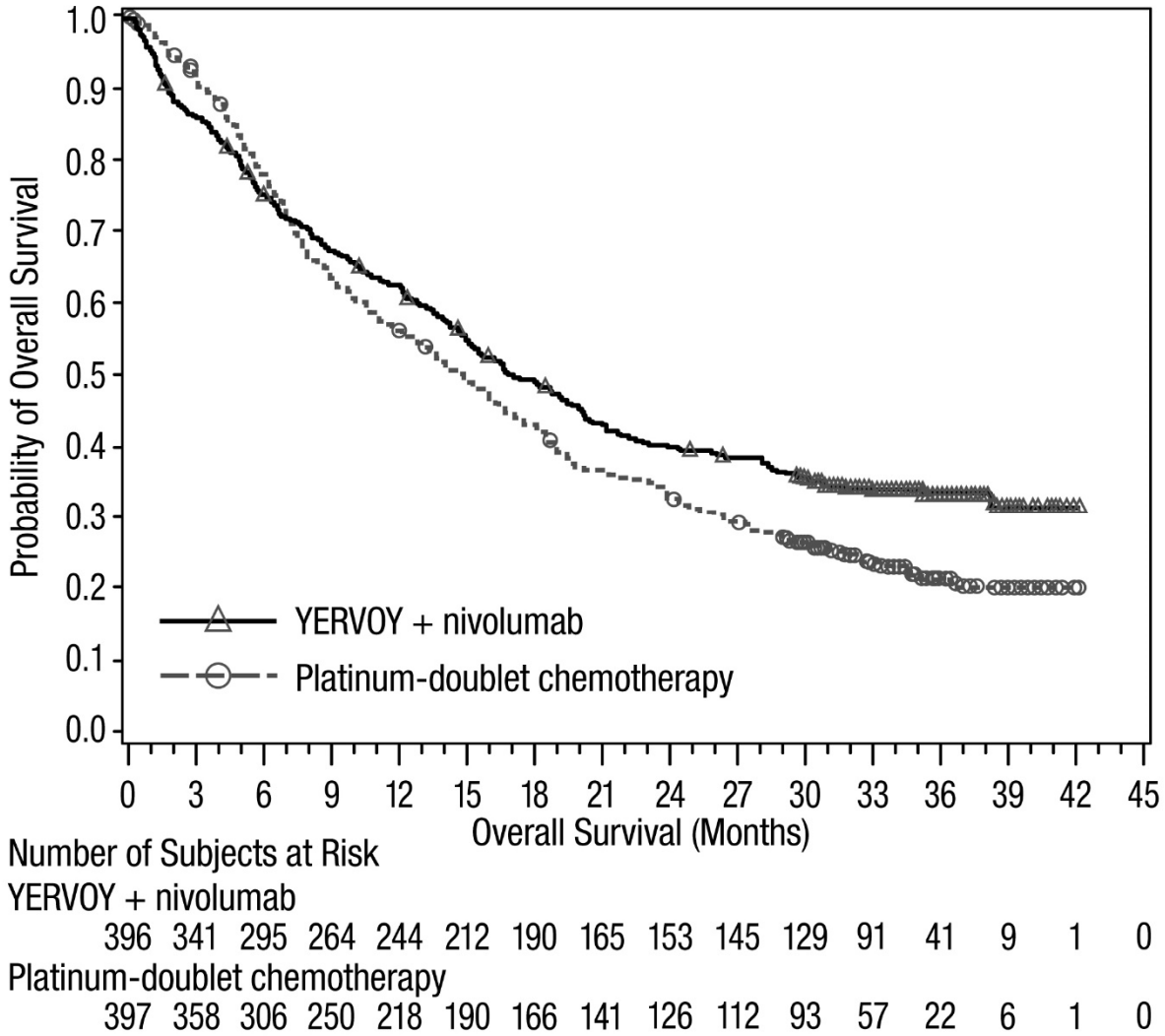
Table 20: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	YERVOY and Nivolumab (n=396)	Platinum-Doublet Chemotherapy (n=397)
Median (months)[a] (95% CI)	17.1 (15, 20.1)	14.9 (12.7, 16.7)
Hazard ratio (95% CI)[b]	0.79 (0.67, 0.94)	
Stratified log-rank p-value	0.0066	

[a] Kaplan-Meier estimate.

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

Figure 4: Overall Survival (PD-L1 ≥1%) - CHECKMATE-227



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BICR-assessed PFS showed a HR of 0.82 (95% CI: 0.69, 0.97), with a median PFS of 5.1 months (95% CI: 4.1, 6.3) in the YERVOY and nivolumab arm and 5.6 months (95% CI: 4.6, 5.8) in the platinum-doublet chemotherapy arm. The BICR-assessed confirmed ORR was 36% (95% CI: 31, 41) in the YERVOY and nivolumab arm and 30% (95% CI: 26, 35) in the platinum-doublet chemotherapy arm. Median duration of response observed in the YERVOY and nivolumab arm was 23.2 months and 6.2 months in the platinum-doublet chemotherapy arm.

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/mg^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

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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 21.

Table 21: 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)
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.

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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 5).

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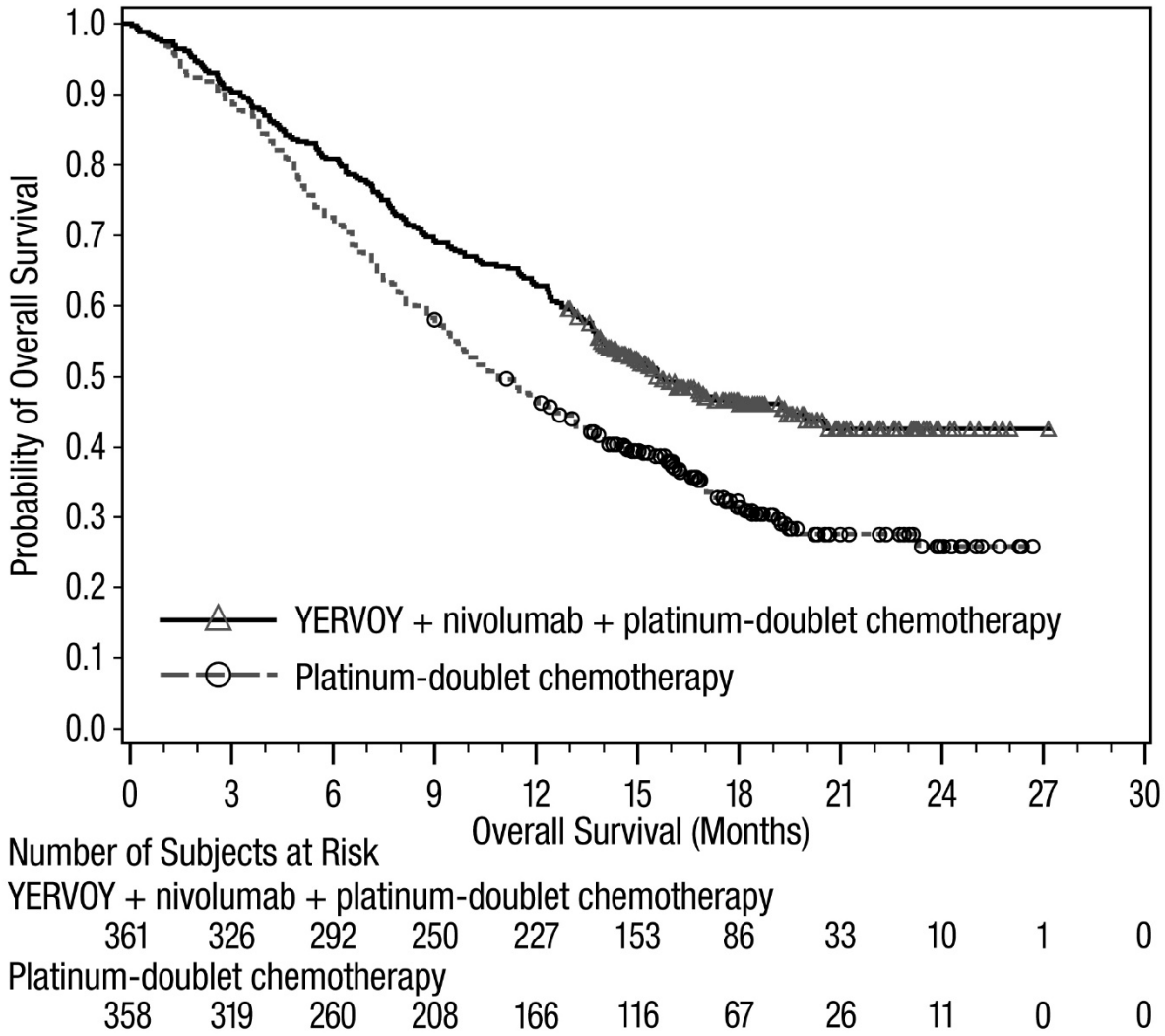
Figure 5: Overall Survival - CHECKMATE-9LA



16 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY (ipilimumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution. YERVOY is available as follows:

Carton Contents	NDC
One 50 mg vial (5 mg/mL), single-dose vial	NDC 0003-2327-11
One 200 mg vial (5 mg/mL), single-dose vial	NDC 0003-2328-22

Store YERVOY under refrigeration at 2°C to 8°C (36°F to 46°F). Protect YERVOY from light by storing in the original carton until time of use. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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Immune-Mediated Adverse Reactions

Advise patients that YERVOY can cause immune-mediated adverse reactions including the following *[see Warnings and Precautions (5.1)]*:

- Immune-Mediated Diarrhea or Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of diarrhea or colitis.
- Immune-Mediated Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Immune-Mediated Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.
- Immune-Mediated Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus
- Immune-Mediated Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening symptoms of pneumonitis.
- Immune-Mediated Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.

Infusion-Related Reactions

- Advise patients who are receiving YERVOY of the potential risk of an infusion-related reaction *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3), Use in Specific Populations (8.3)]*.
- Advise females of reproductive potential to use effective contraception during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations (8.3)]*.
- Advise patients who may have been exposed to YERVOY during pregnancy to contact Bristol-Myers Squibb at 1-844-593-7869 *[see Use in Specific Populations (8.1)]*.

Lactation

- Advise women not to breastfeed during treatment with YERVOY and for 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

[print code]

Reference ID: 4633244

MEDICATION GUIDE
YERVOY® (yur-voi)
(ipilimumab)
injection

Read this Medication Guide before you start receiving YERVOY and before each infusion. There may be new information. If your healthcare provider prescribes YERVOY in combination with nivolumab, also read the Medication Guide that comes with nivolumab. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about YERVOY?

YERVOY can cause serious side effects in many parts of your body which can lead to death. These problems may happen anytime during treatment with YERVOY or after you have completed treatment. Some of these problems may happen more often when YERVOY is used in combination with nivolumab.

Call your healthcare provider right away if you develop any of these signs or symptoms or they get worse. Do not try to treat symptoms yourself.

Intestinal problems (colitis) that can cause tears or holes (perforation) in the intestines. Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- mucus or blood in your stools
- dark, tarry, sticky stools
- stomach pain (abdominal pain) or tenderness
- you may or may not have fever

Liver problems (hepatitis) that can lead to liver failure. Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- dark urine (tea colored)
- nausea or vomiting
- pain on the right side of your stomach
- bleeding or bruise more easily than normal
- decreased energy

Skin problems that can lead to severe skin reaction. Signs and symptoms of severe skin reactions may include:

- skin rash with or without itching
- sores in your mouth
- your skin blisters or peels

Nerve problems that can lead to paralysis. Symptoms of nerve problems may include:

- unusual weakness of legs, arms, or face
- numbness or tingling in hands or feet

Hormone gland problems (especially the pituitary, adrenal, and thyroid glands). Signs and symptoms that your glands are not working properly may include:

- persistent or unusual headaches
- unusual sluggishness
- feeling cold all the time
- weight gain
- changes in mood or behavior such as decreased sex drive, irritability, or forgetfulness
- dizziness or fainting

Lung problems (pneumonitis). Symptoms of pneumonitis may include:

- new or worsening cough
- chest pain
- shortness of breath

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:

- decrease in the amount of urine
- blood in your urine
- swelling in your ankles
- loss of appetite

Inflammation of the brain (encephalitis). Signs and symptoms of encephalitis may include:

- headache
- fever
- tiredness or weakness
- confusion
- memory problems
- sleepiness
- seeing or hearing things that are not really there (hallucinations)
- seizures
- stiff neck

Eye problems. Symptoms may include:

- blurry vision, double vision, or other vision problems
- eye pain or redness

Getting medical treatment right away may keep the problem from becoming more serious.

Your healthcare provider will check you for these problems during treatment with YERVOY. Your healthcare provider may treat you with corticosteroid medicines. Your healthcare provider may need to delay or completely stop treatment with YERVOY if you have severe side effects.

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What is YERVOY?

YERVOY is a prescription medicine used:

- **to treat a kind of skin cancer called melanoma.** YERVOY may be used:
  - in adults and children 12 years of age and older when melanoma has spread or cannot be removed by surgery
  - to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery
- **in people with kidney cancer (renal cell carcinoma).** YERVOY may be used in combination with nivolumab in certain people when their cancer has spread.
- **in adults and children 12 years of age and older, with a type of colon or rectal cancer (colorectal cancer).**
  - YERVOY in combination with nivolumab may be used when your colon or rectal cancer:
    - has spread to other parts of the body (metastatic).
    - is microsatellite stability-high (MSI-H) or mismatch repair deficient (dMMR), **and**
    - You have tried treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, and it did not work or is no longer working.
- **in people with liver cancer (hepatocellular carcinoma).**
  - YERVOY may be used in combination with nivolumab if you have previously received treatment with sorafenib.
- **in adults with a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - YERVOY may be used in combination with nivolumab as your first treatment for NSCLC:
    - when your lung cancer has spread to other parts of your body (metastatic), and
    - your tumors are positive for PD-L1, but do not have an abnormal EGFR or ALK gene.
  - YERVOY may be used in combination with nivolumab and 2 cycles of chemotherapy that contains platinum and another chemotherapy medicine, as the first treatment of your NSCLC when your lung cancer:
    - has spread or grown, or comes back, **and**
    - your tumor does not have an abnormal EGFR or ALK gene.

It is not known if YERVOY is safe and effective in children younger than 12 years of age.

Before you receive YERVOY, tell your healthcare provider about all your medical conditions, including if you:

- have immune system problems (autoimmune disease), such as ulcerative colitis, Crohn's disease, lupus, or sarcoidosis
- have had an organ transplant
- have liver problems
- are pregnant or plan to become pregnant. YERVOY can harm your unborn baby.
  - Females who are able to become pregnant should use effective birth control during treatment with YERVOY and for 3 months after the last dose of YERVOY.
  - If you become pregnant or think you are pregnant, tell your healthcare provider right away. You or your healthcare provider should contact Bristol-Myers Squibb at 1-800-721-5072 as soon as you become aware of the pregnancy.
  - **Pregnancy Safety Surveillance Study: Females** who become pregnant during treatment with YERVOY are encouraged to enroll in a Pregnancy Safety Surveillance Study. The purpose of this study is to collect information about the health of you and your baby. You or your healthcare provider can enroll you in the Pregnancy Safety Surveillance Study by calling 1-844-593-7869.
- are breastfeeding or plan to breastfeed. It is not known if YERVOY passes into your breast milk.
  - **Do not** breastfeed during treatment with YERVOY and for 3 months after the last dose of YERVOY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive YERVOY?

- YERVOY alone is given to you into your vein through an intravenous (IV) line over 90 minutes.
- When YERVOY is used in combination with nivolumab, nivolumab is given to you into your vein through an IV line over 30 minutes. Then YERVOY is also given through an IV over 30 minutes on the same day.
- YERVOY in combination with nivolumab is usually given every 3 weeks for 4 doses. After that, nivolumab alone is usually given every 2 or 4 weeks. For NSCLC that has spread to other parts of your body, YERVOY is given every 6 weeks and nivolumab is given either every 2 or 3 weeks for up to 2 years. Your healthcare provider will determine if you will also need to receive chemotherapy every 3 weeks for 2 cycles.
- Your healthcare provider will decide how many treatments you will need.
- Your healthcare provider will do blood tests before starting and during treatment with YERVOY.
- It is important for you to keep all appointments with your healthcare provider. Call your healthcare provider if you miss an appointment. There may be special instructions for you.

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What are the possible side effects of YERVOY?
YERVOY can cause serious side effects, including:

- **See "What is the most important information I should know about YERVOY?"**
- **Severe infusion reactions. Tell your doctor or nurse right away if you get these symptoms during an infusion of YERVOY:**
  - chills or shaking
  - itching or rash
  - flushing
  - difficulty breathing
  - dizziness
  - fever
  - feeling like passing out

Graft-versus-host disease, a complication that can happen after receiving a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic), may be severe, and can lead to death, if you receive YERVOY either before or after transplant. Your healthcare provider will monitor you for the following signs and symptoms: skin rash, liver inflammation, stomach-area (abdominal) pain, and diarrhea.

The most common side effects of YERVOY when used alone include:

- feeling tired
- diarrhea
- nausea
- itching
- rash
- vomiting
- headache
- weight loss
- fever
- decreased appetite
- difficulty falling or staying asleep

The most common side effects of YERVOY when used in combination with nivolumab include:

- feeling tired
- rash
- itching
- diarrhea
- pain in muscles, bones, and joints
- cough
- fever
- decreased appetite
- nausea
- stomach-area (abdominal) pain
- headache
- vomiting
- shortness of breath
- dizziness
- low thyroid hormone levels (hypothyroidism)
- decreased weight

The most common side effects of YERVOY when used in combination with nivolumab and chemotherapy include:

- feeling tired
- pain in muscles, bones, and joints
- nausea
- diarrhea
- rash
- decreased appetite
- constipation
- itching

These are not all of the possible side effects of YERVOY.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of YERVOY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider or pharmacist for information about YERVOY that is written for healthcare professionals.

What are the ingredients of YERVOY?
Active ingredient: ipilimumab
Inactive ingredients: diethylene triamine pentaacetic acid (DTPA), mannitol, polysorbate 80, sodium chloride, tris hydrochloride, and Water for Injection

Manufactured by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
For more information, call 1-800-321-1335
U.S. License No. 1713
[print code]

YERVOY® and OPDIVO® are trademarks of Bristol-Myers Squ bb Company. All other trademarks are the property of their respective owners.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: June 2020

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125377Orig1s106
CLINICAL REVIEW(S)

Medical Officer Review of Prior Approval Labeling Supplement (Amended)

BLA	125377
Supplement	106
SDN	1589 (original)
	1952 (amended)
SUBMISSION DATE	5/2/2019
	6/9/2020 (amended)
PRODUCTS	Ipilimumab
SPONSOR	Bristol-Myers Squibb Company (BMS)
CLINICAL REVIEWER	Margaret Thompson

I. RECOMMENDED REGULATORY ACTION

The clinical review team recommends approval of the proposed labeling changes.

See the approval letter for final agreed-upon changes to the USPI.

II. REGULATORY HISTORY

On 04/20/2018, BMS submitted efficacy supplement (b) (4) As part of that review, FDA proposed a number of labeling changes intended to bring the ipilimumab label more in alignment with the approach taken in the ongoing harmonization of the PD1/L1 blocking agent labels. The efficacy supplement was subsequently withdrawn for unrelated reasons. BMS was instructed to resubmit the requested labeling changes as a new labeling supplement.

On 5/2/2019 BMS submitted labeling supplement 106, which incorporates the labeling changes requested by the FDA.

On 6/9/2020, BMR submitted an amended labeling supplement 106 which incorporated changes from S_108, S_109, S_110.

III. BACKGROUND AND DISCUSSION

The primary goal of the labeling changes was simplification of the label through:

1) Recognition of a common pathophysiology underlying all immune-mediated adverse reactions (IMARS), allowing for the replacement of redundant text included for each specific IMAR with general text that applies to all IMARS, and

2) Consistent presentation of IMAR specific information.

A key change made in this supplement was removal of the boxed warning for IMARs. The proposed removal of the boxed warning was requested by the FDA as part of our review of efficacy supplement (b) (4) This request was based on a systematic re-assessment by the FDA of product labeling for approved products that are labeled in Section 12.1 of product labeling

as either PD-1 inhibitors or PD-L1 inhibitors. FDA's review of this product class noted that none of them contain a Boxed Warning for IMARs. FDA noted that both CTLA-4 inhibition and PD-1/PD-L1 inhibition serve to inhibit immune checkpoints and enhance immune activity. Further, based on the information contained in the product labeling, the risks of CTLA-4 inhibition by ipilimumab are very similar to those observed with PD-1 and PD-L1 inhibition and are related to the immunostimulatory activity of these agents. Ipilimumab was the first immune checkpoint inhibitor to be approved, and at the time, there was limited experience in clinical practice with this class of drugs and little familiarity with the recognition and management of immune-mediated adverse events. Since ipilimumab was initially approved, the oncology community has developed extensive experience with the identification and management of checkpoint inhibitor-associated IMARs. FDA thus considers that IMARs from the Boxed Warning are well understood and managed by the prescribing community and that including the information in Section 5 of the product labeling is adequate to communicate the risk.

No new data were submitted or reviewed to support the removal of the Boxed Warning other than proposed labeling.

Additional major changes made in this supplement are summarized as follows:

- Section 2.5 Recommended Dose Modifications for Adverse Reactions.
    - The amended label includes a paragraph that states the general dose modification approach for all IMARS. The table includes specific IMARS for which a more or less conservative approach than that specified in the lead in paragraph is indicated.
    - The prior label specified Yervoy to be withheld for Grade 2 IMARs and permanently discontinued for Grade 2 IMARS lasting longer than 6 weeks, inability to wean corticosteroids, and Grade 3 and 4 IMARS. In the prior label, the following exceptions are noted in the dose modification table – endocrine, which requires a less conservative approach and ophthalmologic, which requires a more conservative approach.

      The new label specifies a less conservative default with YERVOY to be withheld for Grade 3 IMARS and discontinued for Grade 4 IMARS, persistent Grade 2 or 3 IMARS, and inability to wean steroids. The dose modification table specifies more conservative guidelines for the following IMARS: colitis/diarrhea, pneumonitis, hepatitis, myocarditis, nephritis with renal dysfunction, exfoliative or bullous dermatologic conditions, and neurological toxicities, and hypophysitis. Less conservative guidelines are specified for endocrinopathies and ophthalmologic adverse reactions.

      The amended table is reviewed and considered adequate.

- Section 5 Warnings and Precautions

    - Major reorganization to consolidate all of the IMARs into one warning, remove repetitive language, and highlight common themes and major deviations from common themes.

    - A general paragraph describing the mechanism of action for Yervoy related IMARs, recommended workup, and general treatment guidelines is added to the amended label at the beginning Section 5.

    - For each specific IMAR (e.g., hepatitis, colitis), the following information is summarized for YERVOY as a single agent (3 mg/kg and 10 mg/kg) and in combination with nivolumab (1 mg/kg ipilimumab and 3 mg/kg nivolumab): incidence for overall and by Grade, frequency of permanent discontinuation and withholding for the specific IMAR, percentage of patients requiring steroids, percentage of patients requiring the addition of another immunosuppressant, and available information regarding rechallenge.

      In some cases, incidence by grade and/or rechallenge information was not adequately captured on the supporting clinical trials to allow reanalysis for the consistent reporting in the amended label. In addition, information regarding specific endocrinopathies was not captured in the clinical trials supporting labeling for single agent YERVOY, and therefore it is reported in the label in as a pooled term.

    - Immune-mediated encephalitis and immune mediated neuropathies were not given their own subsection within Section 5.1 (IMARs) due to their low frequencies of occurrence, but they were retained in the list of rare but serious IMARS ("Other Immune-Mediated Adverse Reactions") that appears at the end of Section 5.1.

    - The risk of reactivation of CMV as a cause for diarrhea/colitis was included with the IMAR colitis/diarrhea as previously agreed to in Supplement 104.

    - Section 5.3 Complications of Allogenic Hematopoietic Stem Cell Transplant was included as previously agreed to in Supplement 102.

Additional changes to the amended label include:

- Highlights of Prescribing Information was updated to reflect changes to the body of the label.

- Section 6.1 was revised to simplify the description of the data source. Tables of adverse reactions were merged with tables of immune-mediated adverse reactions throughout Section 6 for simplicity and ease of reading.

- Titles for Tables in Section 6.1, Clinical Trials Experience, were edited to incorporate all relevant information regarding how adverse reactions were selected in the table.

- Information regarding the tolerability of comparator arms was removed from "Other Clinical Experience" as this subsection typically focuses on the tolerability of the labeled drug.

- Revisions to Section 6.3 (Immunogenicity) that included new data were considered out of the scope for this labeling supplement as no supporting data sets were submitted. FDA requested the proposed changes, supporting datasets, and an integrated written analysis supporting the proposed changes be included in a future labeling supplement. The proposed changes were removed in the final label.

- Revisions to Section 12.3 (Pharmacokinetics) that included new data were considered out of the scope for this labeling supplement as no supporting data sets or analysis were included with the submission. The proposed changes were removed in the final label. However, section 12 was reorganized to improve flow.

- Efficacy tables in Section 14 (Clinical Studies) were consolidated to include all efficacy results for a specific study. These changes did not involve the addition of any new data to the label.

- Color and clarity information was added to Section 16.

- Additional changes made to language for consistency with current DO3 approach.

During labeling negotiations, BMS stated for some of the older trials, information for withholding and restarting ipilimumab for adverse events was not specifically collected. FDA directed BMS to extract the data from information that was collected such as exposure and adverse event data. BMS provided the information; however, during review, FDA noticed that the number of patients who were rechallenged with ipilimumab after holding the drug for a specific IMAR exceeded the number of patients who had had the drug withheld for that IMAR. A TCON was held with the company during which FDA pointed out the discrepancy and requested BMS to formulate an algorithm to correctly identify cases where patients were rechallenged and then had a recurrence of the same IMAR after reinitiating ipilimumab. BMS subsequently submitted an algorithm to which FDA agreed. BMS resubmitted the label with corrected recurrence after rechallenge data for Section 5. FDA did not independently verify the calculations but confirmed they were internally consistent.

The amended S_106 label submitted 6/9/2020 and merged changes from S_108, S_109, S_110. The amended label was reviewed. Several untracked changes were identified in the

highlights but found consistent with current OOD guidelines. Upon final review, minor inconsistencies with formatting were identified. Because these were not substantive, FDA noted these inconsistencies to BMS and recommended the company make the changes as part of a subsequent supplement.

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/s/

MARGARET C THOMPSON
06/23/2020 12:33:24 PM

Medical Officer Review of Prior Approval Labeling Supplement

BLA	125377
Supplement	106
SDN	1589
SUBMISSION DATE	5/2/2019
PRODUCTS	Ipilimumab
SPONSOR	Bristol-Myers Squibb Company (BMS)
CLINICAL REVIEWER	Margaret Thompson
CLINICAL TEAM LEADER	Ashley Ward

I. RECOMMENDED REGULATORY ACTION

The clinical review team recommends approval of the proposed labeling changes.

See the approval letter for final agreed-upon changes to the USPI.

II. REGULATORY HISTORY

On 04/20/2018, BMS submitted efficacy supplement (b) (4) As part of that review, FDA proposed a number of labeling changes intended to bring the ipilimumab label more in alignment with the approach taken in the harmonization of the PD1/L1 blocking agent labels. The efficacy supplement was subsequently withdrawn for unrelated reasons. BMS was instructed to resubmit the requested labeling changes as a new labeling supplement.

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III. BACKGROUND AND DISCUSSION

The primary goal of the labeling changes was simplification of the label through:

1) recognition of a common pathophysiology underlying all immune-mediated adverse reactions (IMARS), allowing for the replacement of redundant text included for each specific IMAR with general text that applies to all IMARS, and

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CTLA-4 inhibition by ipilimumab are very similar to those observed with PD-1 and PD-L1 inhibition and related to the immunostimulatory activity of these agents. Ipilimumab was the first immune checkpoint inhibitor to be approved, and at the time, there was limited experience in clinical practice with this class of drugs and little familiarity with the recognition and management of immune-mediated adverse events. Since ipilimumab was initially approved, the oncology community has developed extensive experience with the identification and management of checkpoint inhibitor-associated IMARs. FDA thus considers that IMARs from the Boxed Warning are well understood and managed by the prescribing community and that including the information in Section 5 of the product labeling is adequate to communicate the risk.

No new data were submitted or reviewed to support the removal of the Boxed Warning other than proposed labeling.

Additional major changes made in this supplement are summarized as follows:

- Section 2.5 Recommended Dose Modifications for Adverse Reactions.
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/s/

MARGARET C THOMPSON
12/19/2019 03:12:08 PM

ASHLEY F WARD
12/20/2019 08:04:05 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125377Orig1s106

<u>OTHER REVIEW(S)</u>

DOP2 Associate Director for Labeling Review

Product Title	**Yervoy (ipilimumab) injection**
Applicant	Bristol-Myers Squibb
Application/Supplement Number	BLA 125377
Type of Application/Submission[1]	Supplement 106
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s) (if applicable)	None
Approved Indication(s) (if applicable)	Melanoma, colorectal cancer and renal cell cancer
Date FDA Received Application	May 2, 2019
Review Classification (Priority/Standard)	Standard
Action Goal Date	November 1, 2019
Review Date	November 1, 2019
Reviewer	Stacy S Shord, Pharm.D.

Background: The applicant submitted a supplemental application to update the package insert. FDA had provided the applicant labeling comments on October 31, 2018 as part of the review of Supplement (b) (4) however, this supplement was subsequently withdrawn on January 24, 2019. This supplement addresses FDA labeling recommendations provided as part of Supplment (b) (4) and includes additional labeling recommendations to update the package insert based on current regulations, recommendations and practices.

Labeling Review:
The approved labeling document was reviewed to help ensure that product information (PI):

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[2]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

The attached PI contains the working version (dated October 29, 2019) of the labeling with my recommended edits (identified by name), as well as comments and edits from other review team members. My labeling recommendations provided in this review (e.g., recommended edits and comments regarding parts of PI) should be considered preliminary and may not represent final recommendations for the labeling.

[2] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.
[3] See *PLR Requirements for PI* website for PLR labeling guidances.

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/s/

STACY S SHORD
06/22/2020 12:29:26 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125377Orig1s106

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

Dec 15, 2020

The below approval letter contained the formatting errors and inconsistencies including outline numbering and text bolding in the Medication Guide.

A courtesy copy of this letter was emailed to the sponsor but the official copy was not mailed. The communication function of this letter has been changed to Advice. A corrected letter was checked in on June 29, 2020.

BLA 125377/S-106

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Noemi Guma, Ph.D.
Director, Global Regulatory and Safety Sciences
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Dr. Guma:

Please refer to your supplemental biologics license application (sBLA), dated and received May 2, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Yervoy (ipilimumab) injection, for intravenous use.

This Prior Approval supplemental biologics application provides for the following changes to the Prescribing Information (PI):

- Removal of the boxed warning for immune-mediated adverse reactions (IMARs);
- Updates to Section 2.5 Recommended Dose Modifications for Adverse Reactions;
- Major reorganization of Section 5 WARNINGS AND PRECAUTIONS to consolidate all the IMARs into one warning;
- Revisions to Efficacy tables in Section 14 CLINICAL STUDIES were consolidated to include all efficacy results for a specific study;
- Additional changes to language in the package insert for consistency and to update based on current regulations, recommendations and labeling practices.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Norma Griffin, Lead Regulatory Health Project Manager, at 301-796-4255.

Sincerely,

{See appended electronic signature page}

Jeffrey Summers, MD
Associate Director for Translational Sciences
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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Reference ID: 4632711

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/s/

JEFFERY L SUMMERS
06/29/2020 10:36:21 AM