CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125554Orig1s080

Trade Name:	OPDIVO
Generic or Proper Name:	nivolumab
Sponsor:	Bristol-Myers Squibb Compnay
Approval Date:	May 15, 2020
Indication:	OPDIVO is a programmed death receptor-1 (PD-1) blocking antibody indicated for the 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 ipilimumab.

CENTER FOR DRUG EVALUATION AND RESEARCH

125554Orig1s080

CONTENTS

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)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s080

APPROVAL LETTER

BLA 125554/S-80

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Hsiao-Ling Hung, Ph.D.
Director, Global Regulatory Lead, Global Regulatory Strategy & Policy
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Dr. Hung:

Please refer to your supplemental biologics license application (sBLA), dated November 15, 2019, 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 Opdivo in combination with ipilimumab, for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test 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,

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

and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

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

The SPL will be accessible via publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this application because studies are impossible or highly impracticable for the for the first-line treatment of adult patients with metastatic or recurrent NSCLC whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test 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 Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Harpreet, Singh, M.D.
Acting, Division Director
Division of Oncologic Diseases 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- 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

---

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
05/15/2020 12:43:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s080

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:

- 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)
- 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)
- 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)
-
- patients with metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy.[a] (1.4)
- 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)
- 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.
- 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)
- 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)
- 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)
- 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 as an intravenous infusion over 30 minutes.
- 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
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 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)

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.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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

Revised: 5/2020

- Lactation: Advise not to breastfeed. (8.2)

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 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/CompanionDiagnostics.

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) Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity

The recommended dosages of OPDIVO in combination with ipilimumab are presented in Table 2. Refer to the ipilimumab Prescribing Information for recommended ipilimumab dosage information.

Table 2: Recommended Dosages of OPDIVO in Combination with Ipilimumab

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
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
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)	

Table 2: Recommended Dosages of OPDIVO in Combination with Ipilimumab

Indication	Recommended OPDIVO Dosage	Duration of Therapy
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	Withhold dose[c]

Table 3: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
	• 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	
	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
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).
- When administered with ipilimumab, administer OPDIVO first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not coadminister 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.

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; and OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks (n=576) in patients enrolled in CHECKMATE-227.

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).

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 14 and 15 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-057.

Table 14: 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 15: 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 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-025.

Table 16: 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 16: 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 17: 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 18 and 19 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in >15% of OPDIVO and ipilimumab-treated patients in CHECKMATE-214.

Table 18: 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 18: 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 19: 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 20 and 21 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-205 and CHECKMATE-039.

Table 20: 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
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 21 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 21: 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

Table 21: 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]
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 22 and 23 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-275.

Table 22: 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

Table 22: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275

Adverse Reaction	OPDIVO (n=270)	
	All Grades (%)	Grades 3-4 (%)
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 23: 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 24 and 25 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 24: 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 25: 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 26 and 27 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 26: 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 26: 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 27: 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
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.

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)]*.

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 was administered in combination with ipilimumab 3 mg/kg, 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 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.

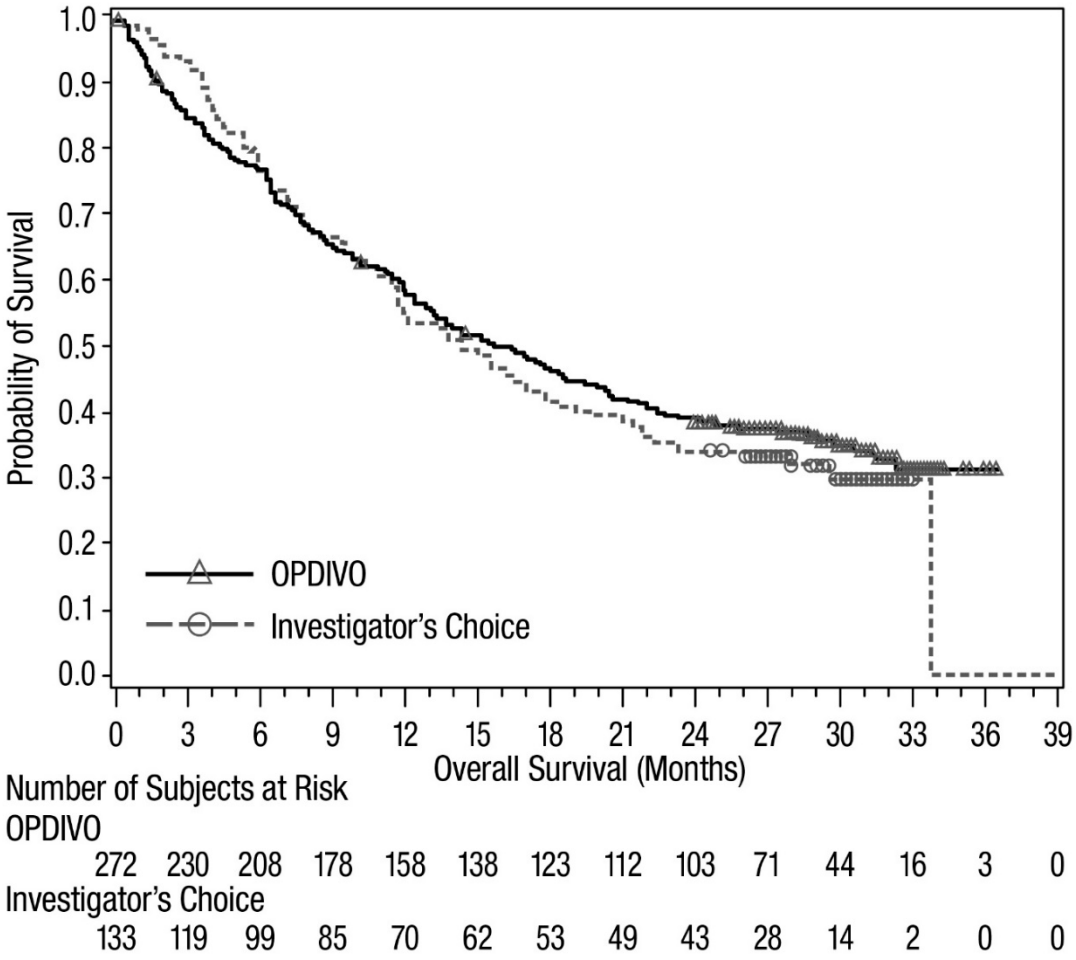
Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in CHECKMATE-037 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed overall response rate (ORR) 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%).

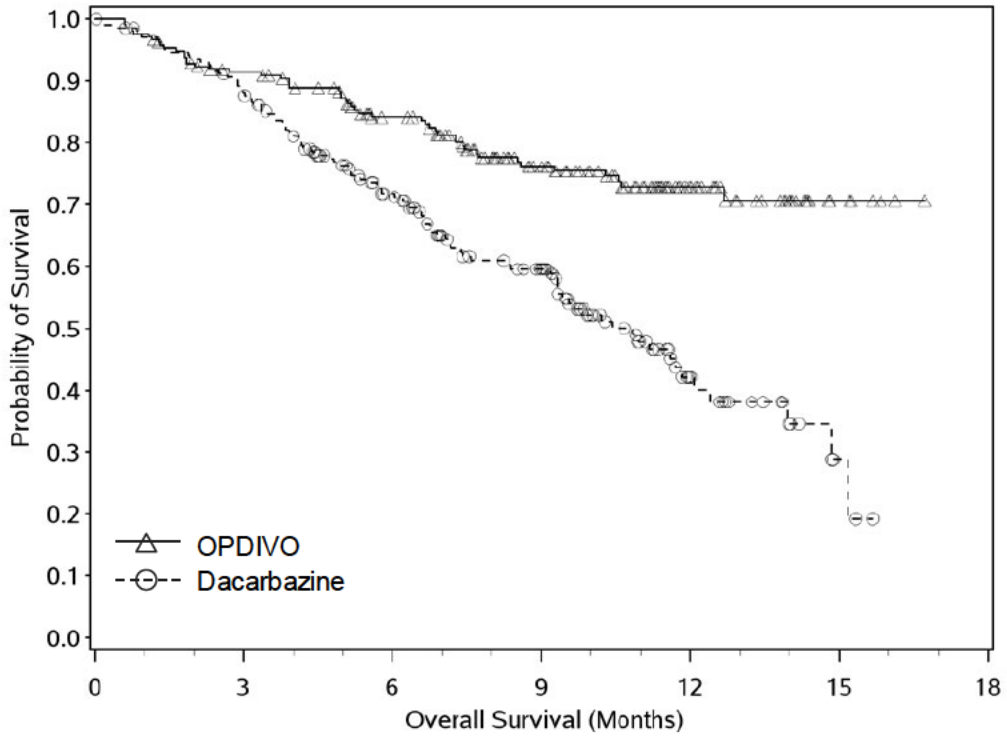
CHECKMATE-066 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. At the time of analysis, 88% (63/72) of OPDIVO-treated patients had ongoing responses, which included 43 patients with ongoing response of 6 months or longer. Efficacy results are shown in Table 28 and Figure 2.

Table 28: 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%).

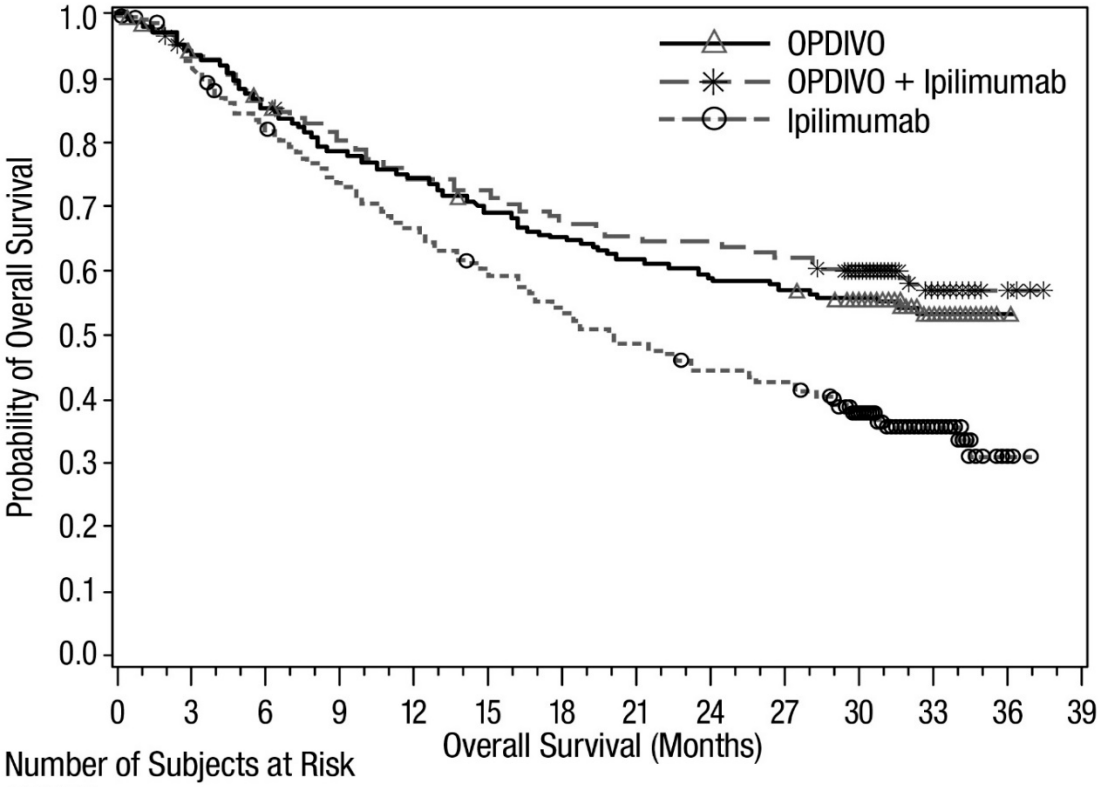
CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. The trial was not designed to assess whether adding ipilimumab to OPDIVO improves PFS or OS compared to OPDIVO as a single agent. Efficacy results are shown in Table 29 and Figure 3.

Table 29: 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%).

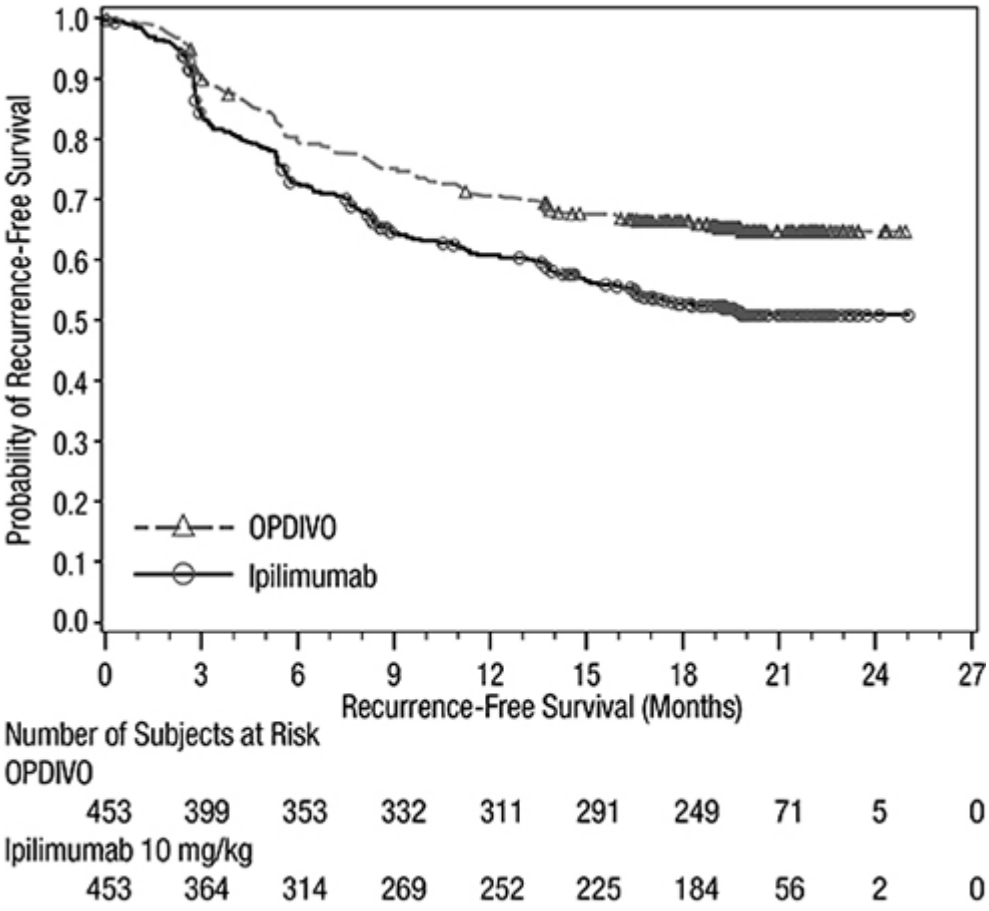
CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the ipilimumab 10 mg/kg arm. Efficacy results are shown in Table 30 and Figure 4.

Table 30: 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 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 31 and Figure 5.

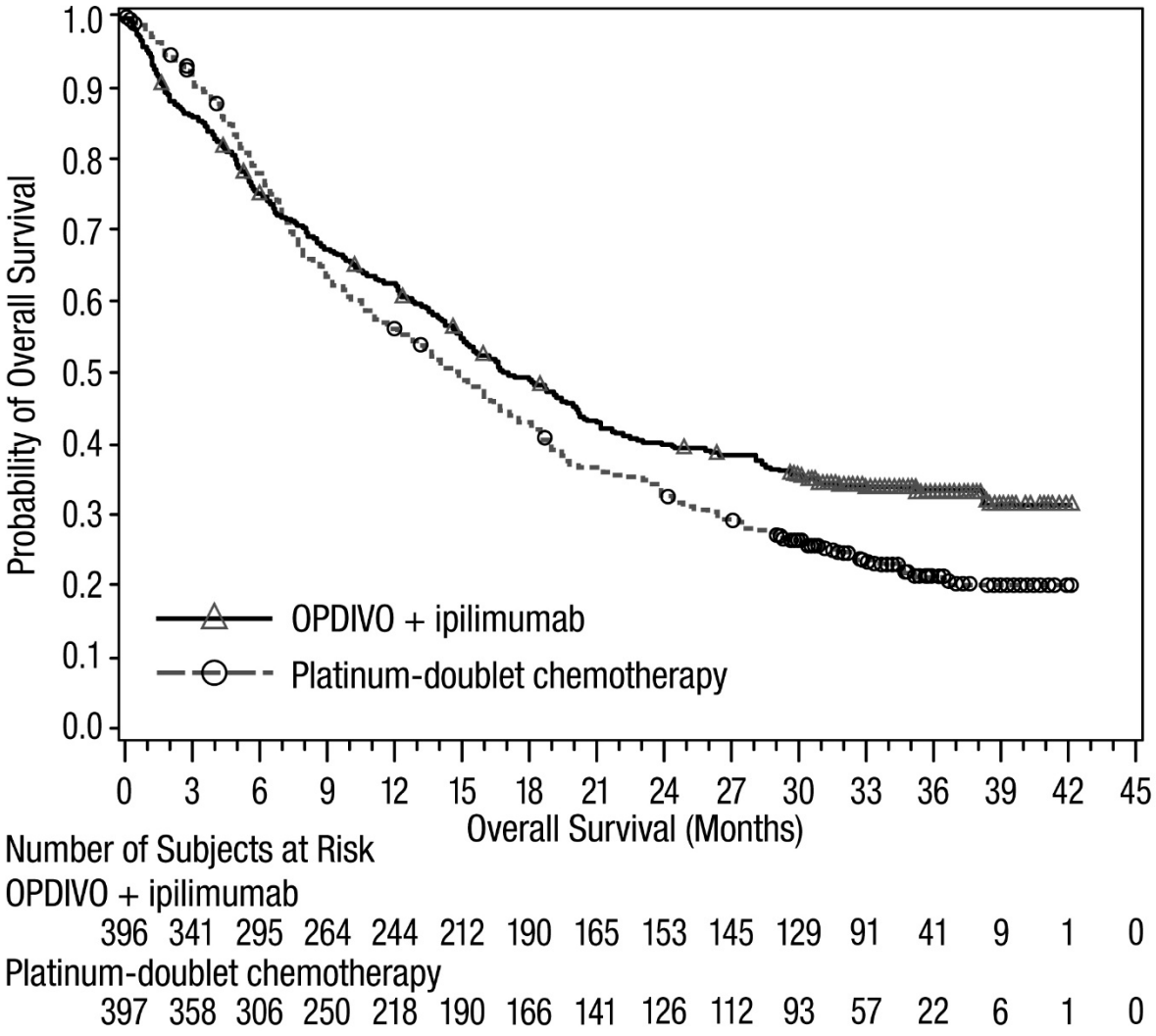
Table 31: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	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.

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 32 and Figure 6.

Table 32: 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

Table 32: Efficacy Results - CHECKMATE-017

	OPDIVO (n=135)	Docetaxel (n=137)
Hazard ratio (95% CI)[a]	0.62 (0.47, 0.81)	
p-value[b]	0.0004	

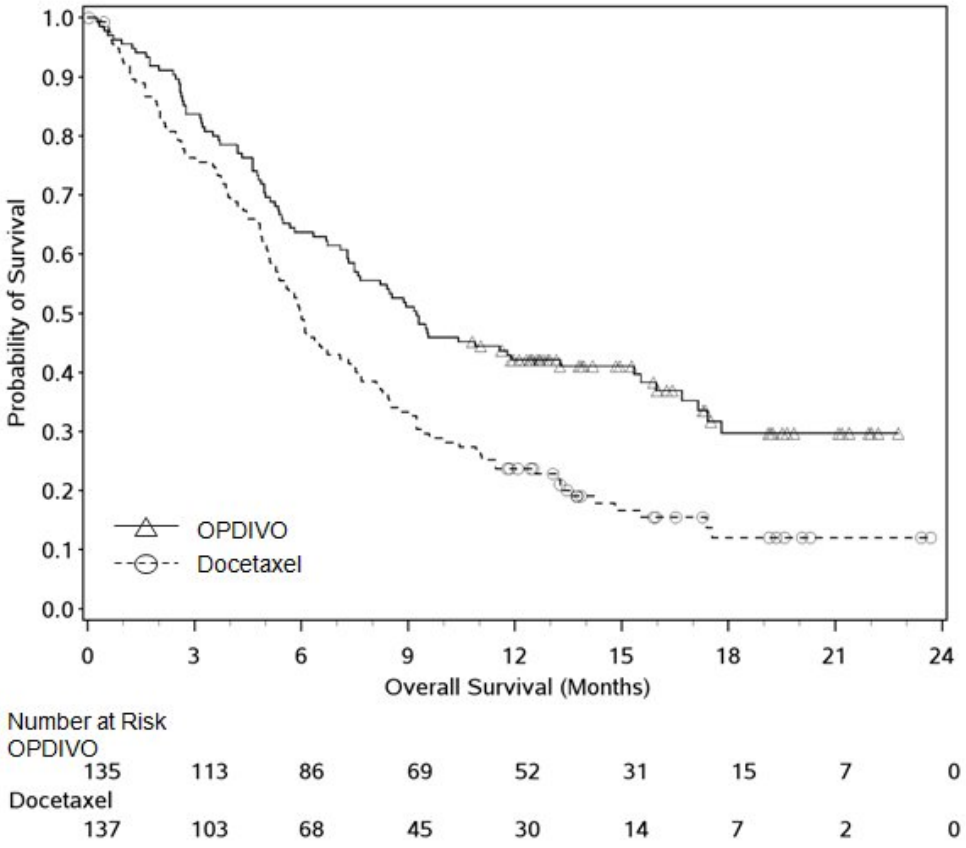
[a] Based on a stratified proportional hazards model.

[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 6: 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 33 and Figure 7.

Table 33: Efficacy Results - CHECKMATE-057

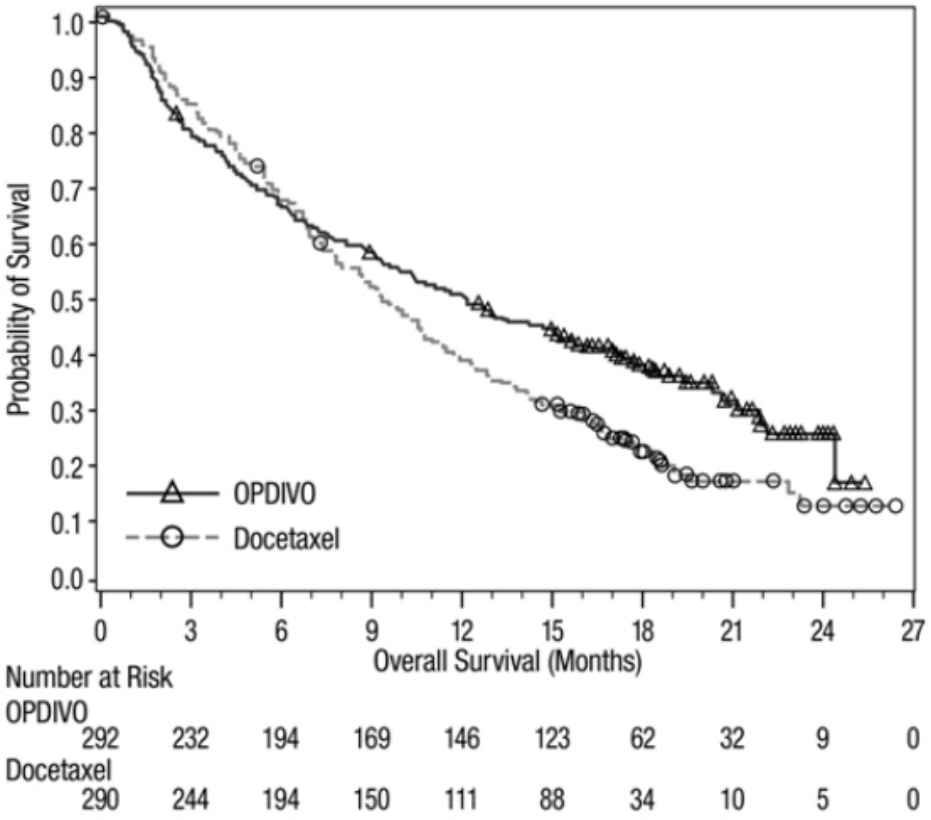
	OPDIVO (n=292)	**Docetaxel (n=290)**
Overall Survival		
Deaths (%)	190 (65%)	223 (77%)
Median (months) (95% CI)	12.2 (9.7, 15.0)	9.4 (8.0, 10.7)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0015	
Overall Response Rate	56 (19%)	36 (12%)
(95% CI)	(15, 24)	(9, 17)
p-value[d]	0.02	
Complete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

Table 33: Efficacy Results - CHECKMATE-057

	OPDIVO (n=292)	Docetaxel (n=290)
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 7: 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 8 and 9 summarize the results of

prespecified analyses of OS and PFS in subgroups determined by percentage of tumor cells expressing PD-L1.

Figure 8: Forest Plot: OS Based on PD-L1 Expression - CHECKMATE-057

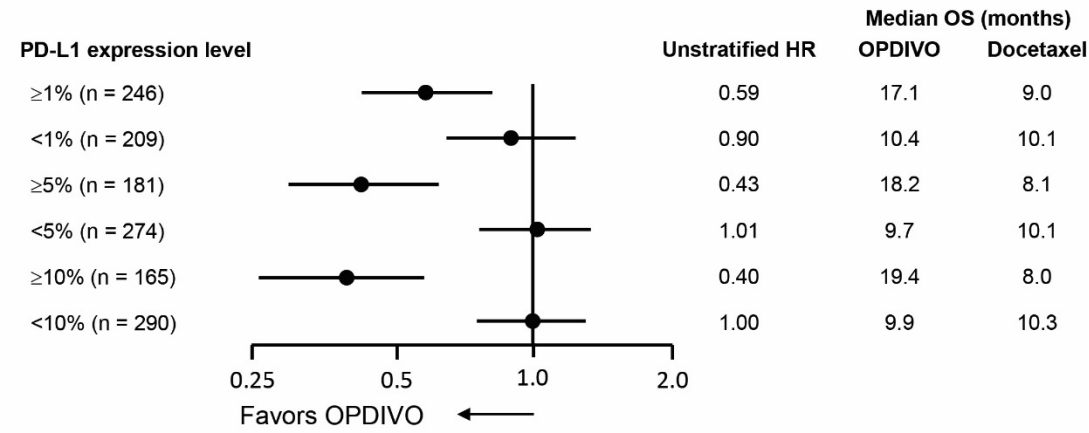
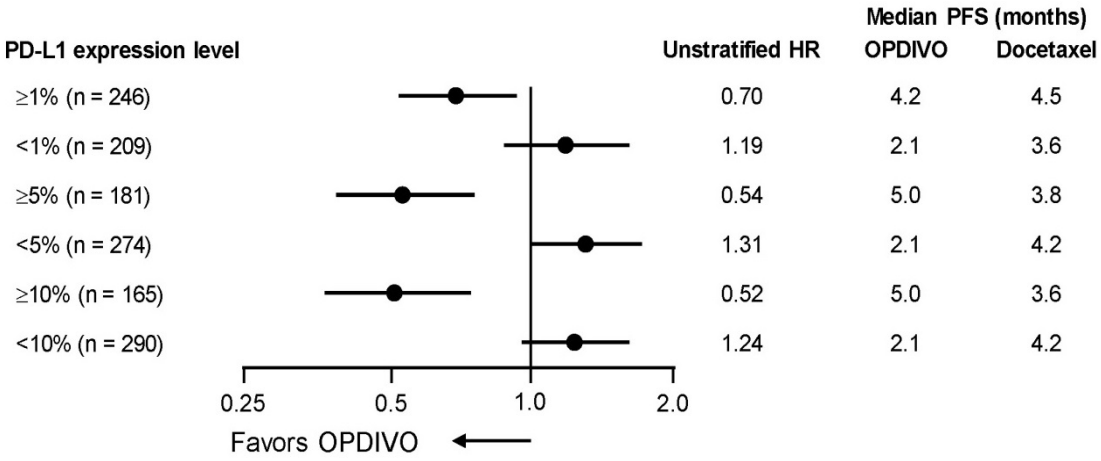


Figure 9: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



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 34.

Table 34: 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 35 and Figure 10.

Table 35: Efficacy Results - CHECKMATE-025

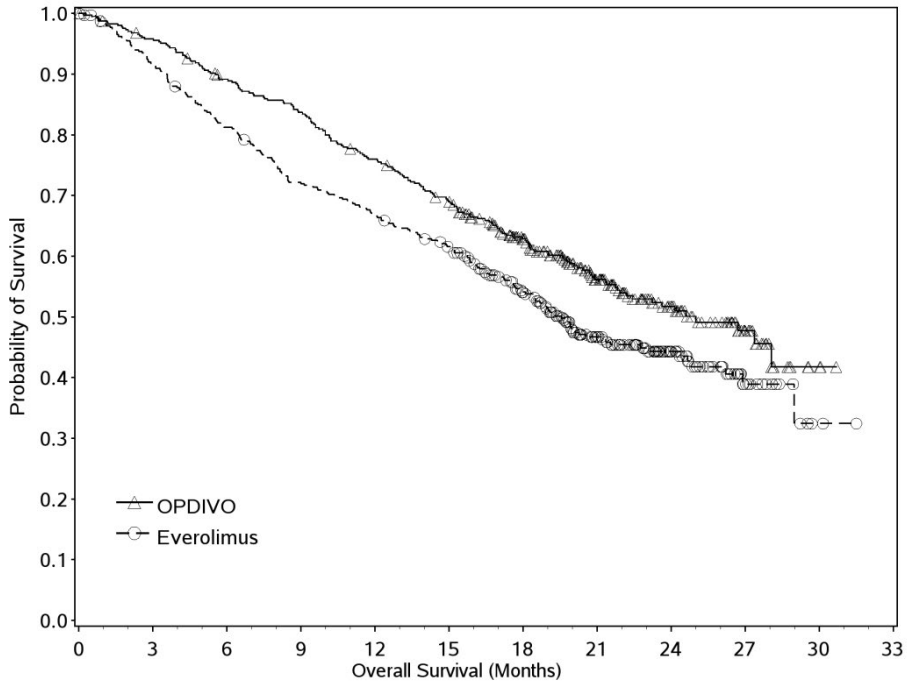
	OPDIVO (n=410)	**Everolimus (n=411)**
Overall Survival		
Deaths (%)	183 (45)	215 (52)
Median survival in months (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0018	
Confirmed Overall Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median 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 10: 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.

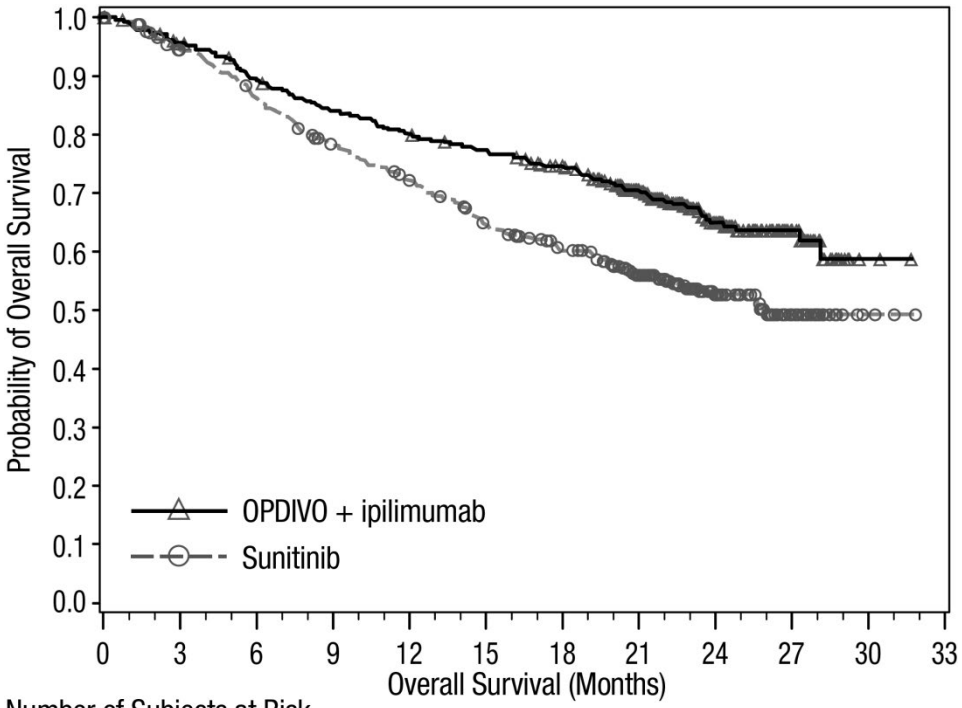
The major efficacy outcome measures were OS, PFS (independent radiographic review committee [IRRC]-assessed) and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to OPDIVO and ipilimumab as compared with sunitinib (Table 36 and Figure 11). 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 36 and Figure 11.

Table 36: 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)	
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 11: Overall Survival (Intermediate/Poor Risk Population) - CHECKMATE-214



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 37.

Table 37: 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 38.

Table 38: 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.

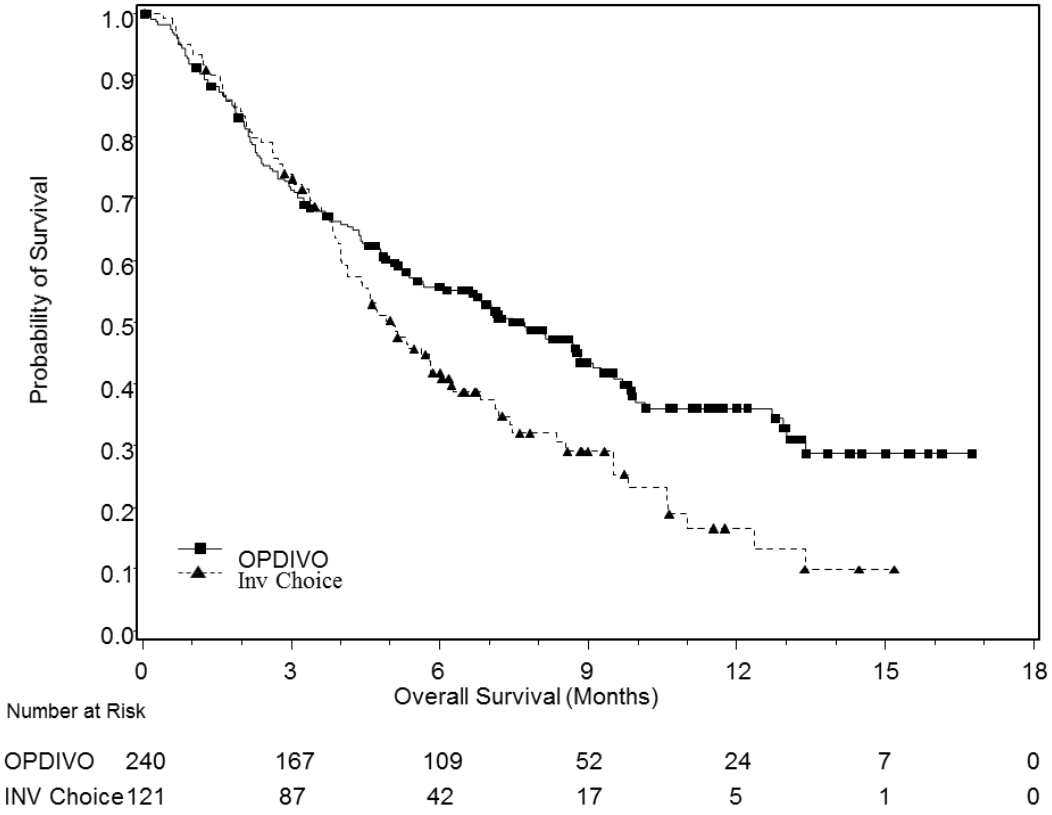
The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). There were no statistically significant differences between the two 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 39 and Figure 12.

Table 39: 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 12: 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 40. 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 40: 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 41.

Table 41: 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 42. 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 42: 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 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.
- 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.
- **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, 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, OPDIVO is given every 2 weeks and ipilimumab is given every 6 weeks for up to 2 years.
- 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
- shortness of breath
- constipation
- decreased appetite

- itchy skin
- diarrhea
- nausea
- weakness
- cough
- back pain
- upper respiratory tract infection
- fever
- headache
- stomach-area (abdominal) pain
- vomiting

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

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

OPDIVO® and YERVOY® are trademarks of Bristol-Myers Squibb Company. Other brands listed are the trademarks of their respective owners.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s080

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

Application Type	Supplemental BLA
Application Number(s)	125554/S-080; 125377/S-109
Priority or Standard	Priority
Submit Date(s)	November 15, 2019
Received Date(s)	November 15, 2019
PDUFA Goal Date	May 15, 2020
Division/Office	DO2/OOD
Review Completion Date	May 11, 2020
Established/Proper Name	Nivolumab, ipilimumab
Trade Name	OPDIVO
Pharmacologic Class	Programmed cell death protein-1 (PD-1) blocking antibody
Code name	Not applicable
Applicant	Bristol-Myers Squibb, Co.
Doseage form	Injection
Applicant proposed Dosing Regimen	Nivolumab 3 mg/kg intravenously every 2 weeks with ipilimumab 1 mg/kg intravenously every 6 weeks
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	OPDIVO, in combination with ipilimumab, is indicated 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 YERVOY, in combination with nivolumab, is indicated 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

Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	Nivolumab 3 mg/kg intravenously every 2 weeks with ipilimumab 1 mg/kg every 6 weeks

APPEARS THIS WAY
ON ORIGINAL

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Table of Tables

Table of Figures

APPEARS THIS WAY
ON ORIGINAL

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Gina Davis
Nonclinical Reviewer	N/A
Nonclinical Team Leader	N/A
Office of Clinical Pharmacology Reviewer(s)	Safaa Burns\Yuan Xu
Office of Clinical Pharmacology Team Leader(s)	Jeanne Fourie-Zirkelbach\Jiang Liu
Clinical Reviewer	Nicole Drezner
Associate Director of Labeling	Ann Marie Trentacosti (acting)
Clinical Team Leader	Erin Larkins
Statistical Reviewer	Mallorie Fiero
Statistical Team Leader	Pallavi Mishra-Kalyani
Cross-Disciplinary Team Leader	Erin Larkins
Division Director (DHOT)	N/A
Division Director (OCP)	N/A
Division Director (OB)	Yuan Li Shen
Division Director (OOD)	Harpreet Singh
Office Director (or designated signatory authority)	Harpreet Singh

Additional Reviewers of Application

OPQ	N/A
Microbiology	N/A
OPDP/DMPP	Sharon Mills/Adesola Adejuwon
OSI	Jenn Sellers
OSE/DEPI	N/A
OSE/DMEPA	N/A
OSE/DRISK	N/A
Other	N/A

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

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Nivolumab (OPDIVO) is a fully human monoclonal 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. Nivolumab is approved for multiple oncologic indications, including the treatment of patients with 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 nivolumab.

Ipilimumab (YERVOY) 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. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, whih may contribute to a general increase in T-cell responsiveness, including the anti-tumor immune response. Ipilimumab is approved for several oncologic indications but is not currently approved for the treatment of patients with NSCLC.

The combination of nivolumab and ipilimumab is currently approved for the following indications:

- for the treatment of patients 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.

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.

The recommended dosage regimen for the proposed indication is nivolumab 3 mg/kg intravenously every 2 weeks (Q2W) with ipilimumab 1 mg/kg intravenously Q6W until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression. The combination is approved at doses of nivolumab 3 mg/kg and ipilimumab 1

mg/kg for renal cell carcinoma and colorectal cancer but with both administered on a Q3W schedule and administration of ipilimumab limited to four doses.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The primary trial supporting this sBLA is Study CA209227 (CheckMate-227), a multicenter, open-label, randomized, three-part (Parts 1a, 1b, 2) study, in which Part 1a contains the primary efficacy population relevant to this review, comparing the combination of nivolumab and ipilimumab to platinum-doublet chemotherapy in support of the indication of nivolumab and ipilimumab in combination for the first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 (≥ 1%), with no EGFR or ALK genomic aberrations.

Study CA209227 demonstrated a hazard ratio (HR) for overall survival (OS) of 0.79 (95% confidence interval [CI] 0.67, 0.94; p-value 0.0066) favoring the nivolumab and ipilimumab arm in patients with PD-L1 tumor expression ≥ 1%; the median OS was 17.1 months (95% CI 15.0, 20.1) in the nivolumab and ipilimumab arm and 14.9 months (95% CI 12.7, 16.7) in the chemotherapy arm. The comparison of PFS for the nivolumab and ipilimumab arm versus the chemotherapy arm was not part of the statistical testing hierarchy, but the hazard ratio for PFS per blinded independent central review (BICR) was 0.82 (95% CI 0.67, 0.99), with a median PFS of 5.1 months (95% CI 4.1, 6.3) in the nivolumab and ipilimumab arm and 5.6 months (95% CI 4.6, 5.8) in the chemotherapy arm. The overall response rate (ORR) per BICR in the nivolumab and ipilimumab arm was 36% (95% CI 31, 41), versus 30% (95% CI 26, 35) in the chemotherapy arm, with a median duration of response (DOR) of 23.2 months in the nivolumab and ipilimumab arm versus 6.2 months in the chemotherapy arm.

The submitted evidence meets the statutory evidentiary standard for regular approval. The observed improvement in OS, with a HR of 0.79 and a 2.2-month difference in median OS, is statistically robust and clinically meaningful. This finding is supported by the improvement in DOR observed in the nivolumab and ipilimumab arm when compared to the chemotherapy arm.

1.3. Benefit-Risk Assessment

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.

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. At the time Study CA209227 was designed, 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 CA209227 (CheckMate-227), a multicenter, international, randomized, three-part (Parts 1a, 1b, and 2), open-label trial, in which the primary analysis population relevant to the supported indication was enrolled in Part 1a. Part 1a is a three-arm substudy in which patients with PD-L1 tumor expression ≥ 1% were randomized (1:1:1) to receive nivolumab as a single agent (Arm A), nivolumab 3 mg/kg every 2 weeks (Q2W) with ipilimumab 1 mg/kg Q6W (Arm B), or platinum-based chemotherapy (Arm C). The primary efficacy population in support of the indication and the basis for conclusions of the substantial evidence of effectiveness for this sBLA is the intent-to-treat population enrolled in Arms B and C of Part 1a of Study CA209227, including a total of 396 patients in the nivolumab and ipilimumab arm and 397 patients in the chemotherapy arm. Efficacy results for the 396 patients enrolled in the nivolumab as a single agent arm provide supportive evidence for the contribution of ipilimumab to the effect of the combination. The primary safety population for the assessment of the safety and tolerability of the recommended dosage regimen of nivolumab and ipilimumab in patients with NSCLC also included patients enrolled in Part 1b of Study CA209227, a three-arm, randomized sub-study of patients with NSCLC with PD-L1 tumor expression status < 1%, which included 187 patients treated with the combination of nivolumab and ipilimumab (Arm D) and 186 treated with platinum-based chemotherapy (Arm F), resulting in a total of 576 patients treated with the combination of nivolumab and ipilimumab and 570 patients treated with platinum-based chemotherapy in the primary safety population.

Study CA209227 demonstrated a HR for overall survival (OS) favoring the nivolumab and ipilimumab arm (Arm B) of 0.79 (95% CI 0.67, 0.94; p-value 0.0066 [compared to allocated alpha 0.0228]) in patients with PD-L1 tumor expression ≥ 1%. The median OS was 17.1 months (95% CI 15.0, 20.1) in the nivolumab and ipilimumab arm and 14.9 months (95% CI 12.7, 16.7) in the chemotherapy arm. The HR for PFS as assessed by

BICR was 0.82 (95% CI 0.67, 0.99) this comparison was not part of the study's statistical testing hierarchy. The ORR as assessed by BICR in the nivolumab and ipilimumab arm was 36% (95% CI 31, 41) with a median DOR of 23.2 months versus 30% (95% CI 26, 35) in the chemotherapy arm with a median DOR of 6.2 months.

Efficacy results for the 396 patients enrolled in the nivolumab as a single agent arm of Part 1a (Arm A) provide evidence for the contribution of ipilimumab to the effect of the combination. Results comparing Arm B (nivolumab and ipilimumab) with Arm A and comparing Arm A with Arm C (chemotherapy) from Part 1a of Study CA209227 were provided. These comparisons were not part of the statistical testing hierarchy for Part 1 of the study; however, these exploratory analyses demonstrate improved efficacy (OS, PFS, and ORR) in patients who received nivolumab and ipilimumab in comparison to those who received nivolumab as a single agent.

The observed safety profile of nivolumab in combination with ipilimumab is acceptable when considered in the context of a life threatening disease. The incidences reported here are for the 576 patients treated with the combination of nivolumab and ipilimumab in Arms B and D of Study CA209227. The most common (≥ 20%) adverse reactions due to any cause were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). Nivolumab and ipilimumab were discontinued due to adverse reactions in 24% of patients; the most common (≥1%) adverse reactions leading to treatment discontinuation were pneumonitis, diarrhea/colitis, hepatitis, and pneumonia. The most frequent (≥ 2%) serious adverse reactions were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis. Deaths considered related or possibly related to nivolumab and ipilimumab were identified in 10 (1.7%) patients; fatal adverse reactions included myocarditis, acute kidney injury, pneumonitis (4 events), hyperglycemia, shock, multi-system organ failure, and renal failure. The incidence and severity of immune-mediated adverse reactions were similar to those reported in the Reference Safety Database and described in the current product labeling for the combination of nivolumab and ipilimumab, with the exception of pneumonitis, which was observed at a higher incidence in patients enrolled on Study CA209227 (9%) than in patients who received the combination of nivolumab 3 mg/kg and ipilimumab 1 mg/kg (renal cell carcinoma [4.4%] and metastatic colorectal cancer [1.7%]). A section describing the risk of pneumonitis in patients with NSCLC receiving nivolumab in combination with ipilimumab has been added to the Warnings and Precautions section of the prescribing information. With this addition, significant and serious adverse reactions, including immune-mediated adverse reactions, are adequately addressed in the Warnings and Precautions section and the dose modification recommendations including in the product labeling. 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 the opinion of the reviewers, the submitted evidence meets the evidentiary standard for regular approval and provides substantial evidence of the effectiveness of nivolumab with ipilimumab for the first-line treatment of 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 magnitude of the treatment effect on OS is statistically robust and clinically meaningful and is consistent with an improvement in the treatment of patients with metastatic NSCLC. This benefit is supported by evidence of a substantial improvement in DOR. The clinical benefits outweigh the risks of nivolumab in combination with ipilimumab, as described above. These risks are considered acceptable in the context of a life-threatening disease and the magnitude of improvement in survival noted. The reviewers recommend granting regular approval of nivolumab and ipilimumab in combination for the following indication: "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."

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 CA209227 (CheckMate-227) 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. • Pembrolizumab as a single agent is an FDA-approved treatment option for patients with NSCLC with PD-L1-positive NSCLC (tumor proportion score [TPS] ≥ 1%).	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 and ipilimumab 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 CA209227, a multicenter, open-label, randomized, three-part (Parts 1a, 1b, and 2), in which Part 1a contains the primary efficacy population relevant to this review, comparing nivolumab with ipilimumab (Arm B) and nivolumab as a single agent (Arm A) to platinum-based chemotherapy (Arm C) in 1189 patients with previously untreated NSCLC with PD-L1 tumor expression ≥ 1%. • Study CA209227 Part 1a demonstrated a HR for overall survival favoring the nivolumab and ipilimumab arm (Arm B) of 0.79 (95% CI 0.67, 0.94; p-value 0.0066 [compared to allocated alpha 0.0228]) in patients with PD-L1 tumor expression ≥ 1%. The median OS was 17.1 months (95% CI 15.0, 20.1) in the nivolumab and ipilimumab arm and 14.9 months (95% CI 12.7, 16.7) in the chemotherapy arm (Arm C). • The HR was 0.82 (95% CI 0.67, 0.99) for PFS as assessed by BICR; this comparison was not part of the study's statistical testing hierarchy. • The ORR as assessed by BICR in the nivolumab and ipilimumab arm was 36% (95% CI 31, 41) with a median DOR of 23.2 months versus 30% (95% CI 26, 35) in the chemotherapy arm with a median DOR of 6.2 months. • Efficacy results for the 396 patients enrolled in the nivolumab as a single agent arm of Part 1a (Arm A) provide evidence for the contribution of ipilimumab to the effect of the combination. Results comparing Arm B (nivolumab and ipilimumab) with Arm A and comparing Arm A with Arm C (chemotherapy) from Part 1a of Study CA209227 were provided. These comparisons were not part of the statistical testing hierarchy for Part 1 of the study; however, these exploratory analyses demonstrate improved efficacy (OS, PFS, and ORR) in patients who received nivolumab and ipilimumab in	The submitted evidence meets the statutory evidentiary standard for regular approval. The observed improvement in OS, with a HR of 0.79 and a 2.2-month difference in median OS, is statistically robust and clinically meaningful. This finding is supported by a substantial improvement in DOR favoring the nivolumab and ipilimumab arm.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	comparison to those who received nivolumab as a single agent.	
Risk and Risk Management	• The safety population from Study CA209227 includes a total of 576 patients - 396 patients with metastatic NSCLC with tumor expression ≥ 1% enrolled on the nivolumab and ipilimumab arm of Part 1a (Arm B) and 190 patients with metastatic NSCLC with tumor expression < 1% enrolled on the nivolumab and ipilimumab arm of Part 1b (Arm D). • Supportive safety data was also provided from three single arm studies of nivolumab and ipilimumab in patients with metastatic NSCLC: Study CA209568 (n=288), Study CA209817 (n=391), and Study CA209012 (n=39). • In addition, safety data was provided from patients renal cell carcinoma (RCC) and metastatic colorectal cancer (mCRC), for which nivolumab 3 mg/kg and ipilimumab 1 mg/kg is an approved treatment combination, enrolled on Studies CA209214 (n=547) and CA209142 (n=119). • The data provided in the following bullets is from the safety population of 576 patients treated with nivolumab and ipilimumab in Study CA209227. • The most common (≥ 20%) adverse reactions due to any cause were fatigue (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%). • Nivolumab and ipilimumab were discontinued in 24% of patients; the most common (≥1%) adverse reactions leading to treatment discontinuation were pneumonitis, diarrhea/colitis, hepatitis, and	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. The incidence and severity of immune-related adverse reactions in patients treated with the combination of nivolumab and ipilimumab in Study CA209227 were similar to those reported in the current labeling with the exception of pneumonitis, which was observed at a higher incidence in patients with NSCLC than in patients with either renal cell carcinoma or metatstic colorectal cancer who received the combination of nivolumab 3 mg/kg and ipilimumab 1 mg/kg. This increased risk of pneumonitis was addressed in the updated Warnings and Precautions section of the product labeling. With this addition, significant and serious adverse reactions, including immune-mediated adverse reactions, are adequately addressed in the Warnings and Precautions section and the dose modification recommendations including in the product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pneumonia. • The most frequent (≥ 2%) serious adverse reactions due to any cause were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, pulmonary embolism, adrenal insufficiency, and hypophysitis (2.3%). • Deaths considered related or possibly related to nivolumab and ipilimumab were identified in 10 (1.7%) patients; fatal adverse events were myocarditis, acute kidney injury, pneumonitis (4 events), hyperglycemia, shock, multi-system organ failure, and renal failure. • The incidence and severity of immune-mediated adverse reactions are similar to those reported in the Reference Safety Database for the combination of nivolumab and ipilimumab with the exception of pneumonitis, which was observed at a higher incidence in patients enrolled on Study CA209227 (9%) than those with other tumor types (renal cell carcinoma [4.4%] and metastatic colorectal cancer [1.7%]) who received the combination of nivolumab 3 mg/kg and ipilimumab 1 mg/kg.	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.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability
		x	Patient reported outcome (PRO)	8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability
		□	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		
	□	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 were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

X Erin Larkins, MD
Cross Discipline Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

There will be approximately 228,000 new cases of lung cancer and 136,000 deaths from lung cancer in the US in 2020.[1] Of these, 85-90% are NSCLC and approximately 80% of patients have locally advanced or metastatic disease at diagnosis; approximately 18% of all patients diagnosed with lung cancer will survive 5 years, with much lower survival rates for patients with metastatic disease at diagnosis. The median survival of patients with advanced NSCLC when managed with supportive care alone is approximately 3-6 months.[2] Treatment with platinum doublet-based chemotherapy, which prior to the advent of immunotherapy was most commonly administered in regimens that included pemetrexed plus cisplatin or carboplatin and carboplatin plus paclitaxel with or without bevacizumab, leads to a median OS of approximately 10 months and a median PFS of approximately 5 months.[3] More recently approved first-line treatment options for patients with metastatic NSCLC include the PD-1-blocking antibody pembrolizumab (for non-squamous and squamous histology) or the PD-L1 blocking antibody atezolizumab (for non-squamous histology) administered with a platinum-based combination regimen, regardless of PD-L1 status, and pembrolizumab as a single agent for patients with NSCLC with PD-L1-positive NSCLC (tumor proportion score [TPS] ≥ 1%).

2.2. Analysis of Current Treatment Options

Table 1: Summary of FDA-approved first-line treatment for metastatic NSCLC

Study	Approval year	Indication	Efficacy Information
Cisplatin-pemetrexed (n=839) vs. cisplatin-gemcitabine (n=830)[2]	2008	Stage IIIB/IV non-squamous NSCLC	Median OS: 10.3 vs. 10.3 mos; HR 0.94 (95% CI 0.84, 1.05) Median PFS: 4.8 vs. 5.1 mos; HR 1.04 (95% CI 0.94, 1.15) ORR: 31% vs. 28% Median DOR: N/A
Platinum-pemetrexed + pembrolizumab (n=410) vs. Platinum-pemetrexed + placbo (n=206)[4]	2017 (AA) 2018 (RA)	Metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	Median OS: NR vs. 11.3 mos; HR 0.49 (95% CI 0.38, 0.64) Median PFS: 8.8 vs. 4.9 mos; HR 0.52 (95% CI 0.43, 0.64) ORR: 48% (95% CI 43, 53) vs. 19% (95% CI 14, 25) Median DOR: 11.2 (range 1.1+, 18.0+) vs. 7.8 mos (range 2.1+, 16.4+)
Carboplatin-paclitaxel/nab-paclitaxel + pembrolizumab (n=278) vs. carboplatin-paclitaxel/nab-paclitaxel (n=281)[5]	2018	Metastatic squamous NSCLC	Median OS: 15.9 vs. 11.3 mos; HR 0.64 (95% CI 0.49, 0.85) Median PFS: 6.4 vs. 4.8 mos; HR 0.56 (95% CI 0.45, 0.70) ORR: 56% (95% CI 48, 68) vs. 35% (95% CI 26, 45) Median DOR: 7.3 (range 2.4, 12.4+) vs. 4.9 mos (range 2.0, 12.4+)
Pembrolizumab (n=637) vs. chemotherapy (n=637)[4]	2019	Advanced NSCLC expressing PD-L1 TPS ≥ 1% with no EGFR or ALK genomic tumor aberrations	Median OS: 16.7 vs. 12.1 mos; HR 0.81 (95% CI 0.71, 0.93) Median PFS: 5.4 vs. 6.5 mos; HR 1.07 (95% CI 0.94, 1.21) ORR: 27% (95% CI 24, 31) vs. 27% (95% CI 23, 30) Median DOR: N/A
Atezolizumab + carboplatin + paclitaxel + bevacizumab (n=359) vs. carboplatin + paclitaxel + bevacizumab (n=337)[6]	2018	Metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	Median OS: 19.2 vs. 14.7 mos; HR 0.78 (95% CI 0.64, 0.96) Median PFS: 8.5 vs. 7.0 mos; HR 0.71 (95% CI 0.59, 0.85) ORR: 55% (95% CI 49. 60) vs. 42% (95% CI 37, 48) Median DOR: 10.8 (range 8.4, 13.9) vs. 6.5 mos (range 5.6, 7.6)
Atezolizumab + nab-paclitaxel + carboplatin (n=453) vs. nab-paclitaxel + carboplatin (n=228)[6]	2019	Metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations	Median OS: 18.6 vs. 13.9 mos; HR 0.80 (95% CI 0.64, 0.99) Median PFS: 7.2 vs. 6.5 mos; HR 0.75 (95% CI 0.63, 0.91) ORR: 46% (95% CI 41, 50) vs. 32% (95% CI 26, 39) Median DOR: 10.8 (range 9.0, 14.4) vs. 7.8 mos (range 6.8, 10.9)

Abbreviations: OS: overall survival, HR: hazard ratio, PFS: progression-free survival; ORR: overall response rate; DOR: duration of response, AA: accelerated approval, RA: regular approval, NR: not reached, TPS: tumor proportion score

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Nivolumab (OPDIVO®) is not a new molecular entity. It is currently marketed in the United States for multiple oncologic indications as discussed in Section 1.1 of this review. Nivolumab was initially approved on December 22, 2014, under the provisions of accelerated approval for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor (BLA 125554). The combination of nivolumab and ipilimumab was first approved on October 1, 2015, for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma under the provisions of accelerated approval (BLAs 125554 and 125377). On March 4, 2015, nivolumab received regular approval as a single agent for the treatment of metastatic NSCLC with progression on or after platinum-based chemotherapy; this remains the only NSCLC indication for which nivolumab is approved (BLA 125554).

Ipilimumab (YERVOY®) is not a new molecular entity. It is currently marketed in the United States for several oncologic indications as discussed in Section 1.1 of this review. Ipilimumab was initially approved on March 25, 2011, for the treatment of patients with unresectable or metastatic melanoma. The combination of nivolumab and ipilimumab was first approved on October 1, 2015, for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma under the provisions of accelerated approval (BLAs 125554 and 125377). Ipilimumab is not currently approved for any NSCLC indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The major regulatory milestones and changes to the statistical analysis plan for Study CA209227 are described in Table 2.

Table 2: Key regulatory activities related to the clinical development of nivolumab in combination with ipilimumab for NSCLC

Date	Discussion	Major Changes to Statistical Analysis Plan
3/18/2015	**IND 125872 Submission.** Original protocol (version date 3/6/15) submitted as IND-enabling study for nivolumab in combination with ipilimumab for the treatment of NSCLC.	• CA209227 was a randomized study in approximately 1200 patients with stage IV or recurrent NSCLC. • Patients were randomly assigned in a 1:1:1:1 ratio to four arms: o Nivo monotherapy (Arm A) o Nivo 1 mg/kg + ipi 1 mg/kg, followed by nivo 3 mg/kg (Arm B) o Nivo 3 mg/kg + ipi 1 mg/kg (Arm C) o Chemo (Arm D)

		• **The primary endpoint was OS for nivo vs. chemo and nivo+ipi vs. chemo.**
6/8/2015	**Revised protocol** (version date 4/15/15). IND amendment based on FDA feedback on multiple arm comparisons to demonstrate additional clinical benefit of ipi in combination with nivo.	• Revised testing procedure to include pairwise comparisons of OS among experimental arms.
6/10/2015	**Revised protocol** (version date 5/29/15). IND amendment based on data from Study CA209057 ("An Open-Label Randomized Phase III Trial of BMS-936558 versus Docetaxel in Previously Treated Metastatic Non-Squamous NSCLC") demonstrating an OS benefit in an interim analysis in patients receiving nivo compared to docetaxel.	• Increased sample size to from 1200 to 1980 patients (990 PD-L1+ (≥ 1%) patients and 990 PD-L1- (< 1%) patients). • Revised treatment arms for PD-L1+ patients assigned (1:1:1) to: o Nivo monotherapy (Arm A), o Nivo 3 mg/kg + ipi 1 mg/kg (Arm B) o Chemo (Arm C) • Revised treatment arms for PD-L1- patients assigned (1:1:1) to: o Nivo 3 mg/kg + ipi 1 mg/kg (Arm D) o Nivo 1 mg/kg + ipi 1 mg/kg followed by nivo 240 mg (Arm E) o Chemo (Arm F) • **Revised co-primary endpoints to OS and PFS in nivo vs. chemo and nivo+ipi vs. chemo separately for PD-L1+ (Part 1a) and PD-L1- (Part 1b).**
11/2/2015	**Revised protocol** (version date 10/21/15). IND amendment based on new data from the ongoing phase 1 study CA209012 examining novel schedules of the nivo+ipi combination for patients with previously untreated NSCLC.	• Dropped Arm E and added nivo 360 mg + chemo (Arm G) in the PD-L1- substudy.
10/24/2016	**Type C meeting.** BMS sought FDA feedback on proposed interim analysis of ORR in PD-L1+ patients followed for at least 6 months. • FDA had no objections but noted that an efficacy supplement based on the results of Study CA209227 should contain data from both control arms (Arms C and F), as well as all nivo containing arms.	• Added descriptive interim analysis of ORR in 484 PD-L1+ (≥ 1% and ≥ 50%) patients followed for at least 6 months (Arms A, B, C).
12/13/2016	**Revised protocol** (version date 11/17/16). IND amendment based on data from CA209012 and CA209026, as well as changing treatment landscape in first-line NSCLC.	• Added Part 2, a randomized study in 480 patients with stage IV or recurrent NSCLC. Eligible patients were randomly assigned in a 1:1 ratio to two arms: o Nivo + platinum doublet chemo (Arm H) o Platinum doublet chemo (Arm I)

		• Revised the sample size in Part 1 to include 1740 patients (increased from 990 to 1200 PD-L1+ patients and decreased from 990 to 540 PD-L1- patients). • **Revised primary endpoint for Part 1a to OS in nivo+ipi (Arm B) vs. chemo (Arm C) in patients with PD-L1 ≥ 50%.** • Revised primary endpoint for Part 1b to PFS in nivo+chemo (Arm G) vs. chemo (Arm F).
3/24/2017	**Type C meeting.** BMS sought FDA feedback on proposed revisions to Part 1b including: • Non-comparative interim analysis of ORR to support an efficacy supplement for nivo+chemo for patients with previously untreated recurrent or metastatic NSCLC whose tumors are PD-L1-. • FDA did not object to the revisions to the final analysis of PFS. FDA also requested additional details regarding the formal statistical testing of the interim and final results of ORR between Arms F and G.	• Decreased the number of events (from 224 to 183 events) required for the final analysis of PFS. • Added non-comparative interim analysis of ORR for chemo (Arm F) and nivo+chemo (Arm G) among PD-L1- patients with minimum 9 months of follow-up.
7/7/2017	**Revised protocol** (version date 6/27/2017). IND amendment to detect smaller effect size.	• Increased sample size of patients from 480 to 750 patients and modified statistical considerations in Part 2.
8/1/2017	**Type C meeting.** BMS sought FDA feedback on proposed revisions to Part 1 including: • Incorporating co-primary analysis of patients with high TMB regardless of PD-L1 expression. o BMS stated that this decision was based on external data including data from CA209026 and CA209568. o FDA expressed concern that the results would rely on a single protocol using a subgroup of less than 60% of the randomized patients (e.g. the TMB evaluable population), and that the proposed treatment effect size, as characterized by an improvement in median PFS of 3.1 months is unlikely to establish the clinical benefit of this treatment regimen, requiring post-marketing trials to verify benefit. o FDA also stated that small treatment effects may not support a request for accelerated approval.	
11/8/2017	**Revised protocol** (version date 10/5/2017). IND amendment based on exploratory post hoc analysis of CA209026.	• Added co-primary endpoint of PFS among patients with TMB ≥ 10 mut/Mb for nivo+ipi (Arms B+D) vs. chemo (Arms C+F). • **Co-primary endpoint in PD-L1 pathway revised to Part 1a to OS in nivo+ipi (Arm B) vs. chemo (Arm C) in patients with PD-L1 ≥ 1%.** • Changed PFS for nivo+chemo vs. chemo from primary to secondary endpoint in PD-L1- patients.

		• Added adjustment of Type I error for early look at ORR in Part 1a.
4/20/2018	**sBLAs submitted** for proposed indication of (b) (4) (b) (4)	
1/27/2019	**sBLAs withdrawn**	
9/19/2019	**Type B pre-sBLA Meeting.** Meeting to discuss the proposal to submit sBLAs for nivo+ipi for the proposed indication of the first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations • FDA did not agree with the proposed indication (b) (4) (b) (4) • FDA did agree that the results of the comparison of nivolumab in combination with ipilimumab versus chemotherapy in patients with NSCLC whose tumors express PD-L1 ≥ 1% (Part 1a), supported by exploratory analyses assessing the contribution of nivolumab and ipilimumab individually to the overall treatment effect, were sufficient to support the filing of the proposed sBLAs. • FDA stated that they would review the data and rationale in support of a resquest for accelerated approval for patients with PD-L1 negative NSCLC.	
11/15/2019	**sBLA 125554/125377 submission.** BMS requested approval for nivolumab in combination with ipilimumab for the treatment of patients with metastatic or recurrent NSCLC with no known EGFR or ALK genomic tumor aberrations.	

APPEARS THIS WAY
ON ORIGINAL

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI performed inspections of BMS and one clinical investigator site in support of the sBLAs. Based on FDA's inspection, the study data derived from the clinical site is considered reliable. Additionally, BMS appeared to maintain adequate oversight of Study CA209227. Based on the results from the two inspections by FDA, the overall survival data from Part 1a of Study CA209227 as submitted by BMS appear reliable. Please see the review by Dr. Jenn Sellers for more information.

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

A supplemental premarket application (sPMA) for the Dako PD-L1 IHC 28-8 pharmDx as a companion diagnostic for use in selecting patients with metastatic NSCLC with PD-L1 tumor expression ≥ 1% was submitted and is planned to be approved concurrently with the approval of sBLAs 125554-s080 and 125537-s109. Please see the review by Dr. Shyam Kalavar for more information.

5 Nonclinical Pharmacology/Toxicology

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.

APPEARS THIS WAY ON ORIGINAL

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology data in support of the use of nivolumab in combination with ipilimumab in patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with **no** EGFR or ALK genomic tumor aberrations are provided from the randomized trial **Study CA209227** (CheckMate-227) at the proposed doses of 3 mg/kg Q2W nivolumab plus 1 mg/kg Q6W ipilimumab.

In **Study CA209227**, the immunogenicity of nivolumab and ipilimumab was assessed in both **Arms B** (programmed death ligand-1 (PD-L1)-positive [≥ 1%]) and **D** (PD-L1-negative [< 1%]) at the proposed doses of 3 mg/kg Q2W nivolumab plus 1 mg/kg Q6W ipilimumab and in **Arm A** (unselected PD-L1 status) at a dose of 240 mg Q2W nivolumab monotherapy in NSCLC patients. The results of this analysis indicate that the incidence of anti-drug antibodies (ADAs) for both nivolumab and ipilimumab tends to be higher when both drugs are given in combination (36.7% and 8.5%, respectively) than to each drug administered alone (23.9% and 6.9%, respectively). The incidence of neutralizing ADAs was 1.4% for nivolumab and 0% for ipilimumab. There was no apparent impact of nivolumab or ipilimumab ADAs on the efficacy or safety.

Updated population pharmacokinetics (PPK) and exposure-response (E-R) efficacy and safety analyses were performed on the data from **Study CA209227** (**Arms A**, **B** and **D**) in NSCLC patients and from other clinical trials in patients with other tumor types at various dosing regimens using the previously developed PPK and E-R models for nivolumab and ipilimumab. The results of these analyses are generally consistent with those currently described in the approved package insert for nivolumab plus ipilimumab (version dated 3/10/2020). These PPK or E-R analyses did not have an impact on labeling and the Applicant has **not** made any labeling claims in their proposed package insert. However, the FDA recommended that addition of a statement to the proposed labeling regarding the changes in clearance (CL) of both nivomumab and ipilimumab when given in combination.

Recommendation

The Office of Clinical Pharmacology have reviewed the clinical pharmacology information in the current application on and conclude that this supplemental BLA is acceptable to support the approval of nivolumab in combination with ipilimumab in the new NSCLC indication.

6.2. Summary of Clinical Pharmacology Assessment

For detailed clinical pharmacology information for both nivolumab and ipilimumab, either as single agents or in combination, refer to the the clinical pharmacology reviews in DARRTS performed for BLAs 125554 (nivolumab) and BLA 124377 (ipilimumab) and to their respective most recently approved labeling versions dated 3/10/2020 at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125554s078lbl.pdf (S-78) and
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s108lbl.pdf

(S-108), respectively.

6.2.1. Pharmacology and Clinical Pharmacokinetics

An updated PPK analysis was performed on the pooled data from the currently submitted **Study CA209227** (Arms A, B and D) in NSCLC patients and other data from 12 clinical trials in patients with other tumor types and various dosing regimens for nivolumab and ipilimumab.
The results from this updated PPK analysis are generally consistent with those described in the currently approved package insert of nivolumab plus ipilimumab combination (version dated 3/10/2020) and with those previously reported by Zhang J *et al.* and by Sanghavi K *et al.* for nivolumab and ipilimumab, respectively. The PKs of both nivolumab and ipilimuab are well-described by a linear 2-compartment model with time-varying clearance and both drugs have elimination half-life ($t_{1/2}$) values similar to those previously reported (nivolumab: $t_{1/2}$=25 days and ipilimumab: $t_{1/2}$=15 days).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Nivolumab is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the programmed death-1 (PD-1) cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Nivolumab **monotherapy** is currently approved at the dosage of 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W) for various indications including patients with metastatic non-small cell cancer (NSCLC) **with** EGFR or ALK genomic tumor aberrations.

Ipilimumab is a fully humanized IgG1 monoclonal antibody binding to the anti-cytotoxic T-cell lymphoma-4 antigen (CTLA-4), an activation-induced T-cell surface molecule. Ipilimumab **monotherapy** is currently approved for the treatment of patients (≥12 years) with unresectable or metastatic melanoma at the dosage of 3 mg/kg every 3 weeks (Q3W) for a total of 4 doses.

The **combination** of **nivolumab** plus **ipilimumab** is currently approved in the following indications:

- **Unresectable or metastatic melanoma:** Nivolumab 1 mg/kg every 2 weeks (Q2W) followed by ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 doses, then nivolumab 240 mg Q2W or 480 mg every 4 weeks (Q4W).
- **Advanced renal cell carcinoma (RCC):** Nivolumab 3 mg/kg Q2W followed by ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W.
- **Hepatocellular carcinoma (HCC):** Nivolumab 1 mg/kg Q2W followed by ipilimumab 3 mg/kg Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W. A combination of nivolumab plus ipilimumab is recently approved on 3/10/2020 at the approved recommended dosage of 1 mg/kg Q2W nivolumab followed by 3 mg/kg Q3W ipilimumab in patients with HCC (S-78).

- **Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer:** Adult and pediatric patients ≥ 40 kg: Nivolumab 3 mg/kg Q2W followed by ipilimumab 1 mg/kg on Q3W for 4 doses, then nivolumab 240 mg Q2W or 480 mg Q4W.

In the current BLA submission, the Applicant expanded the metastatic NSCLC indication of nivolumab monotherapy in patients with EGFR or ALK genomic tumor aberrations to include using a combination of nivolumab plus ipilimumab in NSCLC patients with no EGFR or ALK genomic tumor aberrations based on the efficacy and safety data from Study CA209227. The proposed dosage for the combination is 3 mg/kg Q2W nivolumab followed by 1 mg/kg Q6W ipilimumab; both to be administered intravenously over a 30-minute intravenous infusion. This proposed dosage of nivolumab (3 mg/kg Q2W) followed by ipilimumab (1 mg/kg Q6W) was selected based on the efficacy and safety data from the phase 1 dose-finding Study CA209012 (Cohorts P and Q). In these cohorts, nivolumab 3 mg/kg Q2W (the approved monotherapy dosage) plus ipilimumab 1 mg/kg Q6W or Q12W were found to be well tolerated and showed promising efficacy.

Therapeutic Individualization

As per respective **approved package** insert, there are no clinically relevant differences in nivolumab or ipilimumab CL in patients with renal impairment or patients with mild hepatic impairment compared to those with normal renal or hepatic function. No dose adjustment is required for patients with renal impairment or mild hepatic impairment for both drugs given as monotherapy or in combination.

Immunogenicity Assessment:

The results of immunogenicity analysis of data from **Study CA209227** indicate that the incidence of anti-drug antibodies (ADAs) for both nivolumab and ipilimumab tends to be higher when both drugs given in combination than that after each drug alone treatment.

In **Arm A** when **nivolumab** was administered as monotherapy, 23.9% out of 322 evaluable patients were tested ADA-positive. In Arm B+D of the study, **36.7% of 491** evaluable patients developed ADAs for nivolumab in the presence of ipilimumab. The incidence of nivolumab neutralizing antibodies was 1.6% in Arm A (monotherapy) and **1.4%** in Arms B+D (nivolumab in ccombination with ipilimumab). In **Arms B**+**D**, 8.5% out of 483 evaluable patients treated with **ipilimumab** developed ADAs in the presence of nivolumab. As per the approved package insert for ipilimumab (Version dated 3/10/2020), 4.9% out of 144 evaluable patients with unresectable or metastatic melanoma receiving ipilimumab monotherapy were tested positive for ipilimumab ADAs. No patients tested positive for ipilimumab neutralizing antibodies whether it was administered as monotherapy or in combination with nivolumab. There was no apparent impact of immunogenicity on the safety of nivolumab or ipilimumab. The impact of immunogenicity on efficacy could not be assessed as the number of ADA-positive patients with clinical response was very small.

Drug Drug Interactions (DDIs):

Both nivolumab and ipilimumab are mAbs and are not expected to have a little potential for DDIs. No formal DDIs studies have been conducted for either nivolumab or ipilimumab.

Based on the updated **PPK analysis** conducted in the current supplement, the coadministration of ipilimumab (1 mg/kg Q6W) with nivolumab (3 mg/kg Q2W) resulted in a 14% increase in nivolumab CL compared to nivolumab monotherapy; however, this increase is not clinically significant (<20%). The coadministration of nivolumab (3 mg/kg Q2W) resulted in a significant increase (by 30%) in ipilimumab CL (1 mg/kg Q6W) compared to ipilimumab monotherapy; the clinical relevance of this increase is **not** known. A statement regarding these changes in CL of nivolumab or ipilimumab when given combination were added by the FDA to the proposed Applicant's package insert.

Outstanding Issues

None.

6.2.3. Summary of Labeling Recommendations

The Office of Clinical Pharmacology proposes the following labeling recommendations to be incorporated in t he final package insert.

Labeling Sections	Applicant's Proposed	Clinical Pharmacology Recommendations
Section 6.2	(b) (4)	**6.2 Immunogenicity** **[Applicant's edits are acceptable based on the immunogenicity data submitted in the current sBLA submission]** There was no evidence of increased incidence of infusion-related reactions or (b) (4) with anti-nivolumab antibody development.
Section 12.3		**12.3 Pharmacokinetics**

Labeling Sections	Applicant's Proposed	Clinical Pharmacology Recommendations
	(b) (4)	**[No FDA's updates were made to the approved labeling statements that are related to the PK, distribution and elimination sub-sections]** **FDA's updates were made in the following approved labeling statements that are related to Specificic Populations sub-section:** Specific Populations The following factors had no clinically important effect on the clearance of

Labeling Sections	Applicant's Proposed	Clinical Pharmacology Recommendations
	(b) (4)	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 ≥ 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). (b) (4) (b) (4) Nivolumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST). **FDA's updates were made in the following approved labeling statements that are related to Drug Interaction Studies sub-section:** Drug Interaction Studies When OPDIVO was administered at 3 mg/kg every 3 weeks in combination with ipilimumab 1 mg/kg, the CL of nivolumab and ipilimumab were unchanged. When OPDIVO 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29% compared to OPDIVO administered alone and the CL of ipilimumab was unchanged compared to (b) (4) ipilimumab administered alone. (b) (4) When OPDIVO was administered at 3 mg/kg every 2 weeks 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

Labeling Sections	Applicant's Proposed	Clinical Pharmacology Recommendations
	(b) (4)	ipilimumab was increased by 30% compared to ipilimumab administered alone. When administered in combination, the CL of nivolumab increased by 20% in the presence of antinivolumab antibodies.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

In response to Secions 6.2.3 and 6.2.4, refer to the the clinical pharmacology reviews performed in DARRTS for BLAs 125554 (nivolumab) and BLA 124377 (ipilimumab) and also refer to their respective approved package insert (most recent version dated 3/10/2020) at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125554s078lbl.pdf (S-78) and https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s108lbl.pdf (S-108), respectively.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

An updated PPK analysis was performed on the data from **Study CA209227** (**Arms A, B and D**) in NSCLC patients pooled with other data from 12 clinical trials in patients with other tumor types and various dosing regimens (N=2899) for nivolumab and ipilimumab (N=2602) (*Full model run by Dr. Yuan Xu, Pharmacometrics Division, FDA; refer to **Appendix 19.5** for parameter estimates*) using the previously developed PPK models by Zhang J, *et al.* (*Zhang J, et al., Population Pharmacokinetics of Nivolumab in Combination with Ipilimumab in Patients with Advanced Malignancies. CPT Pharmacometrics Syst Pharmacol 8:962–970, 2019*) and by Sanghavi K, *et al. (Sanghavi K, et al., Population Pharmacokinetics of Ipilimumab in Combination with Nivolumab in Patients With Advanced Solid Tumors. CPT Pharmacometrics Syst Pharmacol 9:29-39, 2020*), respectively. The results from this updated PPK analysis are generally consistent with those described in the currently approved package insert of nivolumab plus ipilimumab combination (version dated 3/10/2020) and with those previously reported by Zhang J *et al.* and by Sanghavi K *et al.* for nivolumab and ipilimumab, respectively. The PKs of both nivolumab and ipilimuab are well-described by a linear 2-compartment model with time-varying clearance and both drugs have elimination half-life ($t_{1/2}$) values similar to those previously reported (nivolumab: $t_{1/2}$=25 days and ipilimumab: $t_{1/2}$=15 days).

Table 3 below summarizes the predicted steady state serum concentrations estimated from the full PPK model for Study CA209227 for nivolumab and ipilimuman when given in combination by PD-L1 status at the proposed dosage (3 mg/kg Q2W + 1 mg/kg Q6W, respectively). The exposure of each of nivolumab and ipilimumab is similar between the PD-L1 positive patients (PD-L1 ≥1%) with PD-L1 negative patients (PD-L <1%).

Table 3: Geometric Mean (%CV) Predicted Steady State PK Parameters by PD-L1 Status in Study CA209227 in NSCLC Patients

	Arm B (PD-L1 ≥ 1%)	Arm D (PD-L1 < 1%)	Monotherapy (Arm A)
	Nivolumab		
N	331	152	328
$C_{min,ss}$ (µg/mL)	59 (53%)	57 (42%)	66 (42%)
$C_{max,ss}$ (µg/mL)	120 (32%)	119 (25%)	135 (28%)
$C_{avg,ss}$ (µg/mL)	78 (44%)	77 (34%)	88 (35%)
	Ipilimumab		
N	315	149	No ipilimumab monotherapy in **Study CA209227**
$C_{min,d4}$ (µg/mL)	1.95 (64%)	2.26 (65%)	
$C_{max,d4}$ (µg/mL)	21.2 (13%)	21.9 (17%)	
$C_{avg,d4}$ (µg/mL)	5.8 (27%)	6.2 (30%)	

Exposure-Response Relationships for Efficacy and Safety:

In the current supplement, an updated exposure-response (E-R) analysis for each of efficacy and safety was performed on the data from **Study CA209227** in patients with advanced NSCLC treated at dosages of 240 mg Q2W nivolumab alone (**Arm A**) and 3 mg/kg Q2W nivolumab plus 1 mg/kg Q6W ipilimumab (**Arms B+D**). The E-R analysis for **efficacy** characterized the relationship between overall survival (OS) and time-averaged serum concentration after the first dosing interval (C_{avg1}). The E-R analysis for **safety** characterized the relationship between the time to first occurrence of Grade ≥2 immune-mediated adverse reactions (Gr.2+IMAEs) and C_{avg1}. The results of this updated E-R analysis are generally consistent with those described in the currently approved package insert of nivolumab plus ipilimumab combination (version dated 3/10/2020) and those reported for nivomumab and ipilimumab by Feng Y, *et al.* (*Feng Y, et al., Nivolumab Exposure–Response Analyses of Efficacy and Safety in Previously Treated Squamous or Nonsquamous Non–Small. Cell Lung Cancer. Clin Cancer Res 23:5394-405, 2017*) and by Feng Y *et al.* (*Feng Y, et al., Exposure–response relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma. Clin Cancer Res 19:3977-3986, 2013*), respectively.

This upated E-R analysis did **not** have an impact on labeling and the Applicant has **not** made any labeling claims in their proposed package insert.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen of nivolumab (3 mg/kg Q2W) followed by ipilimumab (1 mg/kg Q6W) was selected based on the safety and efficacy data obtained from **Study CA209012** (CheckMate 012) (also published by: *Hellmann MD, et al. Nivolumab plus ipilimumab as first-line treatment for advanced Non-Small-Cell Lung Cancer (CheckMate 012): Results of an Open-Label, Phase 1, Multi-cohort Study. Lancet Oncol. 18:31–41, 2017*). **Study CA209012** was a phase 1 multi-cohort study that evaluated the safety and clinical activity of nivolumab in combination with ipilimumab in 197 patients with previously untreated advanced NSCLC regardless of the PD-L1 status. Of six nivolumab+ipilimumab combination cohorts evaluated,

four were excluded from further clinical development because of the poor tolerability or insufficient clinical activity. The two remaining cohorts (**Cohorts P** and **Q**, N=77) of nivolumab 3 mg/kg Q2W (approved dosage) in combination with low dose/less frequent dose of ipilimumab (1 mg/kg Q6W or Q12W) demonstrated to be safe and effective for the treatment of advanced NSCLC (See Applicant's table below).

Table 3.4.1-1: Key Efficacy and Safety Data of Nivolumab in Combination with Ipilimumab in NSCLC - Study CA209012

Cohort[a]	No. Subj.	Regimen[b]	Efficacy and Safety Results (All Treated Subjects)	Interpretation
Pooled G, H	24	N1+ I3 Q3W x 4 then N3 Q2W	• 89.8% drug-related AEs (any grade) • 53.1% drug-related AEs (Grade 3-4) • 38.8% drug-related AEs leading to DC • 3 drug-related deaths • 20.8% ORR (N1 + I3); 24.0% ORR (N3+I1)	High % of AEs leading to discontinuation, which compromised efficacy
Pooled I, J	25	N3 + I1 Q3W x 4 then N3 Q2W		
N	31	N1 + I1 Q3W x 4 then N3 Q2W	• 83.9% drug-related AEs (any grade) • 29.0% drug-related AEs (Grade 3-4) • 9.7% drug-related AEs leading to DC • 0 drug-related deaths • 22.6% ORR	Improved tolerability but the low dose of nivolumab compromises efficacy
O	40	N1 Q2W + I1 Q6W	• 70.0% drug-related AEs (any grade) • 32.5% drug-related AEs (Grade 3-4) • 7.5% drug-related AEs leading to DC • 0 drug-related deaths • 32.5% ORR	
P	38	N3 Q2W + I1 Q12W	• 84.2% drug-related AEs (any grade) • 39.5% drug-related AEs (Grade 3-4) • 15.8% drug-related AEs leading to DC • 0 drug-related deaths • 47.4% ORR • 77.8% DOR (responding ≥ 6 months) • 71.8% DOR (responding ≥ 12 months)	Less frequent and continuous ipilimumab with approved dose of nivolumab results in manageable tolerability and promising efficacy
Q	39	N3 Q2W + I1 Q6W	• 74.4% drug-related AEs (any grade) • 28.2% Grade 3-4 AEs • 17.9% drug-related AEs leading to DC • 0 drug-related deaths • 38.5% ORR • 100% DOR (responding ≥ 6 months) • 75.2% DOR (responding ≥ 12 months)	

Source: Table 7.4.1-1 and Table 7.3-1 (pooled Cohorts GH and IJ); Table 8.4.1-1 and Table 8.3-1 (Cohorts N and O);

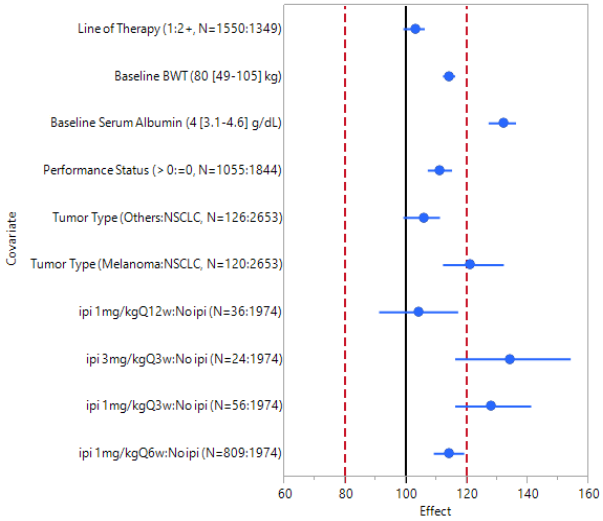
Thus, the data from the combination **Cohorts P** and **Q** of **Study CA209012** supported the proposed recommended dosing regimens of the combination of nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W in **Study CA209227** in NSCLC patients. In the ongoing phase 3 **Study CA209817**, patients with Stage IV or recurrent NSCLC are being treated at nivolumab dosage of 240 mg Q2W (equivalent to 3 mg/kg Q2W for an 80-kg patient) plus ipilimumb dosage of 1 mg

Q6W. The results from the current **Study CA209227** and **Study CA209568** at the doses of 3 mg/kg Q2W nivolumab plus ipilimumb 1 mg Q6W were recently published by Reck M, et al. (*Reck M et al., Nivolumab plus ipilimumab in non-small-cell lung cancer. Future Oncol 15:2287–2302, 2019*).

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

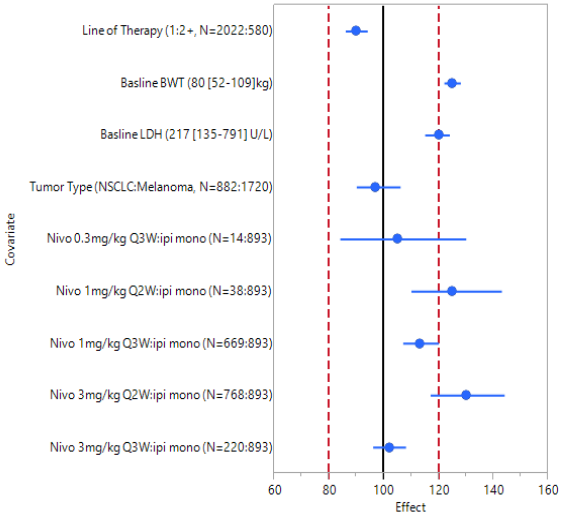
The effects of covariates on the CL of nivolumab and ipilimumab (estimated as geometric mean ratio [95% confidence (CI]) are assessed using the updated PPK analysis (*Full model run by Dr. Yuan Xu, Pharmacometrics Division, FDA; refer to **Appendix 19.5** for parameters estimates*). The results of this covariate analysis for both nivolumab and ipilimumab are generally consistent with those currently described in the approved package insert of the combination (version dated 3/10/2020) and those previously reported by Zhang J, *et al*. (*Zhang J, et al., Population Pharmacokinetics of Nivolumab in Combination With Ipilimumab in Patients with Advanced Malignancies. CPT Pharmacometrics Systs Pharmacol 8:962-970, 2019*) and by Sanghavi K, *et al*. (*Sanghavi, K et al., Population Pharmacokinetics of Ipilimumab in Combination with Nivolumab in Patients With Advanced Solid Tumors. CPT Pharmacometrics Syst Pharmacol 9:29-39, 2020*). A summary of the results of covariates effects (geometric mean ratio [95% CI]) from the PPK analysis is shown in Figure 1 and Figure 2 below for nivolumab and ipilimumab, respectively.

Figure 1. Covariate Effects (95% CI) on Nivolumab CL (Full Nivolumab PPK Model)



Note: Typical reference CL_{REF} value (10.9 mL/h) is for a male patient with NSCLC, white/other race with BBW = 80 kg, PS = 0, eGFR = 90 mL/min/1.73 m^2, and received nivolumab monotherapy.
Parameter estimate in the reference patient is considered as 100% (black solid line) and dashed vertical lines are at 80% and 120% of this value.

Figure 2. Covariate Effects (95% CI) on Ipilimumab CL (Full Ipilimumb PPK Model)



Note: Typical reference CL_{REF} value is for patients with melanoma receiving ipilimumab monotherapy as a 2nd line therapy, weighing 80 kg and baseline lactate dehydro-genase (LDH) of 217 U/L.
Parameter estimate in a reference subject is considered as 100% (black solidline) and dashed vertical lines are at 80% and 120% of this value.

Effect of Covariates on Nivolumab CL:

From Figure 1, it can be seen that:

- Nivolumab CL in patients treated with nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W was 14% higher than patients treated with nivolumab monotherapy; however, the magnitude is considered not clinically relevant (< 20%). The FDA added the following statement regarding the differences in CL of nivolumab when given in combination ipilimumab to the proposed labeling:

  "Coadministration of ipilimumab 1 mg/kg Q6W resulted in a 14% increase in nivolumab CL compared to nivolumab monotherapy".

- Nivolumab CL was higher in patients with higher baseline body weight (BWT); however, the magnitude of the difference is considered not clinically relevant.
- Nivolumab CL was 32% higher in subjects with lower baseline serum albumin.
- Nivolumab CL in patients with melanoma was 21% higher than in patients with NSCLC; the magnitude is considered not clinically relevant.

Effect of Covariates on Ipilimumab CL:

From Figure 2, it can be seen that:

- Ipilimumab CL is 30% higher when administered in combination with nivolumab 3 mg/kg Q2W relative to ipilimumab monotherapy; the clinically relevance of this higher clearace is not known. The FDA added the following statement regarding the differences in CL of nivolumab when given in combination ipilimumab to the proposed labeling:

  "Coadministration of nivolumab 3 mg/kg Q2W resulted in a 30% increase in ipilimumab CL compared to ipilimumab monotherapy."

- Ipilimumab CL was significantly lower in patients who received first-line treatment as compared to second line treatment.
- Ipilimumab CL was increased by baseline BWT consistent with results from the previous analysis describing ipilimumab PK for combination therapy which determined BBWT to be a statistically significant covariate.
- The magnitude of the effect of baseline lactate dehydrogenase (BLDH) was statistically significant; however, magnitude of the effect is unlikely to be clinically significant.

- **Effect of Immunogenicity**

Serum samples collected from patients who enrolled in Part 1 of **Study CA209227** (table below) were evaluated for the presence of nivolumab anti-drug antibodies (ADAs) (**Arms A**, **B** and **D**) and ipilimumab ADAs (**Arm B:** PD-L1 ≥ 1% and **Arm D:** PD-L1 < 1%) using the approved validated electrochemiluminescence [ECL] assay method. The neutralizing activity against nivomulab and ipililumab ADAs was evaluated in serum samples using the approved validated functional cell-based assay method.

Population	Arm A (Nivo)	Arm B (Nivo + Ipi)	Arm C (Chemo)	Arm D (Nivo + Ipi)	Arm G (Nivo+ Chemo)	Arm F (Chemo)	Arms B +D (Pooled Nivo + Ipi)	Arms C + F (Pooled Chemo)	Total n/N (%)
Immunogenicity subjects: treated subjects with baseline and at least 1 post-baseline assessment for anti-drug antibody (ADA) (used for immunogenicity).									
Nivolumab ADA Evaluable	322	334	--	157	148	--	491	--	961
Ipilimumab ADA Evaluable	--	329	--	154	--	--	483	--	483

The results of immunogenicity analysis indicate that the incidence anti-nivolumab and anti-ipilimumab antibodies tends to be higher when given in combination than that after each drug alone treatment This may be due to the different immunostimulatory mechanisms of these immune checkpoint inhibitors (See Table 4 and Table 5 below).

Table 4: Number (%) of Patients with Nivolumab Immunogenicity Assessments Alone and When Given in Combination with Ipilimumab in Part 1 of Study CA209227 (Arms A, B and D)

Preferred Term	Arm A (No PD-L1) (Nivolumab Alone)	Arm B (PD-L1 ≥ 1%) (Nivolumab+ Ipilimumab)	Arm D (PD-L1 < 1%) (Nivolumab+ Ipilimumab)	Arm B + Arm D (Nivolumab+ Ipilimumab)
Total Evaluable Patients, N	322	334	157	491
Baseline ADA Positive, N (%)	33 (10%)	31 (9.3%)	13 (8.3%)	44 (8.9%)
ADA Positive, N (%)	77 (23.9%)	127 (38%)	53 (33.8%)	180 (36.7%)
• Persistent positive (PP), N (%)	2 (0.6%)	7 (2.1%)	0 (0%)	7 (1.4%)
• Not PP-Last sample positive, N (%)	17 (5.3%)	28 (8.4%)	16 (10%)	44 (8.9%)
• Other positive, N (%)	58 (18%)	92 (27%)	37 (23.6%)	129 (26.3%)
• Neutralizing ADA positive, N (%)	5 (1.6%)	6 (1.8%)	1 (0.6%)	7 (1.4%)
ADA Negative, N (%)	245 (76%)	207 (62%)	104 (66%)	311 (63%)

Source: Table S.7.10.1 of the CA209227.
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 PPLast
Sample Positive: Not PP with ADA-positive sample at the last sampling timepoint;
Other Positive: Not PP 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.

Table 5: Number (%) of Patients with Ipilimumab Immunogenicity Assessments When Given in Combination with Nivolumab in Part 1 of Study CA209227 (Arms B and D)

Preferred Term	Arm B (PD-L1 ≥ 1%) (Nivolumab+ Ipilimumab)	Arm D (PD-L1 < 1%) (Nivolumab+ Ipilimumab)	Arm B + Arm D (Nivolumab+ Ipilimumab)
Total Evaluable Patients, N	329	154	483
Baseline ADA Positive, N (%)	12 (3.6%)	8 (5.2%)	20 (4.1%)
ADA Positive, N (%)	30 (9.1%)	11 (7.1%)	41 (8.5%)
• Persistent positive (PP), N (%)	3 (0.9%)	0 (0%)	3 (0.9%)
• Not PP-Last sample positive, N (%)	12 (3.6%)	1 (0.6%)	13 (2.7%)
• Other positive, N (%)	15 (4.6%)	10 (6.5%)	25 (5.2%)
• Neutralizing ADAs positive, N (%)	0 (0%)	0 (0%)	0 (0%)
ADA Negative, N (%)	299 (91%)	143 (93%)	442 (91%)

Source: Table S.7.10.1 of the CA209227.
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 PPLast
Sample Positive: Not PP with ADA-positive sample at the last sampling timepoint;
Other Positive: Not PP 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.

Nivolumab as monotherapy or in combination with ipilimumab:

Out of the 491 evaluable patients for **nivolumab** ADAs in **Arms B and D**, 180 (36.7%) had at least one nivolumab ADA-positive sample relative to baseline at any time after initiation of treatment when given in combination with ipilimumab. Seven (1.4%) patients were neutralizing ADA-positive.

In **Arm A**, out of the 322 evaluable patients for nivolumab ADAs, 77 (23.9%) had at least one nivolumab ADA-positive sample relative to baseline at any time after initiation of treatment when nivolumab was administered as monotherapy. Five (1.6%) patients were neutralizing ADA (Nab)-positive.

Ipilimumab in combination with nivolumab (Arm B + Arm D):

Out pf the 483 evaluable patients for **ipilimumab** ADAs in **Arm B + Arm D**, 41 (8.5%) had at least one ipilimumab ADA-positive sample relative to baseline at any time after initiation of treatment when given in combination with nivolumab. No patients had ipilimumab neutralizing ADAs (0%).

As per the recently approved package insert version for ipilimumab dated 3/10/2020, seven out of 144 (4.9%) patients with unresectable or metastatic melanoma receiving ipilimumab monotherapy were tested positive for ipilimumab ADAs. There were no patients with neutralizing antibodies against ipilimumab monotherapy.

Impact of Immunogenicity on Efficacy

The impact of immunogenicity on efficacy could not be assessed as none of the patients who developed nivolumab or ipilimumab ADAs had any clinical response versus non-responders.

Effect of Immunogenicity on Safety

The incidence of nivolumab or ipilimumab ADAs did not appear to be associated with the occurrence of hypersensitivity and/or infusion-related adverse reactions (See Table 6 and Table 7 below).

Table 6: Number (%) of Patient with Emergent Treatment Related Adverse Reactions by ADA Status for Nivolumab

Preferred Term	Arm A (Nivolumab Alone)		Arm B (PD-L1 ≥ 1%) (Nivolumab+ Ipilimumab)		Arm D (PD-L1 < 1%) (Nivolumab+ Ipilimumab)		Arm B + Arm D (All) (Nivolumab+ Ipilimumab)	
ADAs (N)	Positive (N=77)	Negative (n=245)	Positive (N=127)	Negative (N=207)	Positive (N=53)	Negative (N=104)	Positive (N=180)	Negative (N=311)
Total patients with an event	3 (3.9%)	11 (4.5%)	6 (4.7%)	9 (4.3%)	4 (7.5%)	7 (6.7%)	10 (5.6%)	16 (5.1%)
Anaphylactic reaction	0	1 (0.4%)	0	1 (0.5%)	0	1 (1.0%)	0	2 (0.6)
Bronchospasm	0	2 (0.8%)	2 (1.6%)	0	1 (1.9%)	1 (1.0%)	3 (1.7%	1 (0.3%)
Hypersensitivity	0	2 (0.8%)	0	2 (1%)	1 (1.9%)	0	1 (0.6%)	2 (06%)
Infusion related reaction	3 (3.9%)	6 (2.4%)	4 (3.1)	6 (2.9%)	2 (3.8%)	5 (4.8%)	6 (3.3%)	11 (3.5%)

Source: Refer to Table S.7.238 in the CA209227 Part 1

Table 7: Number (%) of Patient with Emergent Treatment Related Adverse Reactions for Ipilimuab

Preferred Term	Arm B (PD-L1 ≥ 1%) (Nivolumab+ Ipilimumab)		Arm D (PD-L1 < 1%) (Nivolumab+ Ipilimumab)		Arm B + Arm D (All) (Nivolumab+ Ipilimumab)	
ADAs (N)	Positive (N=30)	Negative (N=299)	Positive (N=11)	Negative (N=143)	Positive (N=41)	Negative (N=442)
Total patients with an event	4 (13.3%)	10 (3.3%)	2 (18%)	9 (6.3%)	6 (14.6%)	19 (4.3%)
Anaphylactic reaction	0	1 (0.3%)	1 (9.1%)	0	1 (2.4%)	1 (0.2%)
Bronchospasm	1 (3.3%)	1 (0.3%)	0	2 (1.4%)	1 (2.4%)	3 (0.7%)
Hypersensitivity	0	2 (0.7%)	0	1 (0.7%)	0	3 (0.7%)
Infusion related reaction	3 (10%)	6 (2.0%)	1 (9.1%)	6 (4.2%)	4 (9.8%)	12 (2.7%)

Source: Refer to Table S.7.238 in the CA209227 Part 1

In **Arms B+D** of the study, the proportion of patients with infusion-related reactions was comparable between **nivolumab** ADA-positive and nivolumab ADA-negative subgroups suggesting that the presence of nivolumab ADAs did not appear to be associated with the occurrence of these events. The proportion of patients with infusion reactions was higher in **ipilimumab** ADA-positive patients than in ipilimumab ADA-negative subjects; however, most of these infusion reactions, as per the Applicant, were Grade 1 or 2 and all events have been resolved.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Both nivolumab and ipilimumab are mAbs and are to be administered intravenous, food effect or DDI studies are not required.

Question on clinically relevant specifications (TBD)?

None.

Safaa Burns	Jeanne Zirkelbach Fourie
Primary Reviewer	Team Leader
Xu Yuan	Jiang Liu
Primary Reviewer	Team Leader

APPEARS THIS WAY
ON ORIGINAL

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

This review focuses primarily on the results of **Study CA209227 (CHECKMATE-227)**, entitled, "An Open-Label, Randomized, 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." Study CA209227 has undergone multiple revisions since its original submission to IND 125872 on March 18, 2015; these are described in the section above. In addition, BMS provided supportive summary results from three additional single arm trials (Studies CA209568 [Part 1], CA209817 [Cohort A], and CA209012 [Cohort Q]) evaluating the safety (Studes CA209568, CA209817, and CA209012) and efficacy (Studies CA209568 and CA209817) of nivolumab administered in combination with ipilimumab in patients with previously untreated or chemotherapy-naïve NSCLC. Summary results from an additional randomized trial, Study CA209026, in which patients with previously untreated metastatic NSCLC were randomized to receive either nivolumab as a single agent or chemotherapy, were also provided as supportive data to assess the contribution of ipilimumab to the combination.

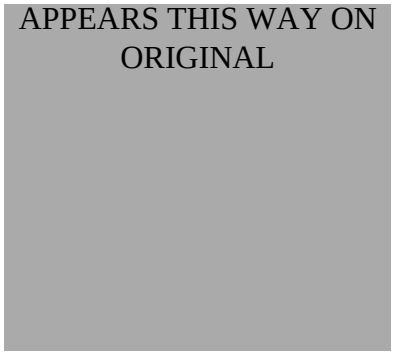


Table 8: Clinical trials supporting the sBLAs

APPEARS THIS WAY ON ORIGINAL

Study ID	Trial Design	# of Patients treated	Treatment Group	Primary Endpoint*
Safety and efficacy (pivotal trial)				
CA209227 **Phase III**	International, multicenter, open-label, randomized, three-part (Parts 1a, 1b, 2) study with three arms in Part 1a (Arms A, B, C) and Part 1b (Arms D, F, G)	Arm A (nivo monotherapy): 396 Arm B (nivo/ipi): 396 Arm C (chemo): 397 Arm D: (nivo/ipi): 180 Arm F (chemo): 173 Arm G (nivo + chemo): 172	Patients with recurrent or metastatic treatment-naïve NSCLC, PD-L1 positive (≥ 1%) (Part 1a) or negative (< 1%) (Part 1b)	***sBLAs:*** Pre-specificed final analysis of OS comparing nivolumab + ipilimumab (Arm B) vs. chemotherapy (Arm C) (alpha=0.0249, Part 1a) and an exploratory analysis of OS comparing nivolumab + ipilimumab (Arm D) vs. chemotherapy (Arm F) (Part 1b)
Supportive studies				
CA209568 **Phase II**	Open-label, two part, single arm, activity estimating study of nivolumab + ipilimumab (Part 1, completed) and nivolumab + ipilimumab + chemotherapy (Part 2, ongoing)	Part 1: 288 PD-L1 ≥ 1%: 138 (nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W)	Previously untreated NSCLC	Part 1: ORR per BICR in patients with PD-L1 expression ≥ 1% and < 1%

CA209817 **Phase II**	Open-label, ongoing, single arm, multiple cohort study of flat dose nivolumab in combination with ipilimumab	Cohort A: 391 (nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W) PD-L1 ≥ 1%: 176	Cohort A: previously untreated NSCLC	Primary: safety of flat dose nivolumab in combination with ipilimumab Secondary: PFS, OS, DOR, ORR
CA209012 (Safety) **Phase I**	Multiple cohort study of nivolumab as monotherapy, in combination with ipilimumab, or in combination with chemotherapy or targeted therapy.	8 nivolumab + ipilimumab cohorts including: Cohort Q (n=39): nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W	Patients with chemotherapy-naïve stage IIIB/IV or recurrent NSCLC regardless of PD-L1 expression	Safety and tolerability of nivolumab in combination with ipilimumab in chemotherapy-naïve patients with stage IIIB/IV NSCLC
CA209026 **Phase III**	International, multicenter, open-label, randomized study of nivolumab vs. investigator's choice chemotherapy	Nivolumab: 267 Chemotherapy: 263	Patients with previously untreated NSCLC with PD-L1 expression ≥ 1%	BICR-assessed PFS of nivolumab vs. chemotherapy in patients with PD-L1 tumor expression ≥ 5%

*Clinical cutoff date: July 2, 2019

The safety analysis of Study CA209227 was evaluated in the context of a side-by-side comparison and pooled analysis of three studies in which patients with NSCLC received nivolumab in combination with ipilimumab (CA209568, CA209817, and CA209012) as well as an integrated comparison of the nivolumab and ipilimumab-containing arms of Study CA209227 (Arms B/D) with data from other approved combination regimens (with similar nivolumab and ipilimumab schedules) in other tumor types (renal cell carcinoma [RCC; Study CA209214] and colorectal cancer [CRC; Study CA209142]). A comparison to safety data from each arm in Part 1A of Study CA209227, including Arm A (nivolumab as a single agent), was also made.

Table 9: Pooled safety dataset for nivolumab in combination with ipilimumab in patients with NSCLC

Study	Number of patients and data cutoff date
CA209227, Part 1	576; July 2, 2019
CA209568, Part 1	288; May 30, 2018
CA209817, Cohort A	391; June 28, 2019
CA209012, Cohort Q	39; September 19, 2016
	Total: 1294

APPEARS THIS WAY
ON ORIGINAL

7.2. Review Strategy

The clinical review of Study CA209227 included review and analysis of the Clinical Study Report (CSR), Summary of Clinical Safety (SCS), Summary of Clinical Efficacy (SCE), BMS' risk:benefit assessment, case report forms (CRFs), narratives, the Integrated Summary of Safety (ISS), the Integrated Summary of Efficacy (ISE), and the submitted datasets. The safety review included reviewer analysis of key safety datasets using the Safety Tool via the safety analysis query request form. The statistical review of efficacy was completed by Mallorie Fiero. The safety review was conducted by Nicole Drezner.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CA209227

Trial Design

Study CA209227 (CHECKMATE-227, NCT02477826) was a randomized, multi-cohort, open-label study in patients with NSCLC. The design of Study CA209227 has undergone multiple revisions since its original submission to IND 125872 on March 18, 2015; major revisions affecting Part 1 of Study CA209227 were incorporated in the protocols submitted to the IND on December 13, 2016 and November 8, 2017. The following description focuses on the current version of the protocol.

The current version of the protocol has multiple independent parts and tests two key hypotheses, the efficacy of nivolumab alone and of nivolumab plus ipilimumab in patients with NSCLC harboring a high level of tumor mutation burden and the efficacy of nivolumab plus chemotherapy and of nivolumab plus ipilimumab in patients with NSCLC based on the intensity of PD-L1 tumor expression. These key hypotheses are described in Table 5. This sBLA is limited to analyses conducted on Part 1a of Study CA209227, which includes patients with NSCLC who express PD-L1.

Table 10 TMB and PD-L1 statistical hierarchies in Study CA209227

TMB hierarchy (alpha = 0.025)	**PD-L1 hierarchy (alpha = 0.0249)***
1. Primary: PFS nivolumab + ipilimumab vs. chemotherapy in patients with TMB ≥ 10 mut/Mb	1. Primary: OS nivolumab + ipilimumab vs. chemotherapy in patients with PD-L1 ≥ 1%
2. PFS nivolumab vs. chemotherapy in patients with TMB ≥ 13 mut/Mb (and PD-L1 ≥ 1%)	2. PFS nivolumab + chemotherapy vs. chemotherapy in patients with PD-L1 < 1%
3. OS nivolumab + ipilimumab vs. chemotherapy in patients with TMB ≥ 10 mut/Mb	3. OS nivolumab + chemotherapy vs. chemotherapy in patients with PD-L1 < 1%
4. OS nivolumab vs. chemotherapy in patients with TMB ≥ 13 mut/Mb (and PD-L1 ≥ 1%)	4. OS nivolumab vs. chemotherapy in patients with PD-L1 ≥ 50%

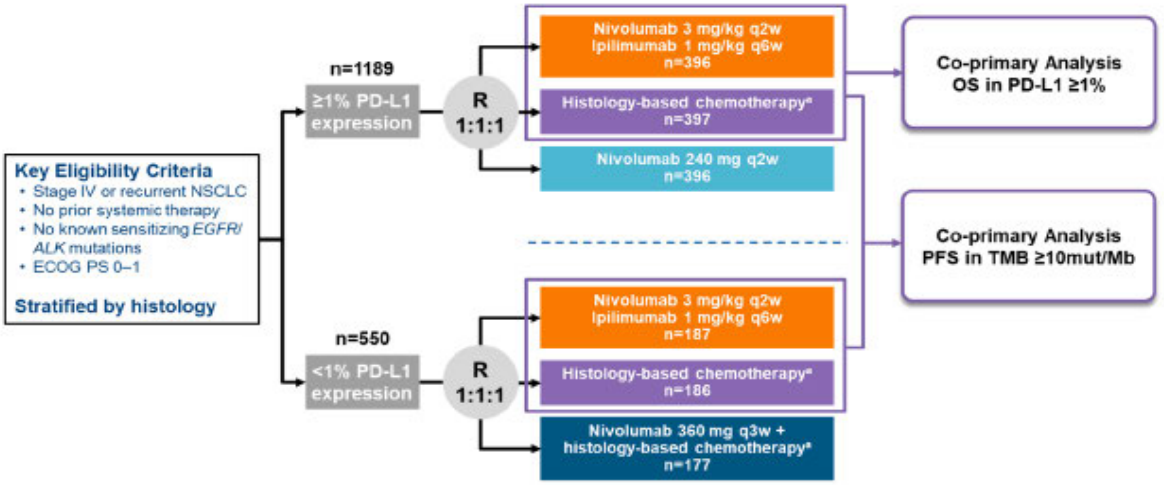
*Alpha of 0.0001 was spent for an interim analysis of ORR for patients with PD-L1 ≥ 1%

Patients were stratified by PD-L1 tumor expression levels (≥ 1% vs. < 1%) and assigned into Parts 1a and 1b based on PD-L1 status during randomization. Key eligibility criteria for Parts 1a and 1b are:

- Part 1a: patients with recurrent or metastatic previously untreated PD-L1 positive (≥1%) NSCLC
- Part 1b: patients with recurrent or metastatic previously untreated PD-L1 negative (<1%) NSCLC

Patients were accrued to Parts 1a and 1b simultaneously; eligibility criteria were the same except for PD-L1 status. In both parts of the study, randomization was stratified by tumor histology (squamous vs. non-squamous) within each PD-L1 group. Figure 3 illustrates the study design for Parts 1a and 1b.

Figure 3: Study CA209227 Schema (Part 1)



[a] Squamous (SQ) histology: gemcitabine with cisplatin or gemcitabine with carboplatin
Non-squamous (NSQ) histology: pemetrexed with cisplatin or pemetrexed with carboplatin. Subjects with stable disease or response after cycle 4 could have continued pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity.

Abbreviations: ALK - anaplastic lymphoma kinase, ECOG - Eastern Cooperative Oncology Group, EGFR - epidermal growth factor receptor, IV - intravenous, mut/Mb - mutations per megabase, NSCLC - non-small cell lung cancer, OS - overall survival, PD-L1 - programmed cell death ligand 1, PFS - progression-free survival, PS - performance status, qXw - every X weeks, TMB - tumor mutational burden

Source: Figure 3.1-1 in Study CA209227 CSR

In Part 1a (PD-L1 ≥ 1%), eligible patients were randomly assigned (1:1:1) to:

- Arm A: nivolumab 240 mg IV every 2 weeks until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue
- Arm B: nivolumab 3 mg/kg IV every 2 weeks and ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue
- Arm C: platinum-doublet chemotherapy; acceptable regimens administered on day 1 of each 21-day cycle for a maximum of 4 cycles, based on tumor histology, as follows:
    - patients with squamous histology may receive:
        - gemcitabine (1000 or 1250 mg/m^2) IV and cisplatin 75 mg/m^2 IV;
        - gemcitabine (1000 mg/m^2) IV and carboplatin (AUC 5) IV; or
        - paclitaxel (200 mg/m^2 IV and carboplatin (AUC 6) IV.
    - patients with non-squamous histology should receive:
        - pemetrexed 500 mg/m^2 IV and either cisplatin (75 mg/m^2); or
        - pemetrexed 500 mg/m^2 IV and carboplatin (AUC 5 or 6).
        - after completion of platinum-doublet chemotherapy, patients with stable or responding disease may receive pemetrexed 500 mg/m^2 IV every 21 days as maintenance therapy until disease progression or unacceptable toxicity.

In Part 1b, eligible patients were randomly assigned (1:1:1) to:

- Arm D: nivolumab 3 mg/kg IV every 2 weeks and ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue
- Arm G: nivolumab 360 mg IV and platinum-doublet chemotherapy on day 1 of each 21-day cycle for 4 cycles then nivolumab 360 IV mg alone every 21-days until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue
- Arm F: platinum-doublet chemotherapy based on tumor histology as described for Arm C in Part 1a.

Tumor re-staging assessments were performed every 6 weeks until Week 48 and every 12 weeks thereafter.

Study Population

Inclusion criteria

1. Signed Written Informed Consent
    a. Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.
    b. Subjects must be willing and able to comply with scheduled visits, treatment schedule, and laboratory testing.
2. Target Population
    a. ECOG Performance Status of ≤ 1
    b. Subjects with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification (IASLC) squamous or non-squamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.
    Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment.
    Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (which ever was given last) occurred at least 6 months prior to enrollment.
    c. Measurable disease by CT or MRI per RECIST 1.1 criteria; radiographic tumor assessment performed within 28 days of randomization.
        i. Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site after the completion of radiation therapy.

d. Subjects must have PD -L1 IHC testing, with results, performed by the central lab during the Screening period. (Note: Although Part 2 allows subjects with unevaluable samples to randomized, PD-L1 testing must have been performed prior to randomization, and the results must be documented as unevaluable). Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to randomization. The tumor tissue sample may be fresh or archival if obtained within 6 months prior to enrollment, and there can have been no systemic therapy (e.g., adjuvant or neoadjuvant chemotherapy) given after the sample was obtained.
   Tissue must be a core needle biopsy, excisional or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins are not considered adequate for biomarker review and randomization. Biopsies of bone lesions that do not have a soft tissue component or decalcified bone tumor samples are also not acceptable.
e. Prior palliative radiotherapy to non-CNS lesions must have been completed at least 2 weeks prior to randomization. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of randomization are strongly encouraged to receive palliative radiotherapy prior to randomization.
f. Screening laboratory values must meet the following criteria (using CTCAE v4):
   i. WBC ≥ 2000/µL
   ii. Neutrophils ≥ 1500/µL
   iii. Platelets ≥ 100 x 10^3/µL
   iv. Hemoglobin ≥ 9.0 g/dL
   v. Serum creatinine ≥ 1.5 x ULN or calculated creatinine clearance ≥ 50 mL/min (using the Cockcroft Gault formula)
   vi. AST/ALT ≤ 3.0 x ULN (≤ 5 x ULN if liver metastases are present)
   vii. Total bilirubin ≤ 1.5 x ULN except subjects with Gilbert Syndrome who must have a total bilirubin level < 3.0 mg/dL).

3. Age and Reproductive Status
   a. Males and Females, ages ≥ 18 years of age
   b. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
   c. Women must not be breastfeeding
   d. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and 5 months after the last dose of nivolumab {i.e., 30 days (duration of ovulatory cycle) plus the time required for nivolumab to undergo approximately five half-lives} (for subjects treated in arms A, B, D, G and H).
      WOCBP must also agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with chemotherapy

plus 5 half-lives of chemotherapy plus 30 days (duration of ovulatory cycle) for a total of 30 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for subjects treated in arms C, F and I).

e. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab and 7 months after the last dose of nivolumab {i.e., 90 days (duration of sperm turnover) plus the time required for nivolumab to undergo approximately five half-lives} (for subjects treated in arms A, B, D, G and H).
Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 90 days (duration of sperm turnover) for a total of 90 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for subjects treated in arms C, F and I).

f. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in these sections.

Exclusion criteria

1) Target Disease Exceptions
    a. Subjects with known EGFR mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. All subjects with non-squamous histology must have been tested for EGFR mutation status; use of an FDA-approved test is strongly encouraged. Subjects with non-squamous histology and unknown or indeterminate EGFR status are excluded.
    b. Subjects with known ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. If tested, use of an FDA-approved test is strongly encouraged. Subjects with unknown or indeterminate ALK status may be enrolled.
    c. Subjects with untreated CNS metastases are excluded.
    d. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of □ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.
    e. Subjects with carcinomatous meningitis
2) Medical History and Concurrent Diseases
    a. Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before randomization.

b. Subjects with previous malignancies (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to randomization and no additional therapy is required or anticipated to be required during the study period.
c. Other active malignancy requiring concurrent intervention.
d. Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
e. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
f. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
g. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
h. Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.

3) Physical and Laboratory Test Findings
    a. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection
    b. Subjects with ≥ Grade 2 peripheral neuropathy
4) Allergies and Adverse Drug Reaction
    a. History of allergy or hypersensitivity to platinum-containing compounds or other study drug components
5) Other Exclusion Criteria
    a. Prisoners or subjects who are involuntarily incarcerated
    b. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

Study Endpoints

Primary endpoints

For the PD-L1 hierarchy, the primary endpoint was OS among patients with tumors expressing PD-L1 ≥ 1% for nivolumab in combination with ipilimumab (Arm B) vs. platinum-doublet chemotherapy (Arm C). BMS defined OS as the time from date of randomization to the date of death due to any cause.

For the TMB hierarchy, the primary endpoint was PFS (based on BICR assessment) among patients with tumors with high baseline TMB (≥ 10 mut/Mb) for nivolumab in combination with ipilimumab (Arms B/D) vs. platinum-doublet chemotherapy (Arms C/F) regardless of PD-L1 expression level. BMS defined PFS as the time from date of randomization to the date of first documented progression or death due to any cause, whichever occurs first.

Secondary endpoints

PD-L1 hierarchy

1. BICR-assessed PFS nivolumab in combination with platinum-doublet chemotherapy (Arm G) vs. platinum-doublet chemotherapy (Arm F) in patients with tumors expressing PD-L1 < 1%
2. OS nivolumab in combination with platinum-doublet chemotherapy (Arm G) vs. platinum-doublet chemotherapy (Arm F) in patients with tumors expressing PD-L1 < 1%
3. OS nivolumab (Arm A) vs. platinum-doublet chemotherapy (Arm C) in patients whose tumors express PD-L1 ≥ 50%

TMB hierarchy

1. BICR-assessed PFS nivolumab monotherapy (Arm A) vs. platinum-doublet chemotherapy (Arm C) in patients whose tumors express PD-L1 ≥ 1% and have high baseline TMB (≥ 13 mut/Mb)
2. OS nivolumab in combination with ipilimumab (Arms B/D) vs. platinum-doublet chemotherapy (Arms C/F) in patients with high baseline TMB (≥ 10 mut/Mb) regardless of PD-L1 expression level
3. OS of nivolumab (Arm A) vs. platinum-doublet chemotherapy (Arm C) in patients whose tumors express PD-L1 ≥ 1% and have high baseline TMB (≥ 13 mut/Mb)

Clinical outcomes assessment (COA) endpoints

Clinial outcomes assessment (COA) endpoints included the proportion of treated patients with disease-related symptom deterioration by 12 weeks as measured by the Lung Cancer Symptom Score (LCSS) average symptom burden index (ASBI) and time-to-deterioration (TTD) in symptoms measured by LCSS ASBI. TTD is defined as time from date of randomization to first date of a 10 point or more increase from baseline. LCSS and EQ-5D were collected every 2 weeks for nivolumab and every 3 weeks in the control arm.

Statistical Analysis Plan

FDA's review of efficacy is limited to the PD-L1 hierarchy (see Table 5).

A total of 800 PD-L1 ≥ 1% patients were planned to be accrued for nivolumab and ipilimumab arm (Arm B) and platinum-doublet chemotherapy arm (Arm C). Assuming the median OS was 13.8 months in the chemotherapy arm and 18.6 months in the nivolumab and ipilimumab arm, a total of 554 events were needed to detect a hazard ratio (HR) of 0.74 with 90% power at a

two-sided alpha level of 2.49%.

One interim ORR was performed when approximately 484 randomized PD-L1+ patients (Arms A, B, and C) had a minimum follow-up of 6 months in Part 1A. An alpha of 0.01% was allocated for this analysis.

One interim analysis for efficacy and futility was performed after 388 (70%) events. The O'Brien Fleming (OBF) boundary method was utilized with respective alpha allocations of 0.56%; the alpha for the final analysis is 2.28%.

If the co-primary endpoint of OS for nivolumab and ipilimumab (Arm B) vs. chemotherapy (Arm C) crossed the boundary for statistical significance, secondary endpoints were tested hierarchically in the following order:

1. BICR-assessed PFS nivolumab in combination with platinum-doublet chemotherapy (Arm G) vs. platinum-doublet chemotherapy (Arm F) in patients with tumors expressing PD-L1 < 1%
2. OS nivolumab in combination with platinum-doublet chemotherapy (Arm G) vs. platinum-doublet chemotherapy (Arm F) in patients with tumors expressing PD-L1 < 1%
3. OS nivolumab (Arm A) vs. platinum-doublet chemotherapy (Arm C) in patients whose tumors express PD-L1 ≥ 50%

The analyses for OS and PFS were log-rank tests stratified by histology (squamous vs. non-squamous) in the intent-to-treat (ITT) population.

Reviewer's Comment: The results were not reported for the interim OS analysis because the Data Monitoring Committee (DMC) determined that the pre-specified boundary for stopping (nominal p ≤ 0.007) was not crossed and recommended that the trial continue to the final OS analysis.

Protocol Amendments

Throughout the conduct of Study CA209227, there were multiple major amendments to the protocol, which was initially submitted to IND 125872 on March 18, 2015, described in Table 6 below. As originally conceived, Study CA209227 was a four arm, randomized (1:1:1:1) study in patients with previously untreated Stage IV or recurrent NSCLC irrespective of PD-L1 status. Patients were randomized to one of the four arms including nivolumab 240 mg IV Q2W (Arm A), nivolumab 1 mg/kg + ipilimumab 1 mg/kg IV Q3W x 4 followed by nivolumab 3 mg/kg Q2W (Arm B), nivolumab 3 mg/kg IV Q2W and ipilimumab 1 mg/kg Q6W (Arm C), and platinum doublet chemotherapy (Arm D). The primary objective was to compare the OS of nivolumab as a single agent (Arm A) and nivolumab in combination with ipilimumab (Arms B and C) to platinum doublet chemotherapy (Arm D) in three separate primary analyses.

Table 11: Protocol amendments for Study CA209227

Date	Description of amendment
10/21/15	• Study redesigned as a six arm trial in two groups categorized by PD-L1 expression with PD-L1-expressing (≥ 1%) patients randomized 1:1:1 to either Arm A (nivolumab monotherapy), Arm B (nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W), or Arm C (chemotherapy), and PD-L1 non-expressing patients (< 1%) randomized 1:1:1 to either Arm D (nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W), Arm F (chemotherapy), or Arm G (nivolumab + chemotherapy). • OS for the comparisons of nivolumab vs. chemotherapy and nivolumab + ipilimumab vs. chemotherapy and PFS for the comparisons of nivolumab vs. chemotherapy and nivolumab + ipilimumab vs. chemotherapy were made co-primary endpoints with separate analyses planned for each PD-L1 three-arm group (e.g. PD-L1 expressors and PD-L1 non-expressors).
11/17/16	• Study reorganized into three distinct parts (Parts 1a, 1b, and 2) with the same eligibility criteria. • Part 1 incorporated previously defined arms with Part 1a including patients with PD-L1 expressing NSCLC randomized to Arms A, B, or C, and Part 1b including patients with PD-L1 non-expressing NSCLC randomized to Arms D, F, and G. • Part 2 was designed as a separately randomized (1:1) substudy in patients with previously untreated NSCLC irrespective of PD-L1 status including two new arms; Arm H (nivolumab + chemotherapy) and Arm I (chemotherapy) with a primary endpoint of OS. • Primary endpoints for Parts 1a and 1b were revised to OS for the comparison of Arm B vs. Arm C in Part 1a and PFS for the comparison of Arm G vs, Arm F.
6/27/17	• Sample size increased for Part 2 only
10/5/17	• PFS for the comparison of nivolumab + ipilimumab (Arms B/D) vs. chemotherapy (Arms C/F) in patients with high tumor mutational burden (TMB) (≥ 10 mutations/megabase [mut/Mb]) was added as a co-primary endpoint. • OS for the comparison of nivolumab + ipilimumab (Arm B) vs. chemotherapy (Arm C) (Part 1a) retained as a co-primary endpoint. • PFS for the comparison of nivolumab + chemotherapy (Arm G) vs. chemotherapy (Arm F) made a secondary endpoint. • Separate hierarchical testing procedures established for the Part 1 TMB co-primary endpoint paradigm and for the Part 1a co-primary endpoint paradigm.
6/1/18	• Interim analysis for OS removed from Part 2

8/15/18	• Hierarchical testing procedure established for the primary endpoint of OS in Part 2 with testing in patients with non-squamous NSCLC first followed by the ITT population. • TMB incorporated as a secondary endpoint.

8.1.2. Study Results

Compliance with Good Clinical Practices

BMS stated that the trial was performed in accordance with the principles of Good Clinical Practice (GCP) and followed the International Conference on Harmonization (ICH)-E6 Guideline for GCP. FDA's review of this supplement identified no substantive protocol deviations that raised concerns regarding adherence to GCP. See Section 4.1 of this review for OSI assessment.

Financial Disclosure

BMS submitted Certification of Financial Interests and Arrangement of Clinical Investigators (Form 3454) for Study CA209227 with a list of all principal investigators and sub-investigators who provided information about financial conflicts of interest as defined in 21 CFR 54.2(1)(b). BMS stated that 2942 of 2959 (99.4%) principal and sub-investigators provided a completed Form 3454; a signed financial disclosure was not provided by 0 principal investigators and 17 sub-investigators despite due diligence efforts. The reasons for the missing financial disclosure form information are provided in the application; the majority were due to addition of the sub-investigator in error. Of the 2942 investigators who responded, 4 principal investigators reported disclosable financial interests; these were due to receipt of significant payments of other sorts. A total of (b) (4) and (b) (4) patients were enrolled at each of the investigators' study sites of 1739 total patients randomized in Part 1 of Study CA209227 (b) (4) respectively, of the total study population). BMS stated that the impact of potential bias of these investigators toward the outcome of Study CA209227 is mitigated by the small number of patients enrolled at each site and by the objective nature of the study design, including co-primary endpoints of OS and BICR-assessed PFS.

Reviewer's comment: There were no financial interests identified for 2938 of the 2959 (99.3%) investigators for Study CA209227. Only 4 principal investigators disclosed financial interests; however, given this small number of investigators who enrolled 2.1% of the randomized study population at their clinical sites, as well as the objective nature of the co-primary endpoint of OS, it is unlikely that these investigators could have substantially biased the results of the study.

Data Quality and Integrity

The clinical reviewer was able to perform the review using the data submitted.

Patient Disposition

The study was initiated on August 5, 2015 and the data cut-off (DCO) date for the final OS analysis was July 2, 2019. Patient disposition is described in Table 12 and Table 13.

Table 12: Patient disposition: treatment discontinuation

	Nivo + ipi (Arms B/D) N=576	Nivolumab (Arm A) N=391	Chemotherapy (Arms C/F) N=570
Total with treatment discontinuation, n (%)	575 (99)	389 (99)	564 (99)
Disease progression, n (%)	305 (53)	240 (61)	295 (52)
Study drug toxicity, n (%)	118 (21)	51 (13)	55 (10)
Death, n (%)	4 (0.7)	7 (1.8)	2 (0.4)
AE unrelated to study therapy, n (%)	41 (7)	29 (7)	36 (6)
Patient request, n (%)	10 (1.7)	3 (0.8)	21 (3.7)
Withdrawal of consent, n (%)	8 (1.4)	5 (1.3)	6 (1.1)
Lost to follow-up, n (%)	1 (0.2)	0	1 (0.2)
Maximum clinical benefit, n (%)	4 (0.7)	3 (0.8)	1 (0.2)
Poor/non-compliance, n (%)	1 (0.2)	0	3 (0.5)
No longer meets study criteria, n (%)	1 (0.2)	1 (0.3)	1 (0.2)
Other, n (%)	12[a] (2.1)	6[b] (1.5)	11[c] (1.9)
Completed treatment, n (%)	59 (10)	36 (9)	126 (22)
Not reported, n (%)	11 (1.9)	5 (1.3)	6 (1.1)
Administrative reason, n (%)	0	3 (0.8)	0

Source: ADaM dataset adsl.xpt

a: Other reasons provided for treatment discontinuation were patient past day of retreatment; investigator's judgment (3); 10 month dose delay; myocardial infarction; pneumonitis; 6 month treatment delay; completion of 2 years of treatment; new primary cancer; sudden death; 6 week treatment delay

b: Other reasons provided for treatment discontinuation were patient decision due to symptomatic deterioration; current state due to WBRT/immunotherapy; received therapy for 2 years (2); patient decision (2)

c: Other reasons provided for treatment discontinuation were lost to follow-up; surgery with no measurable disease; investigator decision (3); possible progression (3); patient decision; neutrophils too low; more than 6 weeks from last treatment dose

Reviewer's comment: More patients in the nivolumab and ipilimumab arms discontinued treatment due to study drug toxicity than in the chemotherapy arms (21% vs. 10%); this is likely due to the differential safety profiles of the two regimens and will be discussed further in the safety portion of this review. More patients in the chemotherapy arms discontinued treatment due to treatment completion than in the nivolumab and ipilimumab arms (22% vs. 10%) due to the shorter duration of protocol-defined chemotherapy regimens vs. the nivolumab and

ipilimumab regimen (4-6 3-week cycles vs. 24 months).

Table 13: Patient disposition: study discontinuation

	Nivo + ipi (Arms B/D) N=576	Nivolumab (Arm A) N=391	Chemotherapy (Arms C/F) N=570
Total with study discontinuation, n (%)	393 (68)	284 (73)	464 (81)
Death, n (%)	355 (62)	260 (66)	431 (76)
Lost to follow-up, n (%)	11 (1.9)	9 (2.3)	8 (1.4)
Other, n (%)	3[a] (0.5)	1[b] (0.2)	3[c] (0.5)
Withdrawal of consent, n (%)	24 (4.2)	14 (3.6)	22 (3.9)

Source: ADaM dataset adsl.xpt
a: Other reasons provided for study discontinuation were patient referred to hospice care; patient refusal; post-surgery poor patient condition
b: Other reason provided for study discontinuation was poor general condition due to disease progression
c: Other reasons provided for study discontinuation were disease progression; patient entered another study (2)

The last patient for Study CA209227 was randomized on (b) (6) and the last patient last visit (LPLV) (clinical cutoff) for the study occurred on (b) (6) providing a minimum follow-up of 28.3 months for all patients in Part 1.

Protocol Violations/Deviations

Major protocol violations were defined as study conduct that differed significantly from the protocol, including GCP compliance; these were described as being within one of the following categories: failure to implement an IRB/IEC approved amendment; failure to obtain written informed consent prior to each subject's participation in the study; failure to report all serious adverse events (SAEs) in accordance with the time period required by GCP, the protocol, BMS and applicable regulations; implementation of protocol changes prior to review by IRB/IEC (except when necessary to eliminate an immediate hazard(s) to trial subjects); inclusion or exclusion deviations; incorrect dosing or study treatment assignment; and other. For the primary analysis population enrolled in Arms B and C, there were 293 and 234 protocol violations, respectively. The highest number of protocol violations occurred within the "other" category; of these, the most common protocol violation was for failure to reconsent patient or reconsent patient in a timely manner for updated informed consent (37 and 43 violations in Arm B and C, respectively, representing 9.3% and 10.8% of the randomized patients).

Relevant protocol deviations are defined as those related to inclusion or exclusion crtieria, study conduct, study management, or subject assessment that were programmable and could potentially affect the interpretability of study results. Relevant protocol deviations were reported in 9 (0.5%) randomized patients overall in Part 1 (Arms A through F), with those occurring in the primary analysis arms (Arms B and C) described in Table 9.

Table 14: Relevant protocol deviations

Patients with at least one protocol deviation, n (%)	Nivo + ipi (Arm B) N=396	Chemo (Arm C) N=397
At study entrance		
Patients without measurable disease at baseline per investigator	2 (0.5)	0
On-treatment deviations		
Patients receiving concurrent anti-cancer therapy	0	2 (0.5)

Source: Study CA209227 Final CSR

Table of Demographic Characteristics

Table 15 and Table 16 summarize the demographics and baseline disease characteristics for the ITT population and the PD-L1-positive population, respectively. A total of 583 patients were randomized to the nivolumab and ipilimumab arms (Arms B/D) and a total of 583 patients were randomized to the chemotherapy arms (Arms C/F). In the ITT population, the median age was 64 years (range: 26-87), 67% were male, 76% were White, and most patients had adenocarcinoma type non-squamous NSCLC (68%). Most patients (65%) had an ECOG performance status of 1 and 85% were former or current smokers. 68% of the patients in the ITT population had a PD-L1 level ≥ 1%. Patient demographics and disease characteristics were generally balanced across arms and similar in the ITT population and the PD-L1 positive population.

Table 15: Demographic and baseline disease characteristics in the ITT population

	Nivolumab + ipilimumab (Arms B/D) N=583	Nivolumab (Arm A) N=396	Chemotherapy (Arms C/F) N=583
Age, years			
Median (range)	64 (26-87)	64 (27-85)	64 (29-87)
Age group, n (%)			
< 65	306 (52)	210 (53)	305 (52)
≥ 65	277 (48)	186 (47)	278 (48)
Sex, n (%)			
Male	393 (67)	272 (67)	385 (66)
Female	190 (33)	124 (33)	198 (34)
Race, n (%)			
White	442 (76)	317 (80)	438 (75)
Black / African American	4 (0.7)	6 (1.5)	7 (1.2)
Asian	125 (21)	67 (17)	127 (22)
Other	12 (2.1)	6 (1.5)	8 (1.4)
Region, n (%)			
North America	56 (10)	39 (10)	70 (12)
Europe	302 (52)	222 (56)	293 (50)
Asia	121 (21)	66 (17)	124 (21)
Rest of world	104 (18)	69 (17)	96 (16)
Histology, n (%)			
Squamous carcinoma	163 (28)	117 (30)	162 (28)
Non-squamous carcinoma			
Adenocarcinoma	399 (68)	267 (67)	404 (69)
Large cell carcinoma	9 (1.5)	5 (1.3)	6 (1.0)
Other/not reported	12 (2.1)	7 (1.8)	11 (1.9)
Metastasis site, n (%)			
Liver	122 (21)	92 (23)	130 (22)
Brain	64 (11)	42 (11)	51 (9)
ECOG performance status, n (%)			
0	204 (35)	142 (36)	191 (33)
1	377 (65)	252 (64)	386 (66)
≥ 2	2 (0.3)	0	4 (0.7)
Smoking status, n (%)			
Never smoker	79 (14)	50 (13)	78 (13)
Former / current smoker	497 (85)	342 (86)	499 (86)
Unknown	7 (1.2)	4 (1.0)	6 (1.0)
PD-L1 status, n (%)			
≥ 1%	396 (68)	391 (100)	397 (68)
< 1%	187 (32)	0	186 (32)

Source: ADaM dataset adsl.xpt

Table 16: Demographics and baseline characteristics in the PD-L1+ population (primary efficacy population)

	Nivolumab + ipilimumab (Arm B) N=396	Chemotherapy (Arm C) N=397
Age, years		
Median (range)	64 (26-84)	64 (29-87)
Age group, n (%)		
< 65	199 (50)	207 (52)
≥ 65	197 (50)	190 (48)
Sex, n (%)		
Male	255 (64)	260 (65)
Female	141 (36)	137 (35)
Race, n (%)		
White	299 (76)	305 (77)
Black / African American	4 (1.0)	5 (1.3)
Asian	84 (21)	82 (21)
Other	9 (2.3)	5 (1.3)
Region, n (%)		
North America	40 (10)	55 (14)
Europe	199 (50)	201 (51)
Asia	81 (20)	81 (20)
Rest of world	76 (19)	60 (15)
Histology, n (%)		
Squamous carcinoma	117 (30)	116 (29)
Non-squamous carcinoma		
Adenocarcinoma	267 (67)	269 (68)
Large cell carcinoma	6 (1.5)	4 (1.0)
Other/not reported	6 (1.5)	8 (2.0)
Metastasis site, n (%)		
Liver	71 (18)	85 (21)
Brain	41 (10)	40 (10)
ECOG performance status, n (%)		
0	135 (34)	134 (34)
1	260 (66)	259 (65)
≥ 2	1 (0.3)	3 (0.8)
Smoking status, n (%)		
Never smoker	56 (14)	51 (13)
Former/ current smoker	334 (84)	340 (86)
Unknown	6 (1.5)	6 (1.5)

Source: ADaM dataset adsl.xpt

Additionally, among the 793 patients randomized to Arms B and C, 50% had tumors with PD-L1 expression ≥50%.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

BMS reports that 9.7% of patients in the nivolumab and ipilimumab arms (Arms B/D) and 7.5%

of patients in the chemotherapy arms (Arms C/F) had deviations from protocol-specified treatment, specifically involving incorrect dosing. Over 99% of treated patients received concomitant medications; 9 patients (1.6%) in the nivolumab and ipilimumab arms and 1 patient (0.2%) in the chemotherapy arms had protocol deviations involving use of prohibited concomitant medications. There were no rescue medications prespecified in the protocol.

Efficacy Results – Primary Endpoint

The efficacy review is based on the data cut-off date of July 2, 2019, for the final analysis of the co-primary endpoint of OS among patients with tumors expressing PD-L1 ≥ 1% for nivolumab in combination with ipilimumab (Arm B) vs. platinum-doublet chemotherapy (Arm C).

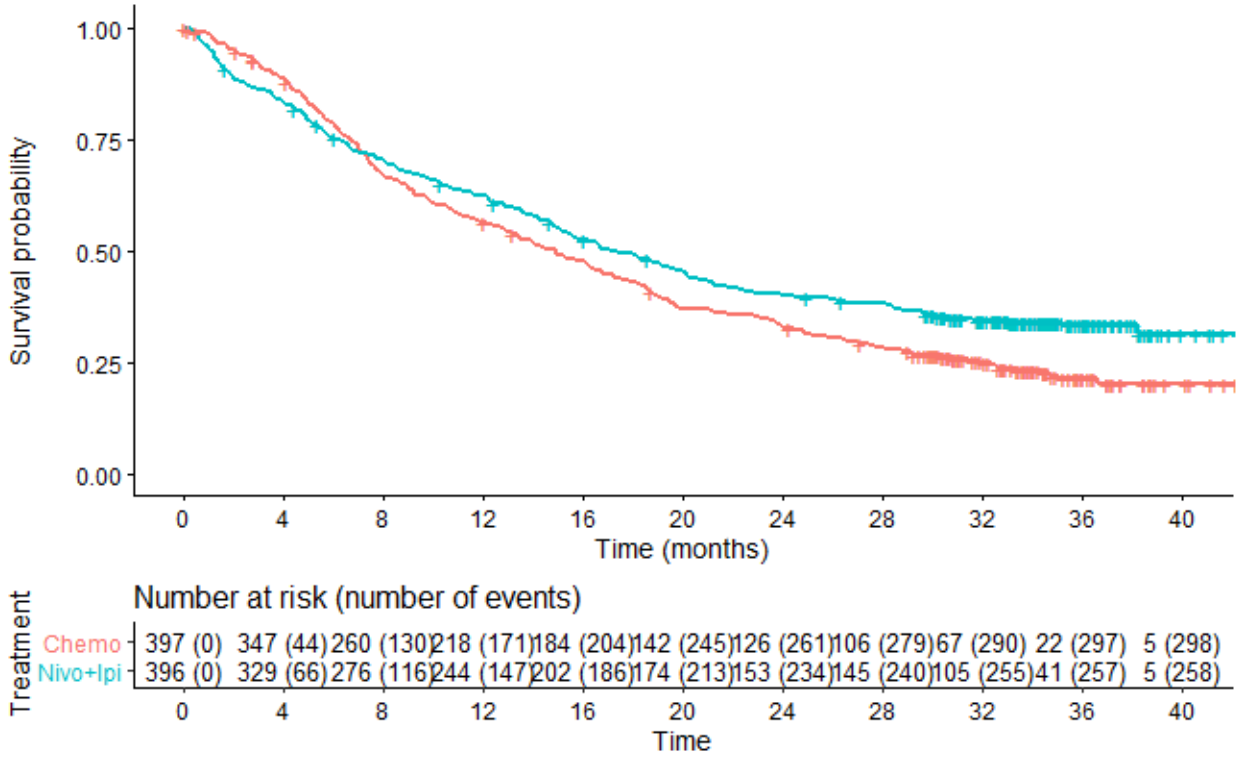
Table 17 presents the analysis of OS in PD-L1 ≥ 1% patients. Figure 4 shows the OS curves estimated using the Kaplan-Meier method.

Table 17: Overall survival in PD-L1 ≥ 1% population

	Nivolumab and Ipilimumab (n=396)	**Chemotherapy (n=397)**
Number of events (%)	258 (65%)	298 (75%)
Median in months (95% CI)[1]	17.1 (15.0, 20.1)	14.9 (12.7, 16.7)
Hazard Ratio (95% CI)[1,2]	0.79 (0.67, 0.94)	
p-value[1,3]	0.0066[4]	

[1] Stratified by histology (squamous vs. non-squamous)
[2] Estimated using a Cox proportional hazards model
[3] Log-rank test
[4] Compared with alpha boundary of 0.0228 (two-sided)

Figure 4: Kaplan-Meier Plot of overall survival in PD-L1 ≥ 1% population

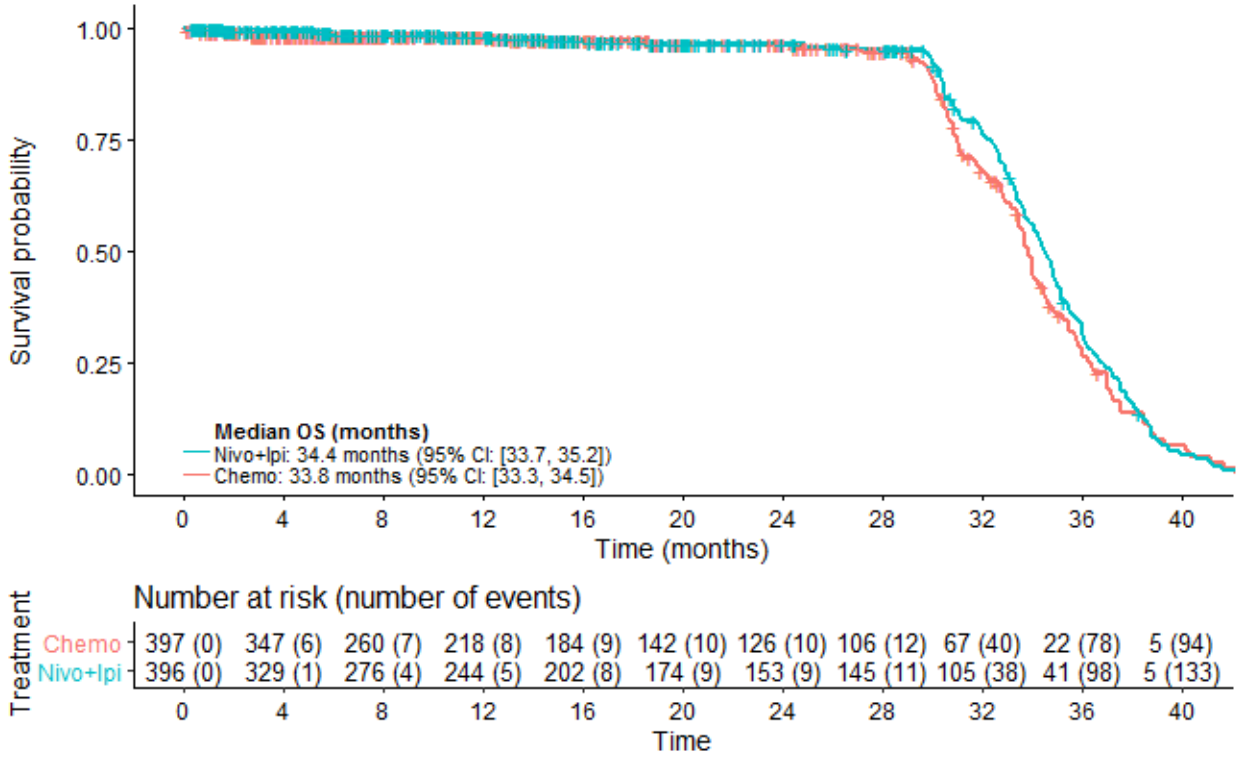


Reviewer's Comments: *The final analysis of the co-primary endpoint shows a statistically and clinically significant improvement in OS among patients with PD-L1 tumor expression ≥1% randomized to the nivolumab and ipilimumab arm compared to the chemotherapy arm at the allocated alpha level of 0.0228.*

Kaplan-Meier curves of OS follow-up were created by treatment arm to evaluate the censoring distribution of OS (Figure 3). The analysis and raw datasets did not show any unusual dropouts occurring in either treatment arm.

Due to concerns of potential study conduct issues, which resulted in multiple protocol amendments (see Table 6), FDA only considers the OS results for the comparison of nivolumab in combination with ipilimumab versus platinum-doublet chemotherapy in patients whose tumors express PD-L1 ≥ 1% to be interpretable. The comparison of OS in patients with PD-L1 < 1% (Part 1b) randomized to the nivolumab and ipilimumab arm versus the chemotherapy arm was not part of the statistical testing hierarchy. Therefore, these results and all other comparisons related to the PD-L1 hierarchy are considered exploratory.

Figure 5: Kaplan-Meier plot of follow-up for overall survival



Efficacy Results – Secondary and other relevant endpoints

PFS nivolumab + chemotherapy vs. chemotherapy in patients with PD-L1 < 1%

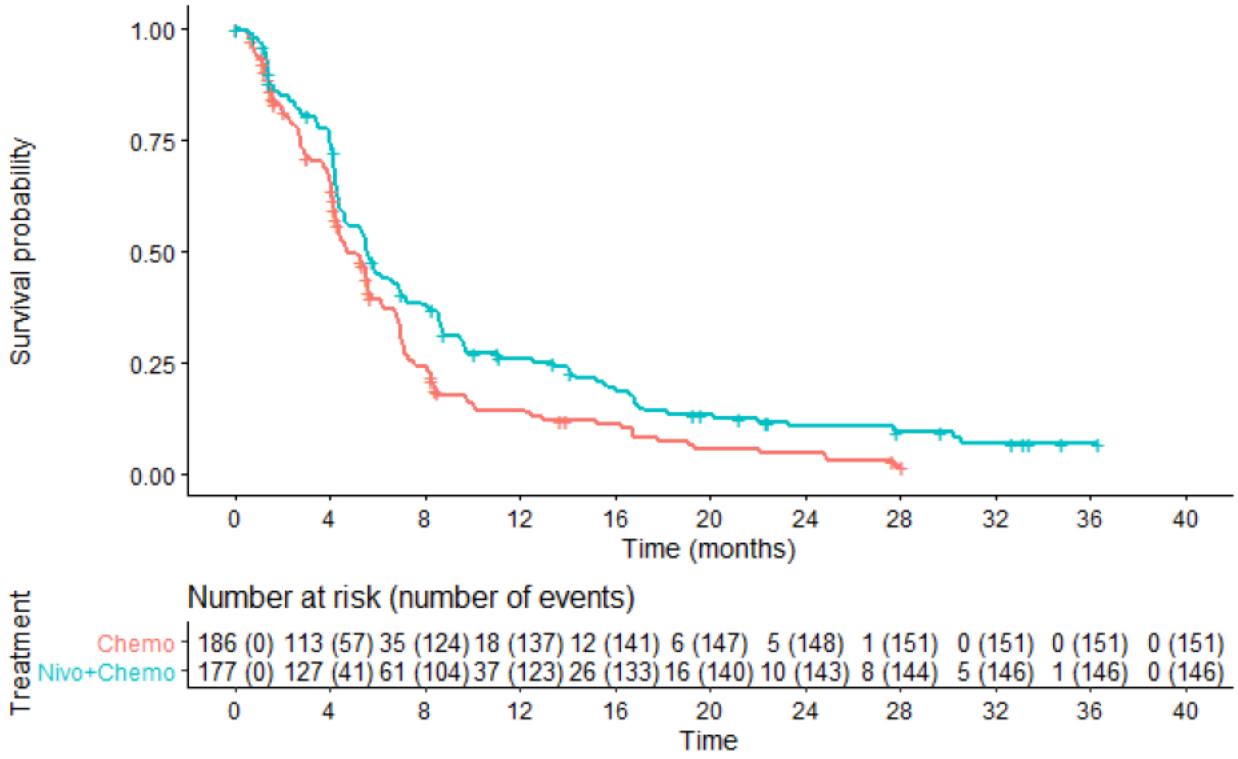
Table 18 presents the analysis of PFS in PD-L1 < 1% patients. Figure 6 shows the PFS curves estimated using the Kaplan-Meier method.

Table 18: Progression-free survival[1] in PD-L1- population

	Nivolumab and Chemotherapy (n=177)	Chemotherapy (n=186)
Number of events (%)	146 (83%)	151 (81%)
Median in months (95% CI)[2]	5.6 (4.6, 6.9)	4.7 (4.2, 5.6)
Hazard Ratio (95% CI)[2,3]	0.73 (0.58, 0.92)	
p-value[2,4]	0.0070[5]	

[1] BICR-assessed
[2] Stratified by histology (squamous vs. non-squamous)
[3] Estimated using a Cox proportional hazards model
[4] Log-rank test
[5] Compared with alpha boundary of 0.0228 (two-sided)

Figure 6: Kaplan-Meier Plot of progression-free survival in PD-L1 < 1% population



Reviewer's Comments: *The analysis of the secondary endpoint shows a statistically significant improvement in BICR-assessed PFS among patients with PD-L1 tumor expression <1% randomized to the nivolumab and chemotherapy arm compared to the chemotherapy arm at the allocated alpha level of 0.0228.* (b) (4)

[redacted]

OS nivolumab + chemotherapy vs. chemotherapy in patients with PD-L1 < 1%

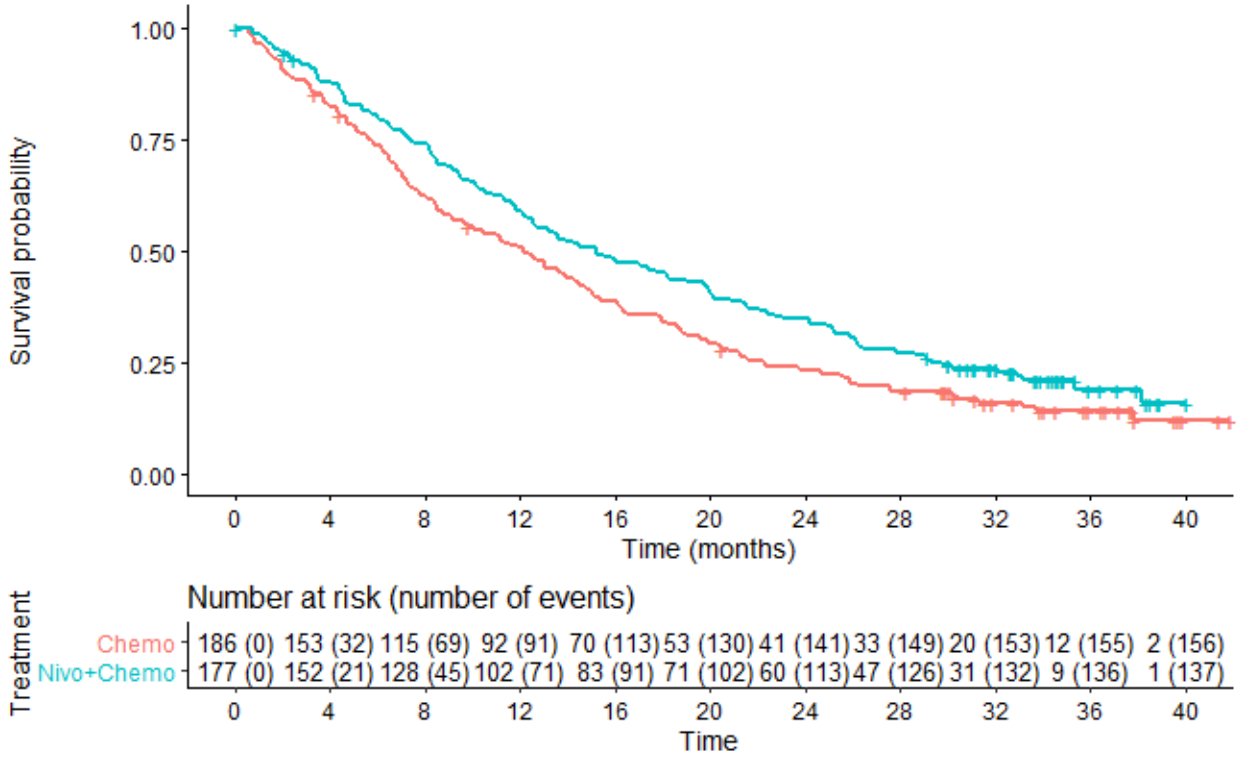
Table 19 presents the analysis of OS in PD-L1 < 1% patients. Figure 4 shows the OS curves estimated using the Kaplan-Meier method.

Table 19: Overall survival in PD-L1 < 1% population

	Nivolumab and Chemotherapy (n=177)	Chemotherapy (n=186)
Number of events (%)	137 (77%)	156 (84%)
Median in months (95% CI)[1]	15.2 (12.3, 19.8)	12.2 (9.2, 14.3)
Hazard Ratio (95% CI)[1,2]	0.78 (0.62, 0.98)	
p-value[1,3]	0.0352[4]	

[1] Stratified by histology (squamous vs. non-squamous)
[2] Estimated using a Cox proportional hazards model
[3] Log-rank test
[4] Compared with alpha boundary of 0.0228 (two-sided)

Figure 7: Kaplan-Meier Plot of overall survival in PD-L1 < 1% population



Reviewer's Comments: *The analysis of the secondary endpoint does not show a statistically significant improvement in OS among patients with PD-L1 tumor expression <1% randomized to the nivolumab and chemotherapy arm compared to the chemotherapy arm at the allocated alpha level of 0.0228. Statistical testing stopped because the boundary for statistical significance was not crossed for this endpoint.*

OS nivolumab vs. chemotherapy in patients with PD-L1 ≥ 50%

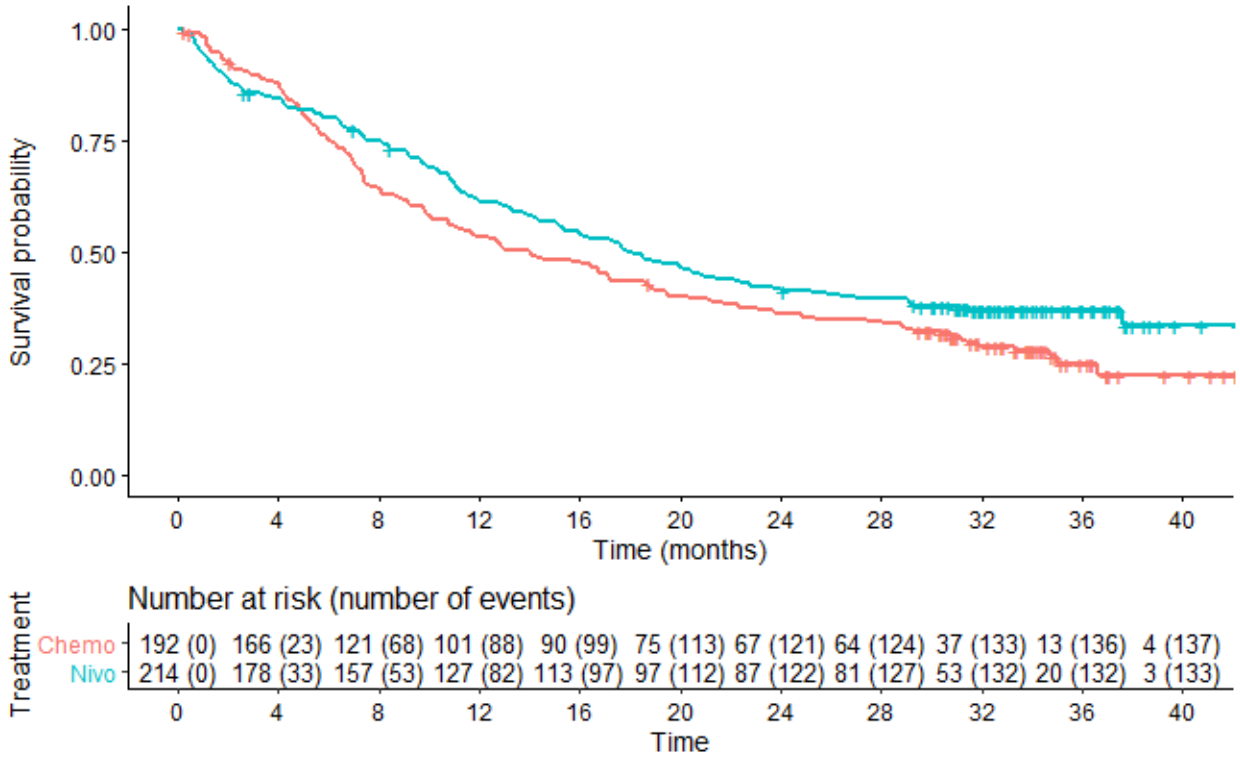
Table 20 presents the analysis of OS in PD-L1 ≥ 50% patients. Figure 8 shows the OS curves estimated using the Kaplan-Meier method.

Table 20: Overall survival in PD-L1 ≥ 50% population

	Nivolumab (n=214)	**Chemotherapy (n=192)**
Number of events (%)	133 (62%)	137 (71%)
Median in months (95% CI)[1]	18.1 (14.4, 22.1)	14 (10.1, 18.6)
Hazard Ratio (95% CI)[1,2]	0.79 (0.62, 1.00)	

[1] Stratified by histology (squamous vs. non-squamous)
[2] Estimated using a Cox proportional hazards model
[3] Log-rank test

Figure 8: Kaplan-Meier Plot of overall survival in PD-L1 ≥ 50% population



Reviewer's Comments: *The analysis of the secondary endpoint of OS among PD-L1 ≥ 50% patients randomized to the nivolumab arm compared to the chemotherapy arm is descriptive because hierarchical testing was stopped at the previous secondary endpoint.*

Dose/Dose Response

See the FDA Clinical Pharmacology review from the original BLA submissions.

Durability of Response

An analysis of ORR and duration of response was not part of the statistical testing hierarchy for patients with PD-L1 tumor expression ≥ 1% for the comparison of nivolumab and ipilimumab versus chemotherapy. However, the ORR was 36% (95% CI: 31, 41) in the nivolumab and ipilimumab arm and 30% (95% CI: 26, 35) in the chemotherapy arm. Median duration of response was 23.2 months in the nivolumab and ipilimumab arm and 6.2 months in the chemotherapy arm. A total of 64% of responding patients in the nivolumab and ipilimumab arm had a response duration of ≥ 12 months compared to 28% in the chemotherapy arm.

Persistence of Effect

This section is not applicable given that patients in the nivolumab and ipilimumab arm continued treatment until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue. See paragraph above for information on durability of response.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Refer to the Section 8.2.6 entitled “Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability” for COA results.

Additional Analyses Conducted on the Individual Trial

Results of subgroup analyses of the co-primary endpoint of OS are presented in Table 21 and Table 22.

Table 21: Subgroup analyses of overall survival

Factor	Nivo+Ipi		Chemo		HR (95% CI)
	Events	N	Events	N	
Overall	258	396	298	397	0.80 (0.68, 0.95)
Age					
< 65	116	199	152	207	0.70 (0.55, 0.89)
>= 65	142	197	146	190	0.91 (0.72, 1.15)
Sex					
Female	94	141	97	137	0.91 (0.69, 1.21)
Male	164	255	201	260	0.75 (0.61, 0.92)
Region					
Asia	37	81	47	81	0.76 (0.49, 1.17)
Europe	138	199	159	201	0.79 (0.62, 0.99)
North America	26	40	40	55	0.85 (0.52, 1.39)
Rest of World	57	76	52	60	0.76 (0.52, 1.1)
Race					
White	210	299	242	305	0.81 (0.67, 0.97)
Asian	39	84	48	82	0.76 (0.50,1.17)
Other	9	13	8	10	0.78 (0.30, 2.03)

Table 22: Subgroup analyses of overall survival for additional subgroups of interest

Factor	Nivo+Ipi		Chemo		HR (95% CI)
	Events	N	Events	N	
Overall	258	396	298	397	0.80 (0.68, 0.95)
ECOG					
0	74	135	96	134	0.66 (0.48, 0.89)
1	183	260	199	259	0.89 (0.73, 1.09)
> 1	1	1	2	3	NA
Not reported	0	0	1	1	NA
Smoking					
Never	38	56	31	51	1.23 (0.76, 1.98)
Current/Former	217	334	262	340	0.77 (0.64, 0.92)
Unknown	3	6	5	6	0.26 (0.06, 1.16)
Histology					
Non-squamous	173	278	195	279	0.85 (0.69, 1.04)
Squamous	85	118	103	118	0.69 (0.52, 0.92)

Reviewer's Comments: *These subgroup analyses were exploratory only. There were generally no outliers in the HRs of OS in these subgroups of interest compared to the primary analysis. The HR for never smokers is above 1. However, sample sizes are small.*

8.1.3 Integrated Review of Effectiveness

Please refer to Section 8.1.4, Integrated Assessment of Effectiveness below.

8.1.4 Integrated Assessment of Effectiveness

BMS provided summary results from two single arm clinical trials, Studies CA209568 and CA209817, to support the anti-tumor activity of nivolumab in combination with ipilimumab in patients with metastatic NSCLC whose tumors express PD-L1 ≥ 1%. In order to support the need for combination immunotherapy in the first-line setting for patients with metastatic NSCLC and demonstrate the contribution of ipilimumab to the combination, BMS also provided summary results from Study CA209026, in which patients with treatment-naïve metastatic NSCLC were randomized to receive either nivolumab as a single agent or chemotherapy.

A brief description of the study designs was provided in Section 7.1.

BMS reports that the median follow-up time for patients enrolled in both Study CA209568 Part 1 and Study CA209817 Cohort A was 15.5 months, compared to 28.3 months in Study CA209227 Part 1a. In general, the demographics of the study populations in Studies CA209227, 209568, and 209871 were similar, with differences observed in sex, race, and region, in part due to fact that Study CA209568 was conducted solely within North America and Study CA209817 was conducted in North America and Europe. Table 23 presents the key demographics for patients enrolled in each of these studies.

APPEARS THIS WAY
ON ORIGINAL

Table 23: Baseline characteristics of patients with treatment-naïve NSCLC with PD-L1 ≥ 1% from Studies CA209227, CA209568, and CA209817

Baseline characteristic	Study CA209227 Part 1a, Arm B N=396	Study CA209568 Part 1 N=138	Study CA209817 Cohort A N=176
Median age (years)	64.0	65.0	66.0
≥ 65 years (%)	50	51	57
Male (%)	64	47	57
Race (%)			
White	76	91	97
Black	1.0	7	1.7
Asian	21	0.7	1.1
Other	1.3	1.4	2.3
Region (%)			
North America	10	100	31
Europe	50	0	69
Asia	21	0	0
Rest of world	19	0	0
Histology (%)			
Squamous	30	27	30
Non-squamous			
Adenocarcinoma	67	68	67
Large cell	1.5	2.9	1.1
ECOG PS (%)			
0	34	37	45
1	66	62	53
Smoking status (%)			
Current/former	84	91	93
Never smoker	14	9	6
Unknown	1.5	0.7	1.1

Source: ADaM dataset adsl.xpt; SCE Table 3.1.1.2-1

Studies CA209568 and CA209817 are both single arm trials; the primary endpoint for Study CA209568 is ORR by BICR assessment in patients with PD-L1 expression status ≥ 1% and < 1%. The primary endpoint for Study CA209817 is to assess the safety of flat dose nivolumab in combination with ipilimumab; secondary endpoints included ORR by investigator assessment and DOR. Given that OS and PFS are difficult to interpret in single arm trials due to the lack of a randomized comparator arm to account for population differences that may affect such time-to-event outcomes, results for ORR and DOR across Studies CA209227, CA209568, and CA209817 are presented in Table 24 to support the anti-tumor activity of nivolumab and ipilimumab in treatment-naïve metastatic NSCLC with PD-L1 tumor expression ≥ 1%.

Table 24: Efficacy results in patients with treatment-naïve NSCLC with PD-L1 ≥ 1% from Studies CA209227, CA209568, and CA209817

Efficacy parameter	Study CA209227 Part 1a, Arm B N=396	Study CA209568 Part 1 N=138	Study CA209817 Cohort A N=176
ORR, % (95% CI)	36%[a] (31, 41)	43%[a] (34, 52)	42%[b] (35, 50)
CR, %	6%	3.6%	4.5%
Median DOR (mos) (Range)	23.2 (1.4+, 37.6+)	NA (1.5, 21.8+)	NA (0.0+, 26.2+)
% of pts with DOR ≥ 6 mos (95% CI)	79% (71, 85)	77% (64, 86)	82% (71, 90)
% of pts with DOR ≥ 12 mos (95% CI)	64% (55, 72)	64% (50, 75)	65% (52, 75)

Source: SCE Tables 3.1.2.1-1 and 3.1.2.2-1; CR: complete response
a: Per BICR assessment
b: Per investigator assessment

Reviewer's comment: ORR results across Studies CA209227, CA209568, and CA209817 were similar, with overlapping 95% confidence intervals, supporting the consistency of the antitumor activity of nivolumab in combination with ipilimumab in patients with treatment-naïve metastatic NSCLC with PD-L1 tumor expression ≥ 1%. By comparison, the ORR observed in patients in the chemotherapy arm (Arm C) of Part 1a of Study CA209227 was 30% (95% CI 25, 35), which is similar to that observed in patients in the nivolumab and ipilimumab arm (Arm B) of Study CA209227. However, the proportion of patients in Arm C with responses at 6 months and 12 months was 53% (95% CI 43, 62) and 28% (95% CI 19, 38), respectively, reflecting the improved durability of responses in patients receiving nivolumab and ipilimumab.

Results comparing Arm B (nivolumab and ipilimumab) with Arm A (nivolumab as a single agent) and Arm A with Arm C (chemotherapy) from Part 1a of Study CA209227 were provided to isolate the contribution of ipilimumab to nivolumab. These comparisons were not part of the statistical testing hierarchy for Part 1 of the study; however, the exploratory analyses presented below demonstrate improved efficacy (OS, PFS, and ORR) in patients who received nivolumab and ipilimumab in comparison to those who received nivolumab as a single agent.

BMS also provided summary results from Studies CA209026 and CA209012, a multicohort, single arm, dose finding study of nivolumab in multiple combinations, for consideration in the totality of the data supporting the contribution of ipilimumab to the combination. Efficacy results from patients with treatment-naïve metastatic NSCLC with PD-L1 tumor expression ≥ 1% from the nivolumab arm of Study CA209026 were similar to those observed in patients enrolled in Arm A of Study CA209227.

These results are presented in Table 25 and Table 26.

Table 25: Exploratory analyses assessing contribution of ipilimumab to nivolumab in Studty CA209227, Part 1a

Efficacy parameter	Study CA209227 Arm B (N/I) N=396	Study CA209227 Arm A (N) N=396	Study CA209227 Arm C (chemo) N=397
OS			
Number of events	258	274	298
mOS (mos)	17.1	15.7	14.9
(95% CI)	(15.0, 20.1)	(13.3, 18.1)	(12.7, 16.7)
Hazard ratio (N/I vs. N) (95% CI)	0.90 (0.76, 1.07)		
Hazard ratio (N vs. chemo) (95% CI)	0.88 (0.75, 1.04)		
PFS			
Number of events	288	311	286
mPFS (mos)	5.1	4.2	5.6
(95% CI)	(4.1, 6.3)	(3.0, 5.3)	(4.6, 5.8)
Hazard ratio (N/I vs. N) (95% CI)	0.83 (0.71, 0.97)		
Hazard ratio (N vs. chemo) (95% CI)	0.99 (0.84, 1.17)		
ORR per BICR, % (95% CI)	36% (31, 41)	28% (23, 32)	30% (26, 35)
Median DOR (mos)[a]	23.2	15.5	6.2

Source: SCE, Table 3.4.1-1
a: Kaplan-Meier estimate

Table 26: Exploratory analyses assessing effect of nivolumab monotherapy vs. chemotherapy in patients with PD-L1 tumor expression ≥ 1% in Studies CA209227 Part 1a and CA209026

Efficacy parameter	Study CA209227 Part 1a		Study CA209026	
	Arm A (Nivo) N=396	Arm C (chemo) N=397	Nivolumab N=271	Chemo N=270
OS				
Number of events	274	298	171	158
mOS (mos)	15.7	14.9	13.7	13.8
(95% CI)	(13.3, 18.1)	(12.7, 16.7)	(11.8, 15.4)	(11.0, 17.0)
Hazard ratio	0.88		1.07	
(95% CI)	(0.75, 1.04)		(0.86, 1.33)	
PFS per BICR				
Number of events	311	286	191	183
mPFS (mos)	4.2	5.6	4.2	5.8
(95% CI)	(3.0, 5.3)	(4.6, 5.8)	(3.1, 5.5)	(5.4, 6.9)
Hazard ratio	0.99		1.17	
(95% CI)	(0.84, 1.17)		(0.95, 1.43)	
ORR per BICR, %	28	30	24	31
(95% CI)	(23, 32)	(26, 35)	(19, 30)	(25, 37)
Median DOR (mos)[a]	15.5	6.2	12.1	5.7
Range	(1.5+, 35.9+)	(1.2+, 34.5+)	(1.7, 19.4+)	(1.4+, 21.0+)

Source: SCE, Table 3.4.4-1
a: Kaplan-Meier estimate

BMS also provided a comparison of anti-tumor activity observed in Study CA209012 in patients enrolled in Cohort Q (nivolumab in combination with ipilimumab, n=39) and Cohort F (nivolumab as a single agent, n=52). The ORR as assessed by investigator in Cohort Q was 39% (95% CI 23, 55) and 23% (95% CI 13, 37) in Cohort F. Median durations of response were not reached in either cohort but ranged from 1.4+ to 20.0+ months in Cohort Q and from 4.2 to 43.4+ months in Cohort F.

There was no ipilimumab monotherapy arm in Study CA209227; however, BMS reports data from the randomized, double-blind study CA184104, in which there was not a statistically significant improvement in OS or PFS in patients with NSCLC receiving ipilimumab 10 mg/kg Q3W for 4 doses then Q12W in combination with platinum-based chemotherapy for up to 6 doses compared to patients receiving chemotherapy alone (OS HR 0.91 [95% CI 0.77, 1.07]; PFS HR 0.87 [95% CI 0.75, 1.01]).[7] BMS also states that in patients with advanced NSCLC with stable disease or clinical response to first-line chemotherapy, maintenance monotherapy with the CTLA-4 inhibitor tremelimumab did not improve PFS over best supportive care.[8] Therefore, BMS does not consider ipilimumab monotherapy to be effective for the treatment of metastatic NSCLC.

Reviewer's comment: In summary, the exploratory analyses comparing nivolumab and ipilimumab (Arm B) to nivolumab as a single agent (Arm A) and nivolumab as a single agent to chemotherapy (Arm C) in Part 1a of Study CA209227, and the efficacy results from the comparison of nivolumab as a single agent to chemotherapy in Study CA209026 demonstrate an improvement in efficacy parameters in patients receiving combination therapy versus those receiving nivolumab as a single agent. These analyses are supportive of the contribution of ipilimumab to the combination resulting in improved efficacy, even in the absence of an ipilimumab monotherapy arm in Study CA209227. The reviewer agrees that based on available data in NSCLC, ipilimumab as a single agent is unlikely to be effective for the treatment of metastatic NSCLC.

8.2 Review of Safety

8.2.1 Safety Review Approach

The clinical safety review of Study CA209227 included review and analysis of the CSR for Study CA209227, BMS' risk:benefit assessment, CRFs, selected narratives, the ISS, the primary datasets for baseline characteristics and adverse events, and the drug product toxicity data submitted by BMS. The clinical reviewer analyzed key safety datasets using several safety analysis queries and the Oncology Center of Excellence (OCE) AutoSafety tool. Subgroup analyses were performed as necessary to further characterize the safety profile of nivolumab in combination with ipilimumab. Adverse events occurring in patients who received nivolumab and ipilimumab were compared with those occurring in patients who received chemotherapy and who received nivolumab as a single agent.

The total population randomized in Part 1 of Study CA209227 includes 1739 patients; of these, 583 were randomized to receive nivolumab and ipilimumab (Arms B/D; 396 in Arm B and 187 in Arm D), 396 patients were randomized to receive nivolumab as a single agent (Arm A), 583 patients were randomized to receive chemotherapy (Arms C/F; 397 in Arm C and 186 in Arm F), and 177 patients were randomized to receive nivolumab in combination with chemotherapy (Arm G). A total of 7 patients in the nivolumab and ipilimumab arms (5 in Arm B and 2 in Arm D), 5 patients in the nivolumab arm, and 13 patients in the chemotherapy arms (10 in Arm C and 3 in Arm F) did not receive any study treatment and are therefore excluded from the safety evaluable population. One patient was randomized twice in error, initially to Arm F without receiving treatment, and subsequently to Arm D with treatment administered. This patient is therefore counted in the safety population as part of Arm D. Thus, the total safety analysis population from Study CA209227 relevant to this sBLA is comprised of 1537 patients; 576 in the nivolumab and ipilimumab arms (Arms B/D; 391 in Arm B and 185 in Arm D), 391 in the nivolumab arm (Arm A), and 570 in the chemotherapy arms (Arms C/F; 387 in Arm C and 183 in Arm F). Safety data from Arm G (nivolumab in combination with chemotherapy) was not considered in the context of this review.

Safety data from Study CA209227 was compared to data from a population of patients who received nivolumab in combination with ipilimumab for the treatment of NSCLC from three

single arm studies, Studies CA209568 (n=288), CA209817 (n=391), and CA209012 (n=39), for further characterize the safety of this combination in the NSCLC patient population; these data are presented separately and as a pooled population. Safety data from Study CA209227 was also compared to data from a population of patients who received nivolumab in combination with ipilimumab for the treatment of other tumor types, including RCC (Study CA209214; n=547), CRC (Study CA209142; n=119), and pooled melanoma studies in which patients received nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W (n=448). Safety data from Study CA209227 was also compared to pooled data from the RCC and CRC populations for immune-mediated adverse events (IMAEs) and other events of special interest (OESIs) to inform the Warnings and Precautions section of the USPI.

8.2.2 Review of the Safety Database

Overall Exposure

In Study CA209227, a total of 576 patients received nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W and a total of 391 patients received nivolumab 3 mg/kg Q2W as a single agent. Treatment in these arms (Arms A, B, and D) was continued until progressive disease, unacceptable toxicity, or up to 24 months, whichever occurred first. Treatment beyond initial investigator-assessed progressive disease was permitted if the patient was deriving clinical benefit from therapy. A total of 570 patients received treatment with investigator's choice chemotherapy. Treatment in these arms (Arms C and F) was continued until progressive disease, unacceptable toxicity, or for 4 cycles, whichever occurred first. Patients with non-squamous NSCLC who had stable disease or any response could continue treatment with pemetrexed after 4 cycles of platinum-based chemotherapy until progressive disease or unacceptable toxicity.

At the time of the data cut-off, a total of 99.8% of patients in the nivolumab and ipilimumab arms, 99.5% of patients in the nivolumab arm, and 98.9% of patients in the chemotherapy arms had discontinued treatment. The median duration of exposure in the nivolumab and ipilimumab arms was 4.2 months (95% CI 3.7, 5.1), including 4.2 months (95% CI 3.7, 5.2) for Arm B and 4.0 months (95% CI 3.0, 5.0) for Arm D. The median duration of exposure in the nivolumab arm was 4.6 months (95% CI 3.8, 5.2), and the median duration of exposure in the chemotherapy arms was 2.6 months (95% CI 2.6, 2.8), including 2.7 months (2.6, 2.8) for Arm C and 2.6 months (2.3, 3.3) for Arm F.

Exposure to nivolumab and ipilimumab (Arms B/D), nivolumab (Arm A), and chemotherapy (Arms C/F) is summarized in Table 27.

Table 27: Summary of treatment exposure

	Nivo + ipi (Arms B/D) N=576	Nivolumab (Arm A) N=391	Chemotherapy (Arms C/F) N=570
Treatment duration (mos)			
Mean (SD)	7.4 (7.8)	4.6 (4.9)	4.8 (5.8)
Median (min-max)	4.2 (0.03, 25.5)	7.6 (0.03, 26.5)	2.6 (0.03, 37.6+)
Number of cycles			
Mean (SD)	10.2 (12.9)	16.4 (16.3)	5.8 (6.0)
Median (min-max)	5.0 (1-55)	9.0 (1-58)	4.0 (1-53)
Duration of exposure, %			
≥ 3 months	59	60	45
≥ 6 months	39	40	24
≥ 12 months	23	23	8

Source: ADaM dataset adex.xpt

A total of 27 patients (4.7%) in the nivolumab and ipilimumab arms discontinued ipilimumab prior to discontinuation of nivolumab. A summary of these patients is provided in Table 28.

Table 28: Summary of partial discontinuation (ipilimumab) in Arms B/D

	Nivo + ipi (Arms B/D) N=576	Nivo + ipi (Arm B) N=391
Pts who discontinued ipilimumab earlier, n (%)	27 (4.7)	22 (6)
Due to adverse event, n (%)	18 (67)	16 (73)
Other, n (%)	9 (33)	6 (27)
Number of doses of nivolumab after ipilimumab stopped		
Mean (SD)	13.1 (12.5)	14.3 (13.3)
Median (min-max)	8.0 (2-42)	8.0 (2-42)
Duration of tx with nivolumab after ipilimumab stopped (days)		
Mean (SD)	223 (195)	238 (204)
Median (min-max)	153 (25-686)	157 (25-686)

Source: Final CSR Table S.4.1.5

The number of doses received for each individual study drug for patients enrolled in the combination therapy arms (Arms B/D and C/F) is summarized in Table 29 and Table 30.

Table 29: Nivolumab and ipilimumab administration

No. of doses	Nivo + ipi (Arms B/D) N=576	
	Nivolumab N=576	Ipilimumab N=576
Mean (SD) Median (min-max)	15.8 (16.1) 9.0 (1-55)	5.5 (5.3) 3.0 (1-19)
1, n (%)	37 (6)	129 (22)
2, n (%)	43 (7)	96 (17)
3, n (%)	56 (10)	81 (14)
4, n (%)	30 (5)	53 (9)
≥ 5, n (%)	410 (71)	217 (38)

Source: ADaM dataset adex.xpt

In Arms C/F, a total of 106 patients (19%) received the combination of gemcitabine/carboplatin, 55 patients (10%) received gemcitabine/cisplatin, 257 patients (45%) received pemetrexed/carboplatin, and 152 patients (27%) received pemetrexed/cisplatin.

Table 30: Chemotherapy administration

No. of doses	Chemotherapy (Arms C/F) N=570			
	Gemcitabine N=161	Cisplatin N= 207	Carboplatin N=378	Pemetrexed N=409
Mean (SD) Median (min-max)	6.2 (2.1) 7.0 (1-8)	3.3 (1.1) 4.0 (1-4)	3.4 (1.0) 4.0 (1-5)	9.0 (9.0) 6.0 (1-53)
1, n (%)	5 (3.1)	23 (11)	36 (10)	31 (8)
2, n (%)	8 (5)	25 (12)	48 (13)	48 (12)
3, n (%)	7 (4.3)	18 (9)	38 (10)	26 (6)
4, n (%)	20 (12)	141 (68)	255 (67)	41 (10)
≥ 5, n (%)	121 (75)	N/A	1 (0.3)	263 (64)

Source: ADaM dataset adex.xpt

Relevant characteristics of the safety population:

The characteristics of the safety population of Study CA209227 are consistent with the epidemiology and natural history of patients with metastatic NSCLC.

Adequacy of the safety database:

Overall, the safety database of 576 patients with metastatic NSCLC treated with nivolumab and

ipilimumab was sufficient to evaluate the safety of the combination given the established safety profiles of nivolumab and ipilimumab, given separately and in combination.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted was adequate to perform a complete review of the safety of nivolumab and ipilimumab. To assess the reliability and quality of the data, the clinical reviewer conducted random cross-validation of datasets with CRFs from Study CA209227; this assessment raised no concerns regarding data integrity. Information requests were sent to BMS during the review period to confirm data or clarify minor discrepencies.

Safety assessments included a review of the cause and frequency of deaths, incidence and severity of AEs and incidence of serious adverse eents (SAEs), AEs leading to discontinuation, AEs leading to dose interruption, reduction, and delay; adverse events of special interest (AESIs); treatment-emergent laboratory abnormalities; and vital sign measurements. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 was used to grade the severity of AEs. Certain MedDRA preferred terms (PTs) were grouped to identify adverse events of special interest.

Reviewer's comment: The corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding. Comparison of BMS' MedDRA PTs to the verbatim terms was undertaken by the reviewer in a sample of approximately 10% of recorded AEs and this review did not reveal significant discrepancies.

Categorization of Adverse Events

Adverse events
An adverse event was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation patient administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to study drug. AEs could be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. BMS considered both serious and non-serious AEs to be included in the term AE; the collection of non-serious AE information began at initiation of study drug and followed to resolution or stabilization. All non-serious AEs (not only those deemed treatment-related) were collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment; they were recorded and described on the non-serious AE page of the CRF.

Serious adverse events

An SAE was defined as any untoward medical occurrence that at any dose fulfilled one or more of the following criteria: results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is an important medical event defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed in the definition. All SAEs, whether related or unrelated to the study drug, that occurred during the screening period and within 100 days of the last dose of study drug, were collected, reported to BMS within 24 hours of awareness of the event, and recorded on the SAE Report Form through the eCRF.

Adverse events of interest: immune-mediated adverse events (IMAEs)

IMAEs were considered specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]) for which patients received immunosuppressive medications for treatment of the event, with the exception of endocrine events, which were included regardless of treatment since these events are often managed without immunosuppression. IMAEs included the following:

- Events occurring within 100 days of the last dose, regardless of causality, with no clear alternate etiology based on investigator assessment, with data collected on a new CRF page.
- Events treated with immune-modulating medication with the exception described above for endocrine events.

Table 31 provides a summary of the IMAEs categories and their respective PTs.

Table 31: Preferred terms included in analysis of IMAEs

IMAE category	PTs included in IMAE category
Pneumonitis	Hypersensitivity pneumonitis, idiopathic interstitial pneumonia, immune-mediated pneumonitis, interstitial lung disease, pneumonitis
Diarrhea/colitis	Autoimmune colitis, autoimmune enteropathy, colitis, colitis ulcerative, diarrhea, enteritis, enterocolitis, enterocolitis hemorrhagic
Hepatitis	Acute hepatic failure, acute on chronic liver failure, ALT increased, AST increased, autommune hepatitis, blood bilirubin increased, drug-induced liver injury, hepatic failure, hepatitis, hepatitis acute, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, transaminases increased
Adrenal insufficiency	Adrenal insufficiency, adrenocortical insufficiency acute,

	hypothalamic pituitary adrenal axis suppression, primary adrenal insufficiency, secondary adrenocortical insufficiency
Hypersensitivity	Anaphylactic reaction, anaphylactic shock, hypersensitivity, infusion related reaction
Hypothyroidism/thyroiditis	Atrophic thyroiditis, autoimmune hypothyroidism, autoimmune thyroiditis, hypothyroidism, primary hypothyroidism, silent thyroiditis, thyroiditis, thyroiditis acute
Hyperthyroidism	Basedow's disease, hyperthyroidism, primary hyperthyroidism
Hypophysitis	Hypophysitis, hypopituitarism, lymphocytic hypophysitis
Diabetes mellitus	Diabetes mellitus, diabetic ketoacidosis, diabetic ketosis, fulminant type 1 diabetes mellitus, latent autoimmune diabetes in adults, type 1 diabetes mellitus
Nephritis and renal dysfunction	Acute kidney injury, autoimmune nephritis, blood creatinine increased, creatinine renal clearance decreased, hypercreatininemia, nephritis, nephritis allergic, paraneoplastic glomerulonephritis, renal failure, renal tubular necrosis, subacute kidney injury, tubulointerstitial nephritis
Rash	Autoimmune dermatitis, dermatitis, dermatitis allergic, dermatitis exfoliative, drug eruption, erythema multiforme, exfoliative rash, fixed eruption, nodular rash, pemphigoid, pemphigus, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash morbilliform, rash papular, rashs pruritic, rash vesicular, Stevens-Johnson syndrome, toxic epidermal necrolysis, toxic skin eruption, urticarial dermatitis

Adverse events of interest: other events of special interest (OESIs)

OESIs were specific events including myasthenic syndrome, pancreatitis, uveitis, encephalitis, myocarditis, myositis, and rhabdomyolysis that were summarized by category regardless of causality or immune-modulating medication treatment in the Applicant's analysis. Table 32 below provides a summary of the OESI categories and their included preferred terms.

Table 32: Preferred terms included in analysis of OESIs

OESI category	PTs included in OESI category
Demyelination	Anti-myelin-associated glycoprotein associated polyneuropathy, autoimmune demyelinating disease, demyelination
Encephalitis	Acute encephalitis with refractory repetitive partial seizures, Bickerstaff's encephalitis, encephalitis, encephalitis allergic, encephalitis autoimmune, encephalitis brain stem, encephalitis hemorrhagic, encephalitis lethargica, encephalitis toxic, limbic encephalitis, lupus encephalitis, noninfective encephalitis, panencephalitis, Rasmussen encephalitis, subacute sclerosing panencephalitis
Guillain-Barre syndrome	Guillain-Barre syndrome, Miller Fisher syndrome
Myasthenic syndrome	Myasthenia gravis, myasthenia gravis crisis, myasthenic syndrome, ocular myasthenia
Myocarditis	Autoimmune myocarditis, eosinophilic myocarditis, hypersensitivity myocarditis, myocarditis
Myositis	Autoimmune myositis, dermatomyositis, inclusion body myositis, paraneoplastic myositis, polymyositis
Pancreatitis	Autoimmune pancreatitis, hemorrhagic necrotic pancreatitis, pancreatitis, pancreatitis acute, pancreatitis necrotizing
Rhabdomyolysis	Rhabdomyolysis
Uveitis	Autoimmune uveitis, chorioretinitis, cyclitis, iridocyclitis, iritis, keratouveitis, uveitis, Vogt-Koyangi-Harada disease

Routine Clinical Tests

At baseline, a medical history was obtained to capture relevant underlying conditions. The baseline examinations should have included weight, height, ECOG performance status, blood pressure (BP), heart rate (HR), temperature, oxygen saturation by pulse oximetry at rest; these were performed within 28 days prior to the first dose. Baseline local laboratory assessments should have been performed within 14 days prior to the first dose and included: complete blood count (CBC) with differential, liver function tests (LFTs) (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase), blood urea nitrogen (BUN) or serum urea level, creatinine, albumin, calcium, magnesium, sodium, potassium, chloride, phosphorous, lactate dehydrogenase (LDH), glucose, amylase, lipase, thyroid function tests (thyroid stimulating hormone [TSH], free T4, free T3). Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA) should have been done within 28 days prior to randomization.

Pregnancy testing for women of childbearing potential (WOCBP) must have been performed within 24 hours prior to Day 1 and then every 4 weeks (2 cycles) ± 3 days for patients in Arms A, B, D and every 3 weeks (each cycle) ± 3 days for patients in Arms C, F, G, H, and I.

While on-study, the following local laboratory assessments were required to be performed within 3 days prior to each dose: CBC with differential, LFTs, BUN or serum urea level, creatinine, albumin, calcium, magnesium, sodium, potassium, chloride, phosphorous, LDH, glucose, amylase, and lipase. TSH testing was done every 6 weeks. On-study weight, ECOG performance status, and vital signs were assessed at each on-study visit prior to dosing; vital signs should also have been taken as per institutional standard of care prior to, during, and after infusions. Oxygen saturation by pulse oximetry at rest and on exertion should have been assessed at each on-study visit prior to dosing; this should also have been obtained any time a patient had any new or worsening respiratory symptoms. All patients who met the eligibility criteria were required to have a 12-lead electrocardiogram (ECG) performed during Screening. If clinically indicated, additional ECGs may have been obtained during the study.

Reviewer's comment: BMS' assessment schedule for routine laboratory and clinical testing was adequate to monitor for the known risks of nivolumab and ipilimumab.

8.2.4 Safety Results

Deaths

In Study CA209227, as of July 2, 2019, there were 372 deaths overall (65%) in the nivolumab and ipilimumab arms (Arms B/D), 270 deaths (69%) in the nivolumab arm, and 445 deaths overall (78%) in the chemotherapy arms (Arms C/F), the majority of which were due to disease progression. Table 33 provides a summary of deaths in all treated patients in Arms A, B/D and C/F.

APPEARS THIS WAY ON ORIGINAL

Table 33: Deaths in all treated patients

	Nivo + ipi (Arms B/D) N=576	Nivo (Arm A) N=391	Chemo (Arms C/F) N=570
Total no. patients who died, n (%)	372 (65%)	270 (69%)	445 (78%)
Due to disease	304 (53%)	219 (56%)	364 (64%)
Due to study drug toxicity	10 (1.7%)	2 (0.5%)	6 (1.1%)
Unknown	14 (2.4%)	12 (3.1%)	27 (4.7%)
Other	46 (8%)	37 (10%)	48 (8%)
Patients who died within 30 days of last dose, n (%)	75 (13%)	51 (13%)	37 (7%)
Due to disease	48 (8%)	31 (8%)	16 (2.8%)
Due to study drug toxicity	5 (0.9%)	1 (0.3%)	5 (0.9%)
Unknown	2 (0.3%)	5 (1.3%)	5 (0.9%)
Other	20 (3.5%)	14 (3.6%)	11 (1.9%)
Patients who died within 100 days of last dose, n (%)	154 (27%)	113 (29%)	144 (25%)
Due to disease	110 (19%)	79 (20%)	105 (18%)
Due to study drug toxicity	7 (1.2%)	2 (0.5%)	6 (1.1%)
Unknown	6 (1.0%)	6 (1.5%)	9 (1.6%)
Other	31 (5.4%)	26 (7%)	24 (4.2%)

Source: CSR Table S.6.16

AEs leading to death, regardless of attribution to study drug, and excluding events of malignant neoplasm progression, are reported in Table 34.

Table 34: Deaths due to AEs

MedDRA SOC/PT	Nivo + ipi (Arms B/D) N=576	Nivo (Arm A) N=391	Chemo (Arms C/F) N=570
Patients with death due to TEAE, n (%)	46 (8)	39 (10)	39 (7)
Blood and lymphatic system disorders	0	1 (0.3)	1 (0.2)
Pancytopenia	0	1 (0.3)	0
Thrombocytopenia	0	0	1 (0.2)
Cardiac disorders	12 (2.1)	6 (1.5)	3 (0.5)
Atrial fibrillation	1 (0.2)	1 (0.3)	0
Cardio-respiratory arrest[a]	2 (0.3)	2 (0.5)	2 (0.4)
Cardiac tamponade	2 (0.3)	0	0
Cardiac failure[b]	2 (0.3)	1 (0.3)	0
Myocardial infarction[c]	4 (0.7)	1 (0.3)	1 (0.2)
Myocarditis	1 (0.2)	0	0

Stress cardiomyopathy	0	1 (0.3)	0
Congenital, familial, and genetic disorders	0	0	1 (0.2)
Tracheo-esophageal fistula	0	0	1 (0.2)
Gastrointestinal disorders	1 (0.2)	1 (0.3)	0
Diverticular perforation	1 (0.2)	0	0
Vomiting	0	1 (0.3)	0
General disorders and administration site conditions	7 (1.2)	8 (2.0)	6 (1.1)
Death[d]	5 (0.9)	7 (1.8)	5 (0.9)
Generalized edema	0	1 (0.3)	0
Hyperthermia	0	0	1 (0.2)
Multiple organ dysfunction syndrome	1 (0.2)	0	0
Hepatobiliary disorders	0	2 (0.5)	0
Cholangitis	0	1 (0.3)	0
Hepatitis	0	1 (0.3)	0
Infections and infestations	14 (2.4)	10 (2.6)	13 (2.3)
Pneumonia[e]	12 (2.1)	7 (1.8)	7 (1.2)
Septic shock[f]	2 (0.3)	3 (0.8)	6 (1.1)
Metabolism and nutrition disorders	1 (0.2)	1 (0.3)	1 (0.2)
Adult failure to thrive	0	0	1 (0.2)
Hyperglycemia	1 (0.2)	0	0
Hyponatremia	0	1 (0.3)	0
Nervous system disorders	2 (0.3)	4 (1.0)	5 (0.9)
Cerebrovascular accident[g]	2 (0.3)	4 (1.0)	5 (0.9)
Renal and urinary disorders	2 (0.3)	0	0
Renal failure	1 (0.2)	0	0
Acute kidney injury	1 (0.2)	0	0
Respiratory, thoracic, and mediastinal disorders	9 (1.6)	16 (4.1)	11 (1.9)
Aspiration pneumonia	0	1 (0.3)	0
Chronic obstructive pulmonary disease	0	0	1 (0.2)
Dyspnea	0	4 (1.0)	1 (0.2)
Esophagobronchial fistula	0	1 (0.3)	0
Hemoptysis	0	1 (0.3)	1 (0.2)
Pneumonitis[h]	4 (0.7)	2 (0.5)	1 (0.2)
Pneumothorax	1 (0.2)	0	1 (0.2)
Pulmonary embolism	3 (0.5)	3 (0.8)	0
Respiratory failure[i]	0	4 (1.0)	5 (0.9)
Lung infiltration	0	0	1 (0.2)
Vascular	2 (0.3)	0	0
Shock	1 (0.2)	0	0
Skin and subcutaneous tissue disorders	0	1 (0.3)	0

Rash	0	1 (0.3)	0

Source ADaM dataset: adae.xpt. and SDTM dataset: ae.xpt.
a: Includes cardiac arrest and cardio-respiratory arrest
b: Includes cardiac failure, cardiopulmonary failure, and cardiac failure acute
c: Includes myocardial infarction and myocardial infarction acute
d: Includes death and sudden death
e: Includes pneumonia, pneumonia viral, pulmonary sepsis lung infection, pleural infection, and respiratory tract infection
f: Includes septic shock, sepsis, and neutropenic sepsis
g: Includes cerebrovascular accident, cerebral infarction, ischemic stroke, and hemorrhagic cerebral infarction
h: Includes pneumonitis and interstitial lung disease
i: Includes respiratory failure and acute respiratory failure

Reviewer's comment: On review of the narratives for the events of fatal AEs, two patients who had events of respiratory failure (patients (b) (6) *and* (b) (6)*) and one patient who had an event of asthenia (patient* (b) (6)*) in the nivolumab and ipilimumab arms were found to have died due to disease progression. Therefore, these preferred terms were excluded from the table above.*

The case narratives and CRFs for patients who experienced an AE resulting in death were reviewed. Deaths considered related or possibly related to either nivolumab and ipilimumab, nivolumab monotherapy, or chemotherapy were identified in 10 (1.7%) patients in the nivolumab and ipilimumab arms including PTs myocarditis, acute kidney injury, pneumonitis (4 events), hyperglycemia, shock, multi-system organ failure, and renal failure; 2 (0.5%) patients in the nivolumab arm including PTs pancytopenia and pneumonitis; and 6 patients in the chemotherapy arms (1.1%) including PTs sepsis (3 events), cerebral infarction, interstitial lung disease, and thrombocytopenia. Brief narratives of the deaths attributed to study drug in the

APPEARS THIS WAY
ON ORIGINAL

nivolumab and ipilimumab arms are provided in Table 35.

Table 35: Adverse events leading to death in the nivolumab and ipilimumab arms

Patient ID	MedDRA PT	Summary	Causal attribution (FDA)
(b) (6)	Myocarditis	78-year-old male developed tachycardia, fatigue, dyspnea, chest and abdominal pain 12 days after the 2nd infusion of nivolumab and 26 days after the 1st infusion of ipilimumab. Lab tests showed an elevated creatine kinase of 2773 U/L (normal range not provided) and troponin I 3.82 µg/mL (range NA-0.06). A CT scan showed no pulmonary embolism or edema. An ECG showed complete atrioventricular block and he underwent pacemaker placement and was treated with corticosteroids. On Day 36 the patient died of myocarditis.	The patient had an exam and lab testing consistent with a diagnosis of myocarditis. Given the known safety profiles of nivolumab and ipilimumab, this event was likely due to study treatment.
(b) (6)	Acute kidney injury	73-year-old male developed worsening acute kidney injury (Grade 2) on Day 183, 42 days after the 11th dose of nivolumab and 56 days after the 4th dose of ipilimumab. Lab test results showed a cortisol level of 3.5 µg/dL (range 3.7-19.4) and an increased creatinine level of 183 µmol/L (range 64-104), after having previously had elevated creatinine levels on Days 155 and 164. The patient died on Day 186 with an autopsy showing acute tubular necrosis.	Given the known safety profile of nivolumab and ipilimumab, autopsy findings consistent with acute tubular necrosis, and lack of any other causative factors or medications, this event was likely due to study treatment.

(b) (6)	Pneumonitis	52-year-old male was diagnosed with PJP pneumonia on Day 34 and treated with sulfamethoxazole/trimethoprim. On Day 36, he developed Grade 3 pneumonitis, 2 days after the 2nd infusion of nivolumab and 35 days after the 1st dose of ipilimumab. A CXR revealed bilateral lung consolidation with bilateral pleural effusions. He was treated with high dose steroids and IV antibiotics, however, on Day 43 he developed fever and worsening CXR findings and he died that day.	There were likely multiple causative factors in this patient's death (including PJP pneumonia, sepsis, and pneumonitis), but given that he received treatment with high dose steroids from Day 10-Day 38, it is likely that pneumonitis due to study medications was a causative factor in his death.
(b) (6)	Pneumonitis	56-year-old male developed Grade 5 pneumonitis 11 days after the 1st infusion of nivolumab and ipilimumab. He presented with 5 days of exertional dyspnea and had an elevated CRP of 30 mg/L (range 0.8-2). He was treated with antibiotics and corticosteroids; a CT angiogram of the thorax showed slight increase in multiple lung metastases, left pleural effusion, and an increase in "frosted glass" abnormalities. He was further treated with infliximab but his CXR continued to show progression. His conditioned worsened and he developed a Grade 4 myocardial infarction on Day 30 and died the same day.	The patient's myocardial infarction was attributed to his worsening pneumonitis, which, given the time course, the CT findings and lack of other infectious markers, likely represents drug-related pneumonitis.

(b) (6)	Pneumonitis	69-year-old female was hospitalized with Grade 2 pneumonitis, reported as related to study therapy on Day 660, for which she received treatment with IV corticosteroids. A CT chest revealed pneumonitis. Study therapy had been discontinued on Day 630 due Grade 3 arthritis (related), with the last dose received on Day 616. The patient was discharged from the hospital 2 months later with a performance status of 3 and an oxygen requirement. No further information was available despite attempts made by BMS to obtain further history; according to the investigator, the patient died of pneumonitis on Day 790.	Despite the lack of information about events occurring between Day 660 and Day 790, given that the investigator's attribution of the fatal event was pneumonitis due to study therapy and that the patient was described as requiring IV corticosteroids, it is likely that this was a fatal event related to study therapy.
(b) (6)	Shock	72-year-old male developed Grade 3 lung infection on Day 155 (14 days after the 10th study drug infusion) and was found to have an increased CRP level of 3.95 mg/dL (range 0-0.14 mg/dL) and a CT chest showing ground glass opacities. He was treated with antibiotics. 10 days later while still hospitalized, he developed Grade 4 shock with chills, fever (41.3^{o}C), hypotension, and decreased consciousness. Blood cultures were negative and the patient required mechanical ventilation. A CT head showed no findings of hemorrhage or infarction, repeat chest CT showed improved lung infection, and a CT abdomen was "unremarkable." He was treated with hydrocortisone x 1 dose, blood products, vasopressors, and IV fluids but he died on Day 165. The investigator attributed his death to cytokine release syndrome related to study therapy.	Although cytokine release syndrome is rare in patients treated with immune checkpoint inhibitors, given the lack of infectious findings at the time of the shock event, it is not possible to rule out study therapy as the causative agent.

(b) (6)	Pneumonitis	63-year old male developed Grade 2 pneumonitis on Day 175 (15 days after the 12th infusion of nivolumab and 5th infusion of ipilimumab) with a CT chest showing bilateral pulmonary consolidation. He was treated with oral corticosteroids and on Day 181 the event was reported as resolved. However, on Day 182, the patient developed worsening pneumonitis for which treatment with oral corticosteroids was continued, and on Day 202 his condition worsened (Grade 4) and he was treated with ceftriaxone and IV corticosteroids. A CT chest revealed an increased number of pulmonary consolidations and on Day 207 the patient died of pneumonitis.	Given the CT findings, prolonged treatment with corticosteroids, and lack of other symptoms of pneumonia (fever, elevated WBC count), this likely represents an event of drug-related pneumonitis.
(b) (6)	*Cardiac tamponade*	*65-year-old male developed retrosternal constrictive pain at home and died on Day 11, 10 days after the 1st infusions of nivolumab and ipilimumab. According to the patient's wife, the patient collapsed after he changed his position from sitting to standing. He was diagnosed with cardiac tamponade by the investigator based on this description. A report from an echocardiogram performed 20 days prior to the fatal event state that "there is severe pulmonary hypertension 94 mmHg (severe PH [sPAP, > 60 mmHg: Group 3]). There is right-sided heart enlargement and heart failure (cor pulmonale)." The patient had a past medical history of hypertension, DVT, and pulmonary embolism. No autopsy was performed and no additional information was able to be obtained from the investigator.*	*Based on the description of the event, the patient's past medical history of DVT, and recent echocardiogram findings of severe pulmonary hypertension, it is unlikely that this event was related to study therapy.*

(b) (6) *	Hyperglycemia	61-year-old male was hospitalized in the intensive care unit on Day 147 (14 days after the 10th infusion of nivolumab and the 4th infusion of ipilimumab) with Grade 4 hyperglycemia with a glucose level of 459 mg/dL (baseline 112 mg/dL; range 70-110). WBC count, BUN, and creatinine were also elevated. Patient also complained of nausea, vomiting, and weight loss. On Day 154 his condition worsened and he required mechanical ventilation; study therapy was discontinued. On Day 155 the patient died.	This patient did not have a past medical history of diabetes mellitus. It is unlikely that the glucose elevation was due to an infectious cause given the lack of fever and height of the glucose level. Given the known safety profiles of nivolumab and ipilimumab, immune-mediated diabetes mellitus cannot be ruled out as the cause of death.
(b) (6) *	Multi-system organ failure	77-year-old female developed Grade 4 AST/ALT/bilirubin elevations on Day 337 with AST 1601 U/L (range 0-40), ALT 1092 U/L (range 0-40), total bilirubin 8.8 mg/dL (range 0-1.5) considered to be related to study therapy. Her most recent doses of nivolumab and ipilimumab were on Day 321. On Day 358, the event was amended to Grade 3 hepatitis related to study therapy and study therapy was discontinued. BMS was unable to obtain further information, including lab results and treatment for the hepatitis prior to the patient withdrawing consent from all follow-up except for survival. On Day 375, the investigator reported an SAE of multiple organ failure resulting in death. No further information was obtained.	Although the event of multi-system organ failure was considered unrelated to study therapy by BMS, given the temporal relationship to treatment-related hepatitis, it is not possible to rule out the causative role of nivolumab and ipilimumab in this fatal event.

(b) (6) *	Renal failure	A 57-year-old male was hospitalized for Grade 4 renal failure on Day 213, 15 days after his 15th infusion of nivolumab and 43 days after the 5th dose of ipilimumab. He presented with "psychomotor agitation" and laboratory tests revealed a creatinine of 13 mg/dL (range 0.7-1.2) and BUN of 223 mg/dL (range 18-55). Previous laboratory values on Day 198 were 0.83 mg/dL and 55 mg/dL, respectively. On Day 214, the patient developed heart failure, was intubated and placed on mechanical ventilation; however, he did not respond to resuscitative measures and died due to renal failure that day. BMS attempted to contact the investigator for further information but was unable to obtain any additional details.	Although the event of renal failure was not attributed to study therapy, given the mechanism of action of nivolumab and ipilimumab, it is not possible to rule out treatment-related nephritis as the cause of renal failure. The patient was not taking any concurrent medications that are known to cause renal failure (cyanocobalamin, folic acid, perindopril).

*Assessed by the clinical reviewer as being related to study therapy

Reviewer's comment: BMS was queried by the clinical reviewer for additional details regarding the fatal events in Patients (b) (6) (multi-system organ failure), (b) (6) (renal failure), (b) (6) (b) (6) (cardiac tamponade), and (b) (6) (pneumonitis). Based on the review of these additional details, the events of multi-system organ failure and renal failure were considered to be at least possibly related to study therapy. Therefore, these events were included in the total number of patients in the nivolumab and ipilimumab arms who died due to an adverse event related to study therapy (10). Additionally, the additional case details regarding the event of cardiac tamponade in patient (b) (6) revealed that the event, attributed as possibly related to study therapy by the investigator, was unlikely to be related to study therapy, and was excluded from the total number of patients in the nivolumab and ipilimumab arms who died due to an adverse event. However, the description of the event is retained in Table 30.

Serious Adverse Events

SAEs occurring in > 2% of patients in the nivolumab and ipilimumab treatment arms (Arms B/D), the nivolumab treatment arm (Arm A), and the chemotherapy treatment arms (Arms C/F), regardless of causality occurring up to 30 days after receipt of last dose of study therapy are listed in Table 36. PTs describing tumor progression-related events, including malignant neoplasm progression, lung cancer metastatic, lymphangiosis carcinomatosa, metastasis, metastases to bone, and neoplasm malignant, were excluded. Overall, 302 (52%) of patients in the nivolumab and ipilimumab arms, 169 (43%) of patients in the nivolumab arm, and 204

(36%) of patients in the chemotherapy arms experienced an SAE. Based on inclusion of SAEs occurring up to 100 days of receipt of last dose of study therapy, SAEs occurred in 58% of patients in the nivolumab and ipilimumab arms.

Table 36: Serious AEs by PT occurring in ≥ 2% of patients in any arm

PT, n (%)	Nivo + Ipi Arms B/D N=576	Nivolumab Arm A N=391	Chemo Arms C/F N=570
Pneumonia[a]	51 (9)	32 (8)	37 (6)
Diarrhea/colitis[b]	29 (5)	7 (1.8)	8 (1.4)
Pneumonitis[c]	29 (5)	11 (2.8)	4 (0.7)
Hepatitis[d]	25 (4.3)	7 (1.8)	1 (0.2)
Adrenal insufficiency	13 (2.3)	1 (0.3)	0
Hypophysitis[e]	13 (2.3)	1 (0.3)	0
Pulmonary embolism	13 (2.3)	5 (1.3)	5 (0.9)
Anemia	3 (0.5)	2 (0.5)	16 (2.8)
Febrile neutropenia	1 (0.2)	0	13 (2.3)

Source ADaM dataset: adae.xpt. and SDTM dataset: ae.xpt.
a: Includes lower respiratory tract infection, lung infection, organizing pneumonia, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia influenzal, pneumonia klebsiella, and pneumonia viral
b: Includes colitis, colitis microscopic, diarrhea, enteritis infectious, enterocolitis, and enterocolitis infectious
c: Includes interstitial lung disease and pneumonitis
d: Includes acute hepatic failure, alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, hepatic enzyme increased, hepatic function abnormal, hepatitis, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased
e: Includes hypophysitis and hypopituitarism

Reviewer's comment: The most common SAE in all three arms was pneumonia which is expected in a population of patients with metastatic NSCLC. Patients in the nivolumab and ipilimumab arms experienced a higher number of SAEs (52% vs. 36%) than those in the chemotherapy arms. PTs for which there was a >2% difference between the nivolumab and ipilimumab arms and the chemotherapy arms were pneumonia, diarrhea/colitis, pneumonitis, hepatitis, adrenal insufficiency, and hypophysitis. More patients in the chemotherapy arm experienced anemia and febrile neutropenia. In addition, more patients in the nivolumab and ipilimumab arms experienced events of pneumonitis, diarrhea/colitis, hepatitis, adrenal insufficiency, and hypophysitis than those in the nivolumab monotherapy arm.

Dropouts and/or Discontinuations Due to Adverse Effects

AEs leading to discontinuation included events in which one or more drugs of a multidrug regimen were discontinued, even if the patient remained on treatment. PTs describing tumor-related events, including malignant neoplasm progression, were excluded. Overall, 140 patients (24%) in the nivolumab and ipilimumab arms, 65 patients (17%) in the nivolumab arm, and 85

patients (15%) in the chemotherapy arms discontinued treatment due to an AE. All-causality AEs occurring within 30 days of follow-up leading to treatment discontinuation in ≥ 3 patients in any arm are summarized in Table 37.

Table 37: AEs leading to discontinuation in ≥ 3 patients in any arm

PT, n (%)	Nivo + Ipi Arms B/D N=576	Nivolumab Arm A N=391	Chemo Arms C/F N=570
Pneumonitis[a]	27 (4.7)	10 (2.6)	3 (0.5)
Diarrhea/colitis[b]	19 (3.3)	6 (1.5)	1 (0.2)
Hepatitis[c]	18 (3.1)	8 (2.0)	2 (0.4)
Pneumonia[d]	6 (1.0)	4 (1.0)	4 (0.7)
Pleural effusion[e]	5 (0.9)	0	1 (0.2)
Adrenal insufficiency	4 (0.7)	1 (0.3)	0
Fatigue[f]	4 (0.7)	3 (0.8)	7 (1.2)
Hypophysitis[g]	4 (0.7)	0	0
Renal impairment[h]	3 (0.5)	1 (0.3)	10 (1.8)
Cerebrovascular accident[i]	3 (0.5)	0	4 (0.7)
Decreased appetite	3 (0.5)	2 (0.5)	3 (0.5)
Rash[j]	3 (0.5)	2 (0.5)	0
Amylase increased	1 (0.2)	3 (0.8)	0
Anemia	0	0	6 (1.1)
Nausea	2 (0.3)	0	3 (0.5)
Neutropenia[k]	0	0	3 (0.5)
Respiratory failure	1 (0.2)	0	3 (0.5)

Source ADaM dataset: adae.xpt. and SDTM dataset: ae.xpt.
a: Includes interstitial lung disease and pneumonitis
b: Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, and enterocolitis
c: Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatocellular injury, hepatotoxicity, immune-mediated hepatitis, and liver function test abnormal
d: Includes lung infection and pneumonia
e: Includes malignant pleural effusion and pleural effusion
f: Includes asthenia and fatigue
g: Includes hypophysitis and hypopituitarism
h: Includes acute kidney injury, blood creatinine increased, creatinine renal clearance decreased, renal failure, tubular interstitial nephritis
i: Includes cerebral infarction, cerebrovascular accident, ischemic stroke, and hemorrhagic cerebral infarction
j: Includea dermatitis bullous, rash, rash maculo-papular and toxic skin eruption
k: Includes neutropenia and neutrophil count decreased

Reviewer's comment: A greater percentage of patients in the nivolumab and ipilimumab arms experienced an AE leading to treatment discontinuation than those in the nivolumab arm or the chemotherapy arms (24% vs. 17% vs. 15%, respectively. The most common AE leading to treatment discontinuation in the nivolumab and ipilimumab arms was pneumonitis (4.7% of

patients) and the most common AE leading to treatment discontinuation in the chemotherapy arms was acute kidney injury (1.8% of patients).

Study drug interruption (Table 38) of any drug in a multidrug combination due to an AE occurred in 303 patients (53%) in the nivolumab and ipilimumab arms, in 168 patients (43%) in the nivolumab arm, and in 261 patients (46%) in the chemotherapy arms, excluding tumor-related PTs (e.g. malignant neoplasm progression).

Table 38: AEs leading to study drug interruption in ≥2% of patients in any arm

PT, n (%)	Nivo + Ipi Arms B/D N=576	Nivolumab Arm A N=391	Chemo Arms C/F N=570
Hepatitis[a]	56 (10)	21 (5)	10 (1.8)
Pneumonia[b]	34 (6)	15 (3.8)	13 (2.3)
Diarrhea/colitis[c]	33 (6)	18 (4.6)	5 (0.9)
Rash[d]	30 (5)	11 (2.8)	2 (0.4)
Fatigue[e]	26 (4.5)	13 (3.3)	23 (4.0)
Pneumonitis[f]	23 (4.0)	20 (5)	0
Pancreatic enzymes increased[g]	17 (3.0)	13 (3.3)	4 (0.7)
Hypothyroidism[h]	15 (2.6)	8 (2.0)	0
Renal impairment[i]	15 (2.6)	6 (1.5)	7 (1.2)
Dyspnea[j]	13 (2.3)	4 (1.0)	3 (0.5)
Neutropenia[k]	2 (0.3)	1 (0.3)	107 (19)
Anemia[l]	9 (1.6)	3 (0.8)	71 (12)
Thrombocytopenia[m]	2 (0.3)	1 (0.3)	41 (7)
Leukopenia[n]	0	0	15 (2.6)

Source ADaM dataset: adae.xpt. and SDTM dataset: ae.xpt.
a: 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, liver function test abnormal, liver function test increased, and transaminases increased
b: Includes atypical pneumonia, lower respiratory tract infection, lung infection, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia influenzal, and pneumonia klebsiella
c: Includes colitis, diarrhea, enteritis infectious, and enterocolitis
d: Includes autoimmune dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative generalized, eczema, rash, rash macular, rash maculo-papular, rash papular
e: Includes fatigue and asthenia
f: Includes interstitial lung disease and pneumonitis
g: Includes amylase increased and lipase increased
h: Includes autoimmune thyroiditis, blood thyroid stimulating hormone decreased, hypothyroidism, thyroiditis
i: Includes acute kidney injury, autoimmune nephritis, blood creatinine increased, creatinine renal clearance

decreased, renal insufficiency, renal failure
j: Includes dyspnea and dyspnea exertional
k: Includes neutropenia and neutrophil count decreased
l: Includes anemia, hematocrit decreased, and hemoglobin decreased
m: Includes platelet count decreased and thrombocytopenia
n: Includes leukopenia and white blood cell count decreased

Significant Adverse Events

Grade 3-5 all-causality AEs reported in ≥ 2% of patients in any arm within 30 days of treatment end are provided in Table 39, excluding tumor progression-related PTs (e.g. malignant neoplasm progression). Overall, 359 patients (62%) in the nivolumab and ipilimumab arms, 213 patients (54%) in the nivolumab arm, and 306 patients (54%) in the chemotherapy arms experienced a Grade 3-5 AE.

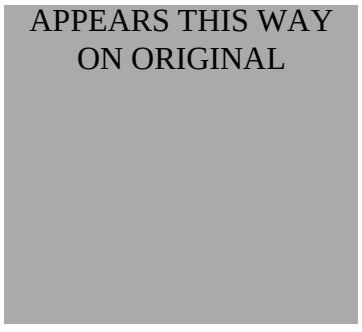


Table 39: All-causality Grade 3-5 AEs in ≥2% of patients in any arm

PT, n (%)	Nivo + Ipi Arms B/D N=576	Nivolumab Arm A N=391	Chemo Arms C/F N=570
Hepatitis[a]	51 (9)	25 (6)	6 (1.1)
Pneumonia[b]	44 (8)	23 (6)	24 (4.2)
Pancreatic enzymes increased[c]	40 (7)	23 (6)	6 (1.1)
Fatigue[d]	32 (6)	15 (3.8)	25 (4.4)
Hyponatremia	32 (6)	12 (3.1)	7 (1.2)
Dyspnea[e]	25 (4.3)	14 (3.6)	12 (2.1)
Rash[f]	25 (4.3)	5 (1.3)	2 (0.4)
Diarrhea/colitis[g]	21 (3.6)	4 (1.0)	5 (0.9)
Pneumonitis[h]	19 (3.3)	1 (0.3)	3 (0.5)
Anemia	18 (3.1)	9 (2.3)	76 (13)
Hyperglycemia	14 (2.4)	4 (1.0)	6 (1.1)
Decreased appetite	13 (2.3)	5 (1.3)	8 (1.4)
Hypokalemia	13 (2.3)	3 (0.8)	5 (0.9)
Pulmonary embolism	13 (2.3)	5 (1.3)	6 (1.1)
Adrenal insufficiency	12 (2.1)	1 (0.3)	0
Pericardial effusion[i]	4 (0.7)	8 (2.0)	1 (0.2)
Neutropenia[j]	2 (0.3)	3 (0.8)	94 (16)
Thrombocytopenia[k]	5 (0.9)	2 (0.5)	45 (8)
Leukopenia[l]	1 (0.2)	1 (0.3)	20 (3.5)
Febrile neutropenia	1 (0.2)	0	16 (2.8)
Nausea	6 (1.0)	2 (0.5)	14 (2.5)
Vomiting	6 (1.0)	4 (1.0)	13 (2.3)

Source ADaM dataset: adae.xpt. and SDTM dataset: ae.xpt.
a: Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatitis, heptatitis E, hepatotoxicity, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal, transaminases increased
b: Includes lower respiratory tract infection, lung infection, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia influenza, pneumonia viral
c: Includes amylase increased and lipase increased
d: Includes asthenia and fatigue
e: Includes dyspnea and dyspnea exertional
f: Includes dermatitis bullous, eczema, rash, rash macular, rash maculo-papular, rash pruritic
g: Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, and enterocolitis
h: Includes interstitial lung disease and pneumonitis
i: Includes pericardial effusion and pericardial effusion malignant
j: Includes neutropenia and neutrophil count decreased
k: Includes platelet count decreased and thrombocytopenia
l: Includes leukopenia and white blood cell count decreased

More patients in the nivolumab and ipilimumab arms were reported to have experienced a Grade 3-5 AE than in the chemotherapy arms (62% vs. 54%). Hepatitis, pneumonia, increased

pancreatic enzymes, fatigue, and hyponatremia were the most common Grade 3-5 events in the nivolumab and ipilimumab arms whereas myelosuppression, i.e. neutropenia, anemia, and thrombocytopenia were the most common Grade 3-5 AEs observed in the chemotherapy arms.

Grade 3-5 AEs occurring at a ≥2% higher frequency in the nivolumab and ipilimumab arms compared to the chemotherapy arms were: hepatitis (9% vs. 1.1%), pneumonia (9% vs. 5%), increased pancreatic enzymes (7% vs. 1.1%), hyponatremia (6% vs. 1.2%), dyspnea (4.3% vs. 2.1%), rash (4.3% vs. 0.4%), diarrhea/colitis (3.6% vs. 0.9%), pneumonitis (3.3% vs. 0.5%), and adrenal insufficiency (2.1% vs. 0). Grade 3-5 AEs occurring at a ≥2% higher frequency in the nivolumab and ipilimumab arms compared to the nivolumab arm were: hepatitis (9% vs. 6%), pneumonia (9% vs. 4.9%), fatigue (6% vs. 3.8%), hyponatremia (6% vs.3.1%), rash (4.3% vs. 1.3%), diarrhea/colitis (3.6% vs. 1.0%), and pneumonitis (3.3% vs. 0.3%).

Reviewer's comment: Although the safety profiles of immunotherapy and chemotherapy are different and largely non-overlapping, more patients overall experienced a Grade 3-5 AE in the nivolumab and ipilimumab arms vs. the chemotherapy arms. Consistent with the known safety profiles of each combination, immune-related events were experienced most frequently in the nivolumab and ipilimumab arms and myelosuppression-related events were experienced most frequently in the chemotherapy arms. The addition of ipilimumab to the combination also appears to increase the overall immune-related toxicity of the nivolumab and ipilimumab regimen in NSCLC patients given the higher frequency of Grade 3-5 hepatitis, rash, diarrhea/colitis, and pneumonitis in those arms when compared with the nivolumab monotherapy arm.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs (all grades and Grades 3-4) occurring in more than 10% of patients in any treatment arm within 30 days of cessation of study therapy are listed in Table 40 by preferred term. The most common adverse reaction reported in the nivolumab and ipilimumab treatment arms was fatigue/asthenia (44%) and the most common adverse reations reported in the chemotherapy treatment arms were fatigue/asthenia and nausea (both 42%).

Among patients treated with nivolumab and ipilimumab, the most common AEs occurring in ≥20% of patients were fatigue/asthenia (44%), rash (34%), decreased appetite (31%), musculoskeletal pain (27%), diarrhea/colitis (26%), dyspnea (26%), cough (23%), hepatitis (21%), nausea (21%), and pruritus (21%).

AEs (all grades) that occurred at a ≥10% incidence in patients in the nivolumab and ipilimumab arms compared to the chemotherapy arms were rash (34% vs. 10%), musculoskeletal pain (27% vs. 16%), diarrhea/colitis (26% vs. 16%), dyspnea (26% vs. 16%), cough (23% vs. 13%), heptatitis (21% vs. 10%), pruritus (21% vs. 3.3%), hypothyroidism (16% vs. 1.1%), and arthralgia (13% vs. 2.5%).

Table 40: All-causality TEAEs in ≥10% of patients in any arm

PT, %	Nivo + Ipi Arms B/D N=576		Nivolumab Arm A N=391		Chemo Arms C/F N=570	
	All grades	Gr 3-4	All grades	Gr 3-4	All grades	Gr 3-4
Any AE	99	66	98	57	97	56
Fatigue[a]	44	6	40	3.8	42	4.4
Rash[b]	34	4.7	21	1.5	10	0.4
Decreased appetite	31	2.3	23	1.3	26	1.4
Musculoskeletal pain[c]	27	1.9	26	1.8	16	0.7
Diarrhea/colitis[d]	26	3.6	22	1.0	16	0.9
Dyspnea[e]	26	4.3	25	3.6	16	2.1
Cough[f]	23	0.2	24	0	13	0
Hepatitis[g]	21	9	16	6	10	1.2
Nausea	21	1.0	18	0.5	42	2.5
Pruritus[h]	21	0.5	11	0	3.3	0
Constipation	18	0.3	15	0.5	27	0.5
Pyrexia	18	0.5	14	0.3	11	0.4
Hypothyroidism[i]	16	0.5	9	0.3	1.2	0
Edema[j]	14	0.2	6	0.3	12	0.5
Arthralgia	13	0.9	10	0.8	2.5	0.2
Pneumonia[k]	13	7	11	6	8	4.0
Vomiting	13	1.0	10	1.0	18	2.3
Headache	11	0.5	9	0	6	0
Abdominal pain[l]	10	0.2	12	1.0	9	0.7
Hyperthyroidism[m]	10	0	5	0	0.5	0

Source ADaM dataset: adae.xpt. and SDTM dataset: ae.xpt.

a: Includes fatigue and asthenia

b: 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

c: Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity

d: Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral

e: Includes dyspnea and dyspnea exertional

f: Includes cough and productive cough

g: 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

h: Includes pruritus and pruritus generalized

i: Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary

hypothyroidism, thyroiditis, and tri-iodothyronine free decreased
j: Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema
k: Includes atypical pneumonia, lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, organizing pneumonia, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral
l: Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness
m: Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased

Reviewer's comment: The adverse reactions that occurred in ≥10% of patients in the nivolumab and ipilimumab arms versus the chemotherapy arms are likely due to the different toxicity profiles of immunotherapy and chemotherapy and are largely reflective of underlying immune-related events, described further in Section 8.2.5.

Laboratory Findings

In Study CA209227, laboratory tests to assess serum chemistry (sodium, potassium, chloride, glucose, BUN, creatinine, magnesium, phosphorous), liver function (AST, ALT, alkaline phosphatase, total bilirubin), albumin, LDH, pancreatic function (amylase and lipase), and thyroid function (TSH, free T4, and free T3), and a complete blood count (CBC) were obtained at screening (within 14 days of the first dose of study therapy) and at the start of every cycle, with the exception of TSH which was evaluated every 6 weeks. Laboratory alterations graded according to NCI CTCAE v4.03 from baseline throughout the course of the study were analyzed; the findings are summarized in the following tables.

Table 41 summarizes the hematologic changes from baseline within 30 days of last dose of study therapy in ≥10% of patients enrolled in Part 1 of Study CA209227 who received at least one dose of study drug.

Table 41: Hematologic laboratory values worsening from baseline in ≥10% of patients

Laboratory abnormality, %	Nivo + Ipi Arms B/D N=576			Nivolumab Arm A N=391			Chemo Arms C/F N=570		
	N*	All grades	Gr 3-4	N*	All grades	Gr 3-4	N*	All grades	Gr 3-4
Anemia	556	46	3.6	369	45	3.8	542	78	14
Lymphopenia	553	46	5	368	45	7	538	60	15
Thrombocytopenia	555	11	0.9	368	9	0.3	546	31	8
Neutropenia	555	10	0.9	370	5	0.3	542	52	18

Source: SCS, ADaM dataset adlb.xpt
*Number of patients with at least one baseline and one post-baseline laboratory measurement; percentages are based on N as the denominatory

Table 42 summarizes the changes in serum chemistry evaluations from baseline in patients

enrolled in Part 1 of Study CA209227 who received at least one dose of study drug.

Table 42: Serum chemistry values worsening from baseline in ≥10% of patients

Laboratory abnormality, %	Nivo + Ipi Arms B/D N=576			Nivolumab Arm A N=391			Chemo Arms C/F N=570		
	N*	All grades	Gr 3-4	N*	All grades	Gr 3-4	N*	All grades	Gr 3-4
Hyponatremia	552	41	12	368	36	10	534	26	4.9
AST increased	551	39	5	368	31	3.5	529	26	0.4
ALT increased	555	36	7	368	32	5	534	27	0.7
Lipase increased	524	35	14	347	25	8	507	14	3.4
Alkaline phosphatase increased	552	34	3.8	366	33	3.0	532	20	0.2
Amylase increased	494	28	9	320	24	4.4	469	18	1.9
Hypocalcemia	545	28	1.7	362	27	0.8	523	17	1.3
Hyperkalemia	551	27	3.4	367	23	2.7	533	22	0.4
Creatinine increased	554	22	0.9	369	17	1.1	536	17	0.2
Hypomagnesemia	542	20	0.6	358	20	0.6	520	25	0.8
Hypokalemia	551	15	4.0	367	9	1.6	533	10	2.3
Hypercalcemia	545	12	1.7	362	12	1.1	523	10	0.6
Hyperbilirubinemia	554	11	1.1	367	10	1.4	533	3.4	0
Hypermagnesemia	542	10	3.7	358	11	3.6	520	7	2.5

Source: SCS, ADaM dataset adlb.xpt
*Number of patients with at least one baseline and one post-baseline laboratory measurement; percentages are based on N as the denominator

Vital Signs

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. No clinically meaningful changes from baseline were noted in the safety population.

Electrocardiograms (ECGs)

Electrocardiograms (12-lead ECGs) were performed at baseline and at any time during the study if clinically indicated. Abnormalities in ECGs were reported as AEs. AEs reflecting potential ECG abnormalities in all treatment arms are listed in Table 43.

Table 43: AEs reflecting potential ECG abnormalities

PT, n (%)	Nivo + Ipi Arms B/D N=576		Nivolumab Arm A N=391		Chemo Arms C/F N=570	
	All grades	Gr 3-5	All grades	Gr 3-5	All grades	Gr 3-5
Atrial fibrillation	21 (3.6)	11 (1.9)	0	0	6 (1.1)	0
Tachycardia	12 (2.1)	0	6 (1.5)	0	11 (1.9)	2 (0.4)
Palpitations	10 (1.7)	0	5 (1.3)	0	1 (0.2)	0
Myocardial infarction[a]	9 (1.6)	9 (1.6)	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)
Sinus tachycardia	7 (1.2)	0	3 (0.8)	0	6 (1.1)	0
Bradycardia	2 (0.3)	0	1 (0.3)	0	0	0
Atrial flutter	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)	2 (0.4)	1 (0.2)
Myocardial ischemia	1 (0.2)	0	0	0	0	0
Sinus bradycardia	1 (0.2)	0	2 (0.5)	0	1 (0.2)	0
Supraventricular tachycardia[b]	1 (0.2)	0	3 (0.8)	1 (0.3)	0	0
Torsades de points	1 (0.2)	1 (0.2)	0	0	0	0
Ventricular arrhythmia	1 (0.2)	0	0	0	1 (0.2)	0
Ventricular extrasystoles	1 (0.2)	0	0	0	0	0
Ventricular tachycardia	1 (0.2)	0	0	0	0	0
Arrhythmia	0	0	1 (0.3)	1 (0.3)	1 (0.2)	0
Atrioventricular block complete	0	0	1 (0.3)	1 (0.3)	0	0
Supraventricular extrasystoles	0	0	0	0	1 (0.2)	0

a: Includes acute myocardial infarction and myocardial infarction
b: Includes supraventricular tachyarrhythmia and supraventricular tachycardia

QT

No dedicated QTc study was submitted with this supplement. Previous analyses have not demonstrated a clinically meaningful effect of nivolumab and/or ipilimumab on the QT interval.

Immunogenicity

In Study CA209227, blood samples for immunogenicity analyses of nivolumab and ipilimumab were collected according to the schedules provided in Table 39 and Table 40. Samples collected from patients in each treatment arm were evaluated for development of Anti-Drug Antibody (ADA) for nivolumab/ipilimumab by validated immunoassays. Samples may also have been analyzed for neutralizing ADA response to nivolumab/ipilimumab.

Table 44: Pharmacokinetic and immunogenicity sample collection schedule (Arm A: nivolumab)

Study Day (1 Cycle = 2 Weeks)	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab
C1D1	Predose[a]	00:00	X	X
C2D1	Predose[a]	00:00	X	X
C4D1	Predose[a]	00:00	X	X
C10D1	Predose[a]	00:00	X	X
D1 of every 9th cycle after C10 D1 until discontinuation of study treatment or maximum up to 2 years of treatment	Predose[a]	00:00	X	X

[a] Predose samples for nivolumab should be taken prior to the start of nivolumab infusion (preferably within 30 minutes). If it is known that a dose is going to be delayed, then predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected.

Source: Clinical protocol for Study CA209227 (Version 6, dated August 15, 2018), Table 5.5.1-1

Table 45: Pharmacokinetic and immunogenicity sample collection schedule (Arms B and D: nivolumab and ipilimumab)

Study Day[a] (1 Cycle = 2 weeks)	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenicity Blood Sample for Ipilimumab
C1D1 (Ipilimumab dose 1)	Predose[b]	00:00	X	X	X	X
C2D1 (Nivolumab dose 2)	Predose[b]	00:00	X	X	X	X
C4D1 (Ipilimumab dose 2)	Predose[b]	00:00	X	X	X	X
C10D1 (Ipilimumab dose 4)	Predose[b]	00:00	X	X	X	X

Study Day[a] (1 Cycle = 2 weeks)	Event (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenicity Blood Sample for Ipilimumab
D1 of every 9th cycle after C10D1 until discontinuation of study treatment (or Ipilimumab Dose 7, 10, 13...etc.) or maximum up to 2 years of treatment	Predose[b]	00:00	X	X	X	X

[a] If ipilimumab is discontinued and nivolumab continues, ipilimumab PK and ADA should be collected only for the next 2 time points (corresponding to nivolumab sample collection) according to the PK table.

[b] Predose samples should be collected just before the administration of the nivolumab (preferably within 30 minutes). If it is known that a dose is going to be delayed, then predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected.

Source: Clinical protocol for Study CA209227 (Version 6, dated August 15, 2018), Table 5.5.1-3

In the nivolumab and ipilimumab arms (Arms B/D), 491 patients (85%) were nivolumab ADA evaluable, defined as patients with a baseline and at least one meaningful nivolumab post baseline immunogenicity assessment. Of these 44 patients (9%) were nivolumab ADA positive at baseline and 180 patients (37%) were nivolumab ADA positive after the start of treatment. A total of 7 patients (1.4%) were considered to have persistent positive nivolumab ADA, defined as ADA to nivolumab positive samples at two or more consecutive timepoints with the first and last ADA-positive samples at least 16 weeks apart. Seven patients (1.4%) were neutralizing ADA positive. The highest titer value observed in nivolumab ADA positive patients was 128, which occurred in one patient.

In the nivolumab and ipilimumab arms (Arms B/D), 483 patients (84%) were ipilimumab ADA evaluable, defined as patients with a baseline and at least one meaningful ipilimumab post baseline immunogenicity assessment. Of these 20 patients (4.1%) were ipilimumab ADA positive at baseline and 41 patients (8.5%) were ipilimumab positive after the start of treatment. A total of 3 patients (0.6%) were considered to have persistent positive ipilimumab ADA and no patients were neutralizing ADA positive.

Table 46 provides a summary of ADA assessements in Study CA209227.

Table 46: Summary of ADA assessments

ADA status, n (%)	Nivo + Ipi Arms B/D N=576		Nivolumab Arm A N=391
	Nivolumab ADA N=491	Ipilimumab ADA N=483	Nivolumab ADA N=322
Baseline ADA positive	44 (9)	20 (4.1)	33 (10)
ADA positive	180 (37)	41 (9)	77 (24)
Persistent positive	7 (1.4)	3 (0.6)	2 (0.6)
Last sample positive	44 (9)	13 (2.7)	17 (5)
Other positive	129 (26)	25 (5)	58 (18)
Neutralizing ADA positive	7 (1.4)	0	5 (1.6)
ADA negative	311 (63)	442 (92)	245 (76)

Source: Final CSR Part 1, ADaM dataset adyi.xpt
Persistent positive: ADA-positive sample at two or more consecutive timepoints where the first and last ADA-positive samples are at least 16 weeks apart
Last sample positive: Not persistent positive with ADA-positive sample at the last sampling timepoint
Other positive: Not persistent positive but some ADA-positive samples with the last sample being negative
Neutralizing ADA positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline
ADA negative: No ADA-positive sample after initiation of treatment

Reviewer's comment: See Section 6 for more details.

APPEARS THIS WAY
ON ORIGINAL

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Immune-mediated adverse events (IMAEs)

IMAEs are known toxicities of checkpoint inhibitor class products including nivolumab and ipilimumab. Please refer to Section 8.2.3 for a detailed description of IMAEs as defined by the Applicant.

Table 47 summarizes the incidence of IMAEs observed in Study CA209227. IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose; these analyses were limited to patients 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. These events were identified by the investigator as IMAEs with no clear alternate etiology and with an immune mediated component.

Overall, 51% of patients in the nivolumab and ipilimumab arms experienced at least one IMAE and 21% of patients in these arms experienced a Grade 3-4 IMAE. In the nivolumab arm, 30% of patients overall experienced at least one IMAE with 9% of patients experiencing a Grade 3-5 IMAE (including one event of Grade 5 pneumonitis). The most common IMAE in both groups was rash (18% vs. 8%) followed by hypothyroidism/thyroiditis (14% vs. 8%).

Table 47: Incidence of IMAEs in Study CA209227

IMAE category, n (%)	Nivo + Ipi Arms B/D N=576		Nivolumab Arm A N=391		Chemo Arms C/F N=570	
	All grades	Gr 3-4	All grades	Gr 3-5	All grades	Gr 3-4
Any IMAE	51	21	30	9	2.3	0.5
Rash	18	3.6	8	0.8	1.1	0
Hypothyroidism/thyroiditis	14	0.7	8	0.3	0.2	0
Pneumonitis	9	4.0	6	2.0	0.5	0.2
Hyperthyroidism	9	0	3.8	0	0.4	0.2
Diarrhea/colitis	8	3.0	4.6	0.8	0	0
Hepatitis	8	6.4	4.1	3.6	0.2	0.2
Adrenal insufficiency	4.7	2.3	0.8	0.3	0	0
Hypophysitis	3.5	1.6	1.0	0	0	0
Diabetes mellitus	1.0	0.9	0.5	0.5	0	0
Nephritis/renal dysfunction	1.0	0.3	1.0	0.8	0.2	0.2
Hypersensitivity	0.7	0	0.8	0.3	0	0

Source: ADaM dataset adaeimm.xpt
See Section 8.2.3 for PTs included in each IMAE category

Table 48 summarizes the management and resolution details for patients experiencing IMAEs within 100 days of the last dose of nivolumab and/or ipilimumab.

Table 48: Management and resolution of IMAEs

IMAE category, %	Pts with IMAE leading to DC/delay	Pts with IMAE receiving IMM/high-dose corticosteroids[a]	Pts with resolution of IMAE	Pts with recurrence after reinitiation
Nivolumab + ipilimumab; Arms B/D; N=576				
Rash	0.7/3.8	100/25	78	5
Hypothyroidism/thyroiditis	0.2/2.3	14/6	33	4.3
Pneumonitis	5.2/3.6	100/94	72	13
Hyperthyroidism	0/1.9	18/8	86	0
Diarrhea/colitis	3.1/4.2	100/85	94	15
Hepatitis	3.1/4.7	100/83	87	8
Adrenal insufficiency	0.9/1.6	93/37	33	0
Hypophysitis	0.9/1.9	85/30	35	0
Diabetes mellitus	0.2/0.5	0/0	0	0
Nephritis/renal dysfunction	0.3/0.7	100/83	83	0
Hypersensitivity	0.2/0	100/50	100	0
Nivolumab; Arm A; N=391				
Rash	0/2.0	100/23	83	0
Hypothyroidism/thyroiditis	0/2.0	3.0/3.0	30	3.2
Pneumonitis	2.8/2.8	100/88	79	42
Hyperthyroidism	0/0.5	0/0	87	0
Diarrhea/colitis	1.8/3.1	100/61	94	23
Hepatitis	1.8/2.0	100/94	81	14
Adrenal insufficiency	0.3/0.3	67/0	67	100
Hypophysitis	0/0.5	100/0	50	0
Diabetes mellitus	0/0	0/0	0	0
Nephritis/renal dysfunction	0.5/0.3	100/100	75	0
Hypersensitivity	0.3/0	100/67	100	0

Source: ADaM dataset adaeimm.xpt
See Section 8.2.3 for PTs included in each IMAE category
a: Denominator is based on the number of patients who experienced the event
IMM: Immune-modulating medication

Reviewer's comment: The proportion of patients with resolution of the most frequently experienced IMAEs was largely similar between the nivolumab and ipilimumab arms and the nivolumab arm. Management of the IMAEs with IMM/high-dose corticosteroids was also similar across arms, likely due to the well-established treatment algorithms for IMAEs.

8.2.5.2 Other events of special interest (OESIs)

Table 49 summarizes the incidence of OESIs in Study CA209227, regardless of causality or immune-modulating medication treatment with extended follow-up (e.g. 100 days). The overall number of OESIs experienced in Study CA209227 was low, with a higher proportion of patients with OESIs in the nivolumab and ipilimumab arms versus the nivolumab arm or the chemotherapy arms (2.3% vs. 0.5% and 0.2%, respectively).

Table 49: Incidence of OESIs in Study CA209227

OESI category, n (%)	Nivo + Ipi Arms B/D N=576		Nivolumab Arm A N=391		Chemo Arms C/F N=570	
	All grades	Gr 3-4	All grades	Gr 3-4	All grades	Gr 3-4
Any OESI	13 (2.3)	8 (1.4)	2 (0.5)	2 (0.5)	1 (0.2)	0
Pancreatitis	6 (1.0)	4 (0.7)	0	0	0	0
Encephalitis	2 (0.3)	2 (0.3)	0	0	0	0
Myocarditis	2 (0.3)	2 (0.3)	0	0	0	0
Myositis	2 (0.3)	1 (0.2)	2 (0.5)	2 (0.5)	1 (0.2)	0
Uveitis	2 (0.3)	0	0	0	0	0
Myasthenic syndrome	1 (0.2)	1 (0.2)	0	0	0	0
Rhabdomyolysis	1 (0.2)	1 (0.2)	0	0	0	0

Source: ADaM dataset adae.xpt
See Section 8.2.3 for PTs included in each OESI category

8.2.5.3 Pneumonitis

Given the higher incidence of pneumonitis observed in patients enrolled on Study CA209227 compared to the incidence of pneumonitis observed in patients receiving nivolumab in combination with ipilimumab in other tumor types (RCC and mCRC), FDA performed a review of all respiratory events experienced by patients enrolled on the nivolumab and ipilimumab arms in Part 1 of Study CA209227. A total of 117 patients (20%) experienced a total of 140 respiratory events that included PTs interstitial lung disease, lower respiratory tract infection, lung disorder, lung infection, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia viral, pneumonitis, respiratory failure, and respiratory tract infection. Patient narratives for all events not coded as pneumonitis or interstitial lung disease were reviewed to confirm the accuracy of their corresponding preferred term with specific attention given to whether corticosteroids were administered as part of the treatment for the event. BMS was queried for additional information on 7 patients who experienced events of pneumonia (3 patients), respiratory failure (2 patients), pneumonia aspiration, and respiratory tract infection (1 patient each); each of the extended narratives was consistent with the assigned preferred term. Overall, a total of 54 patients (9.4%) in the nivolumab and ipilimumab arms experienced an event of pneumonitis, including events that occurred post-100 day follow-up. This is consistent with the incidence of pneumonitis observed in other studies of patients

with NSCLC who received nivolumab and ipilimumab (see Section 8.2.8 Specific Safety Studies/Clinical Trials) and higher than the incidence of pneumonitis observed in patients with other tumor types who received nivolumab and ipilimumab (see 8.2.11 Integrated Assessment of Safety).

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Patient reported outcome (PRO) questionnaires assessing a disease specific measure, the Lung Cancer Symptom Scale (LCSS), and a measure of general health-related quality of life (QoL), the EuroQoL Group's EQ-5D-3L, were administered at pre-specified timepoints during the study. The following PRO exploratory objectives were defined in the protocol for Study CA209227; these results were reported in an addendum to an Interim Study Report based on a database lock of March 15, 2018:

- To evaluate the proportion of treated patients exhibiting disease-related symptom deterioration by 12 weeks, as measured by LCSS average symptom burden index (ASBI)
- To evaluate the time to deterioration (TTD) in symptoms, as measured by the LCSS ASBI
- To assess health utility (quality of life) using the EQ-5D utility index (UI) and overall health status using the EQ-5D visual analogue scale (VAS)

The Applicant reports that the LCSS questionnaire compliance rate while on treatment for all randomized patients in Parts 1a and 1b was ≥ 90% at baseline and ≥ 80% at most subsequent assessments for which ≥ 10 patients were eligible to respond (e.g. through Week 96 in the nivolumab and ipilimumab arm [Arm B] and through Week 84 in the chemotherapy arm [Arm C]). Compliance at Follow-up Visits 1 and 2 after study treatment discontinuation ranged from 51% to 62%.

The Applicant reported that in PD-L1 positive patients enrolled in Part 1a of Study CA209227, the hazard ratio for the time to deterioration of symptoms as measured by the LCSS ABSI for nivolumab and ipilimumab-treated patients (Arm B) versus chemotherapy-treated patients (Arm C) was 0.81 (95% CI: 0.61, 1.07). The proportion of patients with deterioration by Week 12 was similar for the nivolumab and ipilimumab arm and the chemotherapy arm: 31% (95% CI 27, 36) in the nivolumab and ipilimumab arm and 26% (95% CI 31, 40) in the chemotherapy arm. In the nivolumab and ipilimumab arm, the changes from baseline in the EQ-5D UI were mostly improvements; these improvements met or exceeded the minimally important difference (MID) at Weeks 10, 14, and from Week 36 through the remainder of the study when N ≥ 10 (through Week 90). In the chemotherapy arm, clinically meaningful improvements were observed at Weeks 24, 60, and 78.

Reviewer's comment: Since there is no pre-specified statistical testing procedure to control for Type I error, the PRO results reported in the interim CSR for Part 1 of Study CA209227 are exploratory in nature. The PRO analyses appear to show no clinically meaningful difference between the nivolumab and ipilimumab arm and the chemotherapy arm in patients with PD-L1 positive metastatic NSCLC.

8.2.7 Safety Analyses by Demographic Subgroups

Age

In the safety population of Study CA209227, including patients enrolled on Arms A, B, C, D, and F, 47% of patients were age 65 or older. Table 50 summarizes the incidence of AEs by age group (< 65 years vs. ≥ 65 years) with extended follow-up (e.g. 100 days).

Table 50: Overview of adverse events by age group

	Nivo + Ipi Arms B/D N=576		Nivolumab Arm A N=391		Chemo Arms C/F N=570	
	< 65	≥ 65	< 65	≥ 65	< 65	≥ 65
Total N, %	299 (52%)	277 (48%)	210 (54%)	181 (46%)	305 (52%)	278 (48%)
N with any AE	299 (100%)	272 (98%)	208 (99%)	178 (98%)	295 (97%)	263 (95%)
Grade 3-5 AEs	74%	78%	67%	72%	64%	67%
Serious AEs	68%	73%	58%	65%	51%	52%
Died d/t drug-related AE	3 (1.0%)	5 (1.8%)	1 (0.5%)	4 (2.2%)	5 (1.6%)	2 (0.7%)
Discontinued due to an AE	35%	40%	29%	25%	23%	24%

Source: ADaM datasets adsl.xpt, adae.xpt

Overall in the nivolumab and ipilimumab arms, there was a slightly higher proportion of Grade 3-5 AEs, serious AEs, and AEs leading to treatment discontinuation in patients ≥ 65 years when compared with patients < 65 years. However, the difference is small and of unclear clinical significance.

Sex

In the safety population of Study CA209227, including patients enrolled in Arms A, B, C, D, and F, 67% of patients were male and 33% of patients were female. Table 51 summarizes the incidence of AEs by sex with extended follow-up (e.g. 100 days).

Table 51: Overview of adverse events by sex

	Nivo + Ipi Arms B/D N=576		Nivolumab Arm A N=391		Chemo Arms C/F N=570	
	Male	Female	Male	Female	Male	Female
Total N, %	389 (68%)	187 (32%)	268 (69%)	123 (31%)	377 (66%)	193 (34%)
N with any AE	386 (99%)	185 (99%)	264 (99%)	122 (99%)	369 (98%)	189 (98%)
Grade 3-5 AEs	76%	76%	72%	64%	68%	64%
Serious AEs	71%	67%	63%	59%	53%	52%
Died d/t drug-related AE	7 (1.8%)	1 (0.5%)	4 (1.5%)	0	4 (1.1%)	3 (1.6%)
Discontinued due to an AE	39%	34%	25%	30%	23%	26%

Source: ADaM datasets adsl.xpt, adae.xpt

No significant differences were noted in the overall incidence of AEs between males and female patients enrolled in Study CA209227 across treatment arms.

8.2.8 Specific Safety Studies/Clinical Trials

Safety data from patients enrolled in three additional studies, CA209568 (n=288), CA209817 (n=391), and CA209012 (n=39), was submitted to support the safety of nivolumab in combination with ipilimumab in patients with advanced NSCLC (Table 3 and Table 4).

Study CA209568 Part 1

Study CA209568 is an ongoing, multicenter, open-label, single arm study being conducted in two parts in patients with previously untreated stage IV NSCLC, irrespective of PD-L1 status. Patients in Part 1 were enrolled to receive nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W until progression, unacceptable toxicity, or other reasons specified in the protocol, for a maximum of 24 months. Treatment with nivolumab and ipilimumab could be reinitiated according to the original schedule for subsequent disease progression and administered for up to one additional year. The co-primary objectives were to determine the ORR according to RECIST v1.1 as assessed by blinded independent central review (BICR) in all patients treated with nivolumab and ipilimumab with PD-L1 ≥ 1% and to determine the ORR according to RECIST v1.1 as assessed by BICR in all patients treated with nivolumab and ipilimumab with PD-L1 < 1%.

Results from Part 1 are based on an August 25, 2017 database lock: a total of 427 patients were enrolled and 288 were treated with nivolumab and ipilimumab. The median age was 65 years (range: 39-91) with 53% of patients ≥ 65 years, 49% were male, 90% were white, 70% had adenocarcinoma and 26% had squamous cell carcinoma. Sixty-two percent had an ECOG performance status of 1 and 90% were former or current smokers. Baseline demographics and disease characteristics were similar across the PD-L1 subgroups; 48% of patients had PD-L1 expression ≥ 1% and 40% of patients had PD-L1 expression < 1%.

The median exposure to study drugs was reported to be 3.96 months (95% CI 2.89, 5.52; range: 0.03-17.51+). Patients received a median of 8.5 nivolumab doses (range: 1-38) and a median of 3.0 ipilimumab doses (range 1-13). At the time of the database lock, 69% of patients were off treatment.

Summary of safety
All-causality AEs were reported for all patients enrolled in Part 1. Fifty-nine percent of patients experienced an all-causality AE Grade ≥ 3, 43% experienced an SAE, 23% discontinued a study drug due to an AE, and 3 patients (1.0%) died due to study drug toxicity (fatal events reported by the investigator as immune response, dyspnea/hypoxia, and pneumonitis). The most frequently reported SAEs, excluding malignant neoplasm progression, were pneumonia (7%), dyspnea (6%), pneumonitis (3.5%), diarrhea (3.5%), and pulmonary embolism (3.1%). Treatment-related AEs reported in ≥ 15% in any group were fatigue (25%), diarrhea (23%), and pruritus (16%).

All-causality IMAEs reported within 100 days of last dose and treated with immune modulating medication were as follows: rash (14%), diarrhea/colitis (9%), pneumonitis (4.5%), hepatitis (3.8%), hypersensitivity/infusion reactions (1.0%), and nephritis/renal dysfunction (0.7%).

Reviewer's comment: The incidence and severity of TEAEs and IMAEs experienced by patients enrolled in Part 1 of Study CA209568 are consistent with those reported in patients with advanced NSCLC receiving nivolumab and ipilimumab.

Study CA209817 Cohort A
Study CA209817 is an ongoing, multicenter, open-label, single arm study of flat dose nivolumab in combination with ipilimumab in patiens with previously untreated (Cohorts A, A1, and C) or second-line (Cohort B) Stage IV or recurrent NSCLC. Patients in Cohort A were enrolled to receive nivolumab 240 mg Q2W and ipilimumab 1 mg/kg Q6W until disease progression, unacceptable toxicity, withdrawal of consent, 24 months from first dose, or end of study. The primary objective is to characterize the safety of nivolumab administered as a flat dose in combination with weight-based ipilimumab dosing in Cohort A.

Results from Cohort A are based on a database lock of March 1, 2018; approximately 400 patients were planned to be treated in Cohort A and a total of 391 patients received treatment. The median age was 65 years (range: 26-89) with 53% of patients ≥ 65 years, 60% of patients were male, 97% were white, 92% were former or current smokers, and 68% had adenocarcinoma. Forty-five percent of patients had PD-L1 expression ≥ 1% and 46% of patients had PD-L1 expression < 1%.

The median exposure to nivolumab and ipilimumab combination therapy for all treated patients in Cohort A was reported to be 4.11 months (range: 0.03-12.91). The median number of nivolumab doses received was 9.0 (range 1-28) and the median number of ipilimumab doses

received was 3.0 (range: 1-10). At the time of the database lock, 66% of patients were off treatment.

Summary of safety
All-causality AEs were reported in 97% of patients enrolled in Cohort A. Fifty-one percent of patients experienced an all-causality AE of Grade ≥ 3 in severity; 53% of patients experienced an SAE, 23% of patients discontinued a study drug due to an AE, and 2 patients (0.5%) died due to study drug toxicity (fatal events reported by the investigator as heart failure due to rhabdomyolysis and Guillain-Barre syndrome). The most frequently reported SAEs, excluding malignant neoplasm progression, were pneumonitis (4.1%), pneumonia (4.1%), and dyspnea (3.1%). The only treatment-related AE reported at an incidence of ≥ 15% was diarrhea (18%).

All-causality IMAEs reported within 100 days of last dose treated with immune modulating medication were as follows: rash (8%), pneumonitis (7%), diarrhea/colitis (7%), hepatitis (3.6%), hypersensitivity/infusion reactions (2.0%), and nephritis/renal dysfunction (0.5%).

Reviewer's comment: The incidence and severity of TEAEs and IMAEs experienced by patients enrolled in Cohort A of Study CA209817 are consistent with those reported in patients with advanced NSCLC receiving nivolumab and ipilimumab.

Study CA209012 Cohort Q
Study CA209012 is a completed multicenter, multiple cohort study of nivolumab as monotherapy, in combination with ipilimumab, or in combination with chemotherapy or targeted therapy in patients with previously untreated Stage IIIB/IV NSCLC or recurrent disease. Eight cohorts were included in which patients with NSCLC were treated with different dosages and schedules of nivolumab in combination with ipilimumab; in Cohort Q, patients with chemotherapy-naïve NSCLC received nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W. The primary objective was to assess the safety and tolerability of nivolumab in combination with ipilimumab in patients with chemotherapy-naïve Stage IIIB/IV NSCLC.

Results from Cohort Q are based on a database lock of September 19, 2016; a total of 39 patients were treated in Cohort Q. The median age was 62 years (range: 47-87) with 46% of patients ≥ 65 years. A total of 62% of patients were male, 77% had adenocarcinoma, 59% had an ECOG performance status of 1, 74% were current or former smokers, 59% had PD-L1 expression status ≥ 1% and 23% had PD-L1 expression status < 1%.

The median duration of therapy with nivolumab was reported as being 18 weeks (range: 2-103) and the median duration of therapy with ipilumumab was reported as being 15 weeks (range: 6-103). Patients in Cohort Q received a median of 8 doses of nivolumab (range: 1-51) and 2 doses of ipilimumab (range: 1-17). Of note, 23% of patients in Cohort Q received prior systemic therapy, with the majority of therapy administered in the adjuvant setting. Four patients (10%) received prior systemic therapy in the metastatic setting, including one patient each who received erlotinib; afatinib and erlotinib; erlotinib, crizotinib, and an investigational EGFR

inhibitor; and an investigational c-Met inhibitor and erlotinib.

Summary of safety
All-causality AEs were reported in 95% of patients enrolled in Cohort Q. Fifty-one percent of patients experienced an all-causality AE of Grade ≥ 3 in severity, 64% of patients experienced an SAE, 21% of patients discontinued a study therapy due to an AE, and no patients died due to an AE. The most frequently reported SAEs, excluding malignant neoplasm progression, were dyspnea (10%), dehydration (10%), colitis (8%), dysphagia, pyrexia, and adrenal insufficienct (5% each). Treatment-related AEs reported at an incidence of ≥ 10% were fatigue (26%), diarrhea (23%), and pruritus (13%).

In Study CA209012, select AEs were grouped into the following categories, in order of frequency: skin events (including PTs pruritus, rash, rash generalized, rash maculo-papular, erythema, and rash pruritic), 39%; endocrine events (including PTs adrenal insufficiency, hyperthyroidism, hypothyroidism, diabetes mellitus, lymphocytic hypophysitis), 28%; gastrointestinal events (including PTs diarrhea, colitis, and frequent bowel movements), 26%; hepatic events (including PTs ALT increased, AST increased, transaminases increased), 5%; pulmonary events (including PT pneumonitis), 5.1%; renal events (including PTs acute kidney injury and blood creatinine increased), 5.1%; and hypersensitivity/infusion reactions, 0%.

Reviewer's comment: The incidence and severity of TEAEs and select AEs experienced by patients enrolled in Cohort Q of Study CA209012 are consistent with those reported in patients with advanced NSCLC receiving nivolumab and ipilimumab.

Table 52 provides supportive safety results from Part 1 of Study CA209568, Cohort A of Study CA209817, Cohort Q of Study CA209012 side-by-side with results from Part 1 of Study CA209227. The median duration of therapy and minimum follow-up in Study CA209227 were 4.2 and 28.3 months, respectively; 4.0 and 15.5 months, respectively, in Study CA209568; and 4.0 and 21.0 months, respectively, in Study CA209817. The minimum follow-up in Study CA209012 was 16 months.

Table 52: Summary of supportive safety results from Studies CA209568, CA209817, and CA209012 compared to Study CA209227

	CA209227 Part 1 N=576		CA209568 Part 1 N=288		CA209817 N=817		CA209012 N=39	
Death d/t study drug toxicity	10 (1.7%)		4 (1.4%)		4 (1.0%)		0	
%	**Any grade**	**Gr 3-4**	**Any grade**	**Gr 3-4**	**Any grade**	**Gr 3-4**	**Any grade**	**Gr 3-4**
All-causality SAEs	62	45	58	47	60	44	61	45
AEs leading to DC	33	25	31	20	33	22	21	5
All-causality IMAEs within 100 days of last dose treated with IMMs								
Diarrhea/colitis	8	3.0	13	6	10	4.1	13	2.6
Hepatitis	8	6	3.8	2.4	5.1	4.1	2.6	2.6
Pneumonitis	9	4.0	6	2.4	9	4.3	8	2.6
Nephritis/renal dysfunction	1.0	0.3	0.7	0.3	0.5	0.5	0	0
Rash	18	3.6	14	2.4	12	3.1	21	5
Hypersensitivity/ Infusion reactions	0.7	0	2.4	0.3	2.8	1.0	2.6	0

Source: Adapted from Table 7-1, SCS

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No carcinogenicity studies were conducted.

Human Reproduction and Pregnancy

No reproductive toxicity studies were conducted.

Pediatrics and Assessment of Effects on Growth

Not applicable for this supplement. BMS was granted a waiver from the requirement to conduct pediatric studies under PREA based on the low incidence of NSCLC in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Three patients (0.5%) in the nivolumab and ipilimumab arms (2 patients in Arm B and 1 patient

in Arm D) were reported as having an accidental overdose of one of the study drugs. Safety narratives for these events were reviewed; all three events were considered resolved the day of or the day following the event and no actions were taken with the study drug in response to the event. For one event, the error was noted to be due to an incorrectly recorded patient weight.

Based on nivolumab and ipilimumab's mode of administration and pharmacological properties, there are no concerns regarding the potential for abuse, withdrawal, or rebound.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The combination of nivolumab and ipilimumab was first granted marketing authorization in the US on September 30, 2015, for the treatment of patients with unresectable or metastatic melanoma and has since been approved in multiple other countries. The current approved indications for nivolumab and ipilimumab are listed in Section 2.3.

Based on information provided by BMS, as of March 31, 2019, approximately (b) (4) patients have been exposed to commercial nivolumab in the post-marketing setting, either alone or in combination with other agents, and as of December 31, 2018, approximately (b) (4) patients worldwide have been exposed to ipilimumab in the post-marketing setting. Neither nivolumab nor ipilimumab have been withdrawn from investigational use for reasons related to safety or efficacy in any country.

Expectations on Safety in the Postmarket Setting

Nivolumab and ipilimumab in combination have been marketed in the US since 2015, and the safety profile of both agents separately and in combination is well-established. FDA will continue to monitor the safety of nivolumab and ipilimumab in the postmarketing setting.

8.2.11 Integrated Assessment of Safety

In this sBLA, BMS submitted safety data on IMAEs and OESIs from a pooled dataset of 666 patients who received nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W as part of Studies CA209214 (renal cell carcinoma [RCC], n=547) and CA209142 (colorectal cancer [CRC], n=119) to compare the safety profile of nivolumab and ipilimumab across cancer types. Pooled safety data was also provided from patients enrolled in three completed melanoma studies (Studies CA209067, CA209069, and CA209004, n=448); however, these patients received an alternate dosing schedule of nivolumab and ipilimumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W).

Reviewer's comment: The data provided by BMS for the pooled melanoma studies was reviewed separately from data provided from Studies CA209214 and CA209142 given the alternate dosing schedule resulting in both more frequent and higher ipilimumab dosing in the melanoma

studies. According to BMS, the incidence of deaths due to study toxicity was similar between Study CA209227 and the pooled melanoma studies (1.7% vs. 1.1%); however, there was a higher incidence of SAEs (62% vs. 68%), AEs leading to study drug discontinuation (33% vs. 44%), and Grade 3-4 TEAEs (63% vs. 71%) in the pooled melanoma studies than in Study CA209227. Data for IMAEs was not generated for the pooled melanoma studies; however, when comparing select drug-related AEs by category, patients in the pooled melanoma studies experienced a higher incidence of endocrine events (32% vs. 24%), gastrointestinal events (47% vs. 18%), hepatic events (30% vs. 16%), and skin events (65% vs. 34%) than patients enrolled in Study CA209227. The incidence of pulmonary events was similar in both groups of patients (8%). The differences in toxicity, both in frequency and severity of AEs and types of IMAEs, between the two regimens (nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W vs. nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W) has been well-described in the literature and is consistent with the known safety profiles of nivolumab and ipilimumab.[9,10]

Study CA209214 is a multicenter, open label, randomized study of nivolumab in combination with ipilimumab vs. sunitinib in patients with previously untreated advanced or metastatic RCC; the major efficacy outcome measures were OS, PFS, and ORR in intermediate/poor risk patients. The combination of nivolumab and ipilimumab received FDA approval for this indication on April 16, 2018 based on a statistically significant improvement in OS (HR 0.63 [95% CI 0.44, 0.89]). Safety data was derived from 547 patients who received nivolumab and ipilimumab irrespective of International Metastatic RCC Database Consortium (IMDC) prognostic score. The database lock for Study CA209214 occurred on August 7, 2017, with a minimum follow-up time of 17.5 months.

Study CA209142 is a multicenter, non-randomized, multiple parallel-cohort, open-label trial of nivolumab as monotherapy or nivolumab in combination with ipilimumab in patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic CRC who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy; the major efficacy outcome measures were ORR and DOR as assessed by an independent radiologic review committee (IRRC) using RECIST v1.1. Nivolumab in combination with ipilimumab received accelerated approval for this indication on July 10, 2018 based on an ORR of 46% (95% CI 35, 58) with 89% of patients with response durations ≥ 6 months in patients with dMMR/MSI-H metastatic CRC. Safety data was derived from the 119 patients who received nivolumab in combination with ipilimumab irrespective of prior treatment. The database lock for Study CA209142 occurred on August 18, 2017, with a minimum follow-up time of 9 months.

Table 53 summarizes the incidence of AEs across Studies CA209227, CA209214, and CA209142 occurring within 30 days of last dose of study therapy. Overall, the incidence of AEs in Study CA209227 was similar across studies, particularly to Study CA209214. Patients enrolled in Study CA209227 and Study CA209214 experienced a higher proportion of Grade 3-4 AEs, serious AEs, and discontinuations of study therapy due to AE than did those enrolled in Study CA209142.

Table 53: Overview of AEs across tumor types

	Study CA209227 N=576	Study CA209214 N=547	Study CA209142 N=119
% with any AE	99	99	99
Grade 3-4 AEs	66	65	55
Serious AEs	62	59	48
Died d/t drug-related AE	0.9	1.3	0
Discontinued due to an AE	33	31	14

Table 54 summarizes the incidence of IMAEs by grade reported in Studies CA209227, CA209214, and CA209142. Overall, the incidence of IMAEs was similar across tumor types (NSCLC, RCC, and CRC) in which similar dosing schedules of nivolumab and ipilimumab were administered (nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W in Study CA209227 vs. nivolumab 3 mg/kg and ipilimumab 1 mg/kg Q3W x 4 doses followed by nivolumab 3 mg/kg Q2W in Studies CA209214 and CA209142). However, the incidence of pneumonitis overall and of Grades 3-4 was higher in Study CA209227 than in Studies CA209214 and CA209142 (9%/4% vs. 4.4%/1.6% and 1.7%/0, respectively).

Table 54: Incidence of IMAEs requiring immune-modulating medication in patients receiving nivolumab 3 mg/kg and ipilimumab 1 mg/kg across tumor types

IMAE category, %	Study CA209227 N=576		Study CA209214 N=547		Study CA209142 N=119	
	Any gr	Gr 3-4	Any gr	Gr 3-4	Any gr	Gr 3-4
Rash	18	3.6	17	3.3	14	4.2
Hypothyroidism/thyroiditis	14	0.7	22	0.7	15	2.5
Pneumonitis	9	4.0	4.4	1.6	1.7	0
Hyperthyroidism	9	0	12	0.7	12	0
Diarrhea/colitis	8	3.0	10	4.6	7	3.4
Hepatitis	8	6	7	6	8	8
Adrenal insufficiency	4.7	2.3	7	2.7	6	1.7
Hypophysitis	3.5	1.6	3.3	2.4	2.5	1.7
Nephritis/renal dysfunction	1.0	0.3	4.6	1.6	1.7	1.7
Diabetes mellitus	1.0	0.9	2.7	1.1	0	0
Hypersensitivity	0.7	0	1.3	0	2.5	0

Source: ADaM dataset adaeimm.xpt, SCS Part 1 Appendices Tables S.6.202 and S.6.204

Reviewer's comment: The higher incidence of pneumonitis in patients with NSCLC enrolled in Study CA209227 is likely due to several factors, including primary tumor location leading to an immune response in the lungs and prior history of thoracic radiation in some patients. In addition, the older median age of patients with NSCLC and the frequency of cardiovascular and respiratory comorbidities may increase the vulnerability of patients with NSCLC to the

development of pneumonitis when compared to patients with other tumor types.[11]

Table 55 summarizes the incidence of OESIs by grade reported in Studies CA209227, CA209214, and CA209142. Overall, the incidence of OESIs was low and similar across studies.

Table 55: Incidence of OESIs in patients receiving nivolumab 3 mg/kg and ipilimumab 1 mg/kg across tumor types

OESI category, %	Study CA209227 N=576		Study CA209214 N=547		Study CA209142 N=119	
	Any gr	Gr 3-4	Any gr	Gr 3-4	Any gr	Gr 3-4
Myasthenic syndrome	0.2	0.2	0.2	0.2	0	0
Guillain-Barre syndrome	0	0	0	0	0	0
Pancreatitis	1.0	0.7	0	0	0	0
Uveitis	0.3	0	0.4	0	0.8	0.8
Encephalitis	0.3	0.3	0.2	0.2	0.8	0.8
Myocarditis	0.3	0.3	0.2	0.2	0	0
Myositis	0.3	0.2	0.5	0.2	0.8	0.8
Rhabdomyolysis	0.2	0.2	0.2	0.2	0	0

Source: ADaM dataset adaeimm.xpt, SCS Table 7.4-2

8.3 Statistical Issues

BMS submitted data and results from the co-primary analysis of overall survival for the comparison of nivolumab in combination with ipilimumab versus platinum-doublet chemotherapy in patients with metastatic NSCLC whose tumors express PD-L1 ≥ 1% in Study CA209227. Based on the pre-specificed decision rule, the results of this analysis crossed the efficacy boundary for OS. The exploratory analyses of PFS and ORR for this comparison also demonstrated benefit favoring the nivolumab and ipilimumab arm.

Due to concerns of potential study conduct issues, which resulted in multiple protocol amendments (see Table 6), FDA only considers the OS results for the comparison of nivolumab in combination with ipilimumab versus platinum-doublet chemotherapy in patients whose tumors express PD-L1 ≥ 1% to be interpretable. The comparison of OS in patients with PD-L1 < 1% (Part 1b) randomized to the nivolumab and ipilimumab arm versus the chemotherapy arm was not part of the statistical testing hierarchy. Therefore, these results and all other comparisons related to the PD-L1 hierarchy are considered exploratory.

(b) (4)

. In addition, the OS

(b) (4)

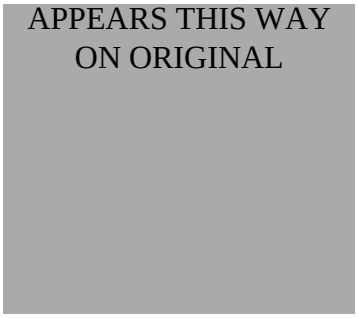
8.4 Conclusions and Recommendations

This application relies on the results of a multicenter, multi-part (Parts 1a and 1b), randomized trial conducted in patients with previously untreated metastatic NSCLC. The efficacy results from the final analysis of the co-primary endpoint of OS among patients with tumors expressing PD-L1 ≥ 1% for nivolumab in combination with ipilimumab (Arm B) vs. platinum-doublet chemotherapy (Arm C) and the safety data from the 576 patients across Parts 1a and 1b who received nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W are intended to support a regular approval for the proposed indication.

Based on the clinical review, the final analysis of OS in patients with tumors expressing PD-L1 ≥ 1% demonstrated a statistically significant and clinically meaningful improvement in OS as compared to available therapy (platinum-based chemotherapy). Nivolumab and ipilimumab was superior to chemotherapy with regard to OS, with an OS HR of 0.79 (95% CI 0.67, 0.94) with a p-value of 0.0066. The median OS for the nivolumab and ipilimumab arm was 17.1 months (95% CI 15, 20.1) compared to 14.9 months (95% CI 12.7, 16.7) in the chemotherapy arm. Additional endpoints comparing the nivolumab and ipilimumab arm to the chemotherapy arm were not part of the statistical testing hierarchy, however, the PFS HR was 0.82 (95% CI 0.69, 0.97), with a median PFS of 5.1 months (95% CI 4.1, 6.3) in the nivolumab and ipilimumab and 5.6 months (95% CI 4.6, 5.8) in the chemotherapy arm. The ORR was 36% (95% CI 31, 41) in the nivolumab and ipilimumab arm and 30% (95% CI 26, 35) in the chemotherapy arm with 64% of patients in the nivolumab and ipilimumab arm having a response duration of ≥ 12 months compared to 28% in the chemotherapy arm. The median duration of response was 23.2 months in the nivolumab and ipilimumab arm compared to 6.3 months in the chemotherapy arm.

The safety profile of nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W is acceptable when considering the clinical benefit demonstrated for the proposed indication. The AEs observed in Study CA209227 are consistent with the known safety profiles of nivolumab and ipilimumab. Based on the safety data from 576 patients enrolled in Parts 1a and 1b of the trial, there was a higher incidence of SAEs (52% vs. 36%), AEs leading to study drug discontinuation (24% vs. 15%), and Grade 3-5 AEs in the nivolumab and ipilimumab arms versus the chemotherapy arms (62% vs. 54%). The most common adverse reactions (≥ 20%) reported in the nivolumab and ipilimumab arms were fatigue, rash, decreased appetite, musculoskeletal pain, diarrhea/colitis, dyspnea, cough, hepatitis, nausea, and pruritus. The incidence of IMAEs in patients enrolled in Study CA209227 was similar to that observed in patients with NSCLC enrolled in other trials and with patients with different tumor types (RCC, CRC) who received the combination of nivolumab 3 mg/kg and ipilimumab 1 mg/kg, with the exception of pneumonitis events, for which the incidence was higher in patients with NSCLC than in patients with other tumor types (9% vs. 4.4% of patients with RCC and 1.7% of patients with CRC).

The review team recommends approval of nivolumab in combination with ipilimumab for the first-line treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥1%), based on the determination that nivolumab in combination with ipilimumab results in a favorable risk/benefit profile for the proposed indication.



X Mallorie Fiero, PhD — Primary Statistical Reviewer

X Pallavi Mishra-Kalyani, PhD — Statistical Team Leader

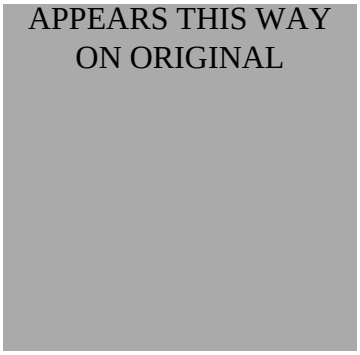
X Nicole Drezner, MD — Primary Clinical Reviewer

X Erin Larkins, MD — Clinical Team Leader

APPEARS THIS WAY ON ORIGINAL

9 Advisory Committee Meeting and Other External Consultations

The Division did not refer this efficacy supplement to an advisory committee because the application did not raise significant public health questions regarding the roles of nivolumab or ipilimumab for the proposed indication. Nivolumab and ipilimumab are marketed biologics approved in combination for the treatment of several solid tumor malignancies and their safety profiles are well established in patients with advanced malignancies. The demonstrated risk-benefit profile for nivolumab and ipilimumab is favorable in patients with previously untreated metastatic NSCLC with tumor PD-L1 expression ≥ 1%.



10 Pediatrics

NSCLC is a rare disease in the pediatric population. According to the World Health Organization, GLOBOCAN 2012, the estimated lung cancer incidence in the pediatric population ages 0-15 is 0.0 in the United States and worldwide.

BMS was granted a waiver from the requirements of the Pediatric Research Equity Act (PREA) to conduct studies with nivolumab and ipilimumab for the treatment of NSCLC in pediatric patients of any age group because it would be highly impracticable or impossible given the small number of pediatric patients with this disease.

11 Labeling Recommendations

11.2 Prescription Drug Labeling

Table 56 Summary of significant labeling changes

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling**
1. Indication and Usage	Indication statement for (b) (4) (b) (4)	• Revised according to FDA review to state that combination is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 (≥ 1%) • Added statement "as determined by an FDA-approved test," given selection of patients with PD-L1 ≥ 1% • Removed (b) (4)
2. Dosage and Administration	Recommended dosage for NSCLC regimen added	Added Section 2.1 with statement about selection of patients with NSCLC whose tumors express PD-L1 ≥ 1% and information on companion diagnostics
5. Warnings and Precautions	Added section on immune-mediated pneumonitis in patients with NSCLC receiving nivolumab 3 mg/kg Q2W with ipilimumab 1 mg/kg Q6W	Accepted BMS' changes

6. Adverse Reactions	Added subsection on adverse reactions in metastatic NSCLC from safety population enrolled in Study CA209227 including population demographics, drug-related serious adverse reactions, drug-related discontinuations for adverse reactions, drug-related interruptions for advserse reactions, drug-related common adverse reactions (with table), and laboratory shift data (with table)	• Revised all adverse reaction statements to include all-causality adverse reactions • Added statement on fatal adverse reactions (therapy related) • Revised common adverse reaction table to include all-causality adverse reactions • Made minor edits to laboratory shift table to round numbers according to FDA convention
8.5 Geriatric Use	Added statement that no overall difference in safety was observed in older patients versus younger patients enrolled in Study CA209227	Added statement about efficacy observed in subgroup analysis of older patients versus younger patients (primary efficacy population)
14. Clinical Studies	Added subsection on efficacy results from Part 1 of Study CA209227, (b) (4) (b) (4)	• Revised description of primary efficacy population to (b) (4) include information from Part 1a of Study CA209227 (b) (4) (b) (4) • •

		(b) (4)

APPEARS THIS WAY
ON ORIGINAL

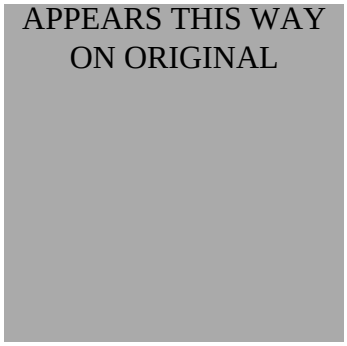
12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team does not recommend a risk evaluation and mitigation strategy (REMS) to ensure the safe and effective use of nivolumab and ipilimumab for the indicated population given the well-established safety profile of nivolumab and ipilimumab and the experience of the medical oncology community in managing immune-mediated adverse reactions. Recommendations for the safe and effective use of nivolumab and ipilimumab, including monitoring for immune-mediated adverse events, are provided in the US prescribing information as well is in the patient medication guide.

APPEARS THIS WAY
ON ORIGINAL

13 Postmarketing Requirements and Commitment

None



14 Division Director (DHOT)

X

15 Division Director (OCP)

X

16 Division Director (OB) Comments

X

17 Division Director (Clinical) Comments

X

18 Office Director (or designated signatory authority) Comments

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 _____

APPEARS THIS WAY ON ORIGINAL

19 Appendices

19.2.2 References

1. National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER): https://seer.cancer.gov/statfacts/html/lungb.html.
2. Marino P, Pampallona S, Preatoni A, et al. Chemotherapy versus supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. *Chest* 1994; 106(3): 861- 865.
3. Kelly K, Crowley J, Bunn PA, et al. Randomized Phase III Trial of Paclitaxel Plus Carboplatin Versus Vinorelbine Plus Cisplatin in the Treatment of Patients with Advanced Non–Small-Cell Lung Cancer: A Southwest Oncology Group Trial. *J Clin Oncol* 2001;19(13):3210–3218.
4. USPI Pembrolizumab, revised August 20, 2018, October 30, 2018, and April 11, 2019: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125514s042lbl.pdf.
5. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small cell lung cancer. *J Clin Oncol* 2008, 26: 3543-3551.
6. USPI Atezolizumab, revised December 3, 2019: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761034s009lbl.pdf.
7. Final Clinical Study Report for Study CA184104. A randomized, multicenter, double-blind, Phase 1 trial comparing the efficacy of ipilimumab in addition to paclitaxel and carboplatin in subjects with stage IV/recurrent non-small cell lung cancer (NSCLC). Bristol-Myers Squibb Company; 2016.
8. Zatloukal P, Heo DS, Park K, et al. Randomized phase II clinical trial comparing tremelimumab (CP-675,206) with best supportive care (BSC) following first-line platinum-based therapy in patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 27: 424s, 2009 (suppl; abstr 8071).
9. Xu H, Tan P, Ai J, et al. Antitumor Activity and Treatment-Related Toxicity Associated With Nivolumab Plus Ipilimumab in Advanced Malignancies: A Systematic Review and Meta-Analysis. *Front Pharmacol* 2019; 10: 1300.
10. Xu C, Chen YP, Du XJ, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. *BMJ* 2018; 363: k4226.
11. Cadranel J, Canellas A, Matton L, et al. Pulmonary complications of immune checkpoint inhibitors in patients with non-small cell lung cancer. *European Respiratory Review* 2019; 28(153): 190058.

19.2.3 Financial Disclosure

Table 57: Financial disclosure summary for Study CA209227

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2959		
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): 4		
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: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0 Sponsor of covered study: 0		
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) 17		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3 Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages]

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

[Add Text and Figures/Tables Here]

19.5 Additional Clinical Outcome Assessment Analyses

[Add Text and Figures/Tables Here]

APPEARS THIS WAY
ON ORIGINAL

Signatures Page

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Safaa Burns	Office of Clinical Pharmacology/ Division of Clinical Pharmacology V	Sections: 6	Select one: x Authored ___ Approved
	Signature: Safaa Burns -S Digitally signed by Safaa Burns -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Safaa Burns -S, 0.9.2342.19200300.100.1.1=1300068123 Date: 2020.05.15 09:27:17 -04'00'			
Clinical Pharmacology Team Leader	Jeanne Fourie-Zirkelbach	Office of Clinical Pharmacology/ Division of Clinical Pharmacology V	Sections: 6	Select one: ___ Authored x Approved
	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300434575, cn=Jeanne Fourie Zirkelbach -S Date: 2020.05.15 09:09:03 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Pharmacometrics Reviewer	Jiang Liu	Office of Clinical Pharmacology/ Division of Clinical Pharmacology V	Sections: 6	Select one: ___ 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: 2020.05.15 08:33:25 -04'00'			
Pharmacometrics Team Leader	Yuan Xu	Office of Clinical Pharmacology/ Division of Clinical Pharmacology V	Sections:6	Select one: x Authored ___ Approved
	Signature: Yuan Xu -S Digitally signed by Yuan Xu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuan Xu -S, 0.9.2342.19200300.100.1.1=2001686060 Date: 2020.05.15 08:27:39 -04'00'			
Clinical Reviewer	Nicole Drezner	Office of Oncologic Disease/Division of Oncologic Disease 2	Sections: All except Section 6	Select one: x Authored ___ Approved
	Signature: Nicole L. Drezner -S Digitally signed by Nicole L. Drezner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002001723, cn=Nicole L. Drezner -S Date: 2020.05.15 10:08:13 -04'00'			

Application Number sBLA 125554/80 (combined review signature page – sBLA 125377/109)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Erin Larkin	Office of Oncologic Disease/ Division of Oncologic Disease 2	Sections: All	**Select one:** X Authored X Approved
	Signature: Erin Larkins, MD Erin A. Larkins -S5 Digitally signed by Erin A. Larkins -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011520339, cn=Erin A. Larkins -S5 Date: 2020.05.15 08:53:25 -04'00'			
Statistical Reviewer	Mallorie Fiero	Office of Biostatistics/Division of Biometrics V	Sections: 8	**Select one:** X Authored ___ Approved
	Signature: Mallorie H. Fiero -S Digitally signed by Mallorie H. Fiero -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002084959, cn=Mallorie H. Fiero -S Date: 2020.05.15 08:00:58 -04'00'			
Statistical Team Leader	Pallavi Mishra-Kalyani	Office of Biostatistics/Division of Biometrics	Sections: 8	**Select one:** X Authored X Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001675542, cn=Pallavi S. Mishra-kalyani -S Date: 2020.05.15 07:56:07 -04'00'			
Deputy Division Director (OB, acting)	Yuan-li Shen	Office of Biostatistics/Division of Biometrics	Sections: 8	**Select one:** ___ Authored X Approved
	Signature: Yuan-li Shen -S Digitally signed by Yuan li Shen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuan li Shen -S, 0.9.2342.19200300.100.1.1=1300142755 Date: 2020.05.15 08:59:08 -04'00'			
Associate Director for Labeling (ADL)	Anne Marie Trentacosti		Sections: 11	**Select one:** x Reviewed x 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: 2020.05.15 07:53:58 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Erin Larkins	Office of Oncologic Disease/ Division of Oncologic Disease 2	Sections: All	**Select one:** x Authored x Approved
	Signature: Erin Larkins, MD Erin A. Larkins -S5 Digitally signed by Erin A. Larkins -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011520339, cn=Erin A. Larkins -S5 Date: 2020.05.15 08:53:54 -04'00'			
Deputy Division Director (Clinical)/ Signatory	Harpreet Singh	Office of Oncologic Disease/ Division of Oncologic Disease 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: 2020.05.15 09:57:18 -04'00'			

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/

GINA M DAVIS
05/15/2020 11:26:43 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s080

OTHER REVIEW(S)

Clinical Inspection Summary

Date	May 6, 2020
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Gina Davis, Pharm.D., Regulatory Project Manager Nicole Drezner, M.D., Clinical Reviewer Erin Larkins, M.D., Clinical Team Leader Harpreet Singh, M.D., Division Director Division of Oncology 2 (DO2)
BLA #	125554-S80
Applicant	Bristol-Myers Squibb Company (BMS)
Drug	Nivolumab and Ipilimumab
NME	No
Therapeutic Classification	Programmed Death Receptor-1 (PD-1) Blocking
Proposed Indication	Treatment of Metastatic or Recurrent Non-Small Cell Lung Cancer (NSCLC)
Consultation Request Date	01/23/2020
Original Summary Goal Date	04/17/2020
Updated Summary Goal Date	05/06/2020
Action Goal Date	05/15/2020
PDUFA Date	05/15/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical site of Dr. Otterson and the sponsor Bristol-Myers Squibb Company (BMS) were inspected by the FDA in support of this supplemental BLA. Based on the results of these inspections, the study (Protocol CA209227 Part 1) appears to have been conducted adequately, and the overall survival data from Part 1a of the study appear acceptable in support of the respective indication.

The European Medicines Agency (EMA) shared with OSI the inspection findings/results of their triggered inspections of the sponsor BMS in the US and two Clinical Research Organizations (CROs), (b) (4) and (b) (4) for Protocol CA209227. The EMA inspection findings presented in this document are based on OSI review of the individual EMA inspection reports (IRs) as well as the integrated inspection report (IIR) (refer to Section III). Although the good clinical practice (GCP) findings identified by EMA are concerning, based on the nature of these findings, they are unlikely to affect the reliability of the overall survival data from Part 1a of the study.

Reference ID: 4604371

II. BACKGROUND

On November 15, 2019, the sponsor BMS submitted BLA 125554-S80 for the combination of Opdivo (nivolumab) and Yervoy (ipilimumab) as a first-line treatment for patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations (Protocol CA209227 Part 1). The GCP inspections were requested only for Part 1a of Protocol CA209227 and for the primary efficacy endpoint for BLA 125554-S80 (i.e., overall survival). The following is a brief description of the Protocol CA209227 Part 1 and 1a:

Protocol CA209227 Part 1

Title: "An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus Platinum Doublet Chemotherapy versus Platinum Doublet Chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)"

Subjects: 2876 enrolled, 1739 randomized, and 1709 treated in Part 1

Study Sites: Total of 239 sites in 32 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea, Lebanon, Mexico, Netherlands, Peru, Poland, Romania, Russian Federation, South Africa, Spain, Switzerland, Taiwan, United Kingdom, and United States)

Study Initiation Date: 05 August 2015

Study Completion Dates: last patient last visit for the final Clinical Study Report was (b) (6) (b) (6) clinical cutoff for overall survival was 18 June 2019

Clinical database lock: 02 July 2019

This was an open-label, randomized, Phase 3 study in adult subjects with stage IV or recurrent NSCLC previously untreated for advanced disease. Enrolled subjects were assessed for PD-L1 expression by immunohistochemical testing of PD-L1 protein in the submitted tumor sample and then categorized into the two following groups using 1% as the PD-L1 cut-off.

- PD-L1 positive (+), PD-L1 expressing tumors: ≥1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells. Subjects in this group were included in Study **Part 1a**.

- PD-L1 negative (-), PD-L1 non-expressing tumors: <1% tumor cell membrane staining in a minimum of 100 evaluable tumor cells. Subjects were included in Study **Part 1b**.

Protocol CA209227 Part 1a

The inspections were requested by DO2 for this part only.

In **Part 1a**, PD-L1+ (≥1%) subjects were randomized in 1:1:1 fashion to the following three open-label treatments (until progression, unacceptable toxicity, or other reasons specified in the protocol):

Reference ID: 4604371

- Arm A (nivolumab only): nivolumab 240 mg IV every 2 weeks

- Arm B: (nivolumab + ipilimumab): nivolumab 3 mg/kg IV every 2 weeks combined with ipilimumab 1 mg/kg IV every 6 weeks

- Arm C (chemotherapy): IV platinum-doublet chemotherapy in 3-week cycles for up to a maximum of 6 cycles.

The primary efficacy endpoint was overall survival for nivolumab + ipilimumab (Arm B) vs. chemotherapy (Arm C) in PD-L1 ≥1% subjects.

Rationale for Site Selection

Inspections were requested for Protocol CA209227 1a, which was the pivotal study for BLA 125554-S80. Three clinical investigators: Drs. Lee (Site 136, South Korea), Ciuleanu (Site 166, Romania), and Pluzanski (Site 59, Poland) were initially selected by the review division and OSI for inspections (on 01/21/2020) due to large enrollments, good treatment effect size, and prior inspection history. Due to the international travel restrictions during the COVID-19 pandemic, the inspection of Dr. Lee was substituted by a US site (Otterson, Site 9), which had a relatively large enrollment (on 2/26/2020). The inspections of Drs. Ciuleanu and Pluzanski were cancelled on 3/16/2020 also because of international travel restrictions.

The sponsor (BMS) inspection was warranted due to the GCP concerns reported for EMA's inspections.

III. RESULTS

FDA Inspections

1. **Gregory A. Otterson, M.D.**
   Site #9
   320 West 10th Ave.
   Columbus, OH 43210
   Inspection dates: 4/13/2020 - 4/24/2020

At this site for all parts/sections of Protocol CA209227, 37 subjects were screened. Eleven subjects were enrolled into **Part 1a** of the protocol. Among these 11 enrolled subjects, one subject ((b) (6) in chemotherapy group) discontinued due to loss to follow up. This subject subsequently died. Nine subjects discontinued due to disease progression (death). One subject ((b) (6) in nivolumab only group) completed the study.

The COVID-19 global pandemic limited FDA's ability to conduct some of the planned on-site clinical investigator GCP inspections for this application, including for this site. Following discussions between OSI, the OND review division, and ORA, the inspection of Dr. Otterson's site was conducted remotely including the review of the site's electronic medical record, scanned copies of relevant subject paper charts, and electronic regulatory records. Specifically, the study records for all 11 subjects enrolled in Part 1a were reviewed. These records included, but were not limited to, informed consent; inclusion/exclusion criteria; randomization, dosing, and study drug administration; primary efficacy endpoint (overall survival); adverse event reporting; protocol compliance; concomitant medications; and other source documents. The study monitoring, ethics committee approval and communications, financial disclosures, FDA 1572s, study staff background

and training, and electronic systems were also reviewed.

The primary efficacy endpoint data, overall survival, as well as progression-free survival data (PFS; as assessed by the investigator), were verifiable. There was no evidence of underreporting of adverse events.

2. Bristol-Myers Squibb (BMS)
3401 Princeton Pike
Lawrenceville, NJ 08648 USA
Inspection dates: 4/8/2020 - 4/22/2020

The sponsor BMS was inspected in accordance with Compliance Program 7348.810 Bioresearch Monitoring (BIMO) for Sponsor, CRO, and Monitors. Activities/records reviewed included, but were not limited to, computer systems and data access, data management, trial monitoring, oversight of vendors, standard operating procedures (SOPs) related to clinical trial activities, clinical investigator (CI) selection and site qualification (such as study specific training and curriculum vitae), drug accountability, drug integrity, adverse event reporting, Institutional Review Board (IRB) compliance, and Forms FDA 1572. No issues of concern were found.

The inspection focused on computer systems and data access. Both the Oracle Clinical Electronic Data system, where all CA209227 study participant level data resided, and the EmBARC system for the conformed data had audit trails to show if and when data were modified, by whom they were modified, and what changes were made (going back to the beginning of the trial).

The SAS Unix system was used by authorized individuals for statistical analysis activities. BMS reported that at the beginning of the study, their SAS Unix system audit trails were not turned on. This audit trail feature was designed to keep track of activities such as who had accessed the system and when. In 2018, the IT team recognized this issue during routine activities and turned on this audit trail (tracking) feature. The sponsor reported that a Corrective and Preventive Action (CAPA) plan for this issue was implemented. During the inspection, the FDA investigator confirmed the existence of SAS Unix system audit trails since September 2018.

Reviewer's comment: Although the lack of SAS Unix system audit trails for much of the study was a critical process issue from the EMA perspective, the observation does not appear to affect significantly the overall reliability of efficacy data for Part 1a of Protocol CA209227, which had overall survival as the primary efficacy endpoint.

According to BMS, their clinical and site monitors reviewed the overall survival data. They stated that they had verified every death and the date of death (100% source verification) to ensure the accuracy of the overall survival data.

Additional Information: Review of EMA Inspection Findings

EMA conducted triggered inspections of the sponsor BMS (May 2019) and the CROs (b) (4) (b) (4) and (b) (4) in connection with a marketing authorization application of Opdivo (nivolumab) and Yervoy (ipilimumab) in Europe.

The reason for these triggered inspections was the concern of the EMA assessors that a protocol amendment that had been submitted by the sponsor to EMA following an interim analysis may

have been made in light of the accumulating trial data, i.e., the inclusion of a primary hypothesis testing the treatment effect on the progression-free survival (PFS) in the tumor mutational burden (TMB) ≥10 mut/mb sub-population.

The EMA shared with OSI their inspection findings/results. OSI reviewed the three individual EMA inspection reports (i.e., BMS, (b) (4) and (b) (4)), the integrated inspection report, the inspected entities' responses to the inspections, and the inspectors' evaluation of these responses. We summarize the findings below:

Note: The information below must be redacted should this CIS be made public as it was received from EMA under the terms of the confidentiality agreement between the two agencies.

A. Bristol-Myers Squibb (BMS)
3401 Princeton Pike
Lawrenceville, NJ 08648 USA
Inspection dates: 07-10 May 2019

The EMA inspection of the sponsor, BMS, for Protocol CA209227, identified one critical and 10 major findings.

Critical Finding: The Trial Master File (TMF) maintained by the sponsor was deficient. Inadequate management and suboptimal processes related to the design, content, maintenance, and handling of the TMF were identified.

Reviewer's comment: This EMA finding related to the TMF would not have been considered a regulatory violation by FDA, as the FDA does not currently have a parallel requirement under 21 CFR 312. This finding appears to us more of a quality/process issue.

Major Finding 1: The oversight by the sponsor of the vendors was inadequate, including:

- The system for managing vendors was not mature enough at the time when the trial started, and no formal quality assurance (QA) audits were performed prior to vendors' selection.
- A risk management system structure across the company was not evident. Some risk-based approaches had been applied but individually and not based on organization´s principles.
- Not all tasks delegated to vendors/service providers/suppliers were sufficiently detailed on contracts to be verified during an inspection.
- No meeting minutes for initial BMS-vendor meetings at the start of the trial were available

Reviewer's comment: This EMA finding would not have been considered a regulatory violation by FDA. It is stated in 21 CFR 312 that the sponsor shall monitor the progress of all clinical investigations being conducted under its IND. However, FDA regulations do not currently require a formal quality assessment (QA) audit prior to a vendor's selection or meeting minutes for initial sponsor-vendor meetings at the start of the trial. We acknowledge that all tasks delegated to vendors should be sufficiently detailed in the contracts. However, 21 CFR 312.52 only has general language that the transfer of responsibility to CROs "shall be described in writing". It does not specify how detailed this language should be. This finding appears to us more of a quality/process issue.

Major Finding 2: A non-optimal process was applied for managing qualification and training related documentation.

Reviewer's comment: This EMA finding would not have been considered a regulatory violation by

Reference ID: 4604371

FDA. The regulation 21 CFR 312.50 states that sponsors are responsible for selecting qualified investigators. It has neither specific requirements regarding the signing or dating of CVs nor the management of CVs or training related documentation by the sponsor. This finding appears to us more of a quality/process issue.

Major Finding 3: Several deficiencies were noted in computerized systems and electronic tools used by the company. These included a TMF-related issue as well as findings that:

- Tools like SharePoint and secure File Transfer Protocol (sFTP) did not have permanent audit trails embedded (when applicable).
- The Unix system was not customized for having an event tracker or audit trail that permitted identification of a user accessing the system at a determined time point or the action the user was performing. This aspect was identified as crucial to determine that individuals having access to the system did not access a layer of the system where specific datasets were hosted. Even though a user role and access privileges were determined for each user, this was not sufficient to rule out access of blinded information by some study staff.

Reviewer's comment: Although FDA intends to exercise enforcement discretion regarding 21 CFR Part 11 requirements for audit trails, the electronic records for a study are required to be maintained in accordance with the underlying predicate rules. In terms of data reliability, sponsors should take a risk-based approach as to what electronic systems for the clinical trial should have audit trails, but audit trails are not required for every electronic system used in the trial. The reported lack of audit trails for the Unix system housing specific datasets is potentially concerning but is addressed in FDA's sponsor (BMS) inspection as summarized above.

Major Finding 4: Deficiencies related to contracts and agreements:

- GCP language was not identified for ten Master Study Agreements provided for the inspection. In addition, there were no GCP statements appearing on protocols or the Clinical Study Report for the trial.

Reviewer's comment: *This EMA finding would not have been considered a regulatory violation by FDA because FDA does not currently have a parallel requirement under 21 CFR. This finding appears to us more of a quality issue.*

Major Finding 5: Deficient management of protocol violations

Reviewer's comment: *The sponsor acknowledged deficiencies in their process to generate the appendix listing in the clinical study report (CSR) of all significant protocol deviations, which inadvertently resulted in inaccurate and incomplete information, including some omissions and duplications. The sponsor reported that a corrective and preventative action (CAPA) plan was instituted to ensure that appropriate corrections were made to the final CSR.*

Major Finding 6: Shortcomings in data management processes were identified, which were mostly related to the reported lack of audit trails or event trackers for the Unix system that hosted the study datasets (as discussed under Major Finding 3).

Major Finding 7: Suboptimal measures were applied to preserve traceability of critical data management and statistics processes as well as the critical data that resulted from these processes.

- Specifically, EMA was concerned that BMS had no way to ensure or demonstrate that only the appropriate staff at BMS had access to the results of the interim analysis
- (b) (4)

Reference ID: 4604371

(b) (4)

Reviewer's comment: This finding was related to the concern of the EMA assessors that a protocol amendment submitted by the sponsor following an interim analysis may have been made in light of the accumulating trial data, i.e., the inclusion of a primary hypothesis testing the treatment effect on PFS in TMB ≥10 mut/mb sub-population. However, of interest to this sBLA is Protocol CA209227 ***Part 1a****, which was an open label study that had an objective measurement, overall survival, as the primary efficacy endpoint that had been a part of the original protocol.*

Major Findings 8 and 9: Deficiencies regarding the interim CSR as well as standard operating procedures in general were identified.

Major Finding 10: Suboptimal management of serious breaches and CAPAs were identified.

Reviewer's comment: Major Findings 8, 9 and 10 appear to OSI more quality/process issues.

(b) (4)

Reviewer's comment: These EMA findings would not have been considered regulatory violations by FDA, as the FDA does not currently have parallel requirements under 21 CFR. These findings appear to OSI more quality/process issues.

(b) (4)

Reviewer's comment: These EMA findings would not have been considered regulatory violations by FDA, as the FDA does not currently have parallel requirements under 21 CFR. These findings appear to OSI more quality/process issues.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. BLA 125554-S80
DO2/Project Manager/Gina Davis
DO2/Division Director/Harpreet Singh
DO2/Medical Officer/Nicole Drezner
DO2/Clinical Team Leader/Erin Larkins
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

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/

JENN W SELLERS
05/06/2020 03:38:27 PM

PHILLIP D KRONSTEIN
05/06/2020 05:08:04 PM

KASSA AYALEW
05/06/2020 05:09:59 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 30, 2020

To: Gina Davis, M.T. Senior 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 080

In response to DO2 consult request dated January 24, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for OPDIVO® (nivolumab) injection, for intravenous use (Opdivo). This supplement (S 080) proposes a new indication for Opdivo (nivolumab), in combination with ipilimumab, for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (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 (Gina Davis) on April 16, 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 April 29, 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.

94 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

ADESOLA F ADEJUWON
04/30/2020 08:20:40 AM

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:	April 29, 2020
To:	Gina M. Davis, MT Senior Regulatory Project Manager **Division of Oncology 2 (DO2)**
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):	OPDIVO (nivolumab)
Dosage Form and Route:	injection
Application Type/Number:	BLA 125554
Supplement Number:	S-080
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On November 15, 2019, Bristol-Myers Squibb Company submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved Biologics License Application (BLA) 125554/S-080 for OPDIVO (nivolumab) injection. With this supplement, the Applicant seeks full approval for OPDIVO, in combination with ipilimumab, for the first-line treatment of patients with metastatic or recurrent NSCLC with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

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 (DO2) on January 24, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPDIVO (nivolumab) injection.

2 MATERIAL REVIEWED

- Draft OPDIVO (nivolumab) injection MG received on November 15, 2019, and received by DMPP on April 16, 2020.
- Draft OPDIVO (nivolumab) injection Prescribing Information (PI) received on November 15, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on April 16, 2020.
- Approved OPDIVO (nivolumab) injection 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.

APPEARS THIS WAY
ON ORIGINAL

9 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

SHARON R MILLS
04/29/2020 02:56:53 PM

ADESOLA F ADEJUWON
04/29/2020 03:04:56 PM

LASHAWN M GRIFFITHS
04/29/2020 03:08:55 PM