CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125554Orig1s091

Trade Name:	OPDIVO
Generic or Proper Name:	(nivolumab)
Sponsor:	Bristol-Myers Squibb Company
Approval Date:	April 16, 2021

Indication:

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

Melanoma

• patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab. (1.1)

• patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting. (1.2)

Non-Small Cell Lung Cancer (NSCLC) • adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab. (1.3)

• adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy. (1.3)

• patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. (1.3)

Malignant Pleural Mesothelioma

• adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab. (1.4)

Renal Cell Carcinoma (RCC)

• patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment in combination with ipilimumab. (1.5)

• patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib. (1.5)

• patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy. (1.5)

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

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

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

Colorectal Cancer
• adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.a (1.9)

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

Esophageal Squamous Cell Carcinoma (ESCC) • patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy. (1.11)

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma
• patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy. (1.12)

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s091

APPROVAL LETTER

U.S. FOOD & DRUG ADMINISTRATION

BLA 125554/S-091

SUPPLEMENT APPROVAL

Bristol Myers Squibb Company
Attention: Sagar Shah, PharmD
Director, US Regulatory Innovation Lead
Global Regulatory Strategy and Policy
P.O Box 4000
Princeton, NJ 08543

Dear Dr. Shah:

Please refer to your supplemental Biologics License Application (sBLA), dated and received November 25, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Opdivo (nivolumab) injection, for intravenous use.

This Prior Approval supplemental biologics application provides for a new indication for Opdivo) in combination with fluoropyrimidine- and platinum-containing chemotherapy for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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

CONTENT OF LABELING

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

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

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

The SPL will be accessible via publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4055-1 Submit the final OS analyses and datasets for nivolumab in combination with chemotherapy vs. chemotherapy alone from the ongoing clinical trial Study CA209649, titled, "A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab Plus Ipilimumab or Nivolumab in Combination with Oxaliplatin Plus Fluoropyrimidine versus Oxaliplatin Plus Fluoropyrimidine in Subjects with Previously Untreated Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer". The results from this study may inform product labeling.

[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.

The timetable you submitted on April 14, 2021 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2019 (completed)
Trial Completion:	05/2021
Final Report Submission:	11/2021

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 126406 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

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

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

REPORTING REQUIREMENTS

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

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

If you have any questions, contact Gina Mehta, Regulatory Health Project Manager, at (301) 796-7910 or via email.

Sincerely,

{See appended electronic signature page}

Lola Fashoyin-Aje, M.D., M.P.H
Deputy Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

IBILOLA A FASHOYIN-AJE
04/16/2021 10:05:56 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

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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, Small Cell Lung Cancer (SCLC) – Accelerated Approval Indication Removed	12/2020
Indications and Usage (1)	4/2021
Dosage and Administration (2)	4/2021
Warnings and Precautions (5)	1/2021

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

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

Melanoma

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

Non-Small Cell Lung Cancer (NSCLC)

- adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab. (1.3)
- adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy. (1.3)
- patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. (1.3)

Malignant Pleural Mesothelioma

- adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab. (1.4)

Renal Cell Carcinoma (RCC)

- patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment in combination with ipilimumab. (1.5)
- patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib. (1.5)
- patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.5)

Classical Hodgkin Lymphoma (cHL)

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

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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

Urothelial Carcinoma

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

Colorectal Cancer

- adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.[a] (1.9)

Hepatocellular Carcinoma (HCC)

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

Esophageal Squamous Cell Carcinoma (ESCC)

- patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy. (1.11)

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy. (1.12)

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

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

- Administer by intravenous infusion based upon recommended infusion rate for each indication. (2)
- Unresectable or metastatic melanoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
  - 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Adjuvant treatment of melanoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Metastatic non-small cell lung cancer
  - 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks. (2.2)
  - 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy. (2.2)
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Malignant pleural mesothelioma
  - 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks. (2.2)
- Advanced renal cell carcinoma
  - 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)
  - 240 mg every 2 weeks or 480 mg every 4 weeks administered in combination with cabozantinib 40 mg once daily without food. (2.2)
  - 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)
- Esophageal squamous cell carcinoma
  - 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC, GEJC, or EAC)
  - 360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks. (2.2)
  - 240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 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 Adverse Reactions: (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis and hepatotoxicity, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, and immune-mediated nephritis and renal dysfunction.

- Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
- Withhold or permanently discontinue based on severity and type of reaction. (2.3)

- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue OPDIVO based on severity of reaction. (5.2)
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patient who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.4, 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. (5.5)

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

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

- As a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, and vomiting. (6.1)
- In combination with ipilimumab: fatigue, diarrhea, rash, pruritus, nausea, musculoskeletal pain, pyrexia, cough, decreased appetite, vomiting, abdominal pain, dyspnea, upper respiratory tract infection, arthralgia, headache, hypothyroidism, decreased weight, and dizziness. (6.1)
- In combination with ipilimumab and platinum-doublet chemotherapy: fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus. (6.1)
- In combination with cabozantinib: diarrhea, fatigue, hepatotoxicity, palmar-plantar erythrodysaesthesia syndrome, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection. (6.1)
- In combination with fluoropyrimidine- and platinum-containing chemotherapy: peripheral neuropathy, nausea, fatigue, diarrhea, vomiting, decreased appetite, abdominal pain, constipation, and musculoskeletal pain. (6.1)

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

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

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

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

1.2 Adjuvant Treatment of Melanoma

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

1.3 Metastatic Non-Small Cell Lung Cancer

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with no EGFR or ALK genomic tumor aberrations.
- OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
- OPDIVO is indicated for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

1.4 Malignant Pleural Mesothelioma

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

1.5 Advanced Renal Cell Carcinoma

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of patients with intermediate or poor risk advanced RCC.
- OPDIVO, in combination with cabozantinib, is indicated for the first-line treatment of patients with advanced RCC.
- 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.

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.

1.11 Esophageal Squamous Cell Carcinoma

OPDIVO is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

1.12 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

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 Esophageal squamous cell 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

Table 1: Recommended Dosages for OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks (30-minute intravenous infusion)	

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

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

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

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

Indication	Recommended OPDIVO Dosage	Duration of Therapy
	6 weeks (30-minute intravenous infusion) and histology-based platinum doublet chemotherapy every 3 weeks	**2 cycles of histology-based platinum-doublet chemotherapy**
Malignant pleural mesothelioma	360 mg every 3 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) Administer OPDIVO in combination with cabozantinib 40 mg orally once daily without food	OPDIVO: Until disease progression, unacceptable toxicity, or up to 2 years Cabozantinib: Until disease progression or unacceptable toxicity
	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 with ipilimumab, 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 Other Therapeutic Agents

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
Gastric cancer, Gastroesophageal junction cancer, and Esophageal adenocarcinoma	240 mg every 2 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks or 360 mg every 3 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks	Until disease progression, unacceptable toxicity, or up to 2 years

2.3 Dose Modifications

No dose reduction for OPDIVO is recommended. In general, withhold OPDIVO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue OPDIVO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for OPDIVO or OPDIVO in combination for adverse reactions that require management different from these general guidelines are summarized in Table 3 and Table 4.

When OPDIVO is administered in combination with ipilimumab, withhold or permanently discontinue both ipilimumab and OPDIVO for an adverse reaction meeting these dose modification guidelines.

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Immune-Mediated Adverse Reactions ***[see Warnings and Precautions (5.1)]***		
Pneumonitis	Grade 2	Withhold[a]
	Grades 3 or 4	Permanently discontinue

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Immune-Mediated Adverse Reactions ***[see Warnings and Precautions (5.1)]***		
Colitis For colitis in patients treated with combination therapy with ipilimumab, see Table 4.	Grade 2 or 3	Withhold[a]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver For liver enzyme elevations in patients treated with combination therapy with ipilimumab, see Table 4.	AST/ALT increases to >3 and ≤8 times ULN or Total bilirubin increases to >1.5 and ≤3 times ULN.	Withhold[a]
	AST or ALT increases to >8 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
Hepatitis with tumor involvement of the liver[b] For liver enzyme elevations in patients treated with combination therapy with ipilimumab, see Table 4.	Baseline AST/ALT is >1 and ≤3 times ULN and increases to >5 and ≤10 times ULN or Baseline AST/ALT is >3 and ≤5 times ULN and increases to >8 and ≤10 times ULN.	Withhold[a]
	AST/ALT increases to >10 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
Endocrinopathies[c]	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grades 2, 3, or 4	Permanently

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Immune-Mediated Adverse Reactions ***[see Warnings and Precautions (5.1)]***		
		discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

[a] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

[b] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue OPDIVO based on recommendations for hepatitis with no liver involvement.

[c] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

Table 4: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with Combination Therapy

Treatment	Adverse Reaction	Severity	Dosage Modification
OPDIVO in combination with ipilimumab	Colitis	Grade 2	Withhold[a]
		Grade 3 or 4	Permanently discontinue
	Hepatitis with no tumor involvement of the liver or Hepatitis with tumor involvement of the liver/non-HCC	AST/ALT increases to >3 times ULN and ≤5 times ULN or Total bilirubin increases to ≥1.5 and ≤3 times ULN.	Withhold[a]
		AST or ALT >5 times ULN or Total bilirubin >3	Permanently discontinue

Table 4: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with Combination Therapy

Treatment	Adverse Reaction	Severity	Dosage Modification
		times ULN.	
	Hepatitis with tumor involvement of the liver[b]/HCC	Baseline AST/ALT is >1 and ≤3 times ULN and increases to >5 and ≤10 times ULN or Baseline AST/ALT is >3 and ≤5 times ULN and increases to >8 and ≤10 times ULN.	Withhold[a]
		AST/ALT increases to >10 times ULN or Total bilirubin increases to >3 times ULN.	Permanently discontinue
OPDIVO in combination with cabozantinib	Liver enzyme elevations	ALT or AST >3 times ULN but ≤10 times ULN with concurrent total bilirubin <2 times ULN	Withhold[c] both OPDIVO and cabozantinib until adverse reactions recover[d] to Grades 0-1
		ALT or AST >10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN	Permanently discontinue[c] both OPDIVO and cabozantinib

[a] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

[b] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue OPDIVO in combination with ipilimumab based on recommendations for hepatitis with no liver involvement.

[c] Consider corticosteroid therapy for hepatic adverse reactions if OPDIVO is withheld or discontinued when administered in combination with cabozantinib.

[d] After recovery, rechallenge with one or both of OPDIVO and cabozantinib may be considered. If rechallenging with cabozantinib with or without OPDIVO, refer to cabozantinib Prescribing Information.

2.4 Preparation and Administration

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

Preparation

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

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

Administration

- Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Administer OPDIVO in combination with other therapeutic agents as follows:
  - With ipilimumab: administer OPDIVO first followed by ipilimumab on the same day.
  - With platinum-doublet chemotherapy: administer OPDIVO first followed by platinum-doublet chemotherapy on the same day
  - With ipilimumab and platinum-doublet chemotherapy: administer OPDIVO first followed by ipilimumab and then platinum-doublet chemotherapy on the same day.
  - With fluoropyrimidine- and platinum-containing chemotherapy: administer OPDIVO first followed by fluoropyrimidine- and platinum-containing chemotherapy on the same day.
- Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.

- Do not co-administer other drugs through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

OPDIVO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.2)]*. In general, if OPDIVO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

OPDIVO can cause immune-mediated pneumonitis, which is defined as requiring use of steroids and no clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

OPDIVO as a Single Agent

Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.9%), and Grade 2 (2.1%) adverse reactions. Pneumonitis led to permanent discontinuation of OPDIVO in 1.1% and withholding of OPDIVO in 0.8% of patients.

Systemic corticosteroids were required in 100% (61/61) of patients with pneumonitis. Pneumonitis resolved in 84% of the 61 patients. Of the 15 patients in whom OPDIVO was withheld for pneumonitis, 14 reinitiated OPDIVO after symptom improvement; of these, 4 (29%) had recurrence of pneumonitis.

OPDIVO with Ipilimumab

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: 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. 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. Pneumonitis resolved in 72% of the patients. Approximately 13% (2/16) of patients had recurrence of pneumonitis after reinitiation of OPDIVO with ipilimumab.

Immune-Mediated Colitis

OPDIVO can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the definition of colitis was diarrhea. 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.

OPDIVO as a Single Agent

Immune-mediated colitis occurred in 2.9% (58/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (1.7%) and Grade 2 (1%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.9% of patients.

Systemic corticosteroids were required in 100% (58/58) of patients with colitis. Four patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 86% of the 58 patients. Of the 18 patients in whom OPDIVO was withheld for colitis, 16 reinitiated OPDIVO after symptom improvement; of these, 12 (75%) had recurrence of colitis.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Immune-mediated colitis occurred in 25% (115/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (0.4%), Grade 3 (14%), and Grade 2 (8%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO with ipilimumab in 14% and withholding of OPDIVO with ipilimumab in 4.4% of patients.

Systemic corticosteroids were required in 100% (115/115) of patients with colitis. Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Colitis resolved in 93% of the 115 patients. Of the 20 patients in whom OPDIVO with ipilimumab was withheld for colitis, 16 reinitiated treatment after symptom improvement; of these, 9 (56%) had recurrence of colitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated colitis occurred in 9% (60/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (4.4%) and Grade 2 (3.7%) adverse reactions. Colitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.2% and withholding of OPDIVO with ipilimumab in 2.7% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (60/60) of patients with colitis. Approximately 23% of patients with immune-mediated colitis required addition of infliximab to high-dose corticosteroids. Colitis resolved in 95% of the 60 patients. Of the 18 patients in whom OPDIVO with ipilimumab was withheld for colitis, 16 reinitiated treatment after symptom improvement; of these, 10 (63%) had recurrence of colitis.

Immune-Mediated Hepatitis and Hepatotoxicity

OPDIVO can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.

OPDIVO as a Single Agent

Immune-mediated hepatitis occurred in 1.8% (35/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (0.2%), Grade 3 (1.3%), and Grade 2 (0.4%) adverse reactions. Hepatitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 0.6% of patients.

Systemic corticosteroids were required in 100% (35/35) of patients with hepatitis. Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 35 patients. Of the 12 patients in whom OPDIVO was withheld for hepatitis, 11 reinitiated OPDIVO after symptom improvement; of these, 9 (82%) had recurrence of hepatitis.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Immune-mediated hepatitis occurred in 15% (70/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (2.4%), Grade 3 (11%), and Grade 2 (1.8%) adverse

reactions. Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 8% or withholding of OPDIVO with ipilimumab in 3.5% of patients.

Systemic corticosteroids were required in 100% (70/70) of patients with hepatitis. Approximately 9% of patients with immune-mediated hepatitis required the addition mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 91% of the 70 patients. Of the 16 patients in whom OPDIVO with ipilimumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement; of these, 8 (57%) had recurrence of hepatitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated hepatitis occurred in 7% (48/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (1.2%), Grade 3 (4.9%), and Grade 2 (0.4%) adverse reactions. Immune-mediated hepatitis led to permanent discontinuation of OPDIVO with ipilimumab in 3.6% and withholding of OPDIVO with ipilimumab in 2.6% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (48/48) of patients with hepatitis. Approximately 19% of patients with immune-mediated hepatitis required addition of mycophenolic acid to high-dose corticosteroids. Hepatitis resolved in 88% of the 48 patients. Of the 17 patients in whom OPDIVO with ipilimumab was withheld for hepatitis, 14 reinitiated treatment after symptom improvement; of these, 10 (71%) had recurrence of hepatitis.

OPDIVO with Cabozantinib

OPDIVO in combination with cabozantinib can cause hepatic toxicity with higher frequencies of Grade 3 and 4 ALT and AST elevations compared to OPDIVO alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt OPDIVO and cabozantinib and consider administering corticosteroids *[see Dosage and Administration (2.3)]*.

With the combination of OPDIVO and cabozantinib, Grades 3 and 4 increased ALT or AST were seen in 11% of patients *[see Adverse Reactions (6.1)]*. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either OPDIVO (n=11) or cabozantinib (n=9) administered as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving OPDIVO, 2 patients receiving cabozantinib, and 7 patients receiving both OPDIVO and cabozantinib.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

OPDIVO can cause primary or secondary adrenal insufficiency. For grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

Adrenal insufficiency occurred in 1% (20/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.6%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.4% of patients.

Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 90% (18/20) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 35% of the 20 patients. Of the 8 patients in whom OPDIVO was withheld for adrenal insufficiency, 4 reinitiated OPDIVO after symptom improvement and all required hormone replacement therapy for their ongoing adrenal insufficiency.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Adrenal insufficiency occurred in 8% (35/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 4 (0.2%), Grade 3 (2.4%), and Grade 2 (4.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO with ipilimumab in 0.4% and withholding of OPDIVO with ipilimumab in 2.0% of patients.

Approximately 71% (25/35) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 37% of the 35 patients. Of the 9 patients in whom OPDIVO with ipilimumab was withheld for adrenal insufficiency, 7 reinitiated treatment after symptom improvement and all required hormone replacement therapy for their ongoing adrenal insufficiency.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Adrenal insufficiency occurred in 7% (48/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (0.3%), Grade 3 (2.5%), and Grade 2 (4.1%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% and withholding of OPDIVO with ipilimumab in 2.1% of patients with RCC or CRC.

Approximately 94% (45/48) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 29% of the 48 patients. Of the 14 patients in whom OPDIVO with ipilimumab was withheld for adrenal insufficiency, 11 reinitiated treatment after symptom improvement; of these, all received hormone replacement therapy and 2 (18%) had recurrence of adrenal insufficiency.

OPDIVO with Cabozantinib

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received OPDIVO with cabozantinib, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of OPDIVO and cabozantinib in 0.9% and withholding of OPDIVO and cabozantinib in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom OPDIVO with cabozantinib was withheld for

adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Hypophysitis

OPDIVO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

Hypophysitis occurred in 0.6% (12/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.2%) and Grade 2 (0.3%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO in <0.1% and withholding of OPDIVO in 0.2% of patients.

Approximately 67% (8/12) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 42% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for hypophysitis, 2 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hypophysitis.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Hypophysitis occurred in 9% (42/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (2.4%) and Grade 2 (6%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO with ipilimumab in 0.9% and withholding of OPDIVO with ipilimumab in 4.2% of patients.

Approximately 86% of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 88% (37/42) of patients with hypophysitis. Hypophysitis resolved in 38% of the 42 patients. Of the 19 patients in whom OPDIVO with ipilimumab was withheld for hypophysitis, 9 reinitiated treatment after symptom improvement; of these, 1 (11%) had recurrence of hypophysitis.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Hypophysitis occurred in 4.4% (29/666) of patients with RCC or CRC receiving OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 4 (0.3%), Grade 3 (2.4%), and Grade 2 (0.9%) adverse reactions. Hypophysitis led to permanent discontinuation of OPDIVO with ipilimumab in 1.2% and withholding of OPDIVO with ipilimumab in 2.1% of patients with RCC or CRC.

Approximately 72% (21/29) of patients with hypophysitis received hormone replacement therapy, including systemic corticosteroids. Hypophysitis resolved in 59% of the 29 patients. Of the 14 patients in whom OPDIVO with ipilimumab was withheld for hypophysitis, 11 reinitiated treatment after symptom improvement; of these, 2 (18%) had recurrence of hypophysitis.

Thyroid Disorders

OPDIVO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management as clinically indicated. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.2)]*.

Thyroiditis

OPDIVO as a Single Agent

Thyroiditis occurred in 0.6% (12/1994) of patients receiving OPDIVO as a single agent, including Grade 2 (0.2%) adverse reactions. Thyroiditis led to permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.2% of patients.

Systemic corticosteroids were required in 17% (2/12) of patients with thyroiditis. Thyroiditis resolved in 58% of the 12 patients. Of the 3 patients in whom OPDIVO was withheld for thyroiditis, 1 reinitiated OPDIVO after symptom improvement without recurrence of thyroiditis.

Hyperthyroidism

OPDIVO as a Single Agent

Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (<0.1%) and Grade 2 (1.2%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.4% of patients.

Approximately 19% of patients with hyperthyroidism received methimazole, 7% received carbimazole, and 4% received propylthiouracil. Systemic corticosteroids were required in 9% (5/54) of patients. Hyperthyroidism resolved in 76% of the 54 patients. Of the 7 patients in whom OPDIVO was withheld for hyperthyroidism, 4 reinitiated OPDIVO after symptom improvement; of these, none had recurrence of hyperthyroidism.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Hyperthyroidism occurred in 9% (42/456) of patients with melanoma or HCC who received OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (0.9%) and Grade 2 (4.2%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of OPDIVO with ipilimumab in no patients and withholding of OPDIVO with ipilimumab in 2.4% of patients.

Approximately 26% of patients with hyperthyroidism received methimazole and 21% received carbimazole. Systemic corticosteroids were required in 17% (7/42) of patients. Hyperthyroidism resolved in 91% of the 42 patients. Of the 11 patients in whom OPDIVO with ipilimumab was withheld for hyperthyroidism, 8 reinitiated treatment after symptom improvement; of these, 1 (13%) had recurrence of hyperthyroidism.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Hyperthyroidism occurred in 12% (80/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (0.6%) and Grade 2 (4.5%) adverse reactions. Hyperthyroidism led to

permanent discontinuation of OPDIVO with ipilimumab in no patients and withholding of OPDIVO with ipilimumab in 2.3% of patients with RCC or CRC.

Of the 80 patients with RCC or CRC who developed hyperthyroidism, approximately 16% received methimazole and 3% received carbimazole. Systemic corticosteroids were required in 20% (16/80) of patients with hyperthyroidism. Hyperthyroidism resolved in 85% of the 80 patients. Of the 15 patients in whom OPDIVO with ipilimumab was withheld for hyperthyroidism, 11 reinitiated treatment after symptom improvement; of these, 3 (27%) had recurrence of hyperthyroidism.

Hypothyroidism

OPDIVO as a Single Agent

Hypothyroidism occurred in 8% (163/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.2%) and Grade 2 (4.8%) adverse reactions. Hypothyroidism led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.5% of patients.

Approximately 79% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 3.1% (5/163) of patients with hypothyroidism. Hypothyroidism resolved in 35% of the 163 patients. Of the 9 patients in whom OPDIVO was withheld for hypothyroidism, 3 reinitiated OPDIVO after symptom improvement; of these, 1 (33%) had recurrence of hypothyroidism.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Hypothyroidism occurred in 20% (91/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (0.4%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to the permanent discontinuation of OPDIVO with ipilimumab in 0.9% and withholding of OPDIVO with ipilimumab in 0.9% of patients.

Approximately 89% of patients with hypothyroidism received levothyroxine. Systemic corticosteroids were required in 2.2% (2/91) of patients with hypothyroidism. Hypothyroidism resolved in 41% of the 91 patients. Of the 4 patients in whom OPDIVO with ipilimumab was withheld for hypothyroidism, 2 reinitiated treatment after symptom improvement; of these, none had recurrence of hypothyroidism.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Hypothyroidism occurred in 18% (122/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (0.6%) and Grade 2 (11%) adverse reactions. Hypothyroidism led to permanent discontinuation of OPDIVO with ipilimumab in 0.2% and withholding of OPDIVO with ipilimumab in 1.4% of patients with RCC or CRC.

Of the 122 patients with RCC or CRC who developed hypothyroidism, approximately 82% received levothyroxine. Systemic corticosteroids were required in 7% (9/122) of patients with hypothyroidism. Hypothyroidism resolved in 27% of the 122 patients. Of the 9 patients in whom

OPDIVO with ipilimumab was withheld for hypothyroidism, 5 reinitiated treatment after symptom improvement; of these, 1 (20%) had recurrence of hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold OPDIVO depending on severity *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

Diabetes occurred in 0.9% (17/1994) of patients receiving OPDIVO as a single agent, including Grade 3 (0.4%) and Grade 2 (0.3%) adverse reactions, and two cases of diabetic ketoacidosis. Diabetes led to the permanent discontinuation of OPDIVO in no patients and withholding of OPDIVO in 0.1% of patients.

No patients (0/17) with diabetes required systemic corticosteroids. Diabetes resolved in 29% of the 17 patients. Of the 2 patients in whom OPDIVO was withheld for diabetes, both reinitiated OPDIVO after symptom improvement; of these, neither had recurrence of diabetes.

Immune-Mediated Nephritis with Renal Dysfunction

OPDIVO can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear alternate etiology.

OPDIVO as a Single Agent

Immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients receiving OPDIVO as a single agent, including Grade 4 (<0.1%), Grade 3 (0.5%), and Grade 2 (0.6%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.4% of patients.

Systemic corticosteroids were required in 100% (23/23) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 78% of the 23 patients. Of the 7 patients in whom OPDIVO was withheld for nephritis or renal dysfunction, 7 reinitiated OPDIVO after symptom improvement; of these, 1 (14%) had recurrence of nephritis or renal dysfunction.

Immune-Mediated Dermatologic Adverse Reactions

OPDIVO can cause immune-mediated rash or dermatitis, defined as requiring the use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue OPDIVO depending on severity *[see Dosage and Administration (2.2)]*.

OPDIVO as a Single Agent

Immune-mediated rash occurred in 9% (171/1994) of patients, including Grade 3 (1.1%) and Grade 2 (2.2%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.5% of patients.

Systemic corticosteroids were required in 100% (171/171) of patients with immune-mediated rash. Rash resolved in 72% of the 171 patients. Of the 10 patients in whom OPDIVO was withheld for immune-mediated rash, 9 reinitiated OPDIVO after symptom improvement; of these, 3 (33%) had recurrence of immune-mediated rash.

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg: Immune-mediated rash occurred in 28% (127/456) of patients with melanoma or HCC receiving OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks, including Grade 3 (4.8%) and Grade 2 (10%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO with ipilimumab in 0.4% and withholding of OPDIVO with ipilimumab in 3.9% of patients.

Systemic corticosteroids were required in 100% (127/127) of patients with immune-mediated rash. Rash resolved in 84% of the 127 patients. Of the 18 patients in whom OPDIVO with ipilimumab was withheld for immune-mediated rash, 15 reinitiated treatment after symptom improvement; of these, 8 (53%) had recurrence of immune-mediated rash.

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg: Immune-mediated rash occurred in 16% (108/666) of patients with RCC or CRC who received OPDIVO 3 mg/kg with ipilimumab 1 mg/kg every 3 weeks, including Grade 3 (3.5%) and Grade 2 (4.2%) adverse reactions. Immune-mediated rash led to permanent discontinuation of OPDIVO with ipilimumab in 0.5% of patients and withholding of OPDIVO with ipilimumab in 2.0% of patients with RCC or CRC.

Systemic corticosteroids were required in 100% (108/108) of patients with immune-mediated rash. Rash resolved in 75% of the 108 patients. Of the 13 patients in whom OPDIVO with ipilimumab was withheld for immune-mediated rash, 11 reinitiated treatment after symptom improvement; of these, 5 (46%) had recurrence of immune-mediated rash.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received OPDIVO or OPDIVO in combination with ipilimumab, or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions,

consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatic

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

5.2 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. Infusion-related reactions occurred in 12% (37/300) of patients with malignant pleural mesothelioma who received OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks.

5.3 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.

5.4 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)]*.

5.5 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.

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

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

227 (n=576) or CHECKMATE-743 (n=300); OPDIVO 360 mg with ipilimumab 1 mg/kg and 2 cycles of platinum-doublet chemotherapy in CHECKMATE-9LA (n=361); and OPDIVO 240 mg with cabozantinib 40 mg in patients enrolled in CHECKMATE-9ER (n=320).

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 5 and 6 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-037.

Table 5: 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 6: 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 7 and 8 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-066.

Table 7: 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

Table 7: 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 (%)
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 8: 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 9 and 10 summarize the incidence of adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-067.

Table 9: 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

Table 9: 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 (%)
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 10: 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 11 and 12 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-238.

Table 11: 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 12: 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 13 and 14 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

Table 13: 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
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 macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.

[d] Includes pruritus and pruritus generalized.

[e] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity.
[f] Includes colitis, colitis microscopic, colitis ulcerative, diarrhea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral.
[g] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.
[h] Includes dyspnea and dyspnea exertional.
[i] Includes cough and productive cough.
[j] Includes alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased.
[k] Includes autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased.
[l] Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased.
[m] Includes lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral, atypical pneumonia, organizing pneumonia.

Other clinically important adverse reactions in CHECKMATE-227 were:

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

Gastrointestinal: stomatitis, pancreatitis, gastritis

Musculoskeletal and Connective Tissue: arthritis, polymyalgia rheumatica, rhabdomyolysis

Nervous System: peripheral neuropathy, autoimmune encephalitis

Blood and Lymphatic System: eosinophilia

Eye Disorders: blurred vision, uveitis

Cardiac: atrial fibrillation, myocarditis

Table 14: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-227

Laboratory Abnormality	OPDIVO and Ipilimumab		Platinum-doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	46	3.6	78	14
Lymphopenia	46	5	60	15
Chemistry				
Hyponatremia	41	12	26	4.9
Increased AST	39	5	26	0.4
Increased ALT	36	7	27	0.7
Increased lipase	35	14	14	3.4
Increased alkaline phosphatase	34	3.8	20	0.2
Increased amylase	28	9	18	1.9
Hypocalcemia	28	1.7	17	1.3
Hyperkalemia	27	3.4	22	0.4
Increased creatinine	22	0.9	17	0.2

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

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

The safety of OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was evaluated in CHECKMATE-9LA *[see Clinical Studies (14.3)]*. Patients received either OPDIVO 360 mg administered every 3 weeks in combination with ipilimumab 1 mg/kg administered every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy was 6 months (range: 1 day to 19 months): 50% of patients received OPDIVO and ipilimumab for >6 months and 13% of patients received OPDIVO and ipilimumab for >1 year.

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

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

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

Table 15: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9

Table 15: Adverse Reactions in >10% of Patients Receiving OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0
Alopecia	11	0.8	10	0.6
Metabolism and Nutrition				
Decreased appetite	28	2.0	22	1.7
Respiratory, Thoracic and Mediastinal				
Cough[g]	19	0.6	15	0.9
Dyspnea[h]	18	4.7	14	3.2
Endocrine				
Hypothyroidism[i]	19	0.3	3.4	0
Nervous System				
Headache	11	0.6	7	0
Dizziness[j]	11	0.6	6	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

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

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

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

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

[f] Includes pruritus and generalized pruritus

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

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

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

[j] Includes dizziness, vertigo and positional vertigo

Table 16: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

Laboratory Abnormality	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16

Table 16: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy - CHECKMATE-9LA

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

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

Second-line Treatment of Metastatic NSCLC

The safety of OPDIVO was evaluated in CHECKMATE-017, a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.3)]*. These trials excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received OPDIVO 3 mg/kg over 60 minutes by intravenous infusion every 2 weeks or docetaxel 75 mg/m^2 intravenously every 3 weeks. The median duration of therapy in OPDIVO-treated patients in CHECKMATE-017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1 year and in CHECKMATE-057, 30% of patients received OPDIVO for >6 months and 20% of patients received OPDIVO for >1 year.

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

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

OPDIVO. OPDIVO was discontinued in 11% of patients and was delayed in 28% of patients for an adverse reaction.

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

Tables 17 and 18 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-057.

Table 17: 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 18: 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.

Malignant Pleural Mesothelioma

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-743, a randomized, open-label trial in patients with previously untreated unresectable malignant pleural mesothelioma *[see Clinical Studies (14.4)]*. Patients received either OPDIVO 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks and ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years; or platinum-doublet chemotherapy for up to 6 cycles. The median duration of therapy in OPDIVO and ipilimumab-treated patients was 5.6 months (range: 0 to 26.2 months); 48% of patients received OPDIVO and ipilimumab for >6 months and 24% of patients received OPDIVO and ipilimumab for >1 year.

Serious adverse reactions occurred in 54% of patients who were treated with OPDIVO in combination with ipilimumab. The most frequent (≥2%) serious adverse reactions were pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism. Fatal adverse reactions occurred in 4 (1.3%) patients and included pneumonitis, acute heart failure, sepsis and encephalitis.

Both OPDIVO and ipilimumab were permanently discontinued due to adverse reactions in 23% of patients and 52% had at least one dose withheld due to an adverse reaction.

The most common (≥20%) adverse reactions were fatigue, musculoskeletal pain, rash, diarrhea, dyspnea, nausea, decreased appetite, cough, and pruritus.

Tables 19 and 20 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-743.

Table 19: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-743

Adverse Reaction	OPDIVO and Ipilimumab (n=300)		Chemotherapy (n=284)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	43	4.3	45	6
Pyrexia[b]	18	1.3	4.6	0.7
Edema[c]	17	0	8	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	38	3.3	17	1.1
Arthralgia	13	1.0	1.1	0
Skin and Subcutaneous Tissue				
Rash[e]	34	2.7	11	0.4
Pruritus[f]	21	1.0	1.4	0
Gastrointestinal				
Diarrhea[g]	32	6	12	1.1
Nausea	24	0.7	43	2.5
Constipation	19	0.3	30	0.7
Abdominal pain[h]	15	1	10	0.7
Vomiting	14	0	18	2.1
Respiratory, Thoracic, and Mediastinal				

Table 19: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Ipilimumab - CHECKMATE-743

Adverse Reaction	OPDIVO and Ipilimumab (n=300)		Chemotherapy (n=284)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Dyspnea[i]	27	2.3	16	3.2
Cough[j]	23	0.7	9	0
Metabolism and Nutrition				
Decreased appetite	24	1.0	25	1.4
Endocrine				
Hypothyroidism[k]	15	0	1.4	0
Infections and Infestations				
Upper respiratory tract infection[l]	12	0.3	7	0
Pneumonia[m]	10	4.0	4.2	2.1

[a] Includes fatigue and asthenia.

[b] Includes pyrexia and tumor-associated fever.

[c] Includes edema, generalized edema, peripheral edema, and peripheral swelling.

[d] Includes musculoskeletal pain, back pain, bone pain, flank pain, involuntary muscle contractions, muscle spasms, muscle twitching, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, polymyalgia rheumatica, and spinal pain.

[e] Includes rash, acne, acneiform dermatitis, allergic dermatitis, atopic dermatitis, autoimmune dermatitis, bullous dermatitis, contact dermatitis, dermatitis, drug eruption, dyshidrotic eczema, eczema, erythematous rash, exfoliative rash, generalized exfoliative dermatitis, generalized rash, granulomatous dermatitis, keratoderma blenorrhagica, macular rash, maculopapular rash, morbilliform rash, nodular rash, papular rash, psoriasiform dermatitis, pruritic rash, pustular rash, skin exfoliation, skin reaction, skin toxicity, Stevens-Johnson syndrome, toxic skin eruption, and urticaria.

[f] Includes pruritus, allergic pruritus, and generalized pruritus.

[g] Includes diarrhea, colitis, enteritis, infectious enteritis, enterocolitis, infectious enterocolitis, microscopic colitis, ulcerative colitis, and viral enterocolitis.

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

[i] Includes dyspnea, dyspnea at rest, and exertional dyspnea.

[j] Includes cough, productive cough, and upper-airway cough syndrome.

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

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

[m] Includes pneumonia, lower respiratory tract infection, lung infection, aspiration pneumonia, and Pneumocystis jirovecii pneumonia.

Table 20: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-743

Laboratory Abnormality	OPDIVO and Ipilimumab		Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Hyperglycemia	53	3.7	34	1.1
Increased AST	38	7	17	0
Increased ALT	37	7	15	0.4
Increased lipase	34	13	9	0.8
Hyponatremia	32	8	21	2.9
Increased alkaline phosphatase	31	3.1	12	0
Hyperkalemia	30	4.1	16	0.7
Hypocalcemia	28	0	16	0
Increased amylase	26	5	13	0.9
Increased creatinine	20	0.3	20	0.4
Hematology				
Lymphopenia	43	8	57	14
Anemia	43	2.4	75	15

[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: 109 to 297 patients) and chemotherapy group (range: 90 to 276 patients).

Advanced Renal Cell Carcinoma

First-line Renal Cell Carcinoma

CHECKMATE-214

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 21 and 22 summarize adverse reactions and laboratory abnormalities, respectively, that occurred in >15% of OPDIVO and ipilimumab-treated patients in CHECKMATE-214.

Table 21: 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
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 22: 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).

CHECKMATE-9ER

The safety of OPDIVO with cabozantinib was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received OPDIVO 240 mg over 30 minutes every 2 weeks with cabozantinib 40 mg orally once daily (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320) *[see Clinical Studies (14.5)]*. Cabozantinib could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in OPDIVO and cabozantinib-treated patients. In this trial, 82% of patients in the OPDIVO and cabozantinib arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving OPDIVO and cabozantinib. The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either OPDIVO or cabozantinib occurred in 20% of patients: 7% OPDIVO only, 8% cabozantinib only, and 6% both drugs due to same adverse reaction at the same time. Adverse reaction leading to dose interruption or reduction of either OPDIVO or cabozantinib occurred in 83% of patients: 3% OPDIVO only, 46% cabozantinib only, and 21% both drugs due to same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with OPDIVO and cabozantinib were diarrhea, fatigue, hepatotoxicity, palmar-plantar erythrodysaesthesia syndrome, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Tables 23 and 24 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-9ER.

Table 23: Adverse Reactions in >15% of Patients Receiving OPDIVO and Cabozantinib - CHECKMATE-9ER

Adverse Reaction	OPDIVO and Cabozantinib (n=320)		Sunitinib (n=320)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal pain[a]	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia[b]	15	0	22	0.3
General				
Fatigue[c]	51	8	50	8
Hepatobiliary				
Hepatotoxicity[d]	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysaesthesia syndrome	40	8	41	8
Stomatitis[e]	37	3.4	46	4.4
Rash[f]	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				
Hypertension[g]	36	13	39	14
Endocrine				
Hypothyroidism[h]	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[i]	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
Respiratory, Thoracic and Mediastinal				
Cough[j]	20	0.3	17	0
Dysphonia	17	0.3	3.4	0
Infections and Infestations				
Upper respiratory tract infection[k]	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

[d] Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.

[e] Includes mucosal inflammation, aphthous ulcer, mouth ulceration.

[f] Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.

[g] Includes blood pressure increased, blood pressure systolic increased.

[h] Includes primary hypothyroidism.

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

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis.

Table 24: Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients on OPDIVO and Cabozantinib - CHECKMATE-9ER

Laboratory Abnormality	OPDIVO and Cabozantinib		Sunitinib	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

[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 cabozantinib group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

Previously Treated Renal Cell Carcinoma

CHECKMATE-025

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 25 and 26 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-025.

Table 25: 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

Table 25: 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 (%)
Pruritus/generalized pruritus	19	0	14	0
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 26: 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).

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 27 and 28 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-205 and CHECKMATE-039.

Table 27: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

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

Table 27: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

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

Toxicity was graded per NCI CTCAE v4.

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

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

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

[d] Includes asthenia.

[e] Includes colitis.

[f] Includes abdominal discomfort and upper abdominal pain.

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

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

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

Additional information regarding clinically important adverse reactions:

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

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

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

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

Table 28 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 28: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-205 and CHECKMATE-039

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

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

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

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

Squamous Cell Carcinoma of the Head and Neck

The safety of OPDIVO was evaluated in CHECKMATE-141, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCHN with progression during or within 6 months of receiving prior platinum-based therapy *[see Clinical Studies (14.7)]*. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma). Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks (n=236) or investigator's choice of either cetuximab (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). 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 29 and 30 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-275.

Table 29: Adverse Reactions Occurring in ≥10% of Patients - CHECKMATE-275

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

Toxicity was graded per NCI CTCAE v4.

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

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

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

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

Table 30: 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. Treatment 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 31 and 32 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 31: 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 32: 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 33 and 34 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 33: 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 33: 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 34: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 or OPDIVO as a Single Agent in Cohorts 1 and 2 of CHECKMATE-040

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

Table 34: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving OPDIVO in Combination with Ipilimumab in Cohort 4 or OPDIVO as a Single Agent in Cohorts 1 and 2 of CHECKMATE-040

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

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

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

Esophageal Squamous Cell Carcinoma

The safety of OPDIVO was evaluated in ATTRACTION-3, a randomized, active-controlled, open-label, multicenter trial in 209 patients with unresectable advanced, recurrent or metastatic ESCC refractory or intolerant to at least one fluoropyrimidine- and platinum-based chemotherapy *[see Clinical Studies (14.11)]*. The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had autoimmune disease, used systemic corticosteroids or immunosuppressants, had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients received OPDIVO 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=209) or investigator's choice: docetaxel 75 mg/m^2 intravenously every 3 weeks (n=65) or paclitaxel 100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off (n=143). Patients were treated until disease progression or unacceptable toxicity. The median duration of exposure was 2.6 months (range: 0 to 29.2 months) in OPDIVO-treated patients and 2.6 months (range: 0 to 21.4 months) in docetaxel- or paclitaxel-treated patients. Among patients who received OPDIVO, 26% were exposed for >6 months and 10% were exposed for >1 year.

Serious adverse reactions occurred in 38% of patients receiving OPDIVO. Serious adverse reactions reported in ≥2% of patients who received OPDIVO were pneumonia, esophageal fistula, interstitial lung disease and pyrexia. The following fatal adverse reactions occurred in patients who received OPDIVO: interstitial lung disease or pneumonitis (1.4%), pneumonia (1.0%), septic shock (0.5%), esophageal fistula (0.5%), gastrointestinal hemorrhage (0.5%), pulmonary embolism (0.5%), and sudden death (0.5%).

OPDIVO was discontinued in 13% of patients and was delayed in 27% of patients for an adverse reaction.

Tables 35 and 36 summarize the adverse reactions and laboratory abnormalities, respectively, in ATTRACTION-3.

Table 35: Adverse Reactions Occurring in ≥10% of Patients Receiving OPDIVO - ATTRACTION-3

Adverse Reaction	OPDIVO (n=209)		Docetaxel or Paclitaxel (n=208)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash[a]	22	1.9	28	1
Pruritus	12	0	7	0
Metabolism and Nutrition				
Decreased appetite[b]	21	1.9	35	5
Gastrointestinal				
Diarrhea[c]	18	1.9	17	1.4
Constipation	17	0	19	0
Nausea	11	0	20	0.5
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	17	0	26	1.4
Infections				
Upper respiratory tract infection[e]	17	1.0	14	0
Pneumonia[f]	13	5	19	9
Respiratory, Thoracic and Mediastinal				
Cough[g]	16	0	14	0.5
General				
Pyrexia[h]	16	0.5	19	0.5
Fatigue[i]	12	1.4	27	4.8
Blood and Lymphatic System				
Anemia[j]	13	8	30	13
Endocrine				
Hypothyroidism[k]	11	0	1.4	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes urticaria, drug eruption, eczema, eczema asteatotic, eczema nummular, palmar-plantar erythrodysaesthesia syndrome, erythema, erythema multiforme, blister, skin exfoliation, Stevens-Johnson syndrome, dermatitis, dermatitis described as acneiform, bullous, or contact, and rash described as maculo-papular, generalized, or pustular.

[b] Includes hypophagia, and food aversion.

[c] Includes colitis.

[d] Includes spondylolisthesis, periarthritis, musculoskeletal chest pain, neck pain, arthralgia, back pain, myalgia, pain in extremity, arthritis, bone pain, and periarthritis calcarea.

[e] Includes influenza, influenza like illness, pharyngitis, nasopharyngitis, tracheitis, and bronchitis and upper respiratory infection with bronchitis.

[f] Includes pneumonia aspiration, pneumonia bacterial, and lung infection. Two patients (1.0%) died of pneumonia in the OPDIVO treatment arm. Two patients (1.0%) died of pneumonia in the chemotherapy treatment arm; these deaths occurred with paclitaxel only.

[g] Includes productive cough.

[h] Includes tumor-associated fever.

[i] Includes asthenia.

[j] Includes hemoglobin decreased, and iron deficiency anemia.

[k] Includes blood thyroid stimulating hormone increased.

Table 36: Laboratory Abnormalities Worsening from Baseline[a] Occurring in ≥10% of Patients - ATTRACTION-3

Laboratory Abnormality	OPDIVO (n=209)		Docetaxel or Paclitaxel (n=208)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased creatinine	78	0.5	68	0.5
Hyperglycemia	52	5	62	5
Hyponatremia	42	11	50	12
Increased AST	40	6	30	1.0
Increased alkaline phosphatase	33	4.8	24	1.0
Increased ALT	31	5	22	1.9
Hypercalcemia	22	6	14	2.9
Hyperkalemia	22	0.5	31	1.0
Hypoglycemia	14	1.4	14	0.5
Hypokalemia	11	2.9	13	3.4
Hematology				
Lymphopenia	46	19	72	43
Anemia	42	9	71	17
Leukopenia	11	0.5	79	45

[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 (209 patients) and Docetaxel or Paclitaxel group (range: 207 to 208 patients).

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

The safety of OPDIVO in combination with chemotherapy was evaluated in CHECKMATE-649, a randomized, multicenter, open-label trial in patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma *[see Clinical Studies (14.12)]*. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases. Patients were randomized to receive OPDIVO in combination with chemotherapy or chemotherapy. Patients received one of the following treatments:

- OPDIVO 240 mg in combination with mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or mFOLFOX6 every 2 weeks.
- OPDIVO 360 mg in combination with CapeOX (capecitabine and oxaliplatin) every 3 weeks or CapeOX every 3 weeks.

Patients were treated with OPDIVO in combination with chemotherapy or chemotherapy until disease progression, unacceptable toxicity, or up to 2 years. The median duration of exposure was 6.8 months (range: 0 to 33.5 months) in OPDIVO and chemotherapy-treated patients. Among patients who received OPDIVO and chemotherapy, 54% were exposed for >6 months and 28% were exposed for >1 year.

Fatal adverse reactions occurred in 16 (2.0%) patients who were treated with OPDIVO in combination with chemotherapy; these included pneumonitis (4 patients), febrile neutropenia (2 patients), stroke (2 patients), gastrointestinal toxicity, intestinal mucositis, septic shock, pneumonia, infection, gastrointestinal bleeding, mesenteric vessel thrombosis, and disseminated

intravascular coagulation. Serious adverse reactions occurred in 52% of patients treated with OPDIVO in combination with chemotherapy. OPDIVO and/or chemotherapy were discontinued in 44% of patients and at least one dose was withheld in 76% of patients due to an adverse reaction.

The most frequent serious adverse reactions reported in ≥2% of patients treated with OPDIVO in combination with chemotherapy were vomiting (3.7%), pneumonia (3.6%), anemia (3.6%), pyrexia (2.8%), diarrhea (2.7%), febrile neutropenia (2.6%), and pneumonitis (2.4%). The most common adverse reactions reported in ≥20% of patients treated with OPDIVO in combination with chemotherapy were peripheral neuropathy, nausea, fatigue, diarrhea, vomiting, decreased appetite, abdominal pain, constipation, and musculoskeletal pain.

Tables 37 and 38 summarize the adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-649.

Table 37: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Chemotherapy - CHECKMATE-649

Adverse Reaction	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	99	69	98	59
Nervous System				
Peripheral neuropathy[a]	53	7	46	4.8
Headache	11	0.8	6	0.3
Gastrointestinal				
Nausea	48	3.2	44	3.7
Diarrhea	39	5	34	3.7
Vomiting	31	4.2	29	4.2
Abdominal pain[b]	27	2.8	24	2.6
Constipation	25	0.6	21	0.4
Stomatitis[c]	17	1.8	13	0.8
General				
Fatigue[d]	44	7	40	5
Pyrexia[e]	19	1.0	11	0.4
Edema[f]	12	0.5	8	0.1
Metabolism and Nutrition				
Decreased appetite	29	3.6	26	2.5
Hypoalbuminemia[g]	14	0.3	9	0.3
Investigations				
Weight decreased	17	1.3	15	0.7
Increased lipase	14	7	8	3.7
Increased amylase	12	3.1	5	0.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[h]	20	1.3	14	2.0
Skin and Subcutaneous Tissue				
Rash[i]	18	1.7	4.4	0.1
Palmar-plantar erythrodysesthesia syndrome	13	1.5	12	0.8

Table 37: Adverse Reactions in ≥10% of Patients Receiving OPDIVO and Chemotherapy - CHECKMATE-649

Adverse Reaction	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Respiratory, Thoracic and Mediastinal				
Cough[j]	13	0.1	9	0
Infections and Infestations				
Upper respiratory tract infection[k]	10	0.1	7	0.1

Toxicity was graded per NCI CTCAE v4.

[a] Includes dysaesthesia, hypoaesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.

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

[c] Includes aphthous ulcer, mouth ulceration, and mucosal inflammation.

[d] Includes asthenia.

[e] Includes tumor associated fever.

[f] Includes swelling, generalized edema, edema peripheral, and peripheral swelling.

[g] Includes blood albumin decreased.

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

[i] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, nodular rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash vesicular.

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, and rhinitis.

Table 38: Laboratory Values Worsening from Baseline[a] Occurring in ≥10% of Patients - CHECKMATE-649

Laboratory Abnormality	OPDIVO and mFOLFOX6 or CapeOX (n=782)		mFOLFOX6 or CapeOX (n=767)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Neutropenia	73	29	62	23
Leukopenia	69	12	59	9
Thrombocytopenia	68	7	63	4.4
Anemia	59	14	60	10
Lymphopenia	59	12	49	9
Chemistry				
Increased AST	52	4.6	47	1.9
Hypocalcemia	42	1.6	37	1.0
Hyperglycemia	41	3.9	38	2.7
Increased ALT	37	3.4	30	1.9
Hyponatremia	34	6	24	5
Hypokalemia	27	7	24	4.8
Hyperbilirubinemia	24	2.8	21	2.0
Increased creatinine	15	1.0	9	0.5
Hyperkalemia	14	1.4	11	0.7
Hypoglycemia	12	0.7	9	0.2
Hypernatremia	11	0.5	7.1	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 mFOLFOX6 or CapeOX group (407 to 767 patients) or mFOLFOX6 or CapeOX group (range: 405 to 735 patients).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of 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, metastatic or recurrent non-small cell lung cancer, and malignant pleural mesothelioma 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) and 25.7% (69/269) with OPDIVO 3 mg/kg every 2 weeks and ipilimumab 1 mg every 6 weeks in non-small cell lung cancer and malignant pleural mesothelioma patients, respectively, 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) and 0.7% (2/269) with OPDIVO 3 mg/kg every 2 weeks and ipilimumab 1 mg every 6 weeks in non-small cell lung cancer and malignant pleural mesothelioma patients, respectively, 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 2 weeks and were evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 45% (20/44) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg and 56% (27/48) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg; the corresponding incidence of neutralizing antibodies against nivolumab was 14% (6/44) and 23% (11/48), respectively.

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

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

6.3 Postmarketing Experience

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

Eye: Vogt-Koyanagi-Harada (VKH) syndrome

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

Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis (HLH) (including fatal cases), autoimmune hemolytic anemia (including fatal cases)

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.

In ATTRACTION-3 (esophageal squamous cell carcinoma), 53% of patients were 65 years or older and 10% 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, and CHECKMATE-040 did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

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

Of the 550 patients randomized to OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg in CHECKMATE-214 (renal cell carcinoma), 38% were 65 years or older and 8% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients. In elderly patients with intermediate or poor risk, no overall difference in effectiveness was reported.

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

Of the 576 patients randomized to OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in CHECKMATE-227 (NSCLC), 48% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (29%) relative to all patients who received OPDIVO with ipilimumab (18%). Of the 396 patients in the primary efficacy population (PD-L1 ≥1%) randomized to OPDIVO 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks in CHECKMATE-227, the hazard ratio for overall survival was 0.70 (95% CI: 0.55, 0.89) in the 199 patients younger than 65 years compared to 0.91 (95% CI: 0.72, 1.15) in the 197 patients 65 years or older *[see Clinical Studies (14.3)]*.

Of the 361 patients randomized to OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in

the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

Of the 303 patients randomized to OPDIVO 3 mg/kg every 2 weeks in combination with ipilimumab 1 mg/kg every 6 weeks in CHECKMATE-743 (malignant pleural mesothelioma), 77% were 65 years old or older and 26% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (68% and 35%, respectively) relative to all patients who received OPDIVO with ipilimumab (54% and 28%, respectively). For patients aged 75 years or older who received chemotherapy, the rate of serious adverse reactions was 34% and the discontinuation rate due to adverse reactions was 26% relative to 28% and 19% respectively for all patients. The hazard ratio for overall survival was 0.76 (95% CI: 0.52, 1.11) in the 71 patients younger than 65 years compared to 0.74 (95% CI: 0.59, 0.93) in the 232 patients 65 years or older randomized to OPDIVO in combination with ipilimumab.

Of the 320 patients who received OPDIVO in combination with cabozantinib in CHECKMATE-9ER (renal cell carcinoma), 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

Of the 1581 patients randomized to OPDIVO 240 mg every 2 weeks or 360 mg every 3 weeks administered in combination with fluoropyrimidine- and platinum-containing chemotherapy in CHECKMATE-649 (GC, GEJC, or EAC), 39% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

11 DESCRIPTION

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

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

12.3 Pharmacokinetics

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent OPDIVO and OPDIVO with ipilimumab. The PK of nivolumab was studied in patients over a dose range of 0.1 mg/kg to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO as a 60-minute intravenous infusion every 2 or 3 weeks. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion. Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold.

Distribution

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

Elimination

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

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

Specific Populations

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

Drug Interaction Studies

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

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

administered alone and the CL of ipilimumab was unchanged compared to ipilimumab administered alone.

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

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

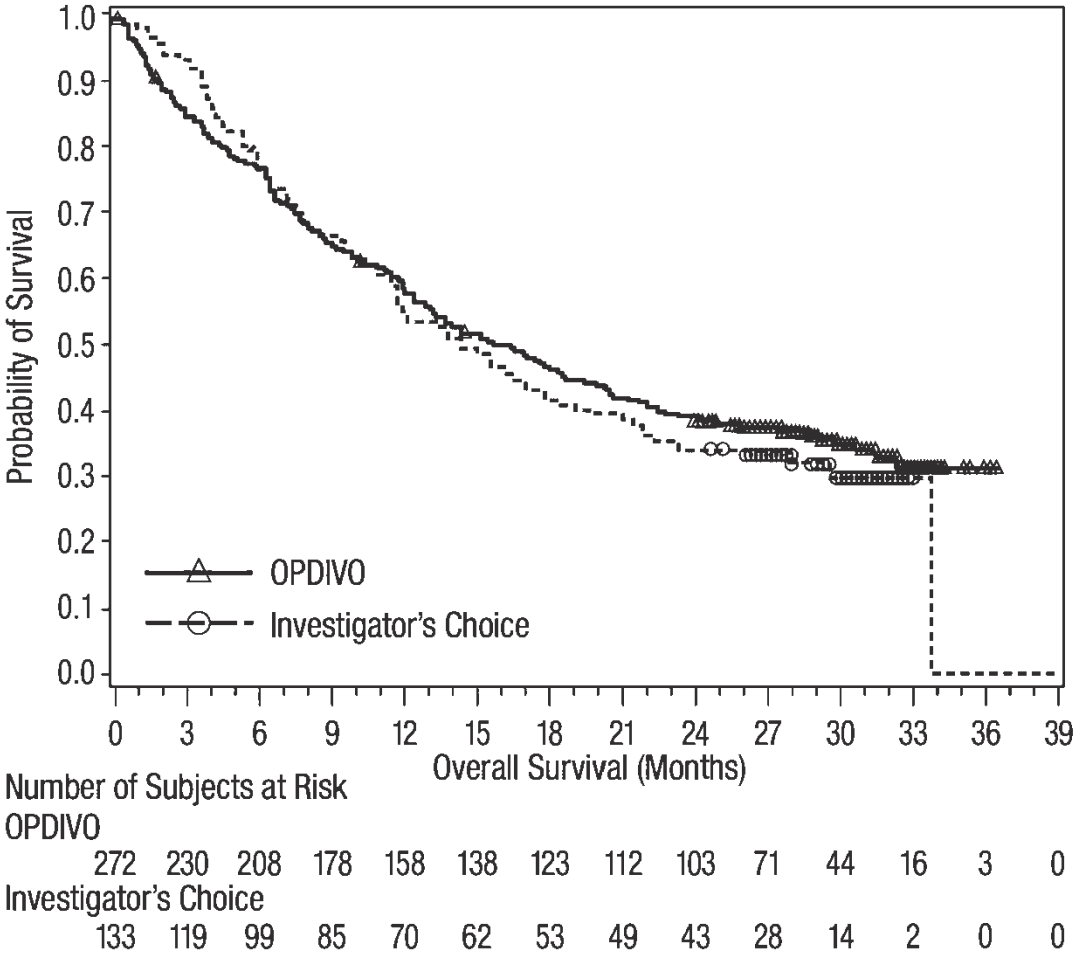
Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in CHECKMATE-037 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed overall response rate (ORR)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

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

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

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

Figure 1: Overall Survival - CHECKMATE-037*



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

Previously Untreated Metastatic Melanoma

CHECKMATE-066

CHECKMATE-066 (NCT01721772) was a multicenter, double-blind, randomized (1:1) trial in 418 patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m^2 intravenously every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (≥5% of tumor cell membrane staining by immunohistochemistry vs. <5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). Key eligibility criteria included histologically confirmed, unresectable or metastatic, cutaneous, mucosal, or acral melanoma; no prior therapy for metastatic disease; completion of prior adjuvant or neoadjuvant therapy at least 6 weeks prior to randomization; ECOG performance status 0 or 1; absence of autoimmune disease; and absence of active brain or leptomeningeal metastases. The trial excluded patients with ocular melanoma. Tumor

assessments were conducted 9 weeks after randomization then every 6 weeks for the first year and then every 12 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Additional outcome measures included investigator-assessed progression-free survival (PFS) and ORR per RECIST v1.1.

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

CHECKMATE-066 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. At the time of analysis, 88% (63/72) of OPDIVO-treated patients had ongoing responses, which included 43 patients with ongoing response of 6 months or longer. Efficacy results are shown in Table 39 and Figure 2.

Table 39: Efficacy Results - CHECKMATE-066

	OPDIVO (n=210)	**Dacarbazine (n=208)**
Overall Survival		
Deaths (%)	50 (24)	96 (46)
Median (months) (95% CI)	NR[a]	10.8 (9.3, 12.1)
Hazard ratio (95% CI)[b]	0.42 (0.30, 0.60)	
p-value[c,d]	<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)[b]	0.43 (0.34, 0.56)	
p-value[c,d]	<0.0001	
Overall Response Rate	34%	9%
(95% CI)	(28, 41)	(5, 13)
Complete response rate	4%	1%
Partial response rate	30%	8%

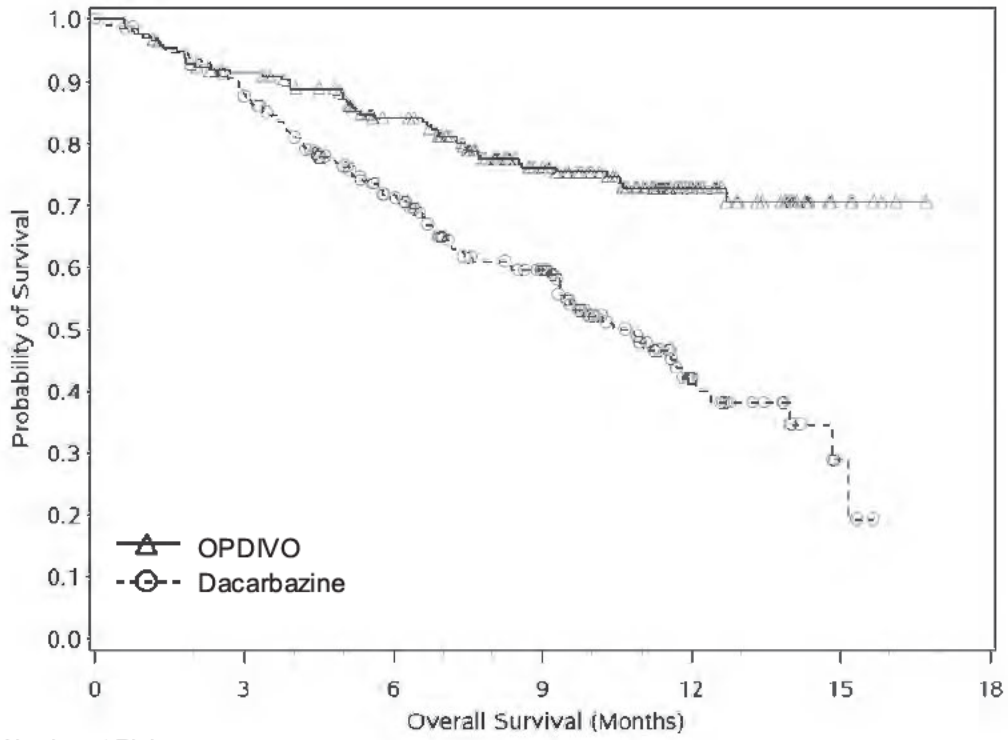
[a] Not Reached

[b] Based on a stratified proportional hazards model.

[c] Based on stratified log-rank test.

[d] 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%).

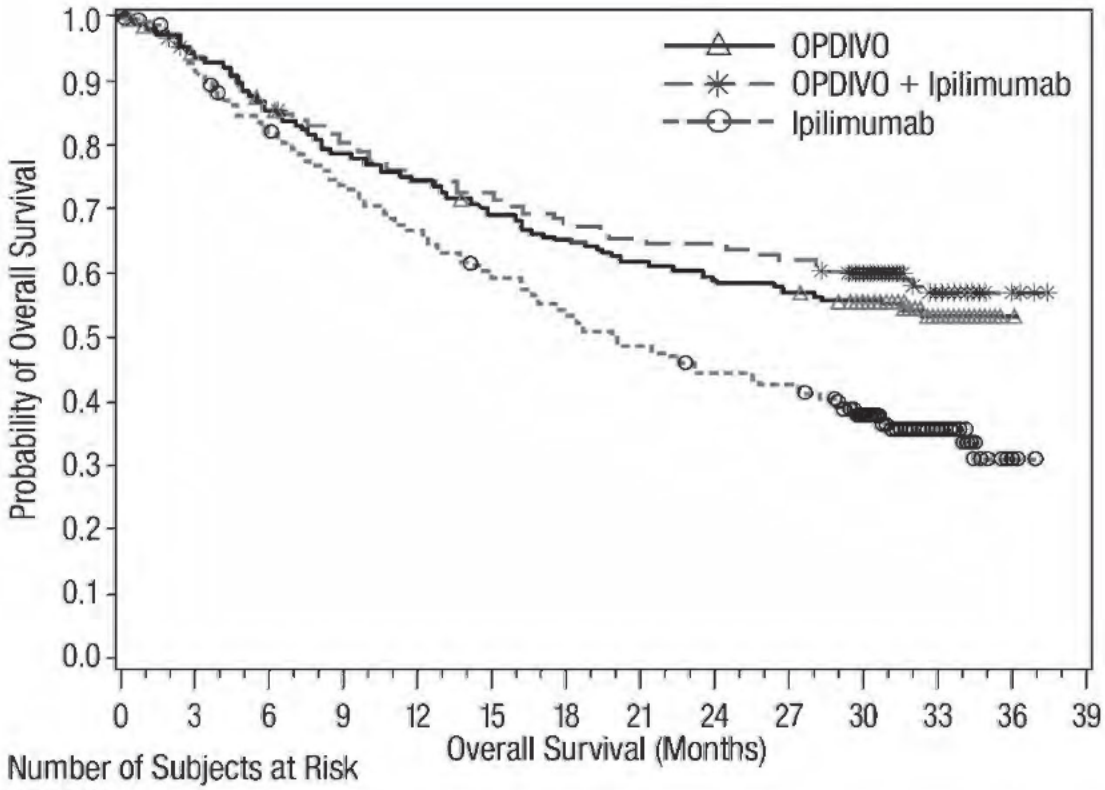
CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. The trial was not designed to assess whether adding ipilimumab to OPDIVO improves PFS or OS compared to OPDIVO as a single agent. Efficacy results are shown in Table 40 and Figure 3.

Table 40: 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 (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%).

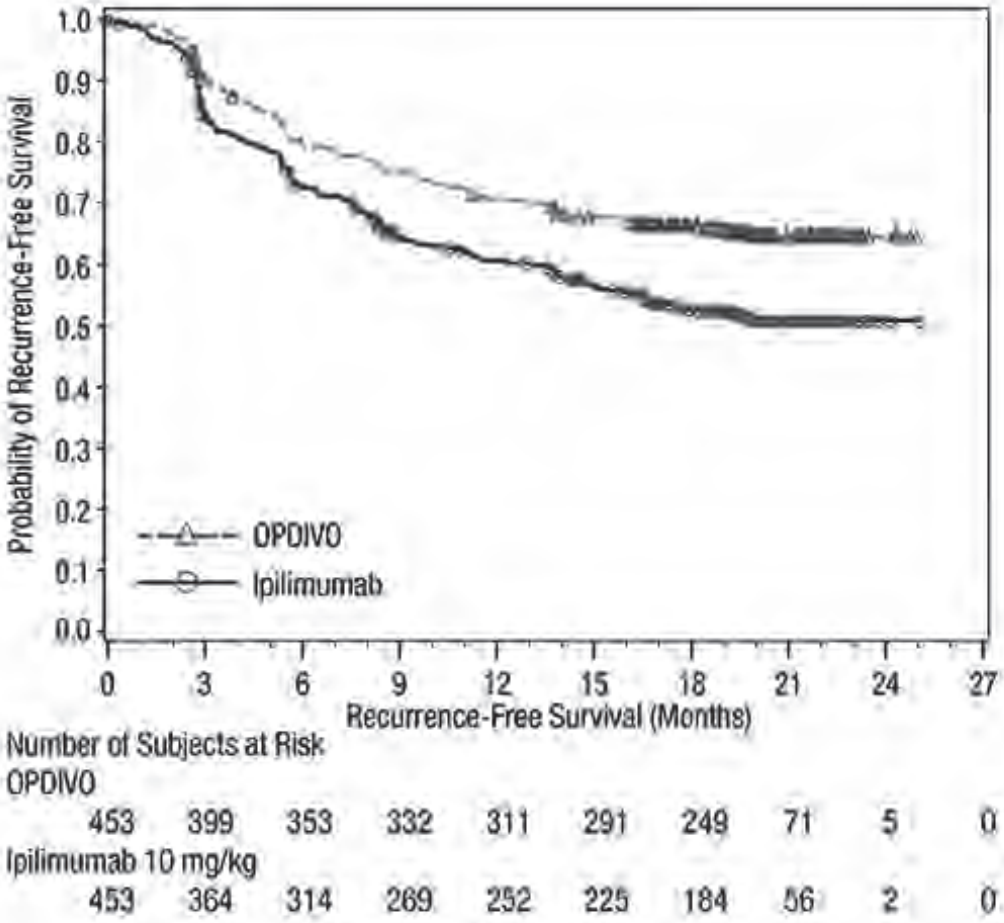
CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the ipilimumab 10 mg/kg arm. Efficacy results are shown in Table 41 and Figure 4.

Table 41: Efficacy Results - CHECKMATE-238

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

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

Figure 4: Recurrence-free Survival -CHECKMATE-238



14.3 Metastatic Non-Small Cell Lung Cancer

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

CHECKMATE-227 (NCT02477826) was a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC. The study included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer [ASLC] classification), ECOG performance status 0 or 1, and no prior anticancer therapy. Patients were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents.

Primary efficacy results were based on Part 1a of the study, which was limited to patients with PD-L1 tumor expression ≥1%. Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. Randomization was stratified by tumor

histology (non-squamous versus squamous). The evaluation of efficacy relied on the comparison between:

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

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

Study treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment continued beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue OPDIVO as a single agent. Tumor assessments were performed every 6 weeks from the first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued. The primary efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response as assessed by BICR.

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

The study demonstrated a statistically significant improvement in OS for PD-L1 ≥1% patients randomized to the OPDIVO and ipilimumab arm compared with the platinum-doublet chemotherapy arm. The OS results are presented in Table 42 and Figure 5.

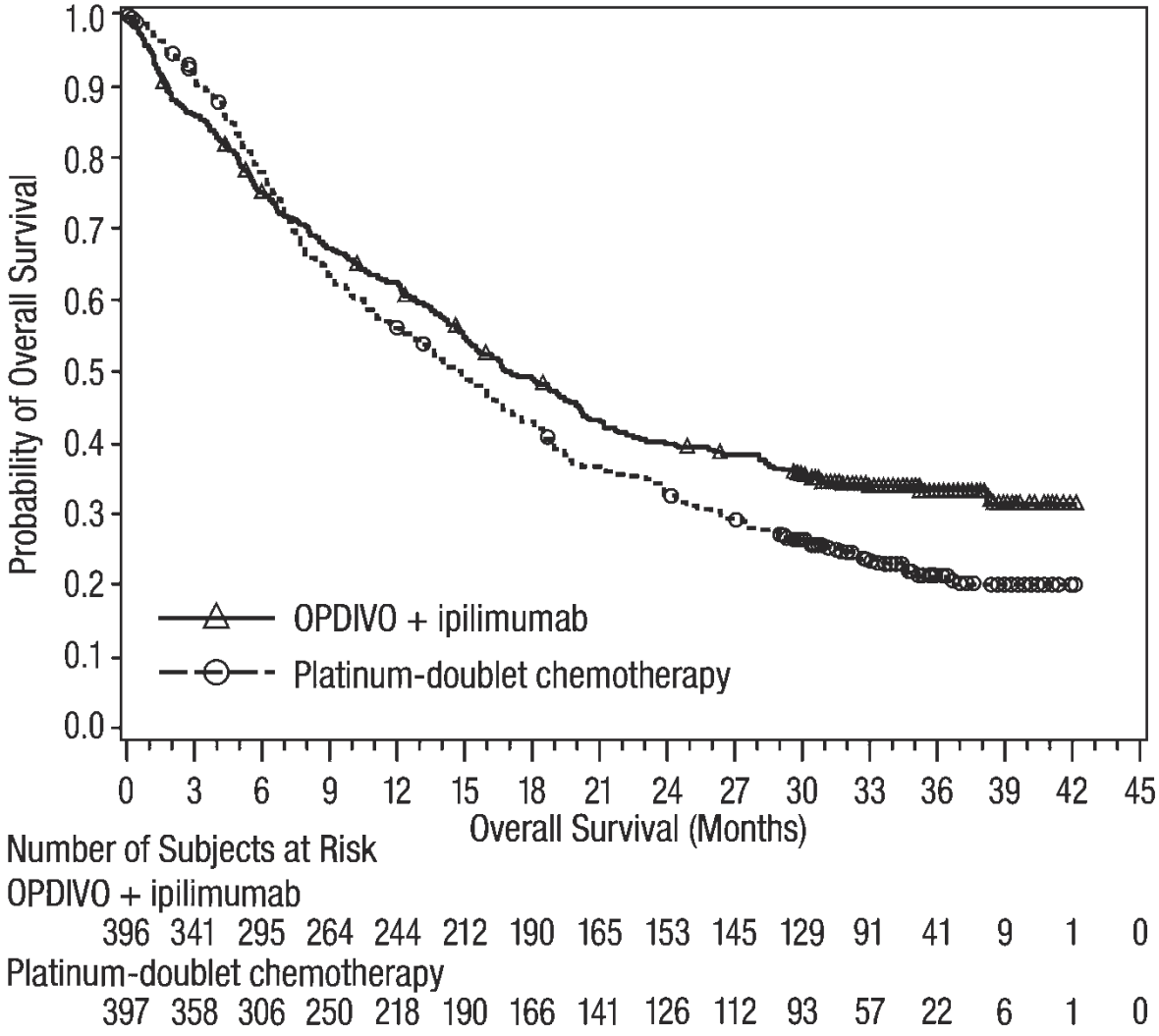
Table 42: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

	OPDIVO and Ipilimumab (n=396)	**Platinum-Doublet Chemotherapy (n=397)**
Overall Survival		
Events (%)	258 (65%)	298 (75%)
Median (months)[a] (95% CI)	17.1 (15, 20.1)	14.9 (12.7, 16.7)
Hazard ratio (95% CI)[b]	0.79 (0.67, 0.94)	
Stratified log-rank p-value	0.0066	

[a] Kaplan-Meier estimate.

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

Figure 5: Overall Survival (PD-L1 ≥1%) - CHECKMATE-227



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

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

CHECKMATE-9LA (NCT03215706) was a randomized, open-label trial in patients with metastatic or recurrent NSCLC. The trial included patients (18 years of age or older) with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification [IASLC]), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors) for metastatic disease. Patients

were enrolled regardless of their tumor PD-L1 status. Patients with known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with stable brain metastases were eligible for enrollment.

Patients were randomized 1:1 to receive either:

- OPDIVO 360 mg administered intravenously over 30 minutes every 3 weeks, ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks, and platinum-doublet chemotherapy administered intravenously every 3 weeks for 2 cycles, or
- platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

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

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

The study demonstrated a statistically significant benefit in OS, PFS, and ORR. Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) are presented in Table 43.

Table 43: Efficacy Results - CHECKMATE-9LA

	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=361)	Platinum-Doublet Chemotherapy (n=358)
Overall Survival		
Events (%)	156 (43.2)	195 (54.5)
Median (months) (95% CI)	14.1 (13.2, 16.2)	10.7 (9.5, 12.5)
Hazard ratio (96.71% CI)[a]	0.69 (0.55, 0.87)	
Stratified log-rank p-value[b]	0.0006	
Progression-free Survival per BICR		
Events (%)	232 (64.3)	249 (69.6)
Hazard ratio (97.48% CI)[a]	0.70 (0.57, 0.86)	
Stratified log-rank p-value[c]	0.0001	
Median (months)[d] (95% CI)	6.8 (5.6, 7.7)	5.0 (4.3, 5.6)
Overall Response Rate per BICR (%)	38	25
(95% CI)[e]	(33, 43)	(21, 30)
Stratified CMH test p-value[f]	0.0003	
Duration of Response per BICR		
Median (months) (95% CI)[d]	10.0 (8.2, 13.0)	5.1 (4.3, 7.0)

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

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

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

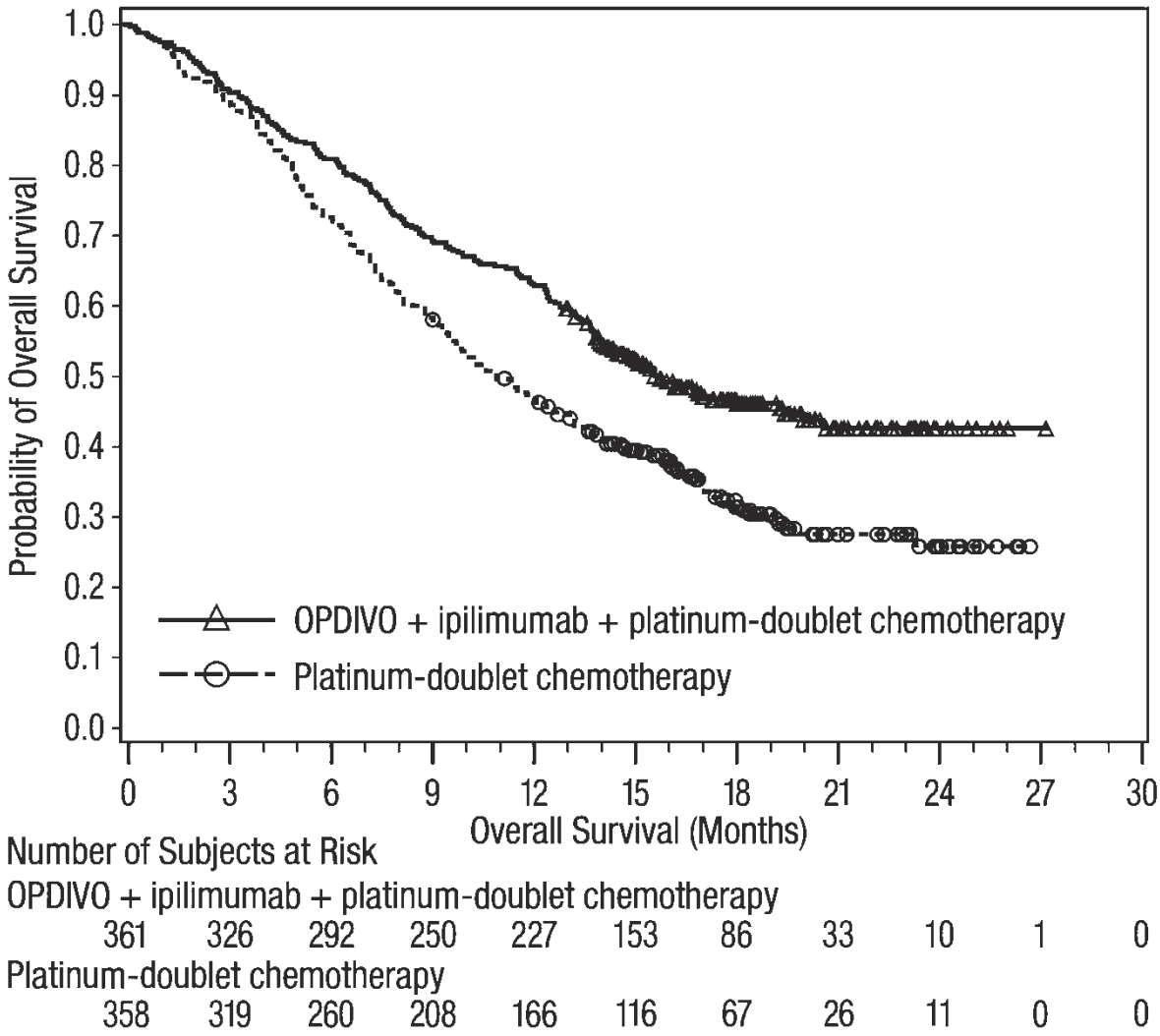
[d] Kaplan-Meier estimate.

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

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

With an additional 4.6 months of follow-up, the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients receiving OPDIVO and ipilimumab and platinum-doublet chemotherapy or platinum-doublet chemotherapy, respectively (Figure 6).

Figure 6: Overall Survival - CHECKMATE-9LA



Second-line Treatment of Metastatic Squamous NSCLC

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

assessed ORR and PFS.

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

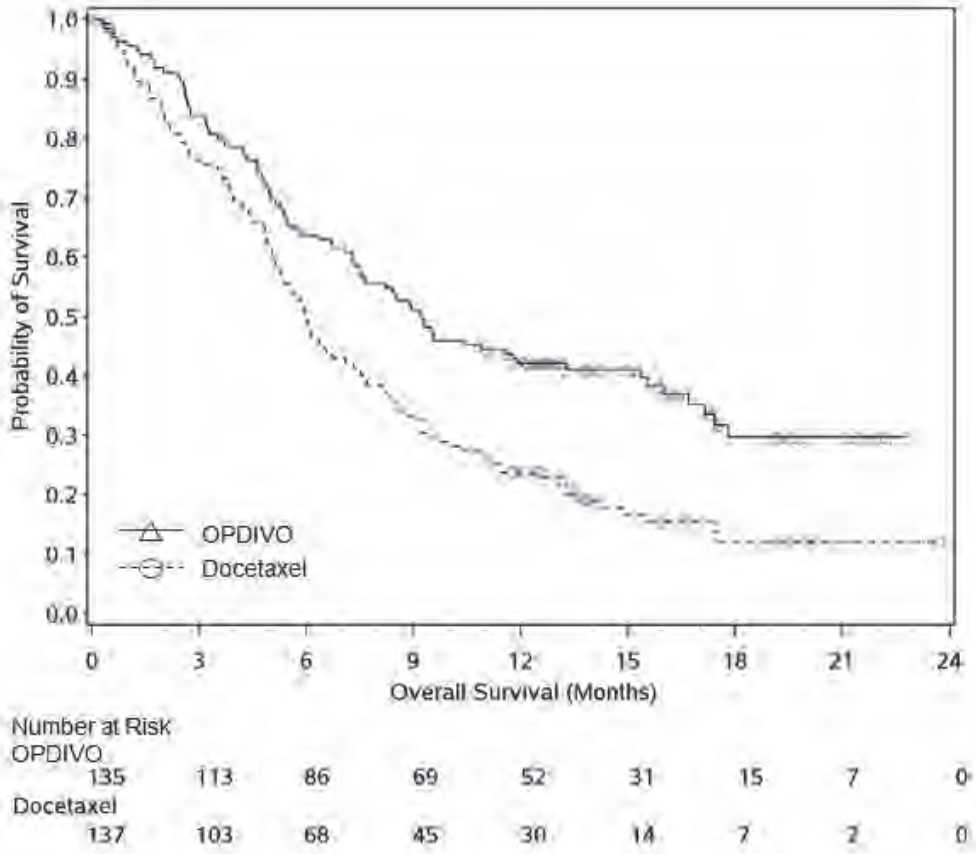
The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 199 events were observed (86% of the planned number of events for final analysis). Efficacy results are shown in Table 44 and Figure 7.

Table 44: 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[e] (9.8, NR[e])	8.4 (3.6, 10.8)
Progression-free Survival		
Disease progression or death (%)	105 (78%)	122 (89%)
Median (months)	3.5	2.8
Hazard ratio (95% CI)[a]	0.62 (0.47, 0.81)	
p-value[b]	0.0004	

[a] Based on a stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with .0315 of the allocated alpha for this interim analysis.
[d] Based on the stratified Cochran-Mantel-Haenszel test.
[e] Not Reached

Figure 7: Overall Survival - CHECKMATE-017



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

Second-line Treatment of Metastatic Non-Squamous NSCLC

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

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

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

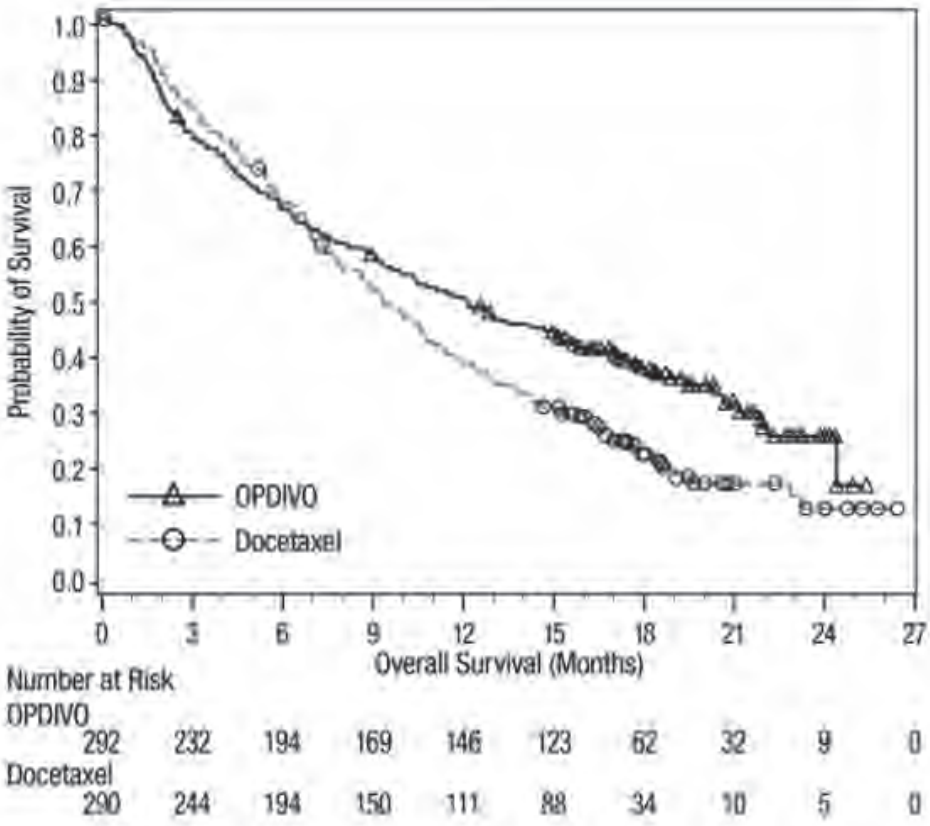
CHECKMATE-057 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 45 and Figure 8.

Table 45: 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[e])	6 (4.4, 7.0)
Progression-free Survival		
Disease progression or death (%)	234 (80%)	245 (84%)
Median (months)	2.3	4.2
Hazard ratio (95% CI)[a]	0.92 (0.77, 1.11)	
p-value[b]	0.39	

[a] Based on a stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with .0408 of the allocated alpha for this interim analysis.
[d] Based on the stratified Cochran-Mantel-Haenszel test.
[e] Not Reached.

Figure 8: Overall Survival - CHECKMATE-057



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

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

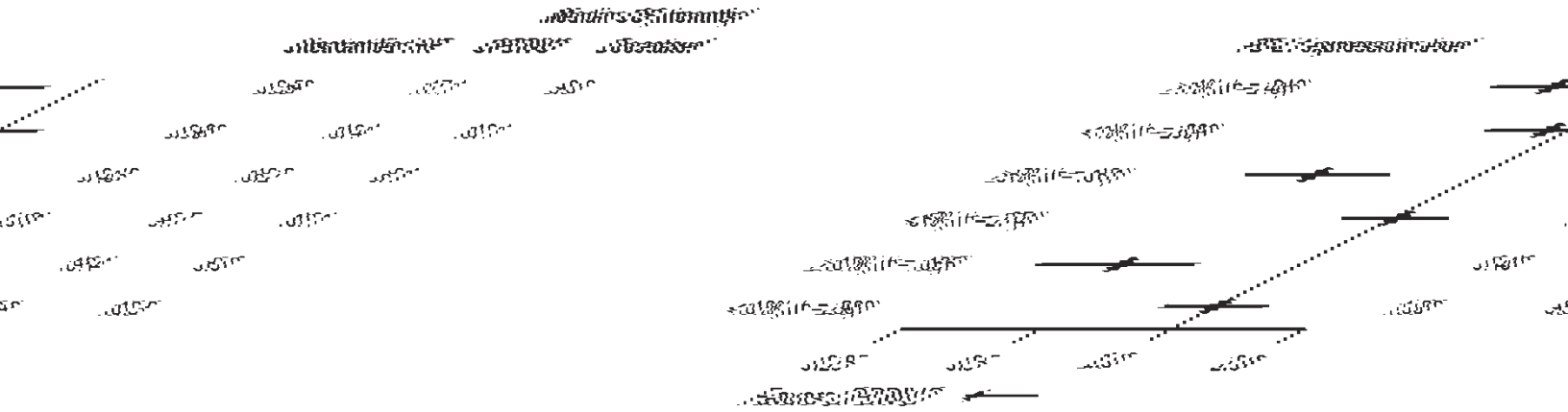
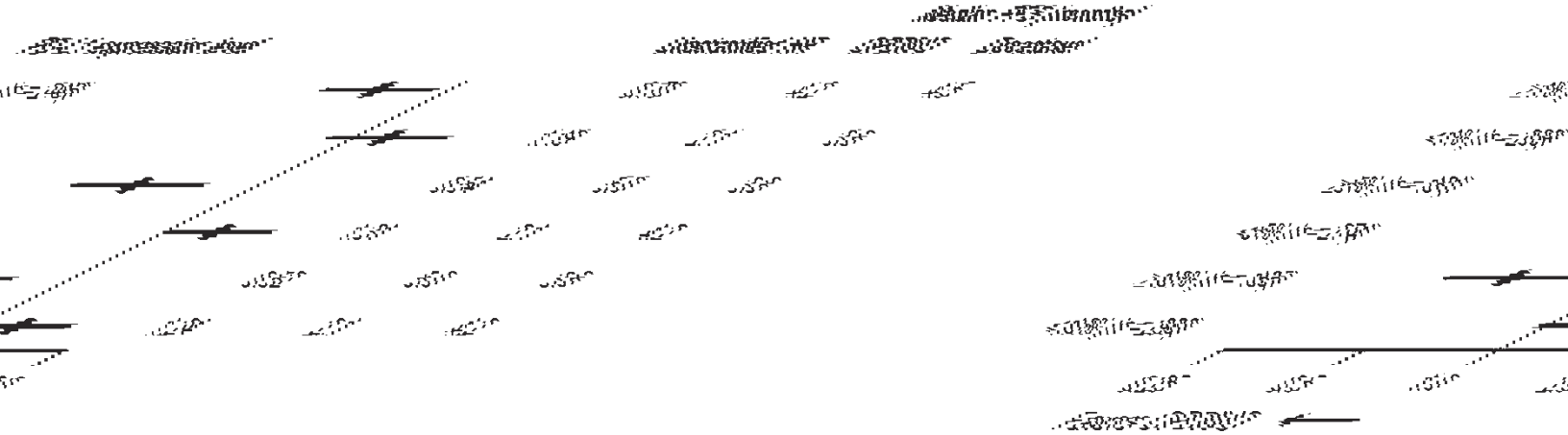


Figure 10: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



14.4 Malignant Pleural Mesothelioma

CHECKMATE-743 (NCT02899299) was a randomized, open-label trial in patients with unresectable malignant pleural mesothelioma. The trial included patients with histologically confirmed and previously untreated malignant pleural mesothelioma with no palliative radiotherapy within 14 days of initiation of therapy. Patients with interstitial lung disease, active autoimmune disease, medical conditions requiring systemic immunosuppression, or active brain metastasis were excluded from the trial.

Patients were randomized 1:1 to receive either:

- OPDIVO 3 mg/kg over 30 minutes by intravenous infusion every 2 weeks and ipilimumab 1 mg/kg over 30 minutes by intravenous infusion every 6 weeks for up to 2 years, or
- cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2, or carboplatin 5 AUC and pemetrexed 500 mg/m^2 administered every 3 weeks for 6 cycles.

Stratification factors for randomization were tumor histology (epithelioid vs. sarcomatoid or mixed histology subtypes) and sex (male vs. female). Study treatment continued for up to 2 years, or until disease progression or unacceptable toxicity. Patients who discontinued combination therapy because of an adverse reaction attributed to ipilimumab were permitted to continue OPDIVO as a single agent. Treatment could continue beyond disease progression if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator. 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 utilizing modified RECIST criteria.

A total of 605 patients were randomized to receive either OPDIVO in combination with ipilimumab (n=303) or chemotherapy (n=302). The median age was 69 years (range: 25 to 89), with 72% of patients ≥65 years and 26% ≥75 years; 85% were White, 11% were Asian, and 77% were male. Baseline ECOG performance status was 0 (40%) or 1 (60%), 35% had Stage III and 51% had Stage IV disease, 75% had epithelioid and 25% had non-epithelioid histology, 75% had tumors with PD-L1 expression ≥1%, and 22% had tumors with PD-L1 expression <1%.

The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO in combination with ipilimumab compared to chemotherapy. Efficacy results from the prespecified interim analysis are presented in Table 46 and Figure 11.

Table 46: Efficacy Results - CHECKMATE-743

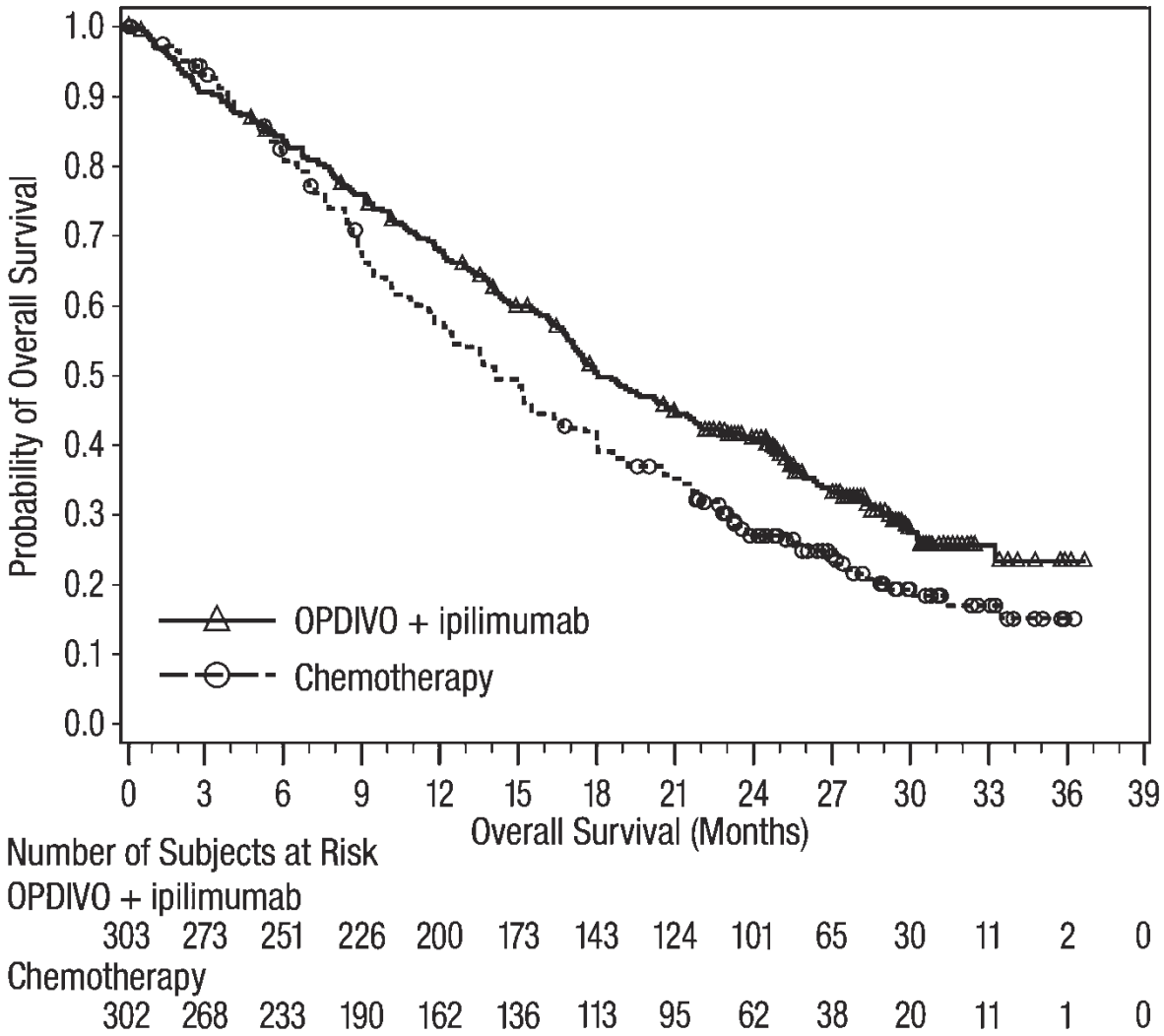
	OPDIVO and Ipilimumab (n=303)	**Chemotherapy (n=302)**
Overall Survival[a]		
Events (%)	200 (66)	219 (73)
Median (months)[b] (95% CI)	18.1 (16.8, 21.5)	14.1 (12.5, 16.2)
Hazard ratio (95% CI)[c]	0.74 (0.61, 0.89)	
Stratified log-rank p-value[d]	0.002	
Progression-free Survival		
Events (%)	218 (72)	209 (69)
Hazard ratio (95% CI)[c]	1.0 (0.82, 1.21)	
Median (months)[b] (95% CI)	6.8 (5.6, 7.4)	7.2 (6.9, 8.1)
Overall Response Rate[e]	40%	43%
(95% CI)	(34, 45)	(37, 49)
Duration of Response		

Table 46: Efficacy Results - CHECKMATE-743

	OPDIVO and Ipilimumab (n=303)	Chemotherapy (n=302)
Median (months)[b]	11.0	6.7
(95% CI)	(8.1, 16.5)	(5.3, 7.1)

[a] At the time of the interim analysis, 419 deaths (89% of the deaths needed for the final analysis) had occurred.
[b] Kaplan-Meier estimate.
[c] Stratified Cox proportional hazard model.
[d] p-value is compared with the allocated alpha of 0.0345 for this interim analysis.
[e] Based on confirmed response by BICR.

Figure 11: Overall Survival - CHECKMATE-743



In a prespecified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology, the hazard ratio (HR) for OS was 0.85 (95% CI: 0.68, 1.06), with median OS of 18.7 months in the OPDIVO and ipilimumab arm and 16.2 months in the chemotherapy

arm. In the subgroup of patients with non-epithelioid histology, the HR for OS was 0.46 (95% CI: 0.31, 0.70), with median OS of 16.9 months in the OPDIVO and ipilimumab arm and 8.8 months in the chemotherapy arm.

14.5 Advanced Renal Cell Carcinoma

First-line Renal Cell Carcinoma

CHECKMATE-214

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 47 and Figure 12). OS benefit was observed regardless of PD-L1 expression level. The trial did not demonstrate a statistically significant improvement in PFS. Efficacy results are shown in Table 47 and Figure 12.

Table 47: Efficacy Results - CHECKMATE-214

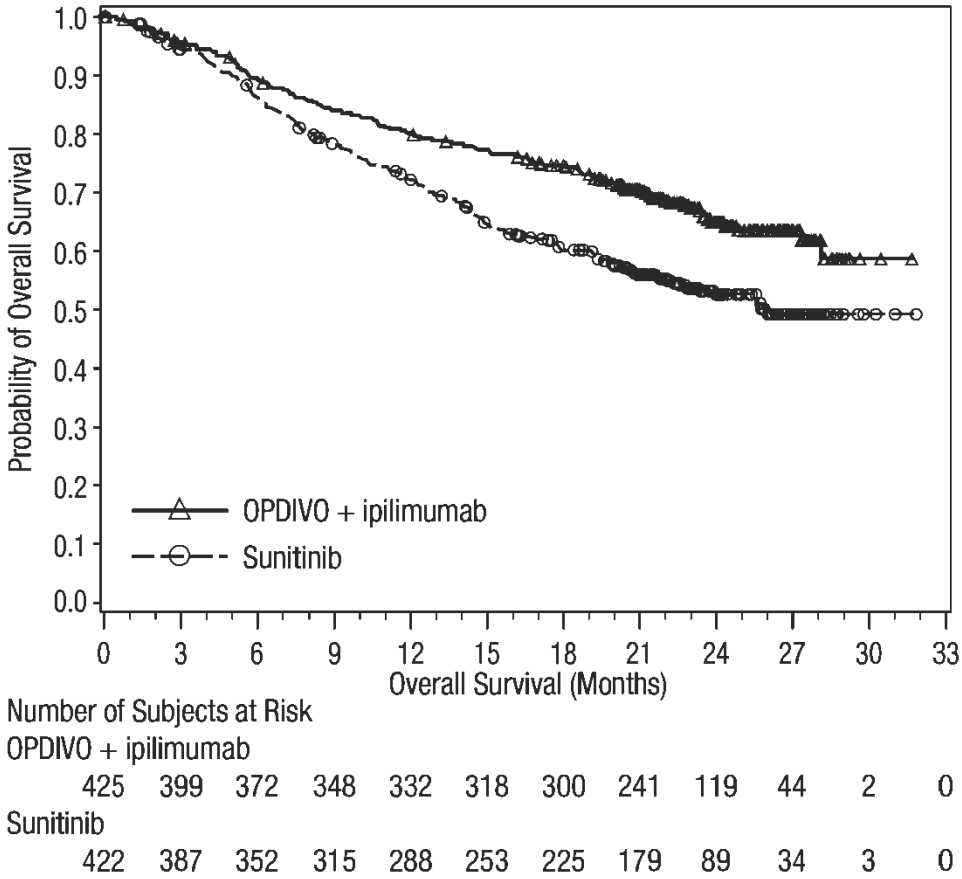
	Intermediate/Poor-Risk	
	OPDIVO and Ipilimumab (n=425)	**Sunitinib (n=422)**
Overall Survival		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (months)	NR[a]	25.9
Hazard ratio (99.8% CI)[b]	0.63 (0.44, 0.89)	
p-value[c,d]	<0.0001	
Confirmed Overall Response Rate (95% CI)	41.6% (36.9, 46.5)	26.5% (22.4, 31.0)
p-value[e,f]	<0.0001	
Complete response (CR)	40 (9.4)	5 (1.2)

Table 47: Efficacy Results - CHECKMATE-214

	Intermediate/Poor-Risk	
	OPDIVO and Ipilimumab (n=425)	**Sunitinib (n=422)**
Partial response (PR)	137 (32.2)	107 (25.4)
Median duration of response (months) (95% CI)	NR[a] (21.8, NR[a])	18.2 (14.8, NR[a])
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[c]	NS[g]	

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

Figure 12: 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.

CHECKMATE-9ER

CHECKMATE-9ER (NCT03141177) was a randomized, open-label study of OPDIVO combined with cabozantinib versus sunitinib in patients with previously untreated advanced RCC. CHECKMATE-9ER excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression. Patients were stratified by IMDC prognostic score (favorable vs. intermediate vs. poor), PD-L1 tumor expression (≥1% vs. <1% or indeterminate), and region (US/Canada/Western Europe/Northern Europe vs. Rest of World).

Patients were randomized to OPDIVO 240 mg intravenously every 2 weeks and cabozantinib 40 mg orally daily (n=323), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328). Treatment continued until disease progression per RECIST v1.1 or unacceptable toxicity. Treatment beyond RECIST-defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter.

The trial population characteristics were: median age 61 years (range: 28 to 90) with 38% ≥65 years of age and 10% ≥75 years of age. The majority of patients were male (74%) and White (82%) and 23% and 77% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. Patient distribution by IMDC risk categories was 22% favorable, 58% intermediate, and 20% poor.

The major efficacy outcome measure was PFS (BICR assessed). Additional efficacy outcome measures were OS and ORR (BICR assessed). The trial demonstrated a statistically significant improvement in PFS, OS, and ORR for patients randomized to OPDIVO and cabozantinib compared with sunitinib. Consistent results for PFS were observed across pre-specified subgroups of IMDC risk categories and PD-L1 tumor expression status. Efficacy results are shown in Table 48 and Figures 13 and 14.

Table 48: Efficacy Results - CHECKMATE-9ER

	OPDIVO and Cabozantinib (n=323)	**Sunitinib (n=328)**
Progression-free Survival		
Disease progression or death (%)	144 (45)	191 (58)
Median PFS (months)[a] (95% CI)	16.6 (12.5, 24.9)	8.3 (7.0, 9.7)
Hazard ratio (95% CI)[b]	0.51 (0.41, 0.64)	
p-value[c,d]	<0.0001	
Overall Survival		
Deaths (%)	67 (21)	99 (30)
Median OS (months)[a] (95% CI)	NR[e]	NR (22.6, NR[e])
Hazard ratio (98.89% CI)[b]	0.60 (0.40, 0.89)	
p-value[c,d,f]	0.0010	

Table 48: Efficacy Results - CHECKMATE-9ER

	OPDIVO and Cabozantinib (n=323)	Sunitinib (n=328)
Confirmed Objective Response Rate (95% CI)[g]	55.7% (50.1, 61.2)	27.1% (22.4, 32.3)
p-value[h]	<0.0001	
Complete Response	26 (8%)	15 (4.6%)
Partial Response	154 (48%)	74 (23%)
Median duration of response in months (95% CI)[a]	20.2 (17.3, NR[e])	11.5 (8.3, 18.4)

[a] Based on Kaplan-Meier estimates.
[b] Stratified Cox proportional hazards model.
[c] Based on stratified log-rank test
[d] 2-sided p-values from stratified log-rank test.
[e] Not Reached
[f] p-value is compared with the allocated alpha of 0.0111 for this interim analysis
[g] CI based on the Clopper-Pearson method.
[h] 2-sided p-value from Cochran-Mantel-Haenszel test.

Figure 13: Progression-free Survival - CHECKMATE-9ER

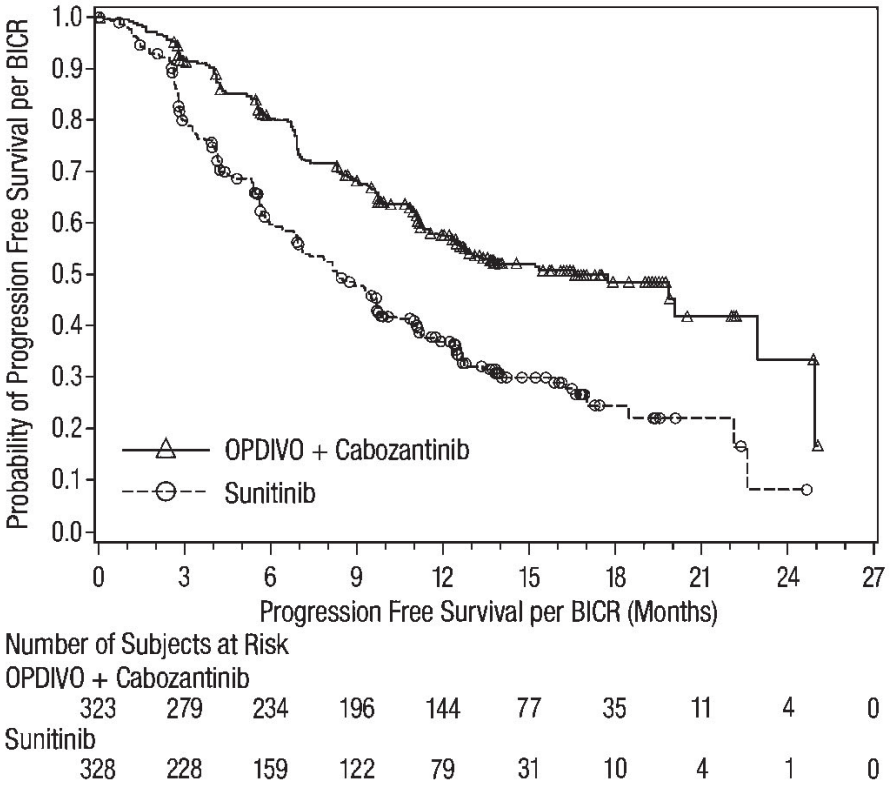
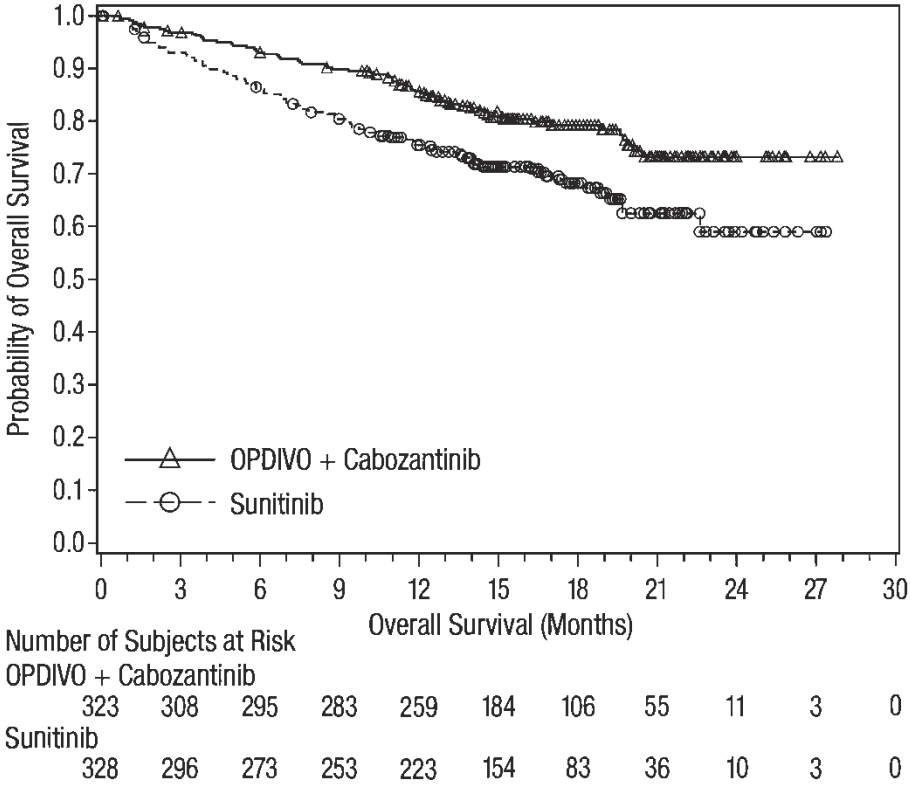


Figure 14: Overall Survival - CHECKMATE-9ER



Previously Treated Renal Cell Carcinoma

CHECKMATE-025

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 49 and Figure 15.

Table 49: Efficacy Results - CHECKMATE-025

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

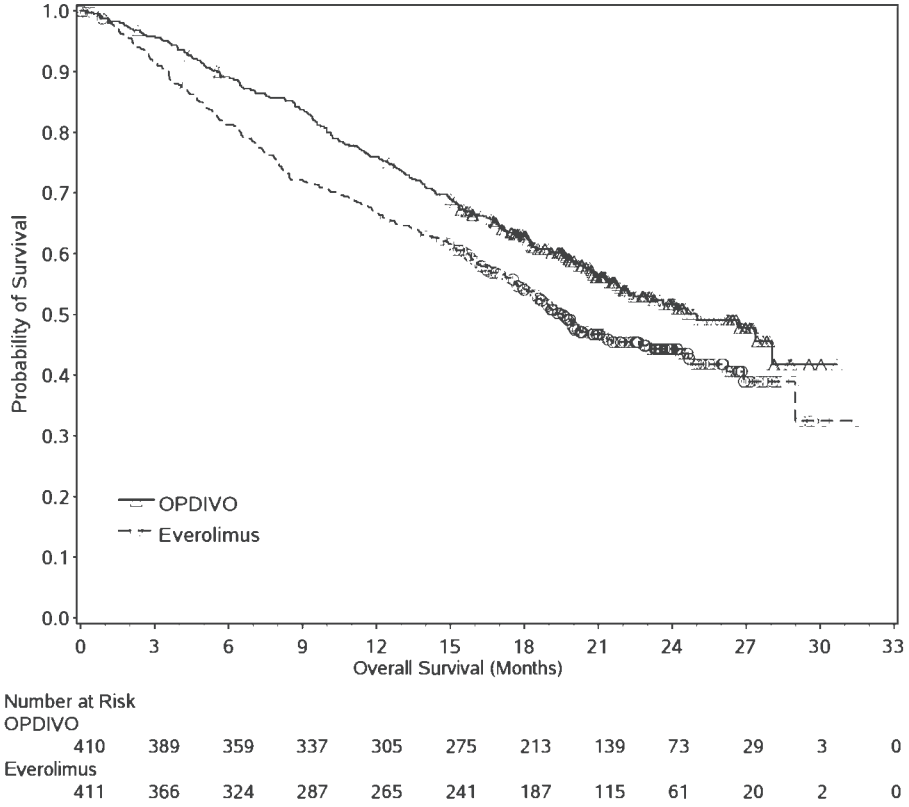
[a] Not Reached

[b] Based on a stratified proportional hazards model.

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

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

Figure 15: Overall Survival - CHECKMATE-025



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 50.

Table 50: 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, NR[d])
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.
[d] Not Reached

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 51.

Table 51: 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]	NR[c]
(95% CI)	(12.0, NR[c])
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.

[c] 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 the OPDIVO arm and 121 patients to the investigator's choice arm (docetaxel: 45%; methotrexate: 43%; and cetuximab: 12%). 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.

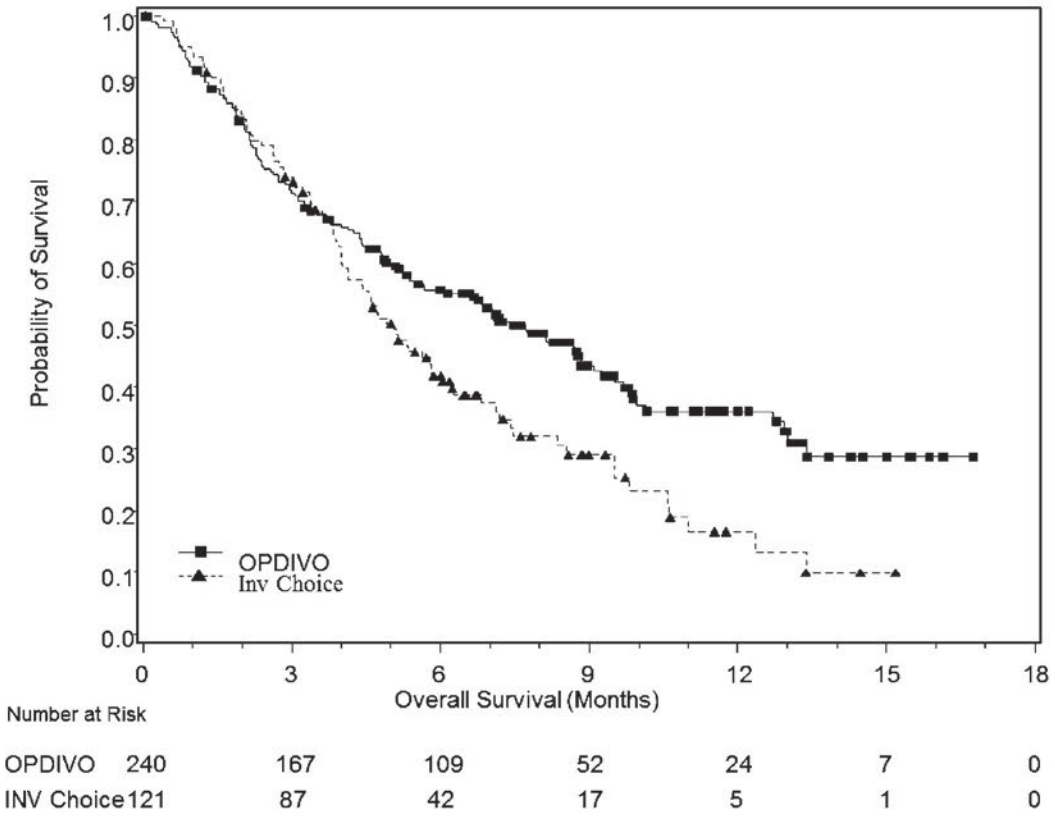
The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). There were no statistically significant differences between the two 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 52 and Figure 16.

Table 52: Overall Survival - CHECKMATE-141

	OPDIVO (n=240)	**Cetuximab, Methotrexate or Docetaxel (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 16: 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 53. 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 53: 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+)	NR[b] (1.9+, 12.0+)

[a] Estimated from the Kaplan-Meier Curve
[b] Not Reached

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 BICR 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 54.

Table 54: Efficacy Results - CHECKMATE-142

	OPDIVO[a] MSI-H/dMMR Cohort		OPDIVO and Ipilimumab[b] 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)**
Overall Response Rate per BICR; n (%)	28 (38%)	17 (32%)	71 (60%)	46 (56%)
(95% CI)[c]	(27, 50)	(20, 46)	(50, 69)	(45, 67)
Complete Response (%)	8 (11%)	5 (9%)	17 (14%)	11 (13%)
Partial Response (%)	20 (27%)	12 (23%)	54 (45%)	35 (43%)
Duration of Response				
Proportion of responders with ≥6 months response duration	86%	94%	89%	87%
Proportion of responders with ≥12 months response duration	82%	88%	77%	74%

[a] Minimum follow-up 33.7 months for all patients treated with OPDIVO (n=74).

[b] Minimum follow-up 27.5 months for all patients treated with OPDIVO and ipilimumab (n=119).

[c] Estimated using the Clopper-Pearson method.

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 55. 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 55: 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.

14.11 Esophageal Squamous Cell Cancer

ATTRACTION-3 (NCT02569242) was a multicenter, randomized (1:1), active-controlled, open-label trial in patients with unresectable advanced, recurrent, or metastatic ESCC, who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen. The trial enrolled patients regardless of PD-L1 status, but tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were refractory or intolerant to taxane therapy, had brain metastases that were symptomatic or required treatment, had autoimmune disease, used systemic corticosteroids or immunosuppressants, or had apparent tumor invasion of organs adjacent to the esophageal tumor or had stents in the esophagus or respiratory tract. Patients were randomized to receive OPDIVO 240 mg by intravenous infusion over 30 minutes every 2 weeks or investigator's choice of taxane chemotherapy consisting of docetaxel (75 mg/m^2 intravenously every 3 weeks) or paclitaxel (100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off).

Randomization was stratified by region (Japan vs. Rest of World), number of organs with metastases (≤1 vs. ≥2), and PD-L1 status (≥1% vs. <1% or indeterminate). Patients were treated until disease progression, assessed by the investigator per RECIST v1.1, or unacceptable toxicity. The tumor assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were ORR and PFS as assessed by the investigator using RECIST v1.1 and DOR.

A total of 419 patients were randomized; 210 to the OPDIVO arm and 209 to the investigator's choice arm (docetaxel: 31%, paclitaxel: 69%). The trial population characteristics were: median age 65 years (range: 33 to 87), 53% were ≥65 years of age, 87% were male, 96% were Asian

and 4% were White. Sixty-seven percent of patients had received one prior systemic therapy regimen and 26% had received two prior systemic therapy regimens prior to enrolling in ATTRACTION-3. Baseline ECOG performance status was 0 (50%) or 1 (50%).

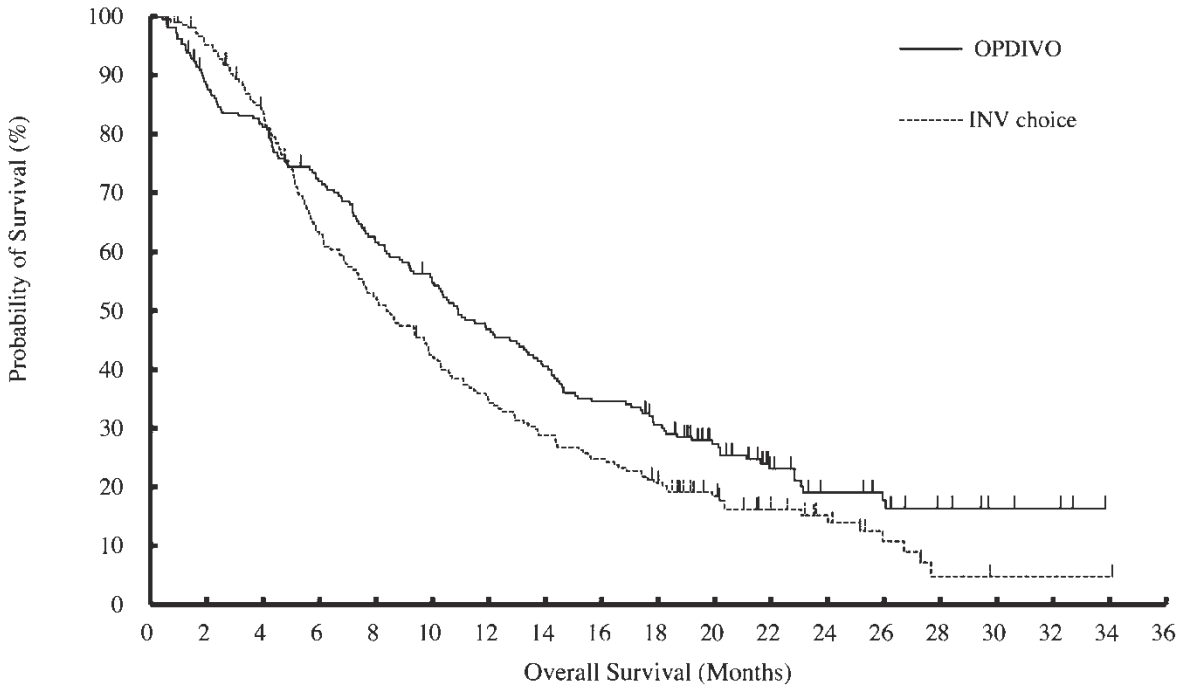
ATTRACTION-3 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice of taxane chemotherapy. OS benefit was observed regardless of PD-L1 expression level. The minimum follow-up was 17.6 months. Efficacy results are shown in Table 56 and Figure 17.

Table 56: Efficacy Results - ATTRACTION-3

	OPDIVO (n=210)	**Docetaxel or Paclitaxel (n=209)**
Overall Survival[a]		
Deaths (%)	160 (76%)	173 (83%)
Median (months) (95% CI)	10.9 (9.2, 13.3)	8.4 (7.2, 9.9)
Hazard ratio (95% CI)[b]	0.77 (0.62, 0.96)	
p-value[c]	0.0189	
Overall Response Rate[d]	33 (19.3)	34 (21.5)
(95% CI)	(13.7, 26.0)	(15.4, 28.8)
Complete response (%)	1 (0.6)	2 (1.3)
Partial response (%)	32 (18.7)	32 (20.3)
Median duration of response (months) (95% CI)	6.9 (5.4, 11.1)	3.9 (2.8, 4.2)
p-value[e]	0.6323	
Progression-free Survival[a, f]		
Disease progression or death (%)	187 (89)	176 (84)
Median (months) (95% CI)	1.7 (1.5, 2.7)	3.4 (3.0, 4.2)
Hazard ratio (95% CI)[b]	1.1 (0.9, 1.3)	

[a] Based on ITT analysis
[b] Based on a stratified proportional hazards model.
[c] Based on a stratified log-rank test.
[d] Based on Response Evaluable Set (RES) analysis, n=171 in OPDIVO group and n=158 in investigator's choice group.
[e] Based on stratified Cochran-Mantel-Haenszel test; p-value not significant.
[f] PFS not tested due to pre-specified hierarchical testing strategy.

Figure 17: Overall Survival - ATTRACTION-3



Number at Risk

OPDIVO	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
INV choice	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

Of the 419 patients, 48% had PD-L1 positive ESCC, defined as ≥1% of tumor cells expressing PD-L1. The remaining 52% had PD-L1 negative ESCC defined as <1% of tumor cells expressing PD-L1.

In a pre-specified exploratory analysis by PD-L1 status, the hazard ratio (HR) for OS was 0.69 (95% CI: 0.51, 0.94) with median survivals of 10.9 and 8.1 months for the OPDIVO and investigator's choice arms, respectively, in the PD-L1 positive subgroup. In the PD-L1 negative subgroup, the HR for OS was 0.84 (95% CI: 0.62, 1.14) with median survivals of 10.9 and 9.3 months for the OPDIVO and investigator's choice arms, respectively.

14.12 Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

CHECKMATE-649 (NCT02872116) was a randomized, multicenter, open-label trial in patients (n=1581) with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.The trial enrolled patients regardless of PD-L1 status, and tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory. The trial excluded patients who were known human epidermal growth factor receptor 2 (HER2) positive, or had untreated CNS metastases. Patients were randomized to receive OPDIVO in combination with chemotherapy (n=789) or chemotherapy (n=792). Patients received one of the following treatments:

- OPDIVO 240 mg in combination with mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) every 2 weeks or mFOLFOX6 every 2 weeks.
- OPDIVO 360 mg in combination with CapeOX (capecitabine and oxaliplatin) every 3 weeks or CapeOX every 3 weeks.

Patients were treated until disease progression, unacceptable toxicity, or up to 2 years. In patients who received OPDIVO in combination with chemotherapy and in whom chemotherapy was discontinued, OPDIVO monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks up to 2 years after treatment initiation.

Randomization was stratified by tumor cell PD-L1 status (≥1% vs. <1% or indeterminate), region (Asia vs. US vs. Rest of World), ECOG performance status (0 vs. 1), and chemotherapy regimen (mFOLFOX6 vs. CapeOX). The major efficacy outcome measures, assessed in patients with PD-L1 CPS ≥5, were PFS assessed by BICR and OS. Additional efficacy outcome measures included OS and PFS in patients with PD-L1 CPS ≥1 and in all randomized patients, and ORR and DOR as assessed by BICR in patients with PD-L1 CPS ≥1 and ≥5, and in all randomized patients. Tumor assessments were conducted per RECIST v1.1 every 6 weeks up to and including week 48, then every 12 weeks thereafter.

The trial population characteristics were: median age 61 years (range: 18 to 90), 39% were ≥65 years of age, 70% were male, 24% were Asian, and 69% were White, and 1% were Black. Baseline ECOG performance status was 0 (42%) or 1 (58%). Seventy percent of patients had adenocarcinoma tumors in the stomach, 16% in the gastroesophageal junction, and 13% in the esophagus.

CHECKMATE-649 demonstrated a statistically significant improvement in OS and PFS for patients with PD-L1 CPS ≥5. Statistically significant improvement in OS was also demonstrated for all randomized patients. The minimum follow-up was 12.1 months. Efficacy results are shown in Table 57 and Figures 18, 19, and 20.

Table 57: Efficacy Results - CHECKMATE-649

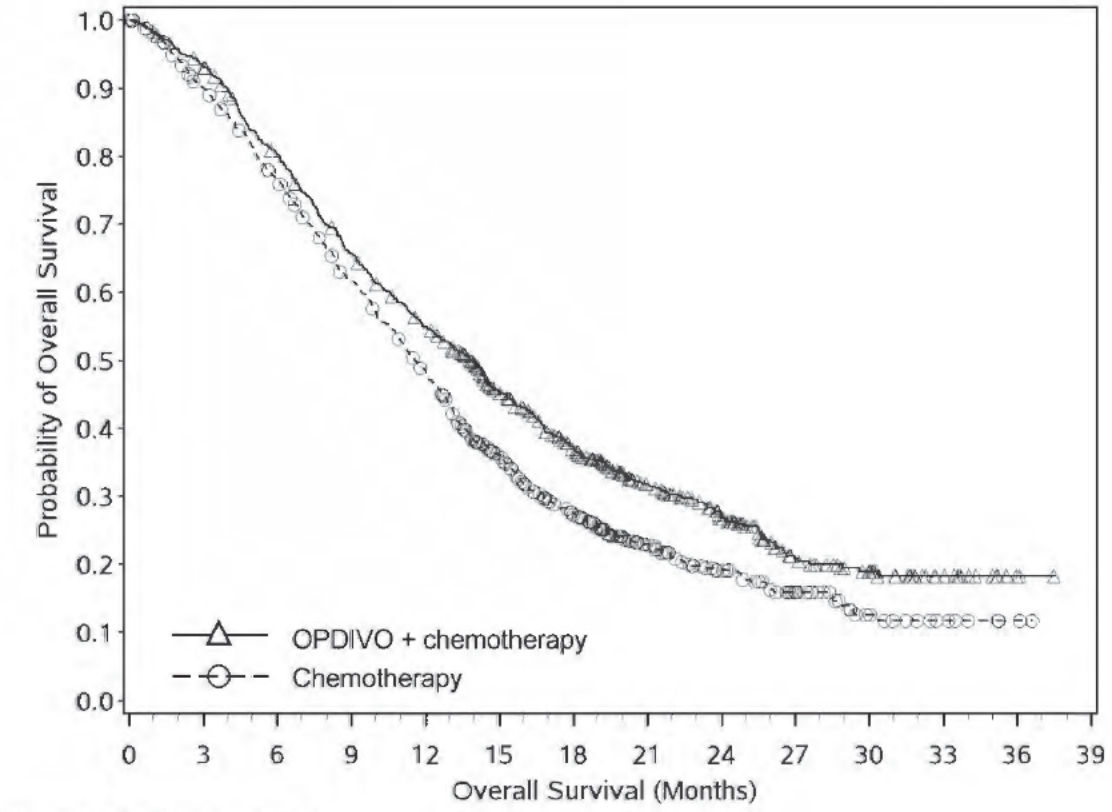
	OPDIVO and mFOLFOX6 or CapeOX (n=789)	mFOLFOX6 or CapeOX (n=792)	OPDIVO and mFOLFOX6 or CapeOX (n=641)	mFOLFOX6 or CapeOX (n=655)	OPDIVO and mFOLFOX6 or CapeOX (n=473)	mFOLFOX6 or CapeOX (n=482)
	All Patients		**PD-L1 CPS ≥1**		**PD-L1 CPS ≥5**	
Overall Survival						
Deaths (%)	544 (69)	591 (75)	434 (68)	492 (75)	309 (65)	362 (75)
Median (months) (95% CI)	13.8 (12.6, 14.6)	11.6 (10.9, 12.5)	14.0 (12.6, 15.0)	11.3 (10.6, 12.3)	14.4 (13.1, 16.2)	11.1 (10.0, 12.1)
Hazard ratio (95% CI)[a]	0.80 (0.71, 0.90)		0.77 (0.68, 0.88)		0.71 (0.61, 0.83)	
p-value[b]	0.0002		<0.0001		<0.0001	
Progression-free Survival[c]						
Disease progression or death (%)	559 (70.8)	557 (70.3)	454 (70.8)	472 (72.1)	328 (69.3)	350 (72.6)
Median (months) (95% CI)	7.7 (7.1, 8.5)	6.9 (6.6, 7.1)	7.5 (7.0, 8.4)	6.9 (6.1, 7.0)	7.7 (7.0, 9.2)	6.0 (5.6, 6.9)
Hazard ratio (95% CI)[a]	0.77 (0.68, 0.87)		0.74 (0.65, 0.85)		0.68 (0.58, 0.79)	
p-value[b]	-[e]		-[e]		<0.0001	
Overall Response Rate, n (%)[c,d]	370 (47)	293 (37)	314 (49)	249 (38)	237 (50)	184 (38)
(95% CI)	(43, 50)	(34, 40)	(45, 53)	(34, 42)	(46, 55)	(34, 43)
Complete response (%)	78 (10)	52 (7)	65 (10)	42 (6)	55 (12)	34 (7)
Partial response (%)	292 (37)	241 (30)	249 (39)	207 (32)	182 (38)	150 (31)
Duration of Response (months)[c,d]						
Median (95% CI) Range	8.5 (7.2, 9.9) 1.0+, 29.6+	6.9 (5.8, 7.2) 1.2+, 30.8+	8.5 (7.7, 10.3) 1.1+, 29.6+	6.9 (5.8, 7.6) 1.2+, 30.8+	9.5 (8.1, 11.9) 1.1+, 29.6+	6.9 (5.6, 7.9) 1.2+, 30.8+

[a] Based on stratified Cox proportional hazard model.
[b] Based on stratified log-rank test.
[c] Assessed by BICR.
[d] Based on confirmed response.
[e] Not evaluated for statistical significance.

In an exploratory analysis in patients with PD-L1 CPS<1 (n=265), the median OS was 13.1 months (95% CI: 9.8, 16.7) for the OPDIVO and chemotherapy arm and 12.5 months (95% CI: 10.1, 13.8) for the chemotherapy arm, with a stratified HR of 0.85 (95% CI: 0.63, 1.15).

In an exploratory analysis in patients with PD-L1 CPS<5 (n=606), the median OS was 12.4 months (95% CI: 10.6, 14.3) for the OPDIVO and chemotherapy arm and 12.3 months (95% CI: 11.0, 13.2) for the chemotherapy arm, with a stratified HR of 0.94 (95% CI: 0.78, 1.14).

Figure 18: Overall Survival (All Patients) - CHECKMATE-649



Number of Subjects at Risk

OPDIVO + chemotherapy	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemotherapy	792	697	586	469	359	239	160	94	59	35	15	7	2	0

Figure 19: Overall Survival (PD-L1 CPS ≥1) - CHECKMATE-649

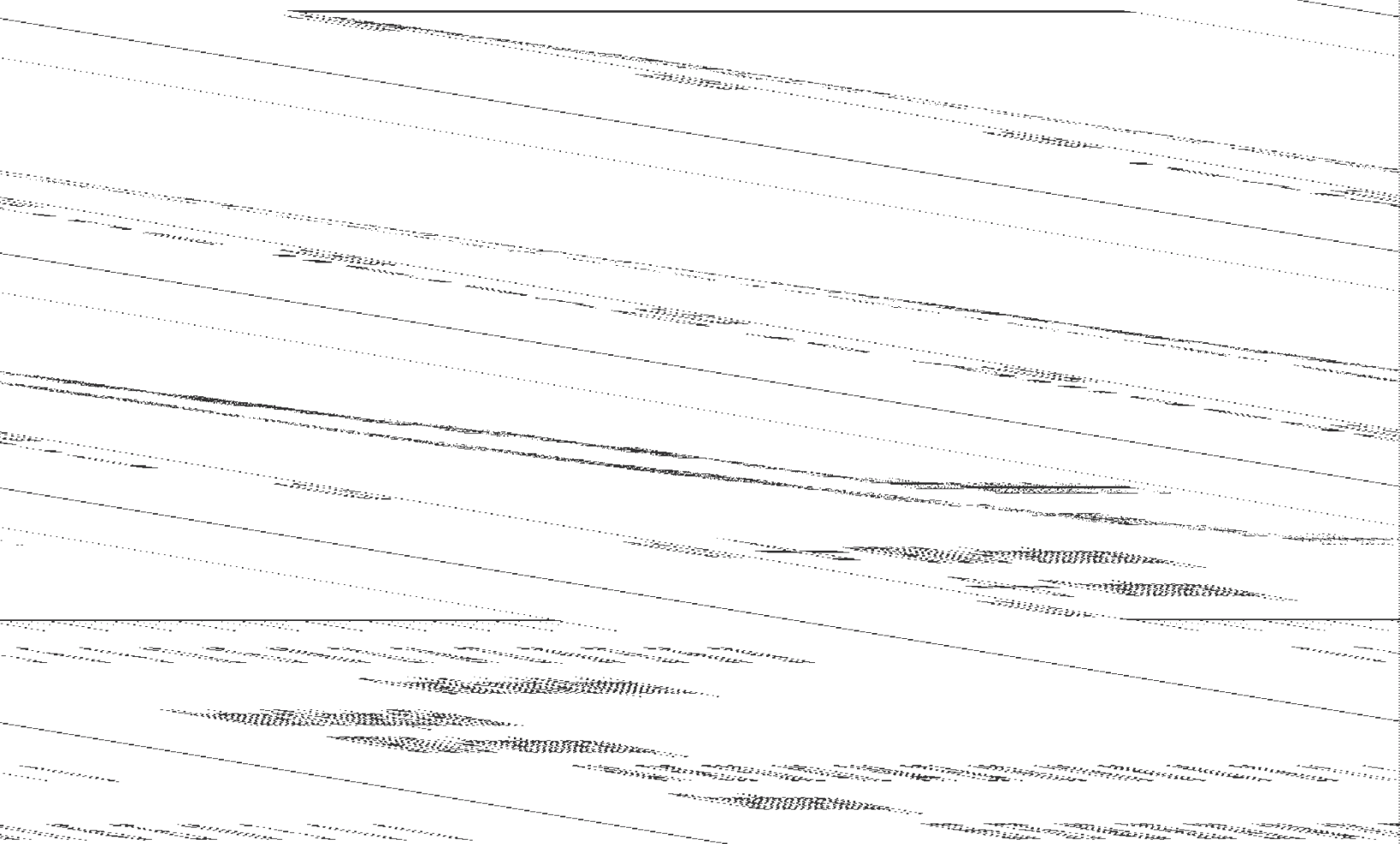
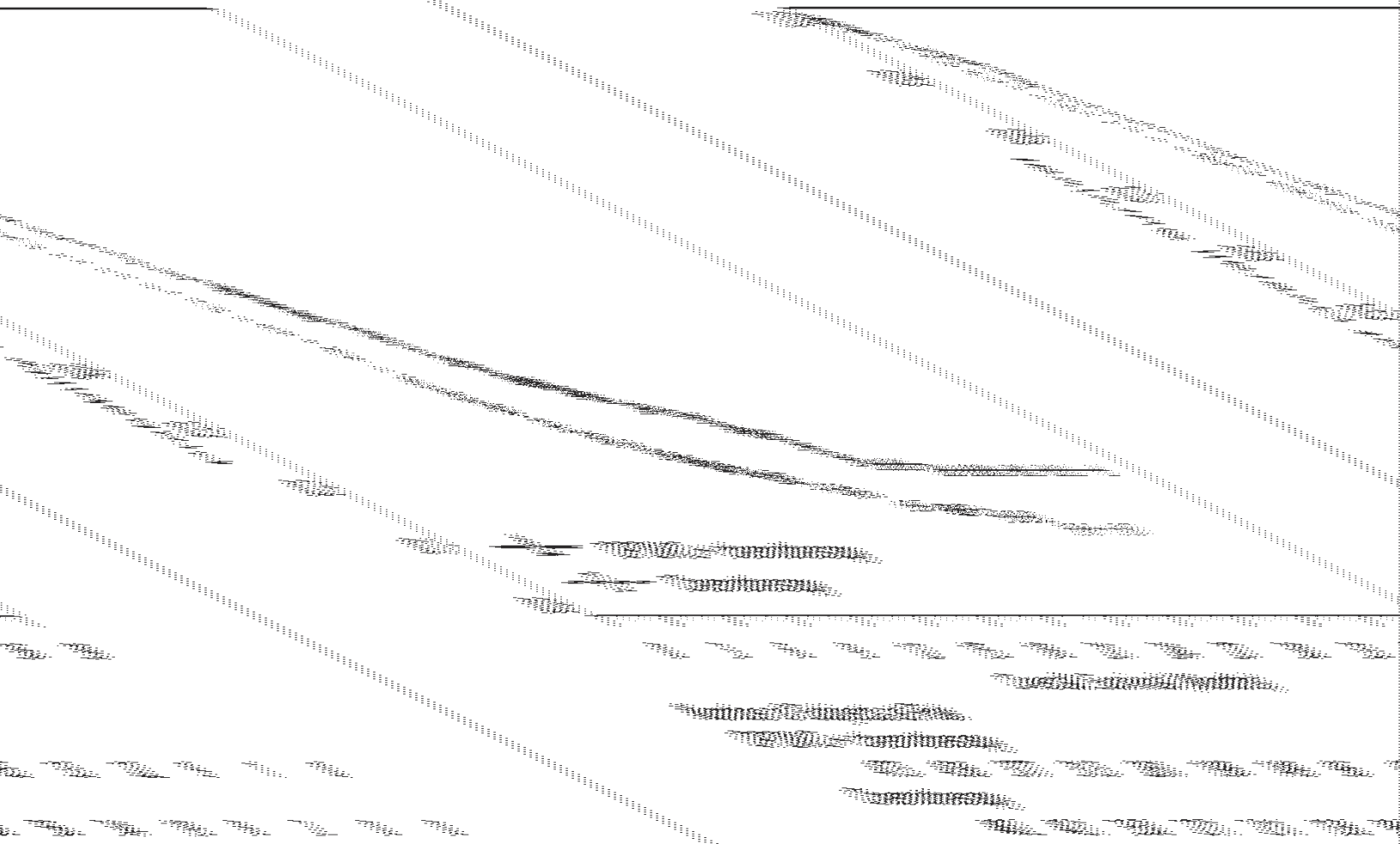


Figure 20: Overall Survival (PD-L1 CPS ≥5) - CHECKMATE-649



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 (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- 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 (5.1)]*.
- 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 (5.1)]*.
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

- Advise patients of the potential risk of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT

- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.3)]*.

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 (5.4), 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. If your healthcare provider prescribes OPDIVO in combination with cabozantinib, also read the Patient Information that comes with cabozantinib. 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 severe or can lead to death. These problems may happen anytime during treatment or even after your treatment has ended. You may have more than one of these problems at the same time. Some of these problems may happen more often when OPDIVO is used in combination with another therapy.

Call or see your healthcare provider right away if you develop any new or worse signs or symptoms, including:

Lung problems.

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

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdominal) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Hormone gland problems.

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heart beat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

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

Skin problems.

- rash
- itching
- skin blistering or peeling
- painful sore or ulcers in mouth or nose, throat, or genital area

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with OPDIVO. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:

- Chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- Double vision, blurry vision, sensitivity to light, eye pain, changes in eye sight
- Persistent or severe muscle pain or weakness, muscle cramps
- Low red blood cells, bruising

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during treatment with OPDIVO. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with OPDIVO, if you have severe side effects.

What is OPDIVO?
OPDIVO is a prescription medicine used to treat:

- **people with a type of skin cancer called melanoma:**
  - OPDIVO may be used alone or in combination with ipilimumab to treat melanoma that has spread or cannot be removed by surgery (advanced melanoma), **or**
  - OPDIVO may be used alone to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.
- **people with a type of advanced stage lung cancer called non-small cell lung cancer (NSCLC).**
  - OPDIVO may be used in combination with ipilimumab as your first treatment for NSCLC:
    - when your lung cancer has spread to other parts of your body (metastatic), and
    - your tumors are positive for PD-L1, but do not have an abnormal EGFR or ALK gene.
  - OPDIVO may be used in combination with ipilimumab and 2 cycles of chemotherapy that contains platinum and another chemotherapy medicine, as the first treatment of your NSCLC when your lung cancer:
    - has spread or grown, or comes back, **and**
    - your tumor does not have an abnormal EGFR or ALK gene.
  - OPDIVO may be used when your lung cancer:
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
    - If your tumor has an abnormal EGFR or ALK gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, **and** it did not work or is no longer working.
- **adults with a type of cancer that affects the lining of the lungs and chest wall called malignant pleural mesothelioma.**
  - OPDIVO may be used in combination with ipilimumab as your first treatment for malignant pleural mesothelioma that cannot be removed by surgery.
- **people with kidney cancer (renal cell carcinoma).**
  - OPDIVO may be used in combination with ipilimumab in certain people when their cancer has spread (advanced RCC), and you have not already had treatment for your advanced RCC.
  - OPDIVO may be used in combination with cabozantinib when your cancer has spread (advanced RCC), and you have not already had treatment for your advanced RCC.
  - OPDIVO may be used alone when your cancer has spread or grown after treatment with other cancer medicines.
- **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 medicine 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.
- **people with cancer of the tube that connects your throat to your stomach (esophageal cancer).**
  - **OPDIVO may be used when your esophageal cancer:**
    - is a type called squamous cell carcinoma, **and**
    - cannot be removed with surgery, **and**
    - has come back or spread to other parts of the body after you have received chemotherapy that contains fluoropyrimidine and platinum.
- **people with cancer of the stomach (gastric cancer), cancer where the esophagus joins the stomach (gastroesophageal junction cancer), and in people with esophageal adenocarcinoma.**
  - OPDIVO may be used in combination with chemotherapy that contains fluoropyrimidine and platinum when your gastric, gastroesophageal junction, or esophageal cancer:
    - cannot be removed with surgery, **or**
    - has spread to other parts of the body.

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.

Before receiving OPDIVO, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area in the past and have received other medicines that are like OPDIVO
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- 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.

How will I receive OPDIVO?

- Your healthcare provider will give you OPDIVO into your vein through an intravenous (IV) line over 30 minutes.
- When OPDIVO is used alone, it is usually given every 2 weeks or 4 weeks depending on the dose you are receiving.
- When OPDIVO is used in combination with ipilimumab (except for treating NSCLC), OPDIVO is usually given every 3 weeks, for a total of 4 doses. Ipilimumab will be given on the same day. After that, OPDIVO will be given alone every 2 weeks or 4 weeks depending on the dose you are receiving.
- For NSCLC that has spread to other parts of your body, when OPDIVO is used in combination with ipilimumab, OPDIVO is given either every 2 weeks or every 3 weeks, and ipilimumab is given every 6 weeks for up to 2 years. Your healthcare provider will determine if you will also need to receive chemotherapy every 3 weeks for 2 cycles.
- For malignant pleural mesothelioma, OPDIVO is given every 3 weeks and ipilimumab is given every 6 weeks for up to 2 years.
- For RCC, when used in combination with cabozantinib, OPDIVO is usually given every 2 weeks or 4 weeks depending on the dose you are receiving. Cabozantinib is given once daily by mouth.
- For gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma, when used in combination with fluoropyrimidine and platinum-containing chemotherapy, OPDIVO is given every 2 weeks or 3 weeks depending on the dose you are receiving. Chemotherapy will be given on the same day.

- 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 healthcare provider or nurse right away if you get these symptoms during an infusion of OPDIVO:
  - chills or shaking
  - itching or rash
  - flushing
  - shortness of breath or wheezing
  - dizziness
  - feel like passing out
  - fever
  - back or neck pain
- **Complications of stem cell transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with OPDIVO. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

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

- feeling tired
- rash
- pain in muscles, bones, and joints
- itchy skin
- diarrhea
- nausea
- weakness
- cough
- vomiting
- shortness of breath
- constipation
- decreased appetite
- back pain
- upper respiratory tract infection
- fever
- headache
- stomach-area (abdominal) pain

The most common side effects of OPDIVO when used in combination with ipilimumab include:

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

The most common side effects of OPDIVO when used in combination with ipilimumab and chemotherapy include:

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

The most common side effects of OPDIVO when used in combination with cabozantinib include:

- diarrhea
- feeling tired or weak
- liver problems. See "What is the most important information I should know about OPDIVO?"
- rash, redness, pain, swelling or blisters on the palms of your hands or soles of your feet
- mouth sores
- rash
- high blood pressure
- low thyroid hormone levels
- pain in muscles, bones, and joints
- decreased appetite
- nausea
- change in the sense of taste
- stomach-area (abdominal) pain
- cough
- upper respiratory tract infection

The most common side effects of OPDIVO when used in combination with fluoropyrimidine and platinum-containing chemotherapy include:

- numbness, pain, tingling, or burning in your hands or feet
- nausea
- feeling tired
- diarrhea
- vomiting
- decreased appetite
- stomach-area (abdominal) pain
- constipation
- pain in muscles, bones, and joints

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. You can ask your pharmacist or healthcare provider for information about OPDIVO that is written for health professionals.

What are the ingredients in OPDIVO?

Active ingredient: nivolumab

Inactive ingredients: mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and Water for Injection. May contain hydrochloric acid and/or sodium hydroxide.

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

For more information, call 1-855-673-4861 or go to www.OPDIVO.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: April 2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s091

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

FDA review was conducted in conjunction with other regulatory authorities under a modified ORBIS. While the application review is completed by the FDA, the application is still under review at the other regulatory agencies (Health Canada, Therapeutic Goods Administration, Brazilian Health Regulatory Agency and Swissmedic).

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	351(a)
Application Number(s)	125554-091
Priority or Standard	Priority
Submit Date(s)	November 25, 2020
Received Date(s)	November 25, 2020
PDUFA Goal Date	May 25, 2021
Division/Office	Division of Oncology 3 / Office of Oncologic Diseases
Review Completion Date	See electronic stamp date
Established Name	Nivolumab
(Proposed) Trade Name	Opdivo
Pharmacologic Class	Programmed death-1 (PD-1) receptor blocking antibody
Applicant	Bristol Myers Squibb (BMS)
Formulation(s)	Single vial solution of 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), and 240 mg/24 mL (10 mg/mL)
Dosing Regimen	240 mg every 2 weeks or 360 mg every 3 weeks
Applicant Proposed Indication(s)/Population(s)	Opdivo, for patients with advanced or metastatic gastric or gastroesophageal junction or esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Opdivo, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

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Pharmacology/Toxicology Team Leader(s)	n/a
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Office of Clinical Pharmacology Team Leader(s)	Jiang Liu, Ph.D., Hong Zhao, Ph.D.
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Additional Reviewers of Application

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OSE/DMEPA	Sali Mahmoud/ Ashleigh Lowery
DMPP	Sharon Mills/Barbara Fuller
OOD Safety	Shaily Arora/ Stacie Woods RPM

OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Project Orbis # 31 - Therapeutic Goods Administration (TGA; Australia) Review team
(b) (6)

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Project Orbis # 31 – Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária {ANVISA}; Brazil) Review team

(b) (6)

Project Orbis #31 - Health Canada (HC; Canada) Review team

(b) (6)

Project Orbis # 31 – Swissmedic (SMC; Switzerland) Review team

(b) (6)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Glossary

AC	adenocarcinoma
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BID	twice daily
BLA	biologics license application
BMS	Bristol-Myers Squibb
BOR	best overall response
BUN	blood urea nitrogen
Cavg1	average concentration within one dosing interval following the 1st dose
Cavgss	steady-state average concentration
CBC	complete blood count
CNS	central nervous system
CF	cisplatin + fluorouracil
CFR	Code of Federal Regulations
Chemo	chemotherapy
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
CLss	clearance at steady state
Cmax1	maximum concentration following the 1st dose
Cmaxss	maximum concentration at steady state
	(b) (4)
Cmin1	minimum concentration following 1st dose
Cminss	minimum concentration at steady state
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DC	discontinuation
DCF	docetaxel + cisplatin + fluorouracil
DMC	data monitoring committee
dMMR	mismatch repair deficient
DOR	duration of response
DRR	durable response rate
EAC	esophageal adenocarcinoma

EC	esophageal cancer
ECG	electrocardiogram
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
E-R	exposure-response
ESCC	esophageal squamous cell carcinoma
ETASU	elements to assure safe use
FACT-Ga	Functional Assessment of Cancer Therapy-Gastric
FDA	Food and Drug Administration
FLP	fluorouracil + leucovorin+ cisplatin
FOLFOX	5-fluorouracil + leucovorin and oxaliplatin
FU	fluorouracil
F/U	follow-up
GaCS	Gastric Cancer Subscale
GC	gastric cancer
GEJC	gastroesophageal junction cancer
HBV	hepatitis B virus
HCC	hepatocellular cancer
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
IMAEs	immune-mediated adverse events
IMM	immune-modulating medication
IND	Investigational New Drug
Ipi	ipilimumab
iPSP	Initial Pediatric Study Plan
IRT	interactive response technology
IV	intravenous
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LLN	lower limit of normal
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
Mono	monotherapy
mOS	median overall survival
MSI	microsatellite instability
MSI-H	microsatellite instability-high
mUC	metastatic urothelial carcinoma
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
Nivo	nivolumab
NR	not reported
NSCLC	non-small cell lung cancer

OESI	other events of special interest
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PFS2	progression-free survival on next line of therapy
PK	pharmacokinetics
PO	orally
PPK	population pharmacokinetics
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PS	performance status
QxW	every x weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
ROW	rest of world
RTOR	Real-Time Oncology Review
S1	tegafur/gimeracil/oteracil potassium
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental biologics license application
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SEER	Surveillance, Epidemiology, and End Results Program
T1/2β,ss	elimination half-life at steady state
ToGA	Trastuzumab for Gastric Cancer study
TSH	thyroid stimulating hormone
TSST	time to second subsequent line therapy
UI	utility index
US	United States
USPI	United States package insert
VAS	visual analogue score
Vss	volume of distribution at steady state
WHO	World Health Organization
XELOX	capecitabine + oxaliplatin

1 Executive Summary

1.1. Product Introduction

Nivolumab is a humanized monoclonal antibody of the IgG4/kappa (IgG4κ) isotype that binds to the programmed death 1 (PD-1) receptor and directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, releasing the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Nivolumab is supplied in single dose vials of 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.

FDA first approved nivolumab on April 14, 2015. Prior to action on this supplement, nivolumab as a single agent or in combination was approved for various lines of treatment and subsets of patients with melanoma, non-small cell lung cancer, malignant pleural mesothelioma, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, microsatellite instability-high (MSI-H) colorectal cancer, gastric cancer, esophageal cancer, hepatocellular carcinoma, and renal cell carcinoma.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted the results of a single adequate and well-controlled study to support the claims of effecitiveness for the proposed indication. Study CA209649 (NCT02872116), a randomized, international, open-label trial, enrolled patients with previously untreated locally advanced unresectable or metastatic gastric cancer, gastroesophageal junction (GEJ) cancer, or esophageal adenocarcinoma (EAC). Patients were eligible if they had histologically confirmed predominant adenocarcinoma and ECOG PS of 0 or 1; patients with known HER2 positive status and patients with untreated central nervous system (CNS) metastases were excluded.

The study design was revised multiple times. The original study was a comparison of immune therapy with nivolumab and ipilimumab vs. standard of care (SOC) chemotherapy; after emerging data from other studies in the same disease setting, a third-arm of nivolumab in combination SOC chemotherapy was added. Enrollment to the nivolumab and ipilimumab arm was closed on June 5, 2018 per the recommendation of the data monitoring committee (DMC) due to increased early toxicity and death rate in this arm. This submission contains only data of the comparison nivolumab/SOC vs SOC.

Patients were randomized (1:1) to receive nivolumab in combination with chemotherapy or chemotherapy alone. The nivolumab dose varied depending on the investigator's choice of chemotherapy; patients randomized to the nivolumab arm received nivolumab 360 mg intravenously (IV) every 3 weeks (Q3W) plus capecitabine and oxaliplatin (XELOX), or nivolumab

240 mg IV Q2W in combination with 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6, FOLFOX); patients randomized to the chemotherapy arm received XELOX or FOLFOX. Patients were treated until disease progression, unacceptable toxicity, or 2 years of nivolumab treatment. The stratification factors for randomization were tumor cell PD-L1 status (≥ 1% vs < 1% [including indeterminate]), region (Asia vs North America [US and Canada] vs Rest of world [ROW]), ECOG performance status (0 vs 1), and chemotherapy (XELOX vs FOLFOX). A total of 1581 patients were randomized, 789 patients into the nivolumab/chemotherapy arm and 792 patients into the chemotherapy arm. The primary endpoints of the trial were progression-free survival (PFS) per RECIST v1.1 as assessed by a blinded independent central review (BIRC) in patients with PD-L1 CPS ≥ 5 and overall survival (OS) in patients with PD-L1 CPS ≥ 5. Additional efficacy outcome measures tested in hierarchical order were OS in patients within patients with PD-L1 CPS ≥ 1 and OS in all patients. Secondary endpoints were OS in patients with PD-L1 CPS ≥ 10, PFS by BIRC in subpopulations defined by CPS scores, overall response rate (ORR), duration of response, and others. Of note, although the stratification factor was based on tumor PD-L1 expression, the primary population for analysis was changed to PD-L1 CPS ≥ 5 (Protocol V7); CPS was generated by rescoring PD-L1 stained slides.

All pre-specified analyses of Study CA209649 included in the statistical plan for which type I error and hierarchical testing were specified were determined to be statistically significant. In the overall population (n: 1581), nivolumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. In FDA's analysis, the OS HR was 0.80 (95% CI: 0.71, 0.90; p: 0.0002) with a median OS of 13.8 months (95% CI: 12.6, 14.6) in the nivolumab/SOC arm and 11.6 months (95% CI: 10.9, 12.5) for the SOC arm. Similarly, clinically meaningful and statistically significant improvements in OS were observed with administration of nivolumab in the planned primary analysis population, patients whose tumors express PD-L1 CPS ≥5 (n: 955) (HR 0.71, 95% CI 0.61, 0.83, p < 0.0001) and also in patients whose tumor express PD-L1 CPS ≥1 (n: 1296) (HR 0.77; 95% CI: 0.68, 0.88; p<0.0001).

The PFS in patients with CPS ≥ 5 crossed the statistical boundary for efficacy (HR 0.68, 95% CI 0.58, 0.79; p: < 0.0001); however, the difference in the magnitude of effect is modest. The median PFS in the nivolumab/SOC arm was 7.7 months (95% CI 7, 9.2) and 6 months (95% CI 5.6, 6.9). In the exploratory analysis of PFS in the ITT, the HR was 0.77 (95% CI 0.68, 0.87) and the median PFS in the nivolumab/SOC arm was 13.8 months (95% CI 12.6, 14.6) and 11.6 months (95% CI 10.9, 12.5). PFS testing, although showing a modest magnitude of effect, confirmed the robustness of the study results and clinical meaningfulness of the effect on survival.

The submitted evidence meets the statutory evidentiary standard for regular approval of nivolumab in combination with chemotherapy for treatment of patients with metastatic or locally advanced gastric, gastroesophageal junction, or esophageal adenocarcinoma who have not received prior systemic treatment for advanced disease. The observed improvement in survival the overall population with a HR of 0.80 is statistically robust and clinically meaningful.

This finding is supported by consistent results on secondary endpoints and analyses.

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1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Nivolumab is a monoclonal antibody that binds to programmed-death receptor 1 (PD-1) and blocks its interactions with both its ligands. This releases the PD-1/PD-L1-mediated inhibition of the immune response, including activation of the anti-tumor immune response. There is extensive clinical experience with nivolumab, which is approved by the FDA for multiple indications, either alone or in combination with other drugs.

The safety and effectiveness of nivolumab for the treatment of patients with metastatic or locally advanced gastric, gastroesophageal junction (GEJ), and esophageal adenocarcinoma is demonstrated by the results of a single multicenter, international, open-label, randomized trial, Study CA209649 (NCT02872116). The study evaluated nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy versus chemotherapy alone
Patients with known HER2 positive status and patients with prior systemic treatment for advanced disease were ineligible. PD-L1 status was centrally determined in tumor specimens in all patients. Randomization (1:1) was stratified by tumor cell PD-L1 status (≥ 1% vs < 1% [including indeterminate]), geographic region Asia vs. North America [US and Canada] vs. Rest of world [ROW]), ECOG performance status (0 vs. 1), and chemotherapy (XELOX vs. FOLFOX). Tumor cell PD-L1 was determined by a central lab using the Agilent/Dako PD-L1 IHC 28-8 pharmDx test). However, efficacy analyses were conducted using the PD-L1 combined positive score (CPS). CPS was generated centrally by rescoring the tumor cell PD-L1 stained slides using the central lab DAKO CPS algorithm, taking into account immunoreactivity for PDL1 in both tumor cells and tumor associated immune cells (restricted to lymphocytes and macrophages) within or directly associated with tumor cell strands. PD-L1 CPS was quantifiable in all but 5 patients on the chemo arm. Results demonstrated PD-L1 CPS of ≥ 1% in approximately 82% of patients and ≥ 5% in 60% of patients across arms. The rates were balanced between arms.

All patients received investigator choice chemotherapy with either XELOX or FOLFOX, selected prior to randomization. The chemotherapy regiments included:

- oxaliplatin 130 mg/m^2 IV on Day 1 of each treatment cycle combined with capecitabine 1000 mg/m^2 orally twice daily (BID) on Days 1 to 14 of each 21-day cycle (XELOX)

- oxaliplatin 85 mg/m^2 IV on Day 1 followed by leucovorin 400 mg/m^2 IV, fluorouracil 400 mg/m^2 bolus IV on Day 1 and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily over 46 hours of each 14-day cycle (mFOLFOX6 [FOLFOX])

Patients randomized to the nivolumab arm received also nivolumab 240 mg IV on Day 1 of each 14-day cycle (if patient was receiving FOLFOX) or 360 mg IV on Day 1 of each 21-day cycle (if patient was receiving XELOX).

Patients were treated until disease progression, unacceptable toxicity, or 2 years of nivolumab treatment. The primary endpoints of the trial were progression-free survival (PFS) per RECIST v1.1 as assessed by a blinded independent central review (BIRC) in patients with PD-L1 CPS ≥ 5 and overall survival (OS) in patients with PD-L1 CPS ≥ 5. Additional efficacy outcome measures tested in hierarchical order were OS in patients within patients with PD-L1 CPS ≥ 1 and OS in all patients. Secondary endpoints were OS in patients with PD-L1 CPS ≥ 10, PFS by BIRC in subpopulations defined by CPS scores, overall response rate (ORR), duration of response, and others.

All pre-specified analyses of Study CA209649 included in the statistical plan for which type I error and hierarchical testing were specified were determined to be statistically significant. In the overall population (n: 1581), nivolumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. In the ITT, the OS HR was 0.80 (95% CI: 0.71, 0.90; p: 0.0002) with a median OS of 13.8 months (95% CI: 12.6, 14.6) in the nivolumab/SOC arm and 11.6 months (95% CI: 10.9, 12.5) for the SOC arm. Similarly, clinically meaningful and statistically significant improvements in OS were observed with administration of nivolumab in the planned primary analysis population, patients whose tumors express PD-L1 CPS ≥5 (n: 473) (HR 0.71, 95% CI 0.61, 0.83, p < 0.0001) and also in patients whose tumor express PD-L1 CPS ≥1 (n: 641) (HR 0.77; 95% CI: 0.68, 0.88; p<0.0001). The PFS in patients with CPS ≥ 5 crossed the statistical boundary for efficacy (HR 0.68, 95% CI 0.58, 0.79; p: < 0.0001).

The adverse reaction profile observed in patients receiving nivolumab in Study CA209649 is consistent with the known nivolumab safety profile. The most common adverse reactions reported in ≥20% of patients treated with nivolumab in combination with chemotherapy were peripheral neuropathy, nausea, fatigue, diarrhea, , vomiting, decreased appetite, abdominal pain, constipation, , and musculoskeletal pain. The most common Grade 3-4 adverse events in the nivolumab arm (incidence ≥ 2%) were peripheral neuropathy, increased lipase, vomiting, decreased appetite, nausea, increased lipase, and abdominal pain. Most of the immune-related AEs were Grade 1-2, and the most common Grade 3-4 immune related AEs were diarrhea/colitis (2.2%), pneumonitis (1.9%), hepatitis (1.7%), and rash (1.2%); all patients with these events received immune-modulating medication. Overall, corticosteroids were administered to treat immune-related AEs in 35% of patients in the nivolumab arm and 20% of patients in the control arm. The incidence and type of immune related AEs observed in Study CA209469 are consistent with the known safety profile of nivolumab.

The review team concluded that the overall risk:benefit assessment favored approval of nivolumab with fluoropyrimidine- and platinum-based chemotherapy, for the first-line treatment of patients with metastatic or locally advanced gastric, gastroesophageal or esophageal adenocarcinoma carcinoma. The demonstrated improvement in survival for patients randomized to nivolumab in combination with chemotherapy compared to patients randomized to chemotherapy is clinically meaningful, statistically significant, and supported by subgroup analyses in Study CA209649. Although the primary endpoint was in the subgroup of patients with PD-L1 CPS ≥ 5, the overall survival results in the ITT population where also statistically significant and clinically meaningful, which supported a favorable benefit:risk decision for the overall population. The adverse reaction profile observed in patients receiving nivolumab is consistent with the adverse reaction profiles observed in prior studies and the disease setting. The most common adverse events and the incidence of these events were similar between arms and the only difference of ≥ 5% was for diarrhea and neutropenia. The rate of immune-related adverse events was consistent with the known incidence for nivolumab. These risks are largely manageable with patient surveillance, treatment delays, and supportive care in most patients. The risks of nivolumab are acceptable considering the life-threatening nature of metastatic or locally advanced gastric, gastroesophageal and esophageal adenocarcinoma.

The application was reviewed under Project Orbis, the real-time oncology review (RTOR) program, and the Applicant submitted an Assessment Aid.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	In the US, it was estimated that there will be 27,600 new cases of gastric cancer in 2020 (1.5% of all new cancer cases) with an estimated 11,010 deaths; the 5-year relative survival rate for metastatic gastric cancer in the US is 32.0% (2009-2016 Surveillance, Epidemiology, and End Results Program [SEER] data). For esophageal cancer, in the US, it is estimated that there will be 18,440 new cases (1% of all new cancer cases) in 2020 with an estimated 16,170 deaths. Approximately two-thirds of patients with esophageal cancer will have adenocarcinomas; ex-US, the most common histology of esophageal cancer is squamous	Metastatic or locally advanced gastric, gastroesophageal junction, and esophageal adenocarcinoma are serious, life-threatening diseases with poor prognosis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cell carcinoma. The median overall survival for patients with unresectable or metastatic gastric or esophageal adenocarcinoma is approximately one year.	
Current Treatment Options	For patients with unresectable or metastatic disease, treatment options are limited to palliative chemotherapy. Combination regimens are generally used and some of the standard combinations most frequently used in the US include fluoropyrimidine and platinum agents. Selection of a regimen for a particular patient is based on the patient's general status, preferences, toxicity, institutional standards, etc. The study supporting this approval is an add-on regimen; patients will continue to receive standard chemotherapy regimens.	Although fluoropyrimidine- and platinum-based chemotherapy improves survival in patients with advanced unresectable or metastatic gastric, gastroesophageal junction, and esophageal adenocarcinoma, there is a need for more effective treatment.
Benefit	The approval is supported by a single study, CA209649 (NCT02872116). CA209649 is a randomized, international, open-label trial in patients with previously untreated locally advanced unresectable or metastatic gastric cancer, gastroesophageal junction or esophageal adenocarcinoma. Patients were eligible if they had histologically confirmed predominant adenocarcinoma, ECOG PS of 0 or 1; patients with known HER2 positive status were excluded. This submission contains only data for two study arms, comparing nivolumab/chemotherapy vs chemotherapy. Patients were randomized (1:1) to receive nivolumab in combination with standard of care (SOC) chemotherapy or SOC. Depending on the investigator's choice of SOC chemotherapy, patients randomized to the nivolumab arm received nivolumab 360 mg intravenously (IV) every 3	The submitted evidence meets the statutory evidentiary standard for regular approval of nivolumab in combination with chemotherapy for treatment of patients with metastatic or locally advanced gastric, gastroesophageal junction, or esophageal adenocarcinoma who have not received prior systemic treatment for advanced disease. The observed improvement in survival the overall population with a HR of 0.80 is statistically robust and clinically meaningful. This finding is supported by consistent results on secondary endpoints and prespecified subgroup analyses.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	weeks (Q3W) plus capecitabine and oxaliplatin (XELOX), or nivolumab 240 mg IV Q2W in combination with 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6, FOLFOX); patients randomized to the SOC arm received XELOX or FOLFOX. Patients were treated until disease progression, unacceptable toxicity, or 2 years of nivolumab treatment. The stratification factors for randomization were tumor cell PD-L1 status (≥ 1% vs < 1% [including indeterminate]), region (Asia vs North America [US and Canada] vs Rest of world [ROW]), ECOG performance status (0 vs 1), and chemotherapy (XELOX vs FOLFOX). A total of 1581 patients were randomized, 789 patients into the nivolumab +chemotherapy arm and 792 patients into the chemotherapy arm. The primary endpoints of the trial were progression-free survival (PFS) per RECIST v1.1 as assessed by a blinded independent central review (BIRC) in patients with PD-L1 CPS ≥ 5 and overall survival (OS) in patients with PD-L1 CPS ≥ 5. Additional efficacy outcome measures tested in hierarchical order were OS in patients within patients with PD-L1 CPS ≥ 1 and OS in all patients. All pre-specified analyses of Study CA209649 included in the statistical plan for which type I error and hierarchical testing were specified were determined to be statistically significant. In the overall population (n: 1581), nivolumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. The OS HR was 0.80 (95% CI: 0.71, 0.90; p: 0.0002) with a median OS of 13.8 months (95% CI: 12.6, 14.6) in the nivolumab+ chemotherapy arm and 11.6 months (95% CI: 10.9, 12.5) for the chemotherapy arm. Similarly, clinically meaningful and statistically	Based on exploratory analyses, there is insufficient data to properly characterize the effect of nivolumab when added to chemotherapy for the treatment of patients with adenocarcinoma or PD-L1 CPS < 5. To inform prescribers of the observed effect in patients with PD-L1 CPS <5, data has been described in the label.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	significant improvements in OS were observed with administration of nivolumab in the planned primary analysis population, patients whose tumors express PD-L1 CPS ≥5 (n: 473) (HR 0.71, 95% CI 0.61, 0.83, p < 0.0001) and also in patients whose tumor express PD-L1 CPS ≥1 (n: 641) (HR 0.77; 95% CI: 0.68, 0.88; p<0.0001). The PFS in patients with CPS ≥ 5 crossed the statistical boundary for efficacy (HR 0.68, 95% CI 0.58, 0.79; p: < 0.0001); however, the difference in the magnitude of effect is modest. The median PFS in the nivolumab/SOC arm was 7.7 months (95% CI 7, 9.2) and 6 months (95% CI 5.6, 6.9). In the exploratory analysis of PFS in the ITT, the HR was 0.77 (95% CI 0.68, 0.87) and the median PFS in the nivolumab/SOC arm was 13.8 months (95% CI 12.6, 14.6) and 11.6 months (95% CI 10.9, 12.5). PFS testing, although showing a modest magnitude of effect, confirmed the robustness of the study results and clinical meaningfulness of the effect on survival. In an exploratory analysis in patients with PD-L1 CPS<1 (n=265), the median OS was 13.1 months (95% CI: 9.8, 16.7) for the nivolumab and arm and 12.5 months (95% CI: 10.1, 13.8) for the chemotherapy arm, with a stratified HR of 0.85 (95% CI: 0.63, 1.15). In patients with PD-L1 CPS <5 (n=606), the median OS was 12.4 months (95% CI: 10.6, 14.3) for the nivolumab arm and 12.3 months (95% CI: 11.0, 13.2) for the chemotherapy arm, with a stratified HR of 0.94 (95% CI: 0.78, 1.14).	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	The observed safety profile of nivolumab in patients with metastatic or unresectable gastric, GEJ, or esophageal adenocarcinoma was consistent with the established safety profile of nivolumab in patients with other types of cancer. The addition of nivolumab to chemotherapy was well tolerated and the only clinically meaningful increase in toxicity was related to immune related adverse reactions. The primary risks of nivolumab are immune-mediated adverse events (IMAEs) and infusion-related reactions (IRRs); IRRs were reported in only 1% of patients in the nivolumab arm. Overall, corticosteroids were administered to treat IMAEs in 35% of patients in the nivolumab arm and 20% of patients in the control arm. Most of the IMAEs were Grade 1-2, and the most common Grade 3-4 IMAEs were diarrhea/colitis (2.2%), pneumonitis (1.9%), hepatitis (1.7%), and rash (1.2%), all patients with these events received immune-modulating medication. The addition of nivolumab to chemotherapy in the setting of treatment of patients with advanced or metastatic esophageal/GEJ or esophageal adenocarcinoma does not appear to significantly increase the toxicity of the backbone therapy and is within the expected range of toxicity for nivolumab when compared with historical data.	The toxicity profile of nivolumab is acceptable when assessed in the context of the life-threatening nature of advanced unresectable or metastatic gastroesophageal adenocarcinoma. No new significant safety concerns were identified during review of this supplemental application that would require a new risk management plan, including a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of pembrolizumab. Significant and serious adverse reactions for nivolumab are predictable based on the antibody mechanism of action and well-known toxicity profiles. These risks are adequately addressed in product labeling, and oncologists who treat patients with gastroesophageal adenocarcinoma are well-trained in the monitoring and treatment of these adverse reactions. The review team determined that standard postmarketing surveillance would be sufficient for continued assessment of the safety of nivolumab in patients with gastric or gastroesophageal adenocarcinoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

1.4. Patient Experience Data

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

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
		Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Section 8.1.2
			□	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 was not submitted in the application, but was considered in this review.				

X

Cross-Disciplinary Team Leader
Refer to signature page

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Gastric cancer (GC) is the 5th leading cancer and the 3rd leading cause of cancer-related deaths worldwide.[1] Esophageal cancer (EC) is the 7th leading cancer and the 6th leading cause of cancer-related deaths worldwide. Adenocarcinoma is the most common (> 90%) histological subtype for GCs worldwide,[2] while approximately 64% of ECs in the United States (US) and 15% of ECs worldwide are adenocarcinomas.[3]

In the US, it is estimated that there will be 27,600 new cases of GC in 2020 with an estimated 11,010 deaths; the 5-year relative survival rate for metastatic GC in the US is 32.0% (2009-2016 Surveillance, Epidemiology, and End Results Program [SEER] data).[4] For EC, it is estimated that there will be 18,440 new cases in the US in 2020 with an estimated 16,170 deaths; the 5-year relative survival rate for metastatic EC in the US is 19.9% (2009-2016 SEER data).[3]

Gastroesophageal junction cancer (GEJC) anatomically straddles the distal esophagus and proximal stomach; due to its location and histology (most GEJ tumors like GC, are adenocarcinomas), GEJ tumors are frequently grouped together with GC. In the US, esophageal adenocarcinoma (EAC), GEJC, and GC are considered similar diseases and the same treatment approach is recommended in the National Comprehensive Cancer Network (NCCN) guidelines.[5,6]

The FDA's Assessment:

FDA generally agrees with the Applicant's opinion; chemotherapy treatment approaches for gastric cancer (GC), gastroesophageal junction cancer (GEJC), and esophageal adenocarcinoma (EAC) are similar in the advanced/unresectable or metastatic setting, but approaches to resectable disease may differ according to tumor location. At the time of diagnosis, 33% of patients will have loco-regional spread and 39% will have metastatic disease. Prognosis in patients with metastatic disease is poor, with median survival of less than a year (Kang Y, 2009).

2.2. Analysis of Current Treatment Options

Data

Table 1: Agents Relevant to First-line Advanced or Metastatic Gastric Cancer, Gastroesophageal Junction Cancer, or Esophageal Adenocarcinoma (GC/GEJC/EAC)

Product (s) Name	Reference	Relevant Indication	Year of Approval Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
HER2 Inhibitor + Chemotherapy						
Herceptin (trastuzumab) + chemotherapy	Van Cutsem E, et al. 2009[7] Trastuzu-mab USPI[8]	HER2-over-expressing metastatic gastric or GEJ AC	2010; Full	Trastuzumab 8 mg/kg Q3W followed by 6 mg/kg Q3W + chemo (cisplatin + capecitabine or 5-FU)	Trastuzumab + chemo mOS: 13.5 months ORR: 47% updated mOS: 13.1 months	Most common Grade 3/4 AEs: neutropenia (27%), anemia (12%), diarrhea (9%), nausea (7%), and anorexia and vomiting (6% each), and asthenia, and febrile neutropenia, and thrombocytopenia (5% each).
Chemotherapy: Platinum Compounds + Fluoropyrimidines						
Fluorouracil (FU)+ leucovorin+ oxaliplatin (FOLFOX) FU + leucovorin+ cisplatin (FLP)	Al-Batran S-E, et al. 2008 [9] Enzinger, et al.[10] NCCN Guidelines 5,6	Untreated gastric or esophago-gastric adeno-carcinoma	2006; Full FU, as a component of a platinum-containing multidrug chemotherapy regimen. FOLFOX is recommended in the NCCN guidelines	FOLFOX: FU 2,600 mg/m^2 via 24-hour infusion, leucovorin 200 mg/m^2 + oxaliplatin 85 mg/m^{2}Q2W FLP: FU 2,000 mg/m^{2}via 24-hour infusion, leucovorin 200 mg/m^2 QW, + cisplatin 50 mg/m^2 Q2W	FOLFOX vs FLP mOS: 10.7 vs 8.8 months ORR: 41.3% vs 16.7%	Most common Grade 3/4 AEs (FLP vs FOLFOX): neutropenia (14.7% vs 11.6%), leukopenia (11.8% vs 6.3%), anemia (6.9% vs 2.7%), nausea (8.8% vs 4.5%), vomiting (5.9% vs 2.7%), thromboembolic (5.9% vs 0.9%), and fatigue (6.9% vs 3.6%).
			Modified FOLFOX6: oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 h (or per local standard) on Days 1 and 2 cycled every 14 days			
Capecitabine (Xeloda) + oxaliplatin (XELOX)	Park YH, et al. 2008[11] Kim GM, et al. 2012[12]	Advanced gastric cancer	Not FDA approved, but XELOX (CapeOx) is recommended in the NCCN guidelines	Capecitabine (1,000 mg/m^2 BID, Days 1–14) + oxaliplatin (130 mg/m^2 IV infusion on Day 1) Q3W	mOS: 11.9 months ORR: 63%	Most common Grade 3/4 AEs: thrombocytopenia (11%), neutropenia (8%), diarrhea and bleeding (7% each), and leukopenia (6%).

Table 1: Agents Relevant to First-line Advanced or Metastatic Gastric Cancer, Gastroesophageal Junction Cancer, or Esophageal Adenocarcinoma (GC/GEJC/EAC)

Product (s) Name	Reference	Relevant Indication	Year of Approval Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Chemotherapy: Platinum Compounds + Fluoropyrimidines (continued)						
Docetaxel + cisplatin + fluorouracil (DCF) Cisplatin + fluorouracil (CF)	Van Cutsem E, et al. 2006[13],	First-line treatment of advanced GC/GEJC	2006; Full Docetaxel +cisplatin + fluorouracil	Docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 (Day 1) + FU 750 mg/m^2/day (Days 1-5) Q3W Cisplatin 100 mg/m^2 (Day 1) + FU 1,000 mg/m^2/day (Days 1-5) Q4W	DCF and CF mOS: 9.2 and 8.6 months ORR: 37% and 25%	Most common Grade 3/4 AEs (DCF vs CF): neutropenia (82% vs 57%), leukopenia (65% vs 31%), anemia (18% vs 26%), stomatitis (21% vs 27%), diarrhea (19% vs 8%), lethargy (19% vs14%), nausea and vomiting (both: 14% vs 17%), and anorexia (10% vs 9%).
Capecitabine + cisplatin	Lordick F, et al. 2013[14] Kang et al. 2009[15]	Previously untreated advanced gastric cancer	Not FDA approved, but capecitabine + cisplatin is recommended in the NCCN guidelines	3-wk cycles of capecitabine BID 1000 mg/m^2 (on Days 1-14) + cisplatin 80 mg/m^2 (on Day 1)	Capecitabine + cisplatin mOS: 10.7 months ORR: 29%	Most common Grade 3/4 AEs: neutropenia (32%), anemia (11%), hypokalemia and nausea (9% each), vomiting (8%), and fatigue, asthenia, hyponatremia, and decreased appetite (6% each).

Abbreviations: AC - adenocarcinoma, AEs - adverse events, BID - twice daily, CF - cisplatin + fluorouracil, chemo - chemotherapy, DCF - docetaxel + cisplatin + fluorouracil, FDA - Food and Drug Administration, FLP - FU + leucovorin+ cisplatin, FU - fluorouracil, GC - gastric cancer, GEJC - gastroesophageal junction cancer, HER2 - human epidermal growth factor receptor 2, IV- intravenous, mOS - median overall survival, NCCN - National Comprehensive Cancer Network, ORR - objective response rate, QXW - every X weeks, USPI - United States Package Insert

The Applicant's Position:

Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil [5-FU], capecitabine, and tegafur/gimeracil/oteracil potassium [S1]) are generally considered first-line, standard-of-care treatment options in metastatic GC/GEJC/EAC across geographic regions (Table 1).[5,6,16,17] These platinum/fluoropyrimidine combinations are generally accepted as active comparators in Phase 2/3 randomized studies by health authorities worldwide.

In the past decade, multiple new investigational drugs with mainly molecular targets have been investigated in the first-line setting as add-ons to backbone platinum and fluoropyrimidine treatment. These agents, with the exception of trastuzumab,[7,8] which targets the human epidermal growth factor receptor 2 (HER2)-positive population, have failed to show a survival benefit in randomized trials. Trastuzumab + chemotherapy provided an improvement in survival over chemotherapy in subjects who were HER2 positive; at a median follow-up of 17.1 months, median OS was 13.5 vs 11.0 months (hazard ratio [HR] = 0.74).[7] At an updated analysis of OS conducted a year later, median OS was 13.1 vs 11.7 months (HR = 0.80).[8]

To date, no immunotherapy agents with or without chemotherapy have demonstrated superior OS versus standard of care chemotherapy or have been approved for the first-line treatment of GC/GEJC/EAC. First-line anti- programmed death receptor-1 (PD-1) monotherapy (pembrolizumab) was shown to be non-inferior to platinum doublet chemotherapy in a programmed death ligand 1 (PD-L1) combined positive score (CPS) selected (≥ 1) GC/GEJC population, with a favorable trend in OS observed at a higher CPS cutoff (≥ 10).[18] However, an early detriment with pembrolizumab monotherapy compared with chemotherapy was observed in this study. Furthermore, first-line anti-PD-1 (pembrolizumab) in combination with cisplatin/fluoropyrimidine did not produce significant improvements in OS or progression free survival (PFS) over chemotherapy.[18] In addition, anti-PD-L1 monotherapy (avelumab) did not improve OS compared with chemotherapy in the first-line maintenance setting after 12 weeks of first-line induction chemotherapy.[19]

Overall, since trastuzumab was approved in 2010 based on the Trastuzumab for Gastric Cancer (ToGA) study,[7] no other drugs have demonstrated superior survival benefits over cytotoxic drugs and no other drugs have been approved in the first-line setting. New treatment options with improved survival benefit are needed in first-line GC/GEJC/EAC.

The FDA's Assessment:

FDA generally agrees with the Applicant's position and notes that tegafur/gimeracil/oteracil potassium (S1) is not approved for marketing in the US. Regarding the Applicant's statement on lack of survival benefit of immunotherapies in the first line setting of gastric, gastroesophageal junction, or esophageal adenocarcinoma, following the submission of this application, on March 22, 2021, FDA approved pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy for the treatment of patients with locally advanced or

metastatic esophageal or gastroesophageal junction carcinoma, which includes patients with esophageal adenocarcinoma. This approval was based on the results of a randomized study, KEYNOTE-590, that compared pembrolizumab vs. placebo in patients receiving standard of care chemotherapy. The hazard ratio for overall survival for the comparison pembrolizumab/chemo vs. placebo/chemo was 0.73 (95% CI 0.62, 0.86); however, only 27% of patients had adenocarcinoma histology.

The backbone chemotherapy regimen selected for Study CA209649 (oxaliplatin plus either 5-fluorouracil [FOLFOX] or capecitabine [CAPEOX or XELOX]) is widely used for the first-line treatment of advanced, unresectable, or metastatic G/GEJ/EAC that is HER2-negative. FOLFOX and CAPELOX are both considered to be similar in efficacy based on literature and professional medical association guidelines and are the preferred options in the US. Decisions regarding the choice between 5-fluorouracil (5-FU) and capecitabine are based on provider- and patient-preference, the toxicity profiles, and the route of administration and are not expected to demonstrate a difference in efficacy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Nivolumab monotherapy was first approved by the US Food and Drug Administration (FDA) for the treatment of melanoma on 22-Dec-2014 and is currently approved for many additional tumor types, including hepatocellular carcinoma (HCC), urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), adjuvant melanoma, esophageal squamous cell carcinoma (ESCC) and microsatellite instability-high/ mismatch repair deficient colorectal cancer (MSI-H/dMMR CRC).

The combination of nivolumab plus ipilimumab was first approved by FDA on 30-Sep-2015 in melanoma, and has subsequently been approved for indications in RCC, MSI-H/dMMR CRC, HCC, NSCLC, and malignant pleural mesothelioma.

Nivolumab in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy was approved on 26-May-2020 for NSCLC.

The FDA's Assessment:

FDA agrees.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 2: Key Regulatory Milestones

05-May-2015	Investigational New Drug (IND) 126406 administratively split from nivolumab Parent IND

	100,052
03-Aug-2016	Initial Protocol for Study CA209649 submitted to IND 126406 (Seq 0112)
22-Aug-2016	Orphan Drug Designation granted for nivolumab for the treatment of esophageal cancer (16-5310)
20-Dec-2016	Orphan Drug Designation granted for nivolumab for the treatment of gastric cancer and gastro-esophageal junction cancer (16-5450)
14-Feb-2020	Agreed Initial Pediatric Study Plan (iPSP-9): Agreement issued by the Food and Drug Administration (FDA) for nivolumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction cancer
08-Sep-2020	Teleconference with FDA to discuss participation in the Real-Time Oncology Review (RTOR), Assessment Aid, and Project Orbis Pilot Programs Agreement with the FDA reached on participation in the RTOR, Assessment Aid, and Project Orbis pilot programs for CA209649, including agreement on the proposed content and timelines for RTOR pre-submission packages
14-Oct-2020	RTOR Pre-Submission Package submitted to Biologics Licensing Application (BLA) 125554 based on Study CA209649
15-Oct-2020	FDA preliminary comments received on the planned Type B Pre-supplemental Biologics Licensing Application (sBLA) meeting: • FDA did not object to submission of the proposed sBLA; the final indication will be determined at the time of the sBLA review. • FDA agreed with the proposed efficacy, safety, and clinical pharmacology presentations, and with the content of the sBLA. • FDA agreed with Bristol-Myers Squibb's (BMS') plan not to submit a safety update report.

The FDA's Assessment:

FDA agrees.

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

4.1. Office of Scientific Investigations (OSI)

FDA clinical and statistical review teams determined that inspections were not needed to confirm the integrity of the data submitted in this application. The decision was based upon the extensive clinical experience with nivolumab, the review teams' audits of the datasets, lack of notable patterns in patient enrollment, protocol deviations, or efficacy and safety data across sites that would raise concerns regarding data integrity.

4.2. Product Quality

No new product quality information was submitted.

4.3. Clinical Microbiology

No new microbiology information was submitted.

4.4. Devices and Companion Diagnostic Issues

There is no companion diagnostic for this indication. Patients were enrolled regardless of PD-L1 status, and stratified based on expression of ≥ 1% combined positive score (CPS) cutoff. PD-L1 status was centrally determined using the Agilent/Dako PD-L1 IHC 28-8 pharmDx test according to the manufacturer's instructions with the DAKO Autostainer Link-48 system.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Office of Clinical Pharmacology has reviewed the information contained in BLA 125554 Supplement 91. This sBLA is approvable from a clinical pharmacology perspective. The key review issues with the specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness came from Study CA209649, which demonstrated statistically significant and clinically meaningful improvements in OS and PFS with the recommended dosage regimens of nivolumab 240 mg every 2 weeks (Q2W) or 360 mg every 3 weeks (Q3W) intravenously (IV) in combination with fluoropyrimidine and platinum-containing chemotherapy in patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma (GC/GEJC/EAC). Refer to the FDA's assessment in Section 8.1.2. Study Results from CA209649 for details.
General dosing instructions	The proposed dosage regimens of nivolumab 240 mg Q2W or 360 mg Q3W IV in combination with the respective fluoropyrimidine and platinum-containing chemotherapy regimens, are efficacious with a manageable safety profile.

	A flat dose-response relationship was observed for OS and PFS between 240 mg Q2W and 360 mg Q3W in study CA209649. The exposures of nivolumab at 240 mg Q2W are comparable to those at 360 mg Q3W in patients with first-line (1L) GC/GEJ/EAC.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended based on intrinsic and extrinsic factors.
Immunogenicity	Following the recommended dosage regimens in Study CA209649, the incidence of anti-nivolumab antibodies was 8.8% (60/681) with 2 (0.3%) patients tested neutralizing ADA positive. The incidence of nivolumab ADA did not appear to affect the PK in patients with 1L GC/GEJC/EAC.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Table 3: Summary Statistics of Nivolumab PK Parameter Estimates in the PPK Analysis

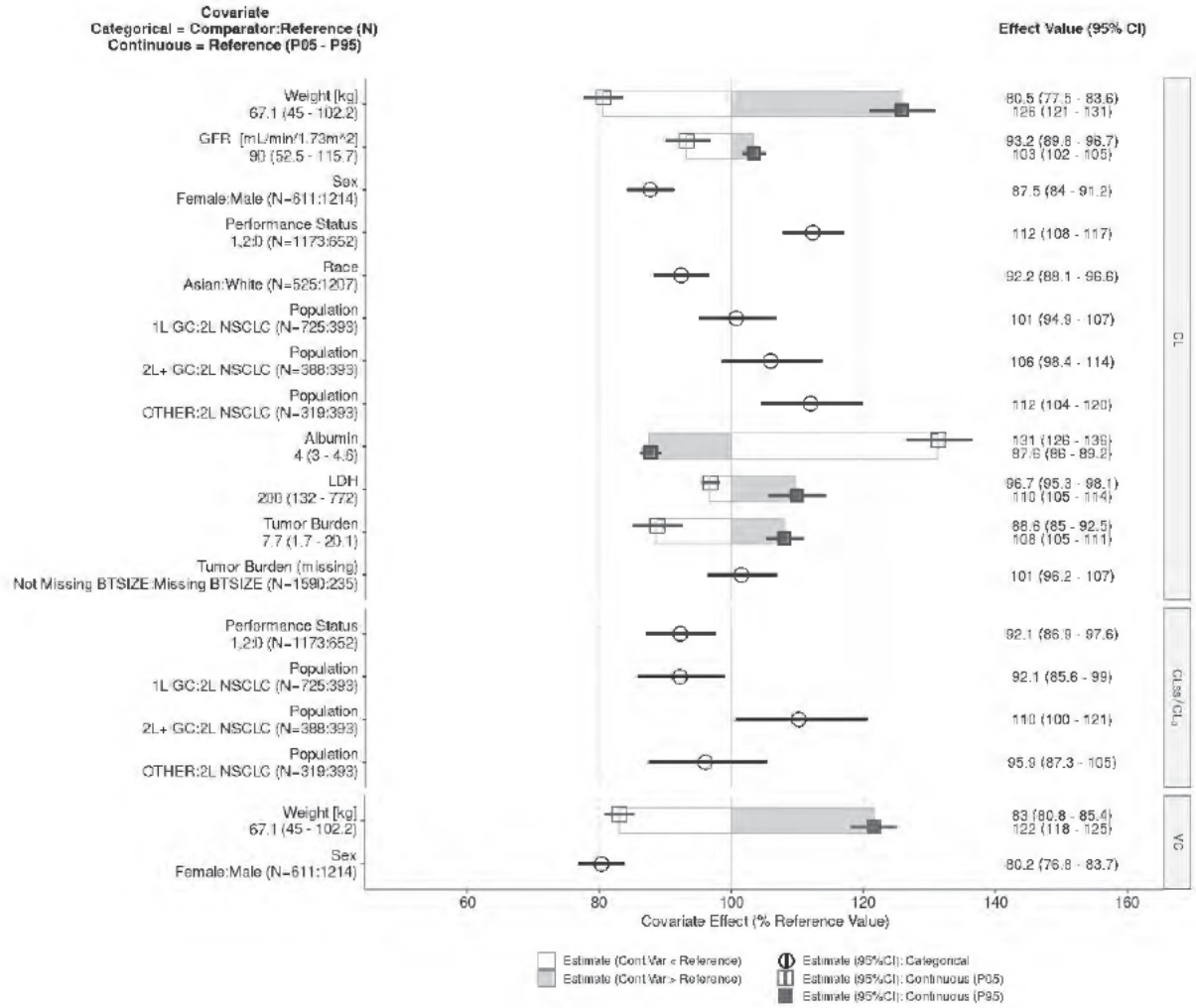
	GeoMean (% CV)		
Nivolumab PK Parameter	**Nivo+Chemo (CA209649) 1L GC/GEJC/EAC (n=725)**	**Nivo Monotherapy (Ono12 and CA209032) 2L+ GC (n=387)**	**All[a] (n=1824)**
CL_{SS} [mL/h]	7.46 (35.0)	9.06 (38.4)	8.25 (46.5)
V_{SS} [L]	6.76 (19.0)	6.51 (21.7)	6.75 (22.7)
$T_{1/2\beta,SS}$[d]	27.4 (25.4)	22.0 (49.7)	24.9 (40.9)

[a] All includes subjects with: 1L GC/GEJC/EAC (n = 725), 2L+ GC (n = 387), NSCLC (n = 393), and other tumor types (n = 319); see Figure 1 for the list of other tumor types.

Abbreviations: 1L - first-line, 2L - second-line, %CV - coefficient of variation expressed as a percentage, CLss - clearance at steady state, EAC - esophageal adenocarcinoma, GC - gastric cancer, GEJC - gastroesophageal junction cancer, PK - pharmacokinetics, PPK - population pharmacokinetics, T1/2β,ss - elimination half-life at steady state Vss - volume of distribution at steady state

Source: Table 5.1.3.1-1 (AdAM dataset: nivoppk.xpt) in CA209649 PPK Report

Figure 1: No Clinically Relevant Covariate Effects on Nivolumab Pharmacokinetic Model Parameters Have Been Identified in the Full Nivolumab Population Pharmacokinetic Model



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is male, PS = 0, eGFR = 90 mL/min/1.73 m2, with baseline albumin of 4.0 g/dL, baseline LDH of 200 IU/L, tumor burden of 7.7 cm, body weight = 67.2 kg, 2L NSCLC tumor type, and race = white or other, defined as not Asian. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Abbreviations: 1L =first-line; 2L = second-line; CI = confidence interval; CL = clearance; CLss = clearance at steady state; CL0 = clearance at time 0; eGFR = estimated glomerular filtration rate; GC = gastric cancer; GFR =

glomerular filtration rate; LDH = lactate dehydrogenase; NSCLC = non small cell lung cancer; PPK = population pharmacokinetic; PS = performance status; VC = volume of the central compartment.

Source: Figure 5.1.1.2-1 (AdAM dataset: nivoppk.xpt) in CA209649 PPK Report

The Applicant's Position:

Pharmacology

Nivolumab is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2. Tumors use PD-L1 expression as defense or escape mechanism against the host's anti-tumor T cell response; inhibiting PD-(L)1 restores the function of these anti-tumor T cells which have become ineffective or suppressed. Therefore, the efficacy of PD-(L)1 inhibition relies on a preexisting immune response.

Chemotherapy is thought to modulate tumor/immune-system interactions in favor of the immune system. Chemotherapy can result in tumor cell death with a resultant increase in tumor antigen delivery to antigen-presenting cells. Tumor cell death may also lead to a reduction in soluble and membrane-bound factors inhibiting tumor-infiltrating T-cells. Chemotherapy may also disrupt immune system regulatory networks by decreasing numbers of T-regulatory cells.[20]

Immunogenic chemotherapy such as oxaliplatin combination with immune checkpoint can trigger T-cell infiltration to tumor and provide additive or synergistic anti-tumor activity in-vivo, and therefore, may contribute to the durable anti-tumor responses.[20,21]

Clinical Pharmacokinetics

A population pharmacokinetic (PPK) analysis was conducted to characterize nivolumab pharmacokinetics (PK) in subjects with previously untreated advanced or metastatic GC, GEJC, or EAC following treatment with nivo+chemo: nivolumab plus capecitabine + oxaliplatin (XELOX) or nivolumab plus leucovorin + fluorouracil + oxaliplatin (FOLFOX). The results from this PPK analysis indicated that nivolumab PK in first-line GC/GEJC/EAC following nivo+chemo is consistent with the known PK characteristics of nivolumab[22] (Table 3; see Figure 1 for the reference population), indicating that co administration with chemotherapy is unlikely to affect nivolumab PK. No covariates were found to have a clinically relevant impact on nivolumab PK (Figure 1).

The FDA's Assessment:

FDA agrees with the Applicant's position that:

- The PK of nivolumab was adequately described by a previously established population PK model which is a linear 2-compartment model with time-varying clearance (CL).
- Co-administration with chemotherapy did not affect the baseline CL of nivolumab. The 21% higher CL at steady state in patients with 2L+ GC compared to patients with 1L GC/GEJ/EAC may hypothetically be due to the difference in tumor burden and less response in patients with 2L+ GC.
- No covariates were found to have a clinically relevant effect on the PK of nivolumab.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data: (supporting the nivo+XELOX and nivo+FOLFOX regimens)

Table 4: OS by Chemotherapy in All Randomized Subjects in CA209649

Chemo Backbone	N	Nivo + Chemo		Chemo		Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs Chemo
		N of events (N of subjects)	mOS (95% CI) (months)	N of events (N of subjects)	mOS (95% CI) (months)	
XELOX	721	255 (360)	14.00 (12.09, 15.57)	272 (361)	11.66 (9.92, 12.78)	0.81 (0.68, 0.96)
FOLFOX	828	283 (422)	13.96 (12.06, 14.82)	300 (406)	11.79 (10.78, 12.62)	0.78 (0.66, 0.91)

Abbreviations: CI - confidence interval, mOS - median overall survival
Source: Figure 7.4.1.1-1 (AdAM datasets: adefttes.xpt, adsl.xpt, adsub.xpt) in CA209649 Primary CSR

Table 5: Grade 3-4 and Grade 5 Safety Summary by Chemotherapy in All Treated Subjects in CA209649

Safety Parameters	No. of Subjects (%)							
	Nivo + XELOX N=360		XELOX N=361		Nivo + FOLFOX N=422		FOLFOX N=406	
	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5
All-causality SAEs	107 (29.7)	44 (12.2)	103 (28.5)	33 (9.1)	174 (41.2)	37 (8.8)	126 (31.0)	30 (7.4)
All-causality AEs	209 (58.1)	44 (12.2)	192 (53.2)	33 (9.1)	331 (78.4)	37 (8.8)	264 (65.0)	30 (7.4)
All-causality AEs leading to discontinuation[a]	94 (26.1)	14 (3.9)	50 (13.9)	7 (1.9)	100 (23.7)	10 (2.4)	63 (15.5)	10 (2.5)
Drug-Related AEs[b]	176 (48.9)	2 (0.6)	140 (38.8)	0	286 (67.8)	2 (0.5)	201 (49.5)	0

[a] Discontinuation could have been discontinuation of 1 or more drugs in the regimen.

[b] AEs could have been related to 1 or more drugs in the regimen.

Abbreviations: AEs - adverse events, SAEs - serious adverse events
Source: Table S.6.1.7.1, Table S.6.1.7.2 (AdAM datasets: adae.xpt, adsl.xpt), Table S.6.1.7.3, and Table S.6.1.7.4 in CA209649 Primary CSR

The Applicant's Position:

Rationale for Dosing Regimen Selection in Pivotal Phase 3 Study CA209649

The selection of the nivolumab dosing regimens for nivo+chemo (nivolumab 360 mg + XELOX every 3 weeks [Q3W] and nivolumab 240 mg + FOLFOX every 2 weeks [Q2W]) for Study CA209649 was informed by the following: clinical efficacy data from the Phase 1/2 study CA209032, clinical safety data from the Phase 1/2 study CA209012, choice of combination

chemotherapy backbone in CA209649, and PK simulation.

Clinical activity of nivolumab monotherapy, 3 mg/kg Q2W, in subjects with previously treated, advanced or metastatic GC or GEJC (n=59) was evaluated in study CA209032. Clinical activity was observed in GC/GEJC patients regardless of PD-L1 expression. Responses (complete responses [CR] or partial responses [PR]) were reported in 6.8% of treated subjects as assessed by blinded independent central review (BICR) (13.6% investigator-assessed) and were durable over time with most responders having a duration of response (DOR) ≥ 6 months. The investigator-assessed median OS was 5.13 months and the OS rates at 3, 6, and 12 months were 70.5%, 50.0%, and 39.4%, respectively. The clinical benefit of nivolumab monotherapy 3 mg/kg Q2W in subjects with metastatic GC/GEJC, who had received 2 or more regimens, was subsequently validated in a double-blind, randomized Phase 3 study ONO-4538-12. In this study, the HR of the nivolumab group relative to the placebo group was 0.60 (95% CI: 0.49, 0.75). The safety profile of nivolumab monotherapy 3 mg/kg Q2W in GC was manageable and consistent with previous reports in other tumor types.
Nivolumab (up to 10 mg/kg Q3W) in combination with platinum doublet chemotherapy was evaluated in chemotherapy-naive subjects with advanced NSCLC in a Phase 1/2 study CA209012. The regimens were well tolerated; no new types of adverse events (AEs) were observed and AEs were manageable with the established treatment algorithms. There were no deaths attributed to study drug toxicity.

Platinum compounds and fluoropyrimidines are generally considered as first-line standard-of-care treatment options in metastatic GC/GEJC/EAC across geographic regions. Two well-established oxaliplatin-based regimens, XELOX (capecitabine + oxaliplatin) Q3W and FOLFOX (5-fluorouracil + leucovorin and oxaliplatin) Q2W, in first-line GC/GEJC/EAC were selected as comparators in CA209649. Investigators could choose either regimen per their local standard.

In order to align nivolumab administration with the administration of the chemotherapy backbone, 2 nivolumab regimens (equivalent to 3 mg/kg Q2W for a patient with body weight 80 kg) were selected: nivolumab 360 mg Q3W to align with the XELOX regimen schedule and nivolumab 240 mg Q2W to align with the FOLFOX regimen schedule. The flat dose was chosen to replace the body weight based regimen in order to reduce the potential for dosing errors. Based on PK simulation, the steady-state average concentration (Cavgss) following administration of nivolumab 240 mg Q2W or 360 mg Q3W are expected to be similar and should still be much lower than the Cavgss for nivolumab 10 mg/kg Q3W in combination with platinum-doublet chemotherapy, which was tested in CA209012. Thus, nivolumab 360 mg + XELOX Q3W and nivolumab 240 mg + FOLFOX Q2W were expected to be efficacious and safe for the treatment of first-line GC/GEJC/EAC subjects and consistent benefit-risk profiles were expected for these 2 regimens. Of note, PK modeling indicated that the overall exposure distribution of 240 mg Q2W or 360 mg Q3W are expected to be similar to that of 3 mg/kg Q2W.

Confirmation of the selected Doses and Regimens
In the pre-specified interim analysis of study CA209649, the nivo+chemo treatments (nivolumab 360 mg + XELOX Q3W and nivolumab 240 mg + FOLFOX Q2W) demonstrated a statistically significant and clinically meaningful improvement in OS and had a clinically manageable safety profile in first-line GC/GEJC/EAC patients. The OS benefit was supported by clinically meaningful improvements in PFS, objective response rate (ORR), and DOR with nivo+chemo vs chemo (see Table 14 and Table 15).

The treatment effect on OS was similar between the 2 regimens with a HR of 0.81 (95% CI: 0.68, 0.96) for the nivolumab 360 mg + XELOX Q3W regimen and a HR (95% CI) of 0.78 (0.66, 0.91) for the nivolumab 240 mg + FOLFOX Q2W regimen (Table 4) in all randomized subjects. From a safety point of view, the safety profile of nivo+chemo was manageable and reflective of the known safety profiles of the nivolumab and chemotherapy components; no new safety signals were identified. It appears that FOLFOX had numerically higher Grade 3/4 toxicity as compared with XELOX, either chemo alone or in combination with nivolumab, but the differences between nivolumab + XELOX and XELOX or nivolumab + FOLFOX and FOLFOX were similar (Table 5). Additionally, results from the PPK analysis also showed comparable nivolumab exposures between these 2 regimens. Taken together, these results support that the 2 recommended nivo+chemo dosing regimens are appropriate as first-line treatment for GC/GEJC/EAC patients and that they offer a consistent benefit-risk profile in the target population.

The FDA's Assessment:

FDA agrees with the Applicant's position that the proposed dosage regimens of nivolumab 240 mg Q2W and 360 mg Q3W in combination with fluoropyrimidine and platinum-containing chemotherapy are acceptable in patients with GC/GEJ/EAC per the following rationales:

- Based on PK simulation, the steady-state average and trough concentrations (Cavgss and Ctroughss) following administration of nivolumab 240 mg Q2W or 360 mg Q3W are expected to be comparable and the steady-state maximum concentration (Cmaxss) is much lower than the Cmaxss achieved with nivolumab 10 mg/kg Q3W.
- A flat dose-response relationship was observed for OS and PFS between 240 mg Q2W and 360 mg Q3W in study CA209649.
- No clear relationship was observed between nivolumab exposure and safety in patients with GC/GEJ/EAC.
- The nivolumab 360 mg Q3W was selected to align with the XELOX regimen schedule and nivolumab 240 mg Q2W was to align with the FOLFOX regimen schedule.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No intrinsic and extrinsic factors were found to have a clinically relevant impact on nivolumab exposures. Therefore, no therapeutic individualization of nivolumab is recommended.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.2.2.3. Outstanding Issues

The Applicant's Position: None

The FDA's Assessment:

FDA concurs.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data

Table 6: Summary of Nivolumab Exposure Following Nivolumab 240 mg + FOLFOX Q2W or 360 mg + XELOX Q3W in First-Line GC/GEJC/EAC

	GeoMean (% CV)[a]		
Summary Exposure (µg/mL)	**240 mg + FOLFOX Q2W (n=392)**	**360 mg + XELOX Q3W (n=333)**	**% Difference GM (G1-G2[a])**
Cavg1	28.5 (21.7)	39.5 (21.2)	-27.8
Cmax1	58.7 (22.5)	93.3 (20.9)	-37.1
Cmin1	18.8 (26.3)	24.1 (27.3)	-22.0
Cavgss	93.2 (33.6)	98.7 (33.3)	-5.57
Cmaxss	134 (28.4)	166 (26.6)	-19.3
Cminss	73.4 (38.5)	70.5 (40.1)	4.11

[a] Geometric mean (GM) difference in percentage of 360 mg Q3W (G2) relative to 240 mg Q2W (G1)

Abbreviations: **%CV**: coefficient of variation expressed as a percentage, **Cavg1**: average concentration within one dosing interval following the 1st dose; **Cmax1**: maximum concentration following the 1st dose; **Cmin1**: minimum concentration following 1st dose; **Cavgss**: average concentration within one dosing interval at steady state; **Cmaxss**: maximum concentration at steady state; **Cminss**: minimum concentration at steady state; **GM**: geometric mean

Source: 5.1.3.1-2 (AdAM dataset: nivoppk.xpt) in CA209649 PPK Report

The Applicant's Position:

Nivolumab PK and Immunogenicity Methods

The following validated methods were used for nivolumab in CA209649: PK concentration measurement: electrochemiluminescence (ECL) Method ICD 416[23] and ECL Method 14BASM122 (China subjects),[24] detection of anti-drug antibodies (ADA): Method ICDIM 140 [25] and 14BASM123 (China subjects), [26] and detection of neutralizing ADA in human serum: Methods 15400[27] and 17BASM155 (China subjects).[28]

The performance of the validated bioanalytical methods used in CA209649 demonstrated that the assays were appropriate for the quantification of nivolumab PK and the assessment of

nivolumab ADAs and neutralizing antibodies in the clinical study serum samples. The human serum assays used for the detection of nivolumab in the clinical trials supporting the PPK analysis were appropriately cross-validated.

Nivolumab PK in First-Line GC/GEJC/EAC patients

Nivolumab PK data from studies CA209649 were pooled with PK data from 6 studies that were conducted in different tumor types (see Figure 1 for the tumor types), including second-line NSCLC (reference population), second-line+ GC/GEJC and others, for an updated PPK analysis. The established nivolumab PPK model, linear 2-compartment time-varying clearance (CL), described nivolumab PK data from Study CA209649 well. Nivolumab PK in first-line GC/GEJC/EAC subjects was consistent with the known nivolumab PK characteristics (Table 6). The geometric mean (CV%) values of nivolumab clearance at steady state (CLss), volume of distribution at steady state (Vss), and elimination half-life at steady state ($T1/2_{\beta,ss}$) following intravenous (IV) administration of nivolumab + chemotherapy in first-line GC/GEJ/EAC subjects were 7.46 mL/h (35.0%), 6.76 L (19.0%), and 27.4 days (25.4%), respectively (Table 3). No covariates were found to have a clinically meaningful effect on nivolumab PK (Figure 1). The difference among the exposure parameters at steady state, including maximum concentration at steady state (Cmaxss), minimum concentration at steady state (Cminss), and Cavgss, was less than 20% between nivolumab 360 mg + XELOX Q3W and nivolumab 240 mg + FOLFOX Q2W (Table 6). In addition, results from the PPK analysis indicated that disease characteristics did not have a clinically meaningful impact on nivolumab exposure in first-line GC/GEJC/EAC subjects, this includes primary tumor location (GC vs GEJ vs EAC), liver metastases (yes/no), and the presence of signet ring cell (yes/no).

Nivolumab Exposure-Response (E-R) Relationships in First-Line GC/GEJC/EAC Patients

E-R analyses of efficacy (OS and PFS) and safety (Grade 2+ immune-mediated adverse events [IMAEs]) will be conducted for CA209649 and the results will be included in the final submission package.

Nivolumab Immunogenicity in First-Line GC/GEJC/EAC patients

Following administration of nivolumab 360 mg Q3W + XELOX or nivolumab 240 mg + FOLFOX, the incidence of nivolumab ADA was 8.8% (10.3% with nivo+XELOX, 7.5% with nivo+FOLFOX) and 0.3% (2 subjects) were neutralizing positive (Table 11.1-1 in the CA209649 Primary CSR). The immunogenicity results observed in CA209649 following nivo+chemo treatment were consistent with those observed in other tumor types following either nivolumab monotherapy or nivolumab in combination with chemotherapy.

Overall, nivolumab immunogenicity did not appear to have an effect on the safety or efficacy of the nivo+chemo regimen in CA209649. The proportions of subjects who experienced AEs in the hypersensitivity/infusion reaction category were similar between ADA positive (18.3%) and ADA

negative (15.8%) subjects. The incidence of ADA did not appear to have negative effects on the efficacy of nivo+chemo in this population as evidenced by the ORR of 56.7% in the ADA positive subjects and 58.0% in the overall nivo+chemo arm. In addition, the overall nivolumab exposure between subjects that were ADA positive were similar to non-ADA positive subjects. The 2 regimens (nivo+XELOX and nivo+FOLFOX) had similar immunogenicity results.

The FDA's Assessment:

FDA agrees with the Applicant's position that

- The assays used in CA209649 are appropriate for the quantification of nivolumab PK and the assessment of nivolumab ADAs and neutralizing antibodies in the clinical study serum samples.
- The PK of nivolumab in first-line GC/GEJC/EAC patients was consistent with the known nivolumab PK characteristics.
- Refer to the FDA's assessment in Section 6.2.2.1. General Dosing for nivolumab Exposure-Response (E-R) analyses in first-line GC/GEJC/EAC patients
- The immunogenicity results observed in Study CA209649 following nivo+chemo treatment were consistent with those observed in other tumor types following either nivolumab monotherapy or nivolumab in combination with chemotherapy. Immunogenicity did not appear to alter the PK of nivolumab in patients with first-line GC/GEJC/EAC.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes, the clinical pharmacology program provides evidence that the selected dosing regimens of nivolumab 360 mg + XELOX Q3W or nivolumab 240 mg + FOLFOX Q2W offers a consistent benefit-risk profile in subjects with previously untreated first-line GC/GEJC/EAC based on statistically significant improvements in OS (HR = 0.80 [95% CI: 0.68, 0.94], p = 0.0002), and PFS per BICR (HR = 0.77 [95% CI: 0.68, 0.87]) with nivo+chemo relative to chemo in Study CA209649. The treatment effect on OS was similar between these 2 regimens: HR (95% CI) of 0.81(0.68, 0.96) for nivolumab 360 mg + XELOX Q3W and HR (95% CI) of 0.78 (0.66, 0.91) for nivolumab 240 mg + FOLFOX Q2W (Table 4) in all randomized subjects. See Section 8.1.2.

The FDA's Assessment:

FDA agrees with the Applicant's position.

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

The Applicant's Position:

Yes, the proposed dosing regimens, nivolumab 360 mg + XELOX Q3W and nivolumab 240 mg + FOLFOX Q2W, are appropriate as first-line therapy in patients with GC/GEJC/EAC, the indication

being sought in this submission. These combination dose regimens were selected based on the observed safety and efficacy data from Studies CA209032 and CA209012, choice of combination chemotherapy backbone in CA209649, and PK simulation (see Section 6.2.2.1). Additionally, the recommended 2 dosing regimens were further supported by the subgroup analyses of clinical efficacy and safety data from first-line GC/GEJC/EAC subjects in the Phase 3 study CA209649 (see Section 6.2.2.1).
In addition, the cumulative dose and relative dose intensity of the individual chemotherapy drugs in the nivo+chemo arm were comparable to that in the chemo arm with the same chemotherapy backbone (Table 6.1.1-1 in the CA209649 Primary CSR). These results indicated that the addition of nivolumab to chemotherapy did not reduce the exposure to the chemotherapy backbone and did not lead to suboptimal chemotherapy doses.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to the FDA's assessment in Section 6.2.2.1. General Dosing for details.

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

The Applicant's Position:

No, an alternative dosing regimen or management strategy is not required for subpopulations based on intrinsic patient factors, which were evaluated in the PPK analysis. Patient intrinsic factors including age, sex, race, and ethnicity did not have a clinically relevant effect on nivolumab PK.

The FDA's Assessment:

FDA concurs with the Applicant's position.

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

The Applicant's Position:

There are no clinically relevant food-drug or drug-drug interactions with nivolumab in combination with chemotherapy in first-line GC/GEJC/EAC patients.

The FDA's Assessment:

FDA concurs with the Applicant's position.

X	X
Primary Reviewer	Team Leader

Refer to signature page

7 Sources of Clinical Data

7.1. Table of Clinical Study (CA209649)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route for this application	Study End-points	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers/ Countries
		Controlled Study to Support Efficacy and Safety*						
CA209-649	NCT02872116	Phase 3, randomized, open-label, 3-arm study of nivo+chemo (nivolumab + oxaliplatin + fluoropyrimidine) or nivo+ipi (nivolumab + ipilimumab) vs chemo (oxaliplatin + fluoropyrimidine) in subjects with previously untreated advanced or metastatic GC/GEJC/EAC	**Nivo+Chemo Arm** Nivolumab + XELOX (Q3W): Nivo 360 mg IV over 30 min on Day 1 + oxaliplatin 130 mg/m^2 IV on Day 1 + capecitabine 1000 mg/m^2 PO BID on Days 1 to 14 Nivolumab + FOLFOX (Q2W): Nivo 240 mg IV over 30 min on Day 1 + oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours or per local standard on Days 1 and 2 **Chemo Arm** XELOX (Q3W): Oxaliplatin 130 mg/m^2 IV on Day 1 + capecitabine 1000 mg/m^2 PO BID on Days 1 to 14 FOLFOX (Q2W): Oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours or per local standard on Days 1 and 2	Efficacy: OS, PFS, ORR, DOR Safety Immuno-genicity, PRO	Until progressive disease, unacceptable toxicity, maximum 2 years of treatment (for nivo only), or subject withdrawal of consent	2687[a] (1581 concurrently randomized: 789 in the nivo+chemo arm and 792 in the chemo arm)	Subjects with previously untreated advanced or metastatic GC/GEJC/EAC	175 sites in 29 countries

[a] The enrolled population contains all concurrently randomized subjects to nivo+chemo and chemo as well as subjects who were screening failures from the start of the 1:1:1 randomization until the end of enrollment.

Abbreviations: BID - twice daily, chemo - chemotherapy, BMS - Bristol-Myers Squibb, DOR - duration of response, EAC - esophageal adenocarcinoma, GC - gastric cancer, GEJC - gastroesophageal junction cancer, IV - intravenous, nivo - nivolumab, ORR - objective response rate, OS - overall survival, PFS - progression-free survival, PO - orally, PRO - patient reported outcomes, QXW - every X weeks

* This submission is only for nivo+chemo vs chemo; BMS remains blinded to the nivo+ipi data.

Source (AdAM datasets): CA209649 Protocol in Appendix 1.1, Table S.2.5.1 (adsl.xpt), Table S.2.6.3 (adsl.xpt), and Table S.3.2.3.1 (adsl.xpt) of the CA209649 Primary CSR

The Applicant's Position:

Efficacy results from the pre-specified analysis of the primary and secondary endpoints comparing the efficacy of nivo+chemo vs chemo in CA209649 provide evidence of efficacy to support the proposed indication of nivolumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the treatment of patients with advanced or metastatic gastric cancer or gastroesophageal junction cancer or esophageal adenocarcinoma (GC/GEJC/EAC). See Section 8.1.2 and Section 8.1.5 for the efficacy results for nivo+chemo vs chemo. Per the statistical analysis plan (SAP), data for the nivo+ipi arm will be analyzed at the time of the final analysis, which is planned in 2021.

The FDA's Assessment:

FDA agrees with the Applicant's summary of Study CA209649.

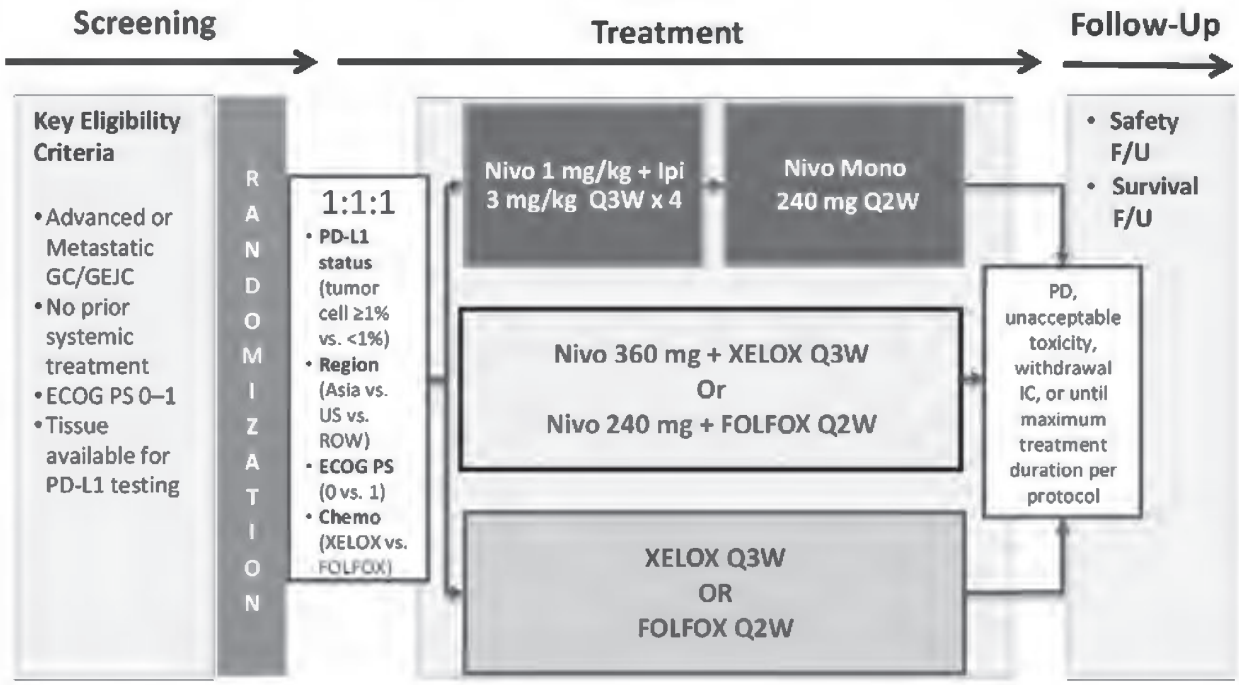
8 Statistical and Clinical Evaluation

8.1. Review of Relevant Trial Used to Support Efficacy -

8.1.1. Study CA209649

Study Design

Figure 2: CA209649 Study Schematic



The Nivo (1 mg/kg) +Ipi (3 mg/kg) arm was closed to enrollment as of 05-Jun-2018.
The study is ongoing and BMS remains blinded to the nivo+ipi data.

Abbreviations: Chemo = chemotherapy, ECOG PS = Eastern Cooperative Oncology Group Performance Status, FOLFOX = leucovorin + fluorouracil + oxaliplatin, F/U = follow-up, GC = gastric cancer, GEJC = gastroesophageal junction cancer, Ipi = ipilimumab, Mono = monotherapy, Nivo = nivolumab, Q2W = every 2 weeks, Q3W = every 3 weeks, PD = progressive disease, PD-L1 = programmed death-ligand 1, ROW = rest of world, XELOX = capecitabine + oxaliplatin

Source: Figure 3.1-1 in Study CA209649 protocol (Appendix 1.1)

The Applicant's Description:

Study CA209649 is a Phase 3, randomized, open-label, 3-arm study of nivo+chemo (nivolumab + oxaliplatin + fluoropyrimidine) or nivo+ipi (nivolumab + ipilimumab) vs chemo (oxaliplatin + fluoropyrimidine) in subjects with previously untreated advanced or metastatic GC/GEJC (Study Design

Figure 2). Note that GEJC largely overlaps with EAC, and per Revised Protocol 04 (Amendment 17), the inclusion criteria were clarified to include EAC in the study population. Subjects in the nivo+chemo arm received nivolumab 360 mg + XELOX (capecitabine + oxaliplatin) Q3W or nivolumab 240 mg + FOLFOX (leucovorin + fluorouracil + oxaliplatin) Q2W.

Efficacy and safety data for nivo+chemo vs chemo from CA209649 support the use of nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with advanced or metastatic GC/GEJC/EAC. Per the SAP, data for the nivo+ipi arm will be analyzed at the time of the final analysis, which is planned in 2021.

In CA209649, subjects were enrolled regardless of PD-L1 expression. Per revised Protocol 07 (dated 14-Sep-2018), the primary population was changed to subjects with PD-L1 CPS ≥ 5 based on the totality of the data (including the correlation with efficacy and the prevalence across CPS cutoffs) from CA209032,[29] KEYNOTE-059[30,] and KEYNOTE-061[31] However, randomization stratified by tumor cell PD-L1 (≥ 1% vs < 1%, including indeterminate) remained unchanged for consistency.

Other stratification factors in CA209649 (in addition to tumor cell PD-L1: ≥ 1% vs < 1%, including indeterminate) were region (Asia [includes China, Japan, Korea, Taiwan, Hong Kong, and Singapore] vs US [includes US and Canada] vs Rest of world [ROW, includes Europe, Australia, and Latin America]), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs 1), and investigator's choice of chemotherapy (XELOX vs FOLFOX).

PD-L1 immunohistochemistry was conducted at a central laborator (b) (4)

(b) (4)

- **Tumor cell PD-L1** was defined as the percent of viable tumor cells with partial or complete membrane staining using the PD-L1 IHC 28-8 pharmDX kit according to the manufacturer's instructions with the DAKO Autostainer Link-48 system (Dako is an Agilent Technologies, Inc. company in Santa Clara, CA).
- **CPS PD-L1** was generated centrally by rescoring PD-L1 stained slides using the CPS algorithm, defined as the number of PD-L1 positive tumor cells (partial or complete

membrane staining), lymphocytes and macrophages (membrane staining and/or intracellular staining) divided by the total number of viable tumor cells multiplied by 100 (PD-L1 IHC 28-8 pharmDx assay).

Enrollment/Assignment to Treatment: After initial eligibility was established and informed consent was obtained, subjects were enrolled into the study via an interactive response technology (IRT) system. Between 17-Apr-2017 and 05-Jun-2018, subjects who met all eligibility criteria were randomized 1:1:1 to treatment with either nivo+chemo (XELOX or FOLFOX), nivo+ipi, or chemo (XELOX or FOLFOX). After 05-Jun-2018 (after the nivo+ipi arm was closed to enrollment per the data monitoring committee [DMC]), eligible subjects were randomized 1:1 to treatment with either nivo+chemo or chemo and stratified using the factors mentioned above.

Trial Locations: 1581 subjects were randomized concurrently to nivo+chemo or chemo at 179 sites in 29 countries: Argentina (82, 5.2%), Australia (38, 2.4%), Brazil (69, 4.4%), Canada (60, 3.8%), Chile (125, 7.9%), China (208, 13.2%), Colombia (31, 2.0%), Czech Republic (15, 0.9%), France (54, 3.4%), Germany (77, 4.9%), Greece (36, 2.3%), Hong Kong (6, 0.4%), Hungary (18, 1.1%), Israel (31, 2.0%), Italy (40, 2.5%), Japan (109, 6.9%), Republic of Korea (8, 0.5%), Mexico (34, 2.2%), Peru (41, 2.6%), Poland (61, 3.9%), Portugal (19, 1.2), Romania (62, 3.9%), Russian Federation (14, 0.9%), Singapore (19, 1.2%), Spain (42, 2.7%), Taiwan (6, 0.4%), Turkey (35, 2.2%), United Kingdom (38, 2.4%), and US (203, 12.8%) (Table S.3.2.3.1 [AdAM dataset: adsl.xpt] in the CA209649 Primary CSR).

Key Inclusion/Exclusion Criteria: The CA209649 study population included adults (≥ 18 years) with inoperable, advanced or metastatic GC/GEJC/EAC, who had histologically confirmed predominant adenocarcinoma and were previously untreated with systemic treatment (including HER2 inhibitors) given as primary therapy for advanced or metastatic disease. Subjects were to have an ECOG PS of 0 or 1. Subjects with known HER2 positive status as well as subjects with untreated central nervous system (CNS) metastases were excluded. Subjects were to have tumor tissue sample available for tumor cell PD-L1 IHC testing at a central laboratory during the screening period, with results to be reported prior to randomization.

***Dose Selection*:** See Section 6.2.2.

Study Treatments

Nivo+Chemo Arm (XELOX or FOLFOX):

- Nivolumab + XELOX (Q3W):
  - nivolumab 360 mg IV over 30 minutes on Day 1
  - oxaliplatin 130 mg/m^2 IV on Day 1
  - capecitabine 1000 mg/m^2 orally twice daily (BID) on Days 1 to 14
- Nivolumab + FOLFOX (Q2W):
  - nivolumab 240 mg IV over 30 minutes on Day 1

- oxaliplatin 85 mg/m^2 IV on Day 1
- leucovorin 400 mg/m^2 IV on Day 1
- fluorouracil 400 mg/m^2 IV on Day 1
- fluorouracil 1200 mg/m^2 IV continuous infusion on Days 1 and 2

Treatment with nivolumab monotherapy (240 mg Q2W, 360 mg Q3W, or 480 mg Q4W) was allowed after treatment with chemo was discontinued.

Chemo Arm (XELOX or FOLFOX):

- XELOX (Q3W):
  - oxaliplatin 130 mg/m^2 IV on Day 1
  - capecitabine 1000 mg/m^2 orally BID on Days 1 to 14
- FOLFOX (Q2W):
  - oxaliplatin 85 mg/m^2 IV on Day 1
  - leucovorin 400 mg/m^2 IV on Day 1
  - fluorouracil 400 mg/m^2 IV on Day 1
  - fluorouracil 1200 mg/m^2 IV continuous infusion on Days 1 and 2

Duration of therapy: Until progressive disease (PD), unacceptable toxicity, a maximum 2-year treatment of nivolumab, or subject withdrawal of consent. Chemotherapy treatment followed local standards. Treatment (nivo or nivo+chemo) beyond initial investigator assessed Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 defined progression was permitted up to 2 years (from the initiation of treatment) in the nivo+chemo arm, if the investigator felt the subject was receiving clinical benefit from treatment and was tolerating treatment [refer to Section 4.5.1.6 of the protocol (Appendix 1.1 of the CA209649 Primary CSR)].

Dose modification: For chemotherapy, dose modification, including dose delay, dose reduction, and discontinuation was allowed per local standards or the package insert. Dose reductions of nivolumab were not permitted. In general for nivolumab, drug-related Grade 2 adverse events (AE)s required a dose delay and Grade 3 or 4 AEs required dose discontinuation. If any component of the chemo regimen was discontinued, the subject could have continued to be treated with the remaining agents. If the chemo regimen was discontinued, the subject could have continued to be treated with nivolumab. Criteria for dose modification are provided in the CA209649 protocol.

***Treatment Compliance*:** Treatment compliance was monitored by drug accountability as well as the subject's medical record and electronic case report form (eCRF).

***Concomitant Medications*:** The following medications are prohibited during the study (unless utilized to treat a drug related adverse event): immunosuppressive agents, immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.2 of the CA209649 Protocol),

any concurrent anti-neoplastic therapy (i.e., surgery, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of GC/GEJC/EAC), Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study. For additional information, refer to Sections 3.4.1 and 3.4.2 of the CA209649 Protocol.

Schedule of Assessments: Assessments for eligibility, safety, efficacy, biomarkers, PK, immunogenicity, and patient reported outcomes (PRO) were performed during screening, on treatment, and follow-up, based on the Schedule of Activities in the protocol. All radiologic tumor imaging from this study were transmitted to a centralized imaging core laboratory for BICR.

***Blinding*:** CA209649 is an open-label study. The study team utilized subject-level data listings only for the purpose of fulfilling Sponsor responsibilities for routine monitoring, assessment of individual patient safety, and data review in accordance with the Data Review Plan. BMS was blinded to aggregated safety and efficacy data by arm. No analyses or summaries by treatment arm were produced during the conduct of the study by the Sponsor. Measures to minimize bias included aspects of the study design and the use of third-parties for critical activities as detailed in Section 4.4.1 of the CA209649 Primary CSR.

Administrative Structure: This study used an independent DMC to ensure the integrity of the study and provide an independent evaluation of the benefit/risk. The DMC Charter outlined the member selection and the process to be followed for communicating recommendations following the DMC meetings. Unblinded data reviewed by DMC at regular safety review meetings were not shared with the Sponsor.
Based on the DMC notification that the PFS and OS at the first formal interim analysis achieved the pre-specified significance levels as specified in the SAP, the study was unblinded for subjects concurrently randomized to the nivo+chemo and chemo arms, and the relevant results are reported in the CA209649 Primary CSR. Note that data to support the nivo + ipi vs chemo comparison are still blinded and will be available at the time of the final analysis in 2021.

The FDA's Assessment:

FDA agrees with the Applicant's description of the trial design.

Study Endpoints

The Applicant's Description:

Key CA209649 objectives/endpoints for nivo+chemo vs chemo are listed in Table 7; the complete list is provided in the CA209649 Primary CSR. A description of the statistical analyses is provided in the section on the SAP below.

Table 7: Key Objectives/Endpoints for Nivo+Chemo vs Chemo (CA209649)

Primary endpoints	• PFS by BICR in subjects with PD-L1 CPS ≥ 5 • OS in subjects with PD-L1 CPS ≥ 5
Secondary endpoints (in hierarchical testing order)	• OS in subjects with PD-L1 CPS ≥ 1 • OS in all randomized subjects.
Secondary endpoints (descriptive)	• OS in subjects PD-L1 CPS ≥ 10 • PFS by BICR in subjects with PD-L1 CPS ≥ 10, 1 or all randomized subjects • ORR by BICR in subjects with PD-L1 CPS ≥ 10, 5, 1 or all randomized subjects
Exploratory Endpoints	• ORR,[a,b] PFS by investigator in subjects with PD-L1 CPS ≥10, 5, 1 or all randomized subjects • OS, PFS,[a] ORR[a,b] in subjects across tumor cell PD-L1 cutoffs • PFS2 or TSST of next line treatment • Duration of response (DOR)[a,b] • Durable response rate (DRR: objective response lasting continuously > 6 months (only in subjects with PD-L1 CPS ≥ 5) [a,b] • PRO in subjects with PD-L1 CPS ≥10, 5, 1, or all randomized subjects • Biomarkers • Safety and tolerability • Immunogenicity

[a] by BICR and investigator

[b] ORR in all randomized subjects; ORR and DOR in subjects with measurable disease

Abbreviations: BICR - blinded independent central review, ORR - objective response rate, OS - overall survival, PD-L1 - programmed death ligand 1, PFS - progression-free survival, PFS2 - PFS after next line of treatment, PRO - patient reported outcomes, TSST - time to second subsequent line therapy

The FDA's Assessment:

FDA agrees with the applicant's description of primary and key secondary endpoints.

Statistical Analysis Plan (SAP) and Amendments

The Applicant's Description:

Power Considerations for the Primary Endpoints

This section summarizes power calculation of the primary endpoints of PFS and OS per Revised Protocol 09 (Amendment 29). The study enrollment was completed prior to Revised Protocol 09 based on the sample size as determined by the Revised Protocol 08 assumptions. Revised Protocol 09 changed the final PFS and interim OS analyses to be conducted at a minimum follow-up time of 12 months and for the final OS analysis to be conducted at a minimum follow-up time of 24 months after the last subject was randomized. Under the assumption that the prevalence of PD-L1 CPS ≥ 5 was 35%, it was estimated that the primary population would consist of 554 subjects concurrently randomized to nivo+chemo and chemo arms. The HR for PFS was modeled as a 2-piece HR with a delayed effect (HR=1) of the first 3 or 6 months followed by a constant HR of 0.56 thereafter. With a type I error of 2% at 12 months minimum follow-up, the expected number of PFS events was estimated to be 497 for a 3-month delay

and approximately 99% power; or 506 for a 6-month delay and approximately 60% power. For OS, the HR was modeled as a 2-piece HR, a delayed effect with a HR of 1 vs chemotherapy for the first 6 months followed by a constant HR of 0.65 thereafter. At 24 months minimum follow-up at final analysis, it was expected that 466 events would be observed providing an adequate power of approximately 85% with a type I error of 3% (2-sided).

The actual observed prevalence of PD-L1 CPS ≥ 5 was 60% in the locked database of 10-Jul-2020 among the randomized subjects pooled over the 3 treatments arms. Therefore, prior to the DMC efficacy review meeting and unblinding of BMS study team, the power for PFS and OS were updated using this actual prevalence of PD-L1 CPS ≥ 5 (reflected in SAP V4.0 Appendix 5 of the CA209649 Primary CSR). Based on randomization schema, the primary population would consist of 949 subjects concurrently randomized to nivo+chemo and chemo. Using the same PFS model as in the design, with 3 months or 6 months delayed treatment effect, the expected number of PFS events would be 841 and 857, with corresponding power of 99.9% and 84%, respectively. For OS, the expected number of events at the final analysis, using the same model as in the design, was 800 events providing a power of 97.9%.

Measures to Ensure Overall Type I Error Control

The hierarchical testing strategy described in Figure 3 ensures a strong control of type I error at a 2-sided significance (alpha) level of 5% for the primary and key secondary endpoints. For the dual primary endpoints of PFS and OS in the comparison of nivo+chemo vs chemo in randomized subjects with PD-L1 CPS ≥ 5, a 2-sided significance level of 2% was allocated to PFS and 3% was allocated to OS. If the OS comparison in subjects with PD-L1 CPS ≥ 5 between nivo+chemo vs chemo was significant, then OS in subjects with PD-L1 CPS ≥ 1 and OS in all randomized were planned to be sequentially tested at a 1.5% significance level.

Figure 3: Testing Procedure for Primary and Secondary Endpoints in CA209649

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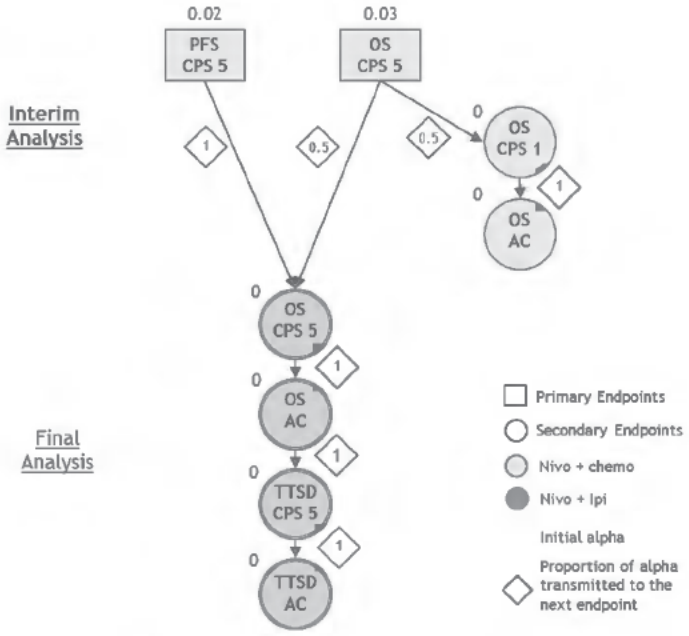

Abbreviations: AC: all comers; chemo: chemotherapy; CPS: combined positive score; ipi: ipilimumab; nivo: nivolumab; OS: overall survival; PFS: progression-free survival; TTSD: time to symptom deterioration.
Source: SAP V4.0 in Appendix 1.11 of the CA209649 Primary CSR

For the OS endpoint which had an interim analysis, the significance levels were distributed using the Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. The nominal significance levels were adjusted according to actual number of events and using the estimated final number of events. For interim analyses of OS in randomized subjects with PD-L1 CPS ≥ 1 and all randomized subjects, the significance levels were obtained using the same information fraction as for randomized subjects with PD-L1 CPS ≥ 5. See Table 13 for the results of the statistical testing hierarchy.

Efficacy Analyses

Efficacy analyses were performed on the population of all subjects randomized (using the IRT) to either the nivo+chemo or chemo arms from 17-Apr-2017 to 27-May-2019. The SAP v3.0 (dated: 03-Jun-2020) was finalized prior to database lock. The SAP v4.0 (dated: 04-Aug-2020), which only updated the power statement based on actual PD-L1 CPS ≥ 5 prevalence, was finalized prior to the DMC meeting.

Primary Endpoints

The dual primary endpoints of PFS by BICR and OS for subjects with PD-L1 CPS ≥ 5 were compared between the nivo+chemo and chemo arms using a 2-sided stratified log rank test. The estimate of the HR between arms was calculated using a stratified Cox proportional hazards model, with treatment as the sole covariate. Ties were handled using the exact method. Confidence intervals (CIs) adjusted for the corresponding significance level for the HR were

provided.
The PFS and OS function for each arm was estimated using the Kaplan-Meier (KM) product limit method and displayed graphically. 2-sided 95% CIs for the median in each arm were obtained via the log-log transformation method. PFS and OS rates at fixed time points were presented along with their associated 95% CIs. These estimates were derived from the KM estimate and corresponding CIs were derived based on the Greenwood[32] formula for variance derivation and on log-log transformation applied on the survivor function.[33] Stratification factors for stratified analyses were region (Asia vs North America [US and Canada] vs ROW), ECOG PS status (0 vs 1), chemotherapy regimen (XELOX vs FOLFOX) and tumor cell PD-L1 (≥ 1% vs < 1% or indeterminate) as recorded in the IRT.

Secondary Endpoints
The analysis methods used for the primary endpoints were also used to analyze OS in subjects with PD-L1 CPS ≥ 1, ≥ 10 (with the exception of log rank test), all randomized subjects, and PFS in PD-L1 CPS ≥ 1, ≥ 10, and all randomized subjects.

Exploratory Endpoints
Best overall response (BOR) was summarized by response category for each arm. ORR (by BICR and investigator) and durable response rate (DRR) (by BICR and investigator) was computed in each arm along with the exact 95% CI using the Clopper-Pearson method. An estimate of the difference in ORRs and DRRs, and corresponding 95% CI was calculated using Cochran-Mantel-Haenszel methodology and adjusted by the randomization stratification factors as recorded IRT. The stratified odds ratios (Mantel-Haenszel estimator) between the arms were provided along with the 95% CI. DOR (BICR and investigator) in each arm was estimated using a KM product-limit method for subjects who achieved PR or CR. Median values along with 2-sided 95% CI were calculated using the KM method. Refer to the CA209649 Primary CSR for information on the analyses of the patient reported outcomes (PRO) data.

Safety: Descriptive statistics of safety were presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. All on-study AEs, drug-related AEs, serious adverse events (SAEs), drug-related SAEs, IMAEs, and other events of special interest (OESIs) were tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study laboratory parameters including hematology, chemistry, liver function and renal function were summarized using worst grade per NCI CTCAE v 4.0 criteria. Frequency, management and resolution of IMAEs were analyzed.

The FDA's Assessment:

FDA generally agrees with the applicant's hierarchical testing plan and multiplicity control for the primary and key secondary endpoints and analysis methods. Regarding the statistical power and sample size calculations, FDA notes that 1581 patients were concurrently randomized 1:1 to nivo + chemo and chemo treatment arms. As stated in the applicant's description, study

enrollment was completed prior to Revised Protocol 09 based on the sample size per the assumptions in Revised Protocol 08. In Revised Protocol 09 and the corresponding SAP amendment 4, the analysis timing was revised to be time-driven rather than event-driven, so the expected number of events for the primary endpoints of PFS and OS in the PDL1 CPS ≥ 5 patient subpopulation were determined based on simulation in EAST 6.4.1. The applicant originally assumed PD-L1 CPS ≥ 5 prevalence of 35% among all randomized patients, and expected 554 concurrently randomized patients with PD-L1 CPS ≥ 5; however, the actual observed prevalence for PDL1 CPS ≥ 5 in the locked database (10-July-2020) was 60%. According to the applicant, prior to DMC efficacy review and unblinding of BMS study team, BMS updated the power calculation for the PFS and OS using the actual prevalence of 60% for the PDL1 CPS ≥ 5 in the randomized patient population in SAP v4.0 Appendix 5 dated 04-Aug-2020. The following table summarizes the key changes in the final SAP amendment related to expected number of events and statistical power.

Table 8: Summary of changes in SAP v4.0

# PD-L1 CPS ≥ 5	554 (based on 35% prevalence)		949 (based on 60% prevalence)	
	PFS	OS	PFS	OS
Min. follow-up/ Expected #events	12 mo./497 (assuming 3 mo. delay) or 506 (assuming 6 mo. delay)	IA: 12 mo./395 Final: 24 mo./466(assuming 6 mo. delay)	12 mo./841 (assuming 3 mo. delay) or 857 (assuming 6 mo. delay)	IA: 12 mo./680 Final: 24 mo./800 (assuming 6 mo. delay)
Average HR	0.66 or 0.80	0.74	0.66 or 0.80	0.74
Control median	5.5 months	11.1 months	5.5 months	11.1 months
Alpha (2-sided)	0.02	0.03 (0.0164 at IA)	0.02	0.03 (0.0164 at IA)
Power	99% or 66%	85% (64% at IA)	99.9% or 84.0%	97.9% (87.3% at IA)

FDA notes that due to the higher than anticipated prevalence of PDL1 CPS ≥ 5 in the randomized patient population, the study may be overpowered for PFS and OS analyses in the PDL1 CPS ≥ 5 patient subpopulation.

FDA further notes that no expected number of events or power specifications were made for testing of the PD-L1 CPS ≥ 1 or the all randomized subjects populations, even though formal tests for PFS and OS were conducted in these populations as per the testing hierarchy. Thus, as stated above, the interim analyses of OS in these populations were tested at significance levels adjusted using the same information fraction as the interim analysis of OS in the PD-L1 CPS ≥ 5

population. While this approach adequately controls type-1 error, FDA notes that it is unlikely that these information fractions would truly be the same across populations. However, given the results (presented later), FDA does not believe any results/conclusions would change even if considering significance levels adjusted using slightly lower information fractions to account for potential differences across populations.

Protocol Amendments (CA209649)

The Applicant's Description:

The original protocol for this study was dated 04-May-2016 (refer to Appendix 1.1A of the CA209649 Primary Clinical Study Report [CSR]). The original study design contained 2 arms: nivo+ipi and chemo (XELOX or FOLFOX); the primary endpoint for the nivo+ipi vs chemo comparison was OS in subjects with tumor cell PD-L1 ≥ 1%.

As of 10-Jul-2020 database lock, there were 29 amendments (including 9 global amendments and 20 country specific amendments) (Table 9). All of the global amendments were based on emerging data external to the CA209649 study. A summary of the 9 global protocol amendments is provided in the table below and additional details on the protocol amendment history and rationale are provided in the CA209649 Primary CSR. Note that the BMS clinical study team remained blinded to the aggregate safety and efficacy data together with treatment assignments up until the 10-Jul-2020 database lock for the protocol-defined interim analysis of OS and the final analysis of PFS.

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Table 9: Summary of the 9 Global Protocol Revisions for CA209649

Document (Amendment) Date	Key Changes in Study Design	Planned Sample Size	Rationale	Total Subjects Randomized at Time of the Amendment
Original Protocol 04-May-2016		750		
Revised Protocol 01 (Amendment 07) 20-Oct-2016	No impact on study design	750	Updated study procedures	0
Revised Protocol 02 (Amendment 08) 07-Dec-2016	Added a new arm nivolumab-plus-chemotherapy (XELOX or FOLFOX) to the study and randomization changed to 1:1:1. OS in subjects with tumor cell PD-L1 ≥ 1% was made the primary endpoint for nivo+chemo vs chemo.	1349	CA209012[34] and KEYNOTE 059[35] data supported the clinical activity of immunotherapy + chemo. The primary endpoint was changed to be consistent for nivo+ipi vs chemo and nivo+chemo vs chemo. Tumor cell PD-L1 ≥ 1% was considered a promising biomarker for immuno-oncology therapy in 2016.	3
Revised Protocol 03 (Amendment 13) 10-May-2017	No impact on study design	1349	Updated study procedures	97
Revised Protocol 04 (Amendment 17) 05-Jan-2018	Changed the primary population to all randomized subjects, and endpoints to OS, PFS and ORR for nivo+chemo vs chemo comparison	1349	Attraction-4 Part 1[36] data supported the clinical activity of nivo+chemo in all randomized subjects with promising ORR and PFS results.	679
Revised Protocol 05 (Amendment 19) 29-May-2018	Increased sample size to 1649	1649	In order to have sufficient sample size for robust analyses at different PD-L1 cutoffs	1158
Revised Protocol 06 (Amendment 20) 11-Jun-2018	Closed nivo+ipi enrollment	1649	Per DMC recommendation: "Due to the concern of the observed increased early death rate in Nivolumab Plus Ipilimumab arm as well as the increased toxicity rate, the DMC recommends to stop the future enrollment of the Nivolumab Plus Ipilimumab arm. The current patients who are already in the Nivolumab Plus Ipilimumab arm should continue as planned, as should the other two arms."	1180

Table 9: Summary of the 9 Global Protocol Revisions for CA209649

Document (Amendment) Date	Key Changes in Study Design	Planned Sample Size	Rationale	Total Subjects Randomized at Time of the Amendment
Revised Protocol 07 (Amendment 23) 14-Sep-2018	Changed the primary population to subjects with PD-L1 CPS ≥ 5 for both comparisons, assumed the prevalence of PD-L1 CPS ≥ 5 as 35% Moved OS to a secondary endpoint for nivo+ipi vs chemo Maintained the primary endpoints of PFS and OS, and moved ORR to secondary endpoint for nivo+chemo vs chemo	1649	CA209032,[29] KEYNOTE-059[30,] and KEYNOTE-061[31] data suggested PD-L1 CPS as a better predictor for efficacy than tumor cell PD-L1 The number of subjects in the nivo+ipi arm was less than targeted due to the early closure of enrollment. Moving the OS endpoint for nivo+ipi vs chemo to a secondary endpoint allocated more alpha to the primary endpoints for nivo+chemo vs chemo. Limited the primary endpoints to PFS and OS for nivo+chemo vs chemo in order to have robust analyses for the primary endpoints.	1462
Revised Protocol 08 (Amendment 26) 15-Nov-2018	Increased sample size to 2005	2005	Initial monitoring of PD-L1 CPS ≥ 5 prevalence in a pooled blinded fashion indicated that the prevalence was lower than the assumed 35%. Increased the total sample size in order to maintain the planned sample size for primary PFS and OS analyses in the primary population	1546
Revised Protocol 09 (Amendment 29) 16-Sep-2019	Changed the primary analyses of nivo+chemo vs chemo from event driven to time-driven with a minimum follow-up of 12 months (for final PFS analysis and interim OS analysis), and 24 months for final OS analysis	2005	KEYNOTE-062[37] study suggested sufficient follow up was needed in order to capture the full treatment effects	2031 (accrual was completed in May 2019)

Abbreviations: chemo: chemotherapy; CPS: combined positive score; DMC: data monitoring committee; FOLFOX: leucovorin + oxaliplatin + 5-fluorouracil; ipi: ipilimumab; nivo: nivolumab; ORR: objective response rate; OS: overall survival; PD-L1: programmed death ligand 1; PFS: progression-free survival; XELOX: oxaliplatin + capecitabine

Source: Appendix 1.1 of the CA209649 Primary CSR

8.1.2. Study Results from CA209649

Compliance with Good Clinical Practices and Methods to Ensure Data Quality and Integrity

The Applicant's Position:

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21 CFR 50).
The protocol, amendments, administrative letters, and subject informed consent form received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Compliance audits were performed as part of implementing quality assurance, and audit certificates are provided as applicable in the individual study reports. The quality of data collected and analyzed was monitored according to BMS standard operating procedures.

CA209649 was conducted as an open-label study; however, the BMS clinical study team was blinded to the aggregate safety and efficacy data together with treatment assignments up until the 10-Jul-2020 database lock for protocol-defined interim analysis of OS and the final analysis of PFS. Measures to minimize bias and preclude dissemination of clinical trial data included procedural and technical access controls and the use of independent third-parties for critical activities; refer to Section 4.4.1 of the CA209649 Primary CSR. For detailed information regarding data collection and quality assurance methods utilized in the study and for more information on the use of a DMC and BICR committee; refer to Section 4.4 of the CA209649 Primary CSR. Significant and relevant protocol deviations are summarized in Section 4.5 of the CA209649 Primary CSR. After review of the reported protocol deviations, it was determined that there was no impact on the interpretability of study results.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Financial Disclosure

The Applicant's Position:

Financial interests or arrangements with clinical investigators have been disclosed (see Appendix 19.2). Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Subinvestigators) participating in the CA209649 clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

The FDA's Assessment:

FDA agrees with the Applicant's description of financial disclosures provided in the application. Additional details are provided in Section 19.2.

Patient Disposition

Data:

The Applicant's Position:

1581 subjects were concurrently randomized (789 to the nivo+chemo arm and 792 to the chemo arm) at 175 sites in 29 countries (see Section 8.1.1 for the trial locations). 1549 subjects were treated: 782 with nivo+chemo and 767 with chemo (Table S.2.6.3 and Table S.2.7.3 in the CA209649 Primary CSR). During the treatment period, the overall rates of discontinuation were 89.3% and 94.9% in the nivo+chemo and chemo arms, respectively. The primary reason in both arms for not completing the treatment period was disease progression.

The FDA's Assessment:

FDA agrees with the Applicant's position. FDA presents details regarding patients who discontinued treatment by study arm, in Table 10 based on a data cutoff of May 27, 2020.

Table 10. Study CA209649: Patient Disposition

n (%)	Nivo + chemo	Chemo	Total
Randomized (efficacy population)	789	792	1581
Treated (safety population)	782 (99)	767 (97)	1549 (98)
Discontinued treatment	698 (89)	728 (95)	1426 (92)
Reason for treatment discontinuation[1]			
Disease progression	515 (66)	528 (69)	1043 (67)
Adverse event	60 (8)	40 (5.2)	100 (6)
Death	0	1 (0.1)	1 (0.06)
Patient request or withdrawal of consent	33 (4.2)	76 (10)	109 (7)
Patient completed treatment	20 (2.6)	0	20 (1.3)
Reason for study discontinuation[1]			
Death	121 (16)	88 (12)	209 (14)
Patient withdrew consent	20 (2.6)	36 (4.7)	56 (3.6)
Lost to follow up / Other	17 (2.2)	18 (10)	35 (2.3)

[1] Percentages based on all treated patients

Source: Reviewer table

At the time of data cutoff, 89% and 95% of patients in the experimental and control arms, respectively, had discontinued treatment. The primary reason for treatment discontinuation was disease progression in both arms. A slightly higher number of adverse events led to treatment discontinuation in the experimental arm (8%) as in the control arm (5.2%).

Protocol Violations/Deviations

The Applicant's Position:

Relevant protocol deviations are deviations related to inclusion or exclusion criteria, study conduct, study management, or subject assessment that were programmable and could potentially affect the interpretability of study results; they are predefined in the SAP.

Overall, relevant protocol deviations (at study entry and on-treatment) were reported in a small number of randomized subjects: 21 (1.3%): 10 (1.3%) in the nivo+chemo arm and 11 (1.4%) in the chemo arm (Table S.2.4.3 [AdAM dataset: adpd.xpt, adsl.xpt] in the CA209649 Primary CSR). After review of the reported protocol deviations, it was determined that there was no impact on the interpretability of study results.

The FDA's Assessment:

FDA reviewed the protocol violations and deviations for Study CA209649 and agrees with the Applicant's assessment. The reported protocol violations and deviation were unlikely to have had an important effect on the overall study results and are unlikely to be a source of bias.

Table of Demographic Characteristics

Data:

Table 11: Frequency of Subjects with Tumor Cell PD-L1 ≥ 1% Among Pre-Specified CPS PD-L1 Populations

	n/N (% of Subjects)		
Pre-Specified Populations	**Nivo+Chemo**	**Chemo**	**Total**
CPS PD-L1 ≥ 5	110/473 (23.3)	120/482 (24.9)	230/955 (24.1)
CPS PD-L1 ≥ 1	122/641 (19.0)	123/655 (18.8)	245/1296 (18.9)
All Randomized	127/789 (16.1)	127/792 (16.0)	254/1581 (16.1)

Tumor cell PD-L1 data are per the IRT system
Abbreviations: Chemo - chemotherapy, CPS - combined positive score, IRT - interactive response technology, Nivo - nivolumab, PD-L1 - programmed death ligand 1
Source: Table S.3.13.1, Table S.3.13.2, Table S.3.13.3 in the CA209649 Primary CSR

Table 12: Key Baseline Characteristics: All Randomized Subjects (CA209649)

	Nivo+Chemo (n = 789)	Chemo (n = 792)
Median age (range)	62.0 (18, 88)	61.0 (21, 90)
Male, n (%)	540 (68.4)	560 (70.7)
Region, n (%)		
Asian	178 (22.6)	178 (22.5)
Asia excluding China	79 (10.0)	69 (8.7)
North America (defined as US and Canada)	131 (16.6)	132 (16.7)
ROW	480 (60.8)	482 (60.9)
Primary Tumor Location at Initial Diagnosis, n (%)		
GC	554 (70.2)	556 (70.2)

	Nivo+Chemo (n = 789)	Chemo (n = 792)
GEJC	132 (16.7)	128 (16.2)
EAC	103 (13.1)	108 (13.6)
Disease Status, n (%)		
Locally recurrent	5 (0.6)	2 (0.3)
Metastatic	757 (95.9)	756 (95.5)
Locally advanced	27 (3.4)	34 (4.3)

Table 10: Key Baseline Characteristics: All Randomized Subjects (CA209649)

	Nivo+Chemo (n = 789)	Chemo (n = 792)
ECOG PS (based on IRT), n (%)		
0	349 (44.2)	349 (44.1)
1	440 (55.8)	443 (55.9)
Subjects with Measurable Disease per BICR, n (%)	603 (76.4)	608 (76.8)
With Liver Metastases, n (%)	301 (38.1)	314 (39.6)
With Peritoneal Metastases, n (%)	188 (23.8)	188 (23.7)
Lauren Classification, n (%)		
Intestinal type	272 (34.5)	267 (33.7)
Diffuse type	254 (32.2)	273 (34.5)
Mixed	58 (7.4)	48 (6.1)
Unknown	205 (26.0)	204 (25.8)
Planned chemotherapy (based on IRT), n (%)		
XELOX	365 (46.3)	370 (46.7)
FOLFOX	424 (53.7)	422 (53.3)
WHO Histological Classification (Cell Type)		
Adenosquamous carcinoma	107 (13.6)	113 (14.3)
Mucinous adenocarcinoma	50 (6.3)	49 (6.2)
Papillary serous adenocarcinoma	7 (0.9)	5 (0.6)
Signet ring Cell	145 (18.4)	136 (17.2)
Tubular adenocarcinoma	128 (16.2)	130 (16.4)
Other	352 (44.6)	357 (45.1)
Not Reported	0	2 (0.3)
HER2 status, n (%)		
Positive	3 (0.4)	4 (0.5)
Negative	459 (58.2)	472 (59.6)
Unknown	5 (0.6)	4 (0.5)
Not reported	322 (40.8)	312 (39.4)
MSI, n (%)		
MSI-H	23 (2.9)	21 (2.7)
MSS	695 (88.1)	682 (86.1)
Invalid	11 (1.4)	17 (2.1)
Not reported	60 (7.6)	72 (9.1)
Tumor cell PD-L1 (based on IRT), n (%)		
>= 1%	127 (16.1)	127 (16.0)
< 1% (or indeterminate)	662 (83.9)	665 (84.0)
Hemoglobin, n (%)		
< 10 g/dl	124 (15.7)	94 (11.9)

	Nivo+Chemo (n = 789)	Chemo (n = 792)
>=10 g/dl	657 (83.3)	669 (84.5)
Not reported	8 (1.0)	29 (3.7)
Albumin, n(%)		
< LLN	179 (22.7)	178 (22.5)
>=LLN	578 (73.3)	581 (73.4)
Not reported	32 (4.1)	33 (4.2)

Abbreviations: BICR - blinded independent central review, EAC - esophageal adenocarcinoma, ECOG - Eastern Cooperative Oncology Group, FOLFOX - 5-fluorouracil + leucovorin and oxaliplatin, GC - gastric cancer, GEJC - gastroesophageal junction cancer, HER2 - human epidermal growth factor receptor 2, IRT - interactive response technology, LLN - lower limit of normal, MSI - microsatellite instability, MSI-H- microsatellite instability high, MSS - microsatellite stable, PD-L1 - programmed death ligand 1, PS - performance status, ROW - Rest of World, WHO - World Health Organization, XELOX - capecitabine + oxaliplatin

Rest of World (ROW) includes Europe, Australia, and Latin America

Source (ADaM datasets): Table S.3.1.3 (adsl.xpt: demographics), Table S.3.3.1.3 (addx.xpt, adsl.xpt: disease characteristics), Table S.3.7.3 (adsl.xpt: lab and tumor assessment), and Table S.5.3.13.3 (PD-L1 and chemo per IRT) in the CA209649 Primary CSR

The Applicant's Position:

Tumor cell PD-L1 at the 1% cutoff was one of the stratification factors (as mentioned in Section 8.1.1); the percentage of subjects with tumor cell ≥ 1% was balanced across the treatment arms in the pre-specified primary efficacy population (subjects with PD-L1 CPS ≥ 5) and in the pre-specified secondary efficacy populations (subjects with PD-L1 CPS ≥ 1 and all randomized subjects) (Table 11).

All Randomized Subjects

Baseline demographic and disease characteristics in all randomized subjects were representative of the advanced or metastatic GC/GEJC/EAC population and balanced between the nivo+chemo and the chemo arms (Table 12).

Overall, the median age of all randomized subjects was 61.0 years (Table 5.2.2-1 in the CA209649 Primary CSR). Most subjects were white (69.4%), male (69.6%) and had an ECOG PS (based on IRT) of 1 (55.9%) (Table S.3.13.3 in the CA209649 Primary CSR). The primary tumor locations were GC (70.2%), GEJC (16.4%), and EAC (13.3%). GEJC represents patients with a diagnosis of GEJ and Siewert-Stein Type II, Type III, or unknown. EAC represents patients with a diagnosis of EAC or GEJC with Siewert-Stein Type I. Most subjects had metastatic disease at initial diagnosis (95.7%). 38.9% and 17.8% of subjects had liver metastases and signet ring cell, respectively.

Per protocol, subjects with known HER2 positive status were excluded. As a HER2 test is a routine diagnostic procedure in first line GC/GEJC across regions, this was not included as a mandatory study procedure in the protocol. 634 out of 1581 randomized subjects (40.1%) did not report HER2 test results, although patients were permitted to have an unknown HER2 status to enroll.

Subjects with PD-L1 CPS ≥ 5

In all randomized subjects, 60.0% (473/789) in the nivo+chemo arm and 60.9% (482/792) in the chemo arm had PD-L1 CPS ≥ 5; PD-L1 CPS ≥ 5 is the primary population. (Table S.9.2.1 [AdAM datasets: adcps.xpt, adsl.xpt] of the CA209649 Primary CSR). Baseline demographic and disease characteristics in subjects with PD-L1 CPS ≥ 5 were consistent with that in all randomized subjects and were balanced between the 2 arms (Table 5.3.2-1 [AdAM datasets: adsl.xpt; addx.xpt, adsl.xpt] of the CA209649 Primary CSR).

The FDA's Assessment:

FDA agrees with the Applicant's description of baseline characteristics with the exception of the PD-L1 status (based on IRT, see below) . FDA notes that the median age of 62 and 61 years (although slightly younger than the median age of diagnosis of gastric cancer, 68 years old) in the nivo+chemo arm and the chemo arm, respectively, and male-predominance in both arms represent the known profile of patients with GC/GEJC/EAC. The chemotherapy regimens XELOX and FOLFOX were administered in approximately 46% and 53% of patients, respectively; the regimens were balanced between study arms.

Patients were enrolled across a broad spectrum of countries with the majority of patients (61% in both arms) being enrolled in countries other than those in North America or Asia and included Australia, South America, Western and Eastern Europe, and Israel. Although only 17% of patients were from North America, the study population does not appear to significantly differ from the US population in terms of disease characteristics.

Tumor cell PD-L1 at 1% cutoff (as determined by a central lab using the Agilent/Dako PD-L1 IHC 28-8 pharmDx test) was one of the stratification factors. However, analyses were conducted using the PD-L1 combined positive score (CPS). CPS was generated centrally by rescoring the tumor cell PD-L1 stained slides using the central lab DAKO CPS algorithm, taking into account immunoreactivity for PDL1 in both tumor cells and tumor associated immune cells (restricted to lymphocytes and macrophages) within or directly associated with tumor cell strands. PD-L1 CPS was quantifiable in all but 5 patients on the chemo arm. Results demonstrated PD-L1 CPS of ≥ 1% in approximately 82% of patients and ≥ 5% in 60% of patients across arms. The rates were balanced between arms.

Microsatellite instability (MSI) status was reported in 91% and 89% of patients in the nivo+chemo and chemo arms, respectively. Approximately 3% of patients in both arms were determined to have MSI-high (MSI-H) tumors. An exploratory analysis suggests that subjects with MSI-H tumors did have a disproportionate OS benefit as compared to subjects with microsatellite stable (MSS) tumors (HR 0.37), but the overall percentage of subjects with MSI-H was low and an exploratory analysis of OS in subjects with MSS alone also demonstrated benefit; see Section 8.1.2.

FDA notes that 7 subjects (3 on the nivo+chemo arm and 4 on the chemo arm) were HER2 positive even though, per protocol, subjects with known HER2+ status were to be excluded from the study. FDA acknowledges that the HER2 status of these subjects could have been

determined post-baseline as HER2 status was not required for randomization. FDA conducted sensitivity analyses excluding these 7 subjects and did not observe a notable impact on the overall study results.

Based on the demographic and baseline characteristics as described, there are no significant imbalances, and this reviewer finds no potential for bias in the safety population or confounders in the efficacy population. As stated in the Applicant's position, FDA acknowledges that baseline demographic and disease characteristics in subjects with PD-L1 CPS ≥5 (n=955) were consistent with those of all randomized subjects and were balanced between arms; FDA further notes that this was also true for subjects with PD-L1 CPS ≥1 (n=1296).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Data and the Applicant's Position of "Other Baseline Characteristics" are provided above and in Table 12. Information on concomitant therapy and subsequent anti-cancer therapy is provided below.

The FDA's Assessment:

See above.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
The Applicant's Position:
Treatment Compliance: Treatment compliance for all treated subjects was monitored by routine monitoring of clinical source documentation and drug accountability, as well as the subject's medical record and CRF.

Concomitant Therapy: Most treated subjects (98.1%) received concomitant medication(s) during the treatment period (Table S.4.8.3 [AdAM datasets: adcm.xpt, adsl.xpt] of the CA209649 Primary CSR). Concomitant immune-modulating medications (IMMs), including corticosteroids, immune-modulating agents, immunosuppressive agents, and glucocorticoids, were administered for management of AEs in 458 (58.6%) subjects in the nivo+chemo arm and 303 (39.5%) subjects in the chemo arm (Table S.6.28.9 [AdAM datasets: adae.xpt, adsl.xpt] of the CA209649 Primary CSR). In subjects with PD-L1 CPS ≥ 5, concomitant medication use was consistent with that for all treated subjects.

Subsequent Anti-Cancer Therapy: In all randomized subjects, subsequent anti-cancer therapy (radiotherapy, surgery, and/or systemic therapy) was received by 297 (37.6%) subjects in the nivo+chemo arm and 326 (41.2%) subjects in the chemo arm (Table S.5.14.3 [AdAM datasets: adcm.xpt; adcms.xpt; adsl.xpt; adxg.xpt; adxp.xpt] of the CA209649 Primary CSR). A numerically higher proportion of subjects in the chemo arm than the nivo+chemo arm received at least 1 subsequent systemic anti-cancer therapy (39.3% vs 34.0%), including immunotherapy (8.1% vs1.5%) and chemotherapy (36.6% vs 32.7%). In subjects with PD-L1 CPS ≥ 5, subsequent anti-cancer therapy use was consistent with that for all randomized subjects.

Rescue Medication Use: Not applicable

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Primary, Secondary, and Other Endpoints (Including Sensitivity Analyses)
Data:

Table 13: Results of the Statistical Testing Hierarchy for OS and PFS (CA209649)

Objectives for Nivo+Chemo vs Chemo	Significance Level	Actual p-Value	Met the Threshold
Primary Objectives			
Compare OS in PD-L1 CPS ≥ 5 subjects	0.016	< 0.0001	Yes
Compare PFS per BICR in PD-L1 CPS ≥ 5 subjects	0.02	< 0.0001	Yes
Secondary Objectives			
Compare OS in PD-L1 CPS ≥ 1 subjects[a]	0.007	< 0.0001	Yes
Compare OS in all randomized subjects	0.007	0.0002	Yes

[a] OS HR = 0.77 (99.3% CI: 0.64, 0.92); median OS for nivo+chemo vs chemo was 13.96 vs 11.33 months

Abbreviations: BICR - blinded independent central review, chemo - chemotherapy, CPS - combined positive score, nivo - nivolumab, OS - overall survival, PD-L1 - programmed death ligand 1, PFS - progression-free survival

Source (AdAM datasets): PD-L1 CPS ≥ 5: Table S.5.22.3 (adefttes.xpt, adsl.xpt: PFS per BICR), Table S.5.22.1 (adefttes.xpt, adsl.xpt: OS); PD-L1 CPS ≥ 1: Table S.5.222.1 (adefttes.xpt, adsl.xpt: OS), all randomized: Table S.5.222.3 (adefttes.xpt, adsl.xpt: OS)

Table 14: Primary Efficacy Endpoints (CA209649)

	All Randomized Subjects with PD-L1 CPS ≥ 5	
Efficacy Parameter	**Nivo+Chemo (N = 473)**	**Chemo (N = 482)**
OS		
Events, n (%)	309 (65.3)	362 (75.1)
Median OS (95% CI)[a], months	14.39 (13.11, 16.23)	11.10 (10.02, 12.09)
HR (CI)[b]	0.71 (98.4% CI: 0.59, 0.86)	
p-value[c]	< 0.0001	
12 month OS Rates (95% CI)[a], %	57.3 (52.6, 61.6)	46.4 (41.8, 50.8)
PFS per BICR (1° Definition)		
Events, n (%)	328 (69.3)	350 (72.6)
Median PFS (95% CI)[a], months	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)
HR (CI)[b]	0.68 (98% CI: 0.56, 0.81)	
p-value[c]	< 0.0001	
12 month PFS Rates (95% CI)[a], %	36.3 (31.7, 41.0)	21.9 (17.8, 26.1)

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. HR is Nivo+Chemo over Chemo.

[c] 2-sided p-value using a stratified log-rank test. Stratified by region (Asia [China, Japan, Korea, Taiwan, Hong Kong, and Singapore] vs US [US and Canada] vs ROW [Europe, Australia, and Latin America]), ECOG (0 vs 1), Tumor Cell PD-L1 (≥ 1% vs <1%/indeterminate) and chemotherapy (XELOX vs FOLFOX).

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months.

Abbreviations: BICR - blinded independent central review, CI - confidence interval, CPS - combined positive score, HR - hazard ratio, OS - overall survival, PD-L1 - programmed death-ligand 1, PFS - progression-free survival

Source (AdAM datasets): Table S.5.22.1 (adefttes.xpt, adsl.xpt: OS), Table S.5.23.1 (adefttes.xpt, adsl.xpt: OS rates), Table S.5.22.3 (adefttes.xpt, adsl.xpt: PFS per BICR), Table S.5.23.3 (adefttes.xpt, adsl.xpt: PFS rates)

Table 15: Efficacy of Nivo+Chemo vs Chemo in All Randomized Subjects (CA209649)

	All Randomized Subjects	
Efficacy Parameter	**Nivo+Chemo (N = 789)**	**Chemo (N = 792)**
OS (formally tested endpoint)		
Events, n (%)	544 (68.9)	591 (74.6)
Median OS (95% CI)[a], months	13.83 (12.55, 14.55)	11.56 (10.87, 12.48)
HR (CI)[b]	0.80 (99.3% CI: 0.68, 0.94)	
p-value[c]	0.0002	
12 month OS rates (95% CI)[a], %	55.0 (51.4, 58.4)	47.9 (44.4, 51.4)
PFS per BICR (1° Definition)		
Events, n (%)	559 (70.8)	557 (70.3)
Median PFS (95% CI)[a], months	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)
HR (CI)[b]	0.77 (95% CI: 0.68, 0.87)	
12 month PFS rates (95% CI)[a], %	33.4 (29.9, 37.0)	23.2 (19.9, 26.7)
ORR per BICR (CR + PR) in Subjects with Measurable Disease		
% (N responders/N)[d]	58.0 (350/603)	46.1 (280/608)
95% CI[d]	(54.0, 62.0)	(42.0, 50.1)
Difference of ORR (95% CI)[e]	12.8 (7.3, 18.2)	
DOR per BICR in Responders with Measurable Disease		
N events/N responders (%)	231/350 (66.0)	206/280 (73.6)
Median (95% CI)[a], months	8.51 (7.23, 9.92)	6.93 (5.82, 7.16)
Min, Max, months	1.0+, 29.6+	1.2+, 30.8+
% with DOR (95% CI)[a] ≥ 12 months	40.4 (34.9, 45.8)	27.9 (22.3, 33.7)

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. HR is Nivo+Chemo over Chemo.

[c] 2-sided p-value using a stratified log-rank test. Stratified by region (Asia [China, Japan, Korea, Taiwan, Hong Kong, and Singapore] vs US [US and Canada] vs ROW [Europe, Australia, and Latin America]), ECOG (0 vs 1), Tumor Cell PD-L1 (≥ 1% vs <1%/indeterminate) and chemotherapy (XELOX vs FOLFOX).

[d] Confirmed CR or PR per RECIST 1.1. CI based on the Clopper and Pearson method.

[e] Strata adjusted difference in response rate (Nivo + Chemo - Chemo) based on DerSimonian and Laird method of

weighting.

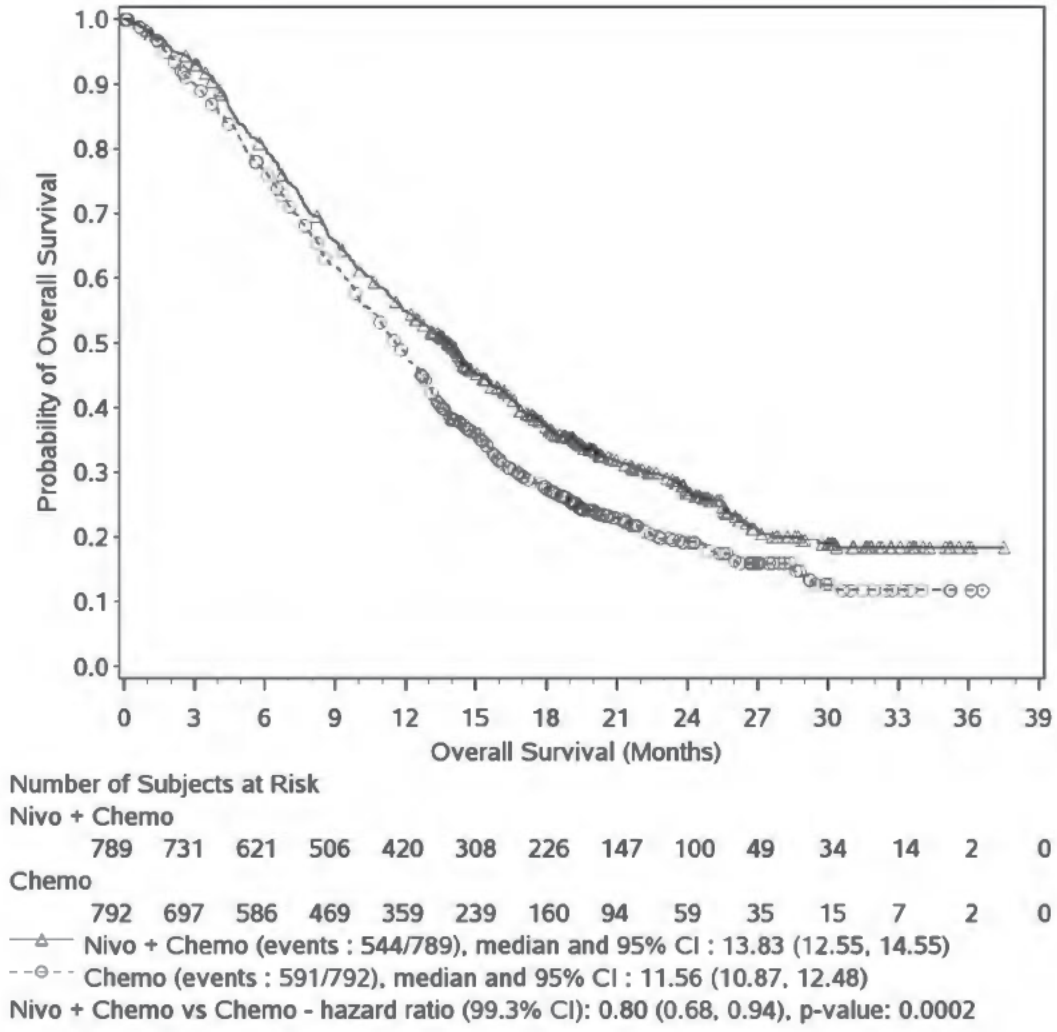
Symbol + indicates a censored value.

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months.

Abbreviations: BICR - blinded independent central review, CI - confidence interval, CR - complete response, DOR - duration of response, ECOG - Eastern Cooperative Oncology Group, HR - hazard ratio, Nivo - nivolumab, ORR - objective response rate, OS - overall survival, PD-L1 - programmed death-ligand 1, PFS - progression-free survival, PR - partial response, RECIST - Response Evaluation Criteria in Solid Tumors, ROW - rest of world

Source (AdAM datasets): Table S.5.222.3 (adefttes.xpt, adsl.xpt: OS), Table S.5.23.16 (adefttes.xpt, adsl.xpt: OS Rates), Table S.5.221.6 (adefttes.xpt, adsl.xpt: PFS per BICR), Table S.5.23.18 (adefttes.xpt, adsl.xpt: PFS rates per BICR), Table S.5.9.13 (adefresp.xpt, adsl.xpt: ORR per BICR, subjects with measurable disease), Table S.5.10.7 (adefresp.xpt, adsl.xpt: DOR per BICR)

Figure 4: Kaplan Meier Plot of Overall Survival - All Randomized Subjects



Symbols represent censored observations. Stratified Cox proportional hazard model for hazard ratio.

Stratified log-rank test for p-value.

Source: Figure 7.4.1-1 (AdAM dataset: adefttes.xpt, adsl.xpt) in the CA209649 Primary CSR

Figure 5 Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - All Randomized Subjects

	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
Overall	1581	544 (789)	13.83 (12.55, 14.55)	591 (792)	11.56 (10.87, 12.48)	0.79 (0.70, 0.89)
Region 1						
Asia	356	116 (178)	16.30 (14.26, 20.21)	129 (178)	12.78 (11.33, 14.62)	0.76 (0.59, 0.97)
US	263	86 (131)	15.11 (11.79, 17.71)	99 (132)	12.09 (10.74, 12.91)	0.67 (0.50, 0.90)
Rest of World	962	342 (480)	12.29 (10.71, 13.83)	363 (482)	10.87 (9.92, 11.76)	0.84 (0.72, 0.97)
Region 2						
Asia [without China]	148	51 (79)	17.97 (16.10, 23.95)	39 (69)	17.05 (13.93, 25.82)	1.19 (0.79, 1.81)
US	263	86 (131)	15.11 (11.79, 17.71)	99 (132)	12.09 (10.74, 12.91)	0.67 (0.50, 0.90)
RoW [including China]	1170	407 (579)	12.62 (11.30, 14.00)	453 (591)	10.84 (9.89, 11.63)	0.79 (0.69, 0.90)
ECOG Performance Status						
0	662	202 (326)	16.69 (14.82, 18.30)	216 (336)	14.09 (12.75, 15.84)	0.86 (0.71, 1.04)
1	914	341 (462)	11.53 (10.22, 13.08)	371 (452)	9.82 (8.41, 10.78)	0.73 (0.63, 0.85)
Not Reported	1	0 (0)	N.A.	1 (1)	7.00 (N.A., N.A.)	
Chemotherapy Regimen						
XELOX	721	255 (360)	14.00 (12.09, 15.57)	272 (361)	11.66 (9.92, 12.78)	0.81 (0.68, 0.96)
FOLFOX	828	283 (422)	13.96 (12.06, 14.82)	300 (406)	11.79 (10.78, 12.62)	0.78 (0.66, 0.91)
Age Categorization						
< 65	961	325 (473)	13.14 (11.66, 14.42)	363 (488)	11.76 (10.87, 12.78)	0.82 (0.71, 0.95)
>= 65 and < 75	466	164 (237)	14.32 (12.19, 16.79)	169 (229)	11.89 (9.99, 13.17)	0.76 (0.61, 0.94)
>= 75	154	55 (79)	14.39 (10.71, 17.18)	59 (75)	9.61 (7.75, 12.71)	0.73 (0.51, 1.06)
>= 65	620	219 (316)	14.39 (12.62, 16.59)	228 (304)	11.27 (9.82, 12.52)	0.75 (0.62, 0.90)
Sex						
Male	1100	367 (540)	14.00 (12.62, 15.28)	414 (560)	11.33 (10.55, 12.48)	0.77 (0.67, 0.88)
Female	481	177 (249)	12.78 (10.84, 14.82)	177 (232)	12.09 (10.48, 12.75)	0.84 (0.69, 1.04)
Race						
Asian	375	121 (186)	16.39 (14.26, 20.21)	138 (189)	12.52 (11.10, 13.96)	0.73 (0.57, 0.93)
White	1097	388 (556)	13.14 (11.63, 14.26)	408 (541)	11.24 (10.15, 12.09)	0.79 (0.69, 0.91)
Other	108	35 (47)	9.69 (6.08, 14.39)	44 (61)	10.87 (8.77, 15.15)	1.05 (0.67, 1.64)
Not Reported	1	0 (0)	N.A.	1 (1)	9.89 (N.A., N.A.)	N.A.
Primary Tumor Location at Initial Diagnosis						
GEJ Cancer (A)	260	92 (132)	13.11 (11.27, 16.23)	89 (128)	12.55 (10.94, 14.09)	0.90 (0.67, 1.21)
Gastric Cancer	1110	379 (554)	14.16 (12.78, 15.28)	424 (556)	11.33 (10.35, 12.52)	0.76 (0.66, 0.87)
Esophageal Adenocarcinoma (B)	211	73 (103)	12.29 (9.89, 15.28)	78 (108)	11.27 (8.48, 12.91)	0.82 (0.60, 1.13)
Disease Stage at Initial Diagnosis						
Stage I-II	76	23 (32)	14.42 (10.55, 24.90)	34 (44)	11.43 (7.00, 14.62)	0.71 (0.42, 1.21)
Stage III	226	74 (108)	14.55 (10.71, 17.51)	88 (118)	11.83 (8.84, 13.54)	0.76 (0.56, 1.04)
Stage IV	1274	446 (646)	13.70 (12.29, 14.49)	468 (628)	11.56 (10.74, 12.52)	0.80 (0.70, 0.91)
Not Reported	5	1 (3)	N.A. (10.84, N.A.)	1 (2)	N.A. (4.01, N.A.)	
Disease Status						
Locally Recurrent/Advanced	68	19 (32)	23.29 (11.76, 27.56)	26 (36)	12.52 (9.56, 18.96)	0.59 (0.33, 1.08)
Metastatic	1513	525 (757)	13.73 (12.32, 14.42)	565 (756)	11.56 (10.81, 12.39)	0.80 (0.71, 0.90)
Prior Surgery Related to Current Cancer						
Yes	336	106 (160)	15.41 (12.06, 16.66)	128 (176)	12.25 (10.84, 13.47)	0.76 (0.59, 0.99)
No	1245	438 (629)	13.57 (11.86, 14.42)	463 (616)	11.33 (10.48, 12.25)	0.79 (0.70, 0.91)
Prior Radiotherapy						
Yes	152	55 (75)	11.79 (7.23, 14.46)	60 (77)	12.09 (8.48, 13.24)	0.92 (0.64, 1.33)
No	1429	489 (714)	14.16 (12.62, 15.01)	531 (715)	11.56 (10.78, 12.52)	0.78 (0.69, 0.88)

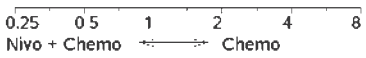


Figure 5: Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - All Randomized Subjects

	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
Lauren Classification						
Intestinal Type	539	173 (272)	15.11 (13.73, 17.97)	197 (267)	12.09 (10.97, 13.27)	0.73 (0.60, 0.90)
Diffuse Type	527	193 (254)	11.63 (9.63, 13.93)	209 (273)	11.20 (9.82, 12.48)	0.91 (0.74, 1.10)
Mixed	106	40 (58)	14.00 (9.89, 17.15)	36 (48)	12.52 (10.02, 13.54)	0.78 (0.50, 1.23)
Unknown	409	138 (205)	13.60 (11.14, 15.28)	149 (204)	10.68 (9.13, 12.94)	0.75 (0.60, 0.95)
WHO Histologic Classification Presence of Signet Ring Cell						
Yes	281	113 (145)	11.04 (8.67, 13.44)	107 (136)	11.24 (9.26, 12.58)	0.96 (0.73, 1.25)
No	1300	431 (644)	14.26 (13.08, 15.57)	484 (656)	11.76 (10.94, 12.62)	0.76 (0.66, 0.86)
TNM Classification Metastasis						
M0	61	17 (30)	16.85 (10.25, 24.90)	22 (31)	13.54 (10.78, 18.96)	0.66 (0.35, 1.25)
M1	1428	499 (715)	13.54 (12.06, 14.39)	530 (713)	11.66 (10.84, 12.52)	0.82 (0.73, 0.93)
Unknown/Mx	22	8 (12)	21.19 (8.05, N.A.)	8 (10)	8.56 (2.17, 15.70)	0.49 (0.18, 1.34)
Not Reported	70	20 (32)	16.23 (10.84, 28.88)	31 (38)	11.01 (7.20, 13.14)	0.47 (0.26, 0.84)
At Least One Target Lesion per BICR						
Yes	1213	416 (605)	13.40 (11.79, 14.49)	466 (608)	10.94 (9.99, 11.66)	0.75 (0.66, 0.86)
No	319	115 (161)	14.00 (11.83, 16.23)	108 (158)	13.54 (12.12, 15.74)	0.99 (0.76, 1.29)
Not Reported	49	13 (23)	24.90 (13.44, 26.55)	17 (26)	17.31 (7.00, 23.26)	0.57 (0.27, 1.20)
Number of Organs with Baseline Lesion Outside Primary Location (Gastric, Gastroesophageal Junction and Esophagus) per BICR						
<= 1	345	105 (166)	16.43 (13.44, 18.40)	124 (179)	15.15 (12.52, 16.79)	0.80 (0.62, 1.04)
>= 2	1236	439 (623)	13.14 (11.66, 14.32)	467 (613)	10.94 (9.95, 11.63)	0.78 (0.69, 0.89)
Time from Initial Disease Diagnosis to Randomization						
< 6 Months	1320	457 (666)	13.80 (12.42, 14.65)	486 (654)	11.47 (10.78, 12.48)	0.78 (0.69, 0.89)
6 Months -< 1 Year	46	11 (15)	10.41 (5.91, 23.39)	24 (31)	15.15 (11.24, 17.74)	1.23 (0.59, 2.55)
>= 1 Year	215	76 (108)	14.29 (9.86, 16.46)	81 (107)	11.37 (8.34, 13.17)	0.77 (0.56, 1.05)
Peritoneal Metastases						
Yes	376	155 (188)	9.49 (8.41, 11.73)	149 (188)	9.95 (8.44, 12.25)	1.03 (0.82, 1.29)
No	1156	376 (578)	14.62 (13.77, 16.46)	425 (578)	11.76 (11.04, 12.62)	0.73 (0.63, 0.84)
Not Reported	49	13 (23)	24.90 (13.44, 26.55)	17 (26)	17.31 (7.00, 23.26)	0.57 (0.27, 1.20)
Liver Metastases						
Yes	615	211 (301)	12.55 (11.24, 14.26)	253 (314)	10.58 (9.17, 11.63)	0.72 (0.60, 0.86)
No	917	320 (465)	14.23 (12.55, 15.51)	321 (452)	12.25 (11.24, 13.11)	0.86 (0.74, 1.00)
Not Reported	49	13 (23)	24.90 (13.44, 26.55)	17 (26)	17.31 (7.00, 23.26)	0.57 (0.27, 1.20)

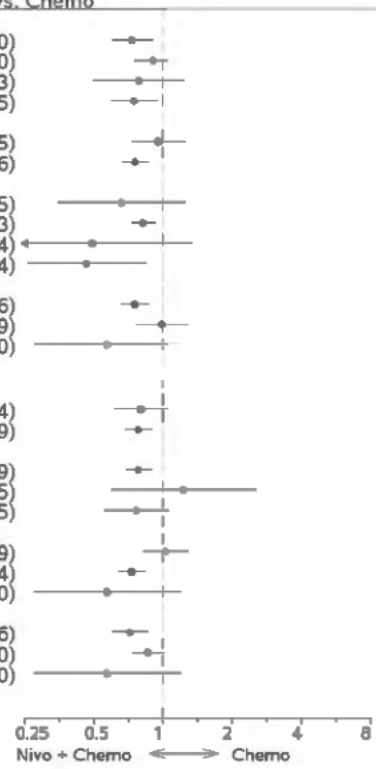
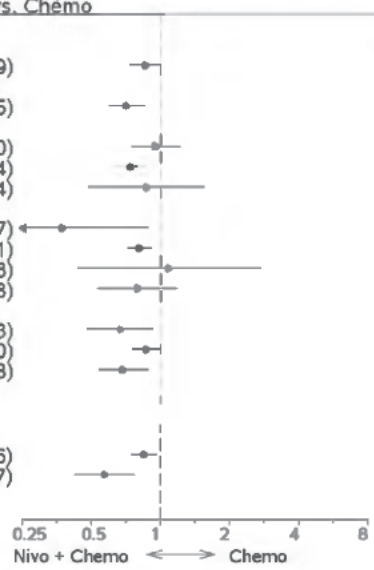


Figure 5: Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - All Randomized Subjects

	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
HER-2 Status at Study Entry						
Positive	7	0 (3)	N.A.	3 (4)	13.34 (7.00, 18.10)	
Negative	931	318 (459)	14.42 (13.57, 16.23)	336 (472)	12.65 (11.89, 13.54)	0.85 (0.73, 0.99)
Unknown	9	4 (5)	10.28 (2.04, 24.15)	3 (4)	6.74 (3.19, N.A.)	
Not Reported	634	222 (322)	11.33 (9.79, 14.00)	249 (312)	9.76 (8.38, 11.04)	0.71 (0.59, 0.85)
Baseline Albumin						
< LLN	357	140 (179)	9.33 (7.66, 11.56)	131 (178)	8.77 (7.20, 9.99)	0.95 (0.75, 1.20)
>= LLN	1159	380 (578)	14.65 (13.96, 16.23)	438 (581)	12.52 (11.63, 13.08)	0.74 (0.64, 0.84)
Not Reported	65	24 (32)	12.12 (7.39, 16.23)	22 (33)	9.13 (6.31, 15.64)	0.86 (0.48, 1.54)
Microsatellite Instability						
MSI-H	44	9 (23)	N.A. (8.38, N.A.)	15 (21)	12.25 (4.11, 21.55)	0.37 (0.16, 0.87)
MSS	1377	483 (695)	13.83 (12.42, 14.62)	507 (682)	11.37 (10.74, 12.48)	0.80 (0.71, 0.91)
Invalid	28	9 (11)	9.26 (4.44, 26.97)	12 (17)	13.70 (7.75, 19.32)	1.08 (0.44, 2.68)
Not Reported	132	43 (60)	11.79 (8.87, 16.66)	57 (72)	11.56 (9.95, 13.54)	0.79 (0.53, 1.18)
H.Pylori						
Yes	210	65 (103)	16.79 (13.60, 20.21)	81 (107)	12.48 (10.78, 14.32)	0.67 (0.48, 0.93)
No	1018	354 (499)	13.08 (11.63, 14.16)	381 (519)	11.37 (10.55, 12.55)	0.86 (0.75, 1.00)
Unknown	352	125 (186)	14.39 (11.73, 16.39)	129 (166)	11.33 (9.30, 12.75)	0.68 (0.53, 0.88)
Not Reported	1	0 (1)	N.A.	0 (0)	N.A.	
Tumor Cell PD-L1 Status						
< 1%	1323	469 (663)	13.60 (12.09, 14.39)	489 (660)	11.99 (11.14, 12.78)	0.85 (0.75, 0.96)
>= 1%	253	75 (126)	15.64 (11.76, 23.06)	97 (127)	9.66 (7.20, 11.24)	0.57 (0.42, 0.77)
Indeterminate/Unevaluable/Not Reported	5	0 (0)	N.A.	5 (5)	9.56 (3.68, 12.52)	

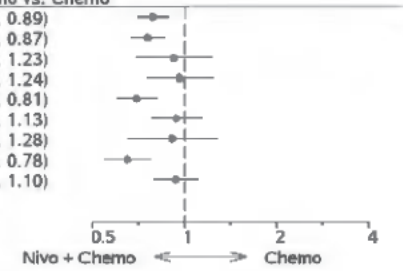


HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.
Rest of World (ROW) includes Europe, Australia, and Latin America.
Asia without China includes Japan, Korea, Taiwan, Hong Kong, and Singapore.
US includes US and Canada.
(A) Gastroesophageal Junction Cancer represents patients with diagnosis GEJ and Siewert-Stein Type II or III or unknown
(B) Esophageal Adenocarcinoma represents patients with diagnosis EAC or Gastroesophageal Junction Cancer with Siewert-Stein Type I

Source: Figure 7.4.1.1-1 (AdAM dataset: adefttes.xpt, adsl.xpt, adsub.xpt) in the CA209649 Primary CSR

Figure 6: Forest Plot of Treatment Effect on OS by PD-L1 CPS Status - All Randomized Subjects

	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
Overall	1581	544 (789)	13.83 (12.55, 14.55)	591 (792)	11.56 (10.87, 12.48)	0.79 (0.70, 0.89)
CPS PD-L1 Expression >= 1	1296	434 (641)	13.96 (12.55, 14.98)	492 (655)	11.33 (10.64, 12.25)	0.76 (0.67, 0.87)
CPS PD-L1 Expression < 1	265	103 (140)	13.08 (9.82, 16.66)	91 (125)	12.48 (10.12, 13.83)	0.92 (0.70, 1.23)
CPS PD-L1 Expression >= 1 and < 5	341	125 (168)	12.29 (9.63, 14.26)	130 (173)	11.99 (10.87, 13.90)	0.97 (0.76, 1.24)
CPS PD-L1 Expression >= 5	955	309 (473)	14.39 (13.11, 16.23)	362 (482)	11.10 (10.02, 12.09)	0.70 (0.60, 0.81)
CPS PD-L1 Expression < 5	606	228 (308)	12.42 (10.61, 14.26)	221 (298)	12.25 (10.97, 13.24)	0.94 (0.78, 1.13)
CPS PD-L1 Expression >= 5 and < 10	187	74 (98)	12.62 (10.71, 16.23)	67 (89)	12.94 (9.40, 14.42)	0.92 (0.66, 1.28)
CPS PD-L1 Expression >= 10	768	235 (375)	15.01 (13.77, 16.79)	295 (393)	10.87 (9.82, 11.83)	0.65 (0.55, 0.78)
CPS PD-L1 Expression < 10	793	302 (406)	12.55 (11.07, 14.19)	288 (387)	12.52 (11.24, 13.27)	0.94 (0.80, 1.10)
CPS PD-L1 Expression Indeterminate/Not Evaluable/Not Reported	20	7 (8)	13.19 (1.22, 19.25)	8 (12)	12.14 (6.97, N.A.)	



HR is not computed for subset category with less than 10 subjects per treatment group.
Program Source: /opt/zfs001/prd/bms237859/stats/ebr2230/prog/figures

Table 16: ORR, CR, and DOR per BICR by CPS PD-L1 Expression at Baseline - All Measurable (BICR) Subjects

CPS Groups	Number of Subjects with Measurable Disease	Nivo + Chemo			Chemo		
	Nivo + Chemo/Chemo Arms	ORR % (95% CI)[a]	CR n/N (%)	DOR (months) Median (95% CI)[b]	ORR % (95% CI)[a]	CR n/N (%)	DOR (months) Median (95% CI)[b]
All Randomized	603/608	58.0 (54.0, 62.0)	59/603 (9.8)	8.51 (7.23, 9.92)	46.1 (42.0, 50.1)	39/608 (6.4)	6.93 (5.82, 7.16)
CPS < 1	93/85	50.5 (40.0, 61.1)	7/93 (7.5)	6.97 (5.16, 11.76)	41.2 (30.6, 52.4)	4/85 (4.7)	6.97 (5.45, 9.69)
CPS ≥ 1	504/515	59.5 (55.1, 63.8)	51/504 (10.1)	8.54 (7.69, 10.22)	46.4 (42.0, 50.8)	32/515 (6.2)	6.93 (5.78, 7.56)
CPS < 5	219/209	55.3 (48.4, 62.0)	14/219 (6.4)	7.69 (6.24, 9.76)	46.4 (39.5, 53.4)	9/209 (4.3)	6.90 (5.72, 8.25)
CPS ≥ 5	378/391	59.8 (54.7, 64.8)	44/378 (11.6)	9.49 (7.98, 11.37)	45.3 (40.3, 50.4)	27/391 (6.9)	6.97 (5.65, 7.85)
CPS < 10	297/281	57.9 (52.1, 63.6)	27/297 (9.1)	7.69 (6.24, 8.64)	47.3 (41.4, 53.3)	15/281 (5.3)	6.90 (5.55, 7.62)
CPS ≥ 10	300/319	58.3 (52.5, 64.0)	31/300 (10.3)	9.82 (8.25, 12.48)	44.2 (38.7, 49.8)	21/319 (6.6)	7.03 (5.65, 8.28)

[a] Confirmed CR or PR per RECIST 1.1. Confidence interval based on the Clopper and Pearson method.

[b] Median computed using Kaplan-Meier method.

Abbreviations: BICR: blinded independent central review; CI : confidence interval; CPS: combined positive score; CR: complete response; DOR: duration of response; ORR: objective response rate; PD-L1: programmed death ligand 1

Source: Table S.5.9.13 (adefresp.xpt, adsl.xpt: ORR per BICR), Table S.5.10.7 (adefresp.xpt, adsl.xpt: DOR per BICR), Table S.9.4.1 (adcps.xpt, adefresp.xpt, adsl.xpt)

The Applicant's Position:
The last subject was randomized on 27-May-2019; the clinical cutoff (last patient last visit [LPLV]) occurred on 27-May-2020, and database lock occurred on 10-Jul-2020. Minimum follow-up (date last subject was randomized to LPLV) was 12.1 months (Table S.5.4.1 [AdAM dataset: adsl.xpt] in the CA209649 Primary CSR). Median follow-up (date of randomization to the last known date alive or death date) was 13.08 months for subjects in the nivo+chemo arm and 11.06 months for subjects in the chemo arm (Table S.5.1.2 [AdAM dataset: adefttes.xpt, adsl.xpt] in the CA209649 Primary CSR).

The pre-specified significance levels for all of the objectives in the statistical testing hierarchy were met at the planned analysis from the 10-July-2020 database lock (Table 13).

Primary Efficacy Endpoint Results
In randomized subjects with PD-L1 CPS $\geq$ 5, statistically significant and clinically relevant improvements in OS and PFS per BICR were observed with nivo+chemo vs chemo (Table 15):

- OS: HR = 0.71 (98.4% CI: 0.59, 0.86); stratified log rank test p value < 0.0001; median OS (95% CI) was 14.39 (13.11, 16.23) vs 11.10 (10.02, 12.09) months
- PFS: HR = 0.68 (98% CI: 0.56, 0.81); stratified log-rank test p value < 0.0001; median PFS (95% CI) was 7.69 (7.03, 9.17) vs 6.05 (5.55, 6.90) months

The robustness of the OS and PFS results for nivo+chemo vs chemo in subjects with PD-L1 CPS $\geq$ 5 were supported by results from pre-specified sensitivity analyses, which were consistent with the primary analyses (refer to Table S.5.322.1 [OS], Table S.5.321.1 [adefttes.xpt, adsl.xpt, adpd.xpt: PFS] in the CA209649 Primary CSR). OS and PFS results in all randomized subjects with PD-L1 CPS $\geq$ 5 for nivo+chemo vs chemo were consistent across most subgroups (refer to Figure 7.2.1.1-1 [adefttes.xpt, adsl.xpt, adsub.xpt: OS], Figure 7.2.2.1-1 [adefttes.xpt, adsl.xpt, adsub.xpt: PFS] in the CA209649 Primary CSR).

Hierarchically Tested Secondary Endpoints
A statistically significant and clinically relevant OS benefit was observed with nivo+chemo vs chemo in subjects with CPS ≥ 1 and in all randomized subjects, the hierarchically tested secondary endpoints (Table 15, Figure 4 [all randomized subjects]; Table 7.1-2 in the CA209649 Primary CSR [subjects with PD-L1 CPS ≥ 1]):

- Subjects with CPS ≥ 1: OS HR = 0.77 (99.3% CI: 0.64, 0.92) stratified log rank test p value < 0.0001; median OS was 13.96 vs 11.33 months, respectively
- All randomized subjects: OS HR = 0.80 (99.3% CI: 0.68, 0.94); stratified log rank test p value = 0.0002; median OS was 13.83 vs 11.56 months, respectively

Other Efficacy Results in All Randomized Subjects
The robustness of the OS results for nivo+chemo vs chemo in all randomized subjects were supported by results from pre-specified sensitivity analyses, which were consistent with the primary analysis (and Table S.5.322.3 [AdAM datasets: adefttes.xpt, adpd.xpt, adsl.xpt] in the

CA209649 Primary CSR).

OS results for nivo+chemo vs chemo in all randomized subjects were consistent across most subgroups including subgroups of region, tumor location, histology type, and metastasis sites (Figure 5).

- The OS HR (95% CI) for nivo+chemo vs chemo was < 1.0 in the following key subgroups: US/Canada (HR = 0.67; 0.50, 0.90), by tumor type, GC (HR =0.76; 0.66, 0.87), GEJC (HR = 0.90; 0.67, 1.21) and EAC (HR= 0.82; 0.60, 1.13), subjects with liver metastases (HR = 0.72; 0.60, 0.86), and tumor cell PD-L1, < 1% (HR = 0.85; 0.75, 0.96) and ≥ 1% (HR = 0.57; 0.42, 0.77).
- A clinically meaningful OS benefit was observed in the subgroup with MSI-H (HR= 0.37; 95% CI: 0.16, 0.87) and the subgroup with microsatellite stable (MSS: HR = 0.80; 95% CI: 0.71, 0.91), although as expected, the benefit was more pronounced in the MSI-H subgroup.
- There were a few subgroups (for example, Asia excluding China) with a small sample size, for which the HR was > 1.0 with wide CIs.

In all randomized subjects, the robust OS benefit was supported by clinically relevant improvements with nivo+chemo vs chemo in all other efficacy endpoints (PFS, ORR, and DOR per BICR) (Table 15).

- PFS (per BICR): HR = 0.77 (95% CI: 0.68, 0.87)
- At baseline, 603 subjects in the nivo+chemo arm and 608 subjects in the chemo arm had measurable disease per BICR. In subjects with measurable disease:
  - ORR per BICR (95% CI) for nivo+chemo vs chemo was 58.0% (54.0, 62.0) vs 46.1% (42.0, 50.1).
  - Median DOR (95% CI) per BICR for nivo+chemo vs chemo was 8.51 (7.23, 9.92) vs 6.93 (5.82, 7.16) months.

In subgroup analyses of OS and PFS by PD-L1 CPS categories, the OS and PFS HRs favored nivo+chemo over chemo (HR < 1.0) across all CPS subgroups, with lower HRs in the CPS ≥ 5 and ≥ 10 subgroups (Figure 6 and Figure S.9.3.5 [PFS: AdAM dataset: adefttes.xpt, adsl.xpt, adsub.xpt] in the CA209649 Primary CSR).

Numerical improvements in ORR and complete response (CR) rates were observed with nivo+chemo vs chemo across CPS subgroups in all randomized subjects with measurable disease, although some CPS subgroups have overlapping 95% CIs (Table 16).

- ORR was numerically higher in the nivo+chemo arm compared with the chemo arm as follows:
  - 13.1%, 14.5%, and 14.1% higher in subjects with PD-L1 CPS ≥ 1, ≥ 5, and ≥ 10, respectively
  - 9.4%, 8.8%, and 10.6% higher in subjects with PD-L1 CPS < 1, < 5 and < 10, respectively
- CR was numerically higher in the nivo+chemo arm compared with the chemo arm as

follows:

- 3.9%, 4.7%, and 3.7% higher in subjects with PD-L1 CPS ≥ 1, ≥ 5, and ≥ 10, respectively
- 2.8%, 2.1%, and 3.8% higher in subjects with PD-L1 CPS < 1, < 5 and < 10, respectively

Median DOR was numerically longer in the nivo+chemo arm compared with the chemo arm as detailed below, although some CPS subgroups have overlapping 95% CIs (Table 16).

- 1.61, 2.52, and 2.79 months longer in subjects with PD-L1 CPS ≥ 1, ≥ 5, and ≥ 10, respectively
- 0.79 months longer in both subjects with PD-L1 CPS < 5 and < 10
- In subjects with PD-L1 CPS < 1, median DOR was 6.97 months in both the nivo+chemo and chemo arms.

In summary, first-line treatment with nivo+chemo demonstrated a statistically significant and clinically relevant OS benefit vs chemo in all randomized subjects with advanced or metastatic GC/GEJC/EAC in the Phase 3 randomized study, CA209649. Results from the subgroup analyses of OS favored nivo+chemo over chemo across most subgroups. In addition, the robust OS benefit that was observed in all randomized subjects was supported by clinically relevant improvements in PFS, ORR, and DOR per BICR.

The FDA's Assessment:

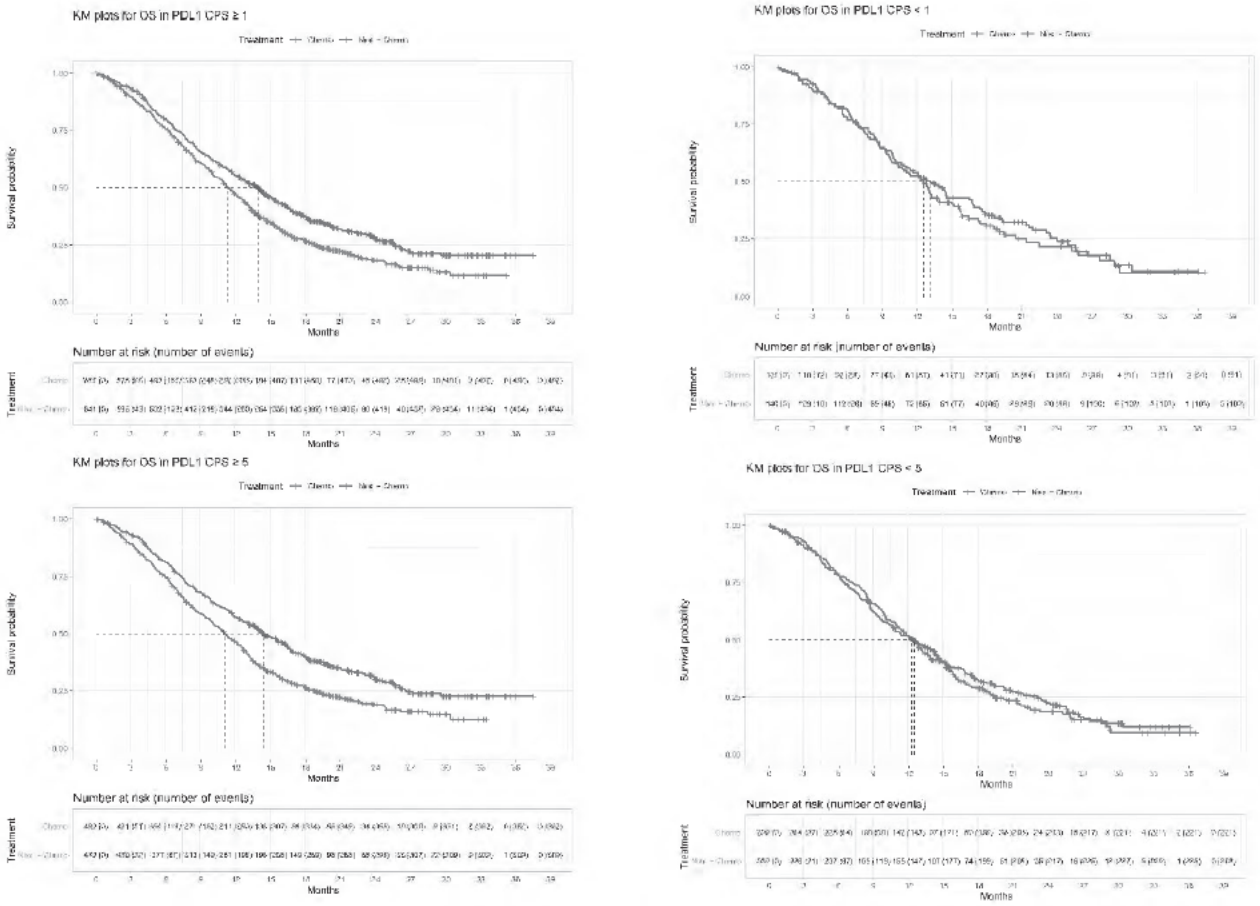
FDA generally agrees with the applicant's primary efficacy results for PFS and OS in the PD-L1 CPS ≥ 5 subgroup. The secondary endpoints that were tested in hierarchy were OS in PD-L1 CPS ≥ 1 and OS in all randomized patients. FDA agrees with the applicant's demonstration of efficacy results based on OS for all randomized patients (HR 0.80, 95% CI 0.71, 0.90). The following table summarizes the OS results by PDL1 subgroups. The stratified HR along with 95% CI were computed for all randomized patients and PDL1 CPS subgroups for consistency and comparability. The OS analyses in PDL1 CPS < 1, <5 <10 and ≥ 10 subpopulations are considered exploratory since no alpha was allocated.

Table 17: Overall Survival Results for all randomized patients and subgroups by PD-L1 CPS status

	Nivo + Chemo		Chemo		Stratified HR (95%CI)	p-value (allocated α)
	Events (N)	mOS (95% CI)	Events (N)	mOS (95% CI)		
All randomized patients	544 (789)	13.8 (12.6, 14.6)	591 (792)	11.6 (10.9, 12.5)	0.80 (0.71, 0.90)	0.0002 (α = 0.007)
PD-L1 Status						
CPS ≥ 1	434 (641)	14 (12.6, 15)	492 (655)	11.3 (10.6, 12.3)	0.77 (0.68, 0.88)	< 0.0001 (α = 0.007)
CPS < 1	103 (140)	13.1 (9.8, 16.7)	91 (125)	12.5 (10.1, 13.8)	0.85 (0.63, 1.15)	-- (α = 0)

CPS ≥ 5	309 (473)	14.4 (13.1, 16.2)	362 (482)	11.1 (10, 12.1)	0.71 (0.61, 0.83)	< 0.0001 (α = 0.016)
CPS < 5	228 (308)	12.4 (10.6, 14.3)	221 (298)	12.3 (11, 13.2)	0.94 (0.78, 1.14)	-- (α = 0)
CPS ≥ 10	235 (375)	15 (13.8, 16.8)	295 (393)	10.9 (9.8, 11.8)	0.66 (0.55, 0.78)	-- (α = 0)
CPS < 10	302 (406)	12.6 (11.1, 14.2)	288 (387)	12.5 (11.2, 13.3)	0.95 (0.8, 1.12)	-- (α = 0)

Figure 7: KM OS Plots in PD-L1 CPS subgroups



FDA did not verify every subgroup result presented by the applicant above. While FDA generally agrees that some OS benefit was observed across most subgroups, the results of these exploratory analyses should be interpreted with caution, and would be considered to be hypothesis generating, particularly in the smaller subgroups with small number of events.

FDA agrees with the applicant's presentation of PFS results for PDL1 CPS ≥ 5 subgroup that was tested as one of the primary endpoints; however, FDA notes that there was only a 1.7 month

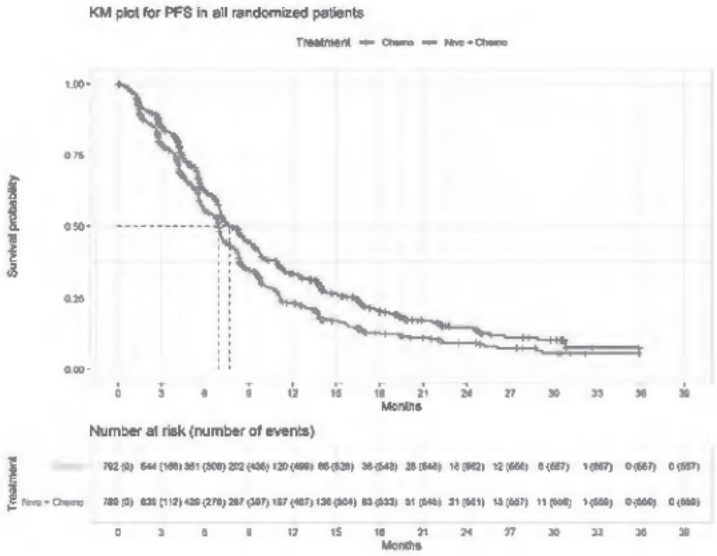
benefit in median PFS for the nivo+chemo arm in the PDL1 CPS ≥ 5 patient subpopulation and that the results were significant potentially due to overpowered hypothesis test. FDA also agrees with the exploratory PFS analysis for all randomized patients; however, the median PFS benefit was only 0.8 months in the nivo + chemo arm compared to chemo. Although the PFS benefit of the addition of nivolumab to chemotherapy appears modest, these results are generally supportive of the benefit observed in overall survival. The following table summarizes the PFS results based on median PFS, stratified HR along with 95% CI in all randomized patients and different PDL1 CPS subgroups. All PFS results except for PDL1 CPS ≥ 5 subpopulation were exploratory since no alpha was allocated.

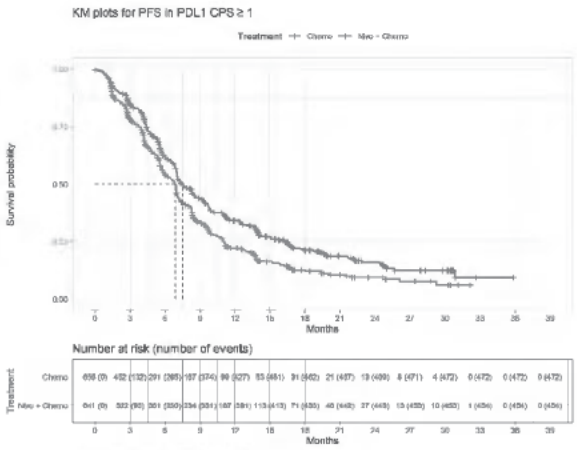
Table 18: PFS results for all randomized patients and PDL1 subgroups

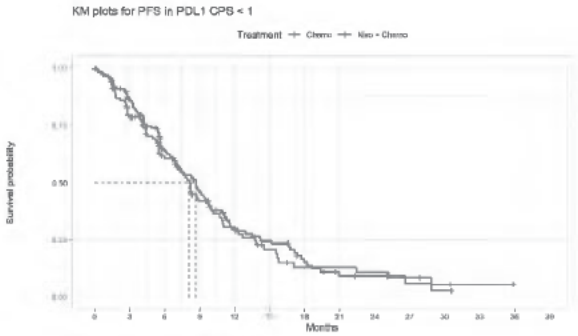
	Nivo + Chemo		Chemo		Stratified HR (95%CI)	p-value (allocated α)
	Events (N)	mPFS (95% CI)	Events (N)	mPFS (95% CI)		
All randomized patients	559 (789)	7.7 (7.1, 8.5)	557 (792)	6.9 (6.6, 7.1)	0.77 (0.68, 0.87)	-- (α = 0)
PD-L1 Status						
CPS ≥ 1	454 (641)	7.5 (7, 8.4)	472 (655)	6.9 (6.1, 7)	0.74 (0.65, 0.85)	-- (α = 0)
CPS < 1	99 (140)	8.7 (6.9, 9.7)	77 (125)	8.1 (6.9, 9.8)	0.83 (0.6, 1.16)	-- (α = 0)
CPS ≥ 5	328 (473)	7.7 (7, 9.2)	350 (482)	6 (5.6, 6.9)	0.68 (0.58, 0.79)	< 0.0001 (α = 0.02)
CPS < 5	225 (308)	7.5 (7, 8.7)	199 (298)	8.1 (7.1, 8.7)	0.93 (0.76, 1.13)	-- (α = 0)
CPS ≥ 10	252 (375)	8.3 (7, 9.7)	289 (393)	5.8 (5.5, 6.9)	0.63 (0.53, 0.75)	-- (α = 0)
CPS < 10	301 (406)	7.5 (7, 8.4)	260 (387)	7.7 (7, 8.3)	0.93 (0.78, 1.1)	-- (α = 0)

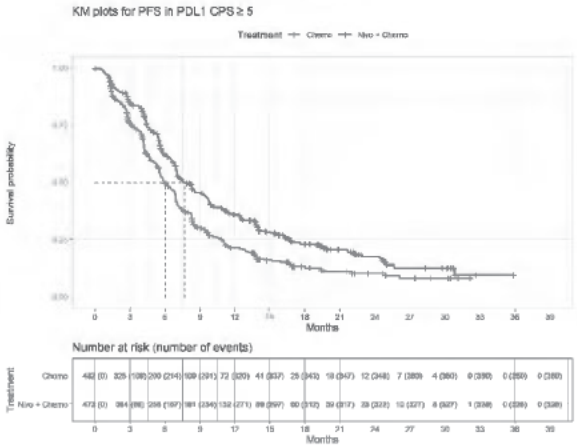
The KM plots for PFS in all randomized patients and in PDL1 CPS subgroups are also presented below in Figure 8.

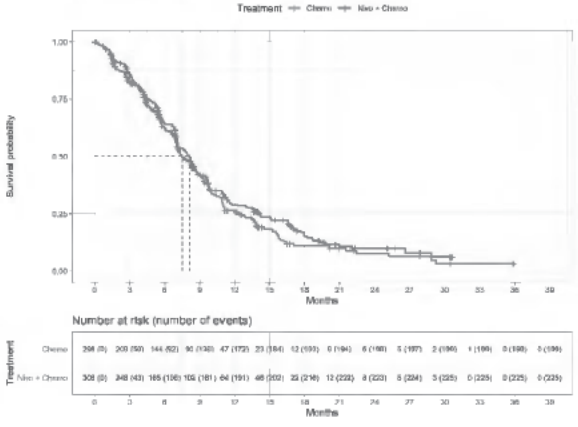
Figure 8: KM PFS Plots in All Randomized Patients and Subpopulations by CPS











FDA acknowledges the applicant's presentation of ORR and DoR results per BICR based on patients with measurable disease at baseline. However, FDA's preferred analysis of ORR and DoR per BICR is based on all randomized patients. All comparative analyses of ORR and DoR are considered exploratory. The following table summarizes the ORR and DoR results for all randomized patients and among patients in the PDL1 CPS subpopulations.

Table 19: ORR and DoR Results for all randomized patients and PDL1 CPS subpopulations

	Nivo + Chemo			Chemo		
	n/N	ORR (95% CI)	Median DoR (95% CI)	n/N	ORR (95% CI)	Median DoR (95% CI)
All randomized patients	370/789	46.89 (43.4, 50.4)	8.5 (7.7, 9.9)	293/792	36.99 (33.6, 40.5)	6.9 (6, 7.6)
CPS ≥ 1	314/641	48.99 (45.1, 52.9)	8.5 (7.9, 10.9)	249/655	38.02 (34.3, 41.9)	6.9 (5.8, 7.6)
CPS < 1	53/140	37.86 (29.8, 46.4)	7 (5.7, 11.8)	38/125	30.4 (22.5, 39.3)	7.1 (5.5, 10.9)
CPS ≥ 5	237/473	50.11 (45.5, 54.7)	9.5 (8.2, 12.2)	184/482	38.17 (33.8, 42.7)	6.9 (5.7, 8)
CPS < 5	130/308	42.21 (36.6, 47.9)	7.7 (6.3, 8.6)	103/298	34.56 (29.2, 40.3)	7 (5.7, 8.3)
CPS ≥ 10	181/375	48.27 (43.1, 53.5)	9.9 (8.5, 12.7)	147/393	37.4 (32.6, 42.4)	7 (5.8, 8.4)
CPS < 10	186/406	45.81 (40.9, 50.8)	7.7 (6.6, 8.5)	140/387	36.18 (31.4, 41.2)	6.9 (5.7, 7.8)

FDA noted in the review of the ORR and DoR results that among all randomized patients (N=1581), there were 33 patients with non-measurable disease at baseline who were reported as responders. FDA sent an IR on 25-Feb-2021 for clarification. BMS' response justified inclusion of these patients in the ORR analyses as patients with non-measurable disease at baseline may still have a complete response based on revised RECIST guideline version 1.1. In addition, FDA verified data for one patient with non-measurable disease at baseline (based on BMS' programmatic definition which considered subjects with baseline efficacy assessments using only PET-CT to be non-measurable) who had a partial response based on measurements from blinded independent review of the CT portion of the PET-CT (allowed by RECIST 1.1, Eisenhauer E., 2009).

The ORR and DoR results for all randomized patients were consistent with the results based on patients with measurable disease. Numerical improvements in magnitude of ORR were observed in the nivo+chemo arm compared to chemo arm based on exploratory analyses.

Overall, all primary and secondary endpoints analyses with pre-specified alpha allocation were

statistically significant. PFS in PDL1 CPS ≥ 5 was tested as a primary endpoint and results were statistically significant. Although the test was overpowered and the median PFS improvement was only 1.7 months for nivo+chemo compared to chemo, the analysis supports the overall survival results. OS results in PDL1 CPS ≥ 5, PDL1 CPS ≥ 1 and all randomized patients, tested in hierarchy, were statistically significant. While the estimation of treatment effect on OS endpoint in PDL1 CPS < 5 (HR: 0.94, 95% CI: 0.78, 1.14) and PDL1 CPS < 1 (HR: 0.85, 95% CI: 0.63, 1.15) were numerically in the same direction and supportive of the OS results in PDL1 CPS ≥ 5, PDL1 CPS ≥ 1 and all randomized patients, the upper limit of the 95% CI of estimated OS HR exceeded 1 for the PDL1 CPS < 5 and < 1 subgroups. However, the study was not designed to study these PD-L1 low populations so these subgroup results are considered exploratory. Furthermore, exploratory subgroup analyses of ORR in the PD-L1 low subgroups showed consistent improvements in anti-tumor activity for nivo+chemo compared to chemo. Given that all pre-specified analyses for which there was alpha allocation were statistically significant and the overall survival analyses were clinically meaningful, FDA is granting the indication to all randomized patients.

Dose/Dose Response

The Applicant's Position:

Results of the E-R analyses supporting the CA209649 clinical efficacy results will be included in the final submission package.

The FDA's Assessment:

See Section 19.4.

Durability of Response

The Applicant's Position:

As of the 10-Jul-2020 database lock (minimum follow-up of 12.1 months), a higher proportion of randomized subjects in the nivo+chemo arm were continuing treatment compared with the chemo arm (10.7% vs 5.1%) (Table 5.2.1-1 [AdAM dataset: adsl.xpt] in the CA209649 Primary CSR).

A statistically significant and clinically relevant improvement in OS was observed with nivo+chemo vs chemo in all randomized subjects: HR = 0.80 (99.3% CI: 0.68, 0.94); stratified log rank test p value = 0.0002 (Table 15). This OS benefit increased over time as evident in the increased separation of the OS KM curves for nivo+chemo vs chemo over time (Figure 4) and the larger difference in OS rates for nivo+chemo vs chemo over time (a difference of 3.8% in the 6-month rates and 7.1% in the 12-month rates). These OS data suggest that the nivo+chemo combination has improved durability compared with chemo.

As described with OS above, the PFS (per BICR) benefit also increased over time. There was

increased separation of the PFS KM curves for nivo+chemo vs chemo over time (Figure 7.4.2-1 [AdAM datasets: adefttes.xpt, adsl.xpt] in the CA209649 Primary CSR). There was a larger difference in PFS rates for nivo+chemo vs chemo over time (a difference of 6.9% in the 6-month rates and 10.2% in the 12-month rates) (Table S.5.23.18 [AdAM dataset: adefttes.xpt, adsl.xpt] in the CA209649 Primary CSR). Note that 70.8% and 70.3% of all randomized subjects in the nivo+chemo and chemo arms, respectively, have had PFS events; therefore, there may be an increased difference in PFS with nivo+chemo vs chemo over time with additional follow-up.

The ORR and DOR data also support an improved durability of response with nivo+chemo vs chemo. In all randomized subjects with measurable disease, ORR was higher with nivo+chemo vs chemo (58.0% vs 46.1%) and the median DOR (95% CI) for all confirmed responders was longer with nivo+chemo than with chemo: 8.51 (7.23, 9.92) vs 6.93 (5.82, 7.16) months; these medians are likely to change with longer follow-up (Table 15). In addition, a higher proportion of responders with measurable disease in the nivo+chemo arm had a DOR $\geq$ 12 months compared with the chemo arm (40.4% vs 27.9%.).

The statistically significant improvement in OS and the clinically relevant treatment response durations and PFS per BICR with nivo+chemo vs chemo in all randomized subjects demonstrate the durability of benefit with nivo+chemo combination treatment. The CA209649 study is ongoing to follow up on the long-term efficacy and safety of nivo+chemo vs chemo.

The FDA's Assessment:

FDA generally does not use landmark analyses for OS and PFS in the evaluation of durability of response. In general, landmark analyses are discouraged as they are performed at a specific time point rather than assessing the entire distribution, and estimates are affected by censoring and length of follow-up. Instead, FDA's assessment of durability of response is based on the exploratory analysis of DoR in all randomized patients. The median DoR was numerically higher in nivo+chemo compared to chemo. The median DoR in the nivo+chemo arm was 8.5 months (95% CI: 7.7, 9.9) and 6.9 months (95% CI: 6, 7.6) in the chemo arm. For additional details see FDA assessment of efficacy above.

Persistence of Effect

The Applicant's Position: Not applicable.

The FDA's Assessment:

Persistence of effect is a term better suited for continuous variables (e.g., hypertension, biomarker assessments, etc.) and is not intended to characterize or compare treatment effects on selected endpoints. Treatment effect and study outcomes are described elsewhere in this section.

Efficacy Results –Exploratory COA (PRO) endpoints

The Applicant's Position:

In all randomized subjects, PRO results for nivo+chemo and chemo were comparable in subjects with advanced or metastatic GC/GEJC/EAC, as measured by the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) total score and Gastric Cancer Subscale (GaCS), the EQ-5D visual analogue score (VAS) and utility index (UI) (Section 11.2.1 of the CA209649 Primary CSR).

The FDA's Assessment:

FDA reviewed the applicant's presentation of PRO results in the CA209649 Primary CSR. As described by the applicant, the study included PRO endpoints as exploratory endpoints as measured by the FACT-Ga including GaCS and EQ-5D-3L. FDA did not conduct independent analyses of the PRO endpoints.

PRO assessments of FACT-Ga and EQ-5D-3L were conducted at baseline and every 6 weeks (±3 days) from Cycle 1 Day 1 (C1D1), regardless of the treatment schedule during the treatment period. Per the applicant, completion rates for the FACT-Ga and EQ-5D-3L were ≥ 90% at baseline and ≥ 80% at most subsequent assessments during the treatment period when at least 10 patients were eligible to respond.

FDA does not agree with the applicant's claim that, in all randomized subjects, PRO results for nivo+chemo and chemo were comparable as measured by the FACT-Ga total score and GaCS, and EQ-5D VAS and UI because failure to demonstrate differences does not imply that the results are comparable. Also, FDA notes that the study was open-label, and therefore patient knowledge of treatment assignment may introduce bias in both the completion of PRO instruments, and in the results. Additionally, there was no alpha allocated to the PRO endpoints, and therefore all PRO results are considered exploratory and therefore comparative claims are unsupported.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position: Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.3. Integrated Review of Effectiveness

The Applicant's Position: Not applicable.

The FDA's Assessment:

All primary and secondary endpoints analyses with pre-specified alpha allocation were statistically significant. OS results appeared consistent based on exploratory subgroups analysis.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position: Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Additional Efficacy Considerations

The Applicant's Position: Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

CA209649, a Phase 3 study in subjects with previously untreated advanced or metastatic GEJC/GC/EAC, met all of the objectives (primary and secondary) in the statistical testing hierarchy at the planned analysis from the 10-July-2020 database lock (minimum follow-up 12.1 months).

In all randomized subjects, a statistically significant and clinically relevant improvement in OS was observed with nivo+chemo vs chemo. This OS benefit of nivo+chemo vs chemo was supported by clinically relevant improvements in PFS, ORR, and DOR per BICR. The OS survival benefit with nivo+chemo vs chemo was also supported by subgroup analyses, which included subgroups of age, gender, tumor location, histology, metastatic sites, and biomarkers (tumor cell PD-L1, PD-L1 CPS, and MSI status). In subgroup analyses of OS and PFS [not shown] by PD-L1 CPS categories, the OS and PFS HRs favored nivo+chemo over chemo (HR < 1.0) across all CPS subgroups, with lower HRs in the CPS $\geq$ 5 and $\geq$ 10 subgroups. In subjects with measurable disease, ORR [including CR rates] also favored nivo+chemo over chemo across all PD-L1 CPS subgroups, with longer DOR with nivo+chemo in most subgroups.
Study CA209649 was an adequate and well-controlled clinical trial and the data submitted meet the statutory evidentiary standard for substantial evidence of effectiveness. The data support the proposed indication of nivolumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the treatment of previously untreated patients with advanced or

metastatic GEJC/GC/EAC.

The FDA's Assessment:

FDA generally agrees with the applicant's position. Also, see FDA assessment in section 8.1.2 and 8.1.3

8.2. Review of Safety

The Applicant's Position:

The overall safety profile of nivo+chemo (nivolumab 240 mg Q2W + FOLFOX Q2W or nivolumab 360 mg Q3W + XELOX Q3W) was manageable using existing treatment algorithms, with no new safety signals identified. The main population for the evaluation of safety (nivo+chemo vs chemo) is all treated subjects (see Section 8.2.4).

The FDA's Assessment:

See subsections below for the review of safety.

8.2.1. Safety Review Approach

The Applicant's Position:

The nivo+chemo safety data are from the pivotal study, CA209649, a randomized Phase 3 trial evaluating nivo+chemo (FOLFOX or XELOX) vs chemo (FOLFOX or XELOX). Data in all treated subjects in the nivo+chemo (N = 782) and chemo (N = 767) arms are based on the clinical cutoff date of 27-May-2020 and a database lock date of 10-Jul-2020, with a minimum follow-up of 12.1 months.

Safety analyses were conducted by treatment arm in all treated subjects who received at least 1 dose of study drug. Safety presentations of AEs, SAEs, AEs leading to discontinuation, and laboratory abnormalities are based on all treated subjects using a safety window of 30 days after last dose. The 30-day safety window was intended to provide a characterization of the safety experience of nivo+chemo and chemo regimens without the influence of AEs associated with subsequent therapies. Additionally, IMAE analyses with extended safety follow-up (using a 100-day window), as well as results of OESIs are provided in the "Safety Results, Significant Adverse Events" subsection.

The FDA's Assessment:

FDA agrees with the Applicant's position. No safety updates were submitted following the final RTOR supplement submission on November 25, 2020, as agreed upon during the October 15, 2020 Type B meeting (minutes issued October 15, 2020).

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 20: Safety Population, Size, and Denominators

Safety Database for the Study Drug[1] Individuals exposed to nivo+chemo (nivolumab 240 mg Q2W + FOLFOX Q2W or nivolumab 360 mg Q3W + XELOX Q3W) in this development program for the indication under review		
Clinical Trial Groups	Nivo+Chemo	Chemo
Controlled trial conducted for this indication (CA209649)[2]	782	767

[1] *study drug* means the drug being considered for approval.

[2] to be used in product's labeling

Source (ADaM dataset): Table S.2.6.3 (adsl.xpt) in the CA209649 Primary CSR

The Applicant's Position:

782 subjects in the nivo+chemo arm and 767 subjects in the chemo arm received at least 1 dose of study drug in CA209649 (Table 20). The median (95% CI) duration of therapy was longer in the nivo+chemo arm than the chemo arm: 6.75 months (6.11, 7.36) months vs 4.86 (4.47, 5.29) months (Figure S.4.1.3, AdAM dataset: adefttes.xpt, adsl.xpt) in the CA209649 Primary CSR). The median duration of the individual chemotherapy drugs was also longer in the nivo+chemo arm than the chemo arm when comparing the same chemotherapy backbone. The cumulative dose and relative dose intensity of the individual chemotherapy drugs in the nivo+chemo arm was comparable to that for the chemo arm with the same chemotherapy backbone (Table 6.1.1-1 [AdAM dataset: adex.xpt, adexs.xpt, adsl.xpt] in the CA209649 Primary CSR). These results indicated that the addition of nivolumab to chemotherapy did not reduce the exposure to the chemotherapy backbone and did not lead to suboptimal chemotherapy doses.
In subjects with PD-L1 CPS ≥ 5, the median (95% CI) duration of therapy was consistent with that for all treated subjects: 7.11 (6.41, 8.15) months in the nivo+chemo arm and 4.53 (4.14, 5.22) months in the chemo arm (Figure S.4.1.1 [AdAM datasets: adefttes.xpt, adsl.xpt] in the CA209649 Primary CSR)

The FDA's Assessment:

FDA agrees with the Applicant's position and presents exposure by arm in Table 21.

Table 21. Study CA 209649: Treatment Exposure by Arm

	Nivo + chemo N = 782	**Chemo N = 767**
Median duration of therapy in months (range)	6.8 (0-34)	4.9 (0-35)
Duration > 6 months (%)	54%	39%
Median duration of therapy by backbone chemotherapy in months		

XELOX (range)	6.5 (0.1-34)	4.9 (0 - 35)
FOLFOX (range)	7 (0-30)	4.8 (0.1 - 33)

Source: Reviewer Table

Relevant characteristics of the safety population:
The Applicant's Position: See Table 12.

The FDA's Assessment:

FDA agrees with the data regarding demographics and baseline tumor characteristics as presented in Table 12. The two arms were well-balanced and represented the known characteristics of a population of patients with advanced or metastatic GC/GEJC/EAC. Only 2% (32 patients) enrolled in the study did not receive study treatment; there are no demographic or baseline tumor characteristic differences between the safety and the ITT populations.

Adequacy of the safety database:
The Applicant's Position:
The population studied in CA209649 is representative of a first-line advanced or metastatic GC/GEJC/EAC population; this is supported by the demographic, disease, and other baseline characteristics, as well as the choice of chemo backbone, which were balanced between the 2 treatment arms. With the large sample size, a minimum follow-up of 12.1 months, and the balance with respect to the chemo backbone received, the exposure to study treatment in Study CA209649 is sufficient to characterize the safety of nivo+chemo. The routine clinical and laboratory evaluations performed in the study were appropriate to evaluate and characterize the safety profile of nivo+chemo.

The FDA's Assessment:

FDA agrees with the Applicant's position and considers that the safety population of 782 patients was sufficient to characterize the safety profile of nivolumab in combination with backbone chemotherapy as first-line therapy in patients with GC/GEJC/EAC.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
The Applicant's Position:
See Section 8.1.2. The quality of data collected and analyzed was monitored according to BMS standard operating procedures. No issues with data quality and integrity have been identified.

The FDA's Assessment:

FDA acknowledges the Applicant's position; the review did not uncover any data integrity issues. FDA agrees that the sBLA submission was complete and of adequate quality.

Categorization of Adverse Event

The Applicant's Position:

Adverse events in CA209649 were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 CTC CTCAE version 4.0, by system organ class and preferred term.

The FDA's Assessment:

FDA conducted an audit of the coding of terms in the safety dataset. Verbatim terms for adverse events were accurately coded using the MedDRA dictionary. FDA analyses were conducted irrespective of attribution, and although the numbers differed from the Applicant's regarding the number of deaths, the review team agrees with the conclusions about differences between arms. See "Deaths" in Section 8.2.4 for further details.

Immune-mediated adverse events (IMAEs) are associated with nivolumab. Analyses of IMAEs are based on a predefined list of preferred AE terms that was developed by the Applicant to assess IMAEs across nivolumab studies.

Routine Clinical Tests

The Applicant's Position:

The following laboratory tests were conducted at Screening: serum hematology (complete blood count [CBC], differential [absolute counts: neutrophils, lymphocytes, monocytes, basophils, eosinophils], and platelets) and serum chemistry (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase (ALP), total bilirubin, albumin, creatinine, blood urea nitrogen [BUN] or serum urea), sodium, potassium, chloride, calcium, fasting glucose, lactate dehydrogenase (LDH), amylase, lipase, thyroid stimulating hormone [TSH], free T4 or T3.

Pregnancy tests for female subjects with childbearing potential were conducted at screening. Testing for hepatitis virus B/C (HBV sAg, HCV antibody or HCV ribonucleic acid [RNA]) was performed within 28 days prior to randomization. Testing for human immunodeficiency virus (HIV) was conducted as per local regulations.

The following laboratory tests were conducted during the treatment period: CBC with differential, serum chemistry (ALT, AST, total bilirubin, creatinine, BUN or serum urea), sodium, potassium, chloride, calcium, glucose, LDH, and TSH for subjects in the nivo+chemo arm). Pregnancy tests for female subjects with childbearing potential were conducted within 24 hours prior to the start of study drug. Additional measures, including non-study required laboratory tests, were to be performed as clinically indicated or to comply with local regulations.

The following laboratory tests were conducted during follow-up: CBC with differential, serum chemistry (ALT, AST, total bilirubin, BUN or serum urea level, creatinine), sodium, potassium, chloride, calcium, glucose, and LDH.

Laboratory tests were graded using the NCI CTCAE, version 4.0.

The FDA's Assessment:

FDA agrees with the sponsor's assessment. Monitoring for safety was adequate and consistent with the standard of care.

8.2.4. Safety Results

Data:

Table 22: Summary of Safety - All Treated Subjects

	No. of Subjects (%)			
Safety Parameters	**Nivo + Chemo (N = 782)**		**Chemo (N = 767)**	
Deaths	538 (68.8)		572 (74.6)	
Primary Reason for Death				
Disease	465 (59.5)		506 (66.0)	
Study Drug Toxicity	12 (1.5)		4 (0.5)	
Unknown	12 (1.5)		18 (2.3)	
Other[a]	49 (6.3)		44 (5.7)	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	423 (54.1)	281 (35.9)	335 (43.7)	229 (29.9)
Drug-related SAEs	172 (22.0)	131 (16.8)	93 (12.1)	77 (10.0)
All-causality AEs leading to DC	371 (47.4)	194 (24.8)	251 (32.7)	113 (14.7)
Drug-Related AEs leading to DC	284 (36.3)	132 (16.9)	181 (23.6)	67 (8.7)
All-causality AEs	776 (99.2)	540 (69.1)	752 (98.0)	456 (59.5)
Drug-Related AEs	738 (94.4)	462 (59.1)	679 (88.5)	341 (44.5)
≥ 20% of Subjects in Any Treatment Group				
Nausea	323 (41.3)	20 (2.6)	292 (38.1)	19 (2.5)
Diarrhea	253 (32.4)	35 (4.5)	206 (26.9)	24 (3.1)
Anemia	203 (26.0)	47 (6.0)	171 (22.3)	21 (2.7)
Neuropathy Peripheral	221 (28.3)	31 (4.0)	190 (24.8)	22 (2.9)
Fatigue	202 (25.8)	30 (3.8)	173 (22.6)	17 (2.2)
Drug-related AEs ≥ 20% of Subjects in Any Treatment Group (continued)				
Vomiting	195 (24.9)	17 (2.2)	166 (21.6)	24 (3.1)
Neutropenia	191 (24.4)	118 (15.1)	181 (23.6)	93 (12.1)

Table 22: Summary of Safety - All Treated Subjects

	No. of Subjects (%)			
Safety Parameters	**Nivo + Chemo (N = 782)**		**Chemo (N = 767)**	
Neutrophil Count Decreased	158 (20.2)	83 (10.6)	118 (15.4)	67 (8.7)
Thrombocytopenia	157 (20.1)	19 (2.4)	145 (18.9)	13 (1.7)
Decreased Appetite	157 (20.1)	14 (1.8)	139 (18.1)	13 (1.7)
All-causality IMAEs within 100 days of last dose				
Treated with Immune Modulating Medication				
Diarrhea/Colitis	26 (3.3)	17 (2.2)	0	0
Hepatitis	19 (2.4)	13 (1.7)	0	0
Pneumonitis	33 (4.2)	15 (1.9)	0	0
Nephritis/Renal Dysfunction	4 (0.5)	2 (0.3)	0	0
Rash	51 (6.5)	11 (1.4)	4 (0.5)	0
Hypersensitivity/Infusion Reactions	6 (0.8)	1 (0.1)	0	0
All-causality Endocrine IMAEs within 100 days of last dose				
With or Without Immune Modulating Medication				
Adrenal Insufficiency	5 (0.6)	1 (0.1)	2 (0.3)	2 (0.3)
Hypophysitis	6 (0.8)	3 (0.4)	0	0
Hypothyroidism/Thyroiditis	74 (9.5)	0	6 (0.8)	0
Hyperthyroidism	23 (2.9)	0	2 (0.3)	0
Diabetes Mellitus	2 (0.3)	1 (0.1)	0	0
All-causality OESIs within 100 days of last dose				
With or Without Immune Modulating Medication				
Pancreatitis	3 (0.4)	2 (0.3)	2 (0.3)	1 (0.1)
Encephalitis	1 (0.1)	1 (0.1)	0	0
Myositis/ Rhabdomyolysis	0	0	2 (0.3)	2 (0.3)
Guillain-Barre Syndrome	1 (0.1)	1 (0.1)	0	0
Uveitis	1 (0.1)	1 (0.1)	0	0
Myocarditis	2 (0.3)	1 (0.1)	0	0

[a] 4 deaths due to other reasons, were reported as related to study drug(s) (nivo, chemo, or both) per the investigator: thrombosis mesenteric vessel, disseminated intravascular coagulation, cerebral infarction and pneumonitis.

MedDRA version 23.0 CTCAE version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months

Abbreviations: AEs - adverse events, CTC - Common Terminology Criteria, DC - discontinuation, IMAEs - immune-mediated adverse events, MedDRA - Medical Dictionary for Regulatory Activities, OESI - other events of special interest, SAEs - serious adverse events

Source (ADaM dataset[s]): Table S.6.15.3 (adsl.xpt; deaths), Table S.6.3.1.2.5 (adae.xpt, adsl.xpt; all-causality SAEs), Table S.6.3.1.2.6 (adae.xpt, adsl.xpt; drug-related SAEs), Table S.6.4.2.5 (adae.xpt, adsl.xpt; all-causality AEs leading to DC), Table S.6.4.2.6 (adae.xpt, adsl.xpt; drug-related AEs leading to DC), Table S.6.1.31.3 (adae.xpt, adsl.xpt; all-causality AEs); Table S.6.1.32.3 (adae.xpt, adsl.xpt; drug-related AEs); Table S.6.202.16 (adae.xpt, adaeimm.xpt, adsl.xpt; non-endocrine IMAEs), Table S.6.202.13 (adae.xpt, adaeimm.xpt, adsl.xpt; endocrine IMAEs), Table S.6.5.3.3.5 (adae.xpt, adaeimm.xpt, adsl.xpt; OESIs)

Deaths

The Applicant's Position:

As of the 10-Jul-2020 database lock, 68.8% of subjects in the nivo+chemo arm and 74.6% of subjects in the chemo arm died (Table 22 and Table S.6.15.3 [ADaM dataset: adsl.xpt] in the CA209649 Primary CSR). Disease progression was the most common cause of death in both arms. 12 subjects in the nivo+chemo arm and 4 subjects in the chemo arm died due to study drug toxicity per investigator assessment.

- 12 deaths due to study drug toxicity in the nivo+chemo arm (3 deaths were related to nivo, 2 were related to both nivo and chemo, and 7 were related to chemo per investigator assessment):
  - Nivo+XELOX: neutropenic fever, intestinal mucositis, stroke, infection, gastrointestinal bleeding, and septic shock
  - Nivo+FOLFOX: pneumonia, pneumonitis/pulmonitis (2 subjects), interstitial lung disease, febrile neutropenia, and gastrointestinal toxicity
- 4 deaths due to study drug toxicity in the chemo arm:
  - XELOX: pulmonary thromboembolism, asthenia and hypoxia, and diarrhea
  - FOLFOX: interstitial pneumonia

Deaths attributed to other reasons were reported in 49 (6.3%) of subjects in the nivo+chemo arm and in 44 (5.7%) of subjects in the chemo arm. Note that 4 deaths in the nivo+chemo arm, which were due to other reasons, were reported as related to study drug(s) (nivo, chemo, or both) per the investigator: thrombosis mesenteric vessel, disseminated intravascular coagulation, cerebral infarction and pneumonitis. Of the 4 deaths, pneumonitis was considered related to nivolumab; the other 3 events were reported as related to both nivo and chemotherapy per investigator.

The FDA's Assessment:

FDA's assessment of deaths related to study drug toxicity differs from that of the Applicant. FDA considers that the 4 deaths in the experimental arm that were attributed to other reasons by the Applicant are at least possibly related to the study drug, as they occurred in relation to an adverse event (thrombosis mesenteric vessel, disseminated intravascular coagulation, cerebral infarction and pneumonitis) and were considered related by the investigator. Of note, pneumonitis and interstitial lung disease should be grouped, as they refer to the same event; therefore, when adding the fatal event of pneumonitis that was attributed as not-related, 4 patients in the nivolumab arm had fatal events of pneumonitis/ILD.

Serious Adverse Events and Discontinuations Due to Adverse Effects (All Causality and Drug-Related)

The Applicant's Position:

The overall frequencies of all causality and drug-related SAEs, and AEs leading to discontinuation were numerically higher with nivo+chemo vs chemo, however, the majority of the events represent typical disease-related and chemotherapy-related toxicities (Table 22). Note that in the nivo+chemo arm, discontinuation was defined as at least 1 drug discontinued.

The most frequently reported SAEs (regardless of causality) were:

- Nivo+chemo: malignant neoplasm progression (13.9%), vomiting (3.2%), anemia (3.1%), pneumonia (2.8%),pyrexia (2.6%), diarrhea (2.4%), febrile neutropenia (2.3%), and pneumonitis (2.2%).
- Chemo: malignant neoplasm progression (11.7%), vomiting (3.1%), and dysphagia (2.1%).

The most frequently reported drug-related SAEs were:

- Nivo+chemo: diarrhea (2.2%), pneumonitis (2.2%), and febrile neutropenia (2.0%).
- Chemo: vomiting (2.3%).

The most common AEs leading to discontinuation (regardless of causality) were:

- Nivo+chemo: neuropathy peripheral (7.8%), malignant neoplasm progression (4.7%), peripheral sensory neuropathy (4.5%), and diarrhea (2.0%.).
- Chemo: neuropathy peripheral (5.3%), peripheral sensory neuropathy (4.7%), and malignant neoplasm progression (3.7%).

The most common drug-related AEs leading to discontinuation were:

- Nivo+chemo: neuropathy peripheral (7.5%) and peripheral sensory neuropathy (4.5%).
- Chemo: neuropathy peripheral (5.2%) and peripheral sensory neuropathy (4.7%).

The FDA's Assessment:

FDA conducted an analysis of SAEs and presents a side-by-side comparison by arm regardless of causality in ≥ 2% of all patients in the safety analysis set (Table 23) to demonstrate the differences between the two arms.

Table 23. Serious Adverse Events in ≥ 2% of Patients by Preferred Term

n (%)	Nivo + chemo (N = 782)		Chemo (N = 767)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Malignant neoplasm progression	109 (14)	45 (6)	90 (12)	33 (4.3)
Vomiting	25 (3.2)	17 (2.2)	24 (3.1)	19 (2.5)
Anemia	24 (3.1)	18 (2.3)	9 (1.2)	8 (1)
Pneumonia	22 (2.8)	16 (2)	2 (0.3)	10 (1.3)

Pyrexia	20 (2.6)	5 (0.6)	10 (1.3)	3 (0.4)
Diarrhea	19 (2.4)	14 (1.8)	12 (1.6)	9 (1.2)
Febrile neutropenia	18 (2.3)	16 (2)	7 (0.9)	7 (0.9)
Pneumonitis	17 (2.2)	11 (1.4)	1 (0.1)	0

Source: reviewer table

All-cause SAEs were numerically higher in the nivo+chemo arm, and that the events for which there was a discrepancy between the two arms are those that have been observed with nivolumab monotherapy (e.g., pyrexia, pneumonia, diarrhea, pneumonitis) and are expected.

Additionally, FDA conducted an analysis of AEs leading to discontinuation (Table 24). The incidence of the most common AEs (peripheral neuropathy, platelet count decreased, and neutrophil count decreased) was similar between arms and these events are well-recognized to be associated with FOLFOX or CAPEOX. AEs that were numerically higher in the nivo+chemo arm were drug hypersensitivity, diarrhea, infusion related reaction and pneumonitis, but the overall incidence was low and consistent with the known toxicity profile of nivolumab.

Table 24. Related AEs Leading to Discontinuation in ≥ 1% of Patients by Preferred Term[1]

n (%)	Nivo + chemo (N = 782)		Chemo (N = 767)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Peripheral neuropathy[2]	94 (12)	28 (3.6)	76 (10)	21 (2.7)
Platelet count decreased[3]	26 (1.7)	6 (0.3)	22 (1.3)	5 (0.3)
Neutrophil count decreased[4]	18 (1.3)	12 (0.9)	16 (1.3)	6 (0.8)
Drug hypersensitivity[5]	17 (2.2)	5 (0.6)	10 (1.3)	0
Diarrhea	15 (1.9)	12 (1.5)	7 (0.9)	4 (0.5)
Pneumonitis[6]	15 (1.9)	11 (1.4)	4 (0.5)	1 (0.1)
Infusion related reaction	14 (1.8)	8 (1)	5 (0.7)	0
Paresthesia	9 (1.2)	0	4 (0.5)	0

[1] Patients may have had more than one AE resulting in discontinuation; [2] includes PTs neuropathy peripheral and peripheral sensory neuropathy; [3] includes PTs platelet count decreased and thrombocytopenia'; [4] Includes neutropenia and neutrophil count decreased; [5] includes PTs drug hypersensitivity and hypersensitivity; [6] includes pneumonitis and interstitial lung disease
Source: ADAE dataset; reviewer table

Overall Adverse Events (All Causality and Drug-Related)

The overall frequencies of all-causality and drug-related AEs were similar between the 2 arms; however, frequencies of Grade 3-4 AEs (all-causality and drug-related) were numerically higher with nivo+chemo compared with chemo (Table 22). The most common drug-related AEs (≥ 20%) in both arms (nivo+chemo and chemo) were: nausea, diarrhea, peripheral neuropathy, neutropenia, anemia, fatigue, and vomiting. In addition, the following drug-related AEs were

reported in ≥ 20% of subjects in the nivo+chemo arm: neutrophil count decreased, thrombocytopenia, and decreased appetite.

Dose Delay or Reduction Due to Adverse Effects

The Applicant's Position:

The most frequently reported drug-related AEs of any grade leading to dose delay or reduction in the nivo+chemo arm were: neutropenia (18.2% vs 15.9%), neutrophil count decreased (13.2% vs 9.9%), platelet count decreased (10.5% vs 8.0%), thrombocytopenia (9.5% vs 6.8%), and diarrhea (7.3% vs 6.4%) (Table S.6.4.3.6 [AdAM dataset: adae.xpt, adsl.xpt] in the CA209649 Primary CSR). Note that these AEs were commonly reported with chemotherapy. No dose reductions were permitted for nivolumab.

The FDA's Assessment:

A total of 524 (67%) patients in the nivolumab plus chemotherapy arm required a dose delay (nivolumab and/or chemotherapy) or reduction (chemotherapy only) due to a related AE vs. 447 (58%) in the chemotherapy arm, as summarized in Table 25.

Table 25. Study CA209649 Dose Delays

	Nivo + chemo (N = 782)		Chemo (N = 767)	
	XELOX (n=360)	FOLFOX (n=422)	XELOX (n=361)	FOLFOX (n=406)
Patients with any Dose Delays n (%)				
Nivolumab	240 (67)	330 (78)	n/a	n/a
Oxaliplatin	214 (59)	315 (75)	174 (48)	285 (70)
Capecitabine	239 (66)	n/a	198 (55)	n/a
5-FU continuous	n/a	333 (79)	n/a	298 (73)
Dose Delays n (%)[1]				
Nivolumab	585/3731 (16)	1170/6825 (17)	n/a	n/a
Oxaliplatin	403/1974 (20)	753/3531 (21)	382/2058 (19)	607/3400 (18)
Capecitabine	582/3558 (16)	n/a	491/2985 (16)	n/a
5-FU continuous	n/a	1063/6014 (18)	n/a	799/4596 (17)
Reason for Delay was AE n (%)				
Nivolumab	381 (65)	547 (47)	n/a	n/a
Oxaliplatin	282 (70)	360 (48)	266 (70)	297 (49)
Capecitabine	0	n/a	0	n/a
5-FU continuous	n/a	483 (45)	n/a	323 (40)

[1] Denominator is the number of doses received

Source: reviewer table

FDA replicated the Applicant's analysis of AEs leading to dose delay or reduction, and agrees

with the Applicant's position. While the incidence of all Grade and Grade 3-4 events is numerically higher in the nivo+chemo arm (67% vs. 58% respectively for all Grades and 39% vs. 29% respectively for Grade 3-4), the most commonly occurring events appeared similar between arms and are consistent with the known toxicity profile of the backbone chemotherapy.

Significant Adverse Events

Data:

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Table 26: Onset/Management/Resolution of All-Causality IMAEs within 100 Days of Last Dose - Nivo+Chemo-Treated Subjects (CA209649)

IMAE Category	% Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAE leading to DC / Dose Delay	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[a]	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE[d,e]	Median[b] Time to Resolution (range), wks[c,d,e]	% Subj. with Recurrence after Reinitiation
Pneumonitis	4.2 / 1.9	25.43 (4.4 - 98.6)	1.8 / 2.0	100 / 84.8	9.29 (0.1 - 94.1)	63.6	14.86 (0.3+ - 66.6+)	28.6 (2 / 7)
Diarrhea/Colitis	3.3 / 2.2	11.29 (1.6 - 59.1)	2.0 / 1.5	100 / 69.2	6.71 (0.3 - 63.9)	84.6	4.57 (0.6 - 52.0+)	33.3 (1 / 3)
Hepatitis	2.4 / 1.7	8.43 (2.1 - 48.0)	0.8 / 1.2	100 / 78.9	6.14 (0.1 - 100.6)	89.5	8.00 (1.0 - 36.1+)	42.9 (3 / 7)
Nephritis/Renal Dysfunction	0.5 / 0.3	14.71 (4.4 - 26.1)	0.4 / 0.4	100 / 50	11.43 (6.1 - 14.4)	75.0	12.07 (1.1 - 26.4+)	50.0 (1 / 2)
Rash	6.5 / 1.4	8.14 (0.1 - 91.3)	0.1 / 1.3	100 / 23.5	7.14 (0.4 - 97.0)	78.4	7.00 (0.7 - 135.9+)	42.9 (3 / 7)
Hypersensitivity	0.8 / 0.1	3.64 (0.1 - 23.3)	0.1 / 0	100 / 83.3	0.21 (0.1 - 6.0)	100	0.14 (0.1 - 8.0)	N.A.
Adrenal Insufficiency	0.6 / 0.1	40.86 (15.0 - 57.4)	0 / 0.1	60 / 0	35.86 (15.1 - 41.0)	20.0	N.A. (1.4 - 52.9+)	0 (0 / 0)
Hypophysitis	0.8 / 0.4	32.86 (16.9 - 49.3)	0 / 0.5	83.3 / 33.3	24.57 (4.7 - 63.1)	66.7	6.93. (0.4 - 61.9+)	0 (0 / 3)
Hypothyroidism/ Thyroiditis	9.5 / 0	17.57 (2.0 - 57.9)	0.3 / 0.9	5.4 / 5.4	4.64 (0.4 - 5.1)	36.5	N.A. (1.4 - 139.1+)	0 (0 / 2)
Hyperthyroidism	2.9 / 0	11.86 (3.3 - 46.3)	0 / 0.3	4.3 / 0	16.00 (16.0 - 16.0)	78.3	10.00 (1.0 - 68.1+)	N.A.
Diabetes Mellitus	0.3 / 0.1	29.64 (15.9 - 43.4)	0 / 0	50 / 0	0.43 (0.4 - 0.4)	0	N.A. (62.7+ - 88.0+)	N.A.

[a] Denominator is based on the number of subjects who experienced the event [b] From Kaplan-Meier estimation.

[c] Symbol + indicates a censored value. [d] Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis.

[e] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

Source (AdAM datasets): Table S.6.202.13 (adae.xpt, adaeimm.xpt, adsl.xpt: endocrine IMAEs), Table S.6.202.14 (adae.xpt, adaeimm.xpt, adsl.xpt: endocrine IMAEs leading to DC), Table S.6.202.15 (adae.xpt, adaeimm.xpt, adsl.xpt: endocrine IMAEs leading to dose delay/reduction), Table S.6.202.16 (adae.xpt, adaeimm.xpt, adsl.xpt: non-endocrine IMAEs), Table S.6.202.17 (adae.xpt, adaeimm.xpt, adsl.xpt: non-endocrine IMAEs leading to DC), Table S.6.202.18 (adae.xpt, adaeimm.xpt, adsl.xpt: non-endocrine IMAEs leading to dose delay/reduction), Table S.6.12.91.3 (adaeimm.xpt, adcmim.xpt, adsl.xpt: duration of IMM for IMAE management), Table S.6.217.5 (adae.xpt, adaette.xpt, adsl.xpt: time to onset of endocrine IMAEs), Table S.6.217.6 (adae.xpt, adaette.xpt, adsl.xpt: time to onset of non-endocrine IMAEs), Table S.6.219.5 (adaette.xpt, adsl.xpt: time to resolution of endocrine IMAEs), Table S.6.219.6 (adaette.xpt, adsl.xpt: time to resolution of non-endocrine IMAEs), Table S.6.223.3 (adaeprc.xpt, adsl.xpt: re-challenge with nivolumab). in the CA209649 Primary CSR

The Applicant's Position:

Immune-mediated Adverse Events: IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (i.e., with extended follow up). These analyses were limited to subjects who received IMM for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. These events were identified by the investigator as IMAEs with no clear alternate etiology and an immune mediated component. As expected, IMAEs occurred more frequently with nivo+chemo relative to chemo. The observed IMAE frequencies and patterns are consistent with those for nivolumab monotherapy.[22] The most frequently reported any-grade IMAEs (by category) in the nivo+chemo arm were hypothyroidism/thyroiditis (9.5%), rash (6.5%), pneumonitis (4.2%) and diarrhea/colitis (3.3%); IMAEs in all other categories were reported in < 3% of subjects (Table 26). Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered (Table 26). Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy.

Other Events of Special Interest (OESIs): OESIs are events that do not fulfill all criteria to qualify as select AEs or IMAEs. They may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs had extended follow-up (100-day window). OESI categories: myasthenic syndrome, demyelination, Guillain-Barré syndrome, pancreatitis, uveitis, encephalitis, myocarditis, myositis, rhabdomyolysis, and graft versus host disease.
OESIs (regardless of causality or IMM treatment, with extended follow-up) were infrequent in both treatment arms (Table 22). Overall, OESIs were reported in 8/782 (1.0%) subjects in the nivo+chemo arm (3 with pancreatitis, 2 with myocarditis, and 1 each with encephalitis, Guillain-Barre syndrome, and uveitis) and 4/767 (0.5%) subjects in the chemo arm (2 with pancreatitis and 2 with myositis).

The FDA's Assessment:

FDA agrees with the Applicant's grouping of terms and categorization of IMAEs. As expected, the incidence of IMAE and OESI as defined by the Applicant was higher in the nivolumab arm. Most of the IMAEs were Grade 1-2, and the most common Grade 3-4 IMAEs were diarrhea/colitis (2.2%), pneumonitis (1.9%), hepatitis (1.7%), and rash (1.2%); all patients with these events received immune-modulating medication. High-dose corticosteroids were administered to 69%, 85%, 79%, and 24% of these patients, respectively. Overall, corticosteroids were administered to treat IMAEs in 35% of patients in the nivolumab arm and 20% of patients in the control arm. The incidence and type of IMAE and OESI observed in Study CA209469 are consistent with the known safety profile of nivolumab.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 27: Adverse Reactions in >10% of Patients Receiving Nivolumab + Chemotherapy (CA209649)

Adverse Reaction	Nivo+Chemo (n=782)		Chemo (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Adverse Reaction	99	69	98	59
Nervous System				
Neuropathy peripheral[a]	53	7	46	4.8
Headache	11	0.8	6	0.3
Gastrointestinal				
Nausea	48	3.2	44	3.7
Diarrhea	39	5	34	3.7
Vomiting	31	4.2	29	4.2
Abdominal pain[b]	27	2.8	24	2.6
Constipation	25	0.6	21	0.4
Stomatitis[c]	17	1.8	13	0.8

Adverse Reaction	Nivo+Chemo (n=782)		Chemo (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and Lymphatic System				
Neutropenia[d]	47	28	40	22
Anemia	41	12	36	8
Thrombocytopenia[e]	39	5	34	4.3
General				
Fatigue[f]	44	7	40	5
Pyrexia[g]	19	1.0	11	0.4
Edema[h]	12	0.5	8	0.1
Metabolism and Nutrition				
Decreased appetite	29	3.6	26	2.5
Hypoalbuminemia[i]	14	0.3	9	0.3
Hypokalemia[j]	12	2.6	9	2.6
Investigations				
Transaminases increased[k]	23	2.6	16	1.6
Weight decreased	17	1.3	15	0.7
White blood cell count decreased	15	3.2	10	1.7
Lipase increased	14	7	8	3.7
Blood alkaline phosphates increased	13	1.3	8	0.7
Amylase increased	12	3.1	5	0.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[l]	20	1.3	14	2.0
Skin and Subcutaneous Tissue				
Rash[m]	18	1.7	4.4	0.1
Palmar-plantar erythrodysesthesia syndrome	13	1.5	12	0.8

Adverse Reaction	Nivo+Chemo (n=782)		Chemo (n=767)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Respiratory, Thoracic and Mediastinal				
Cough[n]	13	0.1	9	0
Infections and Infestations				
Upper respiratory tract infection[o]	10	0.1	7	0.1

Toxicity was graded per NCI CTCAE v4.

[a] Includes dysethesia, hypoesthsia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy.

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

[c] Includes aphthouss ulcer, mouth ulceration, and mucosal inflammation.

[d] Includes neutrophil count decreased.

[e] Includes platelet count decreased.

[f] Includes asthenia.

[g] Includes tumor-associated fever.

[h] Includes swelling, generalized edema, edema peripheral, and peripheral swelling.

[i] Includes blood albumin decreased.

[j] Includes blood potassium decreased.

[k] Includes alanine aminotransferase increased and aspartate aminotransferase increased.

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

[m] Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, drug eruption, exfoliative rash, nodular rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash vesicular.

[n] Includes productive cough.

[o] Includes nasopharyngitis, pharyngitis, and rhinitis.

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months

Source: Appendix GA.USPI.1.5 (ADaM dataset: adaeremp.xpt, adsl.xpt) in the Summary of Clinical Safety

The Applicant's Position:

For labeling purposes, adverse reactions (grouped by system organ class and presented by CTC grade) for the proposed regimen that were reported in > 10% of nivo+chemo-treated subjects in CA209649 were included in Section 6.1 of the United States Prescribing Information (USPI) (Table 27). The most common adverse reactions (reported in ≥ 20% of patients) treated with nivo+chemo were peripheral neuropathy, nausea, neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, vomiting, decreased appetite, abdominal pain, constipation, transaminase increased, and musculoskeletal pain.

The FDA's Assessment:

FDA agrees with the term groupings and was able to replicate the Applicant's analysis. The number of adverse reactions (any Grade and Grade 3-4) in ≥ 10% of patients was generally higher in the nivolumab arm, suggesting that nivolumab increases the overall rate of toxicity of

the chemotherapy regimen. The differences, however, were small given that patients in the control arm were receiving active therapy and the different length of exposure.

Laboratory Findings

Data:

Table 28: Laboratory Abnormalities That Worsened Relative to Baseline (US Conventional Units) Occurring in ≥10% of Patients (CA209649)

Laboratory Abnormality	Percentage of Subjects with Worsening Laboratory Test from Baseline[a]			
	Nivo+Chemo		Chemo	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Hematology				
Neutropenia	73	29	62	23
Leukopenia	69	12	59	9
Thrombocytopenia	68	7	63	4.4
Anemia	59	14	60	10
Lymphopenia	59	12	49	9
Chemistry				
Increased AST	52	4.6	47	1.9
Hypocalcemia	42	1.6	37	1.0
Hyperglycemia	41	3.9	38	2.7
Increased ALT	37	3.4	30	1.9
Hyponatremia	34	6	24	5
Hypokalemia	27	7	24	4.8
Hyperbilirubinemia	24	2.8	21	2.0
Increased creatinine	15	1.0	9	0.5

Laboratory Abnormality	Percentage of Subjects with Worsening Laboratory Test from Baseline[a]			
	Nivo+Chemo		Chemo	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Hyperkalemia	14	1.4	11	0.7
Hypoglycemia	12	0.7	9	0.2
Hypernatremia	11	0.5	7	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 FOLFOX or XELOX (CapeOX) group (407 to 767 patients) or FOLFOX or XELOX (CapeOX) group (range: 405 to 735 patients).

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months

Source: Appendix GA.USPI.6.5 (ADaM dataset: adsl.xpt, adzl.xpt) in the Summary of Clinical Safety

The Applicant's Position:

Laboratory abnormalities (hematology, liver tests, kidney function tests, and electrolytes) in the nivo+chemo arm were primarily Grade 1-2. The types and frequencies of laboratory abnormalities were consistent across the nivo+chemo and chemo arms and were mainly

hematologic abnormalities; these laboratory abnormalities are consistent with the known myelosuppressive toxicity associated with chemotherapy (see Section 8.10 of the CA209649 Primary CSR). The majority of subjects did not have laboratory tests that worsened to Grade 3 or 4 relative to baseline (Table 28). The United States Package Insert (USPI) provides a table summarizing laboratory abnormalities that worsened relative to baseline (US conventional units) in > 10% of nivo+chemo-treated subjects in CA209649.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. As with adverse reactions, the laboratory abnormalities were generally increased in the nivolumab arm relative to the control arm suggesting that nivolumab does contribute to an increased toxicity profile of FOLFOX or XELOX. The magnitude of these differences, however, is small and generally manageable by providers.

Vital Signs
The Applicant's Position:
Vital signs were monitored and recorded at the site per institutional standard of care during screening and treatment visits. These assessments were intended to be used as safety monitoring by the treating physician.

The FDA's Assessment:

FDA agrees.

Electrocardiograms (ECGs) and QT
The Applicant's Position: Not applicable

The FDA's Assessment:

FDA agrees.

Immunogenicity
The Applicant's Position: See Section 6.3.1.

The FDA's Assessment:

FDA agrees and defers to the FDA Assessment in Section 6.3.1.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Comparison with Broader Safety Experience

The Applicant's Position: Not applicable

The FDA's Assessment:

FDA agrees.

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

The Applicant's Position: Not applicable. See Section 8.1.2.

The FDA's Assessment:

FDA agrees and refers to Section 8.1.2.

8.2.7. Safety Analyses by Subgroups

Data:

Table 29: Drug-Related Adverse Events s by Worst CTC Grade and by Age, Gender, Race, Region, and Chemotherapy Backbone - All Treated Subjects (CA209649)

	Drug-related Adverse Events (n/N [%])					
	Nivo+Chemo			Chemo		
	Any Grade	Grade 3-4	Grade 5[a]	Any Grade	Grade 3-4	Grade 5[a]
Total	738/782 (94.4)	462/782 (59.1)	4/782 (0.5)	679/767 (88.5)	341/767 (44.5)	0
By Age (years)						
< 65	445/470 (94.7)	270/470 (57.4)	1/470 (0.2)	419/475 (88.2)	208/475 (43.8)	0
≥ 65	293/312 (93.9)	192/312 (61.5)	3/312 (1.0)	260/292 (89.0)	133/292 (45.5)	0
≥ 65 and < 75	219/235 (93.2)	145/235 (61.7)	2/235 (0.9)	202/221 (91.4)	98/221 (44.3)	0
≥ 75	74/77 (96.1)	47/77 (61.0)	1/77 (1.3)	58/71 (81.7)	35/71 (49.3)	0
≥ 75 and < 85	72/75 (96.0)	46/75 (61.3)	1/75 (1.3)	53/65 (81.5)	33/65 (50.8)	0
≥ 85	2/2 (100.0)	1/2 (50.0)	0	5/6 (83.3)	2/6 (33.3)	0
By Sex						
Male	499/533 (93.6)	294/533 (55.2)	3/533 (0.6)	476/543 (87.7)	218/543 (40.1)	0
Female	239/249 (96.0)	168/249 (67.5)	1/249 (0.4)	203/224 (90.6)	123/224 (54.9)	0
By Race						
White	517/551 (93.8)	332/551 (60.3)	4/551 (0.7)	449/523 (85.9)	228/523 (43.6)	0
Asian (including China)	182/185 (98.4)	104/185 (56.2)	0	174/183 (95.1)	87/183 (47.5)	0
By Region						
North America	125/129 (96.9)	93/129 (72.1)	0	118/124 (95.2)	63/124 (50.8)	0
Rest of the World	439/476 (92.2)	273/476 (57.4)	4/476 (0.8)	396/469 (84.4)	198/469 (42.2)	0

	Drug-related Adverse Events (n/N [%])					
	Nivo+Chemo			Chemo		
	Any Grade	Grade 3-4	Grade 5[a]	Any Grade	Grade 3-4	Grade 5[a]
Asia (including China)	174/177 (98.3)	96/177 (54.2)	0	165/174 (94.8)	80/174 (46.0)	0
By Chemo						
XELOX	342/360 (95.0)	176/360 (48.9)	2/360 (0.6)	314/361 (87.0)	140/361 (38.8)	0
FOLFOX	396/422 (93.8)	286/422 (67.8)	2/422 (0.5)	365/406 (89.9)	201/406 (49.5)	0

[a] 12 subjects in the nivo+chemo arm and 4 subjects in the chemo arm died due to study drug toxicity per investigator assessment. Note that only events that led to death within 24 hours were documented as Grade 5. Events leading to death > 24 hours after onset were reported with the grade at presentation.

MedDRA Version: 23.0; CTC Version 4.0; Includes events reported between first dose and 30 days after last dose of study therapy.

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months

Source (ADaM datasets): Table S.6.1.32.3 (adae.xpt, adsl.xpt; all treated), Table S.6.1.5.7 (age), Table S.6.1.5.5 (sex), Table S.6.1.5.6 (race), Table S.6.1.5.8 (region), and Table S.6.1.7.2 (chemo) in the CA209649 Primary CSR)

Table 30: Summary of Safety - Subjects with PD-L1 CPS ≥ 5 and Subjects with PD-L1 CPS < 5 (CA209649)

	Number (%) of Subjects			
	Subjects with PD-L1 CPS ≥ 5		Subjects with PD-L1 CPS < 5	
Safety Parameters	**Nivo + Chemo (N = 468)**	**Chemo (N = 465)**	**Nivo + Chemo (N = 306)**	**Chemo (N = 290)**
Deaths	305 (65.2)	350 (75.3)	226 (73.9)	214 (73.8)
Primary Reason for Death				
Disease	260 (55.6)	306 (65.8)	199 (65.0)	193 (66.6)
Due to Study Drug Toxicity	8 (1.7)	4 (0.9)	3 (1.0)	0
Unknown	8 (1.7)	11 (2.4)	4 (1.3)	7 (2.4)
Other	29 (6.2)	29 (6.2)	20 (6.5)	14 (4.8)
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All Causality SAEs	250 (53.4)	162 (34.6)	211 (45.4)	141 (30.3)	170 (55.6)	116 (37.9)	119 (41.0)	83 (28.6)
Drug-related SAEs	112 (23.9)	81 (17.3)	64 (13.8)	53 (11.4)	57 (18.6)	47 (15.4)	29 (10.0)	24 (8.3)
All Causality AEs leading to DC	228 (48.7)	120 (25.6)	160 (34.4)	74 (15.9)	139 (45.4)	70 (22.9)	86 (29.7)	38 (13.1)
Drug-Related AEs leading to DC	178 (38.0)	85 (18.2)	115 (24.7)	44 (9.5)	102 (33.3)	43 (14.1)	61 (21.0)	22 (7.6)
All Causality AEs	466 (99.6)	319 (68.2)	456 (98.1)	278 (59.8)	302 (98.7)	215 (70.3)	284 (97.9)	172 (59.3)
Drug-Related AEs	444 (94.9)	277 (59.2)	407 (87.5)	203 (43.7)	286 (93.5)	179 (58.5)	262 (90.3)	135 (46.6)
All Causality IMAEs within 100 days of last dose								
Treated with Immune Modulating Medication								
Diarrhea/Colitis	17 (3.6)	11 (2.4)	0	0	9 (2.9)	6 (2.0)	0	0
Hepatitis	14 (3.0)	10 (2.1)	0	0	2 (0.7)	2 (0.7)	0	0
Pneumonitis	19 (4.1)	11 (2.4)	0	0	12 (3.9)	2 (0.7)	0	0
Nephritis/Renal Dysfunction	3 (0.6)	2 (0.4)	0	0	5 (1.6)	2 (0.7)	0	0
Rash	35 (7.5)	9 (1.9)	4 (0.9)	0	16 (5.2)	2 (0.7)	0	0
Hypersensitivity/Infusion Reactions	3 (0.6)	1 (0.2)	0	0	3 (1.0)	0	0	0

Summary of Safety - Subjects with PD-L1 CPS ≥ 5 and Subjects with PD-L1 CPS < 5 (CA209649)

	Number (%) of Subjects							
	Subjects with PD-L1 CPS ≥ 5				Subjects with PD-L1 CPS < 5			
Safety Parameters	Nivo + Chemo (N = 468)		Chemo (N = 465)		Nivo + Chemo (N = 306)		Chemo (N = 290)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All Causality Endocrine IMAEs within 100 days of last dose With or Without Immune Modulating Medication								
Adrenal Insufficiency	5 (1.1)	1 (0.2)	1 (0.2)	1 (0.2)	0	0	1 (0.3)	1 (0.3)
Hypophysitis	3 (0.6)	3 (0.6)	0	0	3 (1.0)	0	0	0
Hypothyroidism/Thyroiditis	48 (10.3)	0	5 (1.1)	0	27 (8.8)	0	1 (0.3)	0
Hyperthyroidism	17 (3.6)	0	2 (0.4)	0	6 (2.0)	0	0	0
Diabetes Mellitus	2 (0.4)	1 (0.2)	0	0	0	0	0	0
All-causality OESIs within 100 days of last dose With or Without Immune Modulating Medication								
Pancreatitis	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)	2 (0.7)	1 (0.3)	0	0
Encephalitis	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Myositis/ Rhabdomyolysis	0	0	1 (0.2)	1 (0.2)	0	0	1 (0.3)	1 (0.3)
Guillain-Barre Syndrome	0	0	0	0	1 (0.3)	1 (0.3)	0	0
Uveitis	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Myocarditis	1 (0.2)	0	0	0	1 (0.3)	1 (0.3)	0	0

MedDRA version 23.0 CTCAE version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months

Abbreviations: AEs - adverse events, CPS - combined positive score, CTCAE - Common Toxicity Criteria for Adverse Events, DC - discontinuation, IMAEs - immune-mediated adverse events, MedDRA - Medical Dictionary for Regulatory Activities, OESI - other events of special interest, PD-L1 - programmed death ligand 1, SAEs - serious adverse events

Source (ADaM dataset[s]): **PD-L1 CPS ≥ 5:** Table S.6.15.1 (adsl.xpt; deaths), Table S.6.3.1.2.1 (adae.xpt, adsl.xpt; all-causality SAEs), Table S.6.3.1.2.2 (adae.xpt, adsl.xpt; drug-related SAEs), Table S.6.4.2.1 (adae.xpt, adsl.xpt; all-causality AEs leading to DC), Table S.6.4.2.2 (adae.xpt, adsl.xpt; drug-related AEs leading to DC), Table S.6.1.2.1 (all-causality AEs); Table S.6.1.32.1 (adae.xpt, adsl.xpt; drug-related AEs); Table S.6.202.4 (adae.xpt, adaeimm.xpt, adsl.xpt; non-endocrine IMAEs), Table S.6.202.1 (adae.xpt, adaeimm.xpt, adsl.xpt; endocrine IMAEs), Table S.6.5.3.3.1 (OESI) in the CA209649 Primary CSR. **PD-L1 CPS < 5:** Table S.6.15.A.1 (deaths), Table S.6.3.1.2.A.1 (all-causality SAEs), Table S.6.3.1.2.A.2 (drug-related SAEs), Table S.6.4.2.A.1 (all-causality AEs leading to DC), Table S.6.4.2.A. 2 (drug-related AEs leading to DC), Table S.6.203.A.2 (non-endocrine IMAEs), Table S.6.203.A.1 (endocrine IMAEs), Table S.6.5.3.3.A.1 (OESI), Table S.6.1.2.A.1 (all-causality AEs), Table S.6.1.32.A.1 drug-related AEs) in the Summary of Clinical Safety

The Applicant's Position:

The frequencies of drug-related AEs in the nivo+chemo arm for subgroups of age, gender, race, and geographic region were generally consistent to the AE frequencies reported for the overall study populations by treatment, with the following exceptions (Table 29):

- Among all nivo+chemo treated subjects, the frequencies of drug-related Grade 3-4 AEs in the North American region (defined as US and Canada) (72.1%) appeared to be higher than those in other regions (Asia [54.2%] and ROW [57.4%]) and also higher compared with the all-treated population (59.1%). This is likely due to the difference in chemotherapy backbone, as FOLFOX is the most commonly used regimen in the US,[5,6] and drug-related Grade 3-4 AEs were higher with FOLFOX (49.5%) compared with XELOX (38.8%).
- In both treatment arms, the frequencies of Grade 3-4 drug-related AEs appeared to be higher in female subjects compared with male subjects (67.5% vs 55.2% in the nivo+chemo arm, 54.9% vs 40.1% in the chemo arm). In all treated subjects, Grade 3-4 AEs were reported in 59.1% of subjects in the nivo+chemo arm and 44.5% of subjects in the chemo arm.
- The frequencies of drug-related AEs (any grade and Grade 3-4) in the nivo + chemo arm were numerically higher (with at least a 10% difference) compared with the chemo arm for the most of the subgroups of age, gender, race and geographic region; this is consistent with all treated subjects, where drug-related Grade 3-4 AEs were 14.6% higher with nivo+chemo vs chemo.

These differences do not alter the overall benefit/risk profile of nivo+chemo in these demographic subgroups.

The safety profile of nivo+chemo as measured by the frequencies of death, AEs (all causality and drug-related), SAEs (all causality and drug-related), AEs leading to discontinuation (all causality and drug-related), IMAEs, and OESIs was similar in subjects with PD-L1 CPS ≥ 5 and in subjects with PD-L1 CPS < 5 and also consistent with all treated subjects (Table 30).

The FDA's Assessment:

FDA agrees with the Applicant's position. All-causality AEs were mostly consistent across subpopulations defined by age, gender, race and geographic region.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position: Not applicable

The FDA's Assessment:

FDA agrees.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position: There were no findings related to human carcinogenicity for nivo+chemo in study CA209649.

The FDA's Assessment:

FDA agrees.

Human Reproduction and Pregnancy

The Applicant's Position:

In CA209649, pregnancy tests were negative during the study in all female subjects of childbearing potential (Appendix 7.3 in the CA209649 Primary CSR). There is no information to report for use of nivo+chemo in pregnancy or lactation.

The FDA's Assessment:

FDA agrees.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position: Not applicable

The FDA's Assessment:

FDA agrees.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There is no information on overdose or drug abuse. No cases of withdrawal symptoms related to nivolumab were reported in CA209649.

The FDA's Assessment:

FDA agrees.

8.2.10. Safety in the Postmarketing Setting

Safety Concerns Identified Through Postmarketing Experience

The Applicant's Position: Not applicable

The FDA's Assessment:

FDA agrees.

Expectations on Safety in the Postmarketing Setting
The Applicant's Position: Not applicable

The FDA's Assessment:

Not applicable.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Safety data from 782 subjects treated with nivo+chemo from CA209649 demonstrate that the safety profile of nivo+chemo is manageable and reflective of the known safety profile of nivolumab and chemotherapy. There were no new safety signals.

A Risk Management Plan for OPDIVO will be included in this application dossier, and it includes information on the new indication for first-line nivo+chemotherapy for advanced or metastatic GC/GEJC/EAC. No new safety signal was reported, and no changes in risk minimization measures are warranted as per the new pivotal study data.

In summary, the totality of the safety data support the use of nivo+chemo as first-line therapy for advanced or metastatic GC/GEJC/EAC.

The FDA's Assessment:

FDA agrees with the Applicant's position; nivolumab in combination with FOLFOX or XELOX has an acceptable safety profile in patients with advanced unresectable or metastatic GC/GEJC/EAC with no prior therapy in the context of a statistically significant improvement in overall survival regardless of PD-L1 status. The safety profile was consistent with that known to occur in patients receiving nivolumab in combination with cytotoxic chemotherapy.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

1. There were no major statistical issues in FDA's assessment of the application; however, FDA has the following review comments. PFS in PDL1 CPS ≥ 5 was tested as a primary endpoint and results were statistically significant. However, FDA noted that the test was overpowered and the median PFS improvement was only 1.7 months for nivo+chemo compared to chemo. Although the PFS benefit is of modest magnitude, it is supportive of a statistically significant and clinically meaningful effect on overall survival.
2. OS results in PDL1 CPS ≥ 5, PDL1 CPS ≥ 1 and all randomized patients, tested in

hierarchy, were statistically significant. While the estimation of treatment effect on OS endpoint in PDL1 CPS < 5 (HR: 0.94, 95% CI: 0.78, 1.14) and PDL1 CPS < 1 (HR: 0.85, 95% CI: 0.63, 1.15) were numerically in the same direction and supportive of the OS results in PDL1 CPS ≥ 5, PDL1 CPS ≥ 1 and all randomized patients, the upper limit of the 95% CI of estimated OS HR exceeded 1 for the PDL1 CPS < 5 and < 1 subgroups. However, the study was not designed to study these PD-L1 low populations so these subgroup results are considered exploratory. Further, exploratory subgroup analyses of ORR in the PD-L1 low subgroups showed consistent improvements in anti-tumor activity for nivo+chemo compared to chemo. Given that all pre-specified analyses for which there was alpha allocation were statistically significant and the overall survival analyses were clinically meaningful, FDA has granted the indication in all randomized patients.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The clinical and statistical review teams determined that the evidence submitted provides substantial evidence of the effectiveness of nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy for the treatment of patients with advanced or metastatic GC/GEJC/EAC.
The primary support for the effectiveness of nivolumab for the indication was derived from the results of a multicenter, randomized, open-label, active-controlled, randomized trial, Study CA209649. The primary efficacy outcomes were OS and PFS in patients with PD-L1 CPS ≥ 5. FDA agrees with the Applicant's demonstration of efficacy results based on OS for all randomized patients (HR 0.80; 95% CI 0.71, 0.90). The median OS in the nivo + chemo arm was 13.8 months (95% CI: 12.6, 14.6) and in the chemo arm was 11.6 months (95% CI: 10.9, 12.5). FDA also agrees with the Applicant's presentation of PFS results for PD-L1 CPS ≥ 5 subgroup that was tested as one of the primary endpoints.

A statistically significant and clinically relevant benefit was demonstrated in the hierarchically tested secondary endpoints of OS in patients with PD-L1 CPS ≥ 1 and in all randomized patients.

The adverse reaction profile observed in patients receiving nivolumab in Study CA209649 was consistent with the known nivolumab profile in combination with cytotoxic chemotherapy. Although the incidence of adverse reactions was consistently higher with the combination, events were manageable with dose delays and supportive care in most patients.

The review team concluded that the overall risk:benefit assessment favored approval of nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy for the treatment of patients with advanced or metastatic GC/GEJC/EAC.

X	X
Primary Statistical Reviewer ***Refer to signature page***	Statistical Team Leader
X	X
Primary Clinical Reviewer ***Refer to signature page***	Clinical Team Leader ***Refer to signature page***

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No advisory committee was convened for this supplemental application as the application did not raise any issues that warranted the committee's input.

10 Pediatrics

The Applicant's Position:

Nivo+chemo was not studied in pediatric patients with advanced or metastatic GC/GEJC/EAC, as this disease occurs mainly in adults and rarely in children. Nivolumab was granted Orphan Drug Designation for the treatment of gastric and gastro-esophageal junction cancer (#16-5450) on 20-Dec-2016 and for the treatment of esophageal cancer (#16-5310) on 22-Aug-2016, and is therefore exempt from the Pediatric Research Equity Act (PREA) requirement.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

11 Labeling Recommendations

Data:

Table 31: Summary of Significant Labeling Changes (High level changes and not direct quotations)

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
INDICATIONS AND USAGE (1)	Addition of indication for OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction or esophageal adenocarcinoma.	Slight modifications to the wording of the indication
DOSAGE AND ADMINISTRATION (2.2 and 2.4)	Addition of dosing recommendation for ODPVIO in combination with fluoropyrimidine- and platinum-containing chemotherapy and associated text related to the addition of this treatment regimen and administration.	
ADVERSE REACTIONS (6.1)	Addition of clinical safety data from the CA209649 study, including: a brief description of the inclusion/exclusion criteria; duration of therapy; a brief summary of the serious and most common adverse reactions; a table of the adverse reactions occurring at an incidence of 10% or greater; and a table of laboratory abnormalities occurring at an incidence of 20% or greater.	Edits to the proposed language for clarity; changes in the incidences tables to reflect changes in labeling policies.
GERIATRIC USE (8.5)	Addition of data related to Study CA209649.	
CLINICAL STUDIES (14.3)	Addition of clinical efficacy data from the CA209649 study, including: a brief description of the study design and treatment groups; inclusion/exclusion criteria of the study; patient demographics; primary and key secondary efficacy endpoints presented in a table; and a Kaplan-Meier plot of overall survival.	Changes for clarity; changes for consistency with labeling policies (i.e., use of 95% CI, DOR, etc.). Addition of language informing prescribers of the subgroup exploratory analyses of survival in patients with CPS <1 and <5. Inclusion of OS KM for patients with CPS ≥ 1 and ≥5.
MEDGUIDE	Updated with study CA209649 information	Revision of the language for clarity.

Other Prescription Drug Labeling for OPDIVO:
The OPDIVO Medication Guide was updated to include the following additional information in patient-friendly language:

- Under "What is OPDIVO" - Addition of a description of the proposed advanced or metastatic GC/GEJC/EAC indication, consistent with the proposed indication in the Full Prescribing Information.
- Under "How will I receive OPDIVO" - Addition of a description of the dosage and administration information for advanced or metastatic GC/GEJC/EAC indication, consistent with the dosage and administration information in the Full Prescribing Information.
- Under "What are the possible side-effects of OPDIVO" - Addition of a list of the most common adverse reactions observed in the study supporting the advanced or metastatic GC/GEJC/EAC indication, consistent with the adverse reactions information in the Full Prescribing Information.

The Applicant's Position:
The clinical data provided in this supplemental BLA submission demonstrate the clinical benefit and safety of the use of nivolumab + chemotherapy for the treatment of patients with advanced or metastatic GC/GEJC/EAC. Based on these data, the table above provides a high-level summary of the proposed changes to the labeling for OPDIVO (nivolumab).

The FDA's Assessment:

FDA agrees with the updates to the Medication Guide and revised the language for clarity and consistency with current labeling policies.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

No REMS was requested. Nivolumab has been used extensively in patients with cancer.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following Postmarketing Commitment was requested and agreed to by the sponsor. The trial will be completed by May 2021, and the final report will be submitted in November 2021.

"Submit the final OS analyses and datasets for nivolumab in combination with chemotherapy vs. chemotherapy along from the ongoing clinical trial Study CA209649, titled, "A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab Plus Ipilimumab or Nivolumab in Combination with Oxaliplatin Plus Fluoropyrimidine versus Oxaliplatin Plus Fluoropyrimidine in Subjects with Previously Untreated Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer". The results from this study may inform product labeling."

14 Division Director (DHOT) (NME ONLY)

X

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15 Division Director (OCP)

X

Refer to Signature page

16 Division Director (OB)

X

Refer to signature page

17 Division Director (Clinical)

X

Refer to signature page

18 Office Director (or designated signatory authority)

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 _____

Refer to signature page

19 Appendices

19.1. References

The Applicant's References: References are provided in Section 19.6.

The FDA's References:

Not applicable.

19.2. Financial Disclosure

The Applicant's Position:

Financial interests or arrangements with clinical investigators have been disclosed in the table below. Financial disclosure information was collected and reported for the Investigators (Primary Investigators and Sub-investigators) participating in the CA209649 clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: *Financial Disclosure by Clinical Investigators*.

The FDA's Assessment:

FDA agrees with the Applicant's position and has completed the table below.

Covered Clinical Study CA209649

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2195		
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): 5		
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: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 2		

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

	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)

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position: Not applicable.

The FDA's Assessment:

Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

1. Population Pharmacokinetic Analyses

The goal of population PK analysis (popPK) was to apply popPK model to assess sources of variability (intrinsic and extrinsic covariates) of nivolumab in patients with first-line (1L) gastric cancer (GC)/gastroesophageal junction cancer (GEJC)/esophageal adenocarcinoma cancer (EAC).

The popPK) analysis dataset included a total of 9071 nivolumab concentration values from 1825 patients with solid tumors (1L GC/GEJC/EAC, NSCLC, 2L+ GC, and other tumor types) receiving nivolumab either as monotherapy or in combination with chemotherapy in 7 studies. Among these patients 725 patients were treated with nivolumab in combination with chemotherapy in study CA209649.

The popPK analysis was conducted by the applicant and evaluated by the reviewer. The PK of nivolumab was characterized by a two-compartment, zero-order IV infusion PK model and time-varying CL model (sigmoidal-Emax function) with a proportional residual error model, random effect on CL, VC, volume of distribution of peripheral compartment (VP), and EMAX.

A full covariate modeling approach was implemented to investigate the effects of covariates on nivolumab. Parameter estimates of full covariate model were provided in Table 32. The full model included the following covariate effects:

- CL: Baseline bodyweight (BBWT), sex, estimated glomerular filtration rate (eGFR), performance status (PS), race, baseline albumin (BALB), baseline LDH, baseline tumor size, patient population (1L GC/GEJC/EAC, 2L+ GC, and other)

- VC: BBWT and sex
- EMAX (maximal change in CL over time): PS and patient population (1L GC/GEJC/EAC, 2L+ GC, and other)

No signs of model misspecification were identified in the goodness-of-fit plots (Figure 9). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of nivolumab in patients with 1L GC/GEJ/EAC (Figure 10). Bootstrap analyses demonstrated consistency in parameter estimates and indicated the robustness of the model. The effects of all evaluated covariates on the nivolumab clearance were illustrated in the forest plot based on full covariate model (Figure 11).

The magnitude of the effect of covariates on CL, accounting for uncertainty, was within the 20% difference for sex, race (Asian), PS, baseline LDH, tumor burden, and BeGFR. Body weight was associated with a 26% increase in CL with an increase in weight from the median to 95th percentile value. Nivolumab CL increased approximately 31% with a reduction in serum BALB from the median to 5th percentile value. Nivolumab CL in patients with 1L GC/GEJ/EAC was similar to that seen in patients with 2L NSCLC and 2L+ GC (Figure 12).

Patients were randomized to receive nivolumab 240 mg + FOLFOX Q2W or 360 mg + XELOX Q3W in study CA209649. The observed concentration-time (c-t) profiles appeared to be comparable between 240 mg Q2W and 360 mg Q3W in patients with 1L GC/GEJ/EAC in study CA209649 (Figure 13). Simulation was also conducted to predict nivolumab exposures of 240 mg Q2W and 360 mg Q3W in 725 patients with evaluable exposure based on the estimates of individual nivolumab PK parameters. The predicted c-t profiles were used to calculate key summary measures of exposure after first dose (Cmax1, Cmin1, and Cavg1) and at steady-state (Cavgss, Cmaxss, and Cminss).

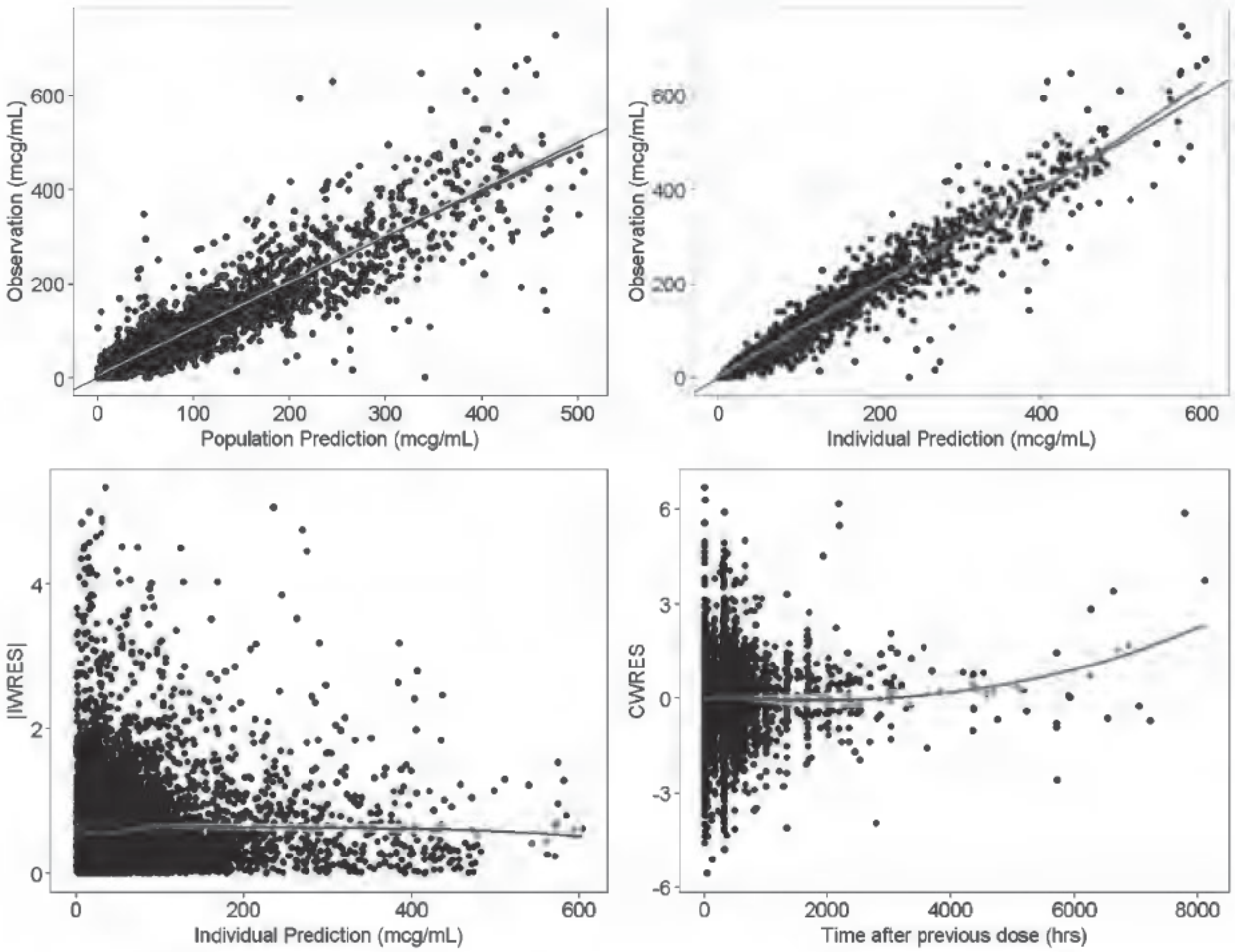
The simulation results show a significant overlap of the c-t profiles between the 360 mg Q3W and 240 mg Q2W at steady state (Figure 14). Summary statistics of these measures of exposure are presented in Table 33. The geometric mean of Cmaxss at nivolumab 360 mg Q3W is comparable (~17% higher) relative to 240 mg Q2W. The Cminss at nivolumab 360 mg Q3W is also comparable (~10% lower) relative to 240 mg Q2W. As expected, there is no exposure difference in Cavgss. The predicted Cmaxss with 360 mg Q3W is well below the median Cmaxss achieved with 10 mg/kg Q2W which is tolerable in the clinical trial.

Table 32: Parameter Estimates of the Full Nivolumab PopPK Model

Name [Units][a]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval (Bootstrap Derived)[d]
Fixed Effects				
CL0 [mL/h][e]	θ_1	10.4	0.386 (3.71)	9.78 - 11.3
VC [L][e]	θ_2	4.64	0.0585 (1.26)	4.54 - 4.75
Q [mL/h][e]	θ_3	33.2	2.56 (7.7)	28.6 - 38.9
VP [L][e]	θ_4	3.02	0.149 (4.94)	2.71 - 3.29
CL_{BBWT}[f]	θ_6	0.543	0.0486 (8.96)	0.442 - 0.636
CL_{GFR}[f]	θ_7	0.131	0.0349 (26.6)	0.0609 - 0.204
CL_{SEX}[g]	θ_8	-0.133	0.0208 (15.6)	(-0.176) - (-0.0959)
CL_{PS}[g]	θ_9	0.115	0.0217 (18.8)	0.0725 - 0.159
CL_{RAAS}[g]	θ_{10}	-0.0808	0.0234 (28.9)	(-0.125) - (-0.0370)
VC_{BBWT}[f]	θ_{11}	0.465	0.0352 (7.58)	0.395 - 0.532
VC_{SEX}[g]	θ_{12}	-0.221	0.0222 (10.1)	(-0.263) - (-0.173)
EMAX[e]	θ_{13}	-0.157	0.0481 (30.5)	(-0.260) - (-0.0678)
T50 [h]	θ_{14}	1550	138 (8.94)	1280 - 1860
HILL [-]	θ_{15}	4.35	2.13 (48.9)	2.34 - 37.8
CL_{BALB}[f]	θ_{16}	-0.945	0.0669 (7.09)	(-1.08) - (-0.811)
CL_{BLDH}[f]	θ_{17}	0.410	0.0894 (21.8)	0.231 - 0.591
CL_{BTSIZE}[f]	θ_{18}	0.0799	0.0143 (17.9)	0.0513 - 0.109
$CL_{MISSBTSIZE}$[g]	θ_{19}	0.0138	0.0269 (195)	(-0.0435) - 0.0680
$CL_{POPGC1L}$[g]	θ_{20}	0.00613	0.0297 (485)	(-0.0470) - 0.0674
$CL_{POPGC2L+}$[g]	θ_{21}	0.0563	0.0369 (65.6)	(-0.0175) - 0.131
CL_{POPOTH}[g]	θ_{22}	0.112	0.0354 (31.6)	0.0384 - 0.181
$EMAX_{PS}$[g]	θ_{23}	-0.0821	0.0295 (36)	(-0.149) - (-0.0262)
$EMAX_{POPGC1L}$[g]	θ_{24}	-0.0824	0.037 (44.9)	(-0.165) - (-0.0124)
$EMAX_{POPGC2L+}$[g]	θ_{25}	0.0963	0.0467 (48.5)	(-0.00138) - 0.182
$EMAX_{POPOTH}$[g]	θ_{26}	-0.0417	0.048 (115)	(-0.143) - 0.0580
Random Effects[h,i]				
ω^2 -CL [-]	$\omega_{1,1}$	0.0874	0.00625 (7.15)	0.0742 - 0.0973
ω^2 -VC [-]	$\omega_{2,2}$	0.0827	0.0092 (11.1)	0.0654 - 0.0994
ω^2 -VP [-]	$\omega_{3,3}$	0.166	0.0386 (23.2)	0.111 - 0.278
ω^2 -EMAX [-]	$\omega_{4,4}$	0.0503	0.0112 (22.2)	0.0319 - 0.0784
ω^2 CL: ω^2 VC [-]	$\omega_{1,2}$	0.0298	0.00409 (13.7)	0.0221 - 0.0384
Residual Error				
Proportional [-]	θ_5	0.197	0.00427 (2.17)	0.188 - 0.205

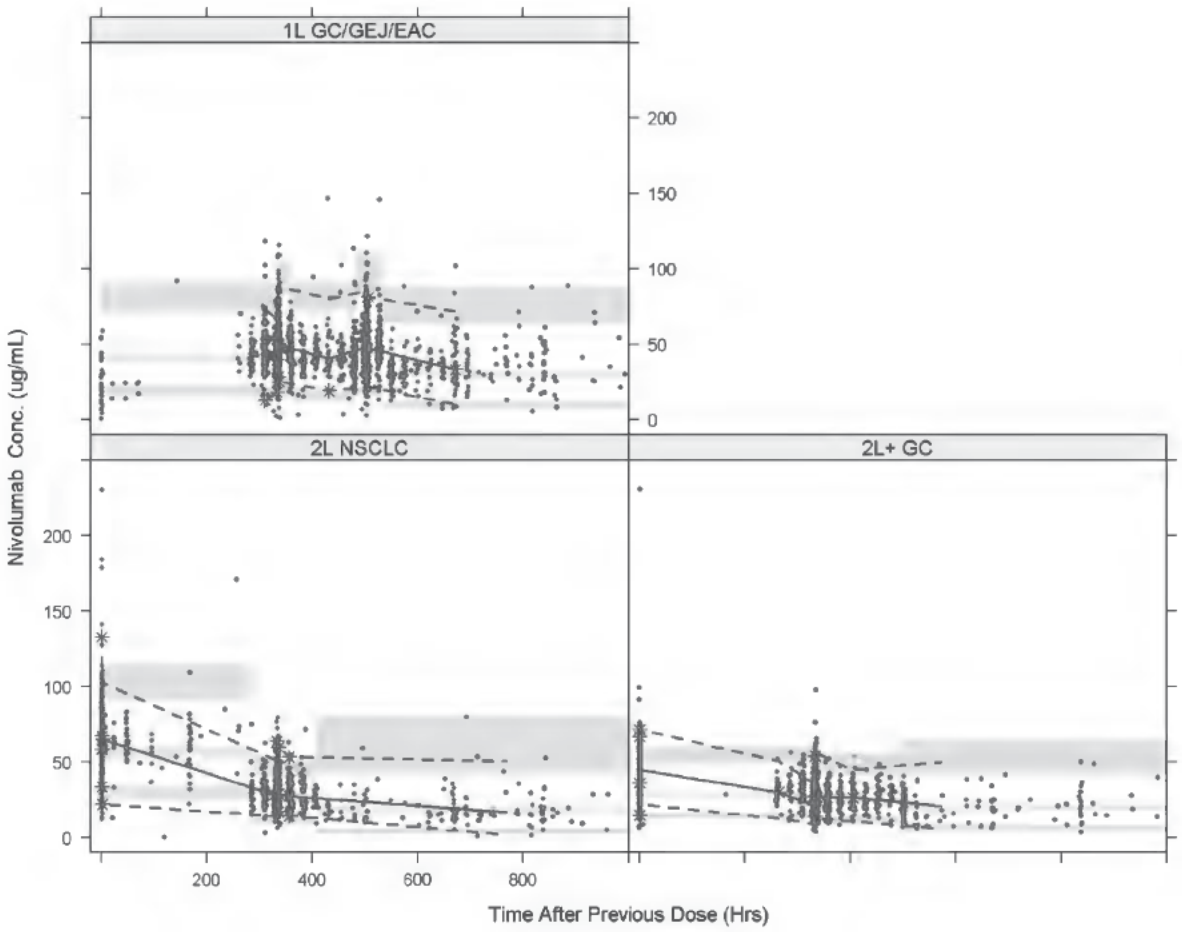
Source: Applicant's popPK report, Table 5.1.1.2-1, Page 50

Figure 9: Goodness of Fit Plots of the Final Model



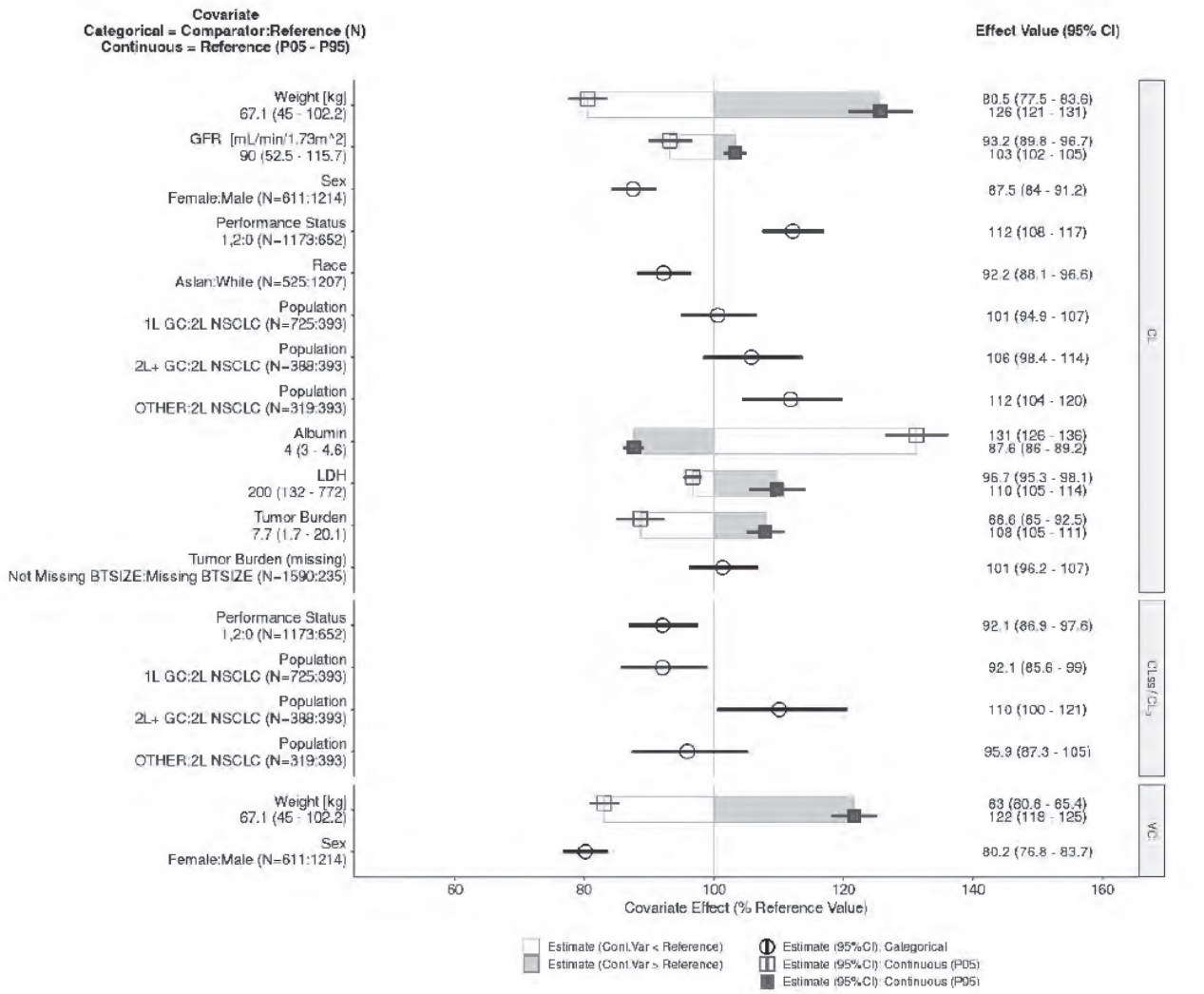
Source: Reviewer's Analysis based on "nivoppk.xpt"

Figure 10: Visual Predictive Checks of nivolumab Concentration-Time Data Stratified by Tumor Type



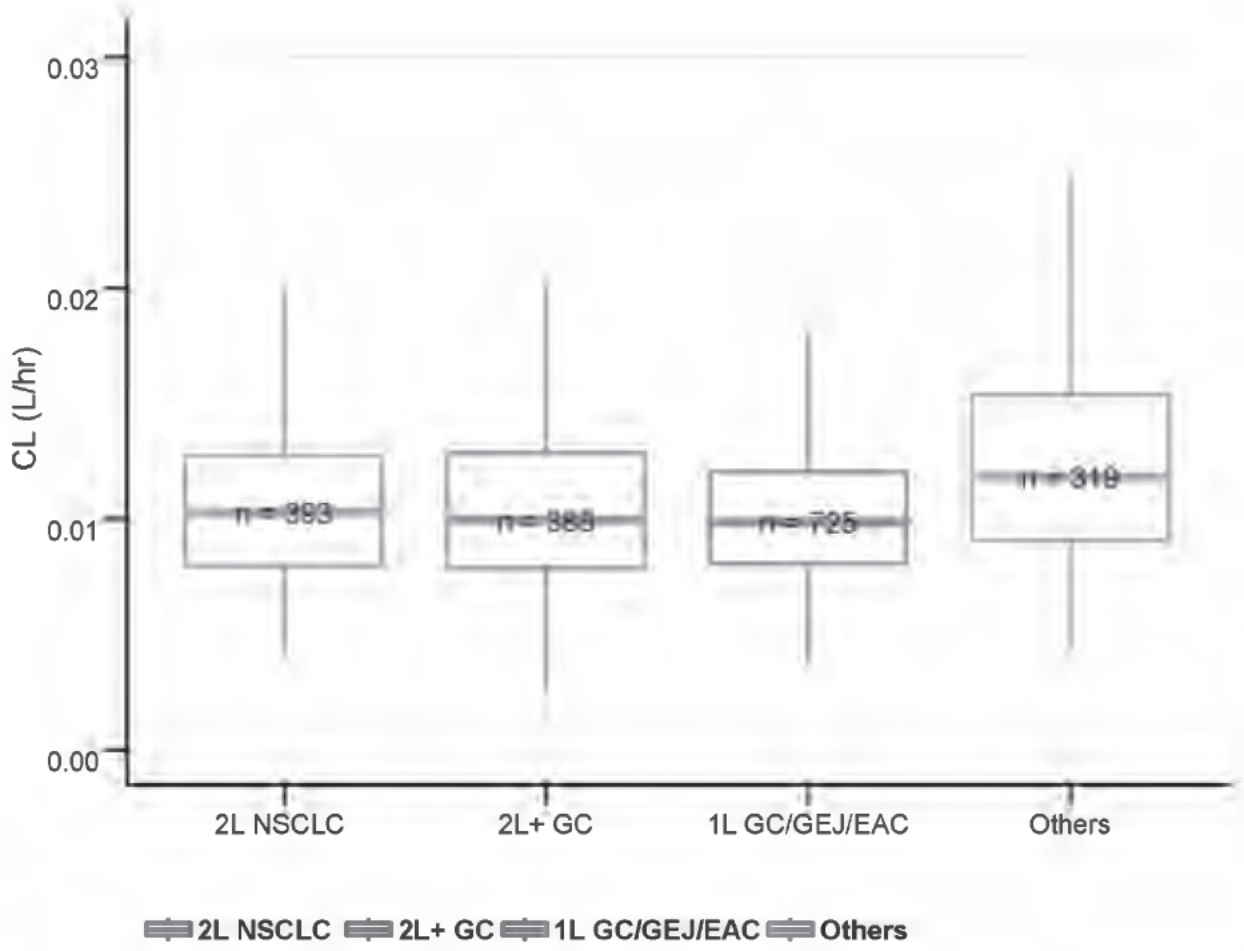
Source: Reviewer's Analysis based on "nivoppk.xpt"

Figure 11: Covariate Effects on Nivolumab Pharmacokinetic Parameters



Source: Source: Applicant's popPK report, Figure 1, Page 5

Figure 12: Comparison of CL across Tumor Types



Source: Reviewer's Analysis based on "nivoppk.xpt"

Figure 13: Comparison of Observed Concentration-Time Profile between 240 mg Q2W or 360 mg Q3W in Patients with 1L GC/GEJ/EAC

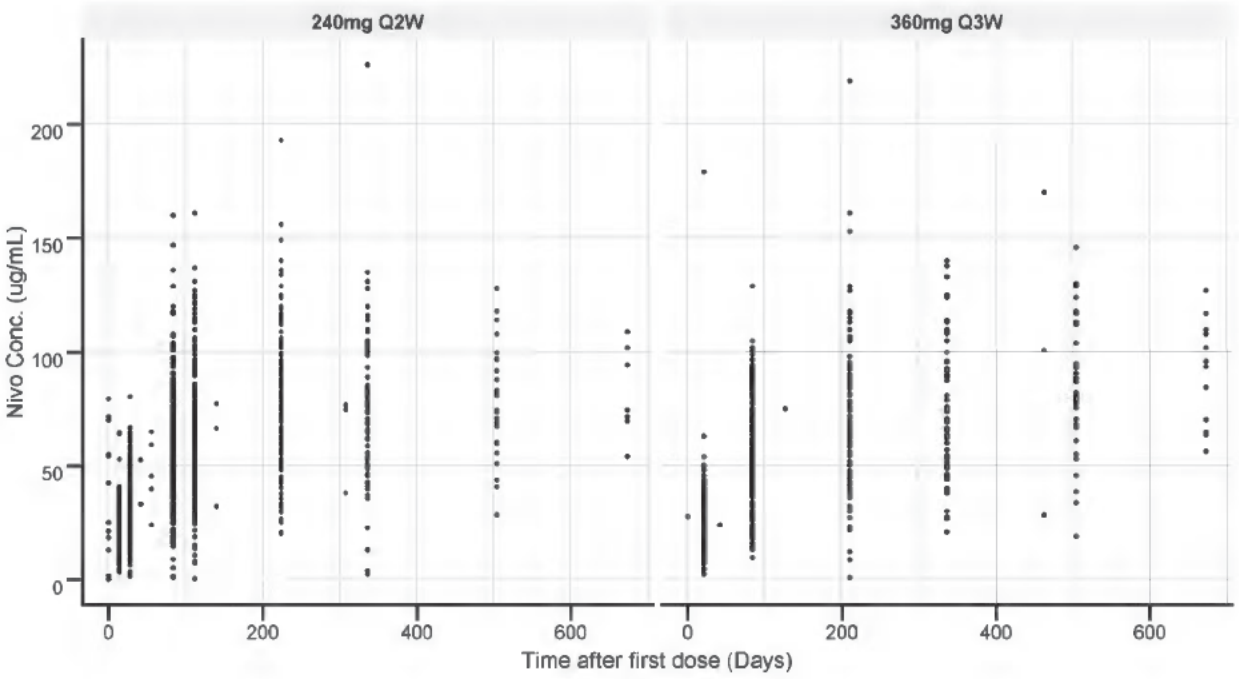
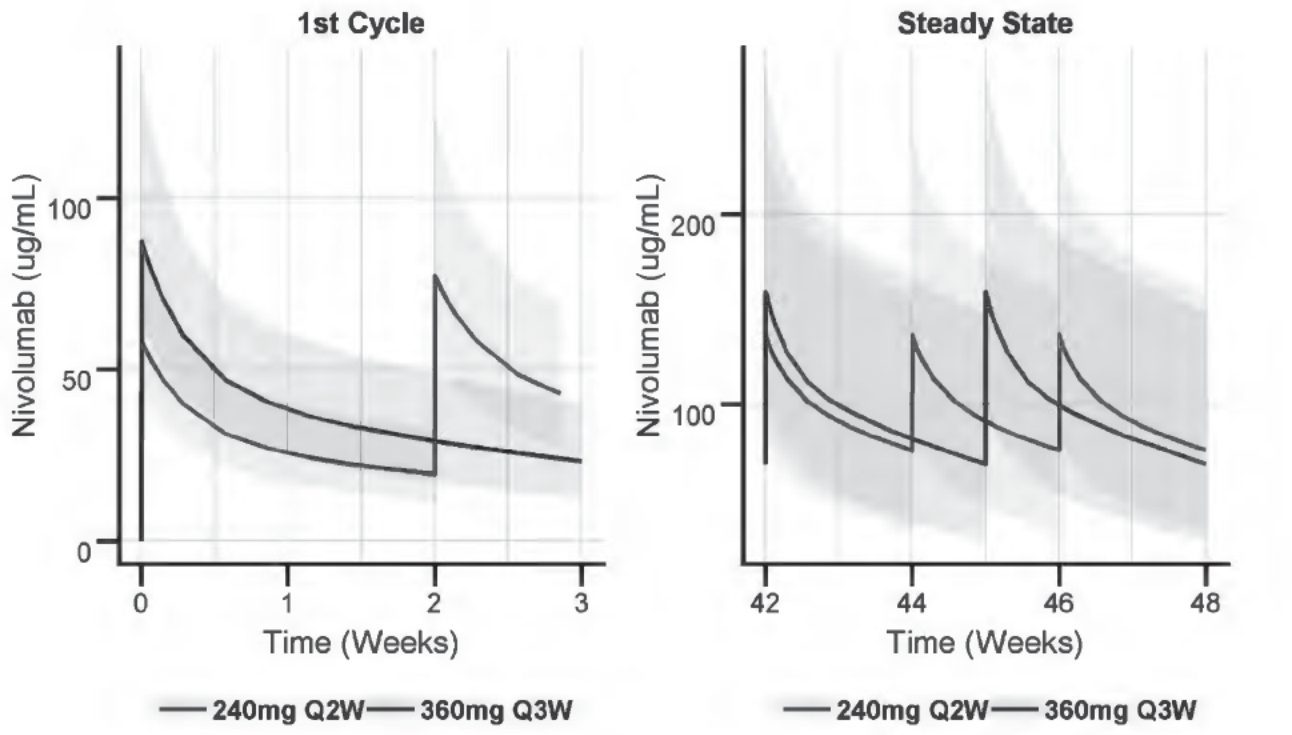


Table 33: Geometric Mean Exposures for Nivolumab after 240 mg Q2W or 360 mg Q3W in 1L GC/GEJ/EAC Patients

Sum	N	Exposure	240mg Q2W	360mg Q3W	Difference (Q3W vs Q2W)
1st	725	Cavg	29.55	38.27	29.51
1st	725	Cmax	60.28	90.42	50
1st	725	Cmin	19.52	23.05	18.08
SS	725	Cavg	95.89	95.9	0.01
SS	725	Cmax	137.57	161.13	17.13
SS	725	Cmin	75.59	68.4	-9.51

Source: Reviewer's Analysis based on "nivoppk.xpt"

Figure 14: Predicted Geometric Mean (with 90% CI) Nivolumab Concentration-Time Profiles (First Cycle and Steady-State), by Dosing Regimen (240 mg Q2W or 360 mg Q3W) in 1L GC/GEJ/EAC Patients



Source: Reviewer's Analysis based on "nivoppk.xpt"

2. Dose/Exposure-Response Analyses
    1) Methods and Data

Dose/Exposure-response (D/E-R) analyses were conducted by the applicant to explore the relationship between exposure of nivolumab and efficacy and safety in 1L GC/GEJ/EAC Patients who received nivolumab in combination with chemotherapy.

The D/E-R analysis of efficacy and E-R analysis of safety included data from 725 patients who received nivolumab 240 mg Q2W or 360 mg Q3W whom estimates of nivolumab exposures (Cavg1) were available in clinical trial CA209649

The endpoints of interest in the D/E-R analysis were overall survival (OS) and progression free survival (PFS) for efficacy and Gr2+ immune-mediated adverse events (IMAE) for safety.

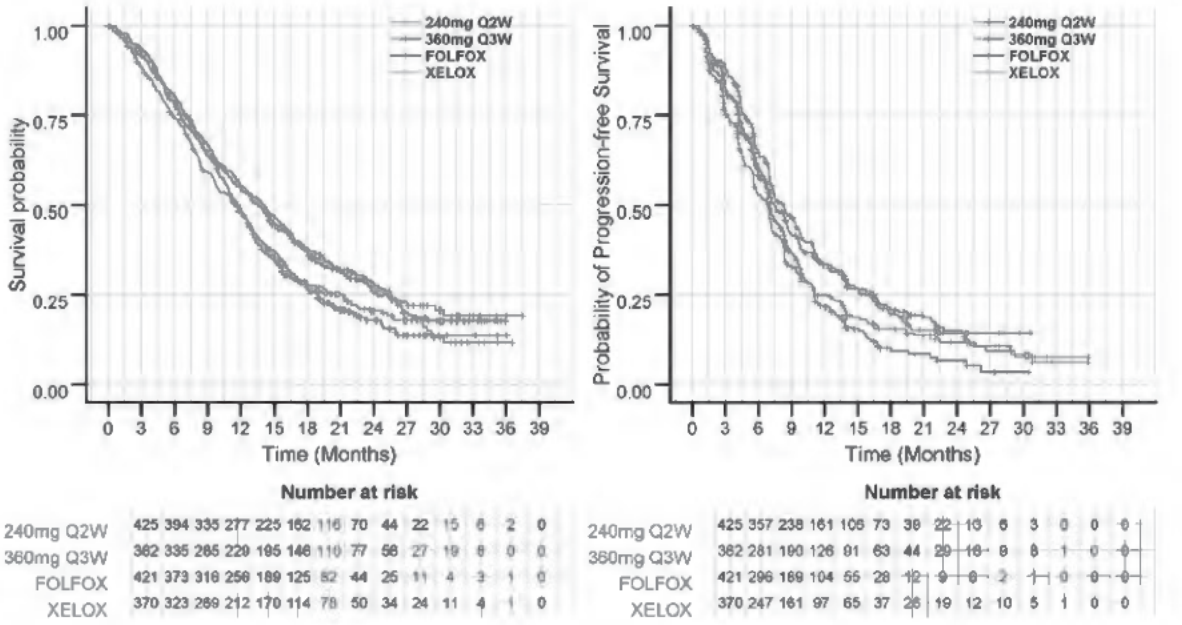
The primary exposure metric is average exposure in the firs cycle (Cave1) for exposure-efficacy analysis and daily average exposure from start of treatment until the event or censoring for exposure-safety assessment. Nivolumab average exposures were predicted by applying the individual PK parameter estimates from the full PopPK model of nivolumab to the actual first dosing history of each patient. The early measure of exposure was chosen for characterization of the E-R relationship for efficacy, as nivolumab CL is known to decrease with time and using the early exposure measurement avoided this confounding effect.

2) Dose/Exposure-Efficacy Relationships

Kaplan-Meier curves of PFS and OS by dose are displayed in Figure 15. OS and PFS appear to be similar between 240 mg + FOLFOX Q2W and 360 mg + XELOX Q3W in trial CA209649. And both Q2W and Q3W dosing regimen appear to provide better OS or PFS compared to the chemotherapy alone (Figure 15).

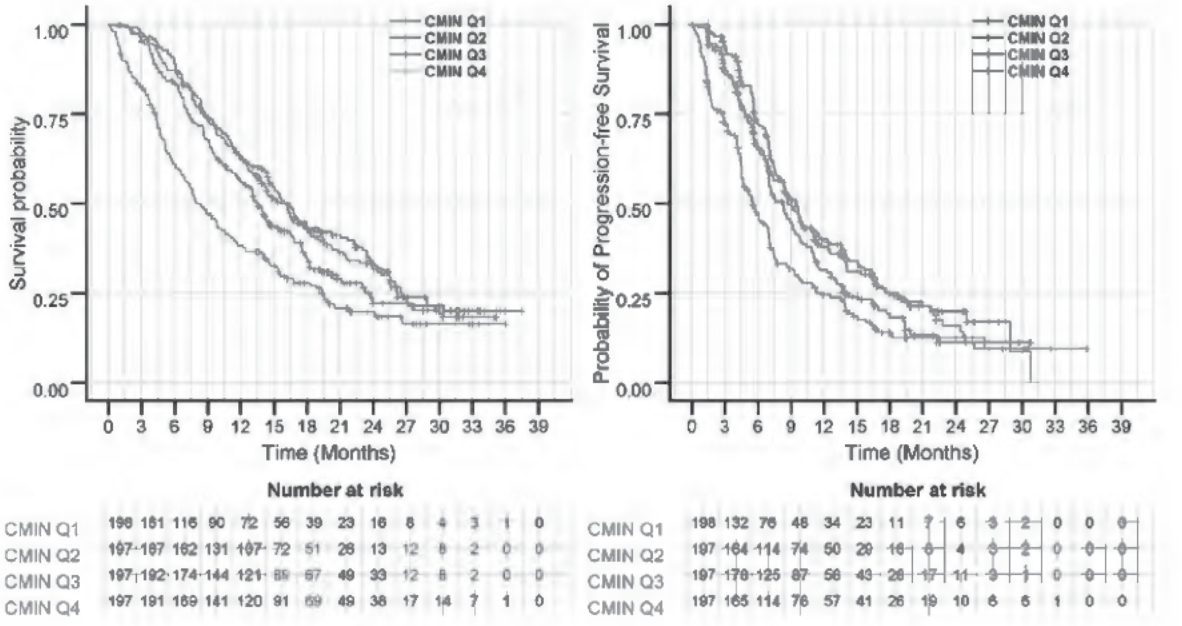
Kaplan-Meier curves of PFS and OS quartiles of nivolumab Cave1 are also displayed in Figure 16. Patients with higher nivolumab exposure (Q3 and Q4) appear to have longer OS or PFS compared to patients in the lowest exposure quartile (Q1). This trend of positive relationship between nivolumab exposure and OS/PFS is inconsistent with the flat dose response relationship for OS/PFS between 240 mg Q2W and 360 mg Q3W observed in trial CA209649. Cumulative experience with nivolumab and other PD-1/PD-L1 antibodies suggests that exposure efficacy relationship based on a narrow range of exposure from a single dose level could be confounded and should be interpreted with caution.

Figure 15: Comparison of PFS/OS between 240 mg + FOLFOX Q2W or 360 mg + XELOX Q3W in 1L GC/GEJ/EAC Patients



Source: Reviewer's Analysis based on "ereff.xpt"

Figure 16: Relationship between Nivolumab Exposure and PFS/OS in 1L GC/GEJ/EAC Patients



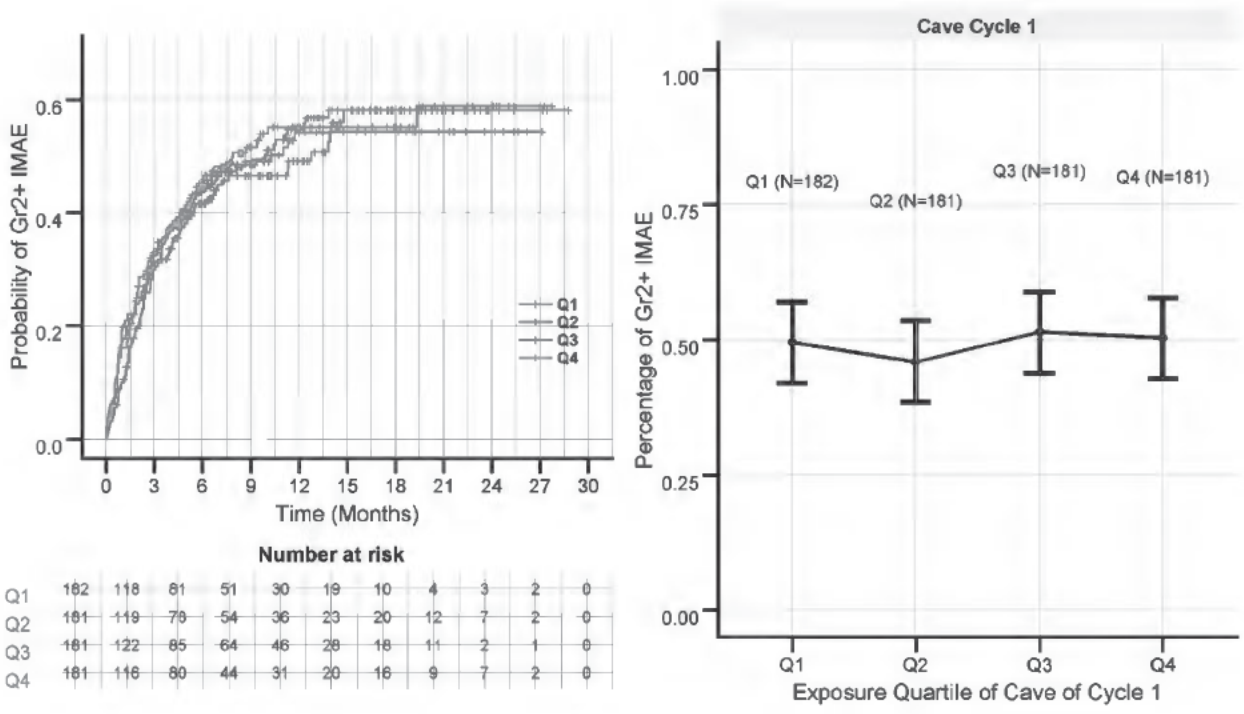
Source: Reviewer's Analysis based on "ereff.xpt"

3) Exposure-safety Relationships

Time-to-event analysis suggests that time to any grade 2+ IMAEs appears to be similar across nivolumab Cave quartiles (Figure 17). The Cave for nivolumab as continuous variable also was found to not correlate with time to grade 2+ IMAEs in a cox proportional hazard model (P-value >0.05). The rate of Grade 2+ IMAEs appears to be similar across nivolumab Cave quartiles. Overall, no significant relationships were found between nivolumab exposure and grade 2+ IMAE in patients with 1L GC/GEJ/EAC.

The D/E-R analyses suggest 360 mg Q3W and 240 mg Q2W should have similar benefit risk profiles in patients with 1L GC/GEJ/EAC.

Figure 17: Relationship between Nivolumab Exposure and Grade 2+ IMAEs in 1L GC/GEJ/EAC Patients



Source: Reviewer's Analysis based on "ersafety.xpt"

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
[FDA will complete this section.]

19.6. References

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[redacted]
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Yibo Wang	CDER/OCP/DCP I	Sections: 6 and 19.4	**Select one:** X Authored ___ Approved
	Signature: Yibo Wang -S Digitally signed by Yibo Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yibo Wang -S, 0.9.2342.19200300.100.1.1=2001497124 Date: 2021.04.14 10:51:07 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	CDER/OCP/DCP II	Sections: 6 and 19.4	**Select one:** X Authored X Approved
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Pharmacometrics Team Leader	Jiang Liu	CDER/OCP/DPM	Sections: 6 and 19.4	**Select one:** x Authored x Approved
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Clinical Reviewer	Naomi Horiba	DO3	Sections: 1, 2, 3, 4, 7, 8.1, 8.2, 8.4, 11, 13, 19.5, 19.6	**Select one:** x Authored ___ Approved
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Clinical Team Leader	Sandra Casak	DO3	Authored: Section 1 Approved Sections: 1, 2, 3, 4.1, 7, 8.1, 8.2, 8.4, 11, 13, 19.5,19.6	**Select one:** X Authored X Approved
	Signature: Refer to final assessment aid.			
Statistical Reviewer	Abhishek Bhattacharjee	OB/DBV	Sections: 1, 7, 8.1. 8.3, 8.4	**Select one:** x Authored x Approved
	Signature: Abhishek Bhattacharjee -S Digitally signed by Abhishek Bhattacharjee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002979095, cn=Abhishek Bhattacharjee -S Date: 2021.04.14 12:33:27 -04'00'			
Statistical Team Leader	Joyce Cheng	OB/DBV	Sections: 1, 7, 8.1. 8.3, 8.4	**Select one:** x Authored x Approved
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Deputy Division Director (OB)	Yuan-Li Shen	OB/DBV	Sections: 1, 7, 8.1. 8.3, 8.4	**Select one:** ___ Authored x Approved
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Associate Director for Labeling (ADL)	William Pierce	OOD/IO	Section: 11, Prescribing Information (USPI)	**Select one:** X Authored X Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2021.04.14 12:26:13 -04'00'			

Cross-Disciplinary Team Leader (CDTL)	Sandra Casak	DO3	Authored Section :1 Approved Section : All	**Select one:** _X_ Authored X Approved
	Signature: Refer to final assessment aid.			
Deputy Division Director (Clinical)	'Lola Fashoyin-Aje	DO3	Sections: All	**Select one:** ___ Authored _X_ Approved
	Signature: Refer to final assessment aid			

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04/16/2021 07:52:06 AM

Clinical Pharmacology Memorandum

BLA #	125554
Type/Category	Efficacy Supplement-91
Brand Name	Opdivo
Generic name	Nivolumab
Proposed Indications	Nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction or esophageal adenocarcinoma.
Dosage Form and Strengths	Nivolumab injection: 40 mg/4 mL, 100 mg/10 mL, and 240 mg/24 mL solution in a single-dose vial
Route of Administration	Intravenous (IV) infusion
Dosing Regimen	Nivolumab: • 360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks. • 240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks.
Sponsor	Bristol-Myers Squibb Company (BMS)
OCP Division	DCP I & II
OND Division	DO3
Submission Date	11/25/2020
PDUFA	5/25/2021
Primary Reviewers	Yibo Wang, Ph.D. and Youwei Bi, Ph.D.
Team Leads	Hong Zhao, Ph.D. and Jiang Liu, Ph.D.

The Clinical Pharmacology Review is complete and has been added to the multidisciplinary review and evaluation document, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details.

Recommendation:
Clinical Pharmacology review team's recommendation for this application is approval.

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/s/

YI-BO WANG
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s091

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 12, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 125554/S-091
Product Name, Dosage Form, and Strength:	Opdivo (nivolumab) Injection, 40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bristol-Myers Squibb
FDA Received Date:	November 25, 2020; January 11, 2021; March 23, 2021
OSE RCM #:	2020-2419
DMEPA Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

Bristol-Myers Squibb submitted BLA 125554/S-091 for revision of the Opdivo (nivolumab) injection Prescribing Information (PI) to add indications and dosing for nivolumab in combination with fluoropyrimidine- and platinum- containing chemotherapy, for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction or esophageal adenocarcinoma. DMEPA was consulted by DO3 to evaluate the PI for areas of vulnerability to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C—N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F—N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed revisions to Section 2 Dosage and administration, and Section 17 Patient counseling/ Medication guide of the Opdivo PI and found the revisions acceptable from a medication error perspective. Therefore, we have no recommendations for the proposed Opdivo PI from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Opdivo Prescribing Information and Medication Guide are acceptable from a medication error perspective.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Opdivo received on January 11, 2021 from Bristol-Myers Squibb.

Table 2. Relevant Product Information for Opdivo

Initial Approval Date	December 22, 2014
Active Ingredient	Nivolumab
Indication	Melanoma; Non-small cell lung cancer; Small cell lung cancer; Malignant pleural mesothelioma; Renal cell carcinoma; Classical Hodgkin lymphoma; Squamous cell carcinoma of the head and neck; Urothelial carcinoma; Colorectal cancer; Hepatocellular carcinoma; Esophageal squamous cell carcinoma; Gastric cancer, Gastroesophageal junction cancer; or Esophageal adenocarcinoma (proposed.)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	40 mg/4 mL, 100 mg/10 mL and 240 mg/24 mL
Dose and Frequency	**Table 1: Recommended Dosages for OPDIVO as a Single Agent**

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma	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
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		
Esophageal squamous cell carcinoma		
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
[redacted]		(b) (4)

Table 1: Recommended Dosages for OPDIVO as a Single Agent

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer	Adult patients and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity
	Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg kg every 2 weeks (30-minute intravenous infusion)	

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

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

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

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Malignant pleural mesothelioma	360 mg every 3 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)	
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

Proposed (March 23, 2021 label)-

Gastric cancer, Gastroesophageal junction cancer, and Esophageal adenocarcinoma	240 mg every 2 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks or 360 mg every 3 weeks (30-minute intravenous infusion) with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks	Until disease progression, unacceptable toxicity, or up to 2 years

How Supplied	40 mg/4 mL single-dose vial 100 mg/10 mL single-dose vial 240 mg/24 mL single-dose vial

Storage	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.
Container Closure	•Nivolumab Injection, 40 mg/4 mL and 100 mg/10 mL (10 mg/mL) are packaged in 10-c (b) (4) glass vials. •Nivolumab Injection, 240 mg/24 mL (10 mg/mL) is packaged i (b) (4) (b) (4) glass vials. •Vials for all three presentations are stoppered with a 20-mm (b) (4) (b) (4) stopper and sealed with a 20-mm aluminum crimp seal with Flip-Off seal.

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APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 4, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Nivolumab, 125554. Our search identified 8 previous reviews[a-h], and we considered our previous recommendations to see if they are applicable for this current review.

[redacted]

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[a] Mahmoud, S. Labeling Review for Opdivo-Cabometyx (BLA 125554/S-090; NDA 208692/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 31. RCM No.: 2020-1812.

[b] Straka, M. Labeling Review for Opdivo (BLA 125554/S-081). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 31. RCM No.: 2020-191.

[c] Straka, M. Labeling Review for Opdivo (BLA 125554/S-073). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 15. RCM No.: 2019-433.

[d] Gao, T. Label and Labeling Review for Opdivo-Yervoy (BLA 125554/S-058; BLA 125377/S-094). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 11. RCM No.: 2017-2323.

[e] Gao, T. Label and Labeling Review for Opdivo (BLA 125554/S-043). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 4. RCM No.: 2017-2016.

[f] Gao, T. Label and Labeling Review for Opdivo (BLA 125554/S-018). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 APR 8. RCM No.: 2016-700.

[g] Gao, T. Label and Labeling Review for Opdivo (BLA 125554/S-012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 26. RCM No.: 2015-2221.

[h] Townsend, O. Label and Labeling Review for Opdivo (BLA 125554). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 22. RCM No.: 2014-1845.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis[i], along with postmarket medication error data, we reviewed the following Opdivo labels and labeling submitted by Bristol-Myers Squibb.

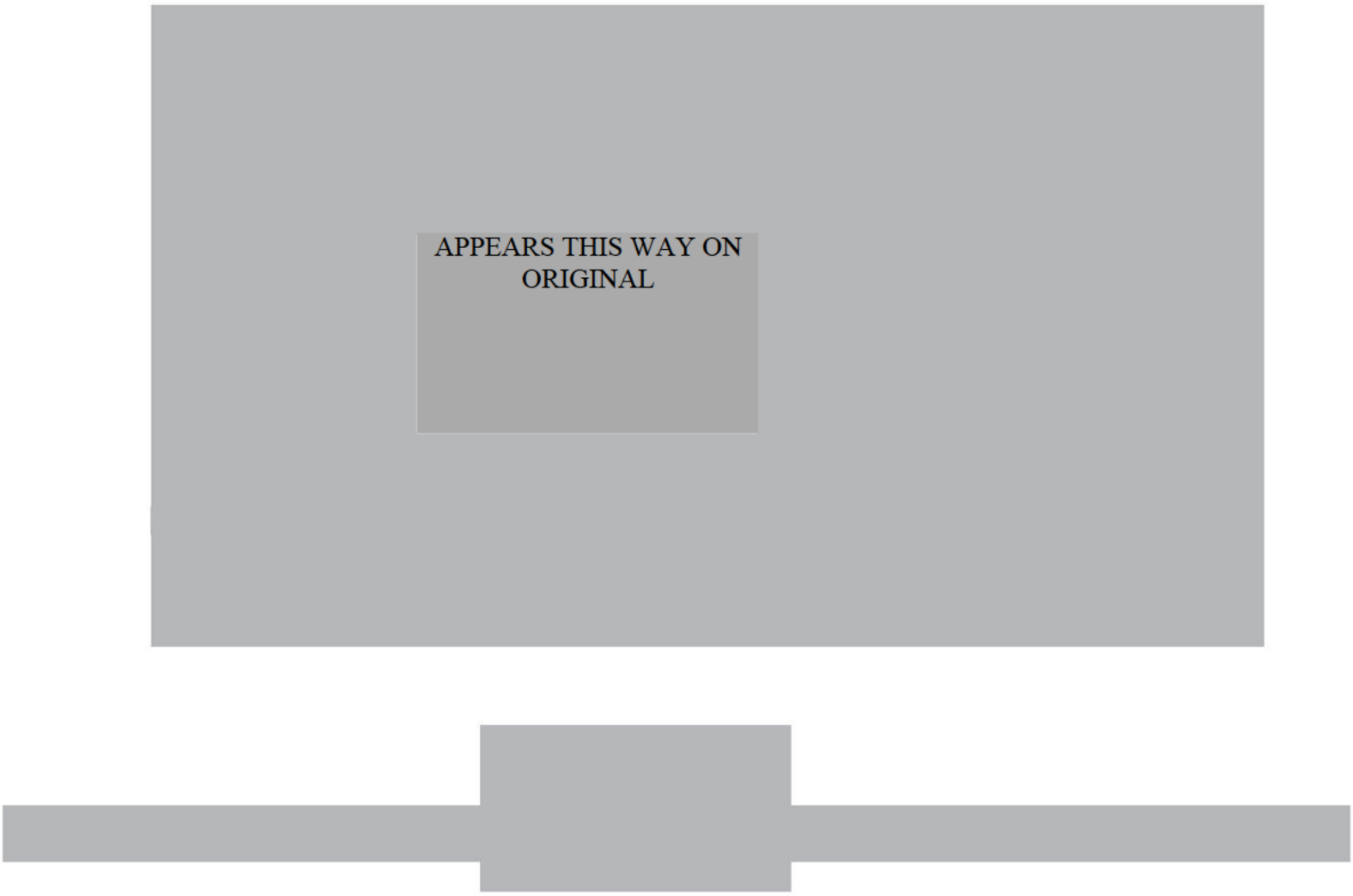
- Prescribing Information (Image not shown) received on March 23, 2021, available from \\CDSESUB1\evsprod\bla125554\0906\m1\us\22mar2021-1l-gc-gejc-eac-649-nivol-markup.docx
- Prescribing Information (Image not shown) received on January 11, 2021, available from \\CDSESUB1\evsprod\bla125554\0878\m1\us\06jan2021-1l-gc-gejc-eac-649-nivol-ann.docx
- Prescribing Information (Image not shown) received on November 25, 2020, available from \\CDSESUB1\evsprod\bla125554\0856\m1\us\1l-gc-gejc-eac-649-nivol-ann.docx

G.2 Label and Labeling Images

N/A

APPEARS THIS WAY ON ORIGINAL

[i]Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



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

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

Memorandum

Date: March 12, 2021

To: Steven Lemery, M.D., Director
Division of Oncology 3 (DO3)

Shubhangi (Gina) Mehta, PharmD, Regulatory Project Manager, DO3

From: Kevin Wright, PharmD, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for Opdivo (nivolumab) injection, for intravenous use

BLA: 125554/Supplement 091

In response to DO3's consult request dated March 11, 2021, OPDP has reviewed the proposed product labeling (PI), and Medication Guide for Opdivo (nivolumab) injection, for intravenous use (Opdivo). This supplement (S-091) proposes a new indication: Opdivo in combination with chemotherapy gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO3 (Gina Mehta) on March 3, 2021, and we have no additional comments at this time.

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 March 11, 2021.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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/s/

KEVIN WRIGHT
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 11, 2021
To:	Shubhangi (Gina) Mehta, PharmD Regulatory Project Manager **Division of Oncology 3 (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kevin Wright, Pharm D Team Leader **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, for intravenous use
Application Type/Number:	BLA 125554
Supplement Number:	S-091
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On November 25, 2020, Bristol-Myers Squibb Company submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved Biologic License Application (BLA) 125554/S-091 for OPDIVO (nivolumab) injection. With this supplement, the Applicant proposes a new indication, in combination with fluoropyrimidine and platinum-containing chemotherapy, for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction or esophageal adenocarcinoma.

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 3 (DO3) on December 2, 2020 and March 11, 2021, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPIVO (nivolumab) injection.

2 MATERIAL REVIEWED

- Draft OPIVO (nivolumab) injection MG received on November 25, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 3, 2021.
- Draft OPIVO (nivolumab) injection Prescribing Information (PI) received on November 25, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 3, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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