CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125377Orig1s110

Trade Name:	Yervoy injection, 50mg/10mL (5mg/mL) and 200mg/40mL 5mg/mL)
Generic or Proper Name:	ipilimumab
Sponsor:	Bristol-Myers Squibb Company
Approval Date:	May 26, 2020
Indication:	For the use of ipilimumab, in combination with nivolumab and 2 cycles of platinum-based chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

CENTER FOR DRUG EVALUATION AND RESEARCH

125377Orig1s110

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Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125377Orig1s110

APPROVAL LETTER

BLA 125377/S-110

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Noemi Guma
Director, Global Regulatory Strategy & Policy
P.O. Box 5326
Princeton, NJ 08543

Dear Ms. Guma:

Please refer to your supplemental biologics license application (sBLA), dated February 6, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Yervoy (ipilimumab), injection, 50mg/10mL (5mg/mL) and 200mg/40mL 5mg/mL).

This Prior Approval supplemental biologics application provides for a new indication for the use of ipilimumab, in combination with nivolumab and 2 cycles of platinum-based chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

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.

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

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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

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,

[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.

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.

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]

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

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 Kwadwo Korsah, Pharm.D., Regulatory Health Project Manager, at (301) 796-6630.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2 (DO 2)
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling

[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/

B HARPREET SINGH
05/26/2020 03:00:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125554Orig1s082

Trade Name:	Opdivo injection, 100 mg/10 mL, 40 mg/4 mL and 240 mg/24 mL.
Generic or Proper Name:	nivolumab
Sponsor:	Bristol-Myers Squibb Company
Approval Date:	May 26, 2020
Indication:	For the use of nivolumab, in combination with ipilimumab and 2 cycles of platinum-based chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

CENTER FOR DRUG EVALUATION AND RESEARCH

125554Orig1s082

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Reviews / Information Included in this NDA Review.

Approval Letter	**X**
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Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
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Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s082

APPROVAL LETTER

BLA 125554/S-082

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Jacqueline Wohlbach
Associate Director, Global Regulatory and Safety Sciences
P.O. Box 5326
Princeton, NJ 08543

Dear Ms. Wohlbach:

Please refer to your supplemental biologics license application (sBLA), dated February 6, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Opdivo (nivolumab), injection, 100 mg/10 mL, 40 mg/4 mL and 240 mg/24 mL.

This Prior Approval supplemental biologics application provides for a new indication for the use of nivolumab, in combination with ipilimumab and 2 cycles of platinum-based chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

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.

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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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

PROMOTIONAL MATERIALS

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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]

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REPORTING REQUIREMENTS

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If you have any questions, call Kwadwo Korsah, Pharm.D., Regulatory Health Project Manager, at (301) 796-6630.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2 (DO 2)
Office of Oncologic Diseases (OOD)
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling

[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/

B HARPREET SINGH
05/26/2020 03:11:50 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125377Orig1s110

LABELING

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

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS
See full prescribing information for complete boxed warning.

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

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. (2.8)

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

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

Indications and Usage (1)	5/2020
Dosage and Administration (2)	5/2020
Warnings and Precautions (5)	5/2020

----------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 of age 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 ipilimumab 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 total of 4 doses. (2.2)
- Adjuvant melanoma:
  - YERVOY 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity. (2.3)
- Advanced renal cell carcinoma:
  - Nivolumab 3 mg/kg followed by YERVOY 1 mg/kg on the same day, every 3 weeks for 4 doses, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks. (2.4)
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer:
  - Nivolumab 3 mg/kg followed by YERVOY 1 mg/kg on the same day every 3 weeks for 4 doses, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks. (2.5)
- Hepatocellular carcinoma:
  - Nivolumab 1 mg/kg followed by YERVOY 3 mg/kg on the same day every 3 weeks for 4 doses, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks. (2.6)
- 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)
- Permanently discontinue for severe adverse reactions. (2.8)

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

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

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

None. (4)

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

Immune-mediated adverse reactions: Permanently discontinue for severe reactions. Withhold dose for moderate immune-mediated adverse reactions until return to baseline, improvement to mild severity, or complete resolution, and patient is receiving less than 7 5 mg prednisone or equivalent per day. Administer systemic high-dose corticosteroids for severe, persistent, or recurring immune-mediated reactions. (5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10)

- Immune-mediated hepatitis: Evaluate liver function tests before each dose of YERVOY. (5.2) Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.2)
- Immune-mediated endocrinopathies: Monitor clinical chemistries, ACTH level, and thyroid function tests prior to each dose. Evaluate at each visit for signs and symptoms of endocrinopathy. Institute hormone replacement therapy as needed. (5.5)
- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.6)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation. (5.7)
- Immune-mediated encephalitis: Monitor for changes in neurologic function. Withhold for new-onset moderate to severe neurological signs or symptoms and permanently discontinue for immune-mediated encephalitis. (5.8)
- Infusion reactions: Discontinue for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. (5.9)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.11, 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: Discontinue breastfeeding during treatment with YERVOY. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2020

FULL PRESCRIBING INFORMATION: CONTENTS *

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

FULL PRESCRIBING INFORMATION

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

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

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions *[see Dosage and Administration (2.8)]*.

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

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

YERVOY is indicated for the treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older) *[see Clinical Studies (14.1)]*.

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 *[see Clinical Studies (14.2)]*.

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) *[see Clinical Studies (14.3)]*.

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

YERVOY, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan *[see Clinical Studies (14.4)]*. 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 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.

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 Dosing for Unresectable or Metastatic Melanoma

The recommended dose of YERVOY is 3 mg/kg administered as an intravenous infusion over 90 minutes every 3 weeks for a maximum of 4 doses. In the event of toxicity, doses may be delayed, but all treatment must be administered within 16 weeks of the first dose *[see Clinical Studies (14.1)]*.

2.3 Recommended Dosing for Adjuvant Treatment of Melanoma

The recommended dose of YERVOY is 10 mg/kg administered as an intravenous infusion over 90 minutes every 3 weeks for 4 doses followed by 10 mg/kg every 12 weeks for up to 3 years *[see Clinical Studies (14.2)]*. In the event of toxicity, doses are omitted, not delayed.

2.4 Recommended Dosing for Renal Cell Carcinoma

The recommended dosage is YERVOY 1 mg/kg administered as an intravenous infusion over 30 minutes, immediately following nivolumab administered on the same day, every 3 weeks for up to 4 doses or until intolerable toxicity or disease progression *[see Clinical Studies (14.3)]*. After completing 4 doses of the combination, administer nivolumab as a single agent. Review the Prescribing Information for nivolumab for full dosing and schedule information.

2.5 Recommended Dosing for Colorectal Cancer

The recommended dosage is YERVOY 1 mg/kg administered as an intravenous infusion over 30 minutes, immediately following nivolumab administered on the same day, every 3 weeks for up to 4 doses or until intolerable toxicity or disease progression *[see Clinical Studies (14.4)]*. After completing 4 doses of the combination, administer nivolumab as a single agent. Review the Prescribing Information for nivolumab for full dosing and schedule information.

2.6 Recommended Dosing for Hepatocellular Carcinoma

The recommended dosage is YERVOY 3 mg/kg administered as an intravenous infusion over 30 minutes, immediately following nivolumab administered on the same day, every 3 weeks for up to 4 doses or until intolerable toxicity or disease progression *[see Clinical Studies (14.5)]*. After completing 4 doses of the combination, administer nivolumab as a single agent. Review the Prescribing Information for nivolumab for full dosing and schedule 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 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 Dose Modifications

Recommendations for YERVOY modifications are provided in Table 1. When YERVOY is administered in combination with nivolumab, if YERVOY is withheld, nivolumab should also be withheld. Review the Prescribing Information for nivolumab for recommended dose modifications.

Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue in patients with severe or life-threatening infusion reactions.

Table 1: Recommended Treatment Modifications for Immune-Mediated Adverse Reactions of YERVOY

Target/Organ System	Adverse Reaction (CTCAE v4)	Treatment Modification
Endocrine	Symptomatic endocrinopathy	Withhold YERVOY Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day.
	• Symptomatic reactions lasting 6 weeks or longer • Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	Permanently discontinue YERVOY
Ophthalmologic	Grade 2 through 4 reactions • not improving to Grade 1 within 2 weeks while receiving topical therapy or • requiring systemic treatment	Permanently discontinue YERVOY

Table 1: Recommended Treatment Modifications for Immune-Mediated Adverse Reactions of YERVOY

Target/Organ System	Adverse Reaction (CTCAE v4)	Treatment Modification
All Other	Grade 2	Withhold YERVOY Resume YERVOY in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving less than 7.5 mg prednisone or equivalent per day.
	• Grade 2 reactions lasting 6 weeks or longer • Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day • Grade 3 or 4	Permanently discontinue YERVOY

2.9 Preparation and Administration

- Do not shake product.
- Inspect parenteral drug products visually 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.

Preparation of Solution

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of YERVOY and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Discard partially used vials or empty vials of YERVOY.

Administration Instructions

- Do not mix YERVOY with, or administer as an infusion with, other medicinal products.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 90 minutes 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) and 200 mg/40 mL (5 mg/mL) as a clear to slightly opalescent, colorless to pale-yellow solution in a single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

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

5.1 Immune-Mediated Enterocolitis/Colitis

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

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating an infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

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

Withhold YERVOY dosing for moderate enterocolitis; administer anti-diarrheal treatment and, if persistent for more than 1 week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent *[see Dosage and Administration (2.8)]*.

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20, severe, life-threatening, or fatal (diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3 to 5) immune-mediated enterocolitis occurred in 34 YERVOY-treated patients (7%), and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 YERVOY-treated patients (5%). Across all YERVOY-treated patients (n=511), 5 patients (1%) developed intestinal perforation, 4 patients (0.8%) died as a result of complications, and 26 patients (5%) were hospitalized for severe enterocolitis.

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

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

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

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3 to 5 immune-mediated enterocolitis occurred in 76 patients (16%) and Grade 2 enterocolitis occurred in 68 patients (14%). Seven patients (1.5%) developed intestinal perforation and 3 patients (0.6%) died as a result of complications *[see Adverse Reactions (6.1)]*.

The median time to onset for Grade 3 to 4 enterocolitis was 1.1 months (range: 1 day to 33.1 months) and for Grade 2 enterocolitis was 1.1 months (range: 1 day to 20.6 months).

Seventy-one patients (95%) with Grade 3 to 4 enterocolitis were treated with systemic corticosteroids. The median duration of treatment was 4.7 months (ranging up to 52.3 months).

Of the 68 patients with moderate enterocolitis, 51 patients (75%) were treated with systemic corticosteroids with a median duration of treatment of 3.5 months (ranging up to 52.2 months). Non-corticosteroids immunosuppression, consisting almost exclusively of infliximab, was used to treat 36% of patients with Grade 3 to 4 enterocolitis and 15% of patients with a Grade 2 event.

Of the 75 patients with Grade 3 to 4 immune-mediated enterocolitis, 86% experienced complete resolution, 3% experienced improvement to Grade 1, and 11% did not improve. Among the 68 patients with Grade 2 enterocolitis, 94% experienced complete resolution, 3% experienced improvement to Grade 1, and 3% did not improve.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Immune-mediated colitis occurred in 10% (52/547) of patients with RCC and 7% (8/119) of patients with CRC. Median time to onset of immune-mediated colitis was 1.7 months (range: 2 days to 19.2 months) in patients with RCC and 2.4 months (range: 22 days to 5.2 months) in patients with CRC.

Immune-mediated colitis led to permanent discontinuation of YERVOY and nivolumab in 3.2% of patients with RCC or CRC (n=666) and withholding of both YERVOY and nivolumab in 3.9% *[see Dosage and Administration (2.8)]*. All patients with colitis required systemic corticosteroids, including 80% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 21 days (range: 1 day to 27 months). Approximately 23% of patients with immune-mediated colitis required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 88% of patients. Two patients with RCC had recurrence of colitis after re-initiation of nivolumab with YERVOY.

YERVOY 3 mg/kg administered with nivolumab 1 mg/kg

Immune-mediated colitis occurred in 10% (5/49) of patients with 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 6% 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 3 patients in whom YERVOY or nivolumab was withheld for colitis, 2 reinitiated treatment after symptom improvement, and none had recurrence of colitis.

5.2 Immune-Mediated Hepatitis

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

Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity before each dose of YERVOY. In patients with hepatotoxicity,

rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.

Permanently discontinue YERVOY in patients with Grade 3 to 4 hepatotoxicity and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for YERVOY, mycophenolate treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids. Withhold YERVOY in patients with Grade 2 hepatotoxicity *[see Dosage and Administration (2.8)]*.

YERVOY as a Single Agent

Metastatic Melanoma

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

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3 to 4 immune-mediated hepatitis occurred in 51 patients (11%) and moderate Grade 2 immune-mediated hepatitis occurred in 22 patients (5%). Liver biopsy performed in 6 patients with Grade 3 to 4 hepatitis showed evidence of toxic or autoimmune hepatitis. The median time to onset for Grade 3 to 4 hepatitis was 2.0 months (range: 1 day to 4.2 months) and for Grade 2 hepatitis was 1.4 months (range: 13 days to 6.5 months). Of the 51 patients with Grade 3 to 4 immune-mediated hepatitis, 94% experienced complete resolution, 4% experienced improvement to Grade 1, and 2% did not improve. Of the 22 patients with Grade 2 immune-mediated hepatitis, 91% experienced complete resolution and 9% did not improve.

Forty-six patients (90%) with Grade 3 to 4 hepatitis were treated with systemic corticosteroids. The median duration of treatment was 4.4 months (ranging up to 56.1 months). Sixteen patients

(73%) with moderate hepatitis were treated with systemic corticosteroids. The median duration of treatment was 2.6 months (ranging up to 41.4 months).

Concurrent Administration with Vemurafenib

In a dose-finding trial, Grade 3 increases in transaminases with or without concomitant increases in total bilirubin occurred in 6 of 10 patients who received concurrent YERVOY (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID).

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Immune-mediated hepatitis occurred in 7% (38/547) of patients with RCC and 8% (10/119) with CRC. Median time to onset was 2 months (range: 14 days to 26.8 months) in patients with RCC and 2.2 months (range: 22 days to 10.5 months) in patients with CRC.

Immune-mediated hepatitis led to permanent discontinuation of YERVOY and nivolumab in 3.6% of patients with RCC or CRC (n=666) and withholding of both YERVOY and nivolumab in 3.5% *[see Dosage and Administration (2.8)]*. All patients with hepatitis required systemic corticosteroids, including 94% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1 month (range: 1 day to 7 months). Approximately 19% of patients with immune-mediated hepatitis required addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 83% of patients. No patients had recurrence of hepatitis after re-initiation of nivolumab with YERVOY or nivolumab alone.

YERVOY 3 mg/kg administered with nivolumab 1 mg/kg

Immune-mediated hepatitis occurred in 20% (10/49) of patients with 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 14.3% 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 7 patients in whom YERVOY or nivolumab was withheld for hepatitis, 4 reinitiated treatment after symptom improvement, and none had recurrence of hepatitis.

5.3 Immune-Mediated Dermatitis/Skin Adverse Reactions

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

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

Permanently discontinue YERVOY in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms *[see Dosage and Administration (2.8)]*.

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

YERVOY as a Single Agent

Metastatic Melanoma

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

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

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

Of the 63 patients with moderate dermatitis, 25 (40%) were treated with systemic corticosteroids (median of 60 mg/day of prednisone or equivalent) for a median of 15 days, 7 (11%) were treated with only topical corticosteroids, and 31 (49%) did not receive systemic or topical corticosteroids. Forty-four patients (70%) with moderate dermatitis were reported to have complete resolution, 7 (11%) improved to mild (Grade 1) severity, and 12 (19%) had no reported improvement.

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3 to 4 immune-mediated dermatitis occurred in 19 patients (4%). There were 99 patients (21%) with moderate (Grade 2) dermatitis. The median time to onset for Grade 3 to 4 dermatitis was 14 days (range: 5 days to 11.3 months) and for Grade 2 dermatitis was 11 days (range: 1 day to 16.6 months).

Sixteen patients (84%) with Grade 3 to 4 dermatitis were treated with systemic corticosteroids for a median of 21 days (ranging up to 49.2 months) resulting in complete resolution of dermatitis within a median time of 4.3 months (range up to 44.4 months). Of the 3 patients (16%) not treated with systemic or topical corticosteroids, 2 (11%) had complete resolution and 1 had improvement to Grade 1.

Of the 99 patients with Grade 2 dermatitis, 67 (68%) were treated with systemic corticosteroids for a median of 2.6 months, 16 (16%) were treated with only topical corticosteroids and 16 (16%) did not receive systemic or topical corticosteroids. Seventy-seven patients (78%) had complete resolution, 15 (15%) improved to mild (Grade 1) severity, and 7 (7%) did not improve.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Immune-mediated rash occurred in 16% (90/547) of patients with RCC and 14% (17/119) of patients with CRC. Median time to onset was 1.5 months (range: 1 day to 20.9 months) in RCC and 26 days (range: 5 days to 9.8 months) in CRC.

Immune-mediated rash led to permanent discontinuation or withholding of YERVOY and nivolumab in 0.5% of patients with RCC or CRC (n=666) and withholding of YERVOY and nivolumab in 2.6% of patients *[see Dosage and Administration (2.8)]*. All patients with immune-mediated rash required systemic corticosteroids, including 19% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 22 days (range: 1 day to 23 months). Complete resolution occurred in 66% of patients. Immune-mediated rash recurred in approximately 3% (3/98) of patients who resumed nivolumab.

YERVOY 3 mg/kg administered with nivolumab 1 mg/kg

Immune-mediated rash occurred in 35% (17/49) of patients with HCC. Median time to onset was 15 days (range: 6 days to 3.1 months). Immune-mediated rash led to withholding of treatment in 6.1% 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, 1 reinitiated treatment after symptom improvement, and none had recurrence of rash.

5.4 Immune-Mediated Neuropathies

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

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue YERVOY in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of

systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Withhold YERVOY dosing in patients with moderate neuropathy (not interfering with daily activities) *[see Dosage and Administration (2.8)]*.

YERVOY as a Single Agent

Metastatic Melanoma

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

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3 to 5 immune-mediated neuropathy occurred in 8 patients (2%); the sole fatality was due to complications of Guillain-Barré syndrome *[see Adverse Reactions (6.1)]*. Moderate Grade 2 immune-mediated neuropathy occurred in 1 patient (0.2%).

The time to onset across the 9 patients with Grade 2 to 5 immune-mediated neuropathy ranged from 1.4 to 27.4 months. All 8 patients with Grade 3 to 5 neuropathy were treated with systemic corticosteroids (range: 3 days to 38.3 months) and 3 also received tacrolimus. Four of the 8 patients with Grade 3 to 5 immune-mediated neuropathy experienced complete resolution, 1 improved to Grade 1, and 3 did not improve. The single patient with Grade 2 immune-mediated neuropathy experienced complete resolution without the use of corticosteroids.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Among 547 RCC patients, there were 3 cases of Grade 3 paresthesia/hypoesthesia.

5.5 Immune-Mediated Endocrinopathies

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

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

Monitor clinical chemistries, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at the start of treatment, before each dose, and as clinically indicated based on symptoms. In

a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

Withhold YERVOY dosing in symptomatic patients and consider referral to an endocrinologist. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy *[see Dosage and Administration (2.8)]*.

YERVOY as a Single Agent

Metastatic Melanoma

In patients receiving YERVOY 3 mg/kg in MDX010-20, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3 to 4) occurred in 9 YERVOY-treated patients (1.8%). All 9 patients had hypopituitarism and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 patients (2.3%) and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and 1 case each of hyperthyroidism and Cushing's syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 2.5 months and ranged up to 4.4 months after the initiation of YERVOY.

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

Adjuvant Treatment of Melanoma

In patients receiving YERVOY 10 mg/kg in CA184-029, Grade 3 to 4 immune-mediated endocrinopathies occurred in 39 patients (8%) and Grade 2 immune-mediated endocrinopathies in 93 patients (20%). Of the 39 patients with Grade 3 to 4 immune-mediated 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. The median time to onset of Grade 3 to 4 immune-mediated endocrinopathy was 2.2 months (range: 2 days to 8 months). Twenty-seven of the 39 patients (69%) were hospitalized for immune-mediated endocrinopathies, and 4 patients (10%) were reported to have resolution.

Of the 93 patients with Grade 2 immune-mediated 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. The median time to onset of Grade 2 immune-mediated endocrinopathy was 2.1 months (range: 9 days to 19.3 months), and 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 immune-mediated endocrinopathy. Of these, 42 (34%) were able to discontinue corticosteroids. Seventy-three patients received thyroid hormones for treatment of Grade 2 to 4 immune-mediated hypothyroidism. Of these, 14 patients (19%) were able to discontinue thyroid replacement therapy.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Hypophysitis. Hypophysitis occurred in 4.6% (25/547) of patients with RCC and 3.4% (4/119) of patients with CRC. Median time to onset was 2.8 months (range: 1.3 months to 7.3 months) in patients with RCC and 3.7 months (range: 2.8 to 5.5 months) in patients with CRC.

Hypophysitis led to permanent discontinuation or withholding of YERVOY and nivolumab in 1.2% and 2.6% of patients with RCC or CRC (n=666), respectively *[see Dosage and Administration (2.8)]*. Approximately 72% of patients with hypophysitis received hormone replacement therapy and 55% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 13 days (range: 1 day to 1.6 months).

Adrenal Insufficiency. Adrenal insufficiency occurred in 7% (41/547) of patients with RCC and 5.9% (7/119) patients with CRC. Median time to onset was 3.4 months (range: 2.0 months to 22.3 months) in RCC and 3.7 months (range: 2.5 to 13.4 months) in CRC.

Adrenal insufficiency led to permanent discontinuation of YERVOY and nivolumab in 1.2% of patients with RCC or CRC (n=666) and withholding of YERVOY and nivolumab in 2.6% *[see Dosage and Administration (2.8)]*. Approximately 94% of patients with adrenal insufficiency received hormone replacement therapy and 27% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 2 days to 5.6 months).

Hypothyroidism and Hyperthyroidism. Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients with RCC and 15% (18/119) of patients with CRC. Median time to onset was 2.2 months (range: 1 day to 21.4 months) in patients with RCC and 2.3 months (range: 22 days to 9.8 months) in patients with CRC. Of the 137 patients with RCC or CRC who developed hypothyroidism, approximately 81% of patients with RCC and 78% with CRC received levothyroxine.

Hyperthyroidism occurred in 12% (66/547) of patients with RCC and 12% (14/119) of patients with CRC. Median time to onset was 1.4 months (range: 6 days to 14.2 months) in RCC and 1.1 months (range: 21 days to 5.4 months) in CRC. Of the 80 patients with RCC or CRC who

developed hyperthyroidism, approximately 15% received methimazole and 2% received carbimazole.

Type 1 Diabetes Mellitus. Diabetes occurred in 2.7% (15/547) of patients with RCC. Median time to onset was 3.2 months (range: 19 days to 16.8 months). Both YERVOY and nivolumab were withheld in 33% of patients and both were permanently discontinued in 20% of patients who developed diabetes *[see Dosage and Administration (2.8)]*.

YERVOY 3 mg/kg administered with nivolumab 1 mg/kg

Hypophysitis. Hypophysitis occurred in 4% (2/49) of patients with 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 with HCC. Median time to onset was 2.8 months (range: 1.4 to 8 months). Adrenal insufficiency led to withholding of treatment in 4% 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 with 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 with HCC. Median time to onset was 1.4 months (range: 1.4 to 2.8 months). Complete resolution occurred in 80% of patients.

5.6 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, including fatal cases, can occur with nivolumab with YERVOY. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY for life-threatening (Grade 4) pneumonitis *[see Dosage and Administration (2.8)]*.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Immune-mediated pneumonitis occurred in 4.4% (24/547) of patients with RCC and 1.7% (2/119) of patients with CRC. Median time to onset of immune-mediated pneumonitis was 2.6 months

(range: 8 days to 9.2 months) in patients with RCC and 1.9 months (range: 27 days to 3 months) in patients with CRC.

Immune-mediated pneumonitis led to permanent discontinuation of YERVOY and nivolumab in 1.8% of patients with RCC or CRC (n=666) and withholding of YERVOY and nivolumab in 1.7% *[see Dosage and Administration (2.8)]*. All patients with pneumonitis required systemic corticosteroids, including 92% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 19 days (range: 4 days to 3.2 months). Approximately 8% required addition of infliximab to high-dose corticosteroids. Complete resolution of pneumonitis occurred in 81% of patients.

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 administered with nivolumab 1 mg/kg

Immune-mediated pneumonitis occurred in 10% (5/49) of patients with 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, 1 reinitiated treatment after symptom improvement, and none had recurrence of pneumonitis.

5.7 Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis can occur with nivolumab with YERVOY. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at

a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents. Withhold YERVOY dosing in patients with moderate to severe signs and symptoms. Permanently discontinue YERVOY for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.8)]*.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients with RCC and 1.7% (2/119) of patients with CRC. Median time to onset was 3 months (range: 1 day to 13.2 months) among these 27 patients.

Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of YERVOY and nivolumab in 1.2% of patients with RCC or CRC (n=666) and withholding of nivolumab and YERVOY in 2.3% of patients with RCC or CRC *[see Dosage and Administration (2.8)]*. Approximately 78% of patients with immune-mediated nephritis and renal dysfunction received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 17 days (range: 1 day to 6 months). Complete resolution occurred in 63% of patients.

5.8 Immune-Mediated Encephalitis

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

Withhold YERVOY in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue YERVOY for immune-mediated encephalitis *[see Dosage and Administration (2.8)]*.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Encephalitis occurred in one patient (0.2%) with RCC approximately 4 months after initiation of YERVOY and in one patient (0.8%) with CRC 15 days after initiation of YERVOY. The patient with CRC required infliximab and high-dose corticosteroids (at least 40 mg prednisone equivalents per day).

5.9 Infusion-Related Reactions

Severe infusion-related reactions can occur with nivolumab with YERVOY. Discontinue YERVOY in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions *[see Dosage and Administration (2.8)]*.

YERVOY 1 mg/kg administered with nivolumab 3 mg/kg

Infusion-related reactions occurred in 5.1% (28/547) of patients with RCC and 4.2% (5/119) of patients with CRC.

YERVOY 3 mg/kg administered with nivolumab 1 mg/kg

Infusion-related reactions occurred in 8% (4/49) of patients with HCC.

5.10 Other Immune-Mediated Adverse Reactions

YERVOY as a Single Agent

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

Monitor patients for signs or symptoms of ocular toxicity, which may include blurred vision and reduced visual acuity. Immune-mediated ocular toxicity may be associated with retinal detachment or permanent vision loss. Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy *[see Dosage and Administration (2.8)]*. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving YERVOY and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive a CTLA-4 receptor blocking antibody either before or after allogeneic hematopoietic stem cell transplantation (HSCT). Follow patients closely for evidence of GVHD and intervene promptly. *[See Adverse Reactions (6.3).]* Consider the benefit versus risks of treatment with a CTLA-4 receptor blocking antibody after allogeneic HSCT.

Metastatic Melanoma

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

Adjuvant Treatment of Melanoma

In CA184-029, the following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients unless specified: cytopenias, eosinophilia (2.1%), pancreatitis (1.3%), meningitis, pneumonitis, sarcoidosis, pericarditis, uveitis, and fatal myocarditis *[see Adverse Reactions (6.1)]*.

Other Clinical Experience

Across 21 dose-ranging trials administering YERVOY at doses of 0.1 to 20 mg/kg (n=2478), the following likely immune-mediated adverse reactions were also reported with less than 1% incidence unless specified: angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, iritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, arthritis, autoimmune thyroiditis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, ocular myositis, cytopenias (2.5%), and nephritis.

YERVOY in Combination with Nivolumab

YERVOY can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of YERVOY therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold YERVOY, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting YERVOY after completion of corticosteroid taper based on the severity of the event.

Across clinical trials of YERVOY administered with nivolumab or in trials of nivolumab administered as a single agent, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in less than 1.0% of patients: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

5.11 Embryo-Fetal Toxicity

Based on its mechanism of action and data 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 a YERVOY-containing regimen and for 3 months after the last dose of YERVOY *[see Use in Specific Populations (8.1, 8.3)]*.

5.12 Risks Associated When Administered in Combination with Nivolumab

When YERVOY is administered in combination with nivolumab, refer to the nivolumab prescribing information for additional risk information that applies to the combination use.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

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

In patients receiving YERVOY 3 mg/kg for unresectable or metastatic melanoma in MDX010-20, 15% of patients receiving monotherapy and 12% of patients treated in combination with gp100 peptide vaccine experienced Grade 3 to 5 immune-mediated reactions. In patients receiving YERVOY 10 mg/kg for adjuvant treatment of melanoma in CA184-029, 41% experienced Grade 3 to 5 immune-mediated reactions.

6.1 Clinical Trials Experience

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

The data described below reflect exposure to YERVOY 3 mg/kg as a single agent in MDX010-20, a randomized trial in patients with unresectable or metastatic melanoma; to YERVOY 10 mg/kg as a single agent in CA184-029, a randomized trial in patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma; to YERVOY 1 mg/kg, administered in combination with nivolumab, in three trials: CHECKMATE-214, a randomized trial in previously untreated patients with advanced renal cell carcinoma, CHECKMATE-142, an open-label, multicenter, non-randomized multiple parallel cohort trial in patients with previously treated, MSI-H or dMMR metastatic colorectal cancer, and CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations; and to YERVOY 3 mg/kg, administered in combination with nivolumab, in CHECKMATE-040, a multicenter, multiple cohort, open-label trial conducted in patients with hepatocellular carcinoma who progressed on or were intolerant to sorafenib; and to YERVOY 1 mg/kg, administered in combination with nivolumab and platinum-doublet chemotherapy in CHECKMATE-9LA, an open-label, multicenter, randomized trial in adult patients with previously untreated metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

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

Unresectable or Metastatic Melanoma

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

MDX010-20 excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation.

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 selected adverse reactions from MDX010-20, which occurred in at least 5% of patients in the YERVOY-containing arms and with at least 5% increased incidence over the control

gp100 arm for all-grade events and at least 1% incidence over the control group for Grade 3 to 5 events.

Table 2: Selected Adverse Reactions in MDX010-20

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

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

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

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

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

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

Adjuvant Treatment of Melanoma

The safety of YERVOY was evaluated in CA184-029, a randomized (1:1), double-blind, placebo-controlled trial in which 945 patients with resected Stage IIIA (>1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) cutaneous melanoma 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 *[see Clinical Studies (14.2)]*. 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).

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.

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%).

YERVOY was discontinued for adverse reactions in 52% of patients.

Table 4 presents selected adverse reactions from CA184-029 which occurred in at least 5% of YERVOY-treated patients and with at least 5% increased incidence over the placebo group for all-grade events.

Table 4: Selected Adverse Reactions in CA184-029

	Percentage (%) of Patients[a]			
	YERVOY 10 mg/kg n=471		Placebo n=474	
System Organ Class/ Preferred Term	Any Grade	Grade 3 to 5	Any Grade	Grade 3 to 5
Skin and Subcutaneous Tissue Disorders				
Rash	50	2.1	20	0
Pruritus	45	2.3	15	0
Gastrointestinal Disorders				
Diarrhea	49	10	30	2.1
Nausea	25	0.2	18	0
Colitis[b]	16	8	1.5	0.4
Vomiting	13	0.4	6	0.2
Investigations				
Weight Decreased	32	0.2	9	0.4
General Disorders and Administration-Site Conditions				
Fatigue	46	2.3	38	1.5
Pyrexia	18	1.1	4.9	0.2
Nervous System Disorders				
Headache	33	0.8	18	0.2
Metabolism and Nutrition Disorders				
Decreased Appetite	14	0.2	3.4	0.2
Psychiatric Disorders				
Insomnia	10	0	4.4	0

[a] Incidences presented in this table are based on reports of adverse events regardless of causality.
[b] Includes 1 death.

Table 5 presents selected laboratory abnormalities from CA184-029 which occurred in at least 10% of YERVOY-treated patients at a higher incidence compared to placebo.

Table 5: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of YERVOY-Treated Patients (CA184-029)[a]

	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	YERVOY		Placebo	
Test	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[b]	26	9	17	4.5
Increased amylase[b]	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).

[b] For lipase and amylase, YERVOY group (range: 447 to 448 patients) and placebo group (range: 462 to 464 patients).

Table 6 presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions from CA184-029.

Table 6: Severe to Fatal Immune-Mediated Adverse Reactions in CA184-029

	Percentage (%) of Patients
	YERVOY 10 mg/kg n=471
Any Immune-Mediated Adverse Reaction	41
Enterocolitis[a,b]	16
Hepatitis	11
Dermatitis	4.0
Neuropathy[a]	1.7
Endocrinopathy	8
Hypopituitarism	7
Primary hypothyroidism	0.2
Hyperthyroidism	0.6

Table 6: Severe to Fatal Immune-Mediated Adverse Reactions in CA184-029

	Percentage (%) of Patients
	YERVOY 10 mg/kg n=471
Other	
Myocarditis[a]	0.2
Meningitis	0.4
Pericarditis[c]	0.2
Pneumonitis	0.2
Uveitis	0.2

[a] Including fatal outcome.

[b] Including intestinal perforation.

[c] Underlying etiology not established.

Other Clinical Experience

Across clinical studies that utilized YERVOY doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were also reported (incidence less than 1% unless otherwise noted): urticaria (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction.

Previously Untreated Renal Cell Carcinoma

The safety of nivolumab 3 mg/kg, administered with YERVOY 1 mg/kg was evaluated in CHECKMATE-214, a randomized open-label trial in which 1082 patients with previously untreated advanced RCC received nivolumab 3 mg/kg in combination with YERVOY 1 mg/kg every 3 weeks for 4 doses followed by nivolumab monotherapy at the 3 mg/kg dose (n=547) every 2 weeks or sunitinib administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle (n=535) *[see Clinical Studies (14.3)]*. The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in nivolumab plus YERVOY-treated patients and 7.8 months (range: 1 day to 20.2+ months) in sunitinib-treated patients. In this trial, 57% of patients in the nivolumab plus YERVOY arm were exposed to treatment for greater than 6 months, and 38% of patients were exposed to treatment for greater than 1 year.

Study therapy was discontinued for adverse reactions in 31% of nivolumab plus YERVOY patients and in 21% of sunitinib patients. Fifty-four percent (54%) of patients receiving nivolumab plus YERVOY and 43% of patients receiving sunitinib had a drug delay for an adverse reaction. In the sunitinib group, 53% of patients required a dose reduction; dose reductions were not permitted in the nivolumab plus YERVOY treatment group. Serious adverse reactions occurred in 59% of patients receiving nivolumab plus YERVOY and in 43% of patients receiving sunitinib. The most

frequent serious adverse reactions reported in at least 2% of patients treated with nivolumab plus YERVOY were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea.

The most common adverse reactions (reported in at least 20% of nivolumab plus YERVOY-treated patients) were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, vomiting, dyspnea, and decreased appetite. Table 7 summarizes adverse reactions that occurred in greater than 15% of nivolumab plus YERVOY-treated patients.

Table 7: Grade 1-4 Adverse Reactions in >15% of Patients Receiving Nivolumab plus YERVOY (CHECKMATE-214)

	Nivolumab plus YERVOY (n=547)		Sunitinib (n=535)	
	Percentage (%) of Patients			
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Adverse Reaction	99	65	99	76
General Disorders 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
Respiratory, Thoracic, and Mediastinal Disorders				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Gastrointestinal Disorders				
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
Skin and Subcutaneous Tissue Disorders				
Rash[c]	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Endocrine Disorders				
Hypothyroidism	18	0.4	27	0.2
Nervous System Disorders				
Headache	19	0.9	23	0.9
Metabolism and Nutrition Disorders				
Decreased appetite	21	1.8	29	0.9
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[d]	37	4.0	40	2.6

Table 7: Grade 1-4 Adverse Reactions in >15% of Patients Receiving Nivolumab plus YERVOY (CHECKMATE-214)

	Nivolumab plus YERVOY (n=547)		Sunitinib (n=535)	
	Percentage (%) of Patients			
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Arthralgia	23	1.3	16	0

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.

The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of nivolumab plus YERVOY-treated patients include increased lipase, anemia, increased creatinine, increased ALT, increased AST, hyponatremia, increased amylase, and lymphopenia. Table 8 summarizes the laboratory abnormalities that occurred in greater than 15% of nivolumab plus YERVOY-treated patients.

Table 8: Grade 1-4 Laboratory Values Worsening from Baseline Occurring in >15% of Patients on Nivolumab plus YERVOY (CHECKMATE-214)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	Nivolumab plus YERVOY		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Hematology				
Anemia	43	3.0	64	9
Lymphopenia	36	5	63	14
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

[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 plus YERVOY group (range: 490 to 538 patients) and sunitinib group (range: 485 to 523 patients).

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

Previously Treated MSI-H or dMMR Metastatic Colorectal Cancer

The safety of YERVOY was evaluated in CHECKMATE-142, an open-label, multicenter, non-randomized, multiple parallel-cohort study. In CHECKMATE-142, 119 patients with previously treated MSI-H or dMMR mCRC received YERVOY, in combination with nivolumab, in a single-arm cohort. 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. *[See Clinical Studies (14.4)]*.

The median duration of exposure for YERVOY was 2.1 months. Serious adverse reactions occurred in 47% of YERVOY-treated patients. The most frequent serious adverse reactions reported in at least 2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. The most common adverse reactions (reported in at least 20% of YERVOY-treated patients) were fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting.

Table 9 summarizes adverse reactions that occurred in greater than 10% of patients receiving YERVOY. Table 10 summarizes laboratory tests that worsened from baseline in greater than 10% of patients receiving YERVOY.

Table 9: 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		
Diarrhea	45	3.4
Abdominal pain[c]	30	5

Table 9: 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**
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
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 less than 10% of patients receiving YERVOY in CHECKMATE-142 were encephalitis (0.8%), necrotizing myositis (0.8%), and uveitis (0.8%).

Table 10: 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 5.1 months (range: 0 to 35+ months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

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

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

Table 11: 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

Table 11: 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 (%)
Nervous System		
Headache	22	0
Dizziness	20	0
Endocrine		
Hypothyroidism	20	0
Adrenal insufficiency	18	4
Investigations		
Weight decreased	20	0
Psychiatric		
Insomnia	18	0
Blood and Lymphatic System		
Anemia	10	4
Infections		
Influenza	10	2
Vascular		
Hypotension	10	0

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

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

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

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

First-line Treatment of Metastatic 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 13 and 14 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 13: 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
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

Table 13: 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 (%)
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.
[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 14: 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				
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 Ipilimumab and Platinum-Doublet Chemotherapy

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

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

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

Tables 15 and 16 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 15: 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

Table 15: 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 (%)
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

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

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

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

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

[f] Includes pruritus and generalized pruritus

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

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

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

[j] Includes dizziness, vertigo and positional vertigo

Table 16: 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 to ipilimumab in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

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

electrochemiluminescent (ECL) based assay. This assay had substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Seven (4.9%) of 144 patients receiving ipilimumab and 7 (4.5%) of 156 patients receiving placebo for the adjuvant treatment of melanoma tested positive for TE-ADAs using an ECL assay with improved drug tolerance. No patients tested positive for neutralizing antibodies. No infusion-related reactions occurred in patients who tested positive for TE-ADAs.

Of 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 503 patients evaluable for anti-nivolumab antibodies in CHECKMATE-214 and CHECKMATE-142 trials, 126 (25%) were positive for anti-nivolumab antibodies and 3 (0.6%) were positive for neutralizing antibodies against nivolumab.

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 disorders: graft-versus-host disease

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action, YERVOY can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. 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 IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. There is insufficient human data for YERVOY exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

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.

A Pregnancy Safety Surveillance Study has been established to collect information about pregnancies in women who have received YERVOY. Healthcare providers are encouraged to enroll patients or have their patients enroll directly by calling 1-844-593-7869.

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 AUC in humans at the 3 mg/kg dose). 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

It is not known whether YERVOY is present in human milk. In monkeys, ipilimumab was present in milk *(see Data)*. There are no data to assess the effects of YERVOY on milk production. Advise women to discontinue breastfeeding during treatment with YERVOY and for 3 months following the final 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.

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

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 microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer 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 metastatic colorectal cancer 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, 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 administered at doses of 1, 3, 5, and 10 mg/kg intravenously over 90 minutes every 3 weeks for 4 doses and then every 12 weeks thereafter until progression or treatment discontinuation.

YERVOY was also evaluated in an open-label, single-arm trial in 12 pediatric patients ≥12 years old (range 12 to 16 years) with previously treated or untreated, unresectable Stage 3 or 4 malignant melanoma. Patients received YERVOY 3 mg/kg (4 patients) or 10 mg/kg (8 patients) intravenously over 90 minutes every 3 weeks for 4 doses.

Of the 17 patients ≥12 years of age with melanoma treated with YERVOY across both studies, two 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.

The overall safety profile of YERVOY in children and adolescents was consistent with the safety profile in adults.

Pediatric Pharmacokinetics (PK)

Based on a population PK analysis using available pooled data from 565 patients from four phase 2 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.

8.5 Geriatric Use

Of the 511 patients treated with YERVOY in MDX010-20 (unresectable or metastatic melanoma), 28% were 65 years and over. No overall differences in safety or efficacy were reported between the elderly patients (65 years and over) and younger patients (less than 65 years).

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 nivolumab 3 mg/kg administered with YERVOY 1 mg/kg 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 reported between elderly patients and younger patients. In elderly patients with intermediate or poor risk, no overall difference in effectiveness was reported.

Of the 49 patients who received nivolumab 1 mg/kg administered with YERVOY 3 mg/kg 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.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

There is no information on overdosage with YERVOY.

11 DESCRIPTION

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

YERVOY is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-use vials of 50 mg/10 mL and 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 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 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. The mean value (percent coefficient of variation) based on population PK analysis for the terminal half-life ($t_{1/2}$) was 15.4 days (34%) and for clearance (CL) was 16.8 mL/h (38%).

YERVOY with nivolumab:

When YERVOY 1 mg/kg was administered in combination 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.

When administered in combination, the CL of ipilimumab was unchanged in the presence of anti-ipilimumab antibodies and the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies.

Specific Populations

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

Renal Impairment: The effect of renal impairment on the CL of ipilimumab was evaluated in patients with mild (GFR <90 and ≥60 mL/min/1.73 m^2; n=349), moderate (GFR <60 and ≥30

mL/min/1.73 m^2; n=82), or severe (GFR <30 and ≥15 mL/min/1.73 m^2; n=4) renal impairment compared to patients with normal renal function (GFR ≥90 mL/min/1.73 m^2; n=350) in population PK analyses. No clinically important differences in the CL of ipilimumab were found between patients with renal impairment and patients with normal renal function *[see Use in Specific Populations (8.6)]*.

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

Pediatric Population: [see Use in Specific Populations (8.4)].

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

The major efficacy outcome measure was overall survival (OS) in the YERVOY plus gp100 arm compared to that in the single-agent gp100 arm. Secondary efficacy outcome measures were OS in the YERVOY plus gp100 arm compared to the YERVOY arm, OS in the YERVOY arm compared to the gp100 arm, best overall response rate (BORR) at week 24 between each of the trial arms, and duration of response.

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

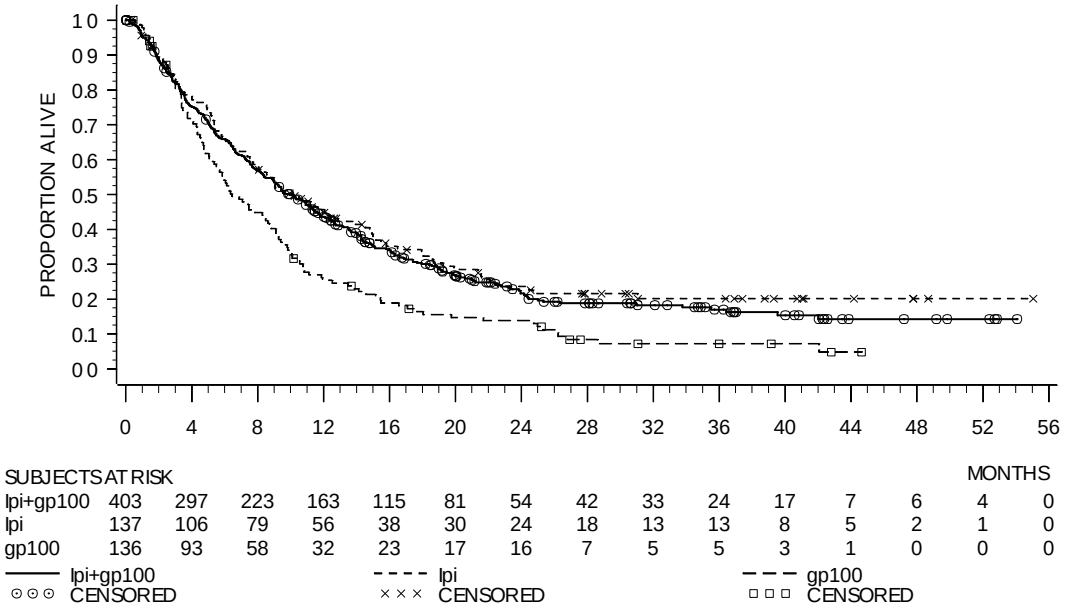
The OS results are shown in Table 17 and Figure 1.

Table 17: Overall Survival Results

	YERVOY n=137	YERVOY+gp100 n=403	gp100 n=136
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)	
Median (months) (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)

[a] Not adjusted for multiple comparisons.

Figure 1: Overall Survival



The best overall response rate (BORR) as assessed by the investigator was 5.7% (95% CI: 3.7%, 8.4%) in the YERVOY plus gp100 arm, 10.9% (95% CI: 6.3%, 17.4%) in the YERVOY arm, and 1.5% (95% CI: 0.2%, 5.2%) in the gp100 arm. The median duration of response was 11.5 months in the YERVOY plus gp100 arm and has not been reached in the YERVOY or gp100 arm.

14.2 Adjuvant Treatment of Melanoma

The safety and efficacy of YERVOY for the adjuvant treatment of melanoma were investigated in 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. 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. 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. 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 old (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 >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%).

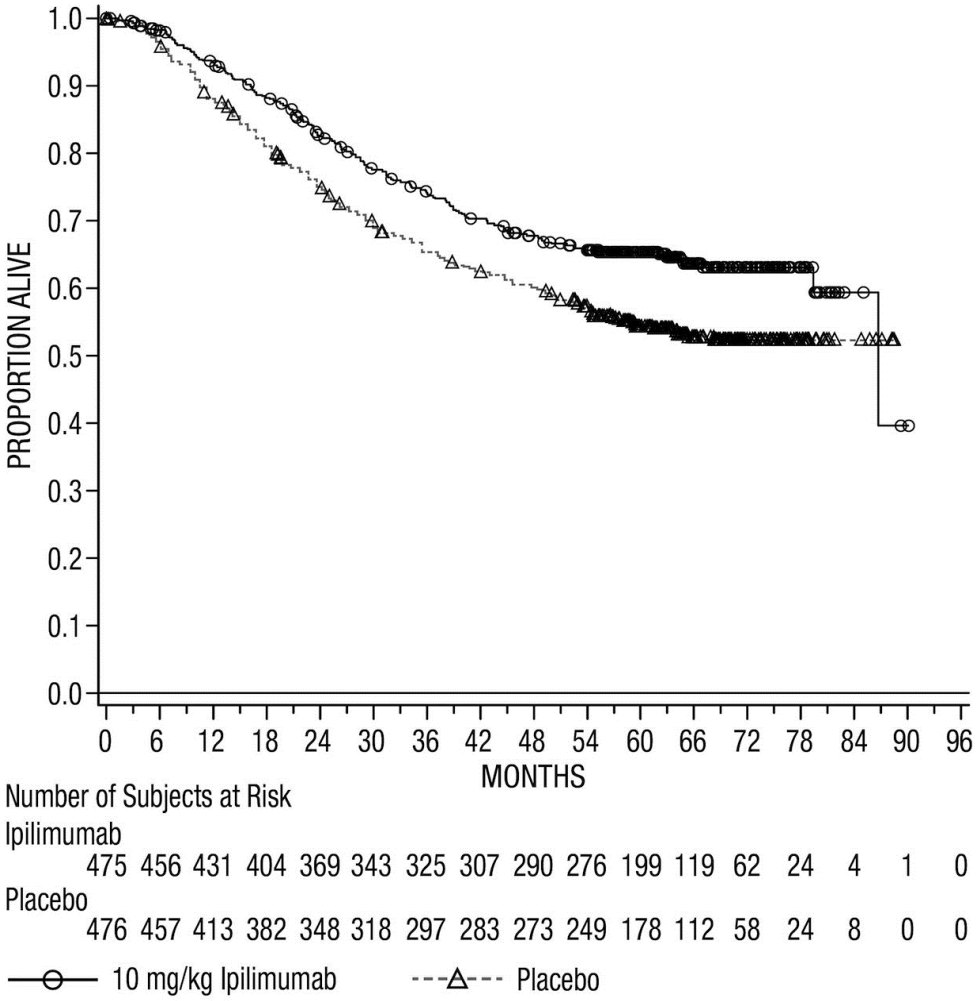
The efficacy results are in Table 18 and in Figure 2.

Table 18: Efficacy Results in CA184-029

	YERVOY N=475		Placebo N=476
Recurrence-Free Survival			
Number of Events, n (%)	234 (49%)		294 (62%)
Recurrence	220		289
Death	14		5
Median (months)	26		17
(95% CI)	(19, 39)		(13, 22)
Hazard Ratio		0.75	
(95% CI)		(0.64, 0.90)	
p-value (stratified log-rank[a])		p<0.002	
Overall Survival			
Number of Events, n (%)			
Death	162 (34%)		214 (45%)
Hazard Ratio		0.72	
(95% CI)		(0.58, 0.88)	
p-value (stratified log-rank[a])		p<0.002	

[a] Stratified by disease stage.

Figure 2: Overall Survival



14.3 Previously Untreated Advanced Renal Cell Carcinoma

CHECKMATE-214 (NCT02231749) was 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 stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region.

Efficacy was evaluated in intermediate/poor-risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status <80%, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal).

Patients were randomized to nivolumab 3 mg/kg plus YERVOY 1 mg/kg (n=425) administered intravenously every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every two weeks or to sunitinib (n=422) administered orally 50 mg daily for 4 weeks followed by 2 weeks off, every cycle. Treatment continued until disease progression or unacceptable toxicity.

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.

The major efficacy outcome measures were OS, PFS (IRRC-assessed), and confirmed ORR (IRRC-assessed) in intermediate/poor-risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to nivolumab plus YERVOY as compared with sunitinib (Table 19 and Figure 3). OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS.

The efficacy results from CHECKMATE-214 are presented in Table 19 and Figure 3.

Table 19: Efficacy Results - CHECKMATE-214

	Intermediate/Poor Risk	
	Nivolumab plus YERVOY (n=425)	**Sunitinib (n=422)**
Overall Survival		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (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)
p-value[d,e]	<0.0001	
Complete Response (CR)	40 (9.4)	5 (1.2)
Partial Response (PR)	137 (32.2)	107 (25.4)
Median duration of response in months (95% CI)	NE (21.8, NE)	18.2 (14.8, NE)
Progression-free Survival		
Disease progression or death (%)	228 (53.6)	228 (54.0)
Median (months)	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	
p-value[b]	NS[f]	

[a] Based on a stratified proportional hazards model.

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

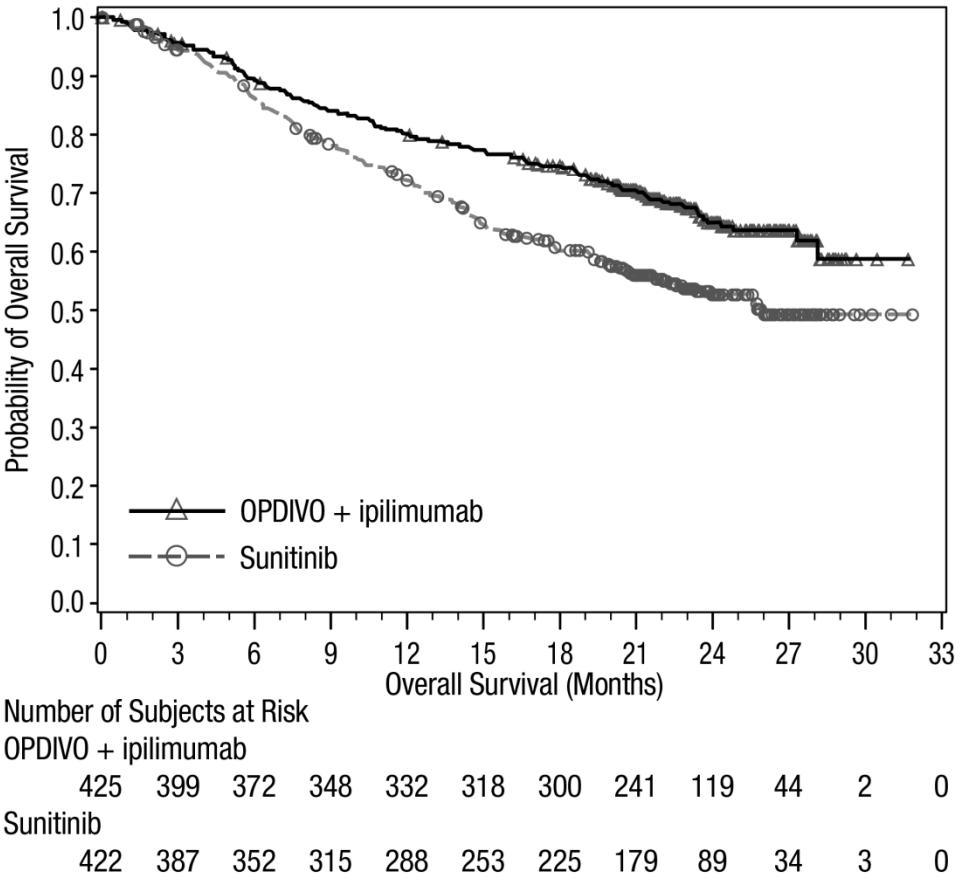
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.

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

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

[f] Not Significant at alpha level of 0.009

Figure 3: Overall Survival (Intermediate/Poor-Risk Population) - CHECKMATE-214



CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to nivolumab plus 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 plus YERVOY compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of nivolumab plus YERVOY in previously untreated renal cell carcinoma with favorable risk disease has not been established.

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

CHECKMATE-142 (NCT02060188) was a multicenter, non-randomized, multiple parallel-cohort, open-label study conducted in patients with locally determined dMMR or MSI-H metastatic CRC (mCRC) who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG 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 mCRC cohort received YERVOY 1 mg/kg and nivolumab 3 mg/kg IV every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg IV as a single agent every 2 weeks.

Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. 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).

A total of 119 patients were enrolled in the YERVOY plus 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 20.

Table 20: Efficacy Results in 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 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 21.

Table 21: 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 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 22 and Figure 4.

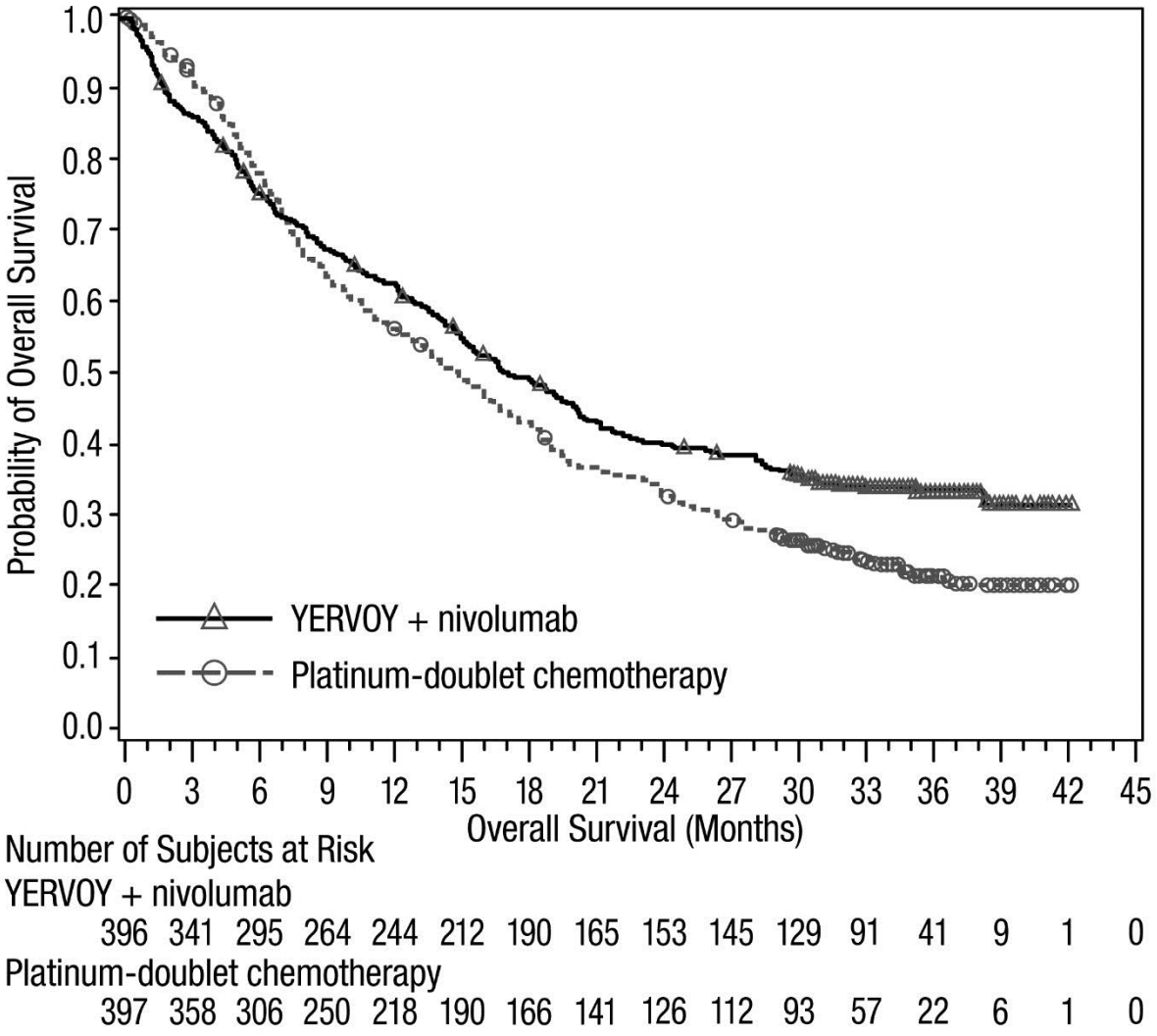
Table 22: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

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



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 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 23.

Table 23: 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.

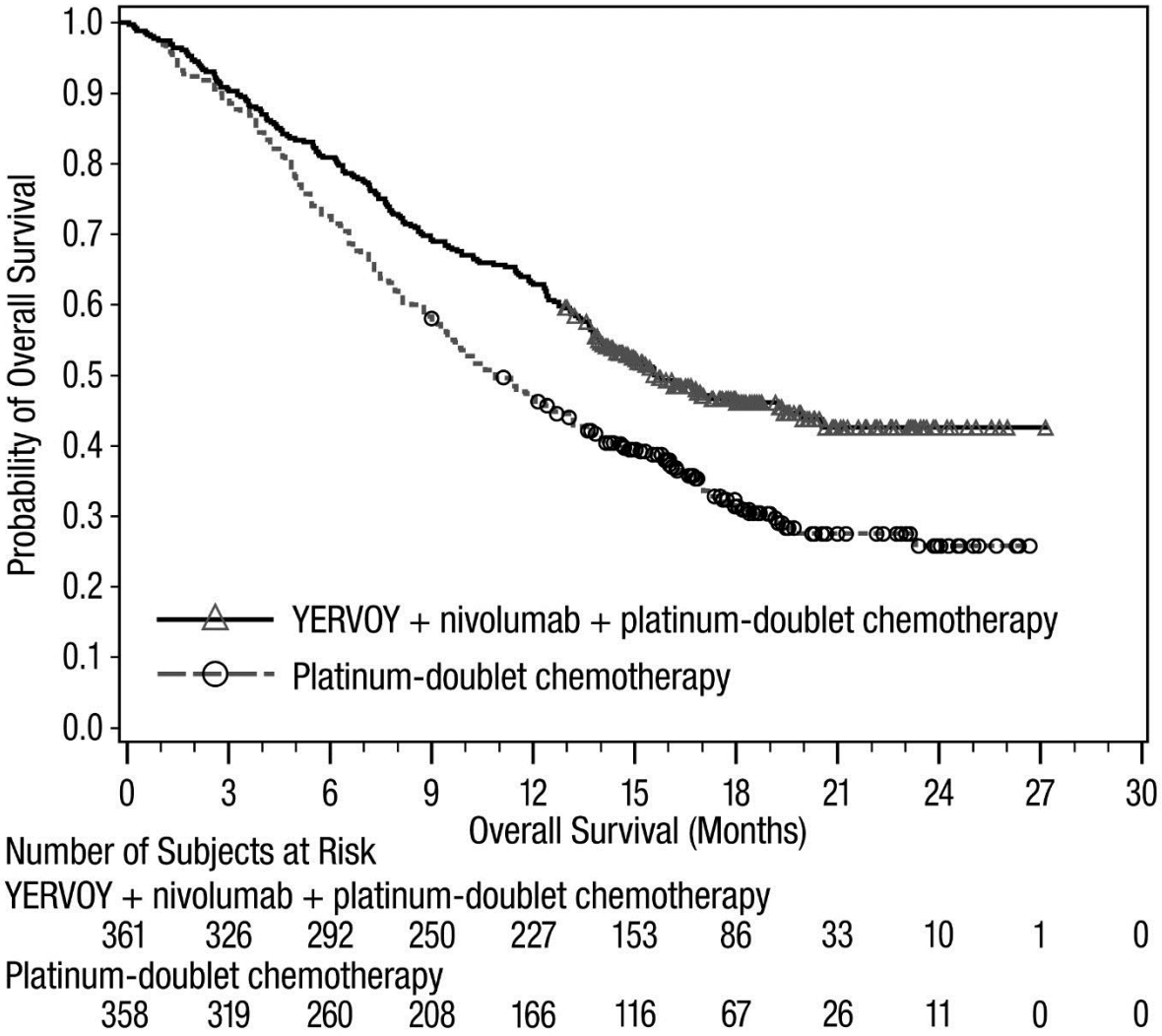
[d] Kaplan-Meier estimate.

[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.

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).

Figure 5: Overall Survival - CHECKMATE-9LA



16 HOW SUPPLIED/STORAGE AND HANDLING

YERVOY (ipilimumab) Injection is available as follows:

Carton Contents	NDC
One 50 mg vial (5 mg/mL), single-use vial	NDC 0003-2327-11
One 200 mg vial (5 mg/mL), single-use 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).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of YERVOY, including:

- Enterocolitis/Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.2)]*.
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions (5.3)]*.
- Neuropathies: Advise patients to contact their healthcare provider immediately for neuropathies *[see Warnings and Precautions (5.4)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.5)]*.
- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.6)]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.7)]*.
- Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis *[see Warnings and Precautions (5.8)]*.

Infusion Reactions

- Advise patients of the potential risk of infusion reaction *[see Warnings and Precautions (5.9)]*.

Females of Reproductive Potential

- Advise female patients that YERVOY can cause fetal harm. 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 female patients to contact their healthcare provider with a known or suspected pregnancy. Advise females who may have been exposed to YERVOY during pregnancy to contact Bristol-Myers Squibb at 1-800-721-5072 *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1, 8.3)]*. Advise patients that there is a Pregnancy Safety

Surveillance Study that monitors pregnancy outcomes in women exposed to YERVOY during pregnancy, and they can be enrolled by calling 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]

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.

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.

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.

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

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/

B HARPREET SINGH
05/26/2020 03:00:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s082

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

OPDIVO (nivolumab) injection, for intravenous use
Initial U.S. Approval: 2014

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

Indications and Usage (1)	5/2020
Dosage and Administration (2)	5/2020
Warnings and Precautions (5)	5/2020

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

OPDIVO is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of:

Melanoma
- patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab. (1.1)
- patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting. (1.2)

Non-Small Cell Lung Cancer (NSCLC)
- 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 ipilimumab. (1.3)
- 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 ipilimumab and 2 cycles of platinum-doublet chemotherapy (1.3)
- patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. (1.3)

Small Cell Lung Cancer (SCLC)
- patients with metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy.[a] (1.4)

Renal Cell Carcinoma (RCC)
- patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.5)
- patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab. (1.5)

Classical Hodgkin Lymphoma (cHL)
- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after[a]: (1.6)
  - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy that includes autologous HSCT.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)
- patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy. (1.7)

Urothelial Carcinoma
- patients with locally advanced or metastatic urothelial carcinoma who[a]:
  - have disease progression during or following platinum-containing chemotherapy
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.8)

Colorectal Cancer
- adult and pediatric (12 years and older) patients 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, as a single agent or in combination with ipilimumab.[a] (1.9)

Hepatocellular Carcinoma (HCC)
- patients with hepatocellular carcinoma who have been previously treated with sorafenib, as a single agent or in combination with ipilimumab.[a] (1.10)

[a] 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.

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

- Administer by intravenous infusion based upon recommended infusion rate for each indication. (2)
- Unresectable or metastatic melanoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Adjuvant treatment of melanoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Metastatic non-small cell lung cancer
  - 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks. (2.2)
  - 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy. (2.2)
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Small cell lung cancer
  - 240 mg every 2 weeks. (2.1)
- Advanced renal cell carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Classical Hodgkin lymphoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Recurrent or metastatic squamous cell carcinoma of the head and neck
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Locally advanced or metastatic urothelial carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
  - Adult and pediatric patients ≥ 40 kg: 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - Pediatric patients < 40 kg: 3 mg/kg every 2 weeks. (2.2)
  - Adult and pediatric patients ≥ 40 kg: 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Hepatocellular carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)

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

- Injection: 40 mg/4 mL, 100 mg/10 mL, and 240 mg/24 mL solution in a single-dose vial. (3)

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

- None. (4)

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

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis: Withhold OPDIVO when given as a single agent for moderate or severe and permanently discontinue for life-threatening colitis. Withhold OPDIVO when given with ipilimumab for moderate and permanently discontinue for severe or life-threatening colitis. (5.2)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.3)
- Immune-mediated endocrinopathies: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis. Withhold for moderate and permanently discontinue for severe or life-threatening adrenal insufficiency. Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. Monitor for hyperglycemia. Withhold for severe and permanently discontinue for life-threatening hyperglycemia. (5.4)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation. (5.5)
- Immune-mediated skin adverse reactions: Withhold for severe and permanently discontinue for life-threatening rash. (5.6)
- Immune-mediated encephalitis: Monitor for changes in neurologic function. Withhold for new-onset moderate to severe neurological signs or symptoms and permanently discontinue for immune-mediated encephalitis. (5.7)
- Infusion-related reactions: Discontinue OPDIVO for severe and life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. (5.9)
- Complications of allogeneic HSCT: Monitor for hyperacute, acute, and chronic graft-versus-host-disease (GVHD), hepatic veno-occlusive disease, and steroid-requiring febrile syndrome. (5.10)

- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and use of effective contraception. (5.11, 8.1, 8.3)
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.12)

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

Most common adverse reactions (incidence ≥20%) in patients were:

- As a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, and vomiting. (6.1)
- In combination with ipilimumab: fatigue, diarrhea, rash, pruritus, nausea, musculoskeletal pain, pyrexia, cough, decreased appetite, vomiting, abdominal pain, dyspnea, upper respiratory tract infection, arthralgia, headache, hypothyroidism, decreased weight, and dizziness. (6.1)
- In combination with ipilimumab and platinum-doublet chemotherapy: 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: 5/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

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

1.2 Adjuvant Treatment of Melanoma

OPDIVO is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

1.3 Metastatic Non-Small Cell Lung Cancer

- OPDIVO, in combination with ipilimumab, 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.
- OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
- OPDIVO is indicated for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

1.4 Small Cell Lung Cancer

OPDIVO is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy.

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 Advanced Renal Cell Carcinoma

- OPDIVO as a single agent is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
- OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with intermediate or poor risk, previously untreated advanced RCC.

1.6 Classical Hodgkin Lymphoma

OPDIVO is indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:

- autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
- 3 or more lines of systemic therapy that includes autologous HSCT.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.6)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.7 Squamous Cell Carcinoma of the Head and Neck

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

1.8 Urothelial Carcinoma

OPDIVO is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14.8)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

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

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.9)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.10 Hepatocellular Carcinoma

OPDIVO, as a single agent or in combination with ipilimumab, 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 (14.10)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with metastatic NSCLC for treatment with OPDIVO in combination with ipilimumab based on PD-L1 expression *[see Clinical Studies (14.3)]*.

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

2.2 Recommended Dosage

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

Table 1: Recommended Dosages for OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma Metastatic non-small cell lung cancer Advanced renal cell carcinoma Classical Hodgkin lymphoma Squamous cell carcinoma of the head and neck Urothelial carcinoma Hepatocellular carcinoma	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity
Adjuvant treatment of melanoma	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Until disease recurrence or unacceptable toxicity for up to 1 year
Small cell lung cancer	240 mg every 2 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks (30-minute intravenous infusion)	

The recommended dosages of OPDIVO in combination with ipilimumab or other therapeutic agents are presented in Table 2. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with OPDIVO for the recommended dosage information, as appropriate.

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

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg intravenously over 90 minutes on the same day	In combination with ipilimumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
Metastatic non-small cell lung cancer expressing PD-L1	3 mg/kg every 2 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion)	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
Metastatic or recurrent non-small cell lung cancer	360 mg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute intravenous infusion) and histology-based platinum doublet chemotherapy every 3 weeks	In combination with ipilimumab until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression
		2 cycles of histology-based platinum-doublet chemotherapy
Advanced renal cell carcinoma	3 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg intravenously over 30 minutes on the same day	In combination with ipilimumab for 4 doses
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity

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

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	3 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 1 mg/kg intravenously over 30 minutes on the same day	In combination with ipilimumab for 4 doses
	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks (30-minute intravenous infusion)	
Hepatocellular carcinoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg intravenously over 30 minutes on the same day	In combination with ipilimumab for 4 doses
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity

2.3 Dose Modifications

Recommendations for OPDIVO modifications are provided in Table 3. When OPDIVO is administered in combination with ipilimumab, if OPDIVO is withheld, ipilimumab should also be withheld. Review the Prescribing Information for ipilimumab for recommended dose modifications.

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions.

Table 3: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis/non-HCC[b]	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose[a]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis/HCC[b]	• If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN • If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN • If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Withhold dose[c]
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[a]
	Serum creatinine more than 6 times the ULN	Permanently discontinue

Table 3: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	 Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

[a] Resume treatment when adverse reaction improves to Grade 0 or 1.

[b] HCC: hepatocellular carcinoma.

[c] Resume treatment when AST/ALT returns to baseline.

2.4 Preparation and Administration

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

Preparation

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

- After preparation, store the diluted solution either:
  - at room temperature for no more than 8 hours from the time of preparation to end of the infusion. Discard diluted solution if not used within 8 hours from the time of preparation; or
  - under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to end of infusion. Discard diluted solution if not used within 24 hours from the time of preparation.
- Do not freeze.

Administration

- Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Administer OPDIVO in combination with other therapeutic agents as follows:
  - With ipilimumab: administer OPDIVO first followed by ipilimumab on the same day.
  - With platinum-doublet chemotherapy: administer OPDIVO first followed by platinum-doublet chemotherapy on the same day
  - With ipilimumab and platinum-doublet chemotherapy: administer OPDIVO first followed by ipilimumab and then platinum-doublet chemotherapy on the same day.
- Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not co-administer other drugs through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), and 240 mg/24 mL (10 mg/mL) clear to opalescent, colorless to pale-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology. Fatal cases have been reported.

Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. The median time to onset of immune-mediated pneumonitis was 3.5 months (range: 1 day to 22.3 months). Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO in 1.1% and withholding of OPDIVO in 1.3% of patients. Approximately 89% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 26 days (range: 1 day to 6 months). Complete resolution of symptoms following corticosteroid taper occurred in 67% of patients. Approximately 8% of patients had recurrence of pneumonitis after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Immune-mediated pneumonitis occurred in 6% (25/407) of patients with melanoma and 10% (5/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 1.6 months (range: 24 days to 10.1 months) in patients with melanoma and 8.3 months (range: 1.2 to 17.5 months) in patients with HCC.

Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO with ipilimumab in 2.9% of patients with melanoma or HCC (n=456) and withholding of OPDIVO with ipilimumab in 3.9%. All patients with pneumonitis required systemic corticosteroids, including 90% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1 month (5 days to 25 months). Complete resolution occurred in 81% of patients. Of the 18 patients in whom OPDIVO or ipilimumab was withheld for pneumonitis, 11 reinitiated treatment after symptom improvement; of these, 18% (2/11) had recurrence of pneumonitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated pneumonitis occurred in 4.4% (24/547) of patients with RCC and 1.7% (2/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset of immune-mediated pneumonitis was 2.6 months (range: 8 days to 9.2 months) in patients with RCC and 1.9 months (range: 27 days to 3 months) in patients with CRC.

Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO with ipilimumab in 1.8% of patients with RCC or CRC (n=666) and withholding of OPDIVO with ipilimumab in 1.7%. All patients with pneumonitis required systemic corticosteroids, including 92% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 19 days (range: 4 days to 3.2 months). Approximately 8% required addition of infliximab to high-dose corticosteroids. Complete resolution of pneumonitis occurred in 81% of patients. Pneumonitis recurred after re-initiation of OPDIVO with ipilimumab in one patient with CRC.

In NSCLC, immune-mediated pneumonitis occurred in 9% (50/576) of patients receiving OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 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 OPDIVO with ipilimumab in 5% of patients and withholding of OPDIVO with ipilimumab 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 OPDIVO with ipilimumab.

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

5.2 Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology.

Monitor patients for signs and symptoms of colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents.

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

Withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon re-initiation of OPDIVO *[see Dosage and Administration (2.3)]*.

When administered in combination with ipilimumab, withhold OPDIVO and ipilimumab for moderate colitis (Grade 2). Permanently discontinue OPDIVO and ipilimumab for severe or life-threatening (Grade 3 or 4) colitis or for recurrent colitis *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, immune-mediated colitis occurred in 2.9% (58/1994) of patients; the median time to onset was 5.3 months (range: 2 days to 20.9 months). Immune-mediated colitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 1% of patients. Approximately 91% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 23 days (range: 1 day to 9.3 months). Four patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 16% of patients had recurrence of colitis after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Immune-mediated colitis occurred in 26% (107/407) of patients with melanoma and 10% (5/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks,

including three fatal cases. Median time to onset was 1.6 months (range: 3 days to 15.2 months) in patients with melanoma and 2 months (range: 1.1 to 19 months) in patients with HCC.

Immune-mediated colitis led to permanent discontinuation of OPDIVO with ipilimumab in 14% of patients with melanoma or HCC (n=456) and withholding of OPDIVO with ipilimumab in 7%. All patients with colitis required systemic corticosteroids, including 92% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1 month (1 day to 30 months). Complete resolution occurred in 77% of patients. Of the 33 patients in whom OPDIVO or ipilimumab was withheld for colitis, 20 reinitiated treatment after symptom improvement; of these, 40% (8/20) had recurrence of colitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated colitis occurred in 10% (52/547) of patients with RCC and 7% (8/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset of immune-mediated colitis was 1.7 months (range: 2 days to 19.2 months) in patients with RCC and 2.4 months (range: 22 days to 5.2 months) in patients with mCRC.

Immune-mediated colitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.2% of patients with RCC or CRC (n=666) and withholding of OPDIVO with ipilimumab in 3.9%. All patients with colitis required systemic corticosteroids, including 80% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 21 days (range: 1 day to 27 months). Approximately 23% of patients with immune-mediated colitis required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 88% of patients. Two patients with RCC had recurrence of colitis after re-initiation of OPDIVO with ipilimumab.

5.3 Immune-Mediated Hepatitis

OPDIVO can cause immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations.

For patients without hepatocellular carcinoma (HCC): withhold OPDIVO for moderate (Grade 2) immune-mediated hepatitis and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.3)]*.

For patients with HCC, permanently discontinue, withhold, or continue OPDIVO based on severity of immune-mediated hepatitis and baseline AST and ALT levels as described in Table 3 *[see Dosage and Administration (2.3)]*. In addition, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper when OPDIVO is withheld or discontinued due to immune-mediated hepatitis.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients; the median time to onset was 3.3 months (range: 6 days to 9 months). Immune-mediated hepatitis led to permanent discontinuation of OPDIVO in 0.7% and withholding

of OPDIVO in 1% of patients. All patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 23 days (range: 1 day to 2 months). Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 29% of patients had recurrence of hepatitis after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Immune-mediated hepatitis occurred in 13% (51/407) of patients with melanoma and 20% (10/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 2.1 months (range: 15 days to 11 months) in patients with melanoma and 1.3 months (range: 22 days to 4.1 months) in patients with HCC.

Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 8% of patients with melanoma or HCC (n=456) and withholding of OPDIVO with ipilimumab in 7%. All patients with hepatitis required systemic corticosteroids, including 90% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1 month (1 day to 34 months). Complete resolution occurred in 77% of patients. Of the 30 patients in whom OPDIVO or ipilimumab was withheld for hepatitis, 13 reinitiated treatment after symptom improvement; of these, 8% (1/13) had recurrence of hepatitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated hepatitis occurred in 7% (38/547) of patients with RCC and 8% (10/119) with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 2 months (range: 14 days to 26.8 months) in patients with RCC and 2.2 months (range: 22 days to 10.5 months) in patients with CRC.

Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.6% of patients with RCC or CRC (n=666) and withholding of OPDIVO and ipilimumab in 3.5%. All patients with hepatitis required systemic corticosteroids, including 94% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1 month (range: 1 day to 7 months). Approximately 19% of patients with immune-mediated hepatitis required addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 83% of patients. No patients had recurrence of hepatitis after re-initiation of OPDIVO with ipilimumab.

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

OPDIVO can cause immune-mediated hypophysitis. Monitor patients for signs and symptoms of hypophysitis. Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3). Permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, hypophysitis occurred in 0.6% (12/1994) of patients; the median time to onset was 4.9 months (range: 1.4 to 11 months). Hypophysitis led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.2% of patients. Approximately 67% of patients with hypophysitis received hormone replacement therapy and 33% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 14 days (range: 5 to 26 days).

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Hypophysitis occurred in 9% (36/407) of patients with melanoma and 4% (2/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 2.7 months (range: 27 days to 5.5 months) in patients with melanoma and 3.7 months (range: 3 to 4.3 months) in patients with HCC.

Hypophysitis led to permanent discontinuation of OPDIVO with ipilimumab in 4 patients with melanoma or HCC (n=456) and withholding of OPDIVO with ipilimumab in 20 patients. Twenty-three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 17 days (1 day to 2 months). Complete resolution occurred in 16 patients.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Hypophysitis occurred in 4.6% (25/547) of patients with RCC and 3.4% (4/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 2.8 months (range: 1.3 months to 7.3 months) in patients with RCC and 3.7 months (range: 2.8 to 5.5 months) in patients with CRC.

Hypophysitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 1.2% and 2.6% of patients with RCC or CRC (n=666), respectively. Approximately 72% of patients with hypophysitis received hormone replacement therapy and 55% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 13 days (range: 1 day to 1.6 months).

Adrenal Insufficiency

OPDIVO can cause immune-mediated adrenal insufficiency. Monitor patients for signs and symptoms of adrenal insufficiency. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, adrenal insufficiency occurred in 1% (20/1994) of patients and the median time to onset was 4.3 months (range: 15 days to 21 months). Adrenal insufficiency led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.5% of patients. Approximately 85% of patients with adrenal insufficiency received

hormone replacement therapy and 25% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 11 days (range: 1 day to 1 month).

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Adrenal insufficiency occurred in 5% (21/407) of patients with melanoma and 18% (9/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 3.0 months (range: 21 days to 9.4 months) in patients with melanoma and 2.8 months (range: 1.4 to 8 months) in patients with HCC.

Adrenal insufficiency led to permanent discontinuation of OPDIVO with ipilimumab in 2 patients with melanoma or HCC (n=456) and withholding of OPDIVO with ipilimumab in 9 patients. Ten patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 8.5 days (1 day to 3 months). Complete resolution occurred in 13 patients.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Adrenal insufficiency occurred in 7% (41/547) of patients with RCC and 5.9% (7/119) patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 3.4 months (range: 2.0 months to 22.3 months) in RCC and 3.7 months (range: 2.5 to 13.4 months) in CRC.

Adrenal insufficiency led to permanent discontinuation of OPDIVO and ipilimumab in 1.2% of patients with RCC or CRC (n=666) and withholding of OPDIVO and ipilimumab in 2.6%. Approximately 94% of patients with adrenal insufficiency received hormone replacement therapy and 27% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 2 days to 5.6 months).

Hypothyroidism and Hyperthyroidism

OPDIVO can cause autoimmune thyroid disorders. Monitor thyroid function prior to and periodically during OPDIVO treatment. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of OPDIVO for hypothyroidism or hyperthyroidism.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients; the median time to onset was 2.9 months (range: 1 day to 16.6 months). Approximately 79% of patients with hypothyroidism received levothyroxine and 4% also required corticosteroids. Resolution occurred in 35% of patients.

Hyperthyroidism occurred in 2.7% (54/1994) of patients who received OPDIVO as a single agent; the median time to onset was 1.5 months (range: 1 day to 14.2 months). Approximately 26% of patients with hyperthyroidism received methimazole, 9% received carbimazole, 4% received propylthiouracil, and 9% received corticosteroids. Resolution occurred in 76% of patients.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients with melanoma and 22% (11/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 2.1 months (range: 1 day to 10.1 months) in patients with melanoma and 3.3 months (range: 1.4 to 16.2 months) in patients with HCC.

Hypothyroidism or thyroiditis resulting in hypothyroidism led to permanent discontinuation of OPDIVO with ipilimumab in 6 patients with melanoma or HCC (n=456) and withholding of OPDIVO with ipilimumab in 14 patients. Six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 27 days (19 days to 1.6 months). Complete resolution occurred in 50 patients.

Hyperthyroidism occurred in 8% (34/407) of patients with melanoma and 10% (5/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 23 days (range: 3 days to 3.7 months) in patients with melanoma and 1.4 months (range: 1.4 to 2.8 months) in patients with HCC.

Hyperthyroidism led to withholding of OPDIVO with ipilimumab in 14 patients with melanoma or HCC (n=456). Five patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 23 days (5 to 29 days). Complete resolution occurred in 38 patients.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (119/547) of patients with RCC and 15% (18/119) of patients with CRC who received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 2.2 months (range: 1 day to 21.4 months) in patients with RCC and 2.3 months (range: 22 days to 9.8 months) in patients with CRC. Of the 137 patients with RCC or CRC who developed hypothyroidism, approximately 81% of patients with RCC and 78% with CRC received levothyroxine.

Hyperthyroidism occurred in 12% (66/547) of patients with RCC and 12% (14/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 1.4 months (range: 6 days to 14.2 months) in RCC and 1.1 months (range: 21 days to 5.4 months) in CRC. Of the 80 patients with RCC or CRC who developed hyperthyroidism, approximately 15% received methimazole and 2% received carbimazole.

Type 1 Diabetes Mellitus

OPDIVO can cause Type 1 diabetes mellitus. Monitor for hyperglycemia. Withhold OPDIVO in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, diabetes occurred in 0.9% (17/1994) of patients including two cases of diabetic ketoacidosis. Median time to onset was 4.4 months (range: 15 days to 22 months).

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Diabetes occurred in 1.5% (6/407) of patients with melanoma who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time to onset was 2.5 months (range: 1.3 to 4.4 months). OPDIVO with ipilimumab was withheld in a patient and permanently discontinued in a second patient who developed diabetes.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Diabetes occurred in 2.7% (15/547) of patients with RCC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks; the median time to onset was 3.2 months (range: 19 days to 16.8 months). OPDIVO with ipilimumab was withheld in 33% of patients and permanently discontinued in 20% of patients who developed diabetes.

5.5 Immune-Mediated Nephritis and Renal Dysfunction

OPDIVO can cause immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents.

Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine. Permanently discontinue OPDIVO for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients; the median time to onset was 4.6 months (range: 23 days to 12.3 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.8% of patients. All patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 21 days (range: 1 day to 15.4 months). Complete resolution occurred in 48% of patients. No patients had recurrence of nephritis or renal dysfunction after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients with melanoma who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks. Median time

to onset was 2.7 months (range: 9 days to 7.9 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.7% and 0.5% of patients, respectively. Approximately 67% of patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 13.5 days (range: 1 day to 1.1 months). Complete resolution occurred in all patients. Two patients resumed OPDIVO with ipilimumab without recurrence of nephritis or renal dysfunction.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated nephritis and renal dysfunction occurred in 4.6% (25/547) of patients with RCC and 1.7% (2/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 3 months (range: 1 day to 13.2 months) among these 27 patients.

Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% of patients with RCC or CRC (n=666) and withholding of OPDIVO and ipilimumab in 2.3%. Approximately 78% of patients with immune-mediated nephritis and renal dysfunction received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 17 days (range: 1 day to 6 months). Complete resolution occurred in 63% of patients. One of 16 patients with RCC had recurrence of nephritis or renal dysfunction after re-initiation of OPDIVO with ipilimumab.

5.6 Immune-Mediated Skin Adverse Reactions

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue OPDIVO *[see Dosage and Administration (2.3)]*.

For immune-mediated rash, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, immune-mediated rash occurred in 9% (171/1994) of patients; the median time to onset was 2.8 months (range: <1 day to 25.8 months). Immune-mediated rash led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.8% of patients. Approximately 16% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 1 day to 8.9 months) and 85% received topical corticosteroids. Complete resolution occurred in 48% of patients. Recurrence of rash occurred in 1.4% of patients who resumed OPDIVO after resolution of rash.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Immune-mediated rash occurred in 22.6% (92/407) of patients with melanoma and 35% (17/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks.

Median time to onset was 18 days (range: 1 day to 9.7 months) in patients with melanoma and 15 days (range: 6 days to 3.1 months) in patients with HCC.

Immune-mediated rash led to permanent discontinuation of OPDIVO with ipilimumab in 0.4% of patients with melanoma or HCC (n=456) and withholding of OPDIVO with ipilimumab in 4.4%. All patients with rash required systemic corticosteroids, including 18% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (1 day to 5.3 months). Complete resolution occurred in 52% of patients. Of the 20 patients in whom OPDIVO or ipilimumab was withheld for rash, 12 reinitiated treatment after symptom improvement; of these, 17% (2/12) had recurrence of rash.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Immune-mediated rash occurred in 16% (90/547) of patients with RCC and 14% (17/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks. Median time to onset was 1.5 months (range: 1 day to 20.9 months) in RCC and 26 days (range: 5 days to 9.8 months) in CRC.

Immune-mediated rash led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.5% of patients with RCC or CRC (n=666) and withholding of OPDIVO with ipilimumab in 2.6% of patients. All patients with immune-mediated rash required systemic corticosteroids, including 19% who received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 22 days (range: 1 day to 23 months). Complete resolution occurred in 66% of patients. Immune-mediated rash recurred in approximately 3% (3/98) of patients who resumed OPDIVO and ipilimumab.

5.7 Immune-Mediated Encephalitis

OPDIVO can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a single agent, encephalitis occurred in 0.2% (3/1994). Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. In the other two patients, encephalitis occurred post-allogeneic HSCT *[see Warnings and Precautions (5.10)]*.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Encephalitis occurred in one patient (0.2%) with melanoma who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks after 1.7 months of exposure.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Encephalitis occurred in one patient (0.2%) with RCC after approximately 4 months of exposure and one patient (0.8%) with CRC after 15 days of exposure. The patient with CRC required infliximab and high-dose corticosteroids (at least 40 mg prednisone equivalents per day).

5.8 Other Immune-Mediated Adverse Reactions

OPDIVO can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.3)]*.

Across clinical trials of OPDIVO administered as a single agent or in combination with ipilimumab, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients who received OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients who received OPDIVO or OPDIVO in combination with ipilimumab and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

5.9 Infusion-Related Reactions

OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions *[see Dosage and Administration (2.3)]*.

OPDIVO as a Single Agent

In patients who received OPDIVO as a 60-minute intravenous infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients.

In a trial assessing the pharmacokinetics and safety of a more rapid infusion, in which patients received OPDIVO as a 60-minute intravenous infusion or a 30-minute intravenous infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

Infusion-related reactions occurred in 2.5% (10/407) of patients with melanoma and in 8% (4/49) of patients with HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

Infusion-related reactions occurred in 5.1% (28/547) of patients with RCC and 4.2% (5/119) of patients with CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, respectively.

5.10 Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1 receptor blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause) *[see Adverse Reactions (6.1)]*. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1 receptor blocking antibody prior to or after an allogeneic HSCT.

5.11 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.12 Increased Mortality in Patients with Multiple Myeloma when OPDIVO Is Added to a Thalidomide Analogue and Dexamethasone

In randomized clinical trials in patients with multiple myeloma, the addition of a PD-1 blocking antibody, including OPDIVO, to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

6 ADVERSE REACTIONS

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

- Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Colitis *[see Warnings and Precautions (5.2)]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions (5.3)]*

- Immune-Mediated Endocrinopathies *[see Warnings and Precautions (5.4)]*
- Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions (5.5)]*
- Immune-Mediated Skin Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Immune-Mediated Encephalitis *[see Warnings and Precautions (5.7)]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.8)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.10)]*

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in WARNINGS AND PRECAUTIONS reflect exposure to OPDIVO as a single agent in 1994 patients enrolled in CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 or a single-arm trial in NSCLC (n=117); OPDIVO 1 mg/kg with ipilimumab 3 mg/kg in patients enrolled in CHECKMATE-067 (n=313), CHECKMATE-040 (n=49), or another randomized trial (n=94); OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg (n=666) in patients enrolled in CHECKMATE-214 or CHECKMATE-142; OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks (n=576) in patients enrolled in CHECKMATE-227; and OPDIVO 360 mg with ipilimumab 1 mg/kg and 2 cycles of platinum-doublet chemotherapy in CHECKMATE-9LA (n=361).

Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

The safety of OPDIVO was evaluated in CHECKMATE-037, a randomized, open-label trial in 370 patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. Patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102): dacarbazine 1000 mg/m^2 intravenously every 3 weeks or carboplatin AUC 6 mg/mL/min and paclitaxel 175 mg/m^2 intravenously every 3 weeks. The median duration of exposure was 5.3 months (range: 1 day to 13.8+ months) in OPDIVO-treated patients and was 2 months (range: 1 day to 9.6+ months) in chemotherapy-treated patients. In this ongoing trial, 24% of patients received OPDIVO for >6 months and 3% of patients received OPDIVO for >1 year.

The population characteristics in the OPDIVO group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% White, baseline Eastern Cooperative Oncology Group (ECOG) performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the OPDIVO group with elevated lactate dehydrogenase (LDH) at baseline (51% vs. 38%).

Serious adverse reactions occurred in 41% of patients receiving OPDIVO. OPDIVO was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving OPDIVO had a dose interruption for an adverse reaction. Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. The most common adverse reaction (reported in ≥20% of patients) was rash.

Tables 4 and 5 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-037.

Table 4: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-037

Adverse Reaction	OPDIVO (n=268)		Chemotherapy (n=102)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	21	0.4	7	0
Pruritus	19	0	3.9	0
Respiratory, Thoracic and Mediastinal				
Cough	17	0	6	0
Infections				
Upper respiratory tract infection[b]	11	0	2.0	0
General				
Peripheral edema	10	0	5	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, and acneiform dermatitis.

[b] Includes rhinitis, pharyngitis, and nasopharyngitis.

Clinically important adverse reactions in <10% of patients who received OPDIVO were:

Cardiac Disorders: ventricular arrhythmia

Eye Disorders: iridocyclitis

General Disorders and Administration Site Conditions: infusion-related reactions

Investigations: increased amylase, increased lipase

Nervous System Disorders: dizziness, peripheral and sensory neuropathy

Skin and Subcutaneous Tissue Disorders: exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis

Table 5: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-037

Laboratory Abnormality	OPDIVO		Chemotherapy	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased AST	28	2.4	12	1.0
Hyponatremia	25	5	18	1.1
Increased alkaline phosphatase	22	2.4	13	1.1
Increased ALT	16	1.6	5	0
Hyperkalemia	15	2.0	6	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 252 to 256 patients) and chemotherapy group (range: 94 to 96 patients).

Previously Untreated Metastatic Melanoma

CHECKMATE-066

The safety of OPDIVO was also evaluated in CHECKMATE-066, a randomized, double-blind, active-controlled trial in 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease and patients requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=206) or dacarbazine 1000 mg/m^2 intravenously every 3 weeks (n=205). The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. In this trial, 47% of patients received OPDIVO for >6 months and 12% of patients received OPDIVO for >1 year.

The trial population characteristics in the OPDIVO group and dacarbazine group: 59% male, median age 65 years, 99.5% White, 61% with M1c stage disease, 74% with cutaneous melanoma, 11% with mucosal melanoma, 4% with brain metastasis, and 37% with elevated LDH at baseline. There were more patients in the OPDIVO group with ECOG performance status 0 (71% vs. 59%).

Serious adverse reactions occurred in 36% of patients receiving OPDIVO. Adverse reactions led to permanent discontinuation of OPDIVO in 7% of patients and dose interruption in 26% of patients; no single type of adverse reaction accounted for the majority of OPDIVO discontinuations. Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO.

The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of patients receiving OPDIVO were increased gamma-glutamyltransferase (3.9%) and diarrhea (3.4%). The most common adverse reactions (reported in ≥20% of patients and at a higher incidence than in the dacarbazine arm) were fatigue, musculoskeletal pain, rash, and pruritus.

Tables 6 and 7 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-066.

Table 6: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-066

Adverse Reaction	OPDIVO (n=206)		Dacarbazine (n=205)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue	49	1.9	39	3.4
Edema[a]	12	1.5	4.9	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	32	2.9	25	2.4
Skin and Subcutaneous Tissue				
Rash[c]	28	1.5	12	0
Pruritus	23	0.5	12	0
Vitiligo	11	0	0.5	0
Erythema	10	0	2.9	0
Infections				
Upper respiratory tract infection[d]	17	0	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes periorbital edema, face edema, generalized edema, gravitational edema, localized edema, peripheral edema, pulmonary edema, and lymphedema.

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

[c] Includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, dermatitis, allergic dermatitis, exfoliative dermatitis, acneiform dermatitis, drug eruption, and skin reaction.

[d] Includes rhinitis, viral rhinitis, pharyngitis, and nasopharyngitis.

Clinically important adverse reactions in <10% of patients who received OPDIVO were:

Nervous System Disorders: peripheral neuropathy

Table 7: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Dacarbazine Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-066

Laboratory Abnormality	OPDIVO		Dacarbazine	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased ALT	25	3.0	19	0.5
Increased AST	24	3.6	19	0.5
Increased alkaline phosphatase	21	2.6	14	1.6
Increased bilirubin	13	3.1	6	0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 194 to 197 patients) and dacarbazine group (range: 186 to 193 patients).

CHECKMATE-067

The safety of OPDIVO, administered with ipilimumab or as a single agent, was evaluated in CHECKMATE-067, a randomized (1:1:1), double-blind trial in 937 patients with previously untreated, unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease, a medical condition requiring systemic treatment with

corticosteroids (more than 10 mg daily prednisone equivalent) or other immunosuppressive medication within 14 days of the start of study therapy, a positive test result for hepatitis B or C, or a history of HIV.

Patients were randomized to receive:

- OPDIVO 1 mg/kg over 60 minutes with ipilimumab 3 mg/kg by intravenous infusion every 3 weeks for 4 doses followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO and ipilimumab arm; n=313), or
- OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (OPDIVO arm; n=313), or
- Ipilimumab 3 mg/kg by intravenous infusion every 3 weeks for up to 4 doses (ipilimumab arm; n=311).

The median duration of exposure to OPDIVO was 2.8 months (range: 1 day to 36.4 months) for the OPDIVO and ipilimumab arm and 6.6 months (range: 1 day to 36.0 months) for the OPDIVO arm. In the OPDIVO and ipilimumab arm, 39% were exposed to OPDIVO for ≥6 months and 30% exposed for >1 year. In the OPDIVO arm, 53% were exposed for ≥6 months and 40% for >1 year.

The population characteristics were: 65% male, median age 61 years, 97% White, baseline ECOG performance status 0 (73%) or 1 (27%), 93% with American Joint Committee on Cancer (AJCC) Stage IV disease, 58% with M1c stage disease; 36% with elevated LDH at baseline, 4% with a history of brain metastasis, and 22% had received adjuvant therapy.

Serious adverse reactions (74% and 44%), adverse reactions leading to permanent discontinuation (47% and 18%) or to dosing delays (58% and 36%), and Grade 3 or 4 adverse reactions (72% and 51%) all occurred more frequently in the OPDIVO and ipilimumab arm relative to the OPDIVO arm.

The most frequent (≥10%) serious adverse reactions in the OPDIVO and ipilimumab arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.2%), colitis (10% and 1.9%), and pyrexia (10% and 1.0%). The most frequent adverse reactions leading to discontinuation of both drugs in the OPDIVO and ipilimumab arm and of OPDIVO in the OPDIVO arm, respectively, were colitis (10% and 0.6%), diarrhea (8% and 2.2%), increased ALT (4.8% and 1.0%), increased AST (4.5% and 0.6%), and pneumonitis (1.9% and 0.3%).

The most common (≥20%) adverse reactions in the OPDIVO and ipilimumab arm were fatigue, diarrhea, rash, nausea, pyrexia, pruritus, musculoskeletal pain, vomiting, decreased appetite, cough, headache, dyspnea, upper respiratory tract infection, arthralgia, and increased transaminases. The most common (≥20%) adverse reactions in the OPDIVO arm were fatigue, rash, musculoskeletal pain, diarrhea, nausea, cough, pruritus, upper respiratory tract infection, decreased appetite, headache, constipation, arthralgia, and vomiting.

Tables 8 and 9 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-067.

Table 8: Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO and Ipilimumab Arm or the OPDIVO Arm and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067

Adverse Reaction	OPDIVO and Ipilimumab (n=313)		OPDIVO (n=313)		Ipilimumab (n=311)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General						
Fatigue[a]	62	7	59	1.6	51	4.2
Pyrexia	40	1.6	16	0	18	0.6
Gastrointestinal						
Diarrhea	54	11	36	5	47	7
Nausea	44	3.8	30	0.6	31	1.9
Vomiting	31	3.8	20	1.0	17	1.6
Skin and Subcutaneous Tissue						
Rash[b]	53	6	40	1.9	42	3.5
Vitiligo	9	0	10	0.3	5	0
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[c]	32	2.6	42	3.8	36	1.9
Arthralgia	21	0.3	21	1.0	16	0.3
Metabolism and Nutrition						
Decreased appetite	29	1.9	22	0	24	1.3
Respiratory, Thoracic and Mediastinal						
Cough/productive cough	27	0.3	28	0.6	22	0
Dyspnea/exertional dyspnea	24	2.9	18	1.3	17	0.6
Infections						
Upper respiratory tract infection[d]	23	0	22	0.3	17	0
Endocrine						
Hypothyroidism	19	0.6	11	0	5	0
Hyperthyroidism	11	1.3	6	0	1	0
Investigations						
Decreased weight	12	0	7	0	7	0.3
Vascular						
Hypertension[e]	7	2.2	11	5	9	2.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia and fatigue.

[b] Includes pustular rash, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, exfoliative dermatitis, psoriasiform dermatitis, drug eruption, exfoliative rash, erythematous rash, generalized rash, macular rash, maculopapular rash, morbilliform rash, papular rash, papulosquamous rash, and pruritic rash.

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

[d] Includes upper respiratory tract infection, nasopharyngitis, pharyngitis, and rhinitis.

[e] Includes hypertension and blood pressure increased.

Clinically important adverse reactions in <10% of patients who received OPDIVO with ipilimumab or OPDIVO as a single agent were:

Gastrointestinal Disorders: stomatitis, intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

Musculoskeletal and Connective Tissue Disorders: myopathy, Sjogren's syndrome, spondyloarthropathy, myositis (including polymyositis)

Nervous System Disorders: neuritis, peroneal nerve palsy

Table 9: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥20% of Patients Treated with OPDIVO with Ipilimumab or Single-Agent OPDIVO and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-067

Laboratory Abnormality	OPDIVO and Ipilimumab		OPDIVO		Ipilimumab	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry						
Increased ALT	55	16	25	3.0	29	2.7
Hyperglycemia	53	5.3	46	7	26	0
Increased AST	52	13	29	3.7	29	1.7
Hyponatremia	45	10	22	3.3	26	7
Increased lipase	43	22	32	12	24	7
Increased alkaline phosphatase	41	6	27	2.0	23	2.0
Hypocalcemia	31	1.1	15	0.7	20	0.7
Increased amylase	27	10	19	2.7	15	1.6
Increased creatinine	26	2.7	19	0.7	17	1.3
Hematology						
Anemia	52	2.7	41	2.6	41	6
Lymphopenia	39	5	41	4.9	29	4.0

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab (range: 75 to 297); OPDIVO (range: 81 to 306); ipilimumab (range: 61 to 301).

Adjuvant Treatment of Melanoma

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-238, a randomized (1:1), double-blind trial in 905 patients with completely resected Stage IIIB/C or Stage IV melanoma received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=452) or ipilimumab 10 mg/kg by intravenous infusion every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year (n=453) *[see Clinical Studies (14.2)]*. The median duration of exposure was 11.5 months in OPDIVO-treated patients and was 2.7 months in ipilimumab-treated patients. In this ongoing trial, 74% of patients received OPDIVO for >6 months.

Serious adverse reactions occurred in 18% of OPDIVO-treated patients. Study therapy was discontinued for adverse reactions in 9% of OPDIVO-treated patients and 42% of ipilimumab-treated patients. Twenty-eight percent of OPDIVO-treated patients had at least one omitted dose for an adverse reaction. Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients.

The most frequent Grade 3 and 4 adverse reactions reported in ≥2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. The most common adverse reactions (at least 20%) were fatigue, diarrhea, rash, musculoskeletal pain, pruritus, headache, nausea, upper respiratory infection, and abdominal pain. The most common immune-mediated adverse reactions were rash (16%), diarrhea/colitis (6%), and hepatitis (3%).

Tables 10 and 11 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-238.

Table 10: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238

Adverse Reaction	OPDIVO (n=452)		Ipilimumab 10 mg/kg (n=453)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	57	0.9	55	2.4
Gastrointestinal				
Diarrhea	37	2.4	55	11
Nausea	23	0.2	28	0
Abdominal pain[b]	21	0.2	23	0.9
Constipation	10	0	9	0
Skin and Subcutaneous Tissue				
Rash[c]	35	1.1	47	5.3
Pruritus	28	0	37	1.1
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	32	0.4	27	0.4
Arthralgia	19	0.4	13	0.4
Nervous System				
Headache	23	0.4	31	2.0
Dizziness[e]	11	0	8	0
Infections				
Upper respiratory tract infection[f]	22	0	15	0.2
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	19	0	19	0
Dyspnea/exertional dyspnea	10	0.4	10	0.2
Endocrine				
Hypothyroidism[g]	12	0.2	7.5	0.4

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.

[c] Includes dermatitis described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.

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

[e] Includes postural dizziness and vertigo.

[f] Includes upper respiratory tract infection including viral respiratory tract infection, lower respiratory tract infection, rhinitis, pharyngitis, and nasopharyngitis.

[g] Includes secondary hypothyroidism and autoimmune hypothyroidism.

Table 11: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients - CHECKMATE-238

Laboratory Abnormality	OPDIVO		Ipilimumab 10 mg/kg	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	27	0.4	12	0.9
Anemia	26	0	34	0.5
Leukopenia	14	0	2.7	0.2
Neutropenia	13	0	6	0.5
Chemistry				
Increased Lipase	25	7	23	9
Increased ALT	25	1.8	40	12
Increased AST	24	1.3	33	9
Increased Amylase	17	3.3	13	3.1
Hyponatremia	16	1.1	22	3.2
Hyperkalemia	12	0.2	9	0.5
Increased Creatinine	12	0	13	0
Hypocalcemia	10	0.7	16	0.5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 400 to 447 patients) and ipilimumab 10 mg/kg group (range: 392 to 443 patients).

Metastatic Non-Small Cell Lung Cancer

First-line Treatment of Metastatic NSCLC: In Combination with Ipilimumab

The safety of OPDIVO in combination with ipilimumab 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 (14.3)]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received OPDIVO 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks and ipilimumab 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO and ipilimumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received OPDIVO and ipilimumab for >6 months and 23% of patients received OPDIVO and ipilimumab 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. OPDIVO and ipilimumab 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 12 and 13 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 12: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-227

Adverse Reaction	OPDIVO and Ipilimumab (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
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

Table 12: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-227

Adverse Reaction	OPDIVO and Ipilimumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
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.
[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 13: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-227

Laboratory Abnormality	OPDIVO and Ipilimumab		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				
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: OPDIVO and ipilimumab 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 Ipilimumab and Platinum-Doublet Chemotherapy

The safety of OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.3)]*. Patients received either OPDIVO 360 mg administered every 3 weeks in combination with ipilimumab 1 mg/kg administered every 6 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 OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received OPDIVO and ipilimumab for >6 months and 13% of patients received OPDIVO and ipilimumab for >1 year.

Serious adverse reactions occurred in 57% of patients who were treated with OPDIVO in combination with ipilimumab 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 OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was permanently discontinued for adverse reactions in 24% of patients and 56% had at least one treatment withheld for an adverse reaction. The most common (>20%) adverse reactions were fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus.

Tables 14 and 15 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9LA.

Table 14: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

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

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

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

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

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

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

[f] Includes pruritus and generalized pruritus

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

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

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

[j] Includes dizziness, vertigo and positional vertigo

Table 15: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	OPDIVO and Ipilimumab 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: OPDIVO and ipilimumab and platinum-doublet chemotherapy group (range: 197 to 347 patients) and platinum-doublet chemotherapy group (range: 191 to 335 patients).

Second-line Treatment of Metastatic NSCLC

The safety of OPDIVO was evaluated in CHECKMATE-017, a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.3)]*. These trials excluded patients with active autoimmune disease, medical conditions requiring

systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received OPDIVO 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks or docetaxel 75 mg/m^2 intravenously every 3 weeks. The median duration of therapy in OPDIVO-treated patients in CHECKMATE-017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1 year and in CHECKMATE-057, 30% of patients received OPDIVO for >6 months and 20% of patients received OPDIVO for >1 year.

Across both trials, the median age of OPDIVO-treated patients was 61 years (range: 37 to 85); 38% were ≥65 years of age, 61% were male, and 91% were White. Ten percent of patients had brain metastases and ECOG performance status was 0 (26%) or 1 (74%).

In CHECKMATE-057, in the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. Serious adverse reactions occurred in 46% of patients receiving OPDIVO. OPDIVO was discontinued in 11% of patients and was delayed in 28% of patients for an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. Across both trials, the most common adverse reactions (≥20%) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

Tables 16 and 17 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-057.

Table 16: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057

Adverse Reaction	OPDIVO (n=418)		Docetaxel (n=397)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Respiratory, Thoracic and Mediastinal				
Cough	31	0.7	24	0
Metabolism and Nutrition				
Decreased appetite	28	1.4	23	1.5
Skin and Subcutaneous Tissue				
Pruritus	10	0.2	2.0	0

Toxicity was graded per NCI CTCAE v4.

Other clinically important adverse reactions observed in OPDIVO-treated patients and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (48% all Grades, 5% Grade 3-4), musculoskeletal pain (33% all Grades), pleural effusion (4.5% all Grades), pulmonary embolism (3.3% all Grades).

Table 17: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% All Grades or ≥2% Grades 3-4) - CHECKMATE-017 and CHECKMATE-057

Laboratory Abnormality	OPDIVO		Docetaxel	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Hyponatremia	35	7	34	4.9
Increased AST	27	1.9	13	0.8
Increased alkaline phosphatase	26	0.7	18	0.8
Increased ALT	22	1.7	17	0.5
Increased creatinine	18	0	12	0.5
Increased TSH[b]	14	N/A	6	N/A

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 405 to 417 patients) and docetaxel group (range: 372 to 390 patients), except for TSH: OPDIVO group n=314 and docetaxel group n=297.

[b] Not graded per NCI CTCAE v4.

Small Cell Lung Cancer

The safety of OPDIVO was evaluated in CHECKMATE-032, a multicenter, multi-cohort, open-label, ongoing trial that enrolled 245 patients with SCLC with disease progression after platinum-based chemotherapy *[see Clinical Studies (14.4)]*. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks. The median duration of therapy in OPDIVO-treated patients was 1 month (range: 0 to 44.2+ months): 17% of patients received OPDIVO for >6 months and 9% of patients received OPDIVO for >1 year.

The population characteristics were: median age 63 years (range: 29 to 83), 92% White, and 60% male. Baseline ECOG performance status was 0 (30%) or 1 (70%), 94% were former/current smokers, 56% received one prior line of therapy, and 44% received two or more prior lines of therapy.

Serious adverse reactions occurred in 45% of patients. OPDIVO was discontinued for adverse reactions in 10% of patients and 25% of patients had at least one dose withheld for an adverse reaction.

The most frequent (≥2%) serious adverse reactions were pneumonia, dyspnea, pneumonitis, pleural effusion, and dehydration. The most common (≥20%) adverse reactions were fatigue, decreased appetite, musculoskeletal pain, dyspnea, nausea, diarrhea, constipation, and cough.

The toxicity profile observed in patients with metastatic SCLC was generally similar to that observed in patients with other solid tumors who received OPDIVO as a single agent.

Advanced Renal Cell Carcinoma

Previously Treated Renal Cell Carcinoma

The safety of OPDIVO was evaluated in CHECKMATE-025, a randomized open-label trial in 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimen received OPDIVO 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.5)]*. The median duration of treatment was 5.5 months (range: 1 day to 29.6+ months) in OPDIVO-treated patients and 3.7 months (range: 6 days to 25.7+ months) in everolimus-treated patients.

Rate of death on treatment or within 30 days of the last dose was 4.7% on the OPDIVO arm. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. Study therapy was discontinued for adverse reactions in 16% of OPDIVO patients. Forty-four percent (44%) of patients receiving OPDIVO had a dose interruption for an adverse reaction.

The most frequent serious adverse reactions in at least 2% of patients were: acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. The most common adverse reactions (≥20%) were fatigue, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of patients include increased creatinine, lymphopenia, anemia, increased AST, increased alkaline phosphatase, hyponatremia, increased triglycerides, and hyperkalemia. In addition, among patients with TSH < ULN at baseline, a greater proportion of patients experienced a treatment-emergent elevation of TSH >ULN in the OPDIVO group compared to the everolimus group (26% and 14%, respectively).

Tables 18 and 19 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-025.

Table 18: Adverse Reactions in >15% of Patients Receiving OPDIVO - CHECKMATE-025

Adverse Reaction	OPDIVO (n=406)		Everolimus (n=397)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Adverse Reaction	98	56	96	62
General				
Fatigue[a]	56	6	57	7
Pyrexia	17	0.7	20	0.8
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	34	0	38	0.5
Dyspnea/exertional dyspnea	27	3.0	31	2.0
Upper respiratory infection[b]	18	0	11	0
Gastrointestinal				
Nausea	28	0.5	29	1
Diarrhea[c]	25	2.2	32	1.8
Constipation	23	0.5	18	0.5
Vomiting	16	0.5	16	0.5
Skin and Subcutaneous Tissue				
Rash[d]	28	1.5	36	1.0
Pruritus/generalized pruritus	19	0	14	0

Table 18: Adverse Reactions in >15% of Patients Receiving OPDIVO - CHECKMATE-025

Adverse Reaction	OPDIVO (n=406)		Everolimus (n=397)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Metabolism and Nutrition				
Decreased appetite	23	1.2	30	1.5
Musculoskeletal and Connective Tissue				
Arthralgia	20	1.0	14	0.5
Back pain	21	3.4	16	2.8

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia, decreased activity, fatigue, and malaise.

[b] Includes nasopharyngitis, pharyngitis, rhinitis, and viral upper respiratory infection (URI).

[c] Includes colitis, enterocolitis, and gastroenteritis.

[d] Includes dermatitis, acneiform dermatitis, erythematous rash, generalized rash, macular rash, maculopapular rash, papular rash, pruritic rash, erythema multiforme, and erythema.

Other clinically important adverse reactions in CHECKMATE-025 were:

General Disorders and Administration Site Conditions: peripheral edema/edema

Gastrointestinal Disorders: abdominal pain/discomfort

Musculoskeletal and Connective Tissue Disorders: extremity pain, musculoskeletal pain

Nervous System Disorders: headache/migraine, peripheral neuropathy

Investigations: weight decreased

Skin Disorders: palmar-plantar erythrodysesthesia

Table 19: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on OPDIVO - CHECKMATE-025

Laboratory Abnormality	OPDIVO		Everolimus	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	42	6	53	11
Anemia	39	8	69	16
Chemistry				
Increased creatinine	42	2.0	45	1.6
Increased AST	33	2.8	39	1.6
Increased alkaline phosphatase	32	2.3	32	0.8
Hyponatremia	32	7	26	6
Hyperkalemia	30	4.0	20	2.1
Hypocalcemia	23	0.9	26	1.3
Increased ALT	22	3.2	31	0.8
Hypercalcemia	19	3.2	6	0.3
Lipids				
Increased triglycerides	32	1.5	67	11
Increased cholesterol	21	0.3	55	1.4

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range: 259 to 401 patients) and everolimus group (range: 257 to 376 patients).

Previously Untreated Renal Cell Carcinoma

The safety of OPDIVO with ipilimumab was evaluated in CHECKMATE-214, a randomized open-label trial in 1082 patients with previously untreated advanced RCC received OPDIVO 3 mg/kg over 60 minutes with ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (n=547) or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=535) *[see Clinical Studies (14.5)]*. The median duration of treatment was 7.9 months (range: 1 day to 21.4+ months) in OPDIVO and ipilimumab-treated patients and 7.8 months (range: 1 day to 20.2+ months) in sunitinib-treated patients. In this trial, 57% of patients in the OPDIVO and ipilimumab arm were exposed to treatment for >6 months and 38% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 59% of patients receiving OPDIVO and ipilimumab. Study therapy was discontinued for adverse reactions in 31% of OPDIVO and ipilimumab patients. Fifty-four percent (54%) of patients receiving OPDIVO and ipilimumab had a dose interruption for an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO and ipilimumab were diarrhea, pyrexia, pneumonia, pneumonitis, hypophysitis, acute kidney injury, dyspnea, adrenal insufficiency, and colitis; in patients treated with sunitinib, they were pneumonia, pleural effusion, and dyspnea. The most common adverse reactions (reported in ≥20% of patients) were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, and decreased appetite. The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of OPDIVO and ipilimumab-treated patients include increased lipase, anemia, increased creatinine, increased ALT, increased AST, hyponatremia, increased amylase, and lymphopenia.

Tables 20 and 21 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in >15% of OPDIVO and ipilimumab-treated patients in CHECKMATE-214.

Table 20: Adverse Reactions in >15% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-214

Adverse Reaction	**OPDIVO and Ipilimumab (n=547)**		**Sunitinib (n=535)**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Adverse Reaction	99	65	99	76
General				
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

Table 20: Adverse Reactions in >15% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-214

Adverse Reaction	OPDIVO and Ipilimumab (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 21: Laboratory Values Worsening from Baseline[a] Occurring in >15% of Patients on OPDIVO and Ipilimumab - CHECKMATE-214

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

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO and ipilimumab 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 OPDIVO and ipilimumab group compared to the sunitinib group (31% and 61%, respectively).

Classical Hodgkin Lymphoma

The safety of OPDIVO was evaluated in 266 adult patients with cHL (243 patients in the CHECKMATE-205 and 23 patients in the CHECKMATE-039 trials) *[see Clinical Studies (14.6)]*. Patients received OPDIVO 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity.

The median age was 34 years (range: 18 to 72), 98% of patients had received autologous HSCT, none had received allogeneic HSCT, and 74% had received brentuximab vedotin. The median number of prior systemic regimens was 4 (range: 2 to 15). Patients received a median of 23 doses (cycles) of OPDIVO (range: 1 to 48), with a median duration of therapy of 11 months (range: 0 to 23 months).

Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last nivolumab dose, 2 from infection 8 to 9 months after completing nivolumab, and 6 from complications of allogeneic HSCT. Serious adverse reactions occurred in 26% of patients. Dose delay for an adverse reaction occurred in 34% of patients. OPDIVO was discontinued due to adverse reactions in 7% of patients.

The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. The most common adverse reactions (≥20%) among all patients were upper respiratory tract infection, fatigue, cough, diarrhea, pyrexia, musculoskeletal pain, rash, nausea, and pruritus.

Tables 22 and 23 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-205 and CHECKMATE-039.

Table 22: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

Adverse Reaction[a]	**OPDIVO (n=266)**	
	All Grades (%)	**Grades 3-4 (%)**
Infections		
Upper respiratory tract infection[b]	44	0.8
Pneumonia/bronchopneumonia[c]	13	3.8
Nasal congestion	11	0
General		
Fatigue[d]	39	1.9
Pyrexia	29	<1
Respiratory, Thoracic and Mediastinal		
Cough/productive cough	36	0
Dyspnea/exertional dyspnea	15	1.5
Gastrointestinal		
Diarrhea[e]	33	1.5
Nausea	20	0
Vomiting	19	<1
Abdominal pain[f]	16	<1
Constipation	14	0.4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[g]	26	1.1
Arthralgia	16	<1

Table 22: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

Adverse Reaction[a]	OPDIVO (n=266)	
	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue		
Rash[h]	24	1.5
Pruritus	20	0
Nervous System		
Headache	17	<1
Neuropathy peripheral[i]	12	<1
Injury, Poisoning and Procedural Complications		
Infusion-related reaction	14	<1
Endocrine		
Hypothyroidism/thyroiditis	12	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes events occurring up to 30 days after last nivolumab dose, regardless of causality. After an immune-mediated adverse reaction, reactions following nivolumab rechallenge were included if they occurred up to 30 days after completing the initial nivolumab course.

[b] Includes nasopharyngitis, pharyngitis, rhinitis, and sinusitis.

[c] Includes pneumonia bacterial, pneumonia mycoplasmal, pneumocystis jirovecii pneumonia.

[d] Includes asthenia.

[e] Includes colitis.

[f] Includes abdominal discomfort and upper abdominal pain.

[g] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, and pain in extremity.

[h] Includes dermatitis, dermatitis acneiform, dermatitis exfoliative, and rash described as macular, papular, maculopapular, pruritic, exfoliative, or acneiform.

[i] Includes hyperesthesia, hypoesthesia, paresthesia, dysesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy. These numbers are specific to treatment-emergent events.

Additional information regarding clinically important adverse reactions:

Immune-mediated pneumonitis: In CHECKMATE-205 and CHECKMATE-039, pneumonitis, including interstitial lung disease, occurred in 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO (one Grade 3 and 12 Grade 2). The median time to onset was 4.5 months (range: 5 days to 12 months). All 13 patients received systemic corticosteroids, with resolution in 12. Four patients permanently discontinued OPDIVO due to pneumonitis. Eight patients continued OPDIVO (three after dose delay), of whom two had recurrence of pneumonitis.

Peripheral neuropathy: Treatment-emergent peripheral neuropathy was reported in 12% (31/266) of all patients receiving OPDIVO. Twenty-eight patients (11%) had new-onset peripheral neuropathy and 3 patients had worsening of neuropathy from baseline. The median time to onset was 50 (range: 1 to 309) days.

Complications of allogeneic HSCT after OPDIVO: Of 17 patients with cHL from the CHECKMATE-205 and CHECKMATE-039 trials who underwent allogeneic HSCT after treatment with OPDIVO, 6 patients (35%) died from transplant-related complications. Five deaths occurred in the setting of severe (Grade 3 to 4) or refractory GVHD. Hyperacute GVHD occurred in 2 patients (12%) and Grade 3 or higher GVHD was reported in 5 patients (29%). Hepatic VOD

occurred in 1 patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure.

Table 23 summarizes laboratory abnormalities in patients with cHL. The most common (≥20%) treatment-emergent laboratory abnormalities included cytopenias, liver function abnormalities, and increased lipase. Other common findings (≥10%) included increased creatinine, electrolyte abnormalities, and increased amylase.

Table 23: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

Laboratory Abnormality	OPDIVO[a] (n=266)	
	All Grades (%)[b]	Grades 3-4 (%)[b]
Hematology		
Leukopenia	38	4.5
Neutropenia	37	5
Thrombocytopenia	37	3.0
Lymphopenia	32	11
Anemia	26	2.6
Chemistry[c]		
Increased AST	33	2.6
Increased ALT	31	3.4
Increased lipase	22	9
Increased alkaline phosphatase	20	1.5
Hyponatremia	20	1.1
Hypokalemia	16	1.9
Increased creatinine	16	<1
Hypocalcemia	15	<1
Hyperkalemia	15	1.5
Hypomagnesemia	14	<1
Increased amylase	13	1.5
Increased bilirubin	11	1.5

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement: range: 203 to 266 patients.

[b] Includes events occurring up to 30 days after last nivolumab dose. After an immune-mediated adverse reaction, reactions following nivolumab rechallenge were included if they occurred within 30 days of completing the initial nivolumab course.

[c] In addition, in the safety population, fasting hyperglycemia (all grade 1-2) was reported in 27 of 69 (39%) evaluable patients and fasting hypoglycemia (all grade 1-2) in 11 of 69 (16%).

Squamous Cell Carcinoma of the Head and Neck

The safety of OPDIVO was evaluated in CHECKMATE-141, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCHN with progression during or within 6 months of receiving prior platinum-based therapy *[see Clinical Studies (14.7)]*. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma). Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=236) or investigator's choice of either:

- cetuximab (n=13), 400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly, or
- methotrexate (n=46) 40 to 60 mg/m^2 intravenously weekly, or
- docetaxel (n=52) 30 to 40 mg/m^2 intravenously weekly.

The median duration of exposure to nivolumab was 1.9 months (range: 1 day to 16.1+ months) in OPDIVO-treated patients. In this trial, 18% of patients received OPDIVO for >6 months and 2.5% of patients received OPDIVO for >1 year.

The median age of all randomized patients was 60 years (range: 28 to 83); 28% of patients in the OPDIVO group were ≥65 years of age and 37% in the comparator group were ≥65 years of age, 83% were male and 83% were White, 12% were Asian, and 4% were Black. Baseline ECOG performance status was 0 (20%) or 1 (78%), 45% of patients received only one prior line of systemic therapy, the remaining 55% of patients had two or more prior lines of therapy, and 90% had prior radiation therapy.

Serious adverse reactions occurred in 49% of patients receiving OPDIVO. OPDIVO was discontinued in 14% of patients and was delayed in 24% of patients for an adverse reaction. Adverse reactions and laboratory abnormalities occurring in patients with SCCHN were generally similar to those occurring in patients with melanoma and NSCLC.

The most frequent serious adverse reactions reported in ≥2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. The most common adverse reactions occurring in ≥10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were cough and dyspnea. The most common laboratory abnormalities occurring in ≥10% of OPDIVO-treated patients and at a higher incidence than investigator's choice were increased alkaline phosphatase, increased amylase, hypercalcemia, hyperkalemia, and increased TSH.

Urothelial Carcinoma

The safety of OPDIVO was evaluated in CHECKMATE-275, a single arm trial in which 270 patients with locally advanced or metastatic urothelial carcinoma had disease progression during or following platinum-containing chemotherapy or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.8)]*. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 3.3 months (range: 0 to 13.4+). Forty-six percent (46%) of patients had a dose interruption for an adverse reaction.

Fourteen patients (5.2%) died from causes other than disease progression. This includes 4 patients (1.5%) who died from pneumonitis or cardiovascular failure which was attributed to treatment with OPDIVO. Serious adverse reactions occurred in 54% of patients. OPDIVO was discontinued for adverse reactions in 17% of patients.

The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. The most common adverse reactions (reported in ≥20% of patients) were fatigue, musculoskeletal pain, nausea, and decreased appetite.

Tables 24 and 25 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-275.

Table 24: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275

Adverse Reaction	OPDIVO (n=270)	
	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	99	51
General		
Asthenia/fatigue/malaise	46	7
Pyrexia/tumor associated fever	17	0.4
Edema/peripheral edema/peripheral swelling	13	0.4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[a]	30	2.6
Arthralgia	10	0.7
Metabolism and Nutrition		
Decreased appetite	22	2.2
Gastrointestinal		
Nausea	22	0.7
Diarrhea	17	2.6
Constipation	16	0.4
Abdominal pain[b]	13	1.5
Vomiting	12	1.9
Respiratory, Thoracic and Mediastinal		
Cough/productive cough	18	0
Dyspnea/exertional dyspnea	14	3.3
Infections		
Urinary tract infection/escherichia/fungal urinary tract infection	17	7
Skin and Subcutaneous Tissue		
Rash[c]	16	1.5
Pruritus	12	0
Endocrine		
Thyroid disorders[d]	15	0

Toxicity was graded per NCI CTCAE v4.

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

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

[c] Includes dermatitis, dermatitis acneiform, dermatitis bullous, and rash described as generalized, macular, maculopapular, or pruritic.

[d] Includes autoimmune thyroiditis, blood TSH decrease, blood TSH increase, hyperthyroidism, hypothyroidism, thyroiditis, thyroxine decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine free increased, tri-iodothyronine increased.

Table 25: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients - CHECKMATE-275

Laboratory Abnormality	OPDIVO[a]	
	All Grades (%)	Grades 3-4 (%)
Chemistry		
Hyperglycemia	42	2.4
Hyponatremia	41	11
Increased creatinine	39	2.0
Increased alkaline phosphatase	33	5.5
Hypocalcemia	26	0.8
Increased AST	24	3.5
Increased lipase	20	7
Hyperkalemia	19	1.2
Increased ALT	18	1.2
Increased amylase	18	4.4
Hypomagnesemia	16	0
Hematology		
Lymphopenia	42	9
Anemia	40	7
Thrombocytopenia	15	2.4
Leukopenia	11	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: range: 84 to 256 patients.

MSI-H or dMMR Metastatic Colorectal Cancer

The safety of OPDIVO administered as a single agent or in combination with ipilimumab was evaluated in CHECKMATE-142, a multicenter, non-randomized, multiple parallel-cohort, open-label trial *[see Clinical Studies (14.9)]*. In CHECKMATE-142, 74 patients with mCRC received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or until intolerable toxicity and 119 patients with mCRC received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for 4 doses, then OPDIVO 3 mg/kg every 2 weeks until disease progression or until unacceptable toxicity.

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

Tables 26 and 27 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-142. Based on the design of CHECKMATE-142, the data below cannot be used to identify statistically significant differences between the two cohorts summarized below for any adverse reaction.

Table 26: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-142

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

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema and peripheral swelling.

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

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

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

[f] Includes nasopharyngitis and rhinitis.

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

Table 27: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-142

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

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

Hepatocellular Carcinoma

The safety of OPDIVO 3 mg/kg every 2 weeks as a single agent was evaluated in a 154-patient subgroup of patients with HCC and Child-Pugh Class A cirrhosis who progressed on or were intolerant to sorafenib. These patients enrolled in Cohorts 1 and 2 of CHECKMATE-040, a multicenter, multiple cohort, open-label trial *[see Clinical Studies (14.10)]*. Patients were required to have an AST and ALT ≤5 x ULN and total bilirubin <3 mg/dL. The median duration of exposure to OPDIVO was 5 months (range: 0 to 22+ months). Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, pneumonia, and anemia.

The toxicity profile observed in these patients with advanced HCC was generally similar to that observed in patients with other cancers, with the exception of a higher incidence of elevations in transaminases and bilirubin levels. Treatment with OPDIVO resulted in treatment-emergent Grade 3 or 4 AST in 27 (18%) patients, Grade 3 or 4 ALT in 16 (11%) patients, and Grade 3 or 4 bilirubin in 11 (7%) patients. Immune-mediated hepatitis requiring systemic corticosteroids occurred in 8 (5%) patients.

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

ipilimumab combination period, 33 of 49 (67%) patients received all 4 planned doses of OPDIVO and ipilimumab. During the entire treatment period, the median duration of exposure to OPDIVO was 5.1 months (range: 0 to 35+ months) and to ipilimumab was 2.1 months (range: 0 to 4.5 months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

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

Tables 28 and 29 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-040. Based on the design of the study, the data below cannot be used to identify statistically significant differences between the cohorts summarized below for any adverse reaction.

Table 28: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 or OPDIVO in Cohorts 1 and 2 of CHECKMATE-040

Adverse Reaction	OPDIVO and Ipilimumab (n=49)		OPDIVO (n=154)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash	53	8	26	0.6
Pruritus	53	4	27	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain	41	2	36	1.9
Arthralgia	10	0	8	0.6
Gastrointestinal				
Diarrhea	39	4	27	1.3
Abdominal pain	22	6	34	3.9
Nausea	20	0	16	0
Ascites	14	6	9	2.6
Constipation	14	0	16	0
Dry mouth	12	0	9	0
Dyspepsia	12	2	8	0
Vomiting	12	2	14	0
Stomatitis	10	0	7	0
Abdominal distension	8	0	11	0
Respiratory, Thoracic and Mediastinal				
Cough	37	0	23	0
Dyspnea	14	0	13	1.9
Pneumonitis	10	2	1.3	0.6
Metabolism and Nutrition				
Decreased appetite	35	2	22	1.3
General				
Fatigue	27	2	38	3.2
Pyrexia	27	0	18	0.6
Malaise	18	2	6.5	0
Edema	16	2	12	0
Influenza-like illness	14	0	9	0

Table 28: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 or OPDIVO in Cohorts 1 and 2 of CHECKMATE-040

Adverse Reaction	OPDIVO and Ipilimumab (n=49)		OPDIVO (n=154)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chills	10	0	3.9	0
Nervous System				
Headache	22	0	11	0.6
Dizziness	20	0	9	0
Endocrine				
Hypothyroidism	20	0	4.5	0
Adrenal insufficiency	18	4	0.6	0
Investigations				
Weight decreased	20	0	7	0
Psychiatric				
Insomnia	18	0	10	0
Blood and Lymphatic System				
Anemia	10	4	19	2.6
Infections				
Influenza	10	2	1.9	0
Upper Respiratory Tract Infection	6	0	12	0
Vascular				
Hypotension	10	0	0.6	0

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

Table 29: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 or OPDIVO as a Single Agent in Cohorts 1 and 2 of CHECKMATE-040

Laboratory Abnormality	OPDIVO and Ipilimumab (n=47)		OPDIVO*	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	53	13	59	15
Anemia	43	4.3	49	4.6
Neutropenia	43	9	19	1.3
Leukopenia	40	2.1	26	3.3
Thrombocytopenia	34	4.3	36	7
Chemistry				
Increased AST	66	40	58	18
Increased ALT	66	21	48	11
Increased bilirubin	55	11	36	7
Increased lipase	51	26	37	14
Hyponatremia	49	32	40	11
Hypocalcemia	47	0	28	0

Table 29: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 or OPDIVO as a Single Agent in Cohorts 1 and 2 of CHECKMATE-040

Laboratory Abnormality	OPDIVO and Ipilimumab (n=47)		OPDIVO*	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alkaline phosphatase	40	4.3	44	7
Increased amylase	38	15	31	6
Hypokalemia	26	2.1	12	0.7
Hyperkalemia	23	4.3	20	2.6
Increased creatinine	21	0	17	1.3
Hypomagnesemia	11	0	13	0

* The denominator used to calculate the rate varied from 140 to 152 based on the number of patients with a baseline value and at least one post-treatment value.

In patients who received OPDIVO with ipilimumab, virologic breakthrough occurred in 4 of 28 (14%) patients and 2 of 4 (50%) patients with active HBV or HCV at baseline, respectively. In patients who received single-agent OPDIVO, virologic breakthrough occurred in 5 of 47 (11%) patients and 1 of 32 (3%) patients with active HBV or HCV at baseline, respectively. HBV virologic breakthrough was defined as at least a 1 log increase in HBV DNA for those patients with detectable HBV DNA at baseline. HCV virologic breakthrough was defined as a 1 log increase in HCV RNA from baseline.

6.2 Immunogenicity

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

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

Of the patients with melanoma, advanced renal cell carcinoma, metastatic colorectal cancer, and metastatic or recurrent non-small cell lung cancer who were treated with OPDIVO and ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26% (132/516) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks, 36.7% (180/491) with OPDIVO 3 mg/kg every 2 weeks and ipilimumab 1 mg every 6 weeks, and 38% (149/394) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralizing antibodies against nivolumab was 0.8% (4/516) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks, 1.4% (7/491) with OPDIVO

3 mg/kg every 2 weeks and ipilimumab 1 mg every 6 weeks, and 4.6% (18/394) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks.

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

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

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

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OPDIVO. 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.

Eye: Vogt-Koyanagi-Harada (VKH) syndrome

Complications of OPDIVO Treatment After Allogeneic HSCT: Treatment refractory, severe acute and chronic GVHD

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *(see Data)*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available data on OPDIVO use in pregnant women to evaluate a drug-associated risk. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to increase fetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. Based on its mechanism of action, fetal exposure to nivolumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

8.2 Lactation

Risk Summary

There are no data on the presence of nivolumab in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment and for 5 months after the last dose of OPDIVO.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

OPDIVO 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 OPDIVO and for at least 5 months following the last dose.

8.4 Pediatric Use

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

to pediatric patients *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.9)]*.

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

8.5 Geriatric Use

Of the 1359 patients randomized to single-agent OPDIVO in CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, and CHECKMATE-067, 39% were 65 years or older and 9% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

In CHECKMATE-275 (urothelial cancer), 55% of patients were 65 years or older and 14% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

In CHECKMATE-238 (adjuvant treatment of melanoma), 26% of patients were 65 years or older and 3% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

CHECKMATE-037, CHECKMATE-205, CHECKMATE-039, CHECKMATE-141, CHECKMATE-142, CHECKMATE-040, and CHECKMATE-032 did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

Of the 314 patients randomized to OPDIVO administered with ipilimumab in CHECKMATE-067, 41% were 65 years or older and 11% were 75 years or older. No overall differences in safety or effectiveness were reported between elderly patients and younger patients.

Of the 550 patients randomized to OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg 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 reported between elderly patients and younger patients. In elderly patients with intermediate or poor risk, no overall difference in effectiveness was reported.

Of the 49 patients who received OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in CHECKMATE-040 (hepatocellular carcinoma), 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of OPDIVO in combination with ipilimumab did not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients.

Of the 576 patients randomized to OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 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 OPDIVO with ipilimumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks 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 (14.3)]*.

Of the 361 patients randomized to OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 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 OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

11 DESCRIPTION

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line.

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles.

OPDIVO (nivolumab) injection for intravenous use is supplied in single-dose vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma and advanced RCC. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.

12.3 Pharmacokinetics

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent OPDIVO and OPDIVO with ipilimumab. The PK of nivolumab was studied in patients over a dose range of 0.1 mg/kg to 20 mg/kg administered as a single dose or as multiple

doses of OPDIVO as a 60-minute intravenous infusion every 2 or 3 weeks. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion. Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold.

Distribution

The geometric mean volume of distribution at steady state (Vss) and coefficient of variation (CV%) is 6.8 L (27.3%).

Elimination

Nivolumab clearance (CL) decreases over time, with a mean maximal reduction from baseline values (CV%) of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady state.

The geometric mean elimination half-life ($t_{1/2}$) is 25 days (77.5%).

Specific Populations

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

Drug Interaction Studies

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis–infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

CHECKMATE-037 (NCT01721746) was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive OPDIVO 3 mg/kg intravenously every 2 weeks or investigator's choice of chemotherapy, either single-agent dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 intravenously every 3 weeks and paclitaxel 175 mg/m^2 intravenously every 3 weeks. Patients were required to have progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

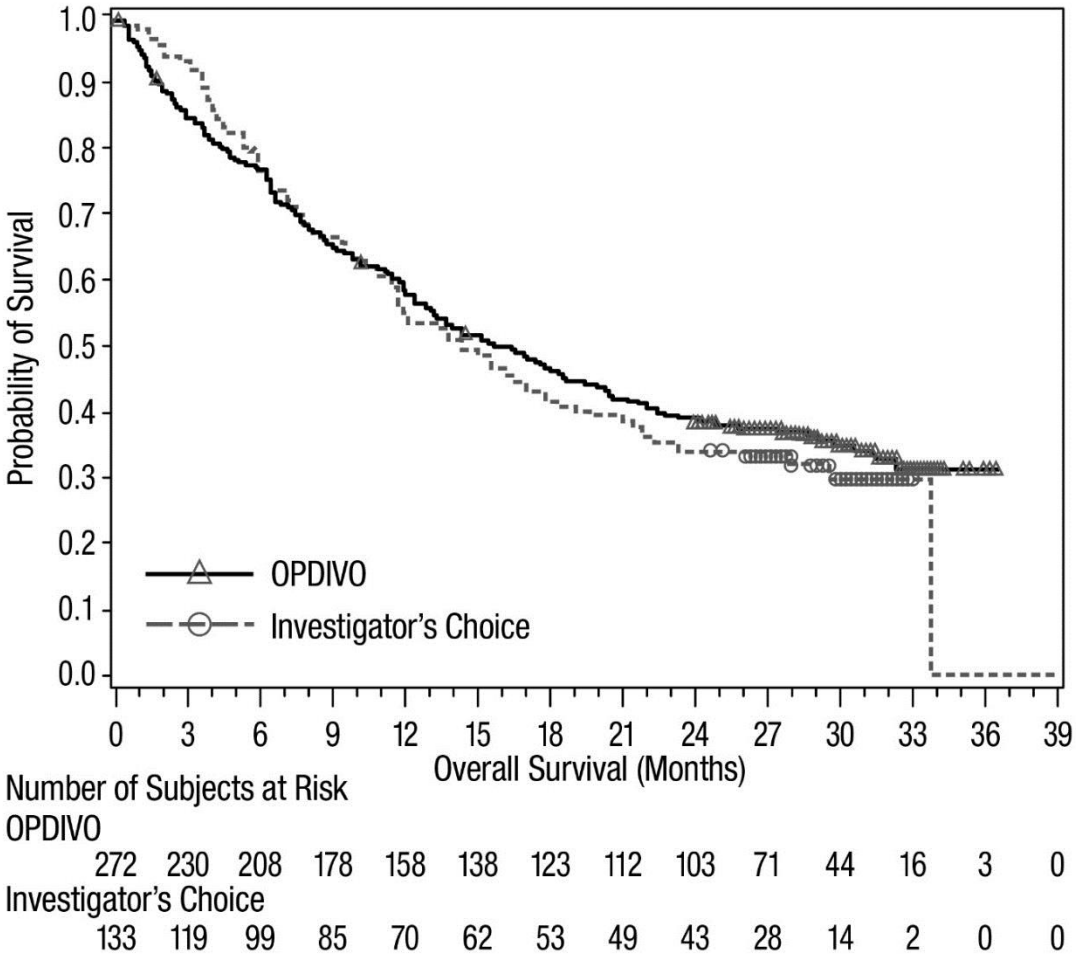
Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in CHECKMATE-037 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed overall response rate (ORR) as measured by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response.

Among the 120 patients treated with OPDIVO, the median age was 58 years (range: 25 to 88), 65% of patients were male, 98% were White, and the ECOG performance score was 0 (58%) or 1 (42%). Disease characteristics were M1c disease (76%), BRAF V600 mutation positive (22%), elevated LDH (56%), history of brain metastases (18%), and two or more prior systemic therapies for metastatic disease (68%).

The ORR was 32% (95% confidence interval [CI]: 23, 41), consisting of 4 complete responses and 34 partial responses in OPDIVO-treated patients. Of 38 patients with responses, 87% had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer.

There were responses in patients with and without BRAF V600 mutation-positive melanoma. A total of 405 patients were randomized and the median duration of OS was 15.7 months (95% CI: 12.9, 19.9) in OPDIVO-treated patients compared to 14.4 months (95% CI: 11.7, 18.2) (HR 0.95; 95.54% CI: 0.73, 1.24) in patients assigned to investigator's choice of treatment. Figure 1 summarizes the OS results.

Figure 1: Overall Survival - CHECKMATE-037*



* The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies, and differences in baseline factors.

Previously Untreated Metastatic Melanoma

CHECKMATE-066

CHECKMATE-066 (NCT01721772) was a multicenter, double-blind, randomized (1:1) trial in 418 patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were

randomized to receive either OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m^2 intravenously every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (≥5% of tumor cell membrane staining by immunohistochemistry vs. <5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). Key eligibility criteria included histologically confirmed, unresectable or metastatic, cutaneous, mucosal, or acral melanoma; no prior therapy for metastatic disease; completion of prior adjuvant or neoadjuvant therapy at least 6 weeks prior to randomization; ECOG performance status 0 or 1; absence of autoimmune disease; and absence of active brain or leptomeningeal metastases. The trial excluded patients with ocular melanoma. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year and then every 12 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Additional outcome measures included investigator-assessed progression-free survival (PFS) and ORR per RECIST v1.1.

The trial population characteristics were: median age was 65 years (range: 18 to 87), 59% were male, and 99.5% were White. Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (11%), elevated LDH level (37%), PD-L1 ≥5% tumor cell membrane expression (35%), and history of brain metastasis (4%). More patients in the OPDIVO arm had an ECOG performance status of 0 (71% vs. 58%).

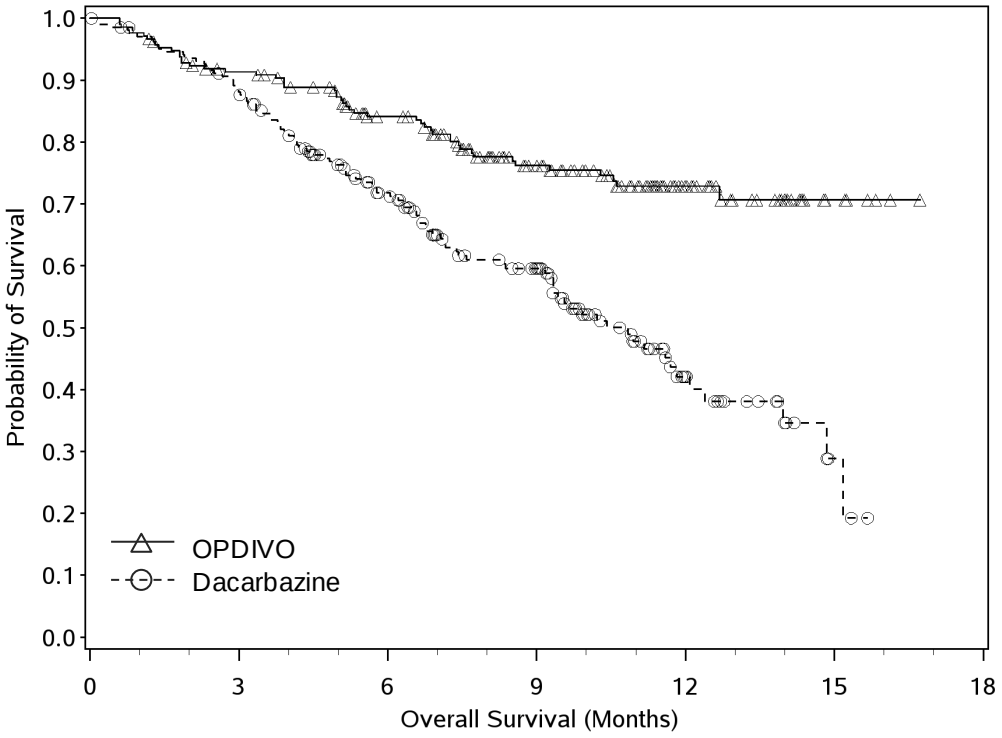
CHECKMATE-066 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. At the time of analysis, 88% (63/72) of OPDIVO-treated patients had ongoing responses, which included 43 patients with ongoing response of 6 months or longer. Efficacy results are shown in Table 30 and Figure 2.

Table 30: Efficacy Results - CHECKMATE-066

	OPDIVO (n=210)	**Dacarbazine (n=208)**
Overall Survival		
Deaths (%)	50 (24)	96 (46)
Median, months (95% CI)	Not Reached	10.8 (9.3, 12.1)
Hazard ratio (95% CI)[a]	0.42 (0.30, 0.60)	
p-value[b,c]	<0.0001	
Progression-free Survival		
Disease progression or death (%)	108 (51)	163 (78)
Median, months (95% CI)	5.1 (3.5, 10.8)	2.2 (2.1, 2.4)
Hazard ratio (95% CI)[a]	0.43 (0.34, 0.56)	
p-value[b,c]	<0.0001	
Overall Response Rate	34%	9%
(95% CI)	(28, 41)	(5, 13)
Complete response rate	4%	1%
Partial response rate	30%	8%

[a] Based on a stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with the allocated alpha of 0.0021 for this interim analysis.

Figure 2: Overall Survival - CHECKMATE-066



Number at Risk						
OPDIVO						
210	185	150	105	45	8	0
Dacarbazine						
208	177	123	82	22	3	0

CHECKMATE-067

CHECKMATE-067 (NCT01844505) was a multicenter, randomized (1:1:1), double-blind trial in 945 patients with previously untreated, unresectable or metastatic melanoma to one of the following arms: OPDIVO and ipilimumab, OPDIVO, or ipilimumab. Patients were required to have completed adjuvant or neoadjuvant treatment at least 6 weeks prior to randomization and have no prior treatment with anti-CTLA-4 antibody and no evidence of active brain metastasis, ocular melanoma, autoimmune disease, or medical conditions requiring systemic immunosuppression.

Patients were randomized to receive:

- OPDIVO 1 mg/kg with ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by OPDIVO as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (OPDIVO and ipilimumab arm),
- OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (OPDIVO arm), or
- Ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by placebo every 2 weeks (ipilimumab arm).

Randomization was stratified by PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay, BRAF V600 mutation status, and M stage per the AJCC staging system (M0, M1a, M1b vs. M1c). Tumor assessments were conducted 12 weeks

after randomization then every 6 weeks for the first year, and every 12 weeks thereafter. The major efficacy outcome measures were investigator-assessed PFS per RECIST v1.1 and OS. Additional efficacy outcome measures were confirmed ORR and duration of response.

The trial population characteristics were: median age 61 years (range: 18 to 90); 65% male; 97% White; ECOG performance score 0 (73%) or 1 (27%). Disease characteristics were: AJCC Stage IV disease (93%); M1c disease (58%); elevated LDH (36%); history of brain metastases (4%); BRAF V600 mutation-positive melanoma (32%); PD-L1 ≥5% tumor cell membrane expression as determined by the clinical trials assay (46%); and prior adjuvant therapy (22%).

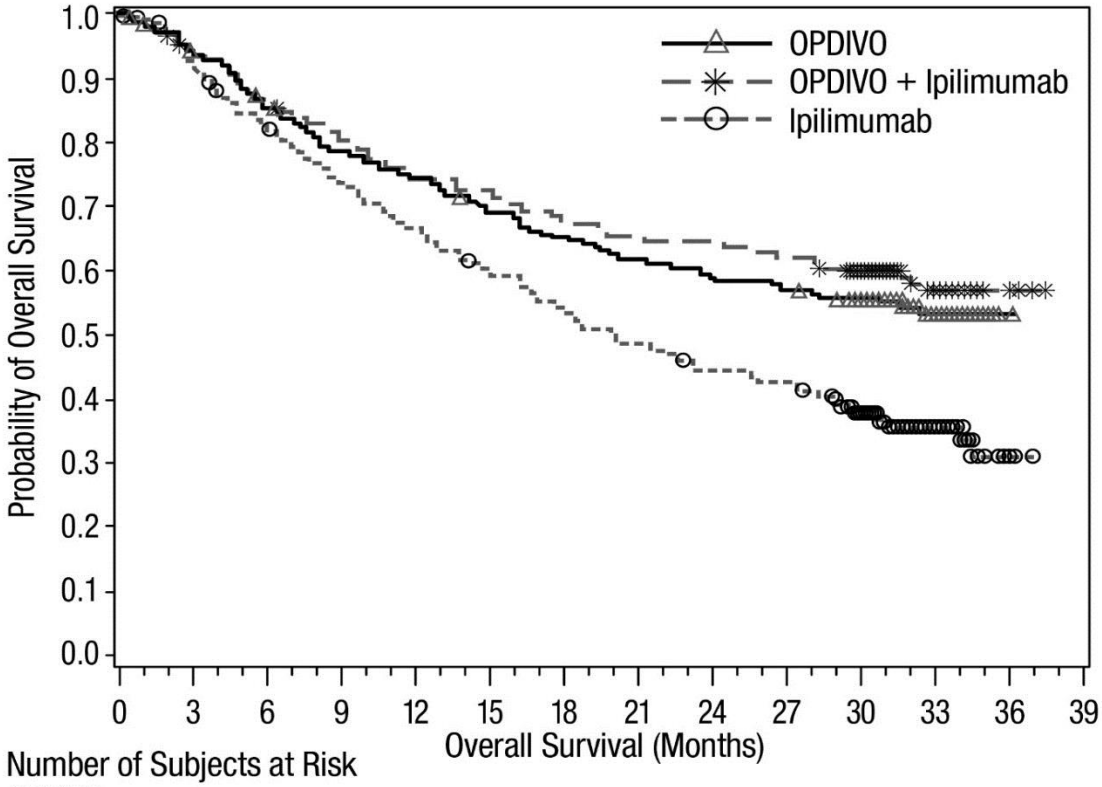
CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. The trial was not designed to assess whether adding ipilimumab to OPDIVO improves PFS or OS compared to OPDIVO as a single agent. Efficacy results are shown in Table 31 and Figure 3.

Table 31: Efficacy Results - CHECKMATE-067

	OPDIVO and Ipilimumab (n=314)	**OPDIVO (n=316)**	**Ipilimumab (n=315)**
Overall Survival[a]			
Deaths (%)	128 (41)	142 (45)	197 (63)
Hazard ratio[b] (vs. ipilimumab) (95% CI)	0.55 (0.44, 0.69)	0.63 (0.50, 0.78)	
p-value[c, d]	<0.0001	<0.0001	
Progression-free Survival[a]			
Disease progression or death	151 (48%)	174 (55%)	234 (74%)
Median in months (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
Hazard ratio[b] (vs. ipilimumab) (95% CI)	0.42 (0.34, 0.51)	0.57 (0.47, 0.69)	
p-value[c, e]	<0.0001	<0.0001	
Confirmed Overall Response Rate[a]	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value[f]	<0.0001	<0.0001	
Complete response	8.9%	8.5%	1.9%
Partial response	41%	31%	12%
Duration of Response			
Proportion ≥6 months in duration	76%	74%	63%
Range (months)	1.2+ to 15.8+	1.3+ to 14.6+	1.0+ to 13.8+

[a] OS results are based on final OS analysis with 28 months of minimum follow-up; PFS (co-primary endpoint) and ORR (secondary endpoint) results were based on primary analysis with 9 months of minimum follow-up.
[b] Based on a stratified proportional hazards model.
[c] Based on stratified log-rank test.
[d] If the maximum of the two OS p-values is less than 0.04 (a significance level assigned by the Hochberg procedure), then both p-values are considered significant.
[e] p-value is compared with .005 of the allocated alpha for final PFS treatment comparisons.
[f] Based on the stratified Cochran-Mantel-Haenszel test.
+ Censored observation

Figure 3: Overall Survival - CHECKMATE-067



Based on a minimum follow-up of 48 months, the median OS was not reached (95% CI: 38.2, NR) in the OPDIVO and ipilimumab arm. The median OS was 36.9 months (95% CI: 28.3, NR) in the OPDIVO arm and 19.9 months (95% CI: 16.9, 24.6) in the ipilimumab arm.

Based on a minimum follow-up of 28 months, the median PFS was 11.7 months (95% CI: 8.9, 21.9) in the OPDIVO and ipilimumab arm, 6.9 months (95% CI: 4.3, 9.5) in the OPDIVO arm, and 2.9 months (95% CI: 2.8, 3.2) in the ipilimumab arm. Based on a minimum follow-up of 28 months, the proportion of responses lasting ≥ 24 months was 55% in the OPDIVO and ipilimumab arm, 56% in the OPDIVO arm, and 39% in the ipilimumab arm.

14.2 Adjuvant Treatment of Melanoma

CHECKMATE-238 (NCT02388906) was a randomized, double-blind trial in 906 patients with completely resected Stage IIIB/C or Stage IV melanoma. Patients were randomized (1:1) to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or ipilimumab 10 mg/kg intravenously every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. Enrollment required complete resection of melanoma with margins negative for disease within 12 weeks prior

to randomization. The trial excluded patients with a history of ocular/uveal melanoma, autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization. Randomization was stratified by PD-L1 status (positive [based on 5% level] vs. negative/indeterminate) and AJCC stage (Stage IIIB/C vs. Stage IV M1a-M1b vs. Stage IV M1c). The major efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurs first and as assessed by the investigator. Patients underwent imaging for tumor recurrence every 12 weeks for the first 2 years then every 6 months thereafter.

The trial population characteristics were: median age was 55 years (range: 18 to 86), 58% were male, 95% were White, and 90% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIB (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%).

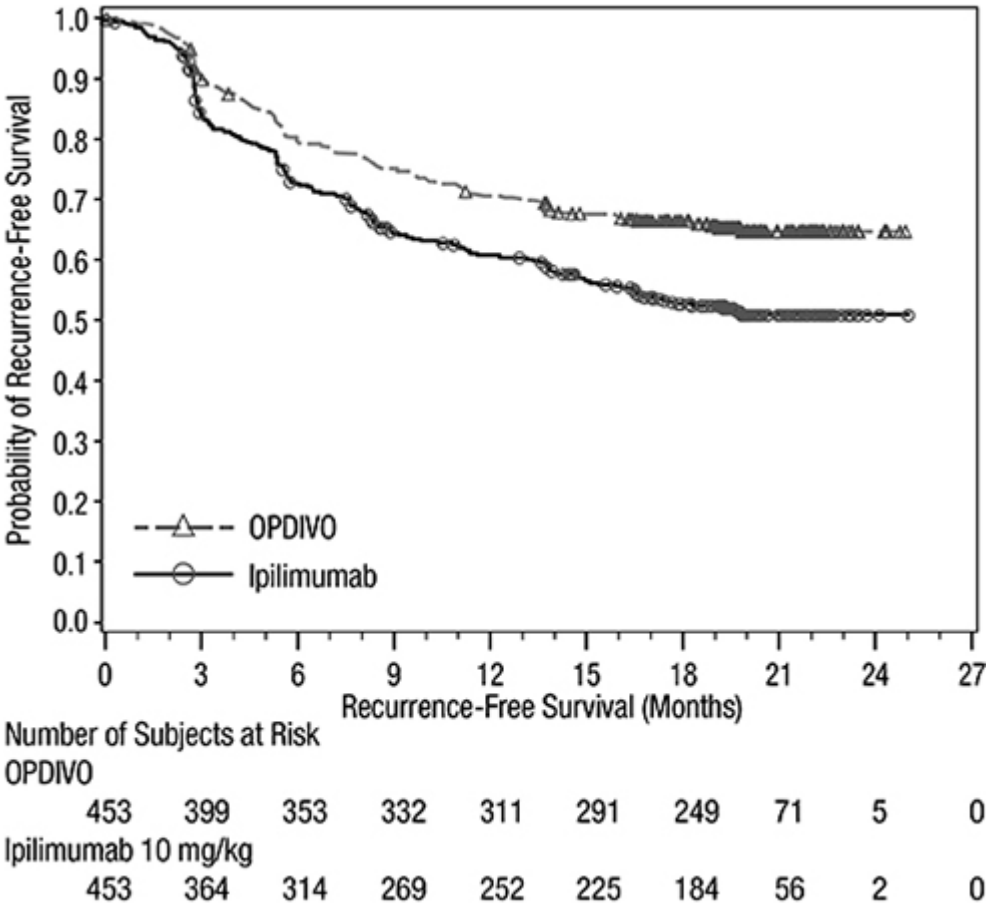
CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the ipilimumab 10 mg/kg arm. Efficacy results are shown in Table 32 and Figure 4.

Table 32: Efficacy Results - CHECKMATE-238

	OPDIVO N=453	**Ipilimumab 10 mg/kg N=453**
Recurrence-free Survival		
Number of Events, n (%)	154 (34%)	206 (45%)
Median (months) (95% CI)	NR[a]	NR[a] (16.56, NR[a])
Hazard Ratio[b] (95% CI) p-value[c,d]	0.65 (0.53, 0.80) p<0.0001	

[a] Not reached.
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] p-value is compared with 0.0244 of the allocated alpha for this analysis.

Figure 4: Recurrence-free Survival -CHECKMATE-238



14.3 Metastatic Non-Small Cell Lung Cancer

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

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 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:

- OPDIVO 3 mg/kg administered intravenously over 30 minutes every 2 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 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 ipilimumab were permitted to continue OPDIVO 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 OPDIVO in combination with ipilimumab (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 OPDIVO and ipilimumab arm compared with the platinum-doublet chemotherapy arm. The OS results are presented in Table 33 and Figure 5.

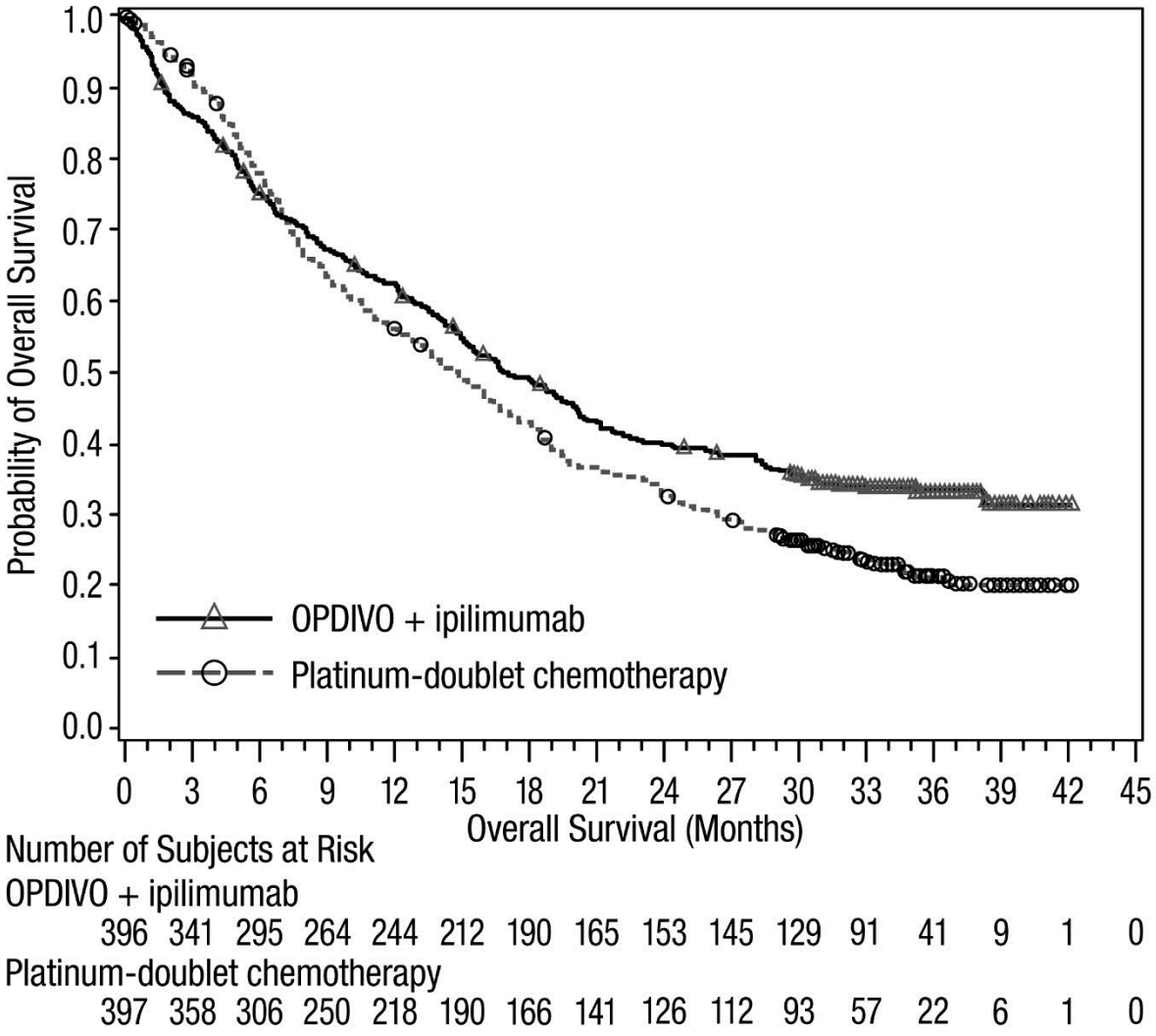
Table 33: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	OPDIVO and Ipilimumab (n=396)	**Platinum-Doublet Chemotherapy (n=397)**
Overall Survival		
Events (%)	258 (65%)	298 (75%)
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 5: Overall Survival (PD-L1 ≥1%) - CHECKMATE-227



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 OPDIVO and ipilimumab 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 OPDIVO and ipilimumab arm and 30% (95% CI: 26, 35) in the platinum-doublet chemotherapy arm. Median duration of response observed in the OPDIVO and ipilimumab 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 Ipilimumab 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:

- OPDIVO 360 mg administered intravenously over 30 minutes every 3 weeks, ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 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 ipilimumab were permitted to continue OPDIVO as a single agent as part of the study. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

A total of 719 patients were randomized to receive either OPDIVO in combination with ipilimumab 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 34.

Table 34: Efficacy Results - CHECKMATE-9LA

	OPDIVO and Ipilimumab 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.

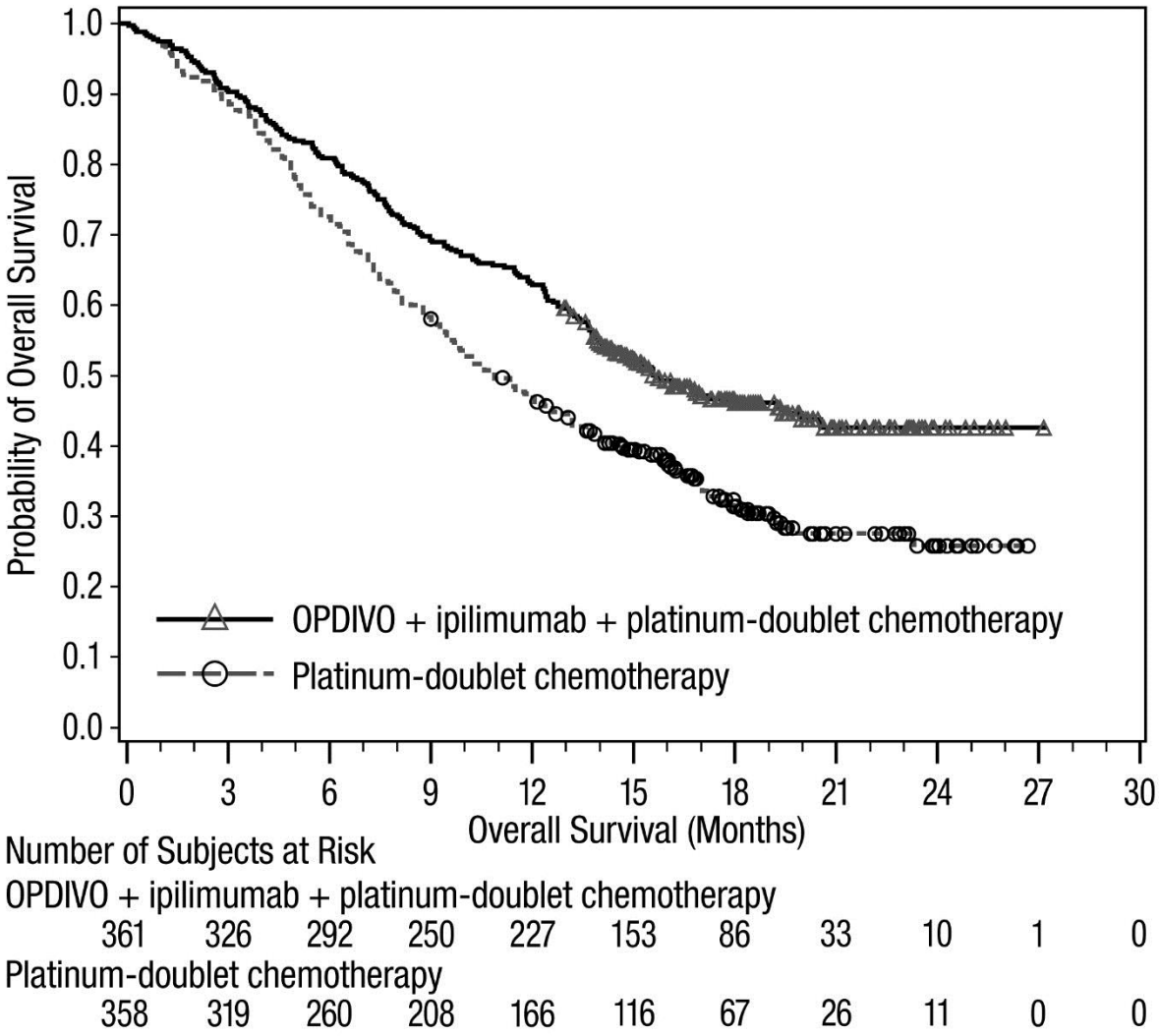
[d] Kaplan-Meier estimate.

[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.

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 OPDIVO and ipilimumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 6).

Figure 6: Overall Survival - CHECKMATE-9LA



Second-line Treatment of Metastatic Squamous NSCLC

CHECKMATE-017 (NCT01642004) was a randomized (1:1), open-label trial in 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=135) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=137). Randomization was stratified by prior paclitaxel vs. other prior treatment and region (US/Canada vs. Europe vs. Rest of World). This trial included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS.

The trial population characteristics were: median age was 63 years (range: 39 to 85) with 44% ≥65 years of age and 11% ≥75 years of age. The majority of patients were White (93%) and male (76%); the majority of patients were enrolled in Europe (57%) with the remainder in US/Canada (32%) and the rest of the world (11%). Baseline ECOG performance status was 0 (24%) or 1 (76%) and 92% were former/current smokers. Baseline disease characteristics of the population as reported by investigators were Stage IIIb (19%), Stage IV (80%), and brain metastases (6%). All patients received prior therapy with a platinum-doublet regimen and 99% of patients had tumors of squamous-cell histology.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis). Efficacy results are shown in Table 35 and Figure 7.

Table 35: Efficacy Results - CHECKMATE-017

	OPDIVO (n=135)	**Docetaxel (n=137)**
Overall Survival		
Deaths (%)	86 (64%)	113 (82%)
Median (months) (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
Hazard ratio (95% CI)[a]	0.59 (0.44, 0.79)	
p-value[b,c]	0.0002	
Overall Response Rate	27 (20%)	12 (9%)
(95% CI)	(14, 28)	(5, 15)
p-value[d]	0.0083	
Complete response	1 (0.7%)	0
Median duration of response, months (95% CI)	NR (9.8, NR)	8.4 (3.6, 10.8)
Progression-free Survival		
Disease progression or death (%)	105 (78%)	122 (89%)
Median (months)	3.5	2.8
Hazard ratio (95% CI)[a]	0.62 (0.47, 0.81)	
p-value[b]	0.0004	

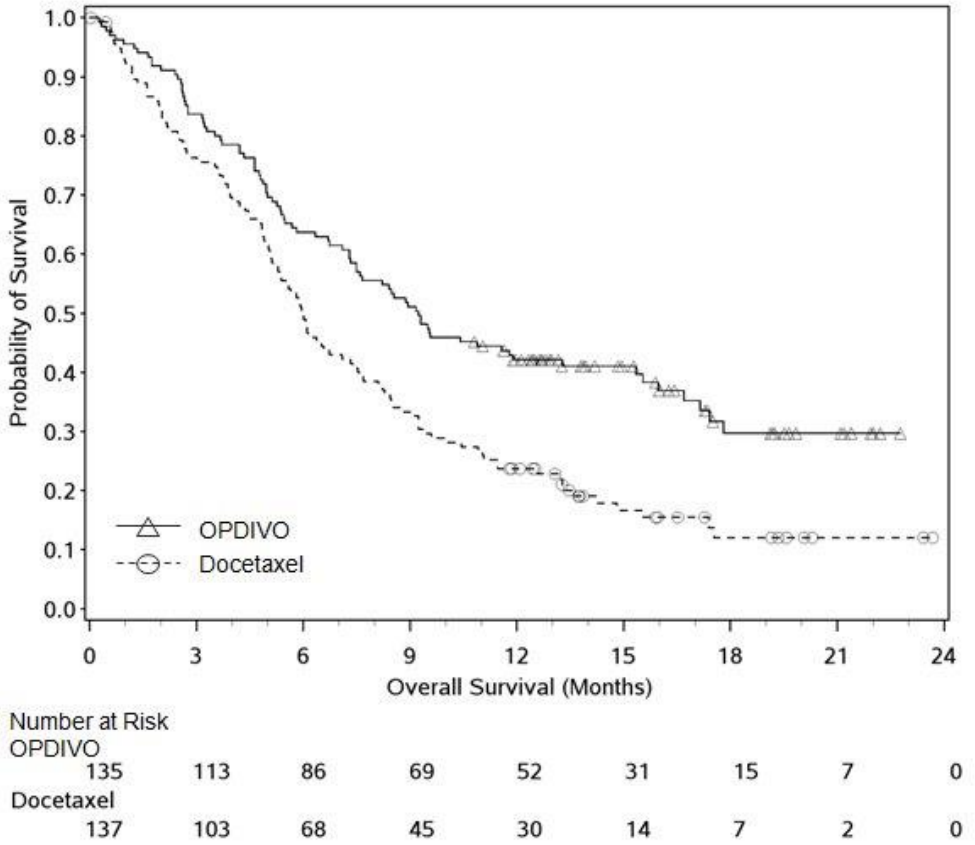
[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

[c] p-value is compared with .0315 of the allocated alpha for this interim analysis.

[d] Based on the stratified Cochran-Mantel-Haenszel test.

Figure 7: Overall Survival - CHECKMATE-017



Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the trial population, 17% of 272 patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1 and 53% had PD-L1 positive squamous NSCLC defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratios for survival were 0.58 (95% CI: 0.37, 0.92) in the PD-L1 negative subgroup and 0.69 (95% CI: 0.45, 1.05) in the PD-L1 positive subgroup.

Second-line Treatment of Metastatic Non-Squamous NSCLC

CHECKMATE-057 (NCT01673867) was a randomized (1:1), open-label trial in 582 patients with metastatic non-squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing EGFR mutation or ALK translocation was allowed. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=292) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=290). Randomization was stratified by prior maintenance therapy (yes vs. no) and number of prior therapies (1 vs. 2). The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional

efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression.

The trial population characteristics: median age was 62 years (range: 21 to 85) with 42% of patients ≥65 years and 7% of patients ≥75 years. The majority of patients were White (92%) and male (55%); the majority of patients were enrolled in Europe (46%) followed by the US/Canada (37%) and the rest of the world (17%). Baseline ECOG performance status was 0 (31%) or 1 (69%), 79% were former/current smokers, 3.6% had NSCLC with ALK rearrangement, 14% had NSCLC with EGFR mutation, and 12% had previously treated brain metastases. Prior therapy included platinum-doublet regimen (100%) and 40% received maintenance therapy as part of the first-line regimen. Histologic subtypes included adenocarcinoma (93%), large cell (2.4%), and bronchoalveolar (0.9%).

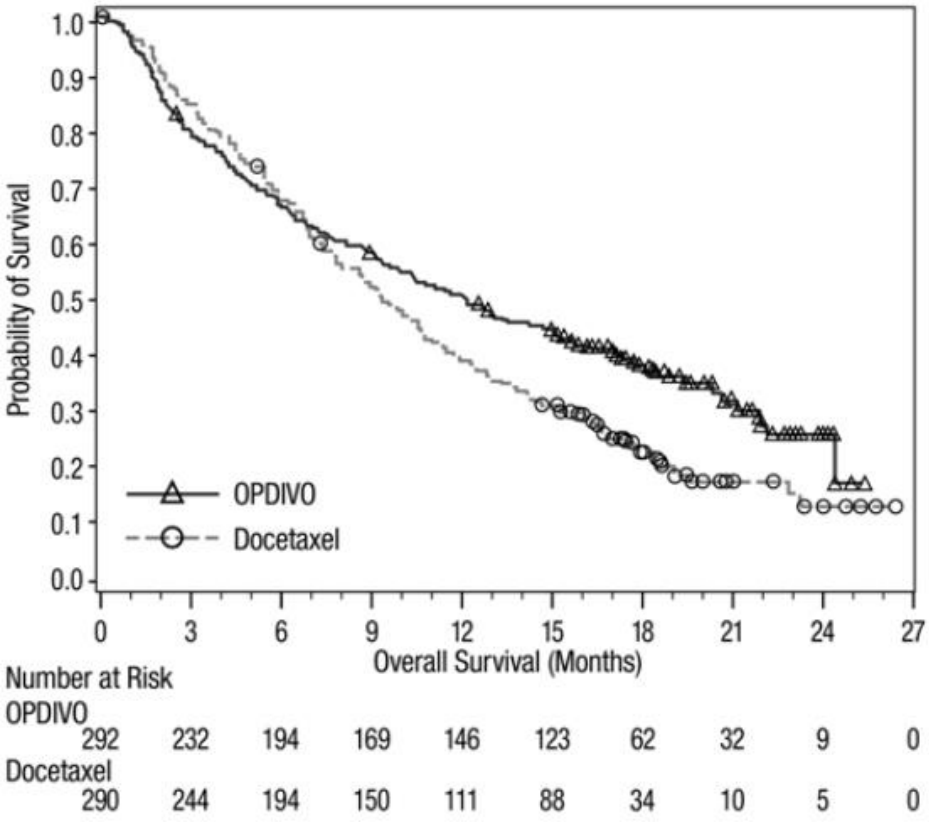
CHECKMATE-057 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 36 and Figure 8.

Table 36: Efficacy Results - CHECKMATE-057

	OPDIVO (n=292)	**Docetaxel (n=290)**
Overall Survival		
Deaths (%)	190 (65%)	223 (77%)
Median (months) (95% CI)	12.2 (9.7, 15.0)	9.4 (8.0, 10.7)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0015	
Overall Response Rate	56 (19%)	36 (12%)
(95% CI)	(15, 24)	(9, 17)
p-value[d]	0.02	
Complete response	4 (1.4%)	1 (0.3%)
Median duration of response (months) (95% CI)	17 (8.4, NR)	6 (4.4, 7.0)
Progression-free Survival		
Disease progression or death (%)	234 (80%)	245 (84%)
Median (months)	2.3	4.2
Hazard ratio (95% CI)[a]	0.92 (0.77, 1.11)	
p-value[b]	0.39	

[a] Based on a stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with .0408 of the allocated alpha for this interim analysis.
[d] Based on the stratified Cochran-Mantel-Haenszel test.

Figure 8: Overall Survival - CHECKMATE-057



Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the trial population, 22% of 582 patients had non-quantifiable results. Of the remaining 455 patients, the proportion of patients in retrospectively determined subgroups based on PD-L1 testing using the PD-L1 IHC 28-8 pharmDx assay were: 46% PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% had PD-L1 expression, defined as ≥1% of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% had ≥1% but <5% tumor cells with positive staining, 7% had ≥5% but <10% tumor cells with positive staining, and 67% had ≥10% tumor cells with positive staining. Figures 9 and 10 summarize the results of prespecified analyses of OS and PFS in subgroups determined by percentage of tumor cells expressing PD-L1.

Figure 9: Forest Plot: OS Based on PD-L1 Expression - CHECKMATE-057

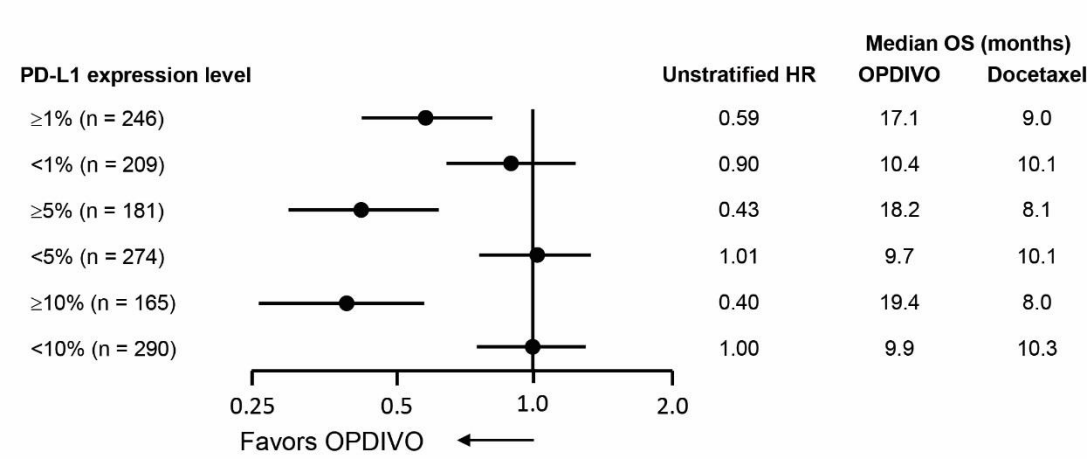
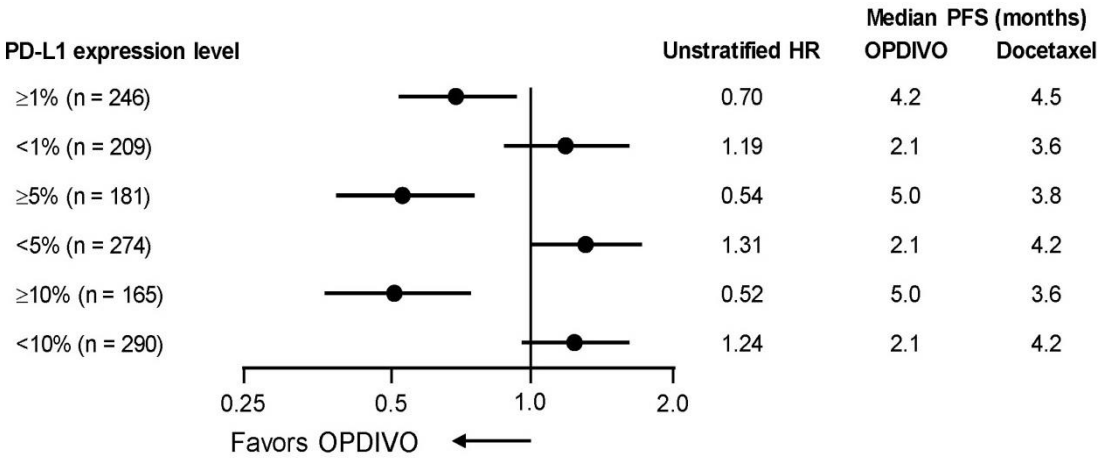


Figure 10: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



14.4 Small Cell Lung Cancer

CHECKMATE-032 (NCT01928394) was a multicenter, open-label, multi-cohort, ongoing trial evaluating nivolumab as a single agent or in combination with ipilimumab in patients with advanced or metastatic solid tumors. Several cohorts enrolled patients with metastatic small cell lung cancer (SCLC), regardless of PD-L1 tumor status, with disease progression after platinum-based chemotherapy to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The major efficacy outcome measures were ORR and duration of response according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR).

A total of 109 patients with SCLC who progressed after platinum-based chemotherapy and at least one other prior line of therapy were enrolled. The trial population characteristics were: median age was 64 years (range: 45 to 81) with 45% of patients ≥65 years and 6% of patients ≥75 years. The majority (94%) of the patients were White, <1% were Asian, and 4% were Black; 56% were male. Baseline ECOG performance status was 0 (29%) or 1 (70%), 93% were former/current smokers, 7% had CNS metastases, 94% received two to three prior lines of therapy and 6% received four to five prior lines of therapy. Approximately 65% of patients had platinum-sensitive SCLC, defined as progression ≥90 days after the last dose of platinum-containing therapy.

Efficacy results are shown in Table 37.

Table 37: Efficacy Results - CHECKMATE-032

	OPDIVO (n=109)
Overall Response Rate	12%
(95% CI)	(6.5, 19.5)
Complete response	0.9%
Partial response	11%
Duration of Response	(n=13)
Range (months)	(3.0, 42.1)
% with duration ≥6 months	77%
% with duration ≥12 months	62%
% with duration ≥18 months	39%

14.5 Advanced Renal Cell Carcinoma

Previously Treated Renal Cell Carcinoma

CHECKMATE-025 (NCT01668784) was a randomized (1:1), open-label trial in patients with advanced RCC who had experienced disease progression during or after one or two prior anti-angiogenic therapy regimens. Patients had to have a Karnofsky Performance Score (KPS) ≥70% and patients were included regardless of their PD-L1 status. The trial excluded patients with any history of or concurrent brain metastases, prior treatment with an mTOR inhibitor, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by region, Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group and the number of prior anti-angiogenic therapies. Patients were randomized OPDIVO 3 mg/kg by intravenous infusion every 2 weeks (n=410) or everolimus 10 mg orally daily (n=411). The first tumor assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. The major efficacy outcome measure was overall survival (OS).

The trial population characteristics were: median age was 62 years (range: 18 to 88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and White (88%) and 34% and 66% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. The majority of patients (77%) were treated with one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 34% favorable, 47% intermediate, and 19% poor.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with everolimus at the prespecified interim analysis when 398 events were

observed (70% of the planned number of events for final analysis). OS benefit was observed regardless of PD-L1 expression level. Efficacy results are shown in Table 38 and Figure 11.

Table 38: Efficacy Results - CHECKMATE-025

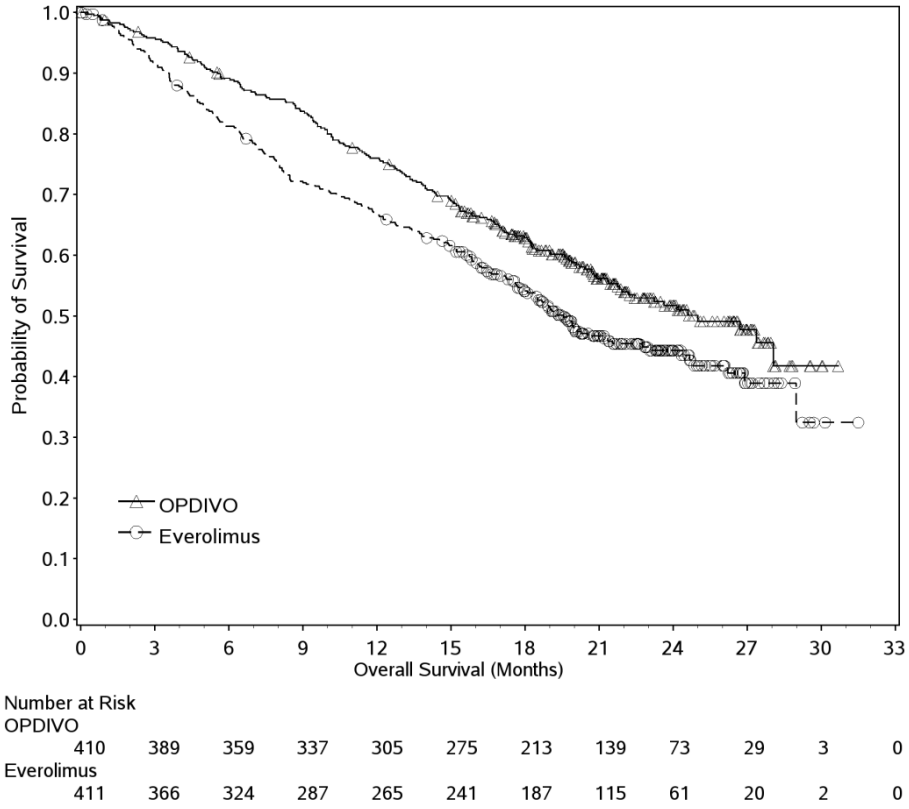
	OPDIVO (n=410)	**Everolimus (n=411)**
Overall Survival		
Deaths (%)	183 (45)	215 (52)
Median survival in months (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0018	
Confirmed Overall Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median duration of response in months (95% CI)	23.0 (12.0, NE)	13.7 (8.3, 21.9)
Median time to onset of confirmed response in months (min, max)	3.0 (1.4, 13.0)	3.7 (1.5, 11.2)

[a] Based on a stratified proportional hazards model.

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

[c] p-value is compared with .0148 of the allocated alpha for this interim analysis.

Figure 11: Overall Survival - CHECKMATE-025



Previously Untreated Renal Cell Carcinoma

CHECKMATE-214 (NCT02231749) was a randomized (1:1), open-label trial 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 stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region.

Efficacy was evaluated in intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the IMDC criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status <80%, hemoglobin less than the lower limit of normal, corrected calcium of >10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal).

Patients were randomized to OPDIVO 3 mg/kg and ipilimumab 1 mg/kg intravenously every 3 weeks for 4 doses followed by OPDIVO 3 mg/kg intravenously every two weeks (n=425), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (n=422). Treatment continued until disease progression or unacceptable toxicity.

The trial population characteristics were: 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.

The major efficacy outcome measures were OS, PFS (independent radiographic review committee [IRRC]-assessed) and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to OPDIVO and ipilimumab as compared with sunitinib (Table 39 and Figure 12). OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS. Efficacy results are shown in Table 39 and Figure 12.

Table 39: Efficacy Results - CHECKMATE-214

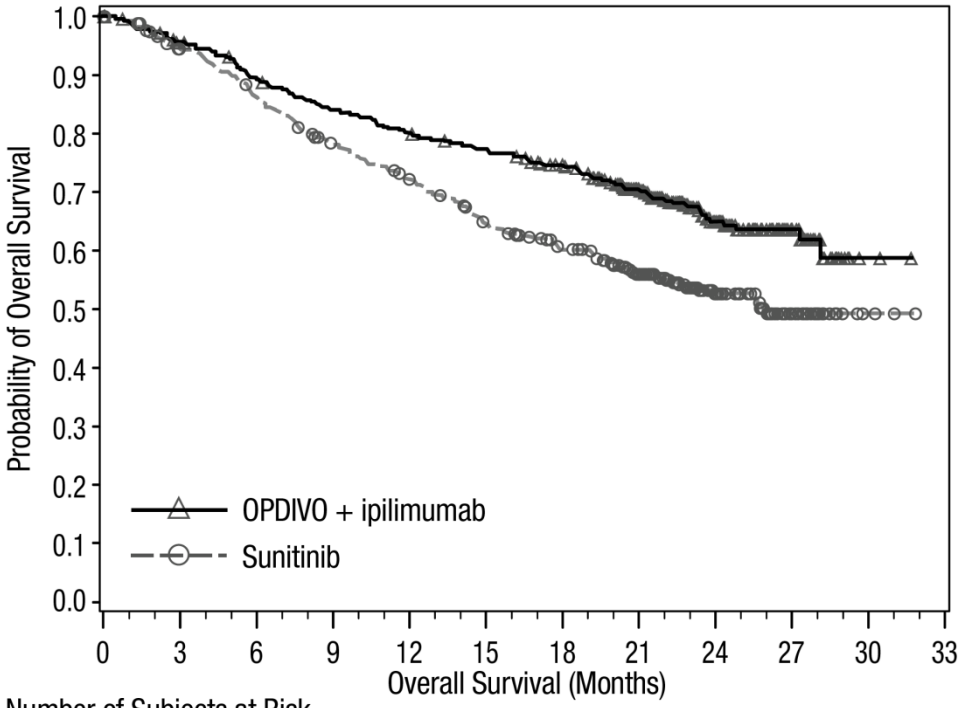
	Intermediate/Poor-Risk	
	OPDIVO and Ipilimumab (n=425)	**Sunitinib (n=422)**
Overall Survival		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (months)	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	
Confirmed Objective Response Rate (95% CI)	41.6% (36.9, 46.5)	26.5% (22.4, 31.0)
p-value[d,e]	<0.0001	
Complete Response (CR)	40 (9.4)	5 (1.2)
Partial Response (PR)	137 (32.2)	107 (25.4)
Median duration of response in months (95% CI)	NE (21.8, NE)	18.2 (14.8, NE)
Progression-free Survival		
Disease progression or death (%)	228 (53.6)	228 (54.0)
Median (months)	11.6	8.4
Hazard ratio (99.1% CI)[a]	0.82 (0.64, 1.05)	

Table 39: Efficacy Results - CHECKMATE-214

	Intermediate/Poor-Risk	
	OPDIVO and Ipilimumab (n=425)	**Sunitinib (n=422)**
p-value[b]	NS[f]	

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[d] Based on the stratified DerSimonian-Laird test.
[e] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[f] Not Significant at alpha level of 0.009.

Figure 12: Overall Survival (Intermediate/Poor Risk Population) - CHECKMATE-214



Number of Subjects at Risk

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

CHECKMATE-214 also randomized 249 favorable risk patients as per IMDC criteria to OPDIVO and ipilimumab (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 OPDIVO and ipilimumab compared to sunitinib has a hazard ratio of 1.45 (95% CI: 0.75, 2.81). The efficacy of OPDIVO and ipilimumab in previously untreated renal cell carcinoma with favorable-risk disease has not been established.

14.6 Classical Hodgkin Lymphoma

Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with cHL after failure of autologous HSCT.

CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort trial in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation trial that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance <40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity.

Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity. A cycle consisted of one dose. Dose reduction was not permitted.

Efficacy was evaluated by ORR as determined by an IRRC. Additional outcome measures included duration of response (DOR).

Efficacy was evaluated in 95 patients in CHECKMATE-205 and CHECKMATE-039 combined who had failure of autologous HSCT and post-transplantation brentuximab vedotin. The median age was 37 years (range: 18 to 72). The majority were male (64%) and White (87%). Patients had received a median of 5 prior systemic regimens (range: 2 to 15). They received a median of 27 doses of OPDIVO (range: 3 to 48), with a median duration of therapy of 14 months (range: 1 to 23 months). Efficacy results are shown in Table 40.

Table 40: Efficacy in cHL after Autologous HSCT and Post-transplantation Brentuximab Vedotin

	CHECKMATE-205 and CHECKMATE-039 (n=95)
Overall Response Rate, n (%)[a]	63 (66%)
(95% CI)	(56, 76)
Complete Remission Rate	6 (6%)
(95% CI)	(2, 13)
Partial Remission Rate	57 (60%)
(95% CI)	(49, 70)
Duration of Response (months)	
Median[b]	13.1
(95% CI)	(9.5, NE)
Range[c]	0+, 23.1+
Time to Response (months)	
Median	2.0
Range	0.7, 11.1

[a] Per 2007 revised International Working Group criteria.
[b] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 9.9 months.
[c] A + sign indicates a censored value.

Efficacy was also evaluated in 258 patients in CHECKMATE-205 and CHECKMATE-039 combined who had relapsed or progressive cHL after autologous HSCT. The analysis included the group described above. The median age was 34 years (range: 18 to 72). The majority were male (59%) and White (86%). Patients had a median of 4 prior systemic regimens (range: 2 to 15), with 85% having 3 or more prior systemic regimens and 76% having prior brentuximab vedotin. Of the 195 patients having prior brentuximab vedotin, 17% received it only before autologous HSCT,

78% received it only after HSCT, and 5% received it both before and after HSCT. Patients received a median of 21 doses of OPDIVO (range: 1 to 48), with a median duration of therapy of 10 months (range: 0 to 23 months). Efficacy results are shown in Table 41.

Table 41: Efficacy in cHL after Autologous HSCT

	CHECKMATE-205 and CHECKMATE-039 (n=258)
Overall Response Rate, n (%) (95% CI)	179 (69%) (63, 75)
Complete Remission Rate (95% CI)	37 (14%) (10, 19)
Partial Remission Rate (95% CI)	142 (55%) (49, 61)
Duration of Response (months)	
Median[a, b]	NE
(95% CI)	(12.0, NE)
Range	0+, 23.1+
Time to Response (months)	
Median	2.0
Range	0.7, 11.1

[a] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 6.7 months.

[b] The estimated median duration of PR was 13.1 months (95% CI, 9.5, NE). The median duration of CR was not reached.

14.7 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

CHECKMATE-141 (NCT02105636) was a randomized (2:1), active-controlled, open-label trial enrolling patients with metastatic or recurrent SCCHN who had experienced disease progression during or within 6 months of receiving platinum-based therapy administered in either the adjuvant, neo-adjuvant, primary (unresectable locally advanced) or metastatic setting. The trial excluded patients with autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. Patients were randomized to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or investigator's choice of:

- cetuximab 400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly, or
- methotrexate 40 to 60 mg/m^2 intravenously weekly, or
- docetaxel 30 to 40 mg/m^2 intravenously weekly.

Randomization was stratified by prior cetuximab treatment (yes/no). The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS and ORR.

A total of 361 patients were randomized; 240 patients to OPDIVO and 121 patients to investigator's choice (45% received docetaxel, 43% received methotrexate, and 12% received cetuximab). The trial population characteristics were: median age was 60 years (range: 28 to 83) with 31% ≥65 years of age, 83% were White, 12% Asian, and 4% were Black, and 83% male.

Baseline ECOG performance status was 0 (20%) or 1 (78%), 76% were former/current smokers, 90% had Stage IV disease, 45% of patients received only one prior line of systemic therapy, the remaining 55% received two or more prior lines of systemic therapy, and 25% had HPVp16-positive tumors, 24% had HPV p16-negative tumors, and 51% had unknown status.

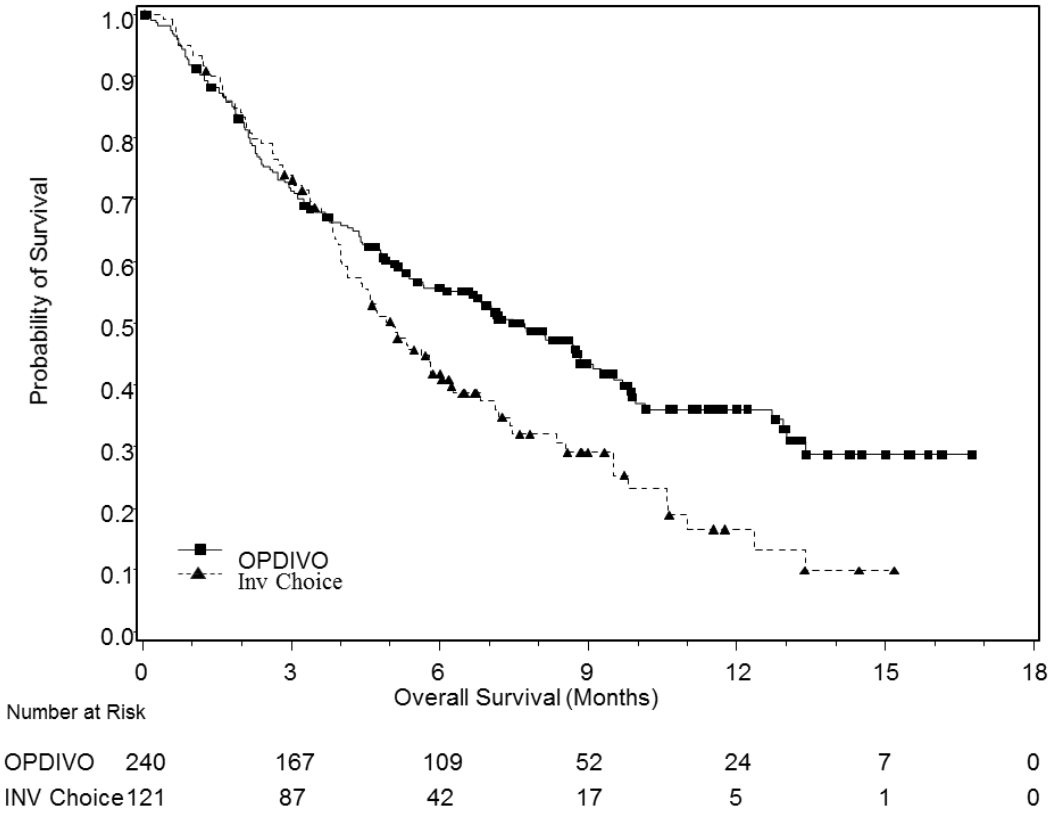
The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). There were no statistically significant differences between the two arms for PFS (HR=0.89; 95% CI: 0.70, 1.13) or ORR (13.3% [95% CI: 9.3, 18.3] vs. 5.8% [95% CI: 2.4, 11.6] for nivolumab and investigator's choice, respectively). Efficacy results are shown in Table 42 and Figure 13.

Table 42: Overall Survival - CHECKMATE-141

	OPDIVO (n=240)	**Investigator's Choice (n=121)**
Overall Survival		
Deaths (%)	133 (55%)	85 (70%)
Median (months) (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
Hazard ratio (95% CI)[a]	0.70 (0.53, 0.92)	
p-value[b,c]	0.0101	

[a] Based on stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with 0.0227 of the allocated alpha for this interim analysis.

Figure 13: Overall Survival - CHECKMATE-141



Archival tumor specimens were retrospectively evaluated for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx assay. Across the trial population, 28% (101/361) of patients had non-quantifiable results. Among the 260 patients with quantifiable results, 43% (111/260) had PD-L1 negative SCCHN, defined as <1% of tumor cells expressing PD-L1, and 57% (149/260) had PD-L1 positive SCCHN, defined as ≥1% of tumor cells expressing PD-L1. In pre-specified exploratory subgroup analyses, the hazard ratio for survival was 0.89 (95% CI: 0.54, 1.45) with median survivals of 5.7 and 5.8 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 negative subgroup. The HR for survival was 0.55 (95% CI: 0.36, 0.83) with median survivals of 8.7 and 4.6 months for the nivolumab and chemotherapy arms, respectively, in the PD-L1 positive SCCHN subgroup.

14.8 Urothelial Carcinoma

CHECKMATE-275 (NCT02387996) was a single-arm trial in 270 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Patients were excluded for active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, and ECOG performance status >1. Patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 8 weeks for the first 48 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed ORR as assessed by IRRC using RECIST v1.1 and DOR.

The median age was 66 years (range: 38 to 90), 78% were male, 86% were White. Twenty-seven percent had non-bladder urothelial carcinoma and 84% had visceral metastases. Thirty-four percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy. Twenty-nine percent of patients had received ≥2 prior systemic regimens in the metastatic setting. Thirty-six percent of patients received prior cisplatin only, 23% received prior carboplatin only, and 7% were treated with both cisplatin and carboplatin in the metastatic setting. Forty-six percent of patients had an ECOG performance status of 1. Eighteen percent of patients had a hemoglobin <10 g/dL, and twenty-eight percent of patients had liver metastases at baseline. Patients were included regardless of their PD-L1 status.

Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are shown in Table 43. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%).

Table 43: Efficacy Results - CHECKMATE-275

	All Patients N=270	**PD-L1 < 1% N=146**	**PD-L1 ≥ 1% N=124**
Confirmed Overall Response Rate, n (%) (95% CI)	53 (19.6%) (15.1, 24.9)	22 (15.1%) (9.7, 21.9)	31 (25.0%) (17.7, 33.6)
Complete Response Rate	7 (2.6%)	1 (0.7%)	6 (4.8%)
Partial Response Rate	46 (17.0%)	21 (14.4%)	25 (20.2%)
Median Duration of Response[a] (months) (range)	10.3 (1.9+, 12.0+)	7.6 (3.7, 12.0+)	NE (1.9+, 12.0+)

[a] Estimated from the Kaplan-Meier Curve

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

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

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

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

A total of 74 patients were enrolled in the single-agent MSI-H mCRC OPDIVO cohort. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% ≥75 years of age, 59% were male and 88% were White. Baseline ECOG performance status was 0 (43%), 1 (55%), or 3 (1.4%) and 36% were reported to have Lynch Syndrome. Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 7%, 30%, 28%, 19%, and 16% received 0, 1, 2, 3, or ≥4 prior lines of therapy for metastatic disease, respectively, and 42% of patients had received an anti-EGFR antibody.

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

Efficacy results for each of these single-arm cohorts are shown in Table 44.

Table 44: Efficacy Results - CHECKMATE-142

	OPDIVO MSI-H/dMMR Cohort		**OPDIVO and Ipilimumab MSI-H/dMMR Cohort**	
	All Patients (n=74)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)**	**All Patients (n=119)**	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
IRRC Overall Response Rate; n (%)	24 (32%)	15 (28%)	58 (49%)	38 (46%)
(95% CI)[a]	(22, 44)	(17, 42)	(39, 58)	(35, 58)
Complete Response (%)	2 (2.7%)	1 (1.9%)	5 (4.2%)	3 (3.7%)
Partial Response (%)	22 (30%)	14 (26%)	53 (45%)	35 (43%)
Duration of Response				
Proportion with ≥6 months response duration	63%	67%	83%	89%
Proportion with ≥12[b] months response duration	38%	40%	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 <12 months from the date of onset of response. In the combination cohort, 78% of the 51 patients with ongoing responses were followed for <12 months from the date of onset of response.

14.10 Hepatocellular Carcinoma

CHECKMATE-040 (NCT01658878) was a multicenter, multiple cohort, open-label trial that evaluated the efficacy of OPDIVO as a single agent and in combination with ipilimumab in patients with hepatocellular carcinoma (HCC) who progressed on or were intolerant to sorafenib.

Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible.

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

The efficacy of OPDIVO as a single agent was evaluated in a pooled subgroup of 154 patients across Cohorts 1 and 2 who received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until disease progression or unacceptable toxicity. The median age was 63 years (range: 19 to 81), 77% were male, and 46% were White. Baseline ECOG performance status was 0 (65%) or 1 (35%). Thirty-one percent (31%) of patients had active HBV infection, 21% had active HCV infection, and 49% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 18% and non-alcoholic fatty liver disease in 6.5% of patients. Child-Pugh class and score was A5 for 68%, A6 for 31%, and B7 for 1% of patients. Seventy-one percent (71%) of patients had extrahepatic spread, 29% had macrovascular invasion, and 37% had alfa-fetoprotein (AFP) levels ≥400 µg/L. Prior treatment history included surgical resection (66%), radiotherapy (24%), or locoregional treatment (58%). All patients had received prior sorafenib, of whom 36 (23%) were unable to tolerate sorafenib; 19% of patients had received 2 or more prior systemic therapies.

The efficacy of OPDIVO in combination with ipilimumab was evaluated in 49 patients (Cohort 4) who received OPDIVO 1 mg/kg and ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, followed by single-agent OPDIVO at 240 mg every 2 weeks until disease progression or unacceptable toxicity. The median age was 60 years (range: 18 to 80), 88% were male, 74% were Asian, and 25% were White. Baseline ECOG performance status was 0 (61%) or 1 (39%). Fifty-seven (57%) percent of patients had active HBV infection, 8% had active HCV infection, and 35% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 16% and non-alcoholic fatty liver disease in 6% of patients. Child-Pugh class and score was A5 for 82% and A6 for 18%; 80% of patients had extrahepatic spread; 35% had vascular invasion; and 51% had AFP levels ≥400 µg/L. Prior cancer treatment history included surgery (74%), radiotherapy (29%), or local treatment (59%). All patients had received prior sorafenib, of whom 10% were unable to tolerate sorafenib; 29% of patients had received 2 or more prior systemic therapies.

Efficacy results are shown in Table 45. Based on the design of this study, the data below cannot be used to identify statistically significant differences in efficacy between cohorts. The results for OPDIVO in Cohorts 1 and 2 are based on a minimum follow-up of approximately 27 months. The results for OPDIVO in combination with ipilimumab in Cohort 4 are based on a minimum follow-up of 28 months.

Table 45: Efficacy Results - Cohorts 1, 2, and 4 of CHECKMATE-040

	OPDIVO and Ipilimumab (Cohort 4) (n=49)	OPDIVO (Cohorts 1 and 2) (n=154)
Overall Response Rate per BICR,[a] n (%), RECIST v1.1	16 (33%)	22 (14%)
(95% CI)[b]	(20, 48)	(9, 21)
Complete response	4 (8%)	3 (2%)
Partial response	12 (24%)	19 (12%)
Duration of Response per BICR,[a] RECIST v1.1	n=16	n=22
Range (months)	4.6, 30.5+	3.2, 51.1+
Percent with duration ≥6 months	88%	91%
Percent with duration ≥12 months	56%	59%
Percent with duration ≥24 months	31%	32%
Overall Response Rate per BICR,[a] n (%), mRECIST	17 (35%)	28 (18%)
(95% CI)[b]	(22, 50)	(12, 25)
Complete response	6 (12%)	7 (5%)
Partial response	11 (22%)	21 (14%)

[a] Confirmed by BICR.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) Injection is available as follows:

Carton Contents	NDC
40 mg/4 mL single-dose vial	0003-3772-11
100 mg/10 mL single-dose vial	0003-3774-12
240 mg/24 mL single-dose vial	0003-3734-13

Store under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the original package 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).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and withholding or discontinuation of OPDIVO, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe

abdominal pain *[see Warnings and Precautions (5.2)]*.

- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.4)]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.5)]*.
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions (5.6)]*.
- Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis *[see Warnings and Precautions (5.7)]*.

Infusion-Related Reactions

- Advise patients of the potential risk of infusion-related reactions *[see Warnings and Precautions (5.9)]*.

Complications of Allogeneic HSCT

- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.10)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with OPDIVO and for 5 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

MEDICATION GUIDE
OPDIVO® (op-DEE-voh)
(nivolumab)
Injection

Read this Medication Guide before you start receiving OPDIVO and before each infusion. There may be new information. If your healthcare provider prescribes OPDIVO in combination with ipilimumab (YERVOY®), also read the Medication Guide that comes with ipilimumab. 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 OPDIVO?

OPDIVO is a medicine that may treat certain cancers by working with your immune system. OPDIVO can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death. These problems may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when OPDIVO is used in combination with ipilimumab.

Call or see your healthcare provider right away if you develop any symptoms of the following problems or these symptoms get worse:

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

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

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- severe stomach-area (abdomen) pain or tenderness

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual
- decreased energy

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

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- hair loss
- feeling cold
- constipation
- voice gets deeper
- excessive thirst or lots of urine
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

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

Skin Problems. Signs of these problems may include:

- rash
- itching
- skin blistering
- ulcers in mouth or other mucous membranes

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

Problems in other organs. Signs of these problems may include:

- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness
- chest pain

Getting medical treatment right away may keep these problems from becoming more serious.
Your healthcare provider will check you for these problems during treatment with OPDIVO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with OPDIVO, if you have severe side effects.

What is OPDIVO?
OPDIVO is a prescription medicine used to treat:

- **people with a type of skin cancer called melanoma:**
  - OPDIVO may be used alone or in combination with ipilimumab to treat melanoma that has spread or cannot be removed by surgery (advanced melanoma), **or**
  - OPDIVO may be used alone to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.
- **people with a type of advanced stage lung cancer called non-small cell lung cancer (NSCLC).**
  - OPDIVO may be used in combination with ipilimumab 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.
  - OPDIVO may be used in combination with ipilimumab 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.
  - OPDIVO may be used when your lung cancer:
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

    If your tumor has an abnormal EGFR or ALK gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, **and** it did not work or is no longer working.
- **people with a type of lung cancer called small cell lung cancer.**
  - OPDIVO may be used when your lung cancer:
    - has spread or grown, **and**
    - you have tried at least two different types of chemotherapy, including one that contains platinum, and it did not work or is no longer working.
- **people with kidney cancer (renal cell carcinoma).**
  - OPDIVO may be used alone when your cancer has spread or grown after treatment with other cancer medicines.
  - OPDIVO may be used in combination with ipilimumab in certain people when their cancer has spread.
- **adults with a type of blood cancer called classical Hodgkin lymphoma.**
  - **OPDIVO may be used if:**
    - your cancer has come back or spread after a type of stem cell transplant that uses your own stem cells (autologous), **and**
    - you used the drug brentuximab vedotin before or after your stem cell transplant, **or**
    - you received at least 3 kinds of treatment including a stem cell transplant that uses your own stem cells (autologous).
- **people with head and neck cancer (squamous cell carcinoma).**
  - **OPDIVO may be used when your head and neck cancer:**
    - has come back or spread, **and**
    - you have tried chemotherapy that contains platinum and it did not work or is no longer working.
- **people with bladder cancer (urothelial carcinoma).**
  - **OPDIVO may be used when your bladder cancer:**
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- **adults and children 12 years of age and older, with a type of colon or rectal cancer (colorectal cancer).**
  - OPDIVO may be used alone or in combination with ipilimumab when your colon or rectal cancer:
    - has spread to other parts of the body (metastatic),

- is microsatellite instability-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.

- **people with liver cancer (hepatocellular carcinoma).**
  - OPDIVO may be used alone or in combination with ipilimumab if you have previously received treatment with sorafenib.

It is not known if OPDIVO is safe and effective when used:
- in children younger than 12 years of age with MSI-H or dMMR metastatic colorectal cancer, or
- in children younger than 18 years of age for the treatment of any other cancers.

What should I tell my healthcare provider before receiving OPDIVO?

Before you receive OPDIVO, tell your healthcare provider if you:
- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. OPDIVO can harm your unborn baby.

  Females who are able to become pregnant:

  Your healthcare provider should do a pregnancy test before you start receiving OPDIVO.
  - You should use an effective method of birth control during and for at least 5 months after the last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant during treatment with OPDIVO.
- are breastfeeding or plan to breastfeed. It is not known if OPDIVO passes into your breast milk. Do not breastfeed during treatment with OPDIVO.

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

Know the medicines you take. Keep a list of them to show your healthcare providers and pharmacist when you get a new medicine.

How will I receive OPDIVO?
- Your healthcare provider will give you OPDIVO into your vein through an intravenous (IV) line over 30 minutes.
- When OPDIVO is used alone, it is usually given every 2 weeks or 4 weeks depending on the dose you are receiving.
- When OPDIVO is used in combination with ipilimumab (except for treating NSCLC), OPDIVO is usually given every 3 weeks, for a total of 4 doses. Ipilimumab will be given on the same day. After that, OPDIVO will be given alone every 2 weeks or 4 weeks depending on the dose you are receiving.
- For NSCLC that has spread to other parts of your body, when OPDIVO is used in combination with ipilimumab, OPDIVO is given either every 2 weeks or every 3 weeks, and ipilimumab is given every 6 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 need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of OPDIVO?

OPDIVO can cause serious side effects, including:
- **See "What is the most important information I should know about OPDIVO?"**
- **Severe infusion reactions.** Tell your doctor or nurse right away if you get these symptoms during an infusion of OPDIVO:
  - chills or shaking
  - itching or rash
  - flushing
  - difficulty breathing
  - dizziness
  - fever
  - feeling like passing out
- **Complications of stem cell transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

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

- feeling tired
- rash
- pain in muscles, bones, and joints
- itchy skin
- diarrhea
- nausea
- weakness
- cough
- vomiting
- shortness of breath
- constipation
- decreased appetite
- back pain
- upper respiratory tract infection
- fever
- headache
- stomach-area (abdominal) pain

The most common side effects of OPDIVO when used in combination with ipilimumab include:

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

The most common side effects of OPDIVO when used in combination with ipilimumab and chemotherapy include:

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

These are not all the possible side effects of OPDIVO.

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 OPDIVO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about OPDIVO, talk with your healthcare provider. You can ask your healthcare provider for information about OPDIVO that is written for health professionals.

What are the ingredients in OPDIVO?

Active ingredient: nivolumab

Inactive ingredients: mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and Water for Injection. May contain hydrochloric acid and/or sodium hydroxide.

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

For more information, call 1-855-673-4861 or go to www.OPDIVO.com.

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

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/

B HARPREET SINGH
05/26/2020 03:11:50 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s082 and 125377Orig1s110

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA or the other Regulatory Authorities. While the application review is completed by the FDA, the application is still under review at the other regulatory agencies.

Application Type	Supplemental BLAs (sBLA)
Application Number(s)	125554/ S-82 and 125377/ S-110
Priority or Standard	Priority
Submit Date(s)	February 6, 2020
Received Date(s)	February 6, 2020
PDUFA Goal Date	August 6, 2020
Division/Office	DO2/ OOD/ OND/ CDER
Review Completion Date	May 26, 2020
Established Name	Nivolumab and Ipilimumab
(Proposed) Trade Name	OPDIVO and YERVOY
Pharmacologic Class	Anti-PD-1 antibody and anti-CTLA-4 antibody
Code name	BMS-936558 and BMS-734016
Applicant	Bristol-Myers Squibb, Co.
Formulation(s)	Nivolumab: Injection; 100 mg/10 mL solution in a single-dose vial Ipilimumab: Injection; 200 mg/40 mL in a single-use vial
Dosing Regimen	Nivolumab 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of histology-based platinum-doublet chemotherapy every 3 weeks
Applicant Proposed Indication(s)/Population(s)	Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (b) (4), for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Nivolumab, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), without EGFR or ALK genomic tumor aberrations.

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Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

[FDA will complete this section.]

Regulatory Project Manager	Kwadwo Korsah
Pharmacology/Toxicology Reviewer(s)	
Pharmacology/Toxicology Team Leader(s)	
Office of Clinical Pharmacology Reviewer(s)	Yibo Wang, Yuan Xu
Office of Clinical Pharmacology Team Leader(s)	Jiang Liu, Hong Zhao
Clinical Reviewer	Paz Vellanki
Clinical Team Leader (Acting)	Adnan Jaigirdar
Safety Analyst (if applicable)	
Statistical Reviewer	Flora Mulkey
Statistical Team Leader	Lisa Rodriguez
Cross-Disciplinary Team Leader (Acting)	Adnan Jaigirdar
Division Director (DHOT)	
Division Director (OCP)	
Deputy Division Director (OB)	Yuan-Li Shen
Division Director (DO2)	Harpreet Singh
Office Director (or designated signatory authority)	

Additional Reviewers of Application

OPQ	
Patient Labeling	Sharon Mills
OPDP	Adesola Adejuwon
OSI	
OSE/DEPI	
OSE/DMEPA	
OSE/DRISK	
Other	

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Project ORBIS Participants

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Project Management	Sereen Akel Vincent Panetta
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Biostatistics Reviewer	Alex Bliu
Clinical Manager	Jian Wang
Oncology Director	Kelly Robinson

Health Science Authority (Singapore) Review Team for Assessment Aid

Regulatory Project Manager	Kalaiselvam Panesilvam
Clinical Reviewer	Choo Qiuyi
External Clinical Reviewer	Ang Mei-Kim
Director	Agnes Chan

Therapeutic Goods Administration (Australia) Review Team for Assessment Aid

Clinical Reviewer	Victoria Mansell
Clinical Team Leader	Michael Coory

Glossary

ADA	anti-drug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ASBI	average symptom burden index
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BBWT	baseline body weight
BICR	blinded independent central review
BLDH	baseline lactate dehydrogenase
BMS	Bristol-Myers Squibb
BOR	best overall response
BUN	blood urea nitrogen
BW	body weight
Cavg1	time-averaged concentration over the first dosing interval
CBC	complete blood count
chemo	Chemotherapy
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL, CL0, CLss	clearance, baseline clearance, clearance at steady-state
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COA	clinical outcome assessment
CPH	Cox Proportional-Hazards model
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CTC	Common Toxicity Criteria
CTLA-4	cytotoxic T-lymphocyte antigen-4
DC	Discontinuation
DCN	document control number
DCR	disease control rate
DDI	drug-drug interaction
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
dMMR	mismatch repair deficient
DoR	duration of response
E-R	exposure response
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate

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EMAX	maximum effect
EQ-5D-3L	EuroQol 5 dimensional 3 level
E-R	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
F/U	follow-up
Gr 2+ IMAEs	Grade ≥ 2 immune-mediated adverse events
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
HR	hazard ratio
IASLC	International Association for the Study of Lung Cancer Classification
IC	investigator's choice
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
IND	Investigational New Drug
ipi	Ipilimumab
iPSP	Initial Pediatric Study Plan
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
KM	Kaplan-Meier
LCSS	Lung Symptom Cancer Scale
LDH	lactate dehydrogenase
LPLV	last patient last visit
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMR	measles, mumps, rubella
mOS	median overall survival
MSI-H	microsatellite instability-high
mut/Mb	mutations per megabase (1 million bases) of exome sequence
NA	not available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
nivo	Nivolumab
nivo + ipi	nivolumab + ipilimumab combination therapy
nivo+ipi+chemo	nivolumab + ipilimumab + 2 cycles of chemotherapy
NR	not reported
NSCLC	non-small cell lung cancer
NSQ	non-squamous
OESI	other event of special interest
ORR	objective response rate
OS	overall survival
OSI	Office of Scientific Investigations

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

PD	pharmacodynamics, progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PFS2	progression-free survival after next line of treatment
PK	Pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
PREA	Pediatric Research Equality Act
PRO	patient reported outcomes
PS	performance status
PTs	preferred terms
Q	inter-compartment clearance
QxW	every x weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RTOR	Real Time Oncology Review
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental Biologics License Application
SCCHN	squamous cell carcinoma of the head and neck
SCE	Summary of Clinical Efficacy
SCLC	small-cell lung cancer
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results Program
SOC	system organ class
SQ	Squamous
TMB	tumor mutational burden
TPS	tumor proportion score
TSH	Thyroid stimulating hormone
TTR	time to response
UC	urothelial carcinoma
UI	utility index
ULN	upper limit of normal
US	United States
UTD	unable to determine
USPI	United States prescribing information
VAS	visual analogue score
VC	volume of distribution of central compartment
VP	volume of distribution of peripheral compartment
WT	wild type

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1. Executive Summary

APPEARS THIS WAY ON ORIGINAL

1.1 Product Introduction

OPDIVO (nivolumab) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed death-1 (PD-1) and blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2, releasing PD-1 pathway mediated inhibition of the immune response. Nivolumab is approved for multiple oncologic indications, including the treatment of patients with non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

YERVOY (ipilimumab) is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (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. Ipilimumab is approved for several oncologic indications but is not currently approved for the treatment of patients with NSCLC as monotherapy.

The combination of nivolumab and ipilimumab is currently approved for the following indications:

- for the treatment of patients with unresectable or metastatic melanoma;
- for the treatment of patients with intermediate- or poor-risk, previously untreated advanced renal cell carcinoma;
- 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 that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan;
- for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib.
- most recently, for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥ 1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

The indications for the combination of nivolumab and ipilimumab for the treatment of patients with MSI-H or dMMR metastatic colorectal cancer and hepatocellular carcinoma are approved under the provisions of accelerated approval based on overall response rate and duration of response.

In this supplemental application, two cycles of histology-based platinum-doublet chemotherapy is administered in combination with nivolumab and ipilimumab (nivo+ipi+chemo). In patients with treatment naïve NSCLC other approved combinations of anti-PD-(L)1 therapy usually include four cycles of platinum-based chemotherapy.

The recommended dosage regimen for the proposed indication is nivolumab 360 mg intravenously (IV) every 3 weeks (Q3W) with ipilimumab 1 mg/kg IV Q6W with two cycles of histology-based platinum-doublet chemotherapy Q3W until disease progression, unacceptable toxicity, or up to two years in patients without disease progression. Nivolumab 360 mg IV Q3W is a dose that, has not been previously approved. Ipilimumab 1 mg/kg in combination with nivolumab has been previously approved for the treatment of advanced renal cell carcinoma and MSI-H or dMMR metastatic colorectal cancer, however administered on a Q3W schedule and limited to four doses.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The primary trial supporting this sBLA for the indication of nivolumab plus ipilimumab with two cycles of chemotherapy as first-line treatment of adult patients with metastatic NSCLC, without EGFR or ALK genomic aberrations is Study CA2099LA (CheckMate-9LA). This is a multicenter, open-label, randomized (1:1) study comparing the combination of nivolumab plus ipilimumab and two cycles of histology-based platinum-doublet chemotherapy (nivo+ipi+chemo) to four cycles of platinum-doublet chemotherapy.

Study CA2099LA demonstrated a hazard ratio (HR) for overall survival (OS) of 0.69 (96.71% CI: 0.55, 0.87; p-value 0.0006) favoring nivo+ipi+chemo; the median OS was 14.1 months (95% CI: 13.2, 16.2) in the nivo+ipi+chemo arm and 10.7 months (95% CI: 9.5, 12.5) in the chemotherapy arm. Based on an updated analysis for overall survival with an additional 4.6 months of follow-up, the HR for OS was 0.66 (95% CI: 0.55, 0.80) with median OS of 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving nivo+ipi+chemo and chemotherapy, respectively. The hierarchically-tested key secondary objectives of the study, progression-free survival (PFS) per blinded independent central review (BICR) and overall response rate (ORR) per BICR, were also statistically significant. The HR for PFS per BICR was 0.70 (97.48% CI: 0.57, 0.86; p-value 0.0001) with a median PFS of 6.8 months (95% CI: 5.6, 7.7) in the nivo+ipi+chemo arm and 5.0 months (95% CI: 4.3, 5.6) in the chemotherapy arm. The ORR per BICR in the nivo+ipi+chemo arm was 38% (95% CI 33, 43) versus 25% (95% CI: 21, 30) in the chemotherapy arm, with a median duration of response (DOR) of 10.0 months (95% CI: 8.2, 13.0) in the nivo+ipi+chemo arm and 5.1 months (95% CI : 4.3, 7.0) in the chemotherapy arm.

The FDA review teams agrees the submitted evidence meets the statutory evidentiary standard for regular approval. The combination of nivo+ipi+chemo showed a survival advantage, with a HR of 0.66 (95% CI: 0.55, 0.80) and a 4.7-month improvement in median OS for nivo+ipi+chemo compared to chemotherapy, a statistically significant and clinically meaningful difference. This finding is supported by statistically significant improvement in PFS, ORR, and DOR observed for nivo+ipi+chemo compared to chemotherapy in Study CA2099LA.

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Nivolumab is a monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2; it is approved for the treatment of multiple solid tumors, including NSCLC. Nivolumab is approved as a single agent for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Ipilimumab is a monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Ipilimumab is not currently approved for the treatment of patients with NSCLC as monotherapy.

Metastatic NSCLC is a life-threatening condition with poor survival. In patients with metastatic NSCLC with no EGFR or ALK genomic tumor aberrations and with tumor PD-L1 expression ≥ 1%, current standard of care treatment options include pembrolizumab (for non-squamous and squamous histology) or atezolizumab (for non-squamous histology) administered with a platinum-based combination regimen and pembrolizumab as a single agent. More recently, the combination of nivolumab and ipilimumab has been approved for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥ 1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. At the time Study CA2099LA was designed, four cycles of platinum-based doublet chemotherapy was an appropriate comparator for the first-line treatment of patients with metastatic NSCLC.

The primary trial supporting this sBLA is Study CA2099LA (CheckMate-9LA); a multicenter, open-label study where a total of 719 patients were randomized to receive either nivolumab in combination with ipilimumab and two cycles of platinum-doublet chemotherapy (n=361) or four cycles of platinum chemotherapy (n=358) as control group. For the primary safety population for the assessment of safety and tolerability of the recommended dose and regimen was derived from the pivotal study CA2099LA on 719 patients, supported by additional 36 patients from study CA209568 who received the same regimen as the one evaluated in the pivotal study.

Study CA2099LA demonstrated a hazard ratio (HR) for overall survival (OS) of 0.69 (96.71% CI: 0.55, 0.87; p-value 0.0006) favoring nivo+ipi+chemo; the median OS was 14.1 months (95% CI: 13.2, 16.2) in the nivo+ipi+chemo arm and 10.7 months (95% CI: 9.5, 12.5) in the chemotherapy arm. Based on an updated analysis for overall survival with an additional 4.6 months of follow-up, the HR for OS was 0.66 (95% CI: 0.55, 0.80) with median OS of 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving nivo+ipi+chemo and chemotherapy, respectively. The hierarchically-tested key secondary objectives of the study, progression-free survival (PFS) per blinded independent central review (BICR) and overall response rate (ORR) per BICR, were also statistically significant. The HR for PFS per BICR was

0.70 (97.48% CI: 0.57, 0.86; p-value 0.0001) with a median PFS of 6.8 months (95% CI: 5.6, 7.7) in the nivo+ipi+chemo arm and 5.0 months (95% CI: 4.3, 5.6) in the chemotherapy arm. The ORR per BICR in the nivo+ipi+chemo arm was 38% (95% CI 33, 43) versus 25% (95% CI: 21, 30) in the chemotherapy arm, with a median duration of response (DOR) of 10.0 months (95% CI: 8.2, 13.0) in the nivo+ipi+chemo arm and 5.1 months (95% CI : 4.3, 7.0) in the chemotherapy arm.

The contribution of components of nivolumab plus ipilimumab with two cycles of chemotherapy in CA2099LA was based largely on external data from Study CA209227. Study CA209227 is a multi-part, randomized study, parts of which compared nivolumab plus ipilimumab (Part 1) and nivolumab plus chemotherapy (Part 2) to chemotherapy alone, in a similar patient population as CA2099LA. The FDA considered the overall survival results from CA209227 supportive in assessing the contribution of nivolumab, ipilimumab, and chemotherapy in CA2099LA. Results from studies in melanoma and RCC were also considered supportive in demonstrating the benefit of combination of ipilimumab to nivolumab.

The observed safety profile of nivolumab in combination with ipilimumab and two cycles of chemotherapy is acceptable when considered in the context of a life threatening disease. The incidences reported here are for the 358 patients treated with the combination of nivolumab and ipilimumab and chemotherapy in Study CA2099LA. The most common (≥ 20%) adverse reactions due to any cause were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%). Nivolumab in combination with ipilimumab and platinum-doublet chemotherapy were discontinued for adverse reactions in 24% of patients. The most common (≥ 2%) serious adverse reactions were anemia, febrile neutropenia, pneumonia, dyspnea, pneumonitis, diarrhea, acute kidney injury, musculoskeletal pain, and hemorrhage. Deaths considered related or possibly related to nivolumab plus ipilimumab and chemotherapy were identified in seven (2%) patients; fatal adverse reactions included acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. The incidence and severity of immune-mediated adverse reactions were comparable to those described in the current product labeling for the combination of nivolumab and ipilimumab. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use.

In summary, the FDA review teams consider that results from the 9LA trial, along with supportive external data, meet the evidentiary standard for regular approval and provides substantial evidence of effectiveness of nivolumab with ipilimumab and two cycles of chemotherapy for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer without EGFR or ALK genomic tumor aberrations. The magnitude of the treatment effect on OS is statistically significant and clinically meaningful and is consistent with an improvement in the

treatment of patients with metastatic NSCLC. This benefit is supported by improvement in PFS, ORR, and DOR.

Based on a favorable risk-benefit profile for this patient population with serious life-threatening disease, the FDA review teams recommend regular approval of nivolumab in combination with ipilimumab and two cycles of platinum chemotherapy for the following indication: *first-line treatment of adult patients with metastatic NSCLC without EGFR or ALK genomic tumor aberrations*.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer death in the US, with 80 - 85% of cases classified as NSCLC. • 85% of cases of NSCLC are diagnosed at later stages and for patients with metastatic disease, the 5-year survival rate is < 10%.	Metastatic NSCLC is a life-threatening condition with poor survival.
Current Treatment Options	• At the time study CA2099LA (CheckMate-9LA) was initiated, platinum based combination chemotherapy was the standard of care option for the first-line treatment of patients with NSCLC; median OS for these regimens is reported as approximately 8-11 months. • Pembrolizumab (for non-squamous and squamous histology) and atezolizumab (for non-squamous histology) administered with a platinum-based combination regimen are current standard of care, FDA-approved treatment options for the first-line treatment of patients with metastatic NSCLC regardless of PD-L1 status. These regimens are associated with both chemotherapy-related toxicities (e.g. myelosuppression) and immune-related toxicities. • The combination of nivolumab and ipilimumab has recently been approved for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥ 1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.	At the time Study CA209227 was designed, platinum-based doublet chemotherapy, which is associated with a median OS of 8-11 months, was an appropriate comparator for the first line treatment of patients with metastatic NSCLC. The combination of nivolumab plus ipilimumab and two cycles of chemotherapy would provide another treatment option for patients with PD-L1-positive NSCLC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The primary trial supporting this sBLA is Study CA2099LA; a multicenter, open-label study where a total of 719 patients were randomized (1:1) to receive either nivolumab in combination with ipilimumab and platinum-doublet chemotherapy (n=361) or four cycles of platinum chemotherapy (n=358) as control group. • Study CA2099LA demonstrated a HR for overall survival of 0.69 (96.71% CI: 0.55, 0.87; p-value 0.0006) favoring nivolumab plus ipilimumab plus chemotherapy; the median OS was 14.1 months (95% CI: 13.2, 16.2) in the nivolumab plus ipilimumab plus chemotherapy arm and 10.7 months (95% CI: 9.5, 12.5) in the chemotherapy arm. • Based on an updated analysis for overall survival with an additional 4.6 months of follow-up, the HR for OS was 0.66 (95% CI: 0.55, 0.80) with median OS of 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving nivolumab plus ipilimumab plus chemotherapy and chemotherapy, respectively. • The hierarchically-tested key secondary objectives of the study, PFS per BICR and ORR per BICR, were also statistically significant. • The HR for PFS per BICR was 0.70 (97.48% CI: 0.57, 0.86; p-value 0.0001) with a median PFS of 6.8 months (95% CI: 5.6, 7.7) in the nivolumab plus ipilimumab plus chemotherapy arm and 5.0 months (95% CI: 4.3, 5.6) in the chemotherapy arm. • The ORR per BICR in the nivolumab plus ipilimumab plus chemotherapy arm was 38% (95% CI 33, 43) versus 25% (95% CI: 21, 30) in the chemotherapy arm, with a median DOR of 10.0 months (95% CI: 8.2, 13.0) in the nivolumab plus ipilimumab plus chemotherapy arm and 5.1 months (95% CI : 4.3, 7.0) in the chemotherapy arm.	The submitted evidence meets the statutory evidentiary standard for regular approval. The observed improvement in OS, with a HR of 0.66 and a 4.7-month difference in median OS, is statistically significant and clinically meaningful. This finding is supported by statistically significant improvement in PFS, ORR, and DOR observed for nivolumab plus ipilimumab plus chemotherapy compared to chemotherapy in Study CA2099LA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• FDA considered results from Study CA209227 supportive in assessing the contribution of nivolumab, ipilimumab, and chemotherapy in CA2099LA. • The survival benefit of adding ipilimumab to nivolumab in NSCLC was demonstrated in CA209227 Part 1. The survival benefit of adding ipilimumab to nivolumab + chemotherapy in NSCLC was assessed based on comparisons of results between CA2099LA and CA209227 Part 2. • The addition of chemotherapy to nivolumab + ipilimumab was also assessed based on comparisons of CA2099LA to CA209227 Part 1 and was supported by the elimination of the early deficit seen with nivolumab + ipilimumab alone compared to chemotherapy.	
Risk and Risk Management	• For the primary safety population for the assessment of safety and tolerability of the recommended dose and regimen was derived from the pivotal study CA2099LA on 719 patients, supported by additional 36 patients from study CA209568 who received the same regimen as the one evaluated in the pivotal study. • Based on the safety population of 719 patients in Study CA2099LA, the most common (≥ 20%) adverse reactions due to any cause were fatigue (49%), musculoskeletal pain (39%), nausea (32%), diarrhea (31%), rash (30%), decreased appetite (28%), constipation (21%), and pruritus (21%). • Nivolumab in combination with ipilimumab and platinum-doublet chemotherapy were discontinued for adverse reactions in 24% of patients. • The most common (≥ 2%) serious adverse reactions were anemia, febrile neutropenia, pneumonia, dyspnea, pneumonitis, diarrhea, acute kidney injury, musculoskeletal pain, and hemorrhage.	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of the combination.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Deaths considered related or possibly related to nivolumab plus ipilimumab and chemotherapy were identified in seven (2%) patients; fatal adverse reactions included acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. • The incidence and severity of immune-mediated adverse reactions were similar to those described in the current product labeling for the combination of nivolumab and ipilimumab. • There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling.	

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:					Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as				8.1.2 Efficacy Results – Secondary or exploratory COA (PRO) endpoints
			X	Patient reported outcome (PRO)		8.1.2 Efficacy Results – Secondary or exploratory COA (PRO) endpoints

		□ Observer reported outcome (ObsRO)	
		□ Clinician reported outcome (ClinRO)	
		□ Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.		

X

Adnan Jaigirdar

Cross-Disciplinary Team Leader

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2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

Lung cancer is the most common cancer worldwide, with 1.8 million new cases diagnosed yearly, and an estimated 1.6 million deaths worldwide.[1] Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancers and includes squamous (SQ) and non-squamous (NSQ) cell carcinoma, which encompasses a variety of histological subtypes including adenocarcinoma, large cell carcinoma, and less common subtypes.[1,2,3,4] In the United States (US), the majority of patients are diagnosed with metastatic disease and the 5-year survival rate for metastatic lung cancer is extremely poor (~ 5%; 2009-2015 Surveillance, Epidemiology, and End Results Program [SEER] data).[5]

The FDA's Assessment:

FDA agrees with the applicant's position.

2.2 Analysis of Current Treatment Options

Data

Table 1: Approved Immuno-Oncology Agents Relevant to First-line NSCLC with nofour EGFR or ALK Genomic Tumor Aberrations

Product (s) Name (Pivotal Study[ies])	Relevant Indication	Year and Type of Approval	Dosing/ Administration	Efficacy Information (Efficacy vs Chemo)	Important Safety and Tolerability
Anti-PD-(L)1 Monotherapy, All in a Subjects with Tumor PD-L1 Expressing Patient Population					
Pembrolizumab (KEYNOTE 042 [6] and KEYNOTE 024) [7]	As a single agent for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test	2019; Full 2016, Full	200 mg every 3 weeks, IV	KEYNOTE 042 (TPS ≥ 1%): Median FU: 12.8 mo. OS rate at 24 mo: 39% vs 28% mOS: 16.7 vs 12.1 mo. HR (95% CI): 0.81 (0.71, 0.93) KEYNOTE 024 (TPS ≥ 50%): Median FU: 18.7mo. OS rate at 12 mo: 69% vs 49% mOS: 22.0 vs 10.7 mo. HR (95% CI): 0.56 (0.45, 0.70)	Immune-mediated adverse events
Anti-PD-(L)1 in Combination with Chemotherapy, All in a Tumor PD-L1 Unselected Patient Population					
Pembrolizumab + pemetrexed and/or platinum chemo (KEYNOTE 189) [8]	In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic NSQ NSCLC.	2017 accelerated; 2018 Full	200 mg every 3 weeks, IV	Median FU: 18.7mo. OS rate at 12 mo: 69% vs 49% mOS: 22.0 vs 10.7 mo. HR (95% CI): 0.56 (0.45, 0.70)	Immune-mediated adverse events
Pembrolizumab + carboplatin and Investigator's choice of paclitaxel or paclitaxel protein-bound (KEYNOTE 407) [9]	In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic SQ NSCLC.	2018; Full	200 mg every 3 weeks, IV	Median FU: 14.3 mo. OS rate at 12 mo: 65% vs 48% mOS: 17.1 vs 11.6 mo. HR (95% CI): 0.71 (0.58, 0.88)	Immune-mediated adverse events
Atezolizumab + bevacizumab + paclitaxel + carboplatin (IMpower 150) [10]	In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic NSQ NSCLC	2018; Full	1200 mg every 3 weeks, IV	Median FU: 15.4 mo. OS rate at 24 mo: 43% vs 34% mOS: 19.2 vs 14.7mo. HR (95% CI): 0.78 (0.64, 0.96)	Immune-mediated adverse events
Atezolizumab + carboplatin + nab-paclitaxel vs carboplatin + nab-paclitaxel (IMPower 130) [11]	In combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic NSQ NSCLC with no EGFR or ALK genomic tumor aberrations	2019; Full	1200 mg every 3 weeks, IV	Min FU: 13 mo. OS rate at 12 mo: 63% vs 56% mOS: 18.6 vs 13.9 mo. HR (95% CI): 0.79 (0.64, 0.98)	Immune-mediated adverse events

The Applicant's Position:

Until recently, platinum-doublet chemotherapy alone was the recommended standard of care for first-line treatment of metastatic NSCLC, with the exception of small subgroups of patients with NSCLC tumors harboring known driver mutations (eg, epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK]) (National Comprehensive Cancer Network guidelines and European Society for Medical Oncology [ESMO] guidelines).[12,13,14,15,16,17,18.19] Chemotherapy alone remains a treatment option in certain cases of advanced NSCLC, such as when patients are not considered candidates to receive immunotherapy.

Platinum doublets are used interchangeably and selected based on physician and patient preferences and comorbidities, with the exception of pemetrexed- and gemcitabine-based doublets, which are reserved for NSQ and SQ histology, respectively. Efforts to improve the efficacy of platinum-based doublet therapies for advanced and metastatic NSCLC have focused on the addition of targeted agents (eg, bevacizumab in NSQ[20,21,22] and necitumumab in SQ[23]) or anti-programmed death ligand-1 (PD-[L]1) immunotherapies and on the use of maintenance therapy (eg, erlotinib or pemetrexed in NSQ[24,25,26,27]) for subjects who did not progress on platinum-based first-line therapy.

First-line anti-PD-1 immunotherapy as monotherapy has been shown to provide survival benefit over chemotherapy in patients with metastatic or recurrent NSCLC whose tumors express PD-L1. This benefit with PD-1 monotherapy has been shown to be mostly driven by patients with high tumor PD-L1 expression (eg, ≥ 50%). Subsequently, first-line combination regimens of anti-PD-(L)1 immunotherapy + chemotherapy have been shown to improve overall survival (OS) over chemotherapy alone in biomarker-unselected NSCLC.

The combination of PD-1 and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibition (nivolumab + ipilimumab [nivo+ipi]) has recently been shown to improve survival across different indications. In metastatic melanoma, the nivo+ipi combination demonstrated superior OS benefit versus nivolumab or ipilimumab as a monotherapy, with a 5-year OS rate of 52%.[28,29] In first-line metastatic or recurrent NSCLC (Phase 3 study CA209227 Part 1), nivo+ipi provided deep and durable responses that translated into a durable survival benefit over chemotherapy in both patients with PD-L1 expressing and PD-L1 non-expressing tumors.[30] The contribution of ipilimumab was demonstrated based on improved OS and progression-free survival (PFS), higher response rates, and longer duration of response with nivo+ipi versus nivolumab monotherapy in PD-L1 ≥ 1% subjects, including across different pre-defined subgroups.

Table 1 shows US-approved anti-PD (L)-1 agents as monotherapy or in combination with chemotherapy for first-line treatments for metastatic NSCLC other than those only approved for subgroups defined by genetic driver mutations. To date, no regimens with 2 immunotherapy agents (anti-PD-(L)1 + anti-CTLA-4) with or without chemotherapy are approved for treatment of first-line NSCLC.

The FDA's Assessment: FDA generally agrees with the data and position presented by the applicant with the following exceptions:

- Based on an updated analysis of KEYNOTE 024 of patients with patients with advanced, unresectable or metastatic NSCLC whose tumors express PD-L1 (TPD ≥50%), FDA notes the following results which differ from the results reported by the Applicant (Reck M. J Clin Oncol, 2019):
    - Median follow-up: 25.2 months
    - Median OS (mOS): 30 months (95% CI: 18.3, not reached [NR]) with pembrolizumab versus 14.2 months (95% CI:9.8, 19.0) with chemotherapy
    - HR for OS (95% CI): 0.63 (0.47, 0.86)
- KEYNOTE 189 was a study of pembrolizumab plus pemetrexed plus platinum chemotherapy for the first-line treatment of patients with metastatic non-squamous NSCLC. FDA agrees with the results reported by the applicant except that FDA notes a median follow-up of 23.1 months as opposed to 18.7 months (Gadgeel S. J Clin Oncol, 2020).

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Nivolumab was first approved in 2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and the European Union (EU), and for other indications, including metastatic NSCLC, small cell lung cancer [SCLC], advanced renal cell carcinoma [RCC], classical Hodgkin lymphoma [cHL], squamous cell carcinoma of the head and neck [SCCHN], metastatic urothelial carcinoma [UC], hepatocellular carcinoma [HCC], microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR] metastatic colorectal cancer [CRC], and adjuvant melanoma.

Ipilimumab was first approved in 2011 in the US for advanced melanoma, and has since been approved for market use in 60 countries worldwide.

Nivolumab + ipilimumab was first approved in the US (2015) and in the EU (2016) for the treatment of patients with unresectable or metastatic melanoma under, respectively, and has since been approved in multiple countries. Nivolumab + ipilimumab was also approved for the treatment of advanced RCC in the US (2018) and the EU (2019), and for the treatment of MSI-H/dMMR metastatic CRC in the US (2018 accelerated approval).

The FDA's Assessment:

FDA agrees with the applicant's position and also notes that nivolumab plus ipilimumab additionally received accelerated approval in 2019 for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib. Most recently, FDA approved the combination of

nivolumab and ipilimumab for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥ 1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Regulatory milestones in Table 2 refer to IND 125872 unless otherwise noted.

Table 2: Key Regulatory Milestones

18-Mar-2015	Initial Application - IND 125872 containing Study Protocol CA209227 Phase 3 Trial of Nivolumab versus Platinum Doublet Chemotherapy and Nivolumab plus Ipilimumab versus Platinum Doublet Chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer
06-Jul-2017	Initial Protocol for Study CA2099LA submitted to IND 125872 Phase 3 Trial of Nivolumab plus Ipilimumab in Combination with Chemotherapy vs Chemotherapy alone as First Line Therapy in Stage IV Non-Small Cell Lung Cancer
01-Nov-2019	Teleconference - Regulatory Review Pilot Programs (Project Orbis, Real-Time Oncology Review [RTOR], Assessment Aid) Agreement with the FDA reached for proposed content and timelines for RTOR pre-submission package, Assessment Aid, and potential participation in Project Orbis
18-Nov-2019	iPSP Amendment - Agreement issued by FDA Sep 2017: iPSP Agreed upon by FDA for nivolumab and ipilimumab Sep 2019: Amended iPSP for NSCLC indications for nivolumab and ipilimumab
06-Dec-2019	Pre-sBLA Meeting - Preliminary Comments issued by FDA: FDA generally agreed to the content of the sBLA submission package, the proposed clinical package, the summaries of clinical efficacy, safety, and pharmacology, proposal for submission of patient narratives and CRFs, proposal for electronic dataset submission, proposal for the safety update, and provided guidance on additional details of the study design to be included in the sBLA FDA reaffirmed participation in the RTOR/Assessment Aid/Project Orbis pilot programs
19-Dec-2019	RTOR Pre-submission Package Submitted to BLA 125554 based on Study CA2099LA
02-Jan-2020	Fast Track Designation Granted by the FDA based on Study CA2099LA

The FDA's Assessment:

FDA agrees with the regulatory timeline and also notes that the applicant submitted the full sBLA applications to the FDA on February 6, 2020. Concerns about demonstration of the contribution of components were discussed by the FDA to the applicant during the November 1, 2019 teleconference and conveyed in the December 6, 2019 pre-sBLA meeting.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

No clinical sites were inspected for the supplemental applications.

4.2 Product Quality

No new CMC information was provided in the supplemental applications. Refer to CDER's Quality Review from the original BLA submissions.

4.3 Clinical Microbiology

No clinical microbiology data were submitted in the supplemental applications.

4.4 Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

The FDA's Assessment:
No new Nonclinical Pharmacology / Toxicology information was provided in the supplemental applications. Refer to CDER's Nonclinical Pharmacology / Toxicology review from the original BLA submissions.

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

The Office of Clinical Pharmacology has reviewed the information contained in BLA 125554 Supplement 82. This sBLA is approvable from a clinical pharmacology perspective. The key review issues with the specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness came from Study CA2099LA, which demonstrated statistically significant and clinically meaningful improvements in OS, PFS, and ORR with the recommended dosage regimen of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy compared to 4 cycles of platinum-doublet chemotherapy in all randomized NSCLC patients : • OS: 14.13 vs 10.74 months, HR = 0.69 (96.71% CI: 0.55, 0.87); p = 0.0006 • PFS: 6.83 vs 4.96 months, HR = 0.70 (97.48% CI: 0.57, 0.86); p= 0.0001 • ORR: 37.7% (95% CI: 32.7, 42.9) vs 25.1% (95% CI: 20.7, 30.0); p = 0.0003
General dosing instructions	The proposed dosage regimen of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of of platinum-doublet chemotherapy is efficacious with a manageable safety profile.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended based on intrinsic and extrinsic factors.
Immunogenicity	Following the recommended dosage regimen in Study CA2099LA, the incidence of anti-nivolumab antibodies was 33.8% (104/308) with 2.6% (8/308) neutralizing antibodies against nivolumab. The incidence of ipilimumab ADA was 7.5% (23/305) and 1.6% (5/305) were neutralizing antibodies against ipilimumab. The incidence of nivolumab and ipilimumab ADA did not appear to affect the efficacy and safety of the combination therapy at the proposed dosage regimen.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

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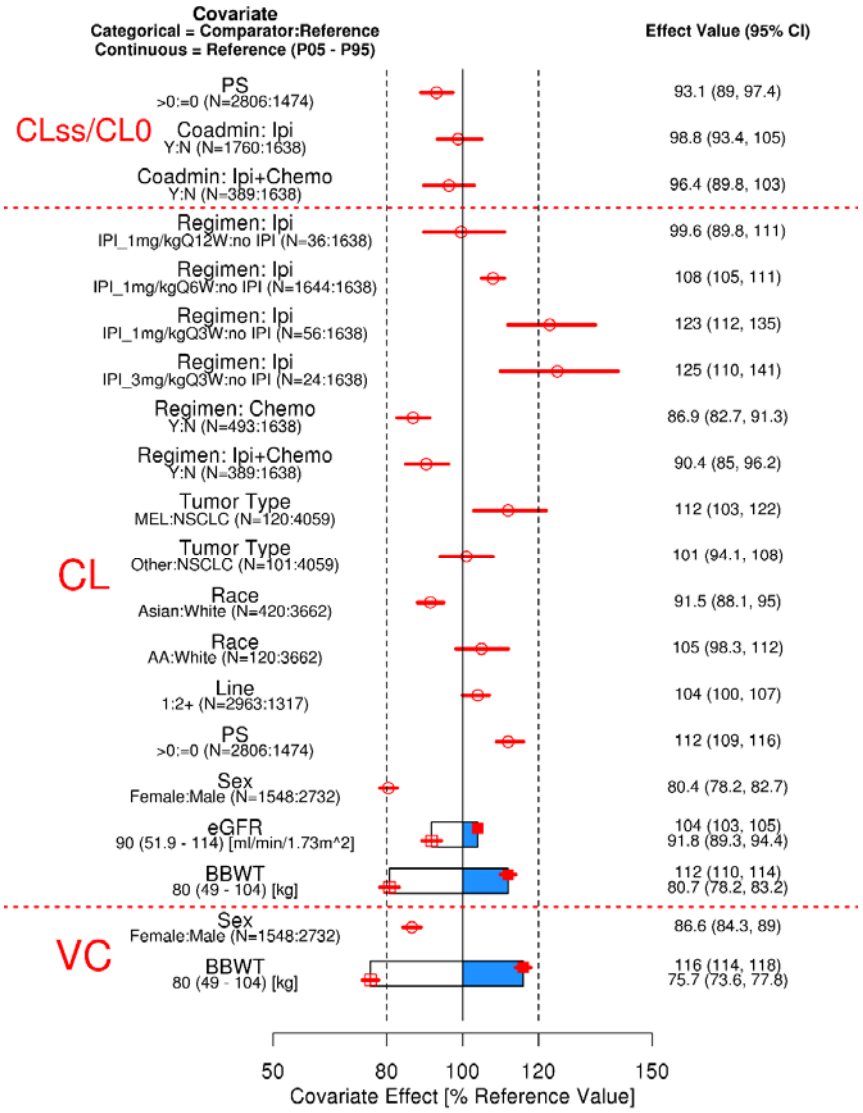
Figure 1: Covariate Effects on Nivolumab Pharmacokinetic Model Parameters (Full Nivolumab Population Pharmacokinetic Model)



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is male, white/other race, BW = 80 kg, PS = 0, eGFR = 90 mL/min/1.73 m2, and received nivolumab monotherapy, with NSCLC as tumor type. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.
Note 4: The effect of BBWT was also added on Q and VP and their estimates were fixed to be similar to that CL and VC, respectively.
Note 5: PS appeared twice in the figure. Baseline CL of nivolumab in subjects with PS > 0 was higher than subjects with PS = 0 by 12%, whereas the reduction of nivolumab CL over time was more significant in subjects with PS > 0 than subjects with PS = 0 by 6.9%.

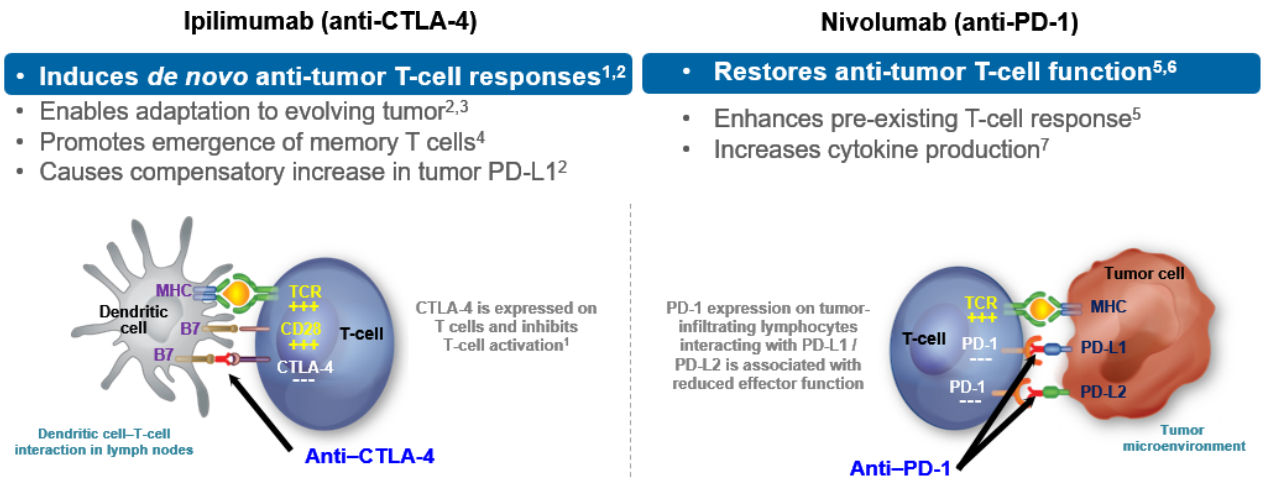
The Applicant's Position:

Pharmacology

Nivolumab is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2 (Figure 2). Tumors use PD-L1 expression as defense or escape mechanism against the host's anti-tumor T cell response; inhibiting PD-(L)1 restores the function of these anti-tumor T cells which have become ineffective or suppressed. Therefore, the efficacy of PD-(L)1 inhibition relies on a preexisting immune response. The clinical benefit from PD-(L)1 inhibition is enhanced with higher PD-L1 expression in the tumor, since tumors with high PD-L1 expression rely more heavily on this escape mechanism.

Ipilimumab is a human monoclonal antibody that targets CTLA-4. CTLA-4 inhibition can induce de novo T-cell responses and recruit novel/additional T cells to the tumor (Figure 2). The ability to induce de novo T-cell responses is likely the underlying mechanism for activity in patients with an absent or insufficient anti-tumor immune response, such as in patients with non PD-L1 expressing tumors. In addition, the recruitment of novel T cells may also allow for the immune response to adapt to an evolving tumor, which together with the generation of memory T cells may be important for durability of response. Importantly, the recruitment of novel T cells to the tumor and the generation of memory T cells through CTLA-4 inhibition is independent of whether the tumor is expressing PD-L1 as defense mechanism. However, the generation of a de novo T-cell response against the tumor frequently leads to compensatory upregulation of PD-(L)1 as an escape mechanism in the tumor, which is likely why CTLA-4 inhibition, without PD-(L)1 inhibition, does not show clinically meaningful activity in NSCLC.

Figure 2: Nivolumab and Ipilimumab Have Distinct but Complementary Mechanisms of Action



Sources: 1. Pardoll DM. Nat Rev Cancer 2012[31] 2. Wei SC, et al. Cancer Discov 2018[32] 3. Wei SC, et al. Immunity 2019[33] 4. Das R, et al. J Immunol 2015[34] 5. Wang C, et al. Cancer Immunol Res 2014[35] 6. Brahmer JR, et al. J Clin Oncol 2010[36] 7. Hamanishi J, et al. Proc Natl Acad Sci USA 2007[37]

Chemotherapy releases neoantigens from apoptosing tumor cells, increasing antigen presentation to dendritic cells, decreasing the myeloid-derived suppressive cells and increasing the ratio of cytotoxic lymphocytes to regulatory T-cells.

Clinical Pharmacokinetics

In the current supplement, a population pharmacokinetics (PPK) analysis characterized the pharmacokinetics (PK) of nivolumab in subjects with previously untreated NSCLC who received nivolumab in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy and determined the effects of covariates on nivolumab PK parameters. This PPK analysis included evaluation of the potential for a drug-drug interaction between nivolumab and ipilimumab. The covariates assessed included ipilimumab dosing regimen (3 mg/kg every 3 weeks [Q3W], 1 mg/kg Q3W, 1 mg/kg every 6 weeks [Q6W], and 1 mg/kg every 12 weeks [Q12W]), chemotherapy, and ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy effect on nivolumab clearance (CL); ipilimumab and ipilimumab + chemotherapy coadministration on maximum effect (EMAX) were also assessed. Consistent with previous PPK analyses, the PK of nivolumab in combination with ipilimumab and 2 cycles of chemotherapy in previously untreated NSCLC subjects was well described by a linear 2 compartment model with time-varying CL. Ipilimumab coadministration (1 mg/kg Q12W), other tumor types (non-melanoma), and African American race, were not statistically significant covariates of nivolumab CL (95% confidence interval [CI] included 1). Coadministration with ipilimumab (1 mg/kg Q6W), chemotherapy, and ipilimumab and chemotherapy, melanoma tumor type, Asian race, performance status (PS), sex, line of therapy, estimated glomerular filtration rate (eGFR), and baseline body weight were statistically significant covariates on nivolumab CL (95% CI did not include 1); however, the magnitude of the differences is not considered to be clinically relevant (< 20%). Nivolumab CL was higher in subjects coadministered ipilimumab 1 mg/kg Q3W and 3 mg/kg Q3W (by ~23% and ~25%, respectively), relative to nivolumab monotherapy. Nivolumab CL was higher in anti-drug antibody (ADA)-positive subjects compared to ADA-negative subjects in Study CA2099LA (by ~29%). There appeared to be no impact on efficacy or safety with increased nivolumab CL in ADA-positive subjects. There were no clinically relevant differences in nivolumab CL by ethnicity.

The FDA's Assessment:

FDA agrees with the Applicant's position that the PK of nivolumab was adequately described by a previously established population PK model which is a linear 2-compartment model with time-varying clearance (CL). The following covariates did not clnically meaningful affect the nivolumab CL: coadministration with ipilimumab (1 mg/kg Q6W and 1 mg/kg Q12W), coadministration with chemotherapy, coadministration with ipilimumab and chemotherapy, tumor type, race, performance status (PS), sex, line of therapy, estimated glomerular filtration rate (eGFR), and baseline body weight. Nivolumab CL was approximately 23% and 25% higher, respectively, in patients coadministered ipilimumab 1 mg/kg Q3W and 3 mg/kg Q3W comparing to nivolumab administered alone. The nivolumab CL was 29% higher in anti-drug antibody (ADA) positive patients compared to ADA-negative patients, which did not appeared to affect the efficacy or safety.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

The Applicant's Position:

Selection of the Doses and Regimen

Nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W was initially selected as the nivo+ipi combination regimen in first-line NSCLC studies based on the totality of available efficacy and safety data from Phase 1 dose-finding study CA209012 showing that this regimen was well tolerated and demonstrated clinically meaningful rates of objective, durable responses in chemotherapy-naive stage IIIB/IV NSCLC subjects.

Nivolumab 360 mg flat dose Q3W in combination with chemotherapy was evaluated because nivolumab 360 mg had similar steady-state nivolumab average exposure compared with the approved 3 mg/kg Q2W dose (at the median body weight of 80 kg). Nivolumab 360 mg was administered at the Q3W interval to align with the dosing of platinum-doublet chemotherapy Q3W.

Two cycles of platinum-doublet chemotherapy were added to the nivo+ipi combination to enhance early disease control, while building on the potential long-term survival benefit with the nivo+ipi combination in first-line NSCLC. In addition, 2 cycles of chemotherapy would likely minimize the chemotherapy-specific toxicities compared with 4 cycles of chemotherapy given as a standard of care either alone or in combination with PD-(L)1 inhibitors currently approved.

The safety and tolerability of the combination of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy was initially evaluated in CA209568 Part 2.[38] The safety profile of nivo+ipi+chemo was manageable and consistent with the safety signals of each individual component. No new safety concerns were identified, and there were no deaths attributed to study drug toxicity. Based on these results, the nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W with 2 cycles of chemotherapy regimen was chosen for the pivotal Phase 3 CA2099LA study. In the pre-specified interim analysis of OS in study CA2099LA, first-line nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy demonstrated statistically significant and clinically meaningful improvements in OS, and blinded independent central review (BICR)-assessed PFS and objective response rate (ORR), compared with 4 cycles of chemotherapy in subjects with metastatic or recurrent NSCLC.

Confirmation of the Doses and Schedule

In the pre-specified interim analysis of study CA2099LA, nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy demonstrated statistically significant and clinically meaningful improvements in efficacy (primary and secondary endpoints) and it had a manageable safety profile. The PPK findings and exposure-response (E-R) data support the combination of nivo+ipi and 2 cycles of chemotherapy.

Results from the PPK analysis showed ipilimumab 1 mg/kg Q6W plus 2 cycles of chemotherapy had a statistically significant effect on nivolumab CL; however, the magnitude of this difference was not considered to be clinically relevant (< 20%). Nivolumab 360 mg Q3W plus 2 cycles of chemotherapy had a statistically significant effect on ipilimumab CL; however the magnitude of this difference was marginal

(~22%).

Exposure-efficacy analyses for first-line NSCLC subjects in CA2099LA showed that the risk of death was not significantly associated with nivolumab or ipilimumab exposure within the dosing regimen of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum doublet chemotherapy (95% CI includes null effect), after adjusting for the effect of nivolumab CL (sensitivity analysis). An exposure-safety analysis of pooled data from subjects in studies CA2099LA and CA209227 showed that both nivolumab and ipilimumab time-averaged concentration over the first dosing interval (Cavg1) exhibited statistically a significant effect on the risk of (Grade $\geq$ 2 immune-mediated adverse events [Gr2+ IMAEs]), compared with chemotherapy, within the treatment regimens. Notably, the risk of Gr2+ IMAEs did not increase with higher nivolumab exposure, but did increase with higher ipilimumab exposure. However, the magnitude of the effects of nivolumab and ipilimumab Cavg1 were similar, indicating that ipilimumab and nivolumab contributed similarly to the increased risk of Gr2+ IMAEs in the treatment regimens.

The results of the E-R analyses of efficacy and safety supported the proposed dosing regimen. Specifically, the E-R relationships of nivolumab and ipilimumab were not associated with efficacy, indicating that the exposures produced by the proposed doses were in the flat part of the efficacy response, within the proposed dosing regimen. The E-R of safety of nivolumab in the combination is similar to that of nivolumab monotherapy, which is well accepted as a safe and tolerable dose. Moreover, although the risk of Gr2+ IMAEs increased with increasing ipilimumab exposure, the magnitude of the effect is similar to that of nivolumab.

In summary, these results support the recommended dose and schedule of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy as first line therapy in patients metastatic or recurrent NSCLC.

The FDA's Assessment:

FDA agrees with the Applicant's selection of the dosage regimen (nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of of platinum-doublet chemotherapy) used in first line NSCLC patients based on the following rationales:

- Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W was initially selected as the combination regimen in first-line NSCLC studies (Phase 1 dose-finding study CA209012, Phase 2 Study CA209568 Part 1 and Phase 3 Study CA209227 Part 1) based on the totality of available efficacy and safety data showing that this regimen was well tolerated and demonstrated clinically meaningful and durable responses in chemotherapy-naive Stage IIIB/IV NSCLC patients.
- Nivolumab 360 mg flat dose Q3W was selected because it achieved similar steady-state nivolumab average exposure compared with the approved 3 mg/kg dose Q2W at the median body weight of 80 kg. The Q3W dosing interval was selected to be align with the platinum doublet chemotherapy ,which was also administered Q3W. Refer to Section 18.4. OCP Appendices for details.
- Two cycles of platinum-doublet chemotherapy were added to the nivo+ipi combination to enhance early disease control, and to complement the durability of response and long-term survival benefit

with the nivo+ipi combination in first-line NSCLC patients and minimize the chemotherapy-specific toxicities compared with 4 cycles of chemotherapy.

- Population PK analyses demonstrated that ipilimumab 1 mg/kg Q6W plus 2 cycles of chemotherapy did not significantly affect the nivolumab CL (<20%) and nivolumab 360 mg Q3W plus 2 cycles of chemotherapy increased the ipilimumab CL by 22%.
- The exposure-efficacy analyses for first-line NSCLC patients in Study CA2099LA showed that the relationship between nivolumab or ipilimumab exposure (Cavg1) and OS appeared flat. The E-R safety analyses showed that the risk of Gr2+ IMAEs increased with higher ipilimumab exposure but did not increase with higher nivolumab exposure.

6.2.2.2 Therapeutic Individualization

The Applicant's Position:
There were no clinically relevant differences in nivolumab PK parameters or exposures identified for the intrinsic and extrinsic factors tested and described below; therefore, therapeutic individualization of nivolumab is not recommended.

The FDA's Assessment:
FDA agrees with the Applicant's position that further therapeutic individualization of nivolumab is not needed as there were no clinically relevant differences in nivolumab PK identified for the intrinsic and extrinsic factors listed in the currently approved labeling.

6.2.2.3 Outstanding Issues

The Applicant's Position:
None

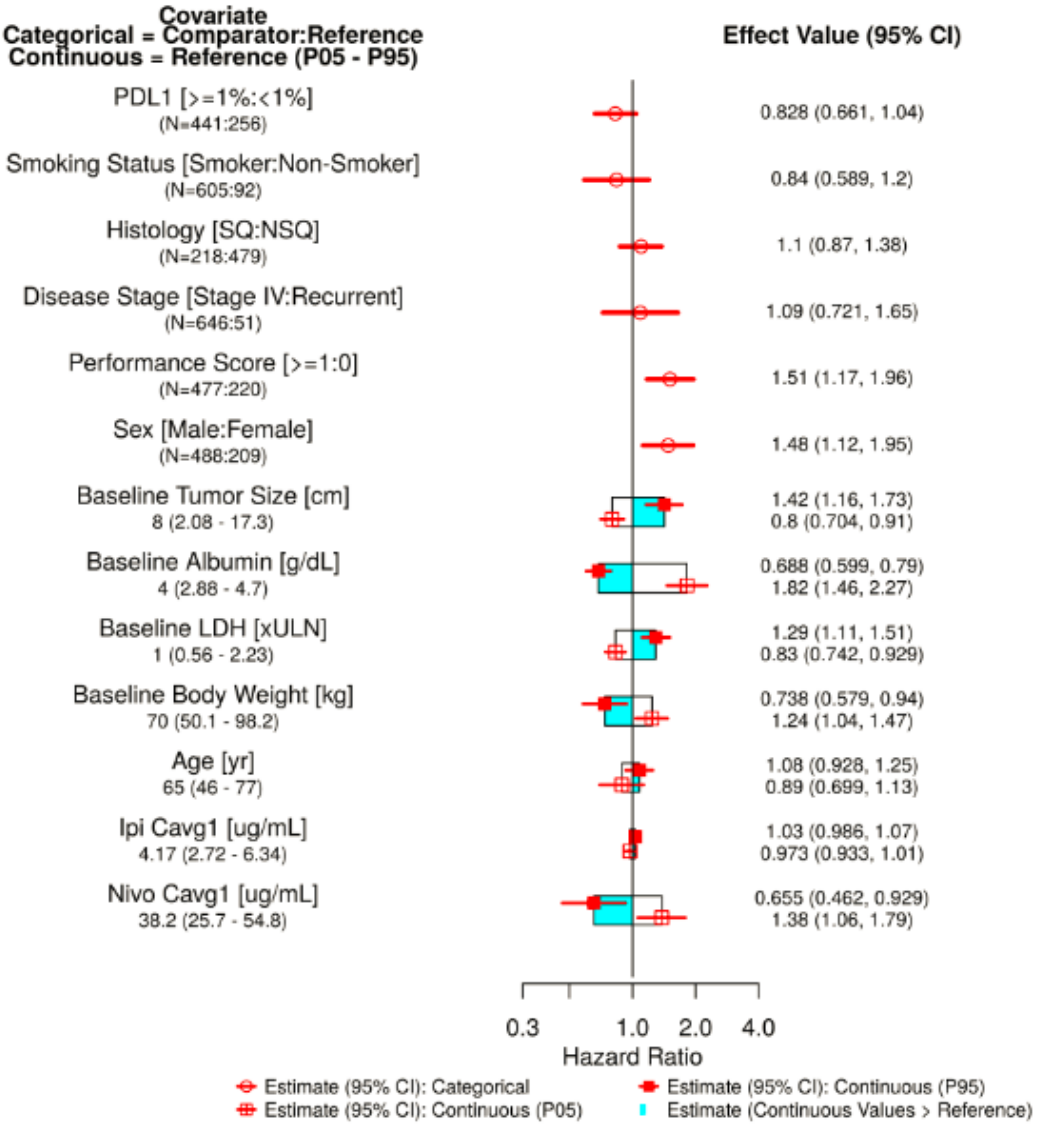
The FDA's Assessment:
FDA concurs.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

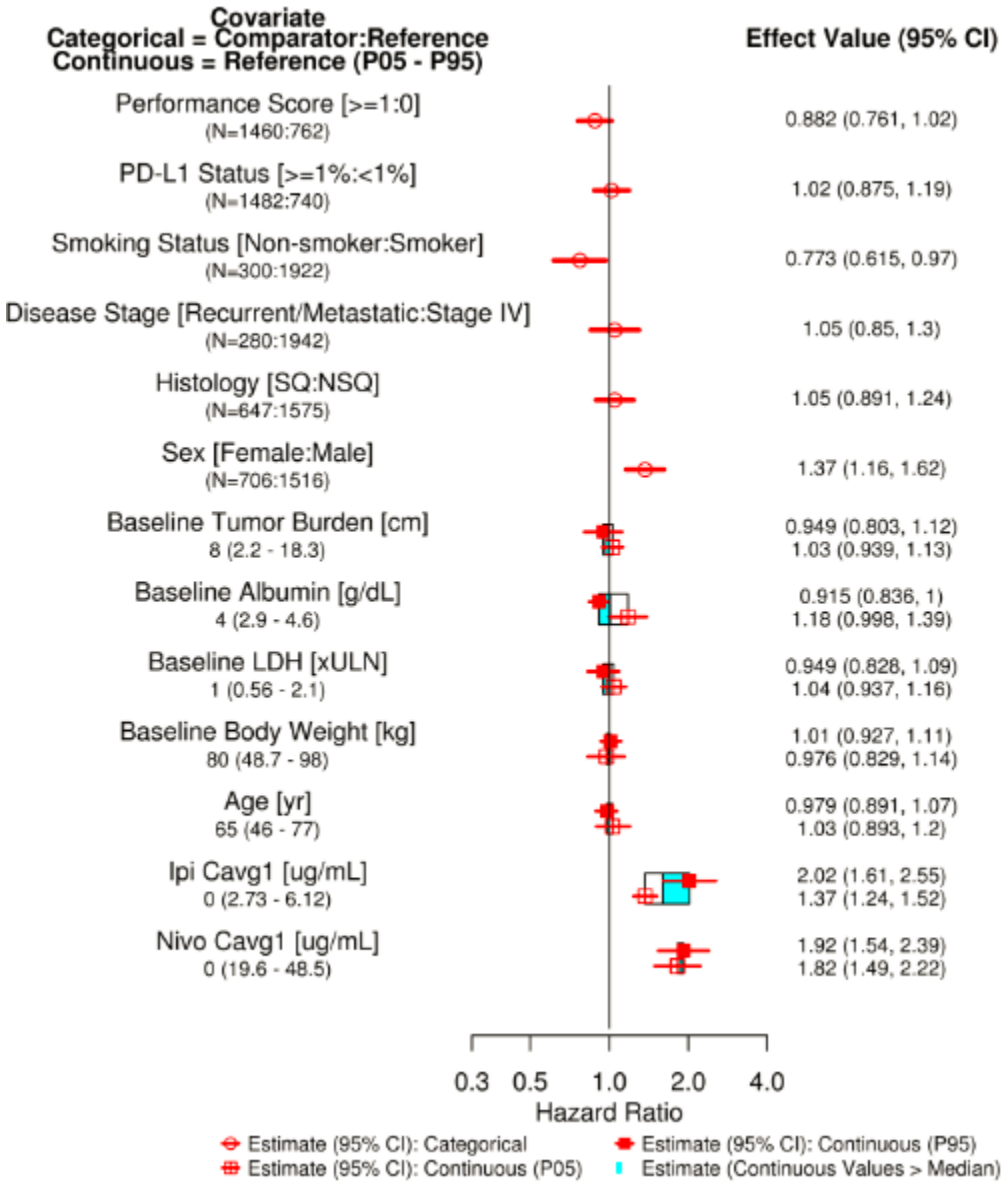
Data:

Figure 3: Estimated Covariate Effects of the Exposure-Response of OS (Full Model)



Note: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate.
Reference subject: subject had median value of nivolumab Cavg1 and ipilimumab Cavg1 who received nivolumab 360 mg Q3W and ipilimumab 1 mg/kg Q6W plus 2 cycles of platinum-doublet chemotherapy in Study CA2099LA, and median value of LDH, albumin, body weight, baseline clearance, baseline tumor size, NSQ, female, non-smoker, PS=0, PD-L1 <1%, and recurrent disease stage subjects.

Figure 4: Estimated Covariate Effects of the Exposure-Response of Gr2+ IMAEs (Revised Full Model)



Note: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate.
Note: The reference value of ipilimumab Cavg1 utilized to calculate the HR is 0.001 µg/mL, as log-transformed value of Cavg1=0 is not defined.

Table 3: ADA Assessments Summary - Nivolumab + Ipilimumab + Chemotherapy Treated Subjects with At Least One Post-Baseline Assessment - CA2099LA

	Nivo+ipi+chemo	
Subject ADA Status (%)	Nivolumab ADA N = 308	Ipilimumab ADA N = 305
BASELINE ADA POSITIVE	19 (6.2)	9 (3.0)
ADA POSITIVE	104 (33.8)	23 (7.5)
PERSISTENT POSITIVE (PP)	1 (0.3)	0
NOT PP - LAST SAMPLE POSITIVE	31 (10.1)	8 (2.6)
OTHER POSITIVE	72 (23.4)	15 (4.9)
NEUTRALIZING ADA POSITIVE	8 (2.6)	5 (1.6)
ADA NEGATIVE	204 (66.2)	282 (92.5)

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (≥) than baseline positive titer) at any time after initiation of treatment;
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart;
Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling timepoint;
Other Positive: Not persistent but some ADA-positive samples with the last sample being negative;
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Post-baseline assessments are assessments reported after initiation of treatment.
Source: Table 7.10.1 (ADaM dataset: adyi.xpt, adsl.xpt)of the CA2099LA CSR

The Applicant's Position:

The following validated methods were used in CA2099LA:

- PK concentration measurement: electrochemiluminescence (ECL) assay Methods BAL-II/MOA/061[39] and 14BASM122[40] for nivolumab and Methods ICD 267[41] and 13BASM127[42] for ipilimumab
- Detection of anti-drug antibodies (ADA): Methods BAL-II/MOA/063[43] and 14BASM123[44] for nivolumab and Methods ICDIM 14[45] and 13BASM128[46] for ipilimumab
- Detection of neutralizing ADA in human serum: Methods 15400[47] and 17BASM155[48] for nivolumab and Method 15818[49] for ipilimumab.

The performance of the validated bioanalytical methods used in CA2099LA demonstrated that the assays were precise and accurate for the quantification of nivolumab and ipilimumab and the assessment of nivolumab and ipilimumab ADAs and neutralizing antibodies in the clinical study serum samples. These bioanalytical methods also met all regulatory requirements for use in clinical studies. The human serum assays used for the detection of nivolumab and ipilimumab in the clinical trials supporting the PPK analysis were appropriately cross-validated and met all regulatory requirements for use in clinical studies.

The nivolumab clinical pharmacology profiles, including single- and multiple-dose PK, pharmacodynamics (PD), pharmacogenomics, drug-drug interaction (DDI) potential, and E-R relationships with safety and efficacy across multiple tumor types have been previously characterized, both as monotherapy and in

combination with ipilimumab. This information was described in the various clinical pharmacology packages that supported the approvals for melanoma, NSCLC, SCLC, RCC, SCCHN, cHL, UC, CRC, and HCC. Clinical pharmacology information are included in the approved product label.

The PPK analysis was updated for this 1L NSCLC submission to include subjects receiving nivolumab + chemotherapy, nivolumab + ipilimumab, and nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy for 1L NSCLC and other solid tumors. The results from the updated analysis are consistent with the previous PPK analyses across tumor types, as well as specific analyses of nivolumab + ipilimumab in 1L NSCLC.

In addition, E-R analyses of efficacy (OS) and safety (Gr2+ IMAEs) were conducted to assess the relationship between nivolumab and ipilimumab exposure (including potential synergistic interaction of exposure/treatment effects) and efficacy and safety in subjects with previously untreated metastatic or recurrent NSCLC. The E-R analyses of efficacy and safety support the proposed dosing regimen of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2-cycles of platinum-doublet chemotherapy.

A semi-parametric Cox Proportional-Hazards (CPH) model was used to characterize the E-R relationship for nivolumab and ipilimumab exposure (Cavg1) and OS. The risk of death was not significantly associated with nivolumab or ipilimumab exposure within the dosing regimen of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy (95% CI includes null effect), after adjusting for the effect of nivolumab CL (sensitivity analysis). The risk of death was higher with higher baseline tumor size, higher baseline lactate dehydrogenase (LDH), lower body weight, lower baseline albumin, subjects with PS $\geq$ 1 (relative to PS = 0), and male subjects (relative to female). The following baseline covariates were not associated with the risk of death: PD-L1 status ($\geq$ 1% vs < 1%), smoking status (smoker vs non-smoker), histology (SQ vs NSQ), disease stage (stage IV vs recurrent), and age.

A semi-parametric CPH model was also used to characterize the E-R relationship for nivolumab and ipilimumab exposure (daily Cavg) and time to first occurrence of Grade 2+ IMAEs. The risk of Gr2+ IMAEs was significantly associated with nivolumab and ipilimumab exposure, resulting in a higher risk compared to chemotherapy. The risk was similar across the range of nivolumab Cavg1 produced by 3 mg/kg Q2W, 240 mg Q2W, and 360 mg Q3W. The risk was higher at the 95th percentile of ipilimumab Cavg1 produced by 1 mg/kg Q6W compared to the 5th percentile. The effects of nivolumab and ipilimumab Cavg1 were additive, and chemotherapy did not have an effect on the risk associated with nivolumab and ipilimumab Cavg1. The risk of Gr2+ IMAEs was higher in females relative to males, and lower in non-smokers relative to current/former smokers. The risk of Gr2+ IMAEs was not significantly associated with the following baseline covariates: PD-L1 status (≥ 1% vs < 1%), histology (SQ vs NSQ), disease stage (recurrent vs stage IV), PS (1+ vs 0), tumor burden, albumin, LDH, body weight, or age.

The immunogenicity of nivolumab and ipilimumab following administration of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy was assessed. The incidence of nivolumab ADA was 33.8% and the incidence of ipilimumab ADA was 7.5%. A total of 8 (2.6%) subjects were nivolumab neutralizing positive and 5 (1.6%) subjects were ipilimumab neutralizing positive (Table 3).[50]

Based on the assessment of the presence of ADA and neutralizing antibodies in relation to PFS, best overall response (BOR) per investigator, and OS, there was no apparent trend showing an effect of ADA or neutralizing antibodies on the efficacy of nivo+ipi+chemo. Of the 104 nivolumab ADA positive subjects, 25 subjects had a BOR of partial response (PR), 66 subjects had stable disease (SD), 9 subjects had progressive disease (PD) and 4 subjects were not evaluable (NE). The ADA titers in these subjects ranged from 1 to 256, the highest titer was in a subject with SD. Of the 23 ipilimumab ADA positive subjects, 8 subjects had a BOR of PR, 12 subjects had SD, 2 subjects had PD and 1 subject was NE. ADA titers in these subjects was low and ranged from 1 to 64; the highest titer was in a subject with PD.

Overall, the incidence of nivolumab and ipilimumab ADA did not appear to have an effect on safety of the tested regimen. Of all the nivo+ipi+chemo-treated subjects who were evaluable for ADA, select AEs in the hypersensitivity/infusion reaction category were experienced by 16 (7.8%) nivolumab ADA-negative subjects, 5 (4.8%) nivolumab ADA-positive subjects, 20 (7.1%) ipilimumab ADA-negative subjects, and 2 (8.7%) ipilimumab ADA-positive subjects.

In summary, these results support the recommended dose and schedule of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy as first line therapy in patients metastatic or recurrent NSCLC.

The FDA's Assessment:
FDA concurs with the Applicant that the results of the PopPK and E-R analyses supported the recommended dosage regimen of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy as first line therapy in patients with metastatic or recurrent NSCLC. Refer to Section 6.2.2.1. General Dosing for details.

Following administration of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy, the incidence of anti-nivolumab antibodies (ADA) was 33.8% (104/308) with 2.6% (8/308) neutralizing antibodies against nivolumab. The incidence of ipilimumab ADA was 7.5% (23/305) and 1.6% (5/305) were neutralizing antibodies against ipilimumab. The incidence of nivolumab and ipilimumab ADAs did not appear to affect the efficacy and safety of the combination therapy at the proposed dosage regimen.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:
Yes, the clinical pharmacology program provides evidence that the selected dose and schedule of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-based chemotherapy offers benefit in subjects with previously untreated metastatic or recurrent NSCLC based on statistically significant improvements in OS (hazard ratio [HR] = 0.69 [96.71% CI: 0.55, 0.87], p = 0.0006), PFS (HR = 0.70 [97.48% CI: 0.57, 0.86], p = 0.0001), and ORR (37.7% vs 25.1%, p = 0.0003) with nivo+ipi+chemo relative to 4 cycles of platinum-based doublet chemotherapy in Study CA2099LA.[50] See Section 8.1.2.

The PPK analysis showed ipilimumab 1 mg/kg Q6W plus 2 cycles of chemotherapy had a statistically significant effect on nivolumab CL; however, the magnitude of this difference was not considered to be clinically relevant (< 20%). Nivolumab 360 mg Q3W plus 2 cycles of chemotherapy had a statistically significant effect on ipilimumab CL; however the magnitude of this difference was marginal (~22%).

Exposure-efficacy analyses for first-line NSCLC subjects in CA2099LA showed that the risk of death was not associated with nivolumab or ipilimumab exposures (sensitivity analysis), within the dosing regimen of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum doublet chemotherapy.

The FDA's Assessment:
Yes, refer to the FDA's assessment in Section 8.1.2 for details.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:
Yes, nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum based chemotherapy is appropriate as first line therapy in patients with metastatic or recurrent NSCLC, the indication being sought in this submission. This combination dose regimen was selected based on the observed safety and efficacy data from CA209012, CA209568 Parts 1 and 2, and CA209227 Parts 1 and 2 (see Section 6.2.2.1). Additionally, this dosing regimen was further supported by the clinical efficacy and safety data from NSCLC subjects in the first-line Phase 3 study CA2099LA (first-line Phase 3 study), and PPK and E-R analyses that included data from CA2099LA (see Section 6.2.2.1).

The FDA's Assessment:
FDA agrees that the Applicant's proposed dosage regimen of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum based chemotherapy is appropriate as first line therapy in patients with metastatic or recurrent NSCLC. Refer to the FDA's assessment in Section 6.2.2.1. General Dosing for details.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:
Both nivolumab and ipilimumab are monoclonal antibodies that are mainly eliminated by intracellular catabolism via the reticuloendothelial system.[51] Thus, the clearance of either nivolumab or ipilimumab is not influenced by ethnically variable genetic polymorphisms of metabolic enzymes or transporters.[52] Neither nivolumab nor ipilimumab pharmacokinetics is ethnically sensitive as monotherapy or combination therapy. No clinically meaningful differences in nivolumab and ipilimumab clearance or exposure have been observed across race and ethnic groups.[53] In the current PPK analysis, African American race and Asian race were incorporated as categorical covariates. African American race was not a statistically significant covariate on nivolumab CL with a 5% (95% CI: 98.3% - 112%) difference compared with White race. The Asian race was a statistically significant covariate on nivolumab CL with a -8.5% (95% CI: 88.1% - 95%) difference, however, the magnitude of the difference was not considered to be clinical

relevant (< 20%).
An alternative dosing regimen or management strategy is not required for subpopulations based on intrinsic patient factors, which were evaluated in the PPK analysis.

The FDA's Assessment:
FDA concurs with the Applicant's position.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:
There are no clinically relevant food-drug or drug-drug interactions with nivolumab in combination with ipilimumab and 2-cycles of chemo in subjects with NSCLC.

The FDA's Assessment:
Both nivolumab and ipilimumab are administered via intravenous infusions and as monoclonal antibodies their potential for PK interaction with chemotherapy is low.

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Yibo Wang
Primary Reviewer

Hong Zhao
Team Leader

7 SOURCES OF CLINICAL DATA

7.1 Table of Clinical Studies

Data:

Table 4: Listing of Clinical Trials Relevant to this sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled (randomized or treated)	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
CA2099LA[50]	NCT03215706	Phase 3, randomized, open label, study of nivo+ipi+chemo vs chemo Stratification factors for randomization were PD-L1 level (≥ 1% vs < 1% or non-quantifiable), histology (SQ vs NSQ), and (male vs female).	**Nivo+ipi+chemo:** nivo 360 mg IV over 30 min Q3W + ipi 1 mg/kg IV over 30 min Q6W + 2 cycles of histology based platinum-based doublet chemo IV **Chemo:** Histology-based, platinum-based doublet chemotherapy IV over 30 min on Day 1 Q3W for 4 cycles (NSQ subjects: optional pemetrexed maintenance)	Efficacy: OS, PFS, ORR, TTR, DoR, PFS2 Safety Immuno-genicity	**Nivo+ipi+chemo:** 2 cycles of histology-based chemo; nivo+ipi until PD, unacceptable toxicity, or up to 24 months. Treatment beyond initial investigator-assessed PD if clinical benefit and tolerating nivo+ipi. **Chemo:** Until PD, unacceptable toxicity or 4 cycles of histology based chemo (NSQ subjects: optional pemetrexed maintenance)	1150 (719 randomized)	Previously untreated stage IV or recurrent NSCLC Patients with EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	103 sites in 19 countries

Table 3: Listing of Clinical Trials Relevant to this sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Other studies pertinent to the review of efficacy or safety						
CA209568 Part 2[38]	NCT02659059	Phase 2 study to assess the safety of nivo + ipi + chemo	**Nivo+ipi+chemo:** All subjects received nivolumab 3 mg/kg IV over 30 min Q2W + ipilimumab 1 mg/kg IV over 30 min Q6W 2 cycles of histology-based platinum-doublet chemotherapy	Safety: incidence of DLT (within 9 weeks after first dose); safety and tolerability Efficacy: ORR and PFS by investigator assessment and OS	2 cycles of histology based chemotherapy; nivo + ipi until PD, unacceptable toxicity, or up to 24 months. Treatment beyond initial investigator-assessed PD permitted if clinical benefit and tolerating nivo + ipi	60 (36 treated)	Previously untreated stage IV or recurrent NSCLC. Patients with activating EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	12 sites in the US

Table 3: Listing of Clinical Trials Relevant to this sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
CA209227 Part 1[30]	NCT02477826	Phase 3, randomized, open label, study of nivo, nivo + ipi, or nivo + chemo vs chemo **Part 1a (PD-L1 ≥ 1%)**: nivo, nivo+ipi, or chemo (randomized 1:1:1; stratified by SQ vs NSQ) **Part 1b (PD-L1 <1%)**: nivo+ipi, nivo+chemo or chemo (randomized 1:1:1; stratified SQ vs NSQ)	**Part 1** **Arm A**: nivo 240 mg IV over 30 min Q2W **Arms B + D**: nivo 3 mg/kg IV over 30 min Q2W + ipi 1 mg/kg IV over 30 min Q6W **Arms C + F**: histology based platinum-doublet chemo up to 4 cycles **Arm G**: nivo 360 mg over 30 min + chemo IV Q3W up to 4 cycles, then nivo 360 mg Q3W **Chemo (Arms C, F, and G)** Optional pemetrexed maintenance (NSQ)	Efficacy: OS, PFS, ORR, TTR, DoR, PFS2 Safety Immuno-genicity	**Nivo + ipi or nivo**: Until PD, unacceptable toxicity, or up to 24 months. Treatment beyond initial investigator assessed PD permitted if clinical benefit and tolerating nivo + ipi or nivo. **Chemo:** Until PD, unacceptable toxicity or completed 4 cycles. (NSQ subjects NSQ pemetrexed maintenance allowed)	2879 (1739 randomized)	Previously untreated stage IV or recurrent NSCLC. Patients with activating EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	239 sites in 32 countries

Table 3: Listing of Clinical Trials Relevant to this sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
CA209-227 Part 2[54]	NCT02477826	Phase 3, randomized, open-label, nivo + chemo vs chemo Stratified by histology (NSQ, SQ), gender (male, female), PD-L1 (≥1%, < 1%)	**Nivo + chemo:** nivo 360 mg IV over 30 min + histology-based platinum-doublet chemo IV Q3W up to 4 (3-week) cycles. Subjects without PD to receive nivo 360 mg IV Q3W. Pemetrexed maintenance allowed for subjects with NSQ histology **Chemo:** histology-based chemo platinum-doublet up to 4 cycles. Optional pemetrexed maintenance (NSQ)	Efficacy: OS (primary endpoint: OS in subjects with NSQ histology), PFS, ORR, TTR, DoR, PFS2 Safety Immuno-genicity	**Chemo:** Chemo until PD, unacceptable toxicity or 4 cycles. (NSQ: optional pemetrexed maintenance) **Nivo + chemo:** see chemo above If SD, PR, or CR after chemo cycle 4 continue nivo Q3W maintenance therapy until PD, unacceptable toxicity or up to 24 months. Nivo beyond initial investigator-assessed PD if clinical benefit and tolerating nivo	1224 (755 randomized)	Previously untreated stage IV or recurrent NSCLC. Patients with activating EGFR mutations or ALK genomic aberrations sensitive to targeted therapy were excluded.	192 sites in 31 countries

Source: Table 1.3-1 in Module 2.5 (Clinical Overview)[55]

The Applicant's Position:
Results from CA2099LA are used in this submission to provide evidence of efficacy to support the proposed indication of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (nivo+ipi+chemo), for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations.
See Section 8.1.4 and Section 8.1.5.

The FDA's Assessment:
Overall, the FDA agrees with the applicant's table of clinical studies and position. Results from CA2099LA provide the main efficacy data to support the proposed indication. Data from studies CA209568 Part 2 and CA209227 Parts 1 and 2 provide supportive efficacy data and are further used to assess the contribution of components in CA2099LA. FDA noted the following minor differences from the table based on the review of the applicant-submitted datasets (ADSL) which are highlighted below:

- For Trial CA209568 Part 2, patients were treated with **nivolumab 360 mg IV every 3 weeks (Q3W)** plus ipilimumab 1 mg/kg Q6W plus two cycles of histology-based platinum-doublet chemotherapy as opposed to dosing with nivolumab 3 mg/kg IV Q2W which is an error in the table.
- For Trial CA209227 Part 1, 2876 patients were enrolled as opposed to 2879 patients as indicated in the table.
- To clarify, the following number of centers and countries were involved for each study:
    - Trial CA2099LA: patients were enrolled from 103 sites and randomized from 91 sites in 19 countries
    - Trial CA209568 Part 2: patients were enrolled from 14 sites and randomized from 12 sites in the U.S.
    - Trial CA209227 Part 1: patients were enrolled from 239 sites and randomized from 224 sites in 32 countries
    - Trial CA209227 Part 2: patients were enrolled from 192 sites and randomized from 170 sites in 32 countries

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Study CA2099LA

Trial Design
The Applicant's Description:
CA2099LA is an open-label, randomized, Phase 3 study of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of histology-based platinum-doublet chemotherapy (nivo+ipi+chemo) versus 4 cycles of

histology based platinum-doublet chemotherapy + optional pemetrexed maintenance therapy in subjects with previously untreated stage IV or recurrent NSCLC (see Figure 5).

Enrollment/Assignment to Treatment: After initial eligibility was established and informed consent obtained, subjects were enrolled into the study via an interactive response technology (IRT). Tumor tissue was required for study enrollment. Subjects were categorized into 3 groups by PD-L1 expression (≥ 1%, < 1%, and not quantifiable) determined by Dako PD-L1 IHC 28-8 pharmDx test for immunohistochemical (IHC) staining of PD-L1 protein in the submitted tumor sample.

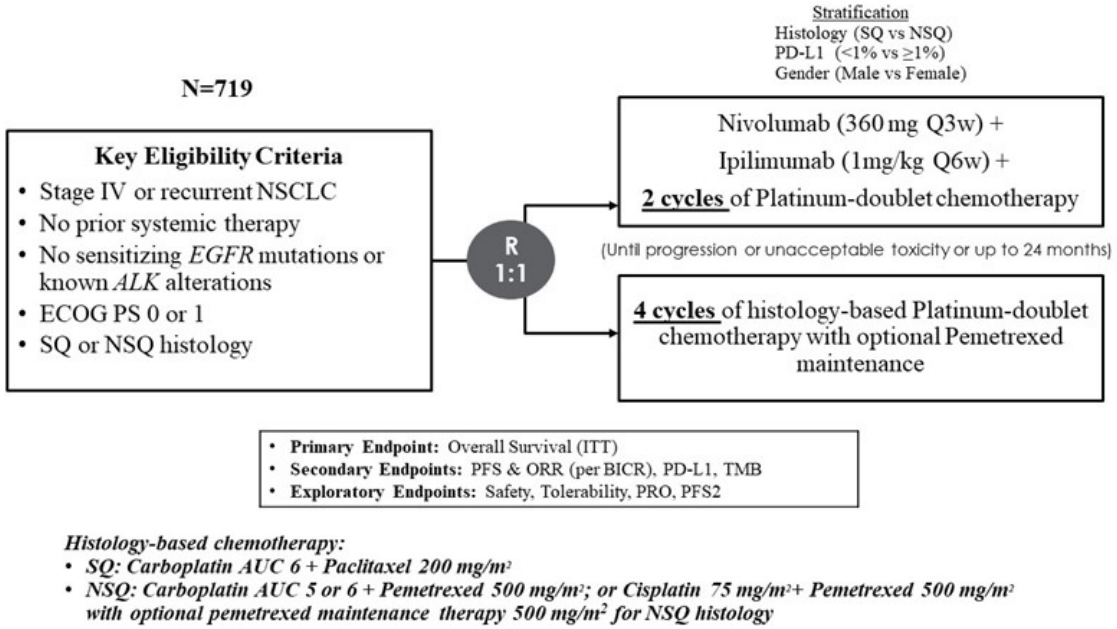
Subjects were randomized 1:1 to treatment with nivo+ipi+chemo or chemotherapy. The stratification factors for randomization were: PD-L1 level (≥ 1% vs < 1% or not quantifiable), histology (SQ vs NSQ), and gender (male vs female). Subjects without quantifiable PD-L1 status were stratified with PD-L1 < 1% population and capped to not exceed 10% of the total study population. Per protocol, the investigator decided prior to randomization if a subject with NSQ histology would receive cisplatin vs carboplatin therapy based on cisplatin eligibility criteria.

Trial Locations: 719 subjects were randomized at 103 sites in 19 countries. Of the 719 subjects, 53 (7.4%) were in Argentina, 15 (2.1%) were in Australia, 9 (1.3%) were in Belgium, 73 (10.2%) were in Brazil, 6 (0.8%) were in Canada, 31 (4.3%) were in Chile, 8 (1.1%) were in China, 65 (9.0%) were in France, 48 (6.7%) were in Germany, 5 (0.7%) were in Ireland, 14 (1.9%) were in Italy, 50 (7.0%) were in Japan, 19 (2.6%) were in Mexico, 36 (5.0%) were in Poland, 114 (15.9%) were in Romania, 15 (2.1%) were in the Russian Federation, 107 (14.9%) were in Spain, 12 (1.7%) were in the United Kingdom (Great Britain and Northern Ireland), and 39 (5.4%) were in the US.

FDA Assessment:
FDA notes that the majority of patients were enrolled in Europe with 5.4% of patients enrolled in the U.S. and that 6.4% of patients had non-quantifiable PD-L1 status.

Key Inclusion/Exclusion Criteria: The CA2099LA study population included adults (≥ 18 years) with histologically confirmed Stage IV NSCLC (per the 7th International Association for the Study of Lung Cancer Classification [IASLC]),[56] SQ or NSQ histology, and with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease. Subjects with known EGFR mutations or ALK translocations sensitive to targeted inhibitor therapy were excluded. Subjects were to have an Eastern Cooperative Oncology Group (ECOG) PS ≤ 1.

Figure 5: CA2099LA Study Design Schematic



Study Treatments

Nivo+ipi+chemo arm: Nivolumab 360 mg intravenous (IV) Q3W was administered over 30 minutes with ipilimumab 1 mg/kg IV over 30 minutes Q6W plus 2 cycles of histology-based platinum-based doublet chemotherapy IV (see the list of chemotherapies below). After 2 cycles of chemotherapy, nivolumab + ipilimumab treatment (nivolumab 360 mg IV Q3W and ipilimumab 1 mg/kg IV Q6W) continued until progression, unacceptable toxicity (or other reasons specified in the protocol) or up to 24 months.

Subjects in the nivo+ipi+chemo arm who had 2 prior dose reductions to any chemotherapy agent and experienced a toxicity that would cause a third dose reduction were to be discontinued from that agent. Subjects who discontinued chemotherapy were to remain on study and receive nivo+ipi therapy. If the investigator assessed the drug-related adverse event (AE) to be related to ipilimumab only and not related to nivolumab, ipilimumab dosing alone could have been discontinued while nivolumab dosing was delayed; nivolumab dosing was to be continued when the subject met the criteria to resume nivolumab treatment. If the investigator was unable to determine whether an AE was due to nivolumab or ipilimumab or chemotherapy, then all drugs were to be discontinued. The assessment for discontinuation of nivolumab and ipilimumab was to be made separately from the assessment made for discontinuation of chemotherapy. If the criteria for discontinuation for nivolumab and ipilimumab were met before the nivo+ipi+chemo cycles have been completed, chemotherapy could have been continued until 2 cycles have been completed.

***Chemotherapy arm (control group)*:** Histology-based, platinum-based doublet chemotherapy options (see below) were selected by the investigator and administered IV on Day 1 Q3W for 4 cycles; subjects with NSQ histology could also receive optional maintenance therapy with 500 mg/m^2 pemetrexed IV alone on Day 1 of each 3 week cycle until disease progression or unacceptable toxicity.

Histology-based platinum-based doublet chemotherapy:

- SQ histology: carboplatin area under the concentration-time curve (AUC) 6 + paclitaxel 200 mg/m^2
- NSQ histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2

Platinum-doublet chemotherapy was chosen because it was the standard of care for first-line treatment of recurrent or metastatic NSCLC in 2017 at the time CA2099LA was initiated.

Dose reductions for nivolumab or ipilimumab were not permitted. Dose reductions for chemotherapy were permitted. Chemotherapy dose reductions were permanent and could not be re-escalated in subsequent cycles except for subjects in the chemotherapy arm who received pemetrexed maintenance therapy (subjects with NSQ histology).

Administrative Structure: An independent data monitoring committee (DMC) reviewed efficacy and safety data from this study in an advisory capacity approximately every 6 months. The DMC provides oversight of safety and efficacy considerations and provides advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the trial. Efficacy is reviewed by the DMC as part of the benefit-to-risk assessment at each 6-monthly safety review, and at one predefined interim analysis, to identify if the predefined threshold for superiority has been crossed.

Dose Selection**:** See Section 6.2.2.

Schedule of Assessments: Assessments for eligibility, safety, efficacy, biomarkers, PK, immunogenicity, and patient reported outcomes (PRO) were performed during screening, on treatment, and follow-up, based on the Schedule of Activities in the protocol.

Contribution of Individual Components, Rationale for the CA2099LA Study Design**:** At the time that CA2099LA was designed, CA209227 was ongoing. CA209227 evaluated the safety and efficacy of first-line nivo+ipi and nivo+chemo vs chemotherapy in subjects with metastatic or recurrent NSCLC. CA2099LA was designed as a 2-arm study (nivo+ipi+ 2 cycles of chemotherapy vs chemotherapy), given that the contribution of each of the components would be available from CA209227. Both CA2099LA and CA209227 were conducted in the same population with histology-based platinum-doublet chemotherapy as a control.

Blinding**:** The treatments in this study were open-label. The personnel who conducted the PD-L1 and TMB testing were blinded to treatment group assignment of individual subjects during the conduct of the study. The whole Bristol-Myers Squibb (BMS) clinical study team was blinded to the aggregate treatment group information up to database lock. Select members of the BMS clinical team were unblinded to the treatment group assignment of individual subjects during the study in order to monitor the safety of individual subjects.

Treatment Compliance**:** Treatment compliance was monitored by drug accountability as well as the subject's medical record and electronic case report form (eCRF).

Concomitant Medications**:** The following medications are prohibited during the study (unless utilized to treat a drug related adverse event): immunosuppressive agents, immunosuppressive doses of systemic

corticosteroids (except topical, ocular, intra-articular, intranasal, and inhalational corticosteroids), any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC), or any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR) during treatment and until 100 days post last dose.

The FDA's Assessment:
Overall, FDA agrees with the applicant's description of the trial design. However, FDA notes that regarding the use of immunosuppressive agents as a concomitant medication, patients were allowed to be on a stable or decreasing dose of ≤10 mg daily of prednisone (or equivalent) for stable and adequately treated CNS metastases or other conditions requiring treatment with corticosteroids. For inhaled or topical steroids, and adrenal replacement steroids, >10 mg daily of prednisone (or equivalent) was permitted in the absence of active autoimmune disease.

Study Endpoints

The Applicant's Description:
The CA2099LA study objectives and endpoints are provided in Table 5 and the definitions of the endpoints are provided below. The parameters used to assess the efficacy profile of nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy in CA2099LA are consistent with other studies exploring the use of anti-cancer agents in subjects with previously untreated stage IV or recurrent NSCLC.

Table 5: Key Objectives and Endpoints in CA2099LA

Objectives	Endpoints
Primary	
To compare the efficacy of nivo+ipi+chemo vs chemotherapy in participants with histologically confirmed stage IV NSCLC	OS
Secondary	
To compare the efficacy of nivo+ipi+chemo vs chemotherapy in participants with histologically confirmed stage IV NSCLC	PFS by BICR ORR by BICR
To evaluate efficacy outcomes in participants with histologically confirmed stage IV NSCLC treated with nivo+ipi+chemo vs chemotherapy with different PD-L1 expression levels	ORR and PFS by BICR and OS in participants with different PD-L1 levels
Key Tertiary/Exploratory	
To evaluate the safety and tolerability of nivo+ipi+chemo	Incidence of AEs, SAEs and select AEs
To characterize the immunogenic potential of nivo and ipi	Anti-nivo and anti-ipi antibodies and their relationship with other outcome measures

OS, the primary endpoint of Study CA2099LA, is the standard measure of efficacy in oncology clinical trials. PFS and ORR per BICR are also common supportive efficacy endpoints in oncology clinical trials.

The FDA's Assessment:
FDA agrees with the endpoints as presented and with their relevancy in assessing efficacy and tolerability for these agents in this patient population.

Statistical Analysis Plan and Amendments

The Applicant's Description:
Efficacy analyses were performed on the population of all randomized subjects (all subjects from the global study population who were randomized using the IRT. The statistical analysis plan (SAP) was finalized prior to the last patient last visit/clinical cut-off. There were no amendments to the SAP.

Primary Endpoint

Overall Survival: The analysis of OS to compare nivo+ipi+chemo and chemotherapy was based on a 2 sided stratified log-rank test stratified by histology (SQ vs NSQ), sex (male vs female), and PD-L1 level (≥ 1% vs < 1% or not quantifiable). A Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary was employed to determine the nominal significance level for the interim analysis (nominal significance level $p < 0.033$ is based on the actual number of OS events of 351). The stratified HR of OS between the treatment groups (nivo+ipi+chemo vs chemotherapy) and corresponding 2-sided 96.71% CI was estimated using a stratified Cox proportional hazard model, with treatment arm as a single covariate. OS curves, OS medians with 95% CIs, and OS rates at fixed time points with their associated 95% CIs were estimated by treatment group using Kaplan-Meier (KM) methodology.

Key Secondary Endpoints (PFS and ORR per BICR)

Hierarchical Testing Procedure for Secondary Endpoints: The key secondary objectives of this study were assessed using a hierarchical testing procedure[57] with an overall experiment-wise 2-sided Type I error rate of 0.05. The hierarchical ordering of the key secondary endpoints was: 1. PFS per BICR and 2. ORR per BICR, where PFS per BICR was to be statistically tested only if the primary efficacy endpoint of OS was statistically significant and subsequently ORR per BICR was to be statistically tested only if PFS per BICR was statistically significant. For PFS per BICR, the type I error rate was controlled using a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) alpha spending function. The significance level for ORR per BICR was pre-specified as $\alpha=0.025$ as an equal Bonferroni splitting of the 2-sided alpha=0.05.

Progression-free survival: PFS (primary definition adjusting for subsequent therapy) was compared between the treatment groups via a stratified log-rank test among all randomized subjects. The stratification factors were histology (SQ vs NSQ), sex (male vs female), and PD-L1 level (≥ 1% vs < 1% or not quantifiable). PFS curves, PFS medians with 95% CIs, and PFS rates at fixed time points with their associated 95% CIs were estimated by treatment group using KM methodology.

Objective Response Rate and Duration of Response: The number and percentage of subjects in each category of BOR per BICR (complete response [CR], PR, SD, PD, or unable to determine [UTD]) were presented, by treatment group. Estimates of response rate, along with its exact 2-sided 95% CI by Clopper and Pearson[58] were presented, by treatment group. An estimate of the difference in response rates between the treatment groups along with the corresponding 2-sided 97.5% CI were computed using the Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for stratification factors.[59] The duration

of response (DoR) for each treatment group was estimated using KM product limit method for subjects who achieved PR or CR, including median values, 2-sided 95% CIs, and range.

Safety (tertiary endpoint): Descriptive statistics of safety were presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. All on-study AEs, drug-related AEs, serious adverse events (SAEs), drug-related SAEs, immune-mediated adverse events (IMAEs), and other events of special interest (OESIs) were tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, liver function and renal function were summarized using worst grade per NCI CTCAE v 4.0 criteria. Frequency, management and resolution of IMAEs were analyzed.

The FDA's Assessment:

FDA agrees with the description of the statistical analysis plan as presented.

FDA adds that the sample size was based on the comparison of OS between nivolumab, ipilimumab and platinum-based chemotherapy doublet and platinum-based chemotherapy doublet alone, assuming a piecewise exponential distribution in the combination arm and an exponential distribution in the platinum-doublet chemotherapy arm. The statistical test for overall survival was based on 700 patients randomized in a 1:1 ratio whereby 402 death events would provide 81% power to detect an average hazard ratio (HR) of 0.75 with a 2-sided type 1 error of 0.05. Here the average HR of 0.75 was determined using a piecewise exponential distribution assuming a 3-month delayed treatment effect for the nivo+ipi+chemo arm, i.e., targeting a HR of 1 for the first three months and 0.68 for the time beyond 3 months. This corresponds to a 33% increase in median OS, assuming 13.9 months with chemotherapy and 18.6 months for the combination arm. It is noted that the current analysis is based on interim results with 351 events or (87% of total events).

In terms of the secondary objective PFS, 596 events would provide approximately 94% power to detect a HR of 0.75 with a 2-sided type 1 error of 0.05. This corresponds to a 33% increase in median PFS assuming 6 months with platinum-doublet chemotherapy and 8 months for the combination arm. One interim analysis of PFS was planned at the same time as the OS interim analysis, conducted in a hierarchical manner. At the time of the interim analysis, there were n=481 events, representing 80.7% of the 596 expected events.

It is noted that the SAP accounts for one interim analysis for OS, PFS and ORR, which would be tested hierarchically in that order, each predicated upon success of the preceding test. Additionally type I error was controlled in separate testing procedures for PFS and ORR, whereby the tests of PFS utilized a group sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending function and tests of ORR used an equal Bonferroni splitting of alpha.

Protocol Amendments

The Applicant's Description:

There were 2 major protocol revisions to the CA2099LA protocol with the following key changes:

- ***Revised Protocol 02*** (issued: 02-Jul-2018): At the time that CA2099LA was designed, the data on the clinical benefit of combining immunotherapy agent with chemotherapy was very limited in first-line

NSCLC. Based on external data, the median OS expectations for the CA2099LA statistical assumptions were revised to reflect the existing experience with PD(L)-1 inhibitors + chemotherapy vs chemotherapy; the resulting HR changed from 0.65 to 0.70, requiring additional events to maintain the original 90% power. The overall sample size was also expanded from 420 to 700 subjects both to compensate for the need for more OS events and to enable subgroup analysis to better characterize the role of nivo+ipi+chemo in different subgroups (eg, by histology and biomarker status).

- ***Revised Protocol 04*** (issued 08-Mar-2019): Findings in other studies in first-line NSCLC, showed that PD-1(L1) inhibitor + chemotherapy (pembrolizumab + chemotherapy and atezolizumab + chemotherapy [plus bevacizumab]), was superior to chemotherapy alone, regardless of PD-L1 expression, with a delayed effect in terms of OS and late separation of the OS.[60,61,62,63] To ensure sufficient power to detect a clinically relevant survival benefit in such a scenario, the protocol was amended to include a 3 month delayed treatment effect for the nivo+ipi+chemo arm. Additionally, given that the 2 interim analyses and the final analysis were anticipated within a couple months of one another, the first planned interim analysis was removed, to allow for sufficient follow-up to characterize efficacy and safety at the time of the planned interim analysis. The resulting HR changed from 0.70 to an average HR of 0.75 (based on an assumed targeted HR of 1 for the initial 3 months from randomization and a target HR of 0.68 for the time beyond 3 months from randomization), requiring an increased number of events for the single interim and final analyses. Because of this HR adjustment, the projected timing of events was updated.

The FDA's Assessment:
FDA agrees that of the four protocol amendments, major revisions impacting statistical assumptions, study size, interim analyses, and study endpoints were contained in amendments 2 and 4 as indicated by the sponsor and were acceptable given the findings in other relevant trials of agents in the same class assessing similar patient populations. It is noted that the revised piecewise hazard ratio assumptions taking into account a potential delayed treatment affect and the removal of one of the pre-planned interim analyses from the protocol were made prior to interim looks at the data.

8.1.2 Study Results from CA2099LA

Compliance with Good Clinical Practices

The Applicant's Position:
The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21 CFR 50).

The FDA's Assessment:
FDA agrees with the Applicant that this study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation and in accordance with the European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21 CFR 50).

Financial Disclosure

The Applicant's Position:

Financial interests or arrangements with clinical investigators have been disclosed (see Appendix 19). Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Subinvestigators) participating in the CA2099LA clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

The FDA's Assessment:

The Applicant's position on financial disclosures were reviewed in Module 1 of the sBLA submission and no concerns were noted. Financial interests were recorded by 2 investigators (1 principal investigator and 1 sub-investigator). The following table summarizes these disclosures:

Protocol/ Site Number	Number of Patients Enrolled at Site	Investigator Name	Investigator Type	Disclosures
[redacted] (b) (6)			Principal Investigator	52,522 USD for speaking engagements for the nivolumab and ipilimumab programs
			Sub-Investigator	- (b) (6) spouse is a (b) (6) and therefore has interest of approximately 50,000 USD. - Investigator-sponsored research grant of 34,000 USD

Source: Module 1 of the sBLA submission from the applicant on February 6, 2020.

Patient Disposition

Data:

Table 6: Subject Disposition - All Enrolled, Randomized, and Treated Subjects

	Nivo+Ipi+Chemo	Chemo	Total
SUBJECTS ENROLLED			1150
SUBJECTS RANDOMIZED	361	358	719
SUBJECTS TREATED[a]	358 (99.2)	349 (97.5)	707 (98.3)
SUBJECTS NOT TREATED[a]	3 (0.8)	9 (2.5)	12 (1.7)
REASON FOR NOT TREATED[a]			
ADVERSE EVENT UNRELATED TO STUDY DRUG	1 (0.3)	0	1 (0.1)
SUBJECT WITHDREW CONSENT	1 (0.3)	3 (0.8)	4 (0.6)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.3)	4 (1.1)	5 (0.7)
OTHER	0	2 (0.6)	2 (0.3)
ONGOING IN THE TREATMENT PERIOD[b]	105 (29.3)	43 (12.3)	148 (20.9)
COMPLETING THE TREATMENT PERIOD[b,c]	16 (4.5)	103 (29.5)	119 (16.8)
NOT COMPLETING THE TREATMENT PERIOD[b]	237 (66.2)	203 (58.2)	440 (62.2)

REASON FOR NOT COMPLETING THE TREATMENT PERIOD[b]			
DISEASE PROGRESSION	150 (41.9)	142 (40.7)	292 (41.3)
STUDY DRUG TOXICITY	53 (14.8)	21 (6.0)	74 (10.5)
DEATH	2 (0.6)	1 (0.3)	3 (0.4)
ADVERSE EVENT UNRELATED TO STUDY DRUG	24 (6.7)	23 (6.6)	47 (6.6)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	1 (0.3)	6 (1.7)	7 (1.0)
SUBJECT WITHDREW CONSENT	3 (0.8)	4 (1.1)	7 (1.0)
LOST TO FOLLOW-UP	0	1 (0.3)	1 (0.1)
OTHER	4 (1.1)	5 (1.4)	9 (1.3)
CONTINUING IN THE STUDY[b]	301 (84.1)	303 (86.8)	604 (85.4)
NOT CONTINUING IN THE STUDY[b]	57 (15.9)	46 (13.2)	103 (14.6)
REASON FOR NOT CONTINUING IN THE STUDY[b]			
DEATH	54 (15.1)	40 (11.5)	94 (13.3)
SUBJECT WITHDREW CONSENT	3 (0.8)	4 (1.1)	7 (1.0)
LOST TO FOLLOW-UP	0	1 (0.3)	1 (0.1)
OTHER	0	1 (0.3)	1 (0.1)

[a] Percentages based on subjects randomized.

[b] Percentages based on subjects treated.

[c] All 16 subjects in the nivo+ipi+chemo arm completed the induction phase (first 6 weeks of nivo+ipi+chemo).

Source (ADaM dataset): Table 2.5.1 (adsl.xpt) for pre-randomized subject status, Table 2.6A.1 (adsl.xpt) for randomized subjects status, Table 2.7A.1 (adsl.xpt) for end of treatment status in the Final CA2099LA CSR

The Applicant's Position:

The last subject was randomized on 30-Jan-2019 and the clinical cutoff occurred on 16-Aug-2019 (last patient last visit [LPLV]). The database lock occurred on 03 Oct 2019. Minimum follow-up (date of the last subject randomized to LPLV) for all data except OS was 6.5 months (Table 5.4.2 of the CA2099LA Final clinical study report [CSR]).[50] Minimum follow-up (date of the last subject randomized to date of the cutoff for OS) for OS was 8.1 months. Median follow-up (date of randomization to the last known date alive or death date) was 10.35 months for the nivo+ipi+chemo arm and 9.07 months for the chemotherapy arm (Table 5.1.1 of the CA2099LA Final CSR).

719 subjects were randomized at 103 sites in 19 countries. 707 subjects were treated: 358 with nivo+ipi+chemo and 349 with chemotherapy. The overall rates of discontinuation during the treatment period were 66.2% and 58.2% in the nivo+ipi+chemo and chemotherapy arm, respectively (Table 6). The primary reason for not completing the treatment period was disease progression (292 subjects, 41.3%): 150 (41.9%) nivo+ipi+chemo treated subjects and 142 (40.7%) chemotherapy-treated subjects.

The FDA's Assessment: In response to an information request to the applicant regarding the 16 patients listed in the table above as having completed treatment with nivolumab plus ipilimumab plus chemotherapy, the applicant clarified that these patients were initially incorrectly reported on the Case Report Forms as having completed treatment with a database lock date of October 3, 2019. However, the disposition of these 16 patients were corrected and updated in the clinical database as of March 9, 2020. The Applicant clarified that of the 16 patients who were incorrectly reported as having completed treatment:

- 15 completed only the induction phase of treatment, but did not receive maintenance therapy with nivolumab and ipilimumab. The primary reasons for not completing the treatment period for these 15 patients, based on the updated March 9, 2020 database lock, were due to disease

progression (n=7), study drug toxicity (n=5), subject request to discontinue study treatment (n=1), subject withdrew consent (n=1), and adverse event unrelated to the study drug (n=1).

- 1 patient received additional cycles of nivolumab and ipilimumab following the induction phase prior to discontinuing treatment due to disease progression, based on the updated March 9, 2020 database lock.

Based on the corrected information, FDA provides the revised table for patient disposition for Study CA2099LA (Table 7).

Table 7: Patient Disposition: CA2099LA-FDA analysis

Characteristics	Nivo+Ipi+Chemo n=361 n (%)	Chemotherapy n=358 n (%)
Treatment ongoing	105 (29)	43 (12)
Treatment completed	-	103 (29)
- Alive	-	51 (14)
Treatment discontinued	253 (70)	203 (57)
- Alive	100 (28)	64 (18)
Total alive	205 (57)	158 (44)
Reason for treatment discontinuation		
Disease progression	158 (44)	142 (40)
Study drug toxicity	58 (16)	21 (6)
AE unrelated to study drug	25 (7)	23 (6)
Death	2 (0.6)	1 (0.3)
Patient withdrawal or request	6 (1.7)	10 (2.8)

Source: FDA analysis of sponsor submitted datasets (ADSL) and IR response dated March 24, 2020.

FDA notes a minor correction to the applicant's position above that 719 patients were enrolled from 103 sites, but randomized from only 91 sites, in 19 countries.

FDA also notes that minimum follow-up represents the shortest amount of follow-up for any one patient. The concept of a theoretical opportunity for follow-up should be clearly indicated as such, it is misleading to present a potential as if it were the actual observed value-- in this case there are 10 censored patients on this study, 3 of which are still receiving treatment (bolded in Table 8), with less than 8.1 months follow-up at the time of the interim analysis. The true minimum follow-up is 6.4 months.

Table 8: Patients with less than 8.1 months follow-up

Unique Subject Identifier	Overall Survival Time (months)
(b) (6)	**7.6**
	7.0
	7.7
	6.9
	7.9
	7.6
	7.0
	6.4*
	7.8
	8.0

Bolded entries represent patients still receiving therapy
*minimum follow-up
Source: FDA analysis of sponsor submitted datasets (ADEFTTES)

Protocol Violations/Deviations

Data:

Table 9: Relevant Protocol Deviations Summary - All Randomized Subjects

	Number of Subjects (%)		
	Nivo+Ipi+Chemo N = 361	Chemo N = 358	Total N = 719
SUBJECTS WITH AT LEAST ONE DEVIATION	7 (1.9)	4 (1.1)	11 (1.5)
AT ENTRANCE			
SUBJECT WITH MISCLASSIFIED PD-L1 STRATIFICATION LEVEL (IRT VS CLINICAL DATABASE)	2 (0.6)	1 (0.3)	3 (0.4)
SUBJECT WITH NO MEASURABLE DISEASE AT BASELINE PER INVESTIGATOR	1 (0.3)	2 (0.6)	3 (0.4)
ON-TREATMENT DEVIATIONS			
SUBJECT WHO RECEIVED ANTI-CANCER THERAPY	4 (1.1)	1 (0.3)	5 (0.7)
SUBJECT TREATED DIFFERENTLY AS RANDOMIZED	0	0	0

Source (ADaM datasets): Table 2.4.1 (adpd.xpt, adsl.xpt) in the CA2099LA Final CSR

The Applicant's Position:

Relevant protocol deviations are those that are related to inclusion or exclusion criteria, study conduct, study management, or subject assessment that were programmable and could potentially affect the interpretability of study results, and are predefined in the SAP. Overall, relevant protocol deviations (at study entry and on-treatment) were reported in a total of 11 (1.5%) randomized subjects: 7 (1.9%) in the nivo+ipi+chemo arm, 4 (1.1%) in the chemotherapy arm (Table 9). After review of the reported protocol deviations, it was determined that there was no impact on the interpretability of study results.

The FDA's Assessment:
FDA agrees with the applicant's listing of relevant protocol deviations in Table 9 and agrees with the position that the reported protocol deviations did not impact the interpretability of the study results.

Table of Demographic and Baseline Characteristics
Data:

Table 10: Key Demographic and Baseline Disease Characteristics - All Randomized Subjects - CA2099LA

	Nivo+Ipi+Chemo (N = 361)	Chemo (N = 358)	Total (N = 719)
Age (years)			
Median	65.0	65.0	65.0
< 65 (n, %)	176 (48.8)	178 (49.7)	354 (49.2)
≥ 65 and < 75 (n, %)	148 (41.0)	147 (41.1)	295 (41.0)
≥ 75 (n, %)	37 (10.2)	33 (9.2)	70 (9.7)
≥ 85 (n, %)	0	2 (0.6)	2 (0.3)
Male (n, %)	252 (69.8)	252 (70.4)	504 (70.1)
Race (n, %)			
White	322 (89.2)	316 (88.3)	638 (88.7)
Black	5 (1.4)	4 (1.1)	9 (1.3)
Asian (including Chinese & Japanese)	30 (8.3)	30 (8.4)	60 (8.3)
All other	4 (1.1)	8 (2.2)	12 (1.7)
Tumor Histology (n, %)			
SQ Carcinoma	113 (31.3)	111 (31.0)	224 (31.2)
NSQ Carcinoma	248 (68.7)	247 (69.0)	495 (68.8)
Metastasis Site			
Liver	68 (18.8)	87 (24.3)	155 (21.6)
CNS	63 (17.5)	58 (16.2)	121 (16.8)
ECOG PS (n, %)			
0	113 (31.3)	112 (31.3)	225 (31.3)
1	247 (68.4)	245 (68.4)	492 (68.4)
Not Reported	1 (0.3)	1 (0.3)	2 (0.3)
Smoking Status (n, %)			
Current/Former	315 (87.3)	305 (85.2)	620 (86.2)
Never smoker	46 (12.7)	53 (14.8)	99 (13.8)

	Nivo+Ipi+Chemo (N = 361)	Chemo (N = 358)	Total (N = 719)
PD-L1 Level (n, %)			
Quantifiable			
< 1%	135 (37.4)	129 (36.0)	264 (36.7)
≥ 1%	203 (56.2)	203 (56.7)	406 (56.5)
1 - 49%	127 (35.2)	106 (29.6)	233 (32.4)
≥ 50%	76 (21.1)	97 (27.1)	173 (24.1)
Not Quantifiable	21 (5.8)	25 (7.0)	46 (6.4)
Not Reported	2 (0.6)	1 (0.3)	3 (0.4)

Source (ADaM datasets): Table 3.2.1.1 (adsl.xpt) demographics, Table 3.2.7.1 (adsl.xpt) disease characteristics in the CA2099LA Final CSR

The Applicant's Position:
Demographic and baseline disease characteristics in all randomized subjects were balanced between the nivo+ipi+chemo and the chemotherapy arms, and were representative of a first-line metastatic or recurrent NSCLC population (Table 10). Of the randomized subjects in CA2099LA, 8.9% (64/719) were from North America (5.4% [39/719] were from the US, 0.8% [6/719] were from Canada, and 2.6% [19/719] were from Mexico).

The FDA's Assessment:
FDA agrees the arms seemed balanced by key demographic and baseline disease characteristics. However, African American patients are underrepresented in this study, accounting for only 1.3% of the study population, compared to the actual proportion of patients with NSCLC who are African American in the U.S. population. Additionally, the median age of patients in this study was 65 years old, however patients with NSCLC in the U.S. are usually older with a median age at diagnosis of approximately 70 years old (Howlader, SEER Cancer Statistics Review, 1975-2017).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Data and the Applicant's Position of "Other Baseline Characteristics" are provided above and in Table 10. See the information on concomitant therapy and subsequent anti-cancer therapy provided below.

The FDA's Assessment:
FDA also refers to Table 10 above and the "Concomitant Therapy" and "Subsequent Anti-Cancer Therapy" sub-sections below.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:
Treatment Compliance: Nivolumab and ipilimumab and chemotherapy were administered IV by trained medical personnel at each site. Treatment compliance was monitored by routine monitoring of clinical source documentation and drug accountability, as well as the subject's medical record and CRF.

Concomitant Therapy: Most subjects (99.7%) received concomitant medication(s) during the treatment period (Table 6.30.1 of the CA2099LA Final CSR). Concomitant immune-modulating medications (IMMs), including corticosteroids, immune-modulating agents, immunosuppressive agents, and glucocorticoids, were administered for management of AEs in 206 (57.5%) subjects in the nivo+ipi+chemo arm and 97 (27.8%) subjects in the chemotherapy arm (Table 6.1.4.1 of the CA2099LA Final CSR).

Subsequent Anti-Cancer Therapy: Subsequent anti-cancer therapy (radiotherapy, surgery, and/or systemic therapy) was received by 104 (28.8%) subjects in the nivo+ipi+chemo arm compared to 147 (41.1%) subjects in the chemotherapy arm (Table 6.6-1 of the CA2099LA Final CSR). Subsequent systemic therapy was received by 90 (24.9%) subjects in the nivo+ipi+chemo arm and 131 (36.6%) subjects in the chemotherapy arm. Subsequent immunotherapy was received by a lower percentage of subjects in the nivo+ipi+chemo arm compared with the chemotherapy arm (3.9% vs 27.9%). A similar percentage of subjects in the nivo+ipi+chemo arm and chemotherapy arm received subsequent chemotherapy (23.8% vs 20.1%).

Rescue Medication Use: Not applicable

The FDA's Assessment:

FDA generally agrees with the applicant's position. However, FDA notes that only 11 out of 361 (3.0%) of patients on the nivolumab plus ipilimumab plus chemotherapy arm, as opposed to 3.9% of patients, received subsequent immunotherapy.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 11: Primary Efficacy Endpoint of OS with Nivolumab + Ipilimumab + Chemotherapy vs Chemotherapy - All Randomized Subjects (CA2099LA)

	Nivo+Ipi+Chemo N = 361	Chemotherapy N = 358
Overall Survival (OS)		
Events, n (%)	156 (43.2)	195 (54.5)
Median OS (95% CI), mo.[a]	14.13 (13.24, 16.16)	10.74 (9.46, 12.45)
HR (96.71% CI)[b]	0.69 (0.55, 0.87); p = 0.0006[c]	
HR (95% CI)[b]	0.69 (0.56, 0.86)	
6-month OS Rates (95% CI), %[a]	80.9 (76.4, 84.6)	72.3 (67.4, 76.7)

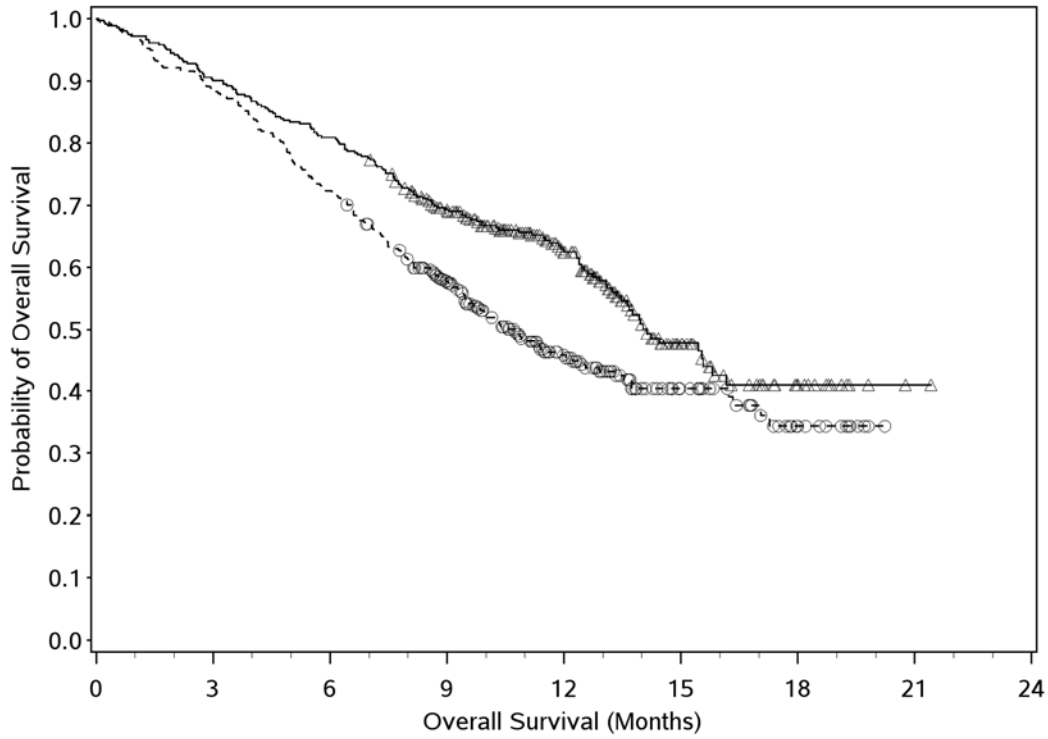
Minimum follow-up (date the last subject randomized to date of the cutoff for OS) was 8.1 months for OS; median follow-up (date of randomization to the last known date alive or death date) was 10.35 months for the nivo+ipi+chemo arm and 9.07 months for the chemo arm. The OS medians would likely be influenced by a high proportion of censored subjects.

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. Hazard Ratio is Nivo+Ipi+Chemo over Chemotherapy.

[c] 2-sided p value from stratified regular log-rank test. The boundary for statistical significance, on the p-value scale, is 0.033. That is, the p-value must be less than 0.033 to show significance for OS.
Source: (ADaM datasets): Table 5.22.1 (adefttes.xpt, adsl.xpt) for OS, Table 5.23.1 (adefttes.xpt, adsl.xpt) for OS rates from the CA2099LA Final CSR

Figure 6: Kaplan Meier Plot of Overall Survival - All Randomized Subjects (CA2099LA)



Statistical model for hazard ratio and p-value: Stratified Cox proportional hazards model and stratified log-rank test.
Symbols represent censored observations.
Source (ADaM datasets): Figure 5.30.1 (adefttes.xpt, adsl.xpt) of the CA2099LA Final CSR

Figure 7: Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - All Randomized Subjects (CA2099LA)

		Nivo+Ipi+Chemo		Chemo		Unstratified
	N	N of Events (N of Subjects)	mOS (95% CI)	N of Events (N of Subjects)	mOS (95% CI)	Hazard Ratio (95% CI) Nivo+Ipi+Chemo vs. Chemo
Overall	719	156 (361)	14.13 (13.24, 16.16)	195 (358)	10.74 (9.46, 12.45)	0.70 (0.57, 0.86)
Age Categorization						
<65	354	74 (176)	13.96 (12.62, N.A.)	100 (178)	10.25 (8.80, 13.73)	0.63 (0.46, 0.85)
>=65 and <75	295	56 (148)	15.80 (14.23, N.A.)	78 (147)	11.86 (9.03, 16.23)	0.64 (0.45, 0.90)
>=75 and <85	68	26 (37)	8.51 (5.59, 13.34)	16 (31)	10.91 (4.96, N.A.)	1.35 (0.72, 2.51)
>=85	2	0 (0)	N.A.	1 (2)	N.A. (5.75, N.A.)	N.A.
>=75	70	26 (37)	8.51 (5.59, 13.34)	17 (33)	10.91 (5.75, N.A.)	1.36 (0.74, 2.52)
>=65	365	82 (185)	14.46 (13.11, N.A.)	95 (180)	11.50 (9.49, 13.54)	0.77 (0.58, 1.04)
Sex						
Male	504	119 (252)	13.77 (12.45, 15.44)	150 (252)	9.69 (8.15, 11.37)	0.69 (0.54, 0.88)
Female	215	37 (109)	15.80 (13.11, N.A.)	45 (106)	N.A. (10.87, N.A.)	0.73 (0.47, 1.13)
Race						
White	638	149 (322)	13.93 (12.91, 15.57)	174 (316)	10.58 (9.43, 12.55)	0.75 (0.61, 0.94)
Black or African American	9	1 (5)	N.A. (2.96, N.A.)	2 (4)	N.A. (6.21, N.A.)	0.42 (0.04, 4.66)
Asian	60	3 (30)	15.44 (11.93, N.A.)	13 (30)	12.22 (7.33, N.A.)	0.11 (0.03, 0.51)
Other	12	3 (4)	3.79 (3.58, N.A.)	6 (8)	4.96 (1.48, N.A.)	1.36 (0.33, 5.61)
Region						
Europe	425	101 (212)	13.93 (12.75, 16.16)	116 (213)	10.58 (9.26, 13.73)	0.76 (0.58, 1.00)
North America	64	19 (36)	13.24 (7.43, N.A.)	18 (28)	8.90 (4.96, N.A.)	0.70 (0.37, 1.34)
Rest of The World	172	33 (85)	N.A. (10.25, N.A.)	48 (87)	10.78 (8.77, 12.45)	0.68 (0.43, 1.05)
Asia	58	3 (28)	15.44 (11.93, 15.44)	13 (30)	12.22 (7.33, N.A.)	0.13 (0.03, 0.57)
Baseline ECOG PS						
0	225	32 (113)	N.A. (15.44, N.A.)	50 (112)	13.31 (10.78, N.A.)	0.53 (0.34, 0.83)
>=1	492	123 (247)	13.11 (11.93, 14.03)	144 (245)	9.46 (7.98, 11.01)	0.77 (0.60, 0.98)
Not Reported	2	1 (1)	9.03 (N.A., N.A.)	1 (1)	4.01 (N.A., N.A.)	
Smoking Status						
Current/Former	620	134 (315)	14.13 (13.34, 16.16)	173 (305)	10.02 (8.97, 12.06)	0.65 (0.52, 0.82)
Never Smoked	99	22 (46)	11.99 (8.02, N.A.)	22 (53)	12.55 (9.46, N.A.)	1.15 (0.64, 2.08)
Unknown	0	0 (0)	N.A.	0 (0)	N.A.	
Histology - per IRT						
Squamous	227	56 (115)	13.67 (12.39, 15.57)	69 (112)	8.97 (7.16, 12.22)	0.65 (0.46, 0.93)
Non-Squamous	492	100 (246)	15.80 (13.08, N.A.)	126 (246)	11.40 (9.69, 16.33)	0.72 (0.55, 0.93)

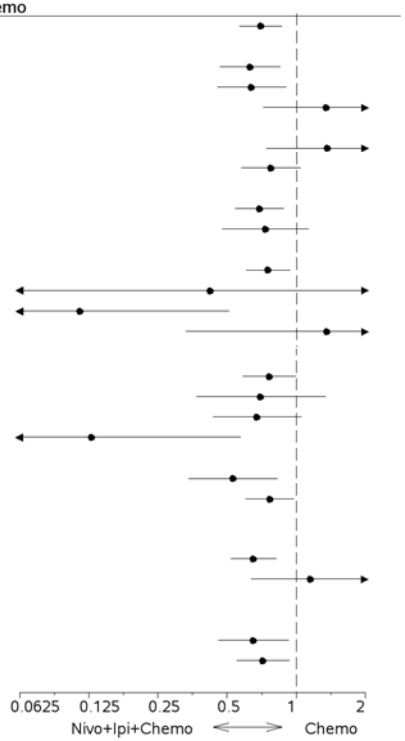
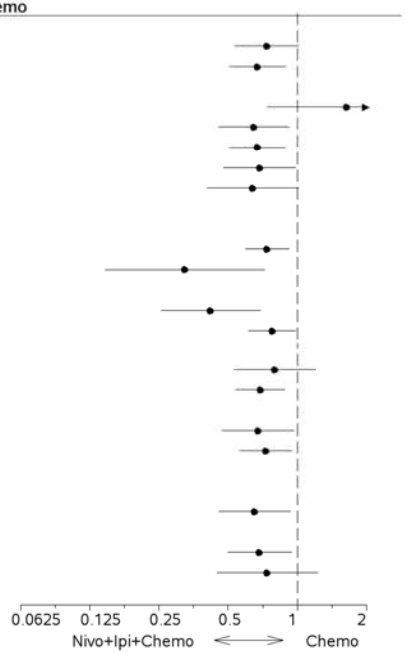


Figure 8: Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - All Randomized Subjects (CA2099LA)

	N	Nivo+Ipi+Chemo N of Events (N of Subjects)	Nivo+Ipi+Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo+Ipi+Chemo vs. Chemo
PD-L1 Status - per IRT						
<1%/Not Quantifiable	311	69 (157)	13.77 (12.32, 16.16)	84 (154)	11.01 (8.57, 16.23)	0.74 (0.54, 1.02)
>=1%	408	87 (204)	14.23 (13.08, N.A.)	111 (204)	10.58 (9.43, 12.91)	0.67 (0.51, 0.89)
PD-L1 Subgroups						
Not Quantifiable	46	14 (21)	10.84 (7.16, 15.57)	12 (25)	17.05 (8.64, N.A.)	1.64 (0.74, 3.63)
<1%	264	55 (135)	14.03 (13.24, N.A.)	72 (129)	9.95 (7.69, 13.73)	0.65 (0.46, 0.92)
>=1%	406	87 (203)	14.23 (13.08, N.A.)	111 (203)	10.58 (9.36, 12.55)	0.67 (0.51, 0.89)
1-49%	233	58 (127)	14.46 (12.45, N.A.)	61 (106)	10.25 (8.67, 12.22)	0.69 (0.48, 0.98)
>=50%	173	29 (76)	14.13 (12.39, N.A.)	50 (97)	11.86 (9.26, N.A.)	0.64 (0.41, 1.02)
Not Reported	3	0 (2)	N.A.	0 (1)	N.A.	
Disease Stage						
Stage IV	668	145 (330)	14.03 (13.11, 16.16)	181 (338)	10.87 (9.46, 13.31)	0.74 (0.59, 0.92)
Recurrent to Metastatic Disease	51	11 (31)	15.57 (12.45, N.A.)	14 (20)	9.05 (6.60, 12.91)	0.32 (0.15, 0.72)
CNS Metastasis						
Yes	121	25 (63)	13.63 (12.32, N.A.)	41 (58)	7.36 (4.99, 10.02)	0.42 (0.26, 0.69)
No	598	131 (298)	14.03 (13.24, 16.16)	154 (300)	11.37 (9.79, 13.73)	0.78 (0.62, 0.98)
Liver Metastasis						
Yes	155	40 (68)	9.89 (7.43, 13.77)	57 (87)	8.02 (6.60, 10.02)	0.80 (0.53, 1.20)
No	564	116 (293)	15.54 (13.67, N.A.)	138 (271)	11.86 (10.25, 16.23)	0.69 (0.54, 0.88)
Bone Metastasis						
Yes	206	51 (96)	11.93 (8.61, 15.80)	72 (110)	8.02 (6.60, 9.46)	0.67 (0.47, 0.97)
No	513	105 (265)	15.44 (13.34, N.A.)	123 (248)	12.06 (10.35, 17.05)	0.73 (0.56, 0.95)
Actual Investigator's Choice Therapy						
Carboplatin/Cisplatin/Pemetrexed	7	1 (1)	4.34 (N.A., N.A.)	4 (6)	10.02 (1.48, N.A.)	
Carboplatin/Paclitaxel	224	55 (114)	13.67 (12.39, 15.57)	67 (110)	8.97 (7.16, 12.22)	0.65 (0.45, 0.93)
Carboplatin/Paclitaxel/Pemetrexed	2	0 (1)	N.A.	1 (1)	10.25 (N.A., N.A.)	
Carboplatin/Pemetrexed	331	68 (168)	15.80 (13.24, N.A.)	86 (163)	10.74 (9.13, 16.33)	0.68 (0.50, 0.94)
Cisplatin/Pemetrexed	142	28 (73)	N.A. (12.32, N.A.)	33 (69)	12.55 (9.46, N.A.)	0.74 (0.45, 1.22)
Paclitaxel/Pemetrexed	1	1 (1)	6.24 (N.A., N.A.)	0 (0)	N.A.	
Not Reported	12	3 (3)	1.74 (0.03, 9.03)	4 (9)	N.A. (1.58, N.A.)	



HR is not computed for subsets (except age, race, region, and sex) category with less than 10 subjects per treatment group.
Source (ADaM datasets): Figure 5.31.1 (adefttes.xpt, adsub.xpt, adsl.xpt) of the CA2099LA Final CSR

The Applicant's Position:

Among all randomized subjects, a statistically significant and clinically meaningful improvement in OS (primary endpoint) was observed with nivo+ipi+chemo compared with chemotherapy: HR = 0.69 (96.71% CI: 0.55, 0.87); stratified log-rank test p value = 0.0006 (Table 11 and Figure 6). OS results with nivo+ipi+chemo vs chemotherapy were consistent across most subgroups, including histology and PD-L1 subgroups (Figure 7):

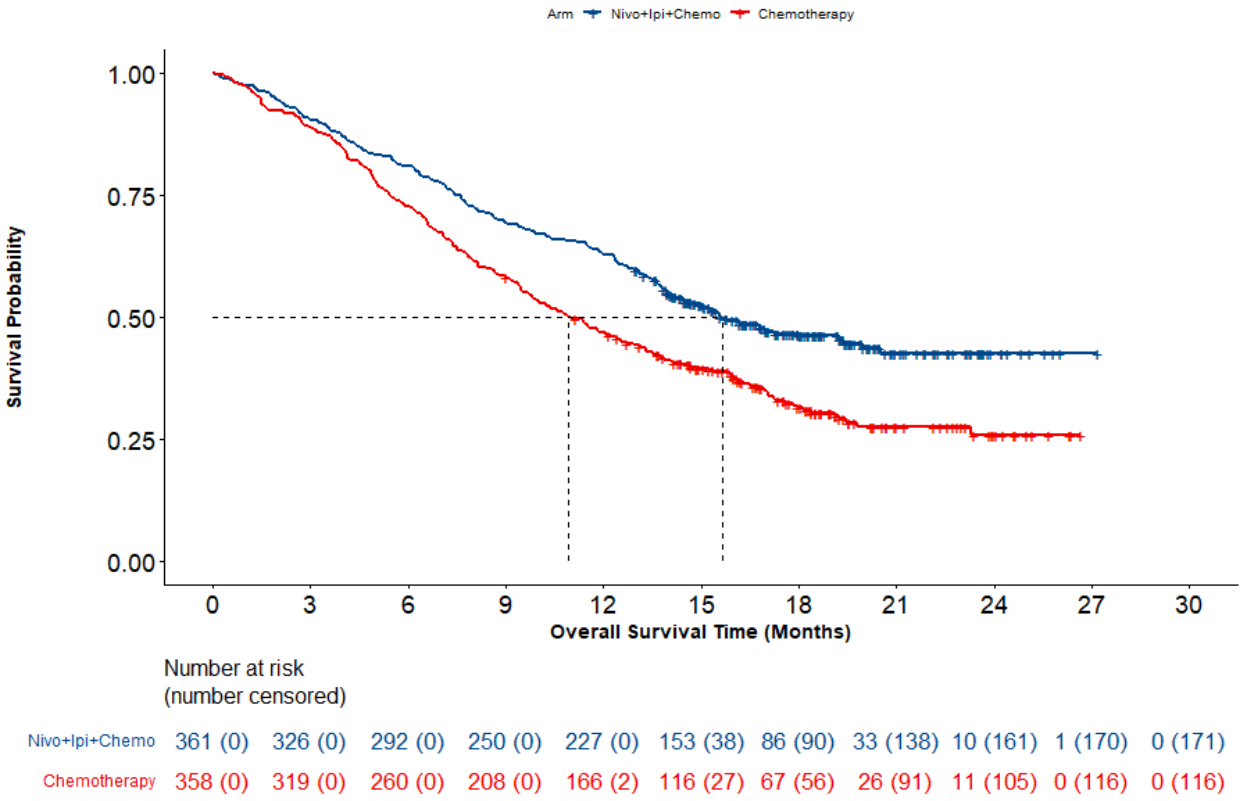
- Histology
  - SQ: HR = 0.65 (95% CI: 0.46, 0.93)
  - NSQ: HR = 0.72 (95% CI: 0.55, 0.93)
- PD-L1 subgroups:
  - PD-L1 < 1%: HR = 0.65 (95% CI: 0.46, 0.92)
  - PD-L1 ≥ 1%: HR = 0.67 (95% CI: 0.51, 0.89)
  - PD-L1 1-49%: HR = 0.69 (95% CI: 0.48, 0.98)
  - PD-L1 ≥ 50%: HR = 0.64 (95% CI: 0.41, 1.02)

While a robust, statistically significant and clinically meaningful improvement was observed across all primary and secondary efficacy endpoints, point estimates for median OS are to be interpreted with caution given the high proportion of censored subjects based on the minimum follow-up (8.1 months for OS).

The FDA's Assessment:

FDA agrees the study met its primary endpoint: Overall Survival estimates crossed the O'Brien-Fleming alpha boundary (with significance level 0.033) with 87% information. However, based on the interim data submitted (database lock 3-Oct-2019) there is evidence of non-proportional hazards in the form of a diminishing effect, specifically the tails of the Kaplan-Meier curves come back together towards the end. Furthermore, the rapid descent of the nivo+ipi+chemo arm at 12 months posed initial concern regarding a potential mortality safety signal (figure 6). The survival update with more mature OS data (database lock 9-Mar-2020) provided in response to FDA's Information Request regarding this issue provided more robust data, which mitigate FDA's initial concerns.(Figure 9).

Figure 9: Updated OS based on 9-Mar-2020 database cut-off



Source: FDA analysis of sponsor submitted datasets: ADEFTTES submitted 6-Apr-2020

Hazard ratios and p-values provide evidence of statistical relevance, but whether this translates into a result being clinically meaningful depends on other measures of magnitude of effect, for example differences in median survival time--estimates which are not mature in this submission. Additionally, to be considered "robust", results should be impervious to stress tests, and in this instance, it is not clear the effect is "robust" across time, given the issues with non-proportionality in the submitted OS data. These types of claims need to be supported by the data and results. With these points in mind, FDA considers the overall survival benefit and HR results presented in Figure 9 as clinically meaningful.

Finally, while FDA does agree that efficacy was observed across most subgroups, these results do need to be interpreted with caution and are only considered hypothesis generating, particularly in smaller groups with small event numbers.

CA2099LA Overall Survival Results by Region

OS point estimates favored nivo+ipi+chemo vs chemotherapy across regions, including the subgroup of subjects in North America (Figure 6, Figure 7, and Figure 7.4.2-1 of the CA2099LA Final CSR[50]).

The FDA's Assessment:

While FDA agrees that overall the estimates generally favor nivo+ipi+chemo across regions, the claim specifying a treatment effect for the subjects in North America is limited by small sample size (n=64 in both arms combined) and relatively large confidence interval which spans 1 (HR: 0.70 (95%CI: 0.37, 1.34))

Data Quality and Integrity

The Applicant's Position:

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21 CFR 50). For the study, the protocol, amendments, administrative letters, and subject informed consent form received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Compliance audits were performed as part of implementing quality assurance, and audit certificates are provided as applicable in the individual study reports. The quality of data collected and analyzed was monitored according to BMS standard operating procedures.

The FDA's Assessment:

The FDA agrees with the applicant's assessment.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 12: Secondary Efficacy Endpoints of Nivolumab + Ipilimumab + Chemotherapy vs Chemotherapy in All Randomized Subjects (CA2099LA)

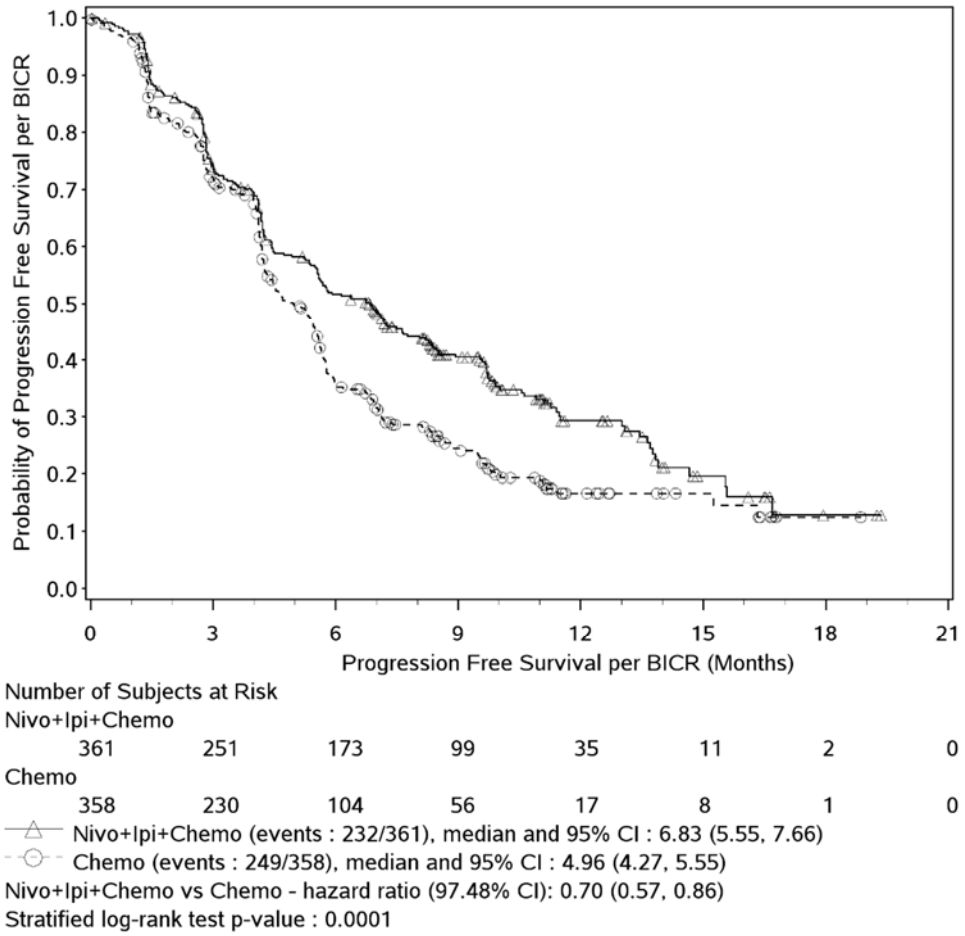
	Nivo+Ipi+Chemo N = 361	Chemotherapy N = 358
Progression-Free Survival (PFS) per BICR (1°Definition)		
Events, n (%)	232 (64.3)	249 (69.6)
Median PFS (95% CI), mo.[a]	6.83 (5.55, 7.66)	4.96 (4.27, 5.55)
HR (97.48% CI)[b]	0.70 (0.57, 0.86); p = 0.0001[c]	
HR (95% CI)[b]	0.70 (0.58, 0.84)	
6-month PFS Rates (95% CI), %[a]	51.7 (46.2, 56.8)	35.9 (30.5, 41.3)
Objective Response Rate (ORR) per BICR (CR + PR)		
N responders (%)	136 (37.7)	90 (25.1)
95% CI[d]	32.7, 42.9	20.7, 30.0
Difference of ORR (97.5% CI), %	12.4 (4.8, 20.0); p = 0.0003[e]	

Table 12: Secondary Efficacy Endpoints of Nivolumab + Ipilimumab + Chemotherapy vs Chemotherapy in All Randomized Subjects (CA2099LA)

	Nivo+Ipi+Chemo N = 361	Chemotherapy N = 358
Confirmed Best Overall Response (BOR) per BICR, n (%)		
Complete Response (CR)	7 (1.9)	3 (0.8)
Partial Response (PR)	129 (35.7)	87 (24.3)
Stable Disease (SD)	166 (46.0)	184 (51.4)
Progressive Disease (PD)	32 (8.9)	45 (12.6)
Unable To Determine (UTD)	24 (6.6)	30 (8.4)
Not Reported (NR)	3 (0.8)	9 (2.5)
Time To Response (TTR) per BICR		
Median (min, max), mo.	2.51 (1.1, 10.6)	1.56 (1.2, 8.3)
Disease Control Rate (CR+PR+SD)		
N responders (%)	302 (83.7)	274 (76.5)
95% CI	(79.4, 87.3)	(71.8, 80.8)
Duration of Response (DoR) per BICR		
N events/N responders (%)	57/136 (41.9)	54/90 (60.0)
Median (95% CI), mo.[a]	10.02 (8.21, 13.01)	5.09 (4.34, 7.00)
Min, Max, mo.	1.0+, 16.5+	1.4+, 15.2+
% of subjects with DoR (95% CI) ≥ 6 months[f]	74 (66, 81)	41 (30, 52)

Symbol + indicates a censored value.
Minimum follow-up (date the last subject randomized to date of the cutoff for OS) was 8.1 months for OS; median follow-up (date of randomization to the last known date alive or death date) was 10.35 months for the nivo+ipi+chemo arm and 9.07 months for the chemo arm. The OS and DoR medians would likely be influenced by a high proportion of censored subjects.
[a] Based on Kaplan-Meier estimates.
[b] Stratified Cox proportional hazards model. Hazard Ratio is Nivo+Ipi+Chemo over Chemotherapy.
[c] 2-sided p value from stratified regular log-rank test. The boundary for statistical significance, on the p-value scale, is 0.0252. That is, the p-value must be less than 0.0252 to show significance for PFS per BICR.
[d] CI based on the Clopper and Pearson method.
[e] 2-sided p value from stratified Cochran-Mantel-Haenszel test. The boundary for statistical significance, on the p-value scale, is 0.025. That is, the p-value must be less than 0.025 to show significance for ORR per BICR.
[f] Based on Kaplan-Meier estimates of duration of response.
Source: (ADaM datasets): Table 5.22.3 (adefttes.xpt, adsl.xpt) for PFS per BICR, Table 5.23.3 (adefttes.xpt, adsl.xpt) for PFS Rates per BICR, Table 5.5.2 (adefresp.xpt, adsl.xpt) for BOR and ORR per BICR, Table 5.10.2 (adefresp.xpt, adsl.xpt) for TTR and DoR, Table 5.12.1 (adefresp.xpt, adsl.xpt) for disease control rate in the CA2099LA Final CSR

Figure 10: Kaplan-Meier Plot of Progression-Free Survival (Primary Definition) per BICR - All Randomized Subjects (CA2099LA)



Statistical model for hazard ratio and p-value: Stratified Cox proportional hazards model and stratified log-rank test.
Symbols represent censored observations.
Source (ADaM datasets): Figure 5.30.3 (adefttes.xpt, adsl.xpt) in the CA2099LA Final CSR

The Applicant's Position:

Results for the primary endpoint of OS were supported by statistically significant improvements in the secondary endpoints (per BICR): PFS (HR = 0.70; 97.48% CI: 0.57, 0.86); stratified log rank test p value = 0.0001 (Table 12 and Figure 10) and ORR (37.7%; 95% CI: 32.7, 42.9 vs 25.1%; 95% CI: 20.7, 30.0); stratified CMH test p value = 0.0003. Efficacy results for PFS and ORR favored nivo+ipi+chemo vs chemotherapy for most subgroups, including histology and PD-L1 subgroups (Figure 7.3.1-1 and Figure 7.4.2-1 of the CA2099LA Final CSR).[50] The disease control rate (DCR) was 83.7% (nivo+ipi+chemo) vs 76.5% (chemotherapy), while the PD rate was 8.9% (nivo+ipi+chemo) vs 12.6% (chemotherapy).

Median DoR was longer for nivo+ipi+chemo than for chemotherapy, with non-overlapping CIs: 10.02 (95% CI: 8.21, 13.01) vs 5.09 (95% CI: 4.34, 7.00) months, respectively (Table 12).

While a robust, statistically significant and clinically meaningful improvement was observed across all primary and secondary efficacy endpoints, point estimates for median DoR are to be interpreted with caution given the high proportion of censored subjects based on the minimum follow-up (6.5 months for DoR).

The FDA's Assessment:
FDA agrees that efficacy results for the secondary endpoints PFS and ORR (both per BICR) were statistically significant. With n=481 events (80.7% information fraction) PFS results passed the O'Brien-Fleming alpha boundary (significance level 0.0252). FDA notes, however, there was only a 1.87 month difference in median PFS times.

It is noted that subgroup analyses across secondary endpoints are considered exploratory, and those results should be interpreted with caution given the small numbers. Furthermore, Disease control rate (DCR) is not considered a relevant endpoint in the regulatory setting as it can be driven by the natural course of the disease and may not represent the therapeutic effect of the agents being evaluated.

Dose/Dose Response
The Applicant's Position:
E-R analyses support theCA2099LA clinical efficacy results. See Section 6.2.2 for details.

The FDA's Assessment:
FDA also refers to Section 6.2.2 of the assessment aid.

Durability of Response
The Applicant's Position:
The median DoR was longer for all confirmed responders treated with nivo+ipi+chemo than with chemotherapy, with non-overlapping CIs: 10.02 (95% CI: 8.21, 13.01) vs 5.09 (95% CI: 4.34, 7.00) months. 74% and 41% of responders in the nivo+ipi+chemo and chemotherapy arms, respectively, had a DoR of at least 6 months (Table 12). The DoR is expected to change with additional follow-up as the minimum follow-up was 8.1 months for OS and 6.5 months for other data including DoR. The study is still ongoing to follow up on the long-term efficacy and safety of the study population.

The long-term efficacy of nivo+ipi has been demonstrated in CA209227 Part 1 with nivo+ipi providing deep and durable responses that translated into long-term survival benefit over chemotherapy in subjects, regardless of PD-L1 status. See Section 8.1.5 for the efficacy data for CA209227 Part 1. CA209227, the difference in OS rates for nivo+ipi versus chemotherapy, nivolumab, or nivo+chemo increased over time, suggesting the combination with ipilimumab had a differential profile with improved durability. The flattening of the OS Kaplan Meier curves for nivo+ipi combination treatment relative to chemotherapy, together with the deep and clinically meaningful treatment response durations demonstrate the durability of benefit with nivo+ipi combination treatment.

The FDA's Assessment:

FDA agrees with the median DoR estimates as presented, and the accuracy of the Kaplan-Meier estimates of DoR at 6 months; however, it is noted that observed estimates of the proportion of patients with a duration of response of at least 6 months provide additional information: 80/136 or 59% of patients responding to nivo+ipi+chemo have a DoR of at least 6 months and 25/90 or 28% of patients receiving platinum-doublet chemotherapy have a DoR of at least 6 months.

Persistence of Effect

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Other than the updated overall survival results as reported in FDA's assessment above for the primary endpoint results, no additional long-term efficacy data have been submitted.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Both nivo+ipi+chemo and chemotherapy resulted in steady on-treatment improvements from baseline in health-related quality-of-life in first line NSCLC, as measured by the Lung Cancer Symptom Scale (LCSS) average symptom burden index (ASBI), EQ-5D visual analogue score (VAS), and EuroQol 5 dimensional 3 level (EQ-5D-3L) utility index (UI) (Section 11.2 of the CA2099LA Final CSR).

The FDA's Assessment:

FDA verified the data presented in the CSR assessing overall health status using the EQ-5D-3L descriptive system, EQ-5D visual analog scale and evaluating disease-related symptoms using the LCSS ASBI, noting that these were exploratory endpoints with no pre-specified statistical testing procedure or alpha-allocation for assessing differences between arms. FDA notes that while there was some fluctuation in mean change from baseline at timepoint assessments in each of these scales, there appeared to be no detriment in LCSS ASBI, EQ-5D VAS,or EQ-5D-3L UI.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA did not conduct any additional analyses other than what is presented elsewhere in the assessment aid.

8.1.3 Integrated Review of Effectiveness

The Applicant's Position:

An assessment of efficacy across CA2099LA and CA209568 Part 2 is provided in Section 8.1.4. In addition, efficacy for CA2099LA and CA209227 Part 1 and Part 2 are provided in Section 8.1.4 to discuss contribution of components.

The FDA's Assessment:

FDA also refers to Section 8.1.4 of the assessment aid.

8.1.4 Assessment of Efficacy Across Trials

Data:

Table 13: Efficacy of Nivo+Ipi+Chemo vs Nivo+Ipi and Nivo+Chemo in First-line NSCLC in Studies CA2099LA, CA209227 Part 1 and CA209227 Part 2: All Randomized Subjects

	CA2099LA		CA209227 Part 1		CA209227 Part 2	
	Nivo+Ipi+Chemo N = 361	Chemo N = 358	Nivo+Ipi N = 583	Chemo N = 583	Nivo+Chemo N = 377	Chemo N = 378
Min. Follow-up for OS, mo	8.1		29.3		19.5	
OS HR (95% CI)[a]	0.69 (0.56, 0.86)		0.73 (0.64, 0.84)		0.81 (0.67, 0.97)	
PFS per BICR HR (95% CI)	0.70 (0.58, 0.84)		0.79 (0.69, 0.91)		0.62 (0.52, 0.73)	
ORR per BICR, %	37.7	25.1	33.1	27.8	51.5	30.2
CR	1.9	0.8	4.6	1.5	4.0	2.1
PR	35.7	24.3	28.5	26.2	47.5	28.0
SD	46.0	51.4	32.4	49.2	36.9	48.9
PD	8.9	12.6	23.2	12.7	6.4	13.0
UTD	6.6	8.4	11.3	10.3	5.3	7.9
NR	0.8	2.5	--	--	--	--
DCR (CR+PR+SD), %	83.7	76.5	65.5	77.0	88.3	79.1
Subsequent immunotherapy, %	3.9	27.9	5.5	40.8	3.7	32.0

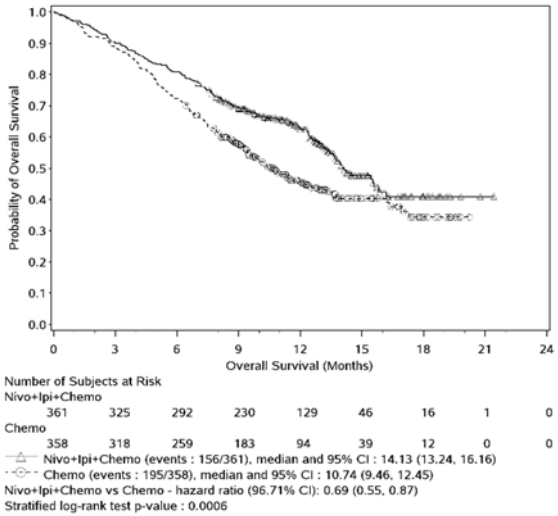
a HR was calculated using stratified Cox proportional hazards model, and 2-sided p value was from stratified regular log-rank test. Data presented for OS are HR (95%CI) for CA2099LA and CA209227 Part 1, and HR (95.62%CI) for CA209227 Part 2.

Source (ADaM datasets): **For CA2099LA**: Table 5.22.1 (adefttes.xpt, adsl.xpt) for OS, Table 5.22.3 (adefttes.xpt, adsl.xpt) for PFS per BICR, Table 5.5.2 (adefresp.xpt, adsl.xpt) for ORR per BICR, Table 5.12.1 (adefresp.xpt, adsl.xpt) for DCR, and Table 6.23.1 (adcms.xpt, adcmatc.xpt, adxp.xpt, adsl.xpt) for subsequent therapy in the CA2099LA Final CSR; **For CA209227 Part 1:** Table S.5.120.1.2 (adefttes.xpt, adsl.xpt) for OS, Table S.5.100.5 (adefttes.xpt, adsl.xpt) for PFS per BICR, Table S.5.109.3 (adefresp.xpt, adsl.xpt) for ORR, Table S.5.121.12 (adcm.xpt, adcms.xpt, adxg.xpt,adsl.xpt) for subsequent therapy in CA209227 Part 1 Final CSR and Table S.5.500.37.1(adefresp.xpt, adsl.xpt) for DCR in Appendix 2 of the SCE, Module 2.7.3; **For CA209227 Part 2**: Table S.5.120.1.1 (adefttes.xpt,

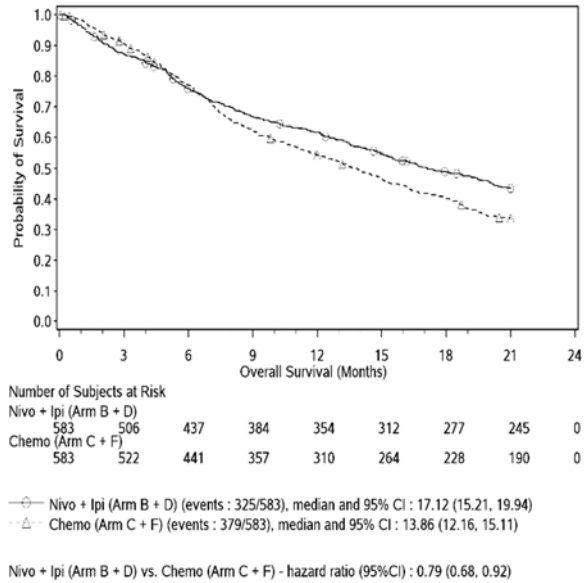
adsl.xpt) for (OS, all randomized), Table S.5.100.1 (adefttes.xpt, adsl.xpt) for (PFS, all randomized), Table S.5.109.1.1 (adefresp.xpt, adsl.xpt) for (ORR, all randomized), and Table S.5.121.8.1 (adcm.xpt, adcms.xpt, adxg.xpt, adsl.xpt) for subsequent therapy in CA209227 Part 2 Final CSR and Table S.5.505.6 (adefresp.xpt, adsl.xpt) for DCR in Appendix 2 of the SCE, Module 2.7.3

Figure 11: Overall Survival Kaplan-Meier Plots in Studies CA2099LA, CA209227 Part 1 and Part 2 to Assess Contribution of Components - All Randomized Subjects

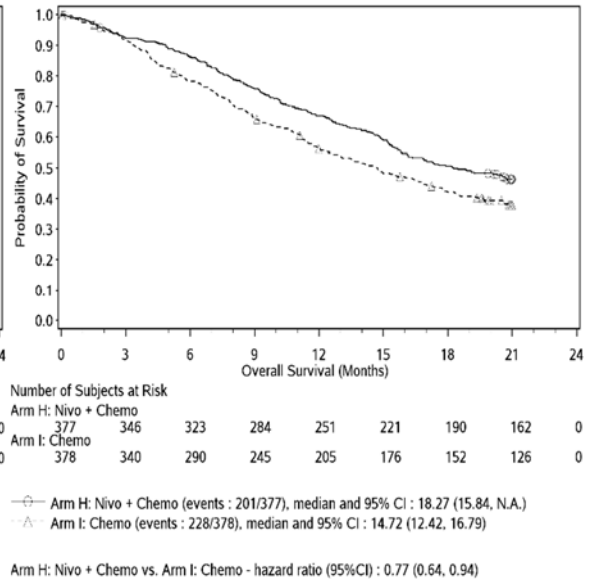
CA2099LA - All Randomized



CA209227 Part 1 - All Randomized



CA209227 Part 2 - All Randomized



Symbols represent censored observations.
Hazard Ratio is based on a stratified Cox proportional hazard model.
OS values censored at 21 months.
Source (ADaM datasets): Figure 5.30.1 (adefttes.xpt, adsl.xpt) of the CA2099LA Final CSR, Figure S.5.500.36.5 (adefttes.xpt, adsl.xpt) in Appendix 2 (for CA209227 Part 1), and Figure S.5.505.4 (adefttes.xpt, adsl.xpt) in Appendix 2 (for CA209227 Part 2) of the SCE, Module 2.7.3

The Applicant's Position:

Efficacy in Study CA209568 Part 2

Safety was the primary endpoint of this single-arm study in 36 subjects. Nivo+ipi+chemo treatment resulted in efficacy outcomes that were consistent with those observed in CA2099LA and support the benefit of first line nivo+ipi+chemo treatment in NSCLC subjects (Table 3-1 of the Summary of Clinical Efficacy [SCE], Module 2.7.3).[64] In CA209568 Part 2 (with a minimum follow-up of 14.9 months), investigator assessed ORR was 44.4% (16/36), with a median DoR of 10.71 months (95% CI: 5.55, not available [N.A.]). Investigator-assessed median PFS was 8.74 months (95% CI: 5.26, 13.83) and median OS was 21.09 months (95% CI: 6.54, N.A.).

Contribution of Individual Components

To establish contribution of components, results from CA2099LA are assessed relative to results from CA209227 Part 1 and Part 2 (Table 13). CA209227 Part 1 and Part 2 are large randomized studies comparing nivo+ipi (Part 1) and nivo+chemo (Part 2) to chemotherapy alone, in a similar patient population as CA2099LA.

Relative to nivo+ipi (CA209227 Part 1), nivo+ipi+chemo results in a considerably earlier separation of OS KM curves versus chemotherapy, without crossing, and a numerically lower HR, despite shorter follow-up: 8.1 months in CA2099LA vs 29.3 months in CA209227 Part 1 (Figure 11). Consistent with the hypothesis that led to the design of CA2099LA, the earlier improvement of OS is likely the result of the improved early disease control with nivo+ipi+chemo relative to nivo+ipi, illustrated by a DCR of 83.7% and a PD rate of 8.9%. Nivo+ipi+chemo was also associated with a significant increase in ORR and PFS versus chemotherapy; increases with nivo+ipi+chemo were of a larger magnitude compared to improvements observed with nivo+ipi vs chemo. The numerically lower CR rate with nivo+ipi+chemo relative to nivo+ipi, may be a function of the relatively short follow-up in CA2099LA (8.1 months for OS and 6.5 months for all other data) compared with CA209227 Part 1 (29.3 months for OS and 28.3 months for all other data); additional subjects in CA2099LA may convert to CR with more follow-up.

Relative to nivo+chemo (CA209227 Part 2), nivo+ipi+chemo demonstrated a statistically significant and clinically meaningful OS improvement versus chemotherapy (HR = 0.69), whereas nivo+chemo did not result in a statistically significant improvement of OS versus chemotherapy in NSQ NSCLC (primary endpoint), and an OS HR of 0.81 in all randomized subjects. Notably, the stronger OS result with nivo+ipi+chemo was observed despite limiting chemotherapy to 2 cycles, clearly demonstrating the effect of the addition of ipilimumab to OS. As expected, nivo+chemo (with 4 cycles of chemotherapy + optional maintenance for subjects with NSQ histology), showed a higher response rate and greater magnitude of PFS benefit versus chemotherapy; however, these benefits appeared to be transient and did not translate into improved survival.

In summary, the totality of the data from CA2099LA, CA209227 Part 1 and Part 2 ~~clearly~~ establish the contribution of individual components to the efficacy of nivo+ipi+chemo regimen.

The FDA's Assessment:

FDA generally agrees with the applicant's description of the contribution of components, which was

based on external data from CA209227. In the assessing the contribution of components, FDA also considered additional supportive results from existing drug approvals with the combination of nivolumab + ipilimumab (nivo+ipi) in other cancer types and highlighted caveats and limitations of cross-trial comparisons.

Cognizant of caveats of cross-trial comparisons, such as variability of performance between trials, FDA considered the OS hazard ratios from CA209227 parts 1 and 2 to be supportive in assessing the contribution of components to the treatment regimen (nivo+ipi+chemo) in CA2099LA as further elaborated below.

- **Nivolumab as a single-agent** was compared to four cycles of platinum-doublet chemotherapy (nivo versus chemo) in the PD-L1 ≥1% population in CA209227 Part 1. OS for nivolumab versus chemotherapy failed to meet statistical significance. However, there was a trend towards improved efficacy of nivolumab with a median OS of 15.7 months (95% CI 13.3, 18.1) over 14.9 months (95% CI 12.7, 16.7) for chemotherapy with a HR of 0.88 (95% CI 0.75, 1.04).

- **Contribution of ipilimumab to nivo+ipi** was assessed based on the results from Study CA209227 Parts 1a and 1b for the PD-L1 ≥1% and PD-L1 <1% populations, respectively. In FDA's review, the data from Parts 1a and 1b were combined for analysis regardless of PD-L1 expression levels, as patients in CA2099LA were not selected based on PD-L1 expression. There was numerically improved efficacy of nivo+ipi versus nivolumab as a single agent across all efficacy endpoints (OS, PFS by BICR, and ORR by BICR). OS was improved for nivo+ipi (17.1 months; 95% CI 15.2, 19.9) compared to nivolumab monotherapy (15.7; 95% CI 13.3, 18.1 months) with HRs versus 4 cycles of platinum-doublet chemotherapy of 0.73 (95% CI 0.64 – 0.84) and 0.88 (95% CI 0.75 – 1.04), respectively. Similarly, the ORR for nivo+ipi was 33.1% (95% CI 29.3, 37.1) compared to 27.5% (95% CI 23.2, 32.2) for nivolumab monotherapy. PFS was also numerically improved for nivo+ipi (5.1 months; 95% CI 4.1, 5.7) over nivolumab monotherapy (4.2 months; 95% CI 3.0, 5.3) with HRs versus 4 cycles of platinum doublet chemotherapy of 0.79 (97.5% CI 0.68, 0.93) and 0.99 (97.5% CI 0.82, 1.19), respectively. Notably, the confidence intervals for all of the point estimates and HRs for these efficacy endpoints are overlapping. However, the trend of improved efficacy of nivo+ipi over nivolumab monotherapy was consistent.

- **Contribution of ipilimumab to nivo+ipi+chemo** was evaluated by cross trial comparisons of nivolumab plus four cycles of platinum-doublet chemotherapy (nivo+chemo) in CA209227 Part 2 and nivo+ipi+chemo in CA2099LA. Importantly, OS for nivolumab plus chemotherapy versus four cycles of platinum-doublet chemotherapy failed to meet statistical significance in CA209227 Part 2. There was a greater magnitude of OS benefit over four cycles of platinum-doublet chemotherapy based on hazard ratios with nivo+ipi+chemo (HR 0.69; 95% CI 0.56, 0.86) compared to nivo+chemo (HR 0.81; 95% CI 0.67, 0.97), despite limiting chemotherapy to 2 cycles in CA2099LA versus four cycles in CA209227 Part 2. Conversely, ORR was improved for nivo+chemo in CA209227 Part 2 (51.5%; 95% CI 46, 57) compared to nivo+ipi+chemo in

CA2099LA (37.7%; 95% CI 33, 43).

- **Contribution of two cycles of platinum-doublet chemotherapy** to nivo+ipi+chemo was evaluated by cross trial comparisons of nivo+ipi in CA209227 Part 1 and nivo+ipi+chemo in CA2099LA. There was a greater magnitude of OS benefit over 4 cycles of platinum-doublet chemotherapy based on hazard ratios with nivo+ipi+chemo (HR 0.69; 95% CI 0.56, 0.86) compared to nivo+ipi (HR 0.73; 95% CI 0.64 – 0.84). Furthermore, there was an initial deficit observed with nivo+ipi compared to chemotherapy as evidenced by early crossing of the OS Kaplan-Meier curves in CA209227 Part 1, a pattern which was not observed with the addition of 2 cycles of chemotherapy to nivolumab plus ipilimumab in CA2099LA.

Caveats of cross-trial comparisons

Although comparisons of OS HRs across trials showed clinical benefit and the contribution of components for nivo+ipi+chemo, the point estimates for median OS and the 6-month and 12-month OS rates were higher for nivo+chemo in CA209227 Part 2 compared to nivo+ipi+chemo in CA2099LA. Notably, the chemotherapy arm in CA209227 Part 2 also had improved OS compared to the chemotherapy arm in CA2099LA. The OS results are shown in the table below:

	Study CA2099LA		**Study CA209227 Part 2**	
	Nivo + Ipi + Chemo N=361	**Chemo N=358**	**Nivo + Chemo N=377**	**Chemo N=378**
Median OS, months (95% CI)	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)	18.3 (15.8, 21.5)	14.7 (12.4, 16.8)
OS HR (95% CI)	0.69 (0.55, 0.87)		0.81 (0.68, 0.98)	
6-month OS rate (95% CI), %	81 (76, 85)	72 (67, 77)	86 (82, 89)	78 (74, 82)
12-month OS rate (95% CI), %	63 (57, 68)	46 (40, 51)	67 62, 71)	56 (51, 61)

Source: FDA analysis of applicant-submitted datasets (ADEFTTES)

Overall, there was variability of performance across trials between CA2099LA and CA209227. The variability in performance may be due to differences in demographics and baseline patient characteristics between trial populations. For instance, fewer patients were Asian, more patients had CNS metastases, and there were more current and former smokers in CA2099LA compared to CA209227. Conversely, more patients had an ECOG performance status of 0 in CA209227 compared to CA2099LA. These key differences are shown in the table below:

	Study CA2099LA		Study CA209227 Part 2	
	Nivo + Ipi + Chemo N=361 n (%)	**Chemo N=358 n (%)**	**Nivo + Chemo N=377 n (%)**	**Chemo N=378 n (%)**
Race				
White	322 (89)	316 (88)	272 (72)	265 (70)
Asian	30 (8)	30 (8)	93 (25)	94 (25)
Black	5 (1)	4 (1)	1 (0)	3 (1)
Other	4 (1)	8 (2)	11 (3)	14 (4)
ECOG				
0	113 (31)	112 (31)	133 (35)	106 (28)
1	247 (68)	245 (68)	243 (64)	267 (71)
Not Reported	1 (0)	1 (0)	-	-
Smoking Status				
Current/Former	315 (87)	305 (85)	316 (84)	299 (79)
Never Smoker	46 (13)	53 (15)	58 (15)	74 (20)
Unknown	-	-	3 (1)	5 (1)
Sites of Metastasis				
Bone	96 (27)	110 (31)	108 (29)	120 (32)
CNS	63 (17)	58 (16)	43 (11)	33 (9)
Liver	68 (19)	87 (24)	86 (23)	82 (22)

Sources: FDA analysis of applicant-submitted datasets (ADSL) and IR response dated March 24, 2020.

In summary, the hazard ratios for OS, provided evidence of benefit of nivo+ipi+chemo over nivo+chemo in cross-trial comparisons. Typically, cross-trial comparisons of medians and landmark analyses are not protected by randomization, whereas within a given trial, randomization ensures equal distribution between treatment arms and protects the relative benefit of the experimental arm versus the control arm. Therefore, for this review, when assessing contribution of components across trials, comparisons of hazard ratios, which remain protected by randomization, seemed acceptable given the totality of information assessed.

Survival benefit of nivolumab plus ipilimumab demonstrated in other cancer types

The combination of nivolumab plus ipilimumab has demonstrated efficacy in other cancer types and provides supportive evidence that ipilimumab contributes to the efficacy of nivolumab plus ipilimumab plus chemotherapy for the treatment of NSCLC. Namely, combinations of nivolumab plus ipilimumab are FDA-approved for the treatment of previously untreated unresectable or metastatic melanoma and previously untreated advanced renal cell carcinoma (RCC).

CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either nivolumab as a single agent or nivolumab plus ipilimumab as compared with ipilimumab as a single agent. Although the trial was not statistically designed to assess whether adding ipilimumab to nivolumab improved OS or PFS compared to nivolumab as a single agent, OS and PFS were numerically better for nivolumab plus ipilimumab versus nivolumab monotherapy. Based on a minimum follow-up of 48 months, the median OS was not reached (95% CI: 38.2, NR) in the nivolumab plus ipilimumab arm, while the median OS was 36.9 months (95% CI: 28.3, NR) in the nivolumab arm. Based on a minimum follow-up of 28 months, the median PFS was 11.7 months (95% CI: 8.9, 21.9) in the nivolumab plus ipilimumab arm and 6.9 months (95% CI: 4.3, 9.5) in the nivolumab arm. Results from this trial led to the approval of nivolumab as a single agent or in combination with ipilimumab for the treatment of previously untreated, unresectable or metastatic melanoma.

CHECKMATE-214 demonstrated statistically significant improvement in OS and ORR for patients randomized to nivolumab + ipilimumab as compared with sunitinib. The median OS for nivolumab + ipilimumab versus sunitinib was not evaluable and 25.9 months, respectively with a HR of 0.63 (99.8% CI 0.44, 0.89). ORR for nivolumab + ipilimumab versus sunitinib was 41.6% (95% CI 36.0, 46.5) and 26.5% (22.4, 31.0), respectively. The contribution of nivolumab and ipilimumab were demonstrated by cross-trial comparisons of studies evaluating nivolumab and ipilimumab as single agents in similar patients populations as to CHECKMATE-214. Results from CHECKMATE-214 led to the approval of nivolumab + ipilimumab for the treatment of previously untreated, intermediate or poor risk RCC.

Although different doses and regimens of nivolumab + ipilimumab are approved for melanoma and RCC, the demonstrated efficacy of the combination of these two drugs support the use of nivolumab + ipilimumab in addition to chemotherapy for the treatment of NSCLC.

Finally, the Applicant submitted Study CA209568 in support of the safety of the proposed regimen of nivo+ipi+chemo in Study CA2099LA. Nonetheless, although this a single-arm safety study of 36 patients with previously untreated metastatic or recurrent NSCLC treated with nivo+ipi+chemo, the investigator-assessed ORR in Study CA209568 was 44.4% (95% CI : 38.1, 72.1) with a median DoR of 10.71 months (95% CI 5.55, NR) which supports the benefit seen in patients treated with nivolumab plus ipilimumab plus chemotherapy in CA2099LA. Additionally, while time-to-event analyses, such as PFS and OS, lack interpretability in single-arm studies, investigator-assessed median PFS was 8.74 months (95% CI: 5.26, 13.83) and median OS was 21.09 months (95% CI: 6.54, NR), along with improved ORR, provide preliminary supportive evidence of the clinical benefit of nivo+ipi+chemo as seen in CA2099LA.

Summary

The contribution of components of nivolumab + ipilimumab + chemotherapy in CA2099LA was assessed with cross-trial comparisons. The benefit of adding ipilimumab to nivolumab + ipilimumab in NSCLC was demonstrated in CA209227 Part 1. The benefit of adding ipilimumab to nivolumab + ipilimumab +

chemotherapy in NSCLC was assessed based on comparisons of results between CA2099LA and CA209227 Part 2. The addition of chemotherapy to nivolumab + ipilimumab + chemotherapy was also assessed based on comparisons of CA2099LA to CA209227 Part 1 and was supported by the elimination of the early deficit seen with nivolumab + ipilimumab alone compared to chemotherapy. While caveats to cross-trial comparisons include differences in baseline characteristics of patient populations leading to overall variability of performance between trials, the FDA considered data from CA209227 supportive in assessing the contribution of nivolumab, ipilimumab, and chemotherapy in CA2099LA. Results from approvals in melanoma and RCC were also informative in demonstrating the benefit of the combination of ipilimumab to nivolumab.

8.1.5 Integrated Assessment of Effectiveness

CA2099LA, a large, randomized Phase 3 study, met its primary endpoint at a pre-planned interim analysis, demonstrating statistically significant and clinically meaningful improvements in OS (primary endpoint), PFS (per BICR), and ORR (per BICR) with nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy, versus platinum based therapy alone, as first-line treatment for NSCLC. The efficacy benefit (OS, PFS, ORR) of nivo+ipi+chemo vs chemotherapy was observed in both subjects with SQ and NSQ histology, in all subjects regardless of PD-L1 status (< 1%, ≥ 1%, 1%-49%, and ≥ 50%), and across most other subgroups. Contribution of individual components was clearly established based on the OS results from CA2099LA relative to CA209227 Part 1 (nivo+ipi) and CA209227 Part 2 (nivo+chemo).

Study CA2099LA was an adequate and well-controlled clinical trial and the data submitted meet the statutory evidentiary standard for substantial evidence of effectiveness. The data support the proposed indication of OPDIVO, in combination with ipilimumab and 2 cycles of platinum-based chemotherapy, is indicated for the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations.

The FDA's Assessment:

Overall, FDA agrees that nivolumab plus ipilimumab plus chemotherapy demonstrated statistically significant and clinically meaningful improvements in efficacy with nivolumab plus ipilimumab plus two cycles of platinum-doublet chemotherapy over four cycles of platinum-doublet chemotherapy alone, as first-line treatment for patients with metastatic NSCLC. CA2099LA met its primary endpoint of OS, and the alpha-controlled key secondary endpoints PFS per BICR and ORR per BICR.

Subgroup analyses were generally consistent with overall findings. However, the Type I error of tests for subgroup analyses were not controlled and often included evaluation of only small numbers of patients. Therefore, FDA considers the presented subgroup analyses as descriptive and hypothesis-generating.

The contribution of individual components was assessed based on cross-trial comparisons of results from CA2099LA relative to CA209227 Parts 1 and 2. As described in greater detail in Section 8.1.4 above, there are caveats to cross-trial comparisons including differences in baseline characteristics of patient

populations leading to overall variability of performance between trials. Nonetheless, FDA considers data from CA209227 Parts 1 and 2 as supportive in assessing the contribution of nivolumab, ipilimumab, and chemotherapy in CA2099LA.

8.2 Review of Safety

The Applicant's Position:

The overall safety profile observed with the combination of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy in CA2099LA (n = 358) and CA209568 Part 2 (n = 36) was manageable and reflective of the known safety profiles of the immunotherapy and chemotherapy components as first-line therapy for NSCLC. There were no new safety concerns identified with the nivo+ipi+chemo combination. In addition, the safety profile of nivo+ipi+chemo in first-line NSCLC (CA2099LA) was consistent with the safety profile of nivo+ipi in first-line NSCLC Study CA209227 Part 1 (nivolumab 3 mg/kg Q2W + ipilimumab Q6W) and other approved indications: RCC Study CA209214 and in CRC Study CA209142 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W). An overall safety summary of nivo+ipi+chemo is presented in Section 8.2.

The FDA's Assessment:

FDA agrees with the applicant's position that the safety review primarily focuses on the randomized study CA2099LA and CA209568, with additional, relevant supportive safety data. For this sBLA, the primary safety results are based upon study CA2099LA. Overall, FDA generally agrees that the safety profile of nivolumab + ipilimumab + chemotherapy for the first-line treatment of NSCLC in CA2099LA was consistent with the safety profiles of the individual immunotherapy and chemotherapy components. Additionally, the safety profile of nivolumab + ipilimumab + chemotherapy in CA2099LA was similar to the safety profile of nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W for the first-line treatment of NSCLC in Study CA209227 Part 1, with a few notable exceptions. Namely, patients treated with nivolumab + ipilimumab + chemotherapy in CA2099LA had higher rates of anemia and nausea compared with patients treated with nivolumab + ipilimumab in CA209227 Part 1 as shown in the table below:

	Study CA2099LA Nivo + Ipi + Chemo N=358 n (%)		**Study CA209227 Part 1 Arm B + Arm D Nivo + Ipi N=576 n (%)**	
	Any Grade	Grade 3 – 4	Any Grade	Grade 3 – 4
Anemia	32	8	12	3.1
Nausea	32	1.7	21	1.0

Source: FDA analysis of sponsor-submitted datasets (ADAE).

The safety profile of nivolumab + ipilimumab + chemotherapy in CA2099LA also seemed similar to the safety profile of nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W for patients with renal cell carcinoma treated in CHECKMATE-214 and patients with MSI-high colorectal cancer in CHECKMATE-142. When comparing nivolumab + ipilimumab + chemotherapy in

CA2099LA to nivolumab 1 mg/kg and ipilimumab 3 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W for patients with melanoma in CHECKMATE-067, there were higher rates of diarrhea and rash for patients in CHECKMATE-067 in the setting of receiving a higher dose of ipilimumab as shown in the table below:

	Study CA2099LA Nivo + Ipi + Chemo N=358 %		**CHECKMATE-067* Nivo + Ipi N=313 %**	
	Any Grade	Grade 3 – 4	Any Grade	Grade 3 – 4
Diarrhea	31	6	54	11
Rash	29	4.7	53	6

Source: FDA analysis of sponsor-submitted datasets (ADAE) and data for CHECKMATE-067 as shown in the U.S. prescribing label for OPDIVO.

8.2.1 Safety Review Approach

The Applicant's Position:

Safety analyses were conducted by treatment arm in all treated subjects who received at least one dose of study drug. Safety presentations of AEs, SAEs, AEs leading to discontinuation, and laboratory abnormalities are based on all treated subjects using a safety window of 30 days after last dose. The 30-day safety window was intended to provide a characterization of the safety experience of nivo+ipi+chemo and chemotherapy regimens without influence of AEs associated with subsequent therapies. Additionally, IMAE analyses with extended safety follow-up (using a 100-day window), as well as results of OESIs are provided in the "Safety Results, Significant Adverse Events" subsection.

Primary nivo+ipi+chemo safety data are from the pivotal study, CA2099LA, a randomized Phase 3 trial evaluating nivo+ipi+chemo versus platinum-doublet chemotherapy. Data in all treated subjects in the nivo+ipi+chemo (N = 358) and chemotherapy (N = 349) arms are based on the clinical cut-off date of 16-Aug-2019 and database lock date of 03-Oct-2019, with a minimum follow-up of 8.1 months for OS and 6.5 months for all other data. Additional first-line safety data are summarized for subjects from Phase 2 study CA209568 Part 2 (N = 36) treated with nivo+ipi+chemo, the same regimen as that evaluated in CA2099LA. CA209568 Part 2 was designed to evaluate the incidence of dose-limiting toxicity (DLT), safety, and tolerability of the nivo+ipi+chemo regimen.

To assess the safety of individual components in the nivo+ipi+chemo regimen, safety data in first line NSCLC are also summarized for subjects treated with nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W (hereafter referred to as nivo+ipi) from CA209227 Part 1 (Arms B + D; N = 576) and subjects treated with nivolumab 360 mg Q3W + 4 cycles of platinum-doublet chemotherapy (hereafter referred to as nivo+chemo) from CA209227 Part 2 (Arm H; N = 375).

In addition, AEs, IMAEs, and OESIs from nivo+ipi+chemo in CA2099LA are assessed relative to those from nivolumab 3 mg/kg + ipilimumab 1 mg/kg regimens studied in NSCLC and other tumor types: NSCLC study

CA209227 Part 1 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q6W), RCC Study CA209214 and CRC Study CA209142 (nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W in both RCC and CRC studies).

The FDA's Assessment:
FDA agrees with the applicant's stated approach for review of safety data.

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Table 14 Safety Population, Size, and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W+2 cycles of platinum-doublet chemotherapy in this development program for the indication under review		
Clinical Trial Groups	Nivo+Ipi+Chemo	Chemo
Controlled trials conducted for this indication (CA2099LA)[2]	358	349
All other than controlled trials conducted for this indication (CA209568 Part 2)[3]	36	--

[1] *study drug* means the drug being considered for approval.

[2] to be used in product's labeling

[3] not used in product's labeling

Source (ADaM dataset): Table 2.6A.1 (adsl.xpt) in the CA2099LA Final CSR

The Applicant's Position:

A total of 358 subjects in the nivo+ipi+chemo group and 349 subjects in the chemotherapy group were administered at least one dose of the investigational product in pivotal Phase 3 study, CA2099LA. The median (95% CI) duration of therapy was 6.05 (4.93, 7.06) months for the nivo+ipi+chemo arm and 2.43 (2.30, 2.83) months in the chemotherapy arm (Table 4.1.1 [ADaM datasets: adexs.xpt, adsl.xpt] in the CA2099LA Final CSR). The median number of doses received was as follows:

- Nivo+ipi+chemo arm: 9 doses for nivolumab, 4 doses for ipilimumab, and 2 doses for each of cisplatin, carboplatin, paclitaxel, and pemetrexed
- Chemotherapy arm: 4 doses for each of cisplatin, carboplatin, and paclitaxel, and 6 doses for pemetrexed.

In the nivo+ipi+chemo arm, 18 (5.0%) subjects discontinued ipilimumab only (Table 4.3.1.1 in the CA2099LA Final CSR). Note that ipilimumab could be discontinued and nivolumab continued; however, if nivolumab was discontinued, ipilimumab could not be continued alone as monotherapy.

In the nivo+ipi+chemo arm, the majority of treated subjects (93.0%) received 2 cycles of chemotherapy (Table 4.4 [ADaM datasets: adexs.xpt, adsl.xpt] in the CA2099LA Final CSR). In the chemotherapy arm, 29.5% of treated subjects received 4 cycles of chemotherapy, and 45.3% of treated subjects received 4 cycles of chemotherapy plus pemetrexed maintenance therapy.

The FDA's Assessment:
FDA agrees with the applicant's position.

Relevant characteristics of the safety population:

The Applicant's Position:
Demographic and baseline disease characteristics in all randomized subjects were balanced between the nivo+ipi+chemo and the chemotherapy arms, and were representative of a first-line recurrent or metastatic NSCLC population (Table 10).

The FDA's Assessment:
FDA agrees with the demographic and baseline disease characteristics of all randomized patients presented by the applicant in Table 8. The median age of patients was 65 for both treatment arms. The majority of patients were male, White, and from Europe. Most patients had a performance status of 1, non-squamous histology, Stage IV disease, and were current or former smokers. A similar proportion of patients between treatment arms had PD-L1 expression <1%, however the chemotherapy control arm had slightly more patients with PD-L1 >50% compared to the nivolumab + ipilimumab + chemotherapy arm (27% versus 21%, respectively). Overall the demographics and baseline characteristics were well-balanced between the treatment arms. In general, the patient population was representative of patients with metastatic NSCLC, although as previously noted, Black patients were underrepresented accounting for only 1.3% of randomized patients in the trial. Additionally, the median age of patients in the trial was 65 years old while patients diagnosed with NSCLC in the U.S. are older with a median age at diagnosis of approximately 70 years old (Howlader, SEER Cancer Statistics Review, 1975-2017).

Adequacy of the safety database:

The Applicant's Position:
The population studied in CA2099LA with previously untreated stage IV or recurrent NSCLC adequately represents the target population, including demographic, disease, and other baseline characteristics. Building on the extensive safety experience of nivo+ ipi (in over 1200 patients) and nivo+chemo in first-line NSCLC as well as nivo+ipi in other tumor types (eg, melanoma, RCC, and CRC), the exposure to study treatment in Study CA2099LA allows for sufficient characterization of the safety of nivolumab 360 mg Q2W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy. The routine clinical and laboratory evaluations performed in the study were appropriate, and overall, the safety profile of nivo+ipi+chemo was manageable using existing algorithms, with no new safety signals identified. Safety data from CA2099LA were further supported by safety data from CA209568 Part 2 designed to evaluate the safety of nivo+ipi+chemo in subjects with previously untreated stage IV or recurrent NSCLC (Section 7.1 of the Summary of Clinical Safety [SCS], Module 2.7.4).[65]

The FDA's Assessment:
FDA agrees with the applicant's assessment. The safety database includes over 1200 patients with NSCLC who have receive nivolumab in combination with ipilimumab, patients with NSCLC treated with nivolumab + chemotherapy, and patients with other tumor types (including melanoma, RCC, and MSI-high CRC) treated with nivolumab in combination with ipilimumab.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21 CFR 50). For CA2099LA, the protocol, amendments, administrative letters, and subject informed consent form received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Compliance audits were performed as part of implementing quality assurance, and audit certificates are provided as applicable in the individual study reports. The quality of data collected and analyzed was monitored according to BMS standard operating procedures. No issues with data quality and integrity have been identified.

The FDA's Assessment:

FDA agrees with the applicant's statement.

Categorization of Adverse Event

The Applicant's Position:

Adverse events in CA2099LA (as well as CA209227 Parts 1 and 2) were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 CTC version 4.0, by system organ class (SOC) and preferred term. Adverse events in CA209568 Part 2 were categorized using MedDRA version 21.1; CTC version 4.0.

The FDA's Assessment:

FDA agrees with the applicant's categorization of adverse events (AEs) for Studies CA2099LA and CA209568. The FDA's safety assessment focused on the frequency and severity of all treatment-emergent AEs from CA2099LA, which were defined as AEs occurring after the first dose of study drug to within 30 days after the last dose of study therapy. Additional analyses included assessment of TEAEs leading to death, serious adverse events (SAEs), TEAEs leading to permanent discontinuation of the study therapy, other events of special interest (OESIs), and immune mediated adverse events (IMAEs). The window for evaluating OESIs and IMAEs was extended to within 100 days after the last dose of study therapy as to not miss any delayed-onset AEs.

Routine Clinical Tests

The Applicant's Position:

The following laboratory tests were conducted at Screening and at each study visit: serum hematology (complete blood count [CBC], differential [ab solute counts: neutrophils, lymphocytes, monocytes, basophils, eosinophils], and platelets) and serum chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, total bilirubin, albumin, creatinine, blood urea nitrogen [BUN] (or urea), sodium, potassium, chloride, calcium, magnesium, glucose, lactate dehydrogenase, amylase, lipase, thyroid stimulating hormone [TSH], free T4 or T3. Pregnancy tests were conducted at

screening and within 24 hours prior to the start of study drug. Testing for hepatitis virus B/C (HBV sAg, HCV antibody or HCV ribonucleic acid [RNA]) was performed within 28 days prior to randomization. Testing for human immunodeficiency virus (HIV) was conducted as per local regulations.

On-treatment laboratory tests were those occurring after the first dose of study treatment and until 30 days after the last dose. Laboratory tests were graded using the NCI CTCAE, version 4.0.

The FDA's Assessment
FDA agrees with the applicant's statement.

8.2.4 Safety Results

Data

Table 15: Overview of CA2099LA Safety - All Treated Subjects

	No. of Subjects (%)			
Safety Parameters	Nivo + Ipi + Chemo (N = 358)		Chemotherapy (N = 349)	
Deaths	153 (42.7)		191 (54.7)	
Primary Reason for Death				
Disease	124 (34.6)		163 (46.7)	
Study Drug Toxicity [a]	7 (2.0)		6 (1.7)	
Unknown	5 (1.4)		4 (1.1)	
Other [b]	17 (4.7)		17 (4.9)	
Not Reported	0		1 (0.3)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	203 (56.7)	157 (43.9)	144 (41.3)	111 (31.8)
Drug-related SAEs	104 (29.1)	90 (25.1)	61 (17.5)	51 (14.6)
All-causality AEs leading to DC	100 (27.9)	77 (21.5)	59 (16.9)	38 (10.9)
Drug-Related AEs leading to DC	68 (19.0)	54 (15.1)	26 (7.4)	14 (4.0)
All-causality AEs	355 (99.2)	228 (63.7)	341 (97.7)	184 (52.7)
Drug-related AEs	322 (89.9)	159 (44.4)	304 (87.1)	129 (37.0)
≥ 15% of Subjects in Any Treatment Group				
Nausea	94 (26.3)	5 (1.4)	126 (36.1)	3 (0.9)
Anemia	80 (22.3)	20 (5.6)	130 (37.2)	48 (13.8)
Asthenia	73 (20.4)	3 (0.8)	61 (17.5)	8 (2.3)
Diarrhea	73 (20.4)	14 (3.9)	42 (12.0)	4 (1.1)
Pruritus	66 (18.4)	3 (0.8)	4 (1.1)	0
Rash	64 (17.9)	5 (1.4)	10 (2.9)	0
Fatigue	59 (16.5)	8 (2.2)	37 (10.6)	2 (0.6)
Decreased Appetite	56 (15.6)	4 (1.1)	53 (15.2)	4 (1.1)
Neutropenia	35 (9.8)	22 (6.1)	58 (16.6)	31 (8.9)

Table 15: Overview of CA2099LA Safety - All Treated Subjects

	No. of Subjects (%)			
Safety Parameters	Nivo + Ipi + Chemo (N = 358)		Chemotherapy (N = 349)	
All-causality IMAEs within 100 days of last dose				
Treated with Immune Modulating Medication				
Diarrhea/Colitis	17 (4.7)	10 (2.8)	0	0
Hepatitis	18 (5.0)	15 (4.2)	0	0
Pneumonitis	18 (5.0)	9 (2.5)	0	0
Nephritis/Renal Dysfunction	5 (1.4)	2 (0.6)	0	0
Rash	50 (14.0)	13 (3.6)	1 (0.3)	1 (0.3)
Hypersensitivity/Infusion Reactions	2 (0.6)	0	0	0
All-causality Endocrine IMAEs within 100 days of last dose				
With or Without Immune Modulating Medication				
Adrenal Insufficiency	12 (3.4)	5 (1.4)	1 (0.3)	0
Hypophysitis	8 (2.2)	5 (1.4)	0	0
	Adverse Events			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hypothyroidism/Thyroiditis	53 (14.8)	2 (0.6)	3 (0.9)	0
Hyperthyroidism	27 (7.5)	0	0	0
Diabetes Mellitus	0	0	0	0
All-causality OESIs within 100 days of last dose				
With or Without Immune Modulating Medication				
Pancreatitis	5 (1.4)	3 (0.8)	0	0
Encephalitis	2 (0.6)	1 (0.3)	0	0
Myositis	0	0	1 (0.3)	0
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0
Uveitis	0	0	0	0
Myocarditis	0	0	0	0
Rhabdomyolysis	0	0	0	0
Graft Versus Host Disease	0	0	0	0

[a] The causes of death per investigator were as follows: in the **nivo+ipi+chemo arm:** 2 deaths were due to nivolumab + ipilimumab (pneumonitis, hepatitis), 1 death was due to ipilimumab (diarrhea), 1 death was due to ipilimumab + chemotherapy (sepsis), 1 death was due to nivo+ipi+chemo (hepatic toxicity), and 2 deaths were due to chemotherapy (acute renal failure, thrombocytopenia) and in the **chemotherapy arm:** sepsis (2 subjects), anemia, pancytopenia, respiratory failure, and neutropenia.

[b] The verbatim terms reported for the 'other' reasons for death were consistent with events expected in the population under study.

Source (ADaM dataset[s]): Table 6.15.1 (adsl.xpt) for deaths, Table 6.3.1.2.1 (adae.xpt, adsl.xpt) for all-causality SAEs, Table 6.3.1.2.2 (adae.xpt, adsl.xpt) for drug-related SAEs, Table 6.4.2.1 (adae.xpt, adsl.xpt) for all-causality

AEs leading to DC, Table 6.4.2.2 (adae.xpt, adsl.xpt) for drug-related AEs leading to DC, Table 6.1.31.1 (adae.xpt, adsl.xpt) for all-causality AEs; Table 6.1.32.1 (adae.xpt, adsl.xpt) for drug-related AEs; Table 6.2.02.4 (adaeimm.xpt, adsl.xpt) for non-endocrine IMAEs, Table 6.2.02.1 (adaeimm.xpt, adsl.xpt) for endocrine IMAEs and Table 6.5.3.3.1 (adaeimm.xpt, adsl.xpt) for OESIs in the CA2099LA Final CSR

Table 16: Select Chemotherapy-related Toxicities, All Nivolumab + Ipilimumab + Chemotherapy and Chemotherapy Treated Subjects in CA2099LA

	Number (%) of Subjects			
	Nivo + Ipi + Chemo (N = 358)		Chemo (N = 349)	
Drug-Related AEs	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Anemia	80 (22.3)	20 (5.6)	130 (37.2)	48 (13.8)
Neutropenia	35 (9.8)	22 (6.1)	58 (16.6)	31 (8.9)
Alopecia	32 (8.9)	3 (0.8)	31 (8.9)	2 (0.6)
Thrombocytopenia	17 (4.7)	10 (2.8)	34 (9.7)	8 (2.3)
Mucosal inflammation	15 (4.2)	2 (0.6)	8 (2.3)	1 (0.3)
Febrile Neutropenia	14 (3.9)	14 (3.9)	11 (3.2)	10 (2.9)
Neuropathy peripheral	9 (2.5)	0	13 (3.7)	1 (0.3)
Pancytopenia	2 (0.6)	1 (0.3)	5 (1.4)	5 (1.4)

MedDRA Version: 22.0. CTC Version 4.0. Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Table 6.1.32.1 (ADaM datasets: adae.xpt, adsl.xpt) in the CA2099LA Final CSR

Table 17: Exposure Adjusted Adverse Event Rates for All Nivolumab + Ipilimumab + Chemotherapy and Chemotherapy Treated Subjects - CA2099LA

	Exposure Adjusted Rates per 100 person-years	
Safety Parameters	**Nivo+Ipi+Chemo (N = 358)**	**Chemotherapy (N = 349)**
Serious Adverse Events (SAEs)	172.0	166.3
Drug-Related SAEs	73.5	63.2
Adverse Events (AEs) Leading to Discontinuation	62.6	53.6
Drug-Related AEs Leading to Discontinuation	41.7	24.1
All AEs	1770.8	1935.6
Drug-Related AEs	866.6	1013.2

Source: (ADaM datasets) Table 6.142.2 (adaeme.xpt, adsl.xpt) for all causality SAEs, Table 6.142.3 (adaeme.xpt, adsl.xpt) for drug-related SAEs, Table 6.142.4 (adaeme.xpt, adsl.xpt) for all-causality AEs leading to discontinuation, Table 6.142.5 (adaeme.xpt, adsl.xpt) for drug-related AEs leading to discontinuation, Table 6.26.1 (adaeme.xpt, adsl.xpt) for all-causality AEs, and Table 6.142.1 (adaeme.xpt, adsl.xpt) for drug-related AEs in the CA2099LA Final CSR

Deaths

The Applicant's Position:

As of the 03-Oct-2019 DBL, 42.7% of subjects in the nivo+ipi+chemo arm and 54.7% of subjects in the chemotherapy arm died (Table 15 and Table 6.15.1 [ADaM dataset: adsl.xpt] in the CA2099LA Final CSR). Disease progression was the most common cause of death in both arms. A similar proportion of subjects in the nivo+ipi+chemo (2.0%) and chemotherapy (1.7%) arms died due to study drug toxicity. Per Investigator, 2 deaths were due to nivo+ipi, 1 death was due to ipilimumab, 1 death was due to ipilimumab + chemotherapy, 1 death was due to nivo+ipi+chemo, and 8 deaths were due to chemotherapy. Deaths attributed to other reasons were reported in 4.7% of subjects in the nivo+ipi+chemo arm and in 4.9% of subjects in the chemotherapy arm. The verbatim terms reported for the 'other' reasons for death were consistent with events expected in the population under study.

The FDA's Assessment:

FDA generally agrees with the applicant's position on the deaths reported for patients treated in Study CA2099LA. Disease progression was the most common cause of death for both treatment arms. However, in review of the death narratives, FDA determined that the cause of death for one patient on the nivolumab plus ipilimumab plus chemotherapy arm that was listed as "other" was actually due to disease progression. Therefore, 35% of patients died due to disease progression and 4.5% of patients died due to "other" causes on the nivolumab plus ipilimumab plus chemotherapy arm. Fatal adverse reactions occurred in seven (2.0%) patients on the nivolumab plus ipilimumab plus chemotherapy arm and included hepatic toxicity (n=2), acute renal failure, sepsis, pneumonitis, diarrhea with hypokalemia, and massive hemoptysis in the setting of thrombocytopenia. FDA provides further details for the "other" causes of death for the nivolumab plus ipilimumab plus chemotherapy arm, based on review of the death narratives, in the table below.

Summary of Deaths in Study CA2099LA

	Nivo+Ipi+Chemo n=358 n (%)	**Chemotherapy n=349 n (%)**
Total Deaths	**153 (43)**	**191 (55)**
Cause of Death		
Disease Progression	125 (35)	163 (47)
Study Drug Toxicity	7 (2.0)	6 (1.7)
Other	16 (4.5)	17 (4.9)
Unknown	5 (1.4)	4 (1.1)

Other Causes of Death		
Infection	5	5
Cardiac arrest (including STEMI)	3	2
Respiratory failure	2	3
Hemorrhage	2	1
VTE/PE	2	1
Bowel occlusion	1	-
Alzheimer's disease	1	-
Multi-organ failure	-	1
Carcinomatosis meningitis	-	1
Superior vena cava syndrome	-	1
Stroke	-	1
Neuropathy	-	1

Source: FDA analysis of sponsor-submitted datasets (ADSL) and sponsor-submitted safety narratives.

Serious Adverse Events

The Applicant's Position:

Any Grade SAEs (regardless of causality) were reported in 56.7% of subjects in the nivo+ipi+chemo arm vs 41.3% of subjects in the chemotherapy arm (Table 15 and Table 6.3.1.2.1 [ADaM datasets: adae.xpt, adsl.xpt]) of the CA2099LA Final CSR) . Grade 3-4 SAEs were reported in 43.9% of subjects in the nivo+ipi+chemo arm and 31.8% of subjects in the chemotherapy arm. The most frequently reported SAEs (regardless of causality) were:

- Nivo+ipi+chemo: malignant neoplasm progression (7.8%), pneumonia (4.5%), diarrhea (3.6%), anemia (3.1%), and febrile neutropenia (3.1%).
- Chemotherapy: malignant neoplasm progression (8.3%), pneumonia (4.6%), anemia (4.0%), and febrile neutropenia (2.6%).

Any-grade drug-related SAEs were reported in 104 (29.1%) subjects in the nivo+ipi+chemo arm, and 61 (17.5%) subjects in the chemotherapy arm (Table 15 and Table 6.3.1.2.2 [ADaM datasets: adae.xpt, adsl.xpt]) of the CA2099LA Final CSR). Grade 3-4 drug-related SAEs were reported in 90 (25.1%) subjects in the nivo+ipi+chemo arm, and 51 (14.6%) subjects in the chemotherapy arm. The most frequently reported drug-related SAEs were:

- Nivo+ipi+chemo: diarrhea (3.1%), febrile neutropenia (3.1%), anemia (2.2%), acute kidney injury (1.7%), colitis (1.4%), and adrenal insufficiency (1.4%).
- Chemotherapy: anemia (3.4%), febrile neutropenia (2.6%), thrombocytopenia (1.7%), and pancytopenia (1.4%).

When incidence rates were exposure-adjusted, the overall rates (all-causality: 172.0 vs 166.3; drug-related: 73.5 vs 63.2) of all causality and drug-related SAEs in the nivo+ipi+chemo arm were comparable to the incidence rates in the chemotherapy arm (all-causality: 172.0 vs 166.3; drug-related: 73.5 vs 63.2) (Table 15).

The FDA's Assessment:

FDA generally agrees with the applicant's assessment of serious adverse events (SAEs). However, FDA grouped preferred terms when completing the analysis of SAEs resulting in slightly different percentages

of events compared with analyses from the applicant. Overall there were more respiratory events and diarrhea as SAEs for patients treated with nivolumab plus ipilimumab plus chemotherapy compared to patients treated on the chemotherapy only arm. As there may be heterogeneity between investigators and difficulty in accurately assigning attribution of adverse events to study therapy, FDA generally does not report drug-related adverse events and did not complete an independent review of drug-related SAEs. Shown below are the most common SAEs (occurring in ≥2% of patients) reported for Study CA2099LA.

Serious Adverse Events (SAEs) in ≥2% of Patients for Study CA2099LA

SAE	Nivo+Ipi+Chemo n=358 n (%)	Chemo n=349 n (%)
Blood adverse events	**22 (6)**	**23 (7)**
Anemia	11 (3.1)	14 (4)
Febrile neutropenia	11 (3.1)	9 (2.6)
Pneumonia[a]	**23 (6)**	**19 (5)**
Respiratory adverse events	**22 (6)**	**13 (3.7)**
Dyspnea	8 (2.2)	7 (2.0)
Pneumonitis[b]	7 (2.0)	5 (1.4)
Respiratory failure	7 (2.0)	1 (0.3)
Diarrhea[c]	**17 (4.7)**	**3 (0.9)**
Acute kidney injury[d]	**11 (3.1)**	**6 (1.7)**
Musculoskeletal pain[e]	**10 (2.8)**	**4 (1.1)**
Hemorrhage[f]	**7 (2.0)**	**6 (1.7)**

Source: FDA analysis of sponsor-submitted datasets (ADAE).

[a] Includes lower respiratory tract infection, lung abscess, lung infection, pneumonia, aspiration pneumonia, and bacterial pneumonia

[b] Includes immune-mediated pneumonitis, interstitial lung disease, and pneumonitis

[c] Includes colitis, diarrhea, and enterocolitis

[d] Includes acute kidney injury and renal failure

[e] Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain

[f] Includes anal hemorrhage, rectal hemorrhage, and upper gastrointestinal hemorrhage

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Adverse events leading to discontinuation included events where 1 or more drugs of a multidrug regimen were discontinued, even if the subject remained on treatment.

Any-grade AEs leading to discontinuation (regardless of causality) were reported in 100 (27.9%) subjects in the nivo+ipi+chemo arm, and 59 (16.9%) subjects in the chemotherapy arm (Table 6.4.2.1 [ADaM datasets: adae.xpt, adsl.xpt] in the CA2099LA Final CSR). Grade 3-4 AEs leading to discontinuation were reported in 77 (21.5%) subjects in the nivo+ipi+chemo arm, and 38 (10.9%) subjects in the chemotherapy arm. The most common AEs leading to discontinuation (regardless of causality) were:

- Nivo+ipi+chemo: malignant neoplasm progression (3.6%), diarrhea (2.5%), pneumonitis (2.0%), and colitis (1.4%).
- Chemotherapy: malignant neoplasm progression (3.4%), general physical health deterioration (1.4%), and anemia (1.1%).

Any-grade drug-related AEs leading to discontinuation were reported in 68 (19.0%) subjects in the nivo+ipi+chemo arm, and 26 (7.4%) subjects in the chemotherapy arm (Table 6.4.2.2 [ADaM datasets: adae.xpt, adsl.xpt] in the CA2099LA Final CSR). Grade 3-4 AEs leading to discontinuation were reported in 54 (15.1%) subjects in the nivo+ipi+chemo arm, and 14 (4.0%) subjects in the chemotherapy arm. The most common drug-related AEs leading to discontinuation were:

- Nivo+ipi+chemo: diarrhea (2.5%), pneumonitis (2.0%), and colitis (1.4%).
- Chemotherapy: anemia (0.9%).

When incidence rates were exposure-adjusted, the overall rates (per 100 person-years) of all causality AEs leading to discontinuation in the nivo+ipi+chemo arm were comparable to the incidence rates in the chemotherapy arm (62.6 vs 53.6). In contrast, the exposure adjusted incidence rates (per 100 person-years) of drug-related AEs leading to discontinuation were higher in nivo+ipi+chemo arm relative to the chemotherapy arm (41.7 vs 24.1) (Table 17) (discontinuation in the nivo+ipi+chemo arm could have been discontinuation of any drug in the regimen).

The FDA's Assessment:

FDA generally agrees with the applicant's position. However, FDA did not include cancer progression as an adverse event (AE). Therefore, FDA calculated that 87 (24%) patients in the nivolumab plus ipilimumab plus chemotherapy arm, and 47 (13%) patients in the chemotherapy arm discontinued study treatment due to any-grade AE. As previously discussed in the section above, FDA generally does not report drug-related AEs and therefore did not complete an independent review of drug-related AEs leading to treatment discontinuation. Additionally, FDA did not perform an independent review of exposure-adjusted incidence rates of AEs leading to discontinuation of study treatment.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

The most frequently reported drug-related AEs of any grade leading to dose delay or reduction in the nivo+ipi+chemo arm were: anemia (4.7%), neutropenia (4.7%), diarrhea (3.6%), pneumonitis (2.8%), and

ALT increased (2.5%) (Table 6.4.2.4 in the CA2099LA Final CSR). No dose reductions were permitted for nivolumab or ipilimumab. The most frequently reported drug-related AEs of any grade leading to dose delay or reduction in the chemotherapy arm were: anemia (12.0%), neutropenia (9.5%), thrombocytopenia (4.6%), platelet count decreased (2.9%), and neutrophil count decreased (2.3%).

The FDA's Assessment:

As explained above, FDA did not complete an independent review of *drug-related* AEs that led to dose delays or dose reductions. However, for all-causality AEs that led to dose delays or dose reductions, FDA presents the table below for the most frequently reports AEs (≥ 2%).

Adverse Events leading to dose delay or reduction in Study CA2099LA

TEAE	Trial arm			
	Nivolumab + Ipilimumab + Platinum Doublet Chemotherapy N = 358		Platinum Doublet Chemotherapy N = 349	
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)
Any TEAE	201 (56)	124 (35)	160 (46)	89 (26)
Anemia	26 (7)	13 (3.6)	47 (13)	30 (9)
Neutropenia[a]	21 (6)	13 (3.6)	44 (13)	20 (6)
Fatigue[b]	18 (5)	7 (2.0)	13 (3.7)	6 (1.7)
Diarrhea	16 (4.5)	3 (0.8)	6 (1.7)	3 (0.9)
Thrombocytopenia[c]	11 (3.1)	5 (1.4)	27 (7.7)	10 (2.9)
Pneumonitis	11 (3.1)	1 (0.3)	2 (0.6)	0
Vomiting	10 (2.8)	2 (0.6)	3 (0.9)	2 (0.6)
Increased alanine aminotransferase	9 (2.5)	2 (0.6)	3 (0.9)	1 (0.3)
Rash	9 (2.5)	2 (0.6)	1 (0.3)	0
Pneumonia	8 (2.2)	7 (2.0)	7 (2.0)	4 (1.1)
Nausea	8 (2.2)	2 (0.6)	3 (0.9)	2 (0.6)
Pyrexia	8 (2.2)	1 (0.3)	6 (1.7)	1 (0.3)
Febrile neutropenia	7 (2.0)	7 (2.0)	7 (2.0)	7 (2.0)
Increased blood creatinine	7 (2.0)	1 (0.3)	5 (1.4)	0
Dyspnea	7 (2.0)	5 (1.4)	7 (2.0)	4 (1.1)

Source: FDA analysis of sponsor-submitted datasets (ADSL).

[a] Includes neutropenia and decreased neutrophil count.

[b] Includes fatigue and asthenia.
[c] Includes thrombocytopenia and decreased platelet count.

Comparison of Chemotherapy-related Toxicities: Nivo+Ipi+Chemo vs Chemotherapy
Consistent with the limited cycles of chemotherapy, several toxicities typically related to chemotherapy were less frequently reported with nivo+ipi+chemo compared to chemotherapy (Table 16).

The FDA's Assessment:
FDA did not complete an independent review of *drug-related* adverse events, including chemotherapy-related toxicities. Please see FDA's table below showing all-causality AEs occurring in > 10% of patients receiving nivolumab plus ipilimumab plus chemotherapy or platinum-doublet chemotherapy in Study CA2099LA.

Significant Adverse Events

Data:

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Table 18: Onset/Management/Resolution of All-Causality IMAEs within 100 Days of Last Dose - Nivo+Ipi+Chemo-Treated Subjects (CA2099LA)

IMAE Category	% Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAE leading to DC / Dose Delay	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[a]	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE[d,e]	Median[b] Time to Resolution (range), wks[c,d,e]	% Subj. with Recurrence after Reinitiation
Pneumonitis	5.0 / 2.5	16.21 (0.6 - 52.4)	2.5 / 2.2	100 / 94.4	7.71 (1.4 - 25.9)	72.2	9.14 (0.7 - 41.1+)	14.3 (1 / 7)
Diarrhea/Colitis	4.7 / 2.8	14.71 (0.4 - 34.4)	2.2 / 2.0	100 / 88.2	5.14 (0.9 - 42.3)	76.5	4.86 (1.1 - 20.4)	12.5 (1 / 8)
Hepatitis	5.0 / 4.2	15.21 (1.3 - 68.3)	2.8 / 2.0	100 / 83.3	5.36 (0.1 - 28.1)	66.7	7.71 (0.3+ - 27.1)	0 (0 / 4)
Nephritis/Renal Dysfunction	1.4 / 0.6	15.14 (10.6 - 24.1)	0.3 / 1.1	100 / 100	7.86 (0.9 - 41.9)	80.0	5.14 (2.4 - 9.7+)	0 (0 / 4)
Rash	14.0 / 3.6	2.93 (0.1 - 51.0)	0.8 / 2.5	100 / 24.0	5.57 (0.1 - 55.6)	74.0	9.14 (0.7 - 55.6+)	2.2 (1 / 46)
Hypersensitivity	0.6 / 0	3.14 (3.1 - 3.1)	0 / 0	100 / 50.0	0.36 (0.1 - 0.6)	100	0.14 (0.1 - 0.1)	0 (0 / 2)
Adrenal Insufficiency	3.4 / 1.4	17.64 (1.9 - 38.4)	1.1 / 1.1	100 / 33.3	12.64 (0.1 - 56.0)	25.0	N.A. (1.0 - 56.1+)	0 (0 / 8)
Hypophysitis	2.2 / 1.4	16.36 (9.0 - 43.0)	0.6 / 0.8	75.0 / 25.0	41.14 (23.3 - 71.9)	37.5	N.A. (0.7 - 72.4+)	0 (0 / 4)
Hypothyroidism/ Thyroiditis	14.8 / 0.6	15.14 (6.0 - 58.3)	0.6 / 1.4	9.4 / 7.5	8.43 (1.1 - 47.4)	26.4	N.A. (1.7+ - 66.3+)	0 (0 / 47)
Hyperthyroidism	7.5 / 0	7.86 (2.3 - 41.9)	0 / 1.4	11.1 / 3.7	2.86 (1.3 - 10.3)	85.2	6.14 (2.1 - 40.1+)	0 (0 / 23)
Diabetes Mellitus	0 / 0	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.

[a] Denominator is based on the number of subjects who experienced the event [b] From Kaplan-Meier estimation.

[c] Symbol + indicates a censored value. [d] Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis.

[e] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

Source (ADaM dataset): Table 6.2.02.1 (adaeimm.xpt, adsl.xpt) for endocrine IMAEs, Table 6.2.02.2 (adaeimm.xpt, adsl.xpt) for endocrine IMAEs leading to DC, Table 6.2.02.3 (adaeimm.xpt, adsl.xpt) for endocrine IMAEs leading to dose delay/reduction, Table 6.2.02.4 (adaeimm.xpt, adsl.xpt) for non-endocrine IMAEs, Table 6.2.02.5 (adaeimm.xpt, adsl.xpt) for non-endocrine IMAEs leading to DC, Table 6.2.02.6 (adaeimm.xpt, adsl.xpt) for non-endocrine IMAEs leading to dose delay/reduction, Table 6.12.91.1 (adcmim.xpt, adsl.xpt) for duration of IMM for IMAE management, Table 6.217.1 (adaette.xpt, adsl.xpt) for time to onset of endocrine IMAEs, Table 6.217.2 (adaette.xpt, adsl.xpt) for time to onset of nonendocrine IMAEs, Table 6.219.1 (adaette.xpt, adsl.xpt) for time to resolution of endocrine IMAEs, Table 6.219.2 (adaette.xpt, adsl.xpt) for time to resolution of non-endocrine IMAEs, Table 6.223.1 (adaerc.xpt, adsl.xp) for rechallenge with nivolumab or ipilimumab. These outputs also include Grade 3-5 and chemotherapy results.of the CA2099LA Final CSR

The Applicant's Position:

Immune-mediated Adverse Events:

IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (ie, with extended follow up). These analyses were limited to subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. In addition, these events were identified by the investigator as IMAEs with no clear alternate etiology and an immune mediated component.

As expected, IMAEs occurred more frequently with nivo+ipi+chemo relative to chemotherapy. The most frequently reported any-grade IMAEs (by category) in the nivo+ipi+chemo arm were hypothyroidism/thyroiditis (14.8%), rash (14.0%), hyperthyroidism (7.5%), hepatitis (5.0%), and pneumonitis (5.0%); IMAEs in all other categories were reported in < 5% of subjects (Table 15).

Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered (Table 15). Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy. The proportion of subjects with IMAEs that resolved, as well as the time to resolution, was generally similar for nivo+ipi+chemo in first-line NSCLC and nivo+ipi in first-line NSCC, and pooled RCC and CRC (Table 7.4-1 of the SCS, Module 2.7.4).

Other Events of Special Interest (OESIs):

OESIs are events that do not fulfill all criteria to qualify as select AEs or IMAEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs had extended follow‑up (100-day window). OESIs included the following categories: myasthenic syndrome, demyelination, Guillain-Barré syndrome, pancreatitis, uveitis, encephalitis, myocarditis, myositis, rhabdomyolysis, and graft versus host disease.

OESIs (regardless of causality or IMM treatment, with extended follow-up) were infrequent in both treatment arms. Overall, OESIs were reported in 7/358 (2.0%) subjects in the nivo+ipi+chemo arm (5 subjects with pancreatitis and 2 subjects with encephalitis)and 1/349 (0.3%) subject with myositis in the chemotherapy arm. 5/7 OESIs in the nivo+ipi+chemo arm and 1/1 OESI in the chemotherapy arm were resolved at the time of DBL. 4/5 events were resolved with IMM treatment in the nivo+ipi+chemo. The only event in the chemotherapy arm resolved without IMM treatment.

The FDA's Assessment:

Overall FDA agrees with the applicant's position. However, Grade 1 immune-mediated adverse events are generally managed without steroids or immune-modulating medications so FDA notes that the applicant's analysis of immune-mediated (non-endocrine) adverse events requiring immune-modulating medications will not capture most Grade 1 events.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 19: Adverse Reactions in >10% of Patients Receiving Nivolumab and Ipilimumab and Platinum-based Doublet Chemotherapy - CA2099LA

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-based Doublet Chemotherapy (n=358)		Platinum-based Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue	(b) (4)			
Pyrexia				
Gastrointestinal				
Nausea				
Diarrhea				
Constipation				
Vomiting				
Abdominal pain				
Musculoskeletal and Connective Tissue				
Musculoskeletal pain	(b) (4)			
Arthralgia				
Metabolism and Nutrition				
Decreased appetite	(b) (4)			
Skin and Subcutaneous Tissue				
Rash	(b) (4)			
Pruritus				
Alopecia				
Respiratory, Thoracic and Mediastinal				
Cough	(b) (4)			
Dyspnea				
Endocrine				
Hypothyroidism	(b) (4)			
Nervous System				
Headache	(b) (4)			
Dizziness				

Source: Appendix L.1.USPI.1 (adaeremp.xpt, adsl.xpt) of the SCS, Module 2.7.4

The Applicant's Position:

For labeling purposes, adverse reactions (grouped by system organ class [SOC] and presented by CTC grade) for the proposed regimen that were reported in > 10% of in nivo+ipi+chemo-treated subjects in CA2099LA were included in Section 6.1 of the United States Prescribing Information (USPI) (see Table 19). The most frequent adverse reactions were fatigue, nausea, and diarrhea in the nivo+ipi+chemo arm and nausea, fatigue, and musculoskeletal pain in the chemotherapy arm (Appendix L.1.USPI.1 (adaeremp.xpt, adsl.xpt) of the SCS, Module 2.7.4). The most frequent Grade 3-4 adverse reactions were hyponatremia,

fatigue, and malignant neoplasm progression in the nivo+ipi+chemo arm and anemia, neutropenia, and thrombocytopenia in the chemotherapy arm (Appendix L.1.USPI.1 (adaeremp.xpt, adsl.xpt) of the SCS, Module 2.7.4).

The FDA's Assessment:
Due to grouping of preferred terms as indicated, FDA calculated slightly different rates of adverse reactions as shown in the table below.

Adverse Reactions in >10% of Patients Receiving Nivolumab and Ipilimumab and Platinum-Doublet Chemotherapy in Study CA2099LA

Adverse Reaction	Nivolumab and Ipilimumab 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[c]	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
Pneumonia[i]	10	4.5	8	4.6
Endocrine				
Hypothyroidism[j]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0

Adverse Reactions in >10% of Patients Receiving Nivolumab and Ipilimumab and Platinum-Doublet Chemotherapy in Study CA2099LA

Adverse Reaction	Nivolumab and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Dizziness[k]	11	0.6	6	0

[a] Includes fatigue and asthenia
[b] Includes myalgia, back pain, pain in extremity, musculoskeletal pain, bone pain, flank pain, muscle spasms, musculoskeletal chest pain, musculoskeletal disorder, osteitis, musculoskeletal stiffness, non-cardiac chest pain, arthralgia, arthritis, arthropathy, joint effusion, psoriatic arthropathy, synovitis
[c] Includes colitis, ulcerative colitis, diarrhea, and enterocolitis
[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, and gastrointestinal pain
[e] Includes acne, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, generalized exfoliative dermatitis , eczema, keratoderma blenorrhagica, palmar-plantar erythrodysaesthesia syndrome, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, urticaria
[f] Includes pruritus and generalized pruritus
[g] Includes cough, productive cough, and upper-airway cough syndrome
[h] Includes dyspnea, dyspnea at rest, and exertional dyspnea
[i] Includes aspiration pneumonia, bacterial pneumonia, lower respiratory tract infection, lung abscess, lung infection, and pneumonia
[j] Includes autoimmune thyroiditis, increased blood thyroid stimulating hormone, hypothyroidism, thyroiditis, and decreased free tri-iodothyronine
[k] Includes dizziness, vertigo and positional vertigo

Laboratory Findings

Data:

Table 20: Laboratory Abnormalities That Worsened Relative to Baseline (US Conventional Units) - CA2099LA

Laboratory Abnormality	Percentage of Subjects with Worsening Laboratory Test from Baseline[a]			
	Niv+Ipi+Chemo		Chemotherapy	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Hematology				
Anemia	(b) (4)			
Lymphopenia				
Neutropenia				
Leukopenia				
Thrombocytopenia				
Chemistry				

Hyperglycemia	(b) (4)
Hyponatremia	
Increased ALT	
Increased lipase	
Increased alkaline phosphatase	
Increased amylase	
Increased AST	
Hypomagnesemia	
Hypocalcemia	
Increased creatinine	
Hyperkalemia	
Hypokalemia	
Hypoglycemia	
Hypercalcemia	
Bilirubin	
Hypermagnesemia	
Hypernatremia	

(b) (4)

The Applicant's Position:

The grades and frequencies of laboratory abnormalities (hematology, liver tests, kidney function tests, and electrolytes) were generally consistent in the nivo+ipi+chemo and chemotherapy arms (see Section 3 of the SCS, Module 2.7.4).[65] However, Grade 3 decreases in hemoglobin levels were less common in the nivo+ipi+chemo arm relative to the chemotherapy arm (9.2% vs 16.4%) and Grade 3 increases in amylase ((b) (4) and lipase (b) (4)% vs 2.2%) levels were more common in the nivo+ipi+chemo arm relative to the chemotherapy arm (Table 7.1.1 [ADaM datasets: adzl.xpt, adsl.xpt] in the CA2099LA Final CSR). The majority of subjects did not have laboratory tests that worsened to Grade 3 or 4 relative to baseline (Table 20). The USPI provides a table summarizing laboratory abnormalities that worsened relative to baseline (US conventional units) in > 20% of nivo+ipi+chemo treated subjects in CA2099LA.

The FDA's Assessment:

Overall, FDA agrees with the applicant's data and position. However, FDA differs from the applicant's position, which should state Grade 3 ***and 4*** decreases in hemoglobin levels were less common in the nivolumab plus ipilimumab plus chemotherapy arm relative to the chemotherapy arm (9.2% vs. 16.4%) and Grade 3 ***and 4*** increases in amylase (***6.7%*** vs. ***1.3%***) and lipase (***11.9%*** vs. 2.2%) levels were more common in the nivolumab plus ipilimumab plus chemotherapy arm relative to the chemotherapy arm. The corrected values match with calculations performed by the FDA as well as the data shown by the applicant in Table 20.

Vital Signs

The Applicant's Position:

Vital signs and oxygen saturation by pulse oximetry were monitored and recorded at the site per institutional standard of care during screening and treatment visits. These assessments were intended to be used as safety monitoring by the treating physician.

The FDA's Assessment:

FDA agrees with the applicant's statement.

Electrocardiograms (ECGs)

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

QT

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

Immunogenicity

The Applicant's Position:

See Section 6.3.1.

The FDA's Assessment:

FDA also refers to Section 6.3.1 of the Assessment Aid.

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Comparison with Broader Safety Experience

Data:

Table 21: Safety of Nivolumab + Ipilimumab + Chemotherapy vs Nivolumab + Ipilimumab and Nivolumab + Chemotherapy in First-line NSCLC - Studies CA2099LA, CA209227 Part 1 (Arms B +D), and CA209227 Part 2 (Part H)

	Number (%) of Subjects					
	Nivolumab + Ipilimumab + Chemotherapy		Nivolumab + Ipilimumab		Nivolumab + Chemotherapy	
Safety Parameters	CA2099LA (N = 358)		CA209227 Part 1 Arm B + Arm D (N = 576)		CA209227 Part 2 Arm H (N = 375)	
Deaths	153 (42.7)		372 (64.6)		223 (59.5)	
Primary Reasons for Death						
Disease	124 (34.6)		304 (52.8)		174 (46.4)	
Due to Study Drug Toxicity	7 (2.0)		8 (1.4)		6 (1.6)	
Unknown	5 (1.4)		14 (2.4)		14 (3.7)	
Other	17 (4.7)		46 (8.0)		29 (7.7)	
	Adverse Event Grades					
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All Causality SAEs	203 (56.7)	157 (43.9)	355 (61.6)	259 (45.0)	195 (52.0)	142 (37.9)
Drug-related SAEs	104 (29.1)	90 (25.1)	141 (24.5)	106 (18.4)	94 (25.1)	75 (20.0)
All Causality AEs leading to DC	100 (27.9)	77 (21.5)	190 (33.0)	141 (24.5)	102 (27.2)	55 (14.7)
Drug-Related AEs leading to DC	68 (19.0)	54 (15.1)	104 (18.1)	71 (12.3)	73 (19.5)	36 (9.6)
All Causality AEs	355 (99.2)	228 (63.7)	568 (98.6)	360 (62.5)	371 (98.9)	223 (59.5)
Drug-Related AEs	322 (89.9)	159 (44.4)	442 (76.7)	189 (32.8)	318 (84.8)	168 (44.8)
≥ 15% of Subjects in Any Treatment Group						
Nausea	94 (26.3)	5 (1.4)	57 (9.9)	3 (0.5)	84 (22.4)	4 (1.1)
Anemia	80 (22.3)	20 (5.6)	22 (3.8)	8 (1.4)	122 (32.5)	39 (10.4)
Asthenia	73 (20.4)	3 (0.8)	59 (10.2)	8 (1.4)	40 (10.7)	5 (1.3)
Diarrhea	73 (20.4)	14 (3.9)	98 (17.0)	10 (1.7)	41 (10.9)	3 (0.8)
Pruritus	66 (18.4)	3 (0.8)	82 (14.2)	3 (0.5)	32 (8.5)	0
Rash	64 (17.9)	5 (1.4)	98 (17.0)	9 (1.6)	50 (13.3)	4 (1.1)
Fatigue	59 (16.5)	8 (2.2)	83 (14.4)	10 (1.7)	58 (15.5)	10 (2.7)
Decreased Appetite	56 (15.6)	4 (1.1)	76 (13.2)	4 (0.7)	60 (16.0)	8 (2.1)

	Number (%) of Subjects					
	Nivolumab + Ipilimumab + Chemotherapy		Nivolumab + Ipilimumab		Nivolumab + Chemotherapy	
Safety Parameters	CA2099LA (N = 358)		CA209227 Part 1 Arm B + Arm D (N = 576)		CA209227 Part 2 Arm H (N = 375)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All Causality IMAEs within 100 days of last dose						
Treated with Immune Modulating Medication						
Diarrhea/Colitis	17 (4.7)	10 (2.8)	48 (8.3)	17 (3.0)	14 (3.7)	5 (1.3)
Hepatitis	18 (5.0)	15 (4.2)	46 (8.0)	37 (6.4)	11 (2.9)	8 (2.1)
Pneumonitis	18 (5.0)	9 (2.5)	50 (8.7)	23 (4.0)	20 (5.3)	7 (1.9)
Nephritis/Renal Dysfunction	5 (1.4)	2 (0.6)	6 (1.0)	2 (0.3)	7 (1.9)	2 (0.5)
Rash	50 (14.0)	13 (3.6)	106 (18.4)	21 (3.6)	25 (6.7)	3 (0.8)
Hypersensitivity/Infusion Reactions	2 (0.6)	0	4 (0.7)	0	0	0
All Causality Endocrine IMAEs within 100 days of last dose						
With or Without Immune Modulating Medication						
Adrenal Insufficiency	12 (3.4)	5 (1.4)	27 (4.7)	13 (2.3)	2 (0.5)	1 (0.3)
Hypophysitis	8 (2.2)	5 (1.4)	20 (3.5)	9 (1.6)	1 (0.3)	1 (0.3)
Hypothyroidism/Thyroiditis	53 (14.8)	2 (0.6)	81 (14.1)	4 (0.7)	31 (8.3)	0
Hyperthyroidism	27 (7.5)	0	50 (8.7)	0	9 (2.4)	0
Diabetes Mellitus	0	0	6 (1.0)	5 (0.9)	0	0
All-causality OESIs within 100 days of last dose						
With or Without Immune Modulating Medication						
Myasthenic Syndrome	0	0	1 (0.2)	1 (0.2)	1 (0.3)	0
Demyelination	0	0	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0	0	0
Pancreatitis	5 (1.4)	3 (0.8)	6 (1.0)	4 (0.7)	3 (0.8)	2 (0.5)
Uveitis	0	0	2 (0.3)	0	1 (0.3)	0
Encephalitis	2 (0.6)	1 (0.3)	2 (0.3)	2 (0.3)	0	0
Myocarditis	0	0	2 (0.3)	2 (0.3)	3 (0.8)	3 (0.8)
Myositis	0	0	2 (0.3)	1 (0.2)	1 (0.3)	0
Rhabdomyolysis	0	0	1 (0.2)	1 (0.2)	0	0

	Number (%) of Subjects					
	Nivolumab + Ipilimumab + Chemotherapy		Nivolumab + Ipilimumab		Nivolumab + Chemotherapy	
Safety Parameters	CA2099LA (N = 358)		CA209227 Part 1 Arm B + Arm D (N = 576)		CA209227 Part 2 Arm H (N = 375)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Graft vs Host Disease	0	0	0	0	0	0

MedDRA version 22.0; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Minimum follow up: 6.5 months (8.1 months for OS) in CA2099LA (03-Oct-2019 database lock); 28.3 months (29.3 months for OS) in CA209227 Part 1 (02-Jul-2019 database lock); and 18.4 months (19.5 months for OS) in CA209227 Part 2 (02-Jul-2019 database lock)

Source: **CA209227 Part 1:** Table S.6.15.1 (adsl.xpt) and Table S.6.15.3 (adsl.xpt) for deaths, Table S.6.18.1.1 (adae.xpt) and Table S.6.18.3.1 (adae.xpt) for all causality SAEs, Table S.6.18.1.3 (adae.xpt) and Table S.6.18.3.3 (adae.xpt) for drug-related SAEs, Table S.6.23.1.1 (adae.xpt) and Table S.6.23.3.1 (adae.xpt) for all causality AEs leading to DC, Table S.6.23.1.2 (adae.xpt) and Table S.6.23.3.2 (adae.xpt) for drug-related AEs leading to DC, Table S.6.2.1 (adae.xpt) and Table S.6.2.3 (adae.xpt) for all causality AEs, Table S.6.3.1 (adae.xpt) and Table S.6.3.3.1 (adae.xpt) for drug-related AEs, Table S.6.204.1 (adaeimm.xpt) and Table S.6.204.3 (adaeimm.xpt) for all causality endocrine IMAEs, Table S.6.202.1 (adaeimm.xpt) and Table S.6.202.3 (adaeimm.xpt) for all causality IMAEs with exception of endocrine, and Table S.6.300.1.1 (adaeimm.xpt) and Table S.6.300.2.1 (adaeimm.xpt) for OESIs; **CA209227 Part 2:** Table S.6.15.1 (adsl.xpt) for deaths, Table S.6.18.1 (adae.xpt) for all causality SAEs, Table S.6.18.3 (adae.xpt) for drug-related SAEs, Table S.6.23.1 (adae.xpt) for all-causality AEs leading to DC, Table S.6.23.3 (adae.xpt) for drug-related AEs leading to DC, Table S.6.2.1 (adae.xpt) for all causality AEs, Table S.6.3.1 (adae.xpt) for drug-related AEs, Table S.6.105.1.1 (adae.xpt) for all causality select endocrine AEs, Table S.6.105.1.3 (adae.xpt) for drug-related select endocrine AEs, Table S.6.101.1.1 (adae.xpt) for all causality select AEs, Table S.6.101.1.3 (adae.xpt) for drug-related select AEs, Table S.6.204.1 (adaeimm.xpt) for endocrine IMAEs, Table S.6.202.1 (adaeimm.xpt) for IMAEs, Table S.6.300.1.1 (adaeimm.xpt) for OESIs

Table 22: Summary of Safety of Nivolumab + Ipilimumab + Chemotherapy in NSCLC vs Nivolumab + Ipilimumab in NSCLC, RCC, and CRC

	NSCLC CA2999LA		NSCLC CA209227		RCC CA209214		CRC CA209142	
	Nivo 360 mg Q3W + Ipi 1 Q6W + Chemo N = 358		Nivo 3 Q2W + Ipi 1 Q6W N = 576		Nivo 3 + Ipi 1 Q3W N = 547		Nivo 3 + Ipi 1 Q3W N = 119	
DEATHS	153 (42.7)		372 (64.6)		159 (29.1)		23 (19.3)	
WITHIN 30 DAYS OF LAST DOSE	40 (11.2)		75 (13.0)		23 (4.2)		2 (1.7)	
WITHIN 100 DAYS OF LAST DOSE	97 (27.1)		154 (26.7)		50 (9.1)		11 (9.2)	
PRIMARY REASON FOR DEATH								
DISEASE PROGRESSION	124 (34.6)		304 (52.8)		124 (22.7)		19 (16.0)	
STUDY DRUG TOXICITY	7 (2.0)		8 (1.4)		7 (1.3)		0	
UNKNOWN	5 (1.4)		14 (2.4)		6 (1.1)		2 (1.7)	
OTHER	17 (4.7)		46 (8.0)		22 (4.0)		2 (1.7)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
ALL-CAUSALITY SAEs	203 (56.7)	157 (43.9)	355 (61.6)	259 (45.0)	305 (55.8)	227 (41.5)	57 (47.9)	45 (37.8)
DRUG-RELATED SAEs	104 (29.1)	90 (25.1)	141 (24.5)	106 (18.4)	162 (29.6)	121 (22.1)	27 (22.7)	24 (20.2)
ALL-CAUSALITY AEs LEADING TO DC	100 (27.9)	77 (21.5)	190 (33.0)	141 (24.5)	168 (30.7)	118 (21.6)	17 (14.3)	12 (10.1)
DRUG-RELATED AEs LEADING TO DC	68 (19.0)	54 (15.1)	104 (18.1)	71 (12.3)	118 (21.6)	84 (15.4)	15 (12.6)	12 (10.1)
ALL-CAUSALITY AEs	355 (99.2)	228 (63.7)	568 (98.6)	360 (62.5)	544 (99.5)	357 (65.3)	118 (99.2)	65 (54.6)
DRUG-RELATED AEs	322 (89.9)	159 (44.4)	442 (76.7)	189 (32.8)	509 (93.1)	250 (45.7)	87 (73.1)	38 (31.9)
Most Frequent Drug-related AEs (≥ 15% of Any Grade in any treatment group								
NAUSEA	94 (26.3)	5 (1.4)	57 (9.9)	3 (0.5)	109 (19.9)	8 (1.5)	15 (12.6)	1 (0.8)
Anaemia	80 (22.3)	20 (5.6)	22 (3.8)	8 (1.4)	34 (6.2)	2 (0.4)	8 (6.7)	3 (2.5)
ASTHENIA	73 (20.4)	3 (0.8)	59 (10.2)	8 (1.4)	72 (13.2)	8 (1.5)	6 (5.0)	1 (0.8)
DIARRHOEA	73 (20.4)	14 (3.9)	98 (17.0)	10 (1.7)	145 (26.5)	21 (3.8)	26 (21.8)	2 (1.7)
RASH	64 (17.9)	5 (1.4)	98 (17.0)	9 (1.6)	118 (21.6)	8 (1.5)	13 (10.9)	2 (1.7)
FATIGUE	59 (16.5)	8 (2.2)	83 (14.4)	10 (1.7)	202 (36.9)	23 (4.2)	21 (17.6)	2 (1.7)
DECREASED APPETITE	56 (15.6)	4 (1.1)	76 (13.2)	4 (0.7)	75 (13.7)	7 (1.3)	10 (8.4)	1 (0.8)
HYPOTHYROIDISM	52 (14.5)	1 (0.3)	72 (12.5)	2 (0.3)	85 (15.5)	2 (0.4)	16 (13.4)	1 (0.8)
PYREXIA	20 (5.6)	0	43 (7.5)	2 (0.3)	79 (14.4)	2 (0.4)	18 (15.1)	0
LIPASE INCREASED	18 (5.0)	13 (3.6)	43 (7.5)	23 (4.0)	90 (16.5)	56 (10.2)	10 (8.4)	5 (4.2)

Table 23: Summary of Safety of Nivolumab + Ipilimumab + Chemotherapy in NSCLC vs Nivolumab + Ipilimumab in NSCLC, RCC, and CRC

	NSCLC CA2099LA		NSCLC CA209227		RCC CA209214		CRC CA209142	
	Nivo 360 mg Q3W + Ipi 1 Q6W + Chemo N = 358		Nivo 3 Q2W + Ipi 1 Q6W N = 576		Nivo 3 + Ipi 1 Q3W N = 547		Nivo 3 + Ipi 1 Q3W N = 119	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ALL-CAUSALITY IMMUNE-MEDIATED ADVERSE EVENTS WITHIN 100 DAYS OF LAST DOSE, BY CATEGORY								
Immune-mediated AEs Treated with Immune-modulating medication								
PNEUMONITIS	18 (5.0)	9 (2.5)	50 (8.7)	23 (4.0)	24 (4.4)	9 (1.6)	2 (1.7)	0
DIARRHEA/COLITIS	17 (4.7)	10 (2.8)	48 (8.3)	17 (3.0)	52 (9.5)	25 (4.6)	8 (6.7)	4 (3.4)
HEPATITIS	18 (5.0)	15 (4.2)	46 (8.0)	37 (6.4)	38 (6.9)	32 (5.9)	10 (8.4)	9 (7.6)
NEPHRITIS AND RENAL DYSFUNCTION	5 (1.4)	2 (0.6)	6 (1.0)	2 (0.3)	25 (4.6)	9 (1.6)	2 (1.7)	2 (1.7)
RASH	50 (14.0)	13 (3.6)	106 (18.4)	21 (3.6)	91 (16.6)	18 (3.3)	17 (14.3)	5 (4.2)
HYPERSENSITIVITY/INFUSION REACTIONS	2 (0.6)	0	4 (0.7)	0	7 (1.3)	0	3 (2.5)	0
Immune-Mediated Endocrine AEs Treated with or without Immune-Modulating Medications								
ADRENAL INSUFFICIENCY	12 (3.4)	5 (1.4)	27 (4.7)	13 (2.3)	41 (7.5)	17 (3.1)	7 (5.9)	2 (1.7)
HYPOPHYSITIS	8 (2.2)	5 (1.4)	20 (3.5)	9 (1.6)	25 (4.6)	15 (2.7)	4 (3.4)	3 (2.5)
HYPOTHYROIDISM/THYROIDITIS	53 (14.8)	2 (0.6)	81 (14.1)	4 (0.7)	119 (21.8)	4 (0.7)	18 (15.1)	3 (2.5)
HYPERTHYROIDISM	27 (7.5)	0	50 (8.7)	0	66 (12.1)	4 (0.7)	14 (11.8)	0
DIABETES MELLITUS	0	0	6 (1.0)	5 (0.9)	15 (2.7)	6 (1.1)	0	0
ALL-CAUSALITY OESIs WITHIN 100 DAYS OF LAST DOSE, BY CATEGORY								
with or without Immune-Modulating Medications								
Myasthenic Syndrome	0	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Guillain-Barre Syndrome	0	0	0	0	0	0	0	0
Pancreatitis	5 (1.4)	3 (0.8)	6 (1.0)	4 (0.7)	13 (2.4)	6 (1.1)	1 (0.8)	1 (0.8)
Uveitis	0	0	2 (0.3)	0	2 (0.4)	0	1 (0.8)	1 (0.8)
Encephalitis	2 (0.6)	1 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	1 (0.8)	1 (0.8)
Myocarditis	0	0	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	0	0
Myositis	0	0	2 (0.3)	1 (0.2)	3 (0.5)	1 (0.2)	1 (0.8)	1 (0.8)
Rhabdomyolysis	0	0	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0

MedDRA version 22.0 for CA2099LA and CA209227, MedDRA version 20.0 for CA209214, and MedDRA version 20.0 for CA209142; CTC version 4.0

All events are within 30 days of the last dose of study drug, unless otherwise indicated. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Source: Table 7.3-1 of the SCS, Module 2.7.4[65]

The Applicant's Position:

Safety Profile of Nivolumab + Ipilimumab + Chemotherapy (Nivo+Ipi+Chemo) is Consistent Across First-Line NSCLC Studies: CA2099LA and CA209568 Part 2

In Part 2 of CA209568, subjects with previously untreated stage IV NSCLC were treated with the same nivo+ipi+chemo regimen and schedule (nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy as that in CA2099LA. In this study evaluating the safety of the nivo+ipi+chemo combination as the primary objective, a DLT was reported in 1 subject (out of 36 subjects), with a DLT incidence rate that was less than the protocol defined 'safe' DLT incidence rate of $\leq$ 25% of evaluated subjects. The reported DLT was Grade 3 increased AST and ALT related to ipilimumab. Subject received second cycle of chemotherapy and continued treatment with nivolumab.

Data from all nivo+ipi+chemo-treated subjects in CA2099LA (N = 358) and CA209568 Part 2 (N = 36) showed that the type, frequency, and severity of AEs with the nivo+ipi+chemo regimen was generally consistent across studies and also consistent with the mechanisms of action of each drug in the regimen. No new safety concerns with nivo+ipi+chemo were identified in CA209568 Part 2 (Table 7.1.1-1 of the SCS, Module 2.7.4[65]).

FDA's Assessment:

FDA agrees that the primary objective of Part 2 of CA209568 was to evaluate the safety of nivolumab 360 mg Q3W plus ipilimumab 1 mg/kg Q6W plus 2 cycles of platinum-doublet chemotherapy, which is the same regimen evaluated in CA2099LA. Overall, the type, frequency, and severity of AEs for the nivolumab plus ipilimumab plus chemotherapy regimen were consistent across Studies CA209568 and CA2099LA.

Safety Profile of Nivolumab + Ipilimumab + Chemotherapy is Consistent with the Established Safety Profile of Each Drug in the Regimen

A side-by-side comparison of safety data for nivo+ipi+chemo from CA2099LA, nivo+ipi from CA209227 Part 1, and nivo+chemo from CA209227 Part 2, provided in Table 21 shows that the overall safety profile of nivo+ipi+chemo was consistent with the established safety profile of each drug in the regimen.

- The frequencies of deaths attributed to study drug toxicity were comparable with nivo+ipi+chemo (2.0%), nivo+ipi (1.4%), and nivo+chemo (1.6%).
- Frequencies of all-causality AEs, SAEs (all causality and drug-related), and AEs leading to discontinuation (all causality and drug-related) were similar between nivo+ipi+chemo, nivo+ipi, and nivo+chemo, although the types of AEs differed, which was consistent with the mechanism of action of each regimen. The frequencies of any grade and Grade 3-4 drug-related AEs were similar between nivo+ipi+chemo and nivo+chemo but were lower with nivo+ipi.
  - Rash, diarrhea, and pruritus, AEs typical of immunotherapy, were more frequent with nivo+ipi+chemo and nivo+ipi than with nivo+chemo, whereas nausea and anemia, AEs typical of chemotherapy, were more common with nivo+ipi+chemo and nivo+chemo than with nivo+ipi.
- All-causality and drug-related select AEs in the categories of endocrine, gastrointestinal and skin were reported at higher frequencies with nivo+ipi+chemo and nivo+ipi than with nivo+chemo.

- IMAEs in the categories of endocrine, diarrhea/colitis, hepatitis, and rash were reported at higher frequencies with nivo+ipi+chemo and nivo+ipi than with nivo+chemo.
- OESIs were infrequent across all 3 regimens.

FDA's Assessment:

FDA largely agrees with the data presented in Table 21 regarding the primary reasons of death for patients, however as already discussed in Section 8.2.4 of the Assessment Aid, FDA determined that the cause of death for one patient on the nivolumab plus ipilimumab plus chemotherapy arm in Study CA2099LA that was listed as "other" was actually due to disease progression.

FDA notes that drug-related AEs were not assessed, but rather provides the table below which provides side-by-side comparisons of all-causality AEs for Studies CA2099LA and CA209227. Rash, diarrhea, and pruritus were more frequent with nivo+ipi+chemo, and nivo+ipi compared to nivolumab plus chemotherapy. Nausea and alopecia were more common with nivo+ipi+chemo and Nivo+chemo than with nivo+ipi.

FDA also agrees that other events of special interest were infrequent across all three regimens.

Adverse Reactions in ≥10% of Patients Receiving Nivolumab + Ipilimumab + Chemotherapy vs Nivolumab + Ipilimumab and Nivolumab + Chemotherapy in First-line NSCLC - Studies CA2099LA, CA209227 Part 1 (Arms B +D), and CA209227 Part 2 (Part H)

Adverse Reaction	Nivolumab and Ipilimumab and Platinum-Doublet Chemotherapy CA2099LA (n=358)		Nivolumab and Ipilimumab CA209227 Part 1 Arms B and D (n=576)		Nivolumab and Platinum-Doublet Chemotherapy CA209227 Part 2 Arm H (n=375)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General						
Fatigue[a]	49	5	44	6	40	6
Pyrexia	14	0.6	18	0.5	15	0
Edema[b]	8	0.6	14	0.3	11	0
Musculoskeletal and Connective Tissue						
Musculoskeletal pain[c]	39	4.5	39	3.3	37	2.7
Gastrointestinal						
Nausea	32	1.7	21	1	33	1.3
Diarrhea[d]	31	6	26	3.6	20	2.1
Constipation	21	0.6	18	0.3	22	0.3

Adverse Reaction	Nivolumab and Ipilimumab and Platinum-Doublet Chemotherapy CA2099LA (n=358)		Nivolumab and Ipilimumab CA209227 Part 1 Arms B and D (n=576)		Nivolumab and Platinum-Doublet Chemotherapy CA209227 Part 2 Arm H (n=375)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Vomiting	18	2.0	13	1	14	1.1
Abdominal pain[e]	12	0.6	11	0.2	13	0.8
Skin and Subcutaneous Tissue						
Rash[f]	30	4.7	35	4.7	23	2.4
Pruritus[g]	21	0.8	21	0.5	9	0
Alopecia	11	0.8	1.7	0	11	0.3
Metabolism and Nutrition						
Decreased appetite	28	2.0	31	2.3	27	2.9
Respiratory, Thoracic and Mediastinal						
Cough[h]	19	0.6	23	0.2	21	0.3
Dyspnea[i]	18	4.7	26	4.3	21	2.9
Pneumonia[j]	10	4.5	13	7	13	6
Endocrine						
Hypothyroidism[k]	19	0.3	16	0.5	10	0.3
Nervous System						
Headache	11	0.6	11	0.5	9	0
Dizziness[l]	11	0.6	8	0.2	10	0
Peripheral neuropathy[m]	8	0	6	0.3	17	0.3
Blood and lymphatic system disorders						
Anemia	32	8	12	3.1	45	14
Neutropenia[n]	15	9	1.7	0.3	30	17
Thrombocytopenia[o]	9	3.6	2.1	0.9	22	8
Leukopenia[p]	4.7	1.7	1.0	0.2	14	4.3
Investigations						
Increased Lipase	8	5	10	5	6	3.5

Adverse Reaction	Nivolumab and Ipilimumab and Platinum-Doublet Chemotherapy CA2099LA (n=358)		Nivolumab and Ipilimumab CA209227 Part 1 Arms B and D (n=576)		Nivolumab and Platinum-Doublet Chemotherapy CA209227 Part 2 Arm H (n=375)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased ALT	8	1.1	12	4	12	1.1
Increased AST	6	1.1	12	3.5	11	0.8
Increased Creatinine	6	0.3	6	0.2	11	0.8
Psychiatric Disorders						
Insomnia	6	0.6	10	0	8	0

Source: FDA analysis of sponsor-submitted datasets (ADAE).

[a] Includes fatigue and asthenia

[b] Includes edema, eyelid edema, face edema, generalized edema, localized edema, periorbital edema, and peripheral edema

[c] 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

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

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

[f] 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

[g] Includes pruritus and generalized pruritus

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

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

[j] Includes aspiration pneumonia, bacterial pneumonia, lower respiratory tract infection, lung abscess, lung infection, and pneumonia

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

[l] Includes dizziness, vertigo and positional vertigo

[m] Includes dysesthesia, hyperesthesia, hypoesthesia, neuralgia, paresthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy

[n] Includes decreased neutrophil count and neutropenia

[o] Includes decreased platelet count and thrombocytopenia

[p] Includes decreased white blood cell count and leukopenia

Safety of Nivolumab + Ipilimumab + Chemotherapy and Nivolumab + Ipilimumab Across Tumor Types (NSCLC, RCC, and CRC)

The safety profile of nivo+ipi+chemo in first-line NSCLC (CA2099LA) was consistent with the safety profile of nivo+ipi in other studies/other indications: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W in first-line NSCLC (CA209227 Part 1) and nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W in RCC (CA209214) and in CRC (CA209142) with no new safety concerns (Table 22). Note that there were differences in minimum follow-up across studies: CA2099LA (NSCLC: 6.5 months), CA209227 Part 1 (NSCLC: 28.3 months), CA209214 (RCC: 17.5 months), and CA209142 (CRC: 9 months).

- Deaths attributed to study drug toxicity occurred in ≤ 2% with both nivo+ipi+chemo and nivo+ipi across tumor types.
- All-causality and drug-related SAEs, all-causality and drug-related AEs leading to discontinuation, and all-causality AEs were reported at similar frequencies with nivo+ipi+chemo in CA299LA NSCLC and CA209227 Part 1 NSCLC, RCC, and CRC.
- Drug-related AEs (any-grade and Grade 3-4) were more frequent with nivo+ipi+chemo in CA2099LA NSCLC (89.9% and 44.4%) than with nivo+ipi in CA209227 Part 1 NSCLC (76.7% and 32.8%) and CRC (73.1% and 31.9%), but were similar to nivo+ipi in RCC (93.1% and 45.7%).
- IMAEs and OESIs were reported at similar or lower frequencies with nivo+ipi+chemo in CA2099LA NSCLC relative to nivo+ipi in CA209227 Part 1 NSCLC, RCC, and CRC. Note that drug-related skin select AEs occurred at a similar frequency with nivo+ipi+chemo in CA2099LA NSCLC and nivo+ipi CA209227 Part 1 NSCLC (37.7% vs 34.0%), but they occurred at a higher frequency with nivo+ipi+chemo in CA2099LA NSCLC than with nivo+ipi in CA209142 CRC (37.7% vs 28.6%).

Information to Support Section 5 of the USPI (Warnings and Precautions)

Key findings are as follows (source: Table 7.4-1 of the SCS, Module 2.7.4):

- In NSCLC subjects, any-grade and Grade 3-4 IMAEs were reported at similar or lower frequencies with nivo+ipi+chemo (CA2099LA) than with nivo+ipi (CA209227 Part 1) in all IMAE categories except for the nephritis/renal category (Any-grade: 1.4% vs 1.0%; Grade 3-4: 0.6% vs 0.3%).
- Any-grade and Grade 3-4 IMAEs were reported at lower frequencies with nivo+ipi+chemo (CA2099LA) relative to pooled RCC and CRC in all IMAE categories, except for the pneumonitis category (any-grade: 5.0% vs 3.9%; Grade 3-4: 2.5% vs 1.4%).
- OESIs (regardless of causality or IMM) within 100 days after the last dose were reported at similar or lower frequencies in NSCLC with either nivo+ipi+chemo or nivo+ipi relative to pooled RCC and CRC (source: Table 7.4-2 of the SCS, Module 2.7.4).

Based on these data, no amendments or changes in the Warnings and Precautions sections of the USPI (Section 5) are proposed in the current application.

The FDA's Assessment:

Overall, FDA agrees with the applicant that the safety profile of nivolumab plus ipilimumab plus chemotherapy for the first-line treatment of NSCLC in CA2099LA was consistent with the safety profile of nivolumab plus ipilimumab in other studies for other indications, including nivolumab plus ipilimumab for NSCLC in CA209227 Part 1, renal cell carcinoma (RCC) in CA209214, and colorectal cancer (CRC) in CA209142 with no new safety concerns. While FDA completed an independent review of the data from CA209227 Part 1 for review of this application, FDA relied on prior assessments from the FDA as included in the U.S. prescribing label for OPDIVO when evaluating results from Studies CA209214 and CA209142. FDA agrees that no major amendments to the Warnings and Precautions section of the U.S. prescribing label are necessary. However, FDA proposes to include the rates of pneumonitis for nivolumab plus ipilimumab plus chemotherapy from CA2099LA in Section 5 of the label for OPDIVO as pneumonitis is a particularly relevant adverse event for lung cancer patients, who often have impaired pulmonary function at baseline due to their underlying cancer and other comorbidities such as COPD.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
Not applicable. See Section 8.1.2.

The FDA's Assessment:
FDA also refers to Section 8.1.2.

8.2.7 Safety Analyses by Demographic Subgroups

Data:

Table 24: Drug-related AEs Classified by the Worst CTC Grade and by Age, Gender, Race, and Region - All Treated Subjects - CA2099LA

	Drug-related AEs (n/N [%])					
	Nivo+Ipi+Chemo			Chemo		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Total	322/358 (89.9)	159/358 (44.4)	1/358 (0.3)	304/349 (87.1)	129/349 (37.0)	3/349 (0.9)
By Age						
< 65 yrs	157/174 (90.2)	80/174 (46.0)	0	151/174 (86.8)	57/174 (32.8)	1/174 (0.6)
≥ 65 yrs	165/184 (89.7)	79/184 (42.9)	1/184 (0.5)	153/175 (87.4)	72/175 (41.1)	2/175 (1.1)
≥ 65 and < 75	131/147 (89.1)	61/147 (41.5)	0	124/143 (86.7)	60/143 (42.0)	1/143 (0.7)
≥ 75	34/37 (91.9)	18/37 (48.6)	1/37 (2.7)	29/32 (90.6)	12/32 (37.5)	1/32 (3.1)
≥ 75 and < 85	34/37 (91.9)	18/37 (48.6)	1/37 (2.7)	27/30 (90.0)	11/30 (36.7)	1/30 (3.3)
By Sex						
Male	221/251 (88.0)	107/251 (42.6)	1/251 (0.4)	210/245 (85.7)	83/245 (33.9)	2/245 (0.8)
Female	101/107 (94.4)	52/107 (48.6)	0	94/104 (90.4)	46/104 (44.2)	1/104 (1.0)
By Race						
White	283/319 (88.7)	142/319 (44.5)	1/319 (0.3)	263/307 (85.7)	104/307 (33.9)	2/307 (0.7)
Black or African American	5/5 (100.0)	1/5 (20.0)	0	4/4 (100.0)	3/4 (75.0)	0
Asian	30/30 (100.0)	16/30 (53.3)	0	29/30 (96.7)	17/30 (56.7)	1/30 (3.3)
By Region						
Europe	185/210 (88.1)	96/210 (45.7)	0	171/206 (83.0)	67/206 (32.5)	1/206 (0.5)
North America	34/36 (94.4)	14/36 (38.9)	0	27/27 (100.0)	12/27 (44.4)	1/27 (3.7)

	Drug-related AEs (n/N [%])					
	Nivo+Ipi+Chemo			Chemo		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Rest of the World	75/84 (89.3)	34/84 (40.5)	1/84 (1.2)	77/86 (89.5)	33/86 (38.4)	0
Asia	28/28 (100.0)	15/28 (53.6)	0	29/30 (96.7)	17/30 (56.7)	1/30 (3.3)

MedDRA Version: 22.0; CTC Version 4.0; Includes events reported between first dose and 30 days after last dose of study therapy.
Source (ADaM datasets): Table 6.1.32.1 (adae.xpt, adsl.xpt; total); Table 6.1.5.7 (adae.xpt;, adsl.xpt; age); Table 6.1.5.5 (adae.xpt, adsl.xpt; sex), Table 6.1.5.6 (adsl.xpt, adsl.xpt; race), Table 6.1.5.8 (8 (adae.xpt, adsl.xpt; region) of the CA2099LA Final CSR

The Applicant's Position:

The frequencies of all-causality AEs (Table 6.1.5.1, Table 6.1.5.3, and Table 6.1.5.4 [ADaM datasets: adae.xpt, adsl.xpt] in the CA2099LA Final CSR) and drug-related AEs in the nivo+ipi+chemo arm for subgroups of age, gender, and geographic region were similar to the AE frequencies reported for the overall study populations by treatment.

No overall difference in all-causality AEs (Table 6.1.5.3 [ADaM datasets: adae.xpt, adsl.xpt] in the CA2099LA Final CSR) and drug-related AEs (Table 24) was reported in older subjects compared with younger subjects treated with nivo+ipi+chemo. However, the frequency of AEs leading to discontinuation with nivo+ipi+chemo were higher in subjects ≥ 75 years of age (43.2%) compared with: subjects < 65 years (25.3%), subjects ≥ 65 and < 75 years (27.2%), and all subjects treated with nivo+ipi+chemo (27.9%) (Table 6.1.6.1 [ADaM datasets: adae.xpt, adsl.xpt] in the CA2099LA Final CSR).

Both treatment arms had higher frequencies of SAEs with fatal (death) outcome in the 75-84 years age subgroup relative to the overall population (nivo+ipi+chemo 29.7% vs 12.8%; chemotherapy 26.7% vs 14.3%) (Table 5.1.1-1 in the SCS, Module 2.7.4). Interpretation of these data is limited by small numbers of subjects in the 75-84 years age subgroup (n = 37 in the nivo+ipi+chemo arm and n = 30 in the chemotherapy arm).

For subgroups based on race, most participants were clustered in a single category (White) (Table 6.1.5.6 [ADaM datasets: adsl.xpt, adsl.xpt] in the CA2099LA Final CSR). Very low sample sizes in other categories of race limit the interpretability of potential differences.

Among all nivo+ipi+chemo treated subjects in CA2099LA, the frequencies of all-causality and drug-related Grade 3-4 AEs in the North American region (63.9% [23/36] all causality and 38.9% [14/36] drug-related) were generally consistent with those in other regions (Europe, Asia, and Rest of World) and those in the all-treated population (63.7% [228/358] all causality and 44.4% [159/358] drug-related) (Appendix 1 of the Clinical Overview, Module 2.7.5). The frequencies of all-causality and drug-related AEs in the chemotherapy arm for the subgroup of geographic region were similar to the AE frequencies reported for the overall study populations by treatment.

These differences do not alter the overall safety profile of nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy or 4 cycles of platinum-doublet chemotherapy in these subgroups.

The FDA's Assessment:

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 nivolumab with ipilimumab and chemotherapy (24%). (FDA notes that the applicant reports that 27.9%, as opposed to 24%, of all patients who received nivo+ipi+chemo in CA2099LA discontinued treatment due to adverse reactions. After discussion of this discrepancy with the applicant, this likely represents events of cancer progression being misclassified as AEs by the applicant for this analysis.) Alternatively, the discontinuation rate due to adverse reactions was similar for patients aged 75 years or older who received chemotherapy only (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 nivolumab in combination with ipilimumab and platinum-doublet chemotherapy in CA2099LA, 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; for the 37 patients 75 years or older, the hazard ratio for overall survival was 1.21 (95% CI 0.69, 2.12). It should be noted this sub-group analysis is limited by the small number of patients who are 75 years older.

FDA agrees that most patients in CA2099LA were White, limiting the interpretability of results when evaluating for differences in safety and AEs between races of patients.

Overall, the safety of nivolumab plus ipilimumab plus chemotherapy in CA2099LA did not vary significantly across demographic subgroups.

8.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position: Not applicable

The FDA's Assessment:
Not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:
There were no new findings related to human carcinogenicity for nivolumab and ipilimumab in study CA2099LA.

The FDA's Assessment:
FDA agrees with the applicant's statement.

Human Reproduction and Pregnancy

The Applicant's Position:

In CA2099LA, pregnancy tests were negative during the study in all but 1 female subject of childbearing potential (Appendix 7.3.1 in the CA2099LA Final CSR). One subject had a positive pregnancy test during the study which was retested after 5 days and was then negative. There is no new information to report for use of nivolumab and/or ipilimumab in pregnancy or lactation.

The FDA's Assessment:

FDA agrees with the applicant's statement.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable as the study was in adult patients 18 years or older.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There is no information on overdose or drug abuse. No cases of withdrawal symptoms related to nivolumab and/or ipilimumab were reported during human clinical trials. Nivolumab and/or ipilimumab has minor influence on the ability to drive and use machines. Fatigue is a very common side effect which may also impair the ability to drive and use machines. Patients should be advised not to drive or use machines if they feel tired.

The FDA's Assessment:

FDA agrees with the applicant's position.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Nivolumab

Based on pharmacovigilance activities conducted by BMS Worldwide Patient Safety, review of postmarketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab. The safety profile of nivolumab in the postmarketing setting supports the favorable benefit-risk profile of nivolumab established during clinical trials. Postmarketing data for nivolumab are subject to continued active pharmacovigilance monitoring and are reported as per applicable post-marketing safety reporting requirements, as well as periodically to global health authorities.

Ipilimumab

Based on pharmacovigilance activities conducted by BMS Worldwide Patient Safety, review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for ipilimumab. The safety profile of ipilimumab in the post-marketing setting supports the benefit-risk profile of

ipilimumab established during clinical trials. Qualitative and quantitative safety information received to date does not raise any significant new safety concerns or substantially alter the overall known safety profile of ipilimumab as described in the prescribing information.

Nivolumab + Ipilimumab

Based on pharmacovigilance activities conducted by BMS Worldwide Patient Safety, review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab + ipilimumab. The safety profile of nivolumab + ipilimumab in the post-marketing setting supports the favorable benefit-risk profile of nivolumab + ipilimumab established during clinical trials.

For additional details and context of the marketing history of nivolumab and ipilimumab, see Section 3.1.

The FDA's Assessment:
FDA agrees with the applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:
Not applicable

The FDA's Assessment:
Neither post-marketing requirements nor post-marketing commitments for safety are expected in the post-marketing setting for CA2099LA.

8.2.11 Integrated Assessment of Safety

The Applicant's Position:

Safety data from 358 subjects from CA2099LA and 36 subjects from CA209568 Part 2 demonstrate that the safety profile of nivo+ipi+chemo is manageable and reflective of the known safety profiles of the immunotherapy and chemotherapy components as first-line therapy for NSCLC. The addition of 2 cycles of chemotherapy to nivo+ipi did not result in new safety signals relative to the well-established safety profile of nivo+ipi in first-line NSCLC, which is based on over 1,200 subjects (576 subjects from CA209227 Part 1 with a minimum follow up of 29.3 months,[30] 288 subjects from CA209568 Part 1,[66] 39 subjects from CA209012 Cohort Q,[67] and 391 subjects from CA209817 Cohort A[68]) In addition, the safety profile of nivo+ipi+chemo in first-line NSCLC (CA2099LA) was consistent with the safety profile of nivo+ipi in other indications: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W in RCC (CA209214) and in CRC (CA209142).

Risk Management Plans for OPDIVO and YERVOY are included in this application dossier, and include information concerning the addition of the new indication for nivo+ipi+chemo in first-line NSCLC. No new safety signal is reported, and no changes in risk minimization measures are warranted as per new pivotal study data, and safety data provided.

In summary, the totality of the safety data support the use of nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of platinum-doublet chemotherapy combination therapy, followed by nivolumab

360 mg Q3W + ipilimumab 1 mg/kg Q6W, as first-line treatment of patients with metastatic or recurrent NSCLC.

The FDA's Assessment:
FDA agrees with the applicant's integrated assessment of safety. Overall, the safety profile of the combination of nivolumab plus ipilimumab plus platinum-doublet chemotherapy is consistent with the known safety profile of each of the agents. No new safety issues were identified.

SUMMARY AND CONCLUSIONS

The FDA's Assessment:

8.3 Statistical Issues

While the submitted data from the pre-specified interim analysis met its primary OS endpoint (HR: 0.69 (96.71% CI: 0.55, 0.87); p-value=0.0006) and through hierarchical testing, was supported by secondary endpoints PFS per BICR (HR: 0.70 (97.48%CI: 0.57, 0.86); p-value=0.0001) followed by ORR per BICR (37.7% vs. 25%; p-value 0.0003) , there was concern regarding non-proportionality as characterized by the diminishing effect in the tails of the Kaplan-Meier survival curves due to a higher mortality rate (per FDA's analysis) in the experimental arm relative to the control arm at approximately 12 months. However upon review of mature OS data, submitted upon FDA request, we no longer have this concern as the behavior of the OS Kaplan-Meier curves does not appear to contradict proportionality, while still providing evidence of survival advantage (HR: 0.66 (95% CI: 0.55, 0.80)).

X X

Flora Mulkey
Primary Statistical Reviewer

Lisa Rodriguez
Statistical Team Leader

X X

Paz Vellanki
Primary Clinical Reviewer

Adnan Jaigirdar
Clinical Team Leader

The FDA's Assessment:

8.4 Conclusions and Recommendations

Study CA2099LA is a global, multicenter, randomized, open-label trial of 719 patients with advanced, unresectable, recurrent or metastatic NSCLC who were previously untreated for recurrent or metastatic NSCLC. Patients were randomized 1:1 to nivolumab plus ipilimumab plus two cycles of platinum-doublet chemotherapy or 4 cycles of platinum-doublet chemotherapy. Treatment with nivolumab plus ipilimumab plus chemotherapy demonstrated statistically significant and clinically meaningful improvement in the primary efficacy outcome (overall survival) over four cycles of platinum-doublet chemotherapy; the alpha-controlled key secondary endpoints (PFS per BICR and ORR per BICR) were also statistically significant favoring treatment with nivolumab plus ipilimumab plus chemotherapy. The safety profile of nivolumab plus ipilimumab plus chemotherapy is acceptable for the intended population, and is manageable with product labeling. Based on a favorable risk-benefit assessment of nivolumab plus ipilimumab plus chemotherapy, the FDA review teams recommend regular approval for the following indication:

Nivolumab (OPDIVO) in combination with ipilimumab (YERVOY) and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), without EGFR or ALK genomic tumor aberrations.

9 Advisory Committee Meeting and Other External Consultations

10 Pediatrics

The Applicant's Position:
Nivolumab in combination with ipilimumab and chemotherapy was not studied in pediatric patients with NSCLC, as this disease occurs mainly in adults and rarely in children. Due to the low incidence in the pediatric population, BMS submitted full disease specific waivers from the pediatric study (PREA) requirements for nivolumab (FDA Agreement letter for Initial Pediatric Study Plan [iPSP-12] received 18-Nov-2019).

The FDA's Assessment:
FDA agrees with the applicant.

11 Labeling Recommendations

Data:

Table 25: Summary of Significant Labeling Changes (High level changes and not direct quotations)

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
INDICATIONS AND USAGE (1.3)	Addition of indication for OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for the first line treatment of patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.	FDA added "adult" patients to the indication statement.
DOSAGE AND ADMINISTRATION (2.1)	Addition of dose dosage recommendation for ODPVIO in combination with ipilimumab and 2 cycles of histology-based platinum doublet chemotherapy and associated text related to the addition of this treatment regimen.	Overall, FDA agreed with the applicant's proposed labeling. To highlight that only two cycles of chemotherapy are a part of this treatment regimen, FDA recommended that text describing this was bolded in the label.
ADVERSE REACTIONS (6.1)	Addition of clinical safety data from the CA2099LA study, including: a brief description of the inclusion/exclusion criteria of the study; duration of therapy; patient demographics; a brief summary of the serious and most common adverse reactions; a table of the adverse reaction occurring at an incidence of 10% or greater; and a table of laboratory abnormalities occurring at an incidence of 20% or greater.	FDA recommended the following revisions: • Addition of CHECKMATE-9LA as one of the trials used to provide data in Section 5 of the label (Warnings an Precautions) as FDA proposes that rates of pneumonitis reported in CHECKMATE-9LA are included. • Inclusion of a summary of the fatal adverse events for patients treated with nivolumab plus ipilimumab plus chemotherapy. • FDA grouped MedDRA preferred terms when reporting AEs and SAEs and recommended that the label was updated to reflect these grouped terms. • Rates of permanent discontinuation of nivolumab plus ipilimumab plus chemotherapy were modified to exclude events of cancer progression which were misclassified as adverse events.

ADVERSE REACTIONS (6.2)	Addition of a brief summary of immunogenicity data arising from the CA2099LA study, including incidence rate of anti-nivolumab antibodies and neutralizing antibodies against nivolumab.	FDA recommended stylistic changes to the text but overall agreed with the applicant's data and summary.
USE IN SPECIFIC POPULATIONS (8.5)	Addition of information related to patients 65-years-of-age and older arising from the CA2099LA study, including a statement regarding discontinuation rates in patients 75-years-of-age and older.	For comparison, FDA included a statement regarding discontinuation of chemotherapy for patients 75 years and older. Additionally, FDA recommended including hazard ratios for overall survival to compare efficacy of nivolumab plus ipilimumab plus chemotherapy across age groups for patients less than 65 years old, 65 years and older, and 75 years and older.
CLINICAL PHARMACOLGY (12.3)	Addition of Pharmacokinetic information arising from the CA2099LA study, including relative nivolumab and ipilimumab clearance information.	FDA recommended describing less than 20% change in clearance (CL) of nivolumab as "unchanged".
CLINICAL STUDIES (14.3)	Addition of clinical efficacy data from the CA2099LA study, including: a brief description of the study design and treatment groups; inclusion/exclusion criteria of the study; patient demographics; primary and key secondary efficacy endpoints presented in a table; and a Kaplan-Meier plot of overall survival.	FDA recommended the following revisions: • Inclusion of updated overall survival data. • Exchange of the Kaplan-Meier curve for overall survival using data from the primary analysis with data from the updated analysis. • (b) (4)

Other Prescription Drug Labeling for OPDIVO:

The OPDIVO Medication Guide was updated to include the following additional information in patient-friendly language:

- Under "What is OPDIVO" - Addition of a description of the proposed non-small lung cancer indication, consistent with the proposed indication in the Full Prescribing Information.
- Under "How will I receive OPDIVO" - Addition of a description of the dosage and administration information for the non-small cell lung cancer indication, consistent with the dosage and administration information in the Full Prescribing Information.
- Under "What are the possible side-effects of OPDIVO" - Addition of a list of the most common adverse reactions observed in the study supporting the non-small cell lung cancer indication, consistent with the adverse reactions information in the Full Prescribing Information.

The Applicant's Position:
The clinical data provided in this supplemental BLA submission demonstrate the clinical benefit and safety of the use of nivolumab in combination with ipilimumab and 2 cycles of chemotherapy for the treatment of patients with previously untreated metastatic or recurrent NSCLC. Based on these data, the table above provides a high-level summary of the proposed changes to the labeling for OPDIVO (nivolumab).

The FDA's Assessment:
FDA proposed the revisions to the prescribing label as indicated in the table above. For the OPDIVO Medication Guide, FDA recommended the following indication statement:

OPDIVO is a prescription medication used to treat people with a type of advanced stage lung cancer called non-small cell lung cancer (NSCLC).

- *OPDIVO may be used in combination with ipilimumab 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.*

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
No REMS are indicated.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
As the applicant has submitted the final overall survival analysis and other updated efficacy results with

the associated datasets for Study CA2099LA, there are no post-marketing requirements or commitments for this supplemental application.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

X

X

X

X

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Appendices

18.1 References

The Applicant's References:
References are provided in Section 18.6.

The FDA's References:

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Reck M, *et al*. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019; 37:537-546.

Gadgeel SM, *et al*. Updated Analysis from KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2020; 38(14): 1505-1517.

18.2 Financial Disclosure

The Applicant's Position:
Financial interests or arrangements with clinical investigators have been disclosed in the table below. Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the CA2099LA clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators*.

The FDA's Assessment:
FDA reviewed the financial disclosures below and has no concerns.

Covered Clinical Study (Name and/or Number):* CA2099LA

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 983		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

18.3 Nonclinical Pharmacology/Toxicology

Not applicable.

18.4 OCP Appendices (Technical documents supporting OCP recommendations)

(b) (4)

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From an efficacy perspective, the E-R analyses for efficacy showed that baseline body weight was not a significant covariate for overall survial (OS) and the relationship between nivolumab exposure (Cavg1) and OS is flat in the nivolumab Cavg1 range of 25.7 - 54.8 µg/mL.

Therefore, FDA agrees with the Applicant that there is no concern of overdosing in patients with low body weight and under-dosing in patients with high body weight with the flat dose of nivolumab 360 mg Q3W.

18.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment: No additional safety analyses were conducted by the FDA other than what was already described above in the assessment aid.

18.6 Additional Meetings Conducted by FDA and other Regulatory Agencies (Project Orbis)

The FDA's Assessment:

In review of this application and assessment aid, the FDA held additional meetings and collaborated with the (b) (4) and Singapore's Health Sciences Authority (HSA) as part of Project Orbis as outlined below.

- On April 17, 2020, the FDA held the first Project Orbis meeting the Regulatory Agencies listed above to discuss the overall efficacy results submitted in the application. In addition to Sections 7 and 8.1 from the assessment aid, additional topics discussed during this meeting include the following:
  - Observed clinical benefit from Study CA2099LA (CheckMate-9LA)
  - Proportionality of OS Kaplan-Meier curves and review of additional 4.6-month follow-up results
  - Efficacy assessment in subgroups and
  - Assessment of contribution of components
- On April 29, 2020, FDA held the second Project Orbis meeting to discuss the safety results and overall safety consideration for this application. Along with Section 8.2 from the assessment aid, the following safety topics were discussed at this meeting:
  - Discussion whether two cycles of chemotherapy change the known safety profile of nivolumab and ipilimumab
  - Treatment Emergent Adverse Events (TEAEs), across trial CA2099LA and CA209227
  - Comparison of Serious Adverse Events (SAE) ≥2% in trial CA2099LA and CA209227
  - Immune-mediated adverse events, and other events of special interest
  - Reasons for treatment discontinuation
  - Summary of deaths and TEAEs resulting in death
  - Safety assessments in subgroups and demographics

- The final Project Orbis meeting was held on May 4, 2020 to discuss additional safety considerations related to immune mediated toxicities, acute kidney injury, and review of the final product label.

(b) (4)

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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Yi-bo Wang	Office of Clinical Pharmacology/ Division of Clinical Pharmacology V	Sections: 6	**Select one:** x Authored ___ Approved
	Signature: Yibo Wang -S Digitally signed by Yibo Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yibo Wang -S, 0.9.2342.19200300.100.1.1=2001497124 Date: 2020.05.22 22:35:56 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	Office of Clinical Pharmacology/ Division of Clinical Pharmacology V	Sections:	**Select one:** X Authored X Approved
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Pharmacometrics Reviewer	Yuan Xu	Office of Clinical Pharmacology/ Division of Clinical Pharmacology V	Sections: 6	**Select one:** x Authored ___ Approved
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Pharmacometrics Team Leader	Jiang Liu	Office of Clinical Pharmacology/ Division of Clinical Pharmacology V	Sections: 6	**Select one:** x Authored x Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.05.23 11:04:08 -04'00'			
Clinical Reviewer	Paz Vellanki	Office of Oncologic Disease/Division of Oncology 2	Sections: 1.1, 1.2, 1.4, 2, 3, 4, 5, 7, 8, 11, 12, 13	**Select one:** X Authored ___ Approved
	Signature: Paz J. Vellanki -S Digitally signed by Paz J. Vellanki -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002846954, cn=Paz J. Vellanki -S Date: 2020.05.26 07:40:47 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Flora Mulkey	Office of Biostatistics/Division of Biometrics V	Sections: 7, 8	**Select one:** X Authored ___ Approved
	Signature: Flora M. Mulkey -S Digitally signed by Flora M. Mulkey -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001984421, cn=Flora M. Mulkey -S Date: 2020.05.23 07:20:00 -04'00'			
Statistical Team Leader	Lisa Rodriguez	Office of Biostatistics/Division of Biometrics V	Sections: 7, 8	**Select one:** ___ Authored X Approved
	Signature: Lisa R. Rodriguez -S Digitally signed by Lisa R. Rodriguez -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001011155, cn=Lisa R. Rodriguez -S Date: 2020.05.26 10:03:17 -04'00'			
Deputy Division Director (OB)	Yuan-Li Shen	Office of Biostatistics/Division of Biometrics V	Sections: 7, 8	**Select one:** ___ Authored X Approved
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Associate Director for Labeling (ADL)	Ann Marie Trentacosti (acting ADL)	Office of New Drugs Policy/Division of Clinical Policy/Labeling Policy Team	Sections: 11	**Select one:** X Reviewed ___ Approved
	Signature: Ann M. Trentacosti -S Digitally signed by Ann M. Trentacosti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300216343, cn=Ann M. Trentacosti -S Date: 2020.05.24 09:29:00 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Adnan Jaigirdar	Office of Oncologic Disease/Division of Oncology 2	Sections: All	**Select one:** X Authored X Approved
	Signature: Adnan A. Jaigirdar -S Digitally signed by Adnan A. Jaigirdar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000999266, cn=Adnan A. Jaigirdar -S Date: 2020.05.26 07:45:07 -04'00'			
Division Director (Clinical)	Harpreet Singh	Office of Oncologic Disease/Division of Oncology 2	Sections: All	**Select one:** X Authored X Approved
	Signature: Bonnie H. Moore -S Digitally signed by Bonnie H. Moore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001042285, cn=Bonnie H. Moore -S Date: 2020.05.23 13:37:35 -04'00'			

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s082 and 125377Orig1s110

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 18, 2020

To: Kwadwo Korsah, PharmD, MS, Regulatory Project Manager
Division of Oncology 2 (DO2)

Ann Marie Trentacosti, M.D., Associate Director for Labeling, DO2

From: Adesola Adejuwon, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for YERVOY® (ipilimumab) injection, for intravenous use

BLA: 125377/Supplement 110

OPDP received a DO2 consult request dated March 4, 2020 for the proposed product labeling (PI) and Medication Guide for YERVOY® (ipilimumab) injection, for intravenous use (Yervoy). This supplement (S-110) proposes a new indication in combination with nivolumab and 2 cycles of platinum-based chemotherapy, for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

Reference is made to DO2's consult request dated March 4, 2020, for BLA 125554/S-82 for OPDIVO® (nivolumab) injection, for intravenous use (Opdivo) and consult response dated May 4, 2020. Reference is also made to the combined OPDP and Division of Medical Policy Programs (DMPP) review of the proposed Medication Guide for Opdivo consult response dated May 1, 2020.

Per email correspondence from DO2 (Kwadwo Korsah) dated April 24, 2020, DO2 would revise the Yervoy PI and Medication Guide to include all changes agreed to during the review of the Opdivo PI and Medication Guide.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at (240) 402-5773 or Adesola.Adejuwon@fda.hhs.gov.

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ADESOLA F ADEJUWON
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 4, 2020

To: Kwadwo Korsah, PharmD, MS, Regulatory Project Manager
Division of Oncology 2 (DO2)

Ann Marie Trentacosti, M.D., Associate Director for Labeling, (DO2)

From: Adesola Adejuwon, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for OPDIVO® (nivolumab) injection, for intravenous use

BLA: 125554/Supplement 082

In response to DO2 consult request dated March 4, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for OPDIVO® (nivolumab) injection, for intravenous use (Opdivo). This supplement (S 082) proposes a new indication for the use of nivolumab, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DO2 (Kwadwo Korsah) on April 24, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on May 1, 2020.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at (240) 402-5773 or Adesola.Adejuwon@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 1, 2020
To:	Kwadwo Korsah, PharmD, MS Regulatory Project Manager **Division of Oncology 2 (DO 2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route, Application Type/Number, Applicant	OPDIVO (nivolumab) injection, for intravenous use BLA 125554/S-082, Bristol-Myers Squibb Company YERVOY (ipilimumab) injection, for intravenous use BLA 125377/S-110, Bristol-Myers Squibb Company

1 INTRODUCTION

On February 6, 2020, Bristol-Myers Squibb Company simultaneously submitted for the Agency's review two Prior Approval Supplements (PAS)- Efficacy to their approved Biologics License Application BLA 125554/S-082 for OPDIVO (nivolumab) injection and BLA 125377/S-110 for YEROVY (ipilimumab) injection, respectively.

With BLA 125554/S-082, the Applicant proposes OPDIVO (nivolumab) injection in combination with ipilimumab, and 2 cycles of platinum-based chemotherapy, for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations, based on the results of Phase 3 study CCA2099LA.

With BLA 125377/S-110, the Applicant proposes YERVOY (ipilimumab) injection in combination with nivolumab, and 2 cycles of platinum-based chemotherapy, for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic aberrations, based on the results of Phase 3 study CCA2099LA.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 2 (DO 2) on March 4, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guides (MG) for OPDIVO (nivolumab) injection and YERVOY (ipilimumab) injection. On April 24, 2020 DO 2 notified DMPP and OPDP that all agreed upon changes to the OPDIVO (nivolumab) injection S-082 labeling will be applied to the YERVOY (ipilimumab) injection S-110 labeling. Therefore, only a review of the OPDIVO (nivolumab) injection MG is needed at this time.

2 MATERIAL REVIEWED

- Draft OPDIVO (nivolumab) injection MG received on February 6, 2020 and revised on March 23, 2020, and received by DMPP on April 24, 2020.
- Draft OPDIVO (nivolumab) injection Prescribing Information (PI) received on February 6, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on April 24, 2020.
- Approved OPDIVO (nivolumab) labeling dated March 10, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
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