CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125554Orig1s081

Trade Name: OPDIVO

Generic or Proper Name: nivolumab

Sponsor: Bristol-Myers Squibb Company

Approval Date: June 10, 2020

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

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.
- 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.
- patents 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.

Small Cell Lung Cancer (SCLC)

- patients with metastatic small cell lung cancer with progression after

platinum-based chemotherapy and at least one other line of therapy.[a]

Renal Cell Carcinoma (RCC)

- patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.
- patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab.

Classical Hodgkin Lymphoma (cHL)

- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after[a]:
    - 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.

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.

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]

Hepatocellular Carcinoma (HCC)

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

Esophageal Squamous Cell Carcinoma (ESCC)

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

[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.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s081

APPROVAL LETTER

BLA 125554/S-081

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Adrian Cheung, Ph.D., R.A.C.
Associate Director, Global Regulatory, Safety and Biometrics, US Oncology
P.O. Box 5326
Princeton, NJ 08543

Dear Dr. Cheung:

Please refer to your supplemental biologics license application (sBLA), dated and received December 11, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Opdivo (nivolumab), injection, for intravenous infusion.

This Prior Approval supplemental biologics application provides for a new indication for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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

CONTENT OF LABELING

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

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

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

The SPL will be accessible via publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

PROMOTIONAL MATERIALS

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

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

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

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

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

If you have any questions, call Maryam Khazraee, Regulatory Health Project Manager, at (301) 796-7119.

Sincerely,

{See appended electronic signature page}

Lola Fashoyin-Aje, M.D., M.P.H
Deputy Director (Acting)
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
06/10/2020 04:25:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s081

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

Indications and Usage (1)	6/2020
Dosage and Administration (2)	6/2020
Warnings and Precautions (5)	5/2020

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

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

Melanoma

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

Non-Small Cell Lung Cancer (NSCLC)

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

Small Cell Lung Cancer (SCLC)

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

Renal Cell Carcinoma (RCC)

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

Classical Hodgkin Lymphoma (cHL)

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

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

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

Urothelial Carcinoma

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

Colorectal Cancer

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

Hepatocellular Carcinoma (HCC)

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

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)

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

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

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

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

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

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

- None. (4)

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

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis: Withhold OPDIVO when given as a single agent for moderate or severe and permanently discontinue for life-threatening colitis. Withhold OPDIVO when given with ipilimumab for moderate and permanently discontinue for severe or life-threatening colitis. (5.2)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.3)
- Immune-mediated endocrinopathies: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis. Withhold for moderate and permanently discontinue for severe or life-threatening adrenal insufficiency. Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. Monitor for hyperglycemia. Withhold for severe and permanently discontinue for life-threatening hyperglycemia. (5.4)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation. (5.5)
- Immune-mediated skin adverse reactions: Withhold for severe and permanently discontinue for life-threatening rash. (5.6)
- Immune-mediated encephalitis: Monitor for changes in neurologic function. Withhold for new-onset moderate to severe neurological signs or symptoms and permanently discontinue for immune-mediated encephalitis. (5.7)

- Infusion-related reactions: Discontinue OPDIVO for severe and life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. (5.9)
- Complications of allogeneic HSCT: Monitor for hyperacute, acute, and chronic graft-versus-host-disease (GVHD), hepatic veno-occlusive disease, and steroid-requiring febrile syndrome. (5.10)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and use of effective contraception. (5.11, 8.1, 8.3)
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.12)

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

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

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

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

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

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

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

1.2 Adjuvant Treatment of Melanoma

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

1.3 Metastatic Non-Small Cell Lung Cancer

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

1.4 Small Cell Lung Cancer

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

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

1.5 Advanced Renal Cell Carcinoma

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

1.6 Classical Hodgkin Lymphoma

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

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

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

1.7 Squamous Cell Carcinoma of the Head and Neck

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

1.8 Urothelial Carcinoma

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

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

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

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

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

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

1.10 Hepatocellular Carcinoma

OPDIVO, as a single agent or in combination with ipilimumab, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.10)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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.

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
Small cell lung cancer	240 mg every 2 weeks (30-minute intravenous infusion)	Until disease progression or unacceptable toxicity

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

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

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

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

Indication	Recommended OPDIVO Dosage	Duration of Therapy
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

2.3 Dose Modifications

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

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

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

Table 3: Recommended Dose Modifications for OPDIVO

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

Table 3: Recommended Dose Modifications for OPDIVO

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

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

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

[b] HCC: hepatocellular carcinoma.

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

2.4 Preparation and Administration

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

Preparation

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

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

Administration

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

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

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

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

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

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

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

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

5.2 Immune-Mediated Colitis

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

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

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

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

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

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

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

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

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

5.3 Immune-Mediated Hepatitis

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

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

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

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

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

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

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

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

Adrenal Insufficiency

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

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

Hypothyroidism and Hyperthyroidism

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

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

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

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

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

Type 1 Diabetes Mellitus

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

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

5.5 Immune-Mediated Nephritis and Renal Dysfunction

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

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

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

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

5.6 Immune-Mediated Skin Adverse Reactions

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

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

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

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

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

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

5.7 Immune-Mediated Encephalitis

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

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

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

5.8 Other Immune-Mediated Adverse Reactions

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

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

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

5.9 Infusion-Related Reactions

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

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

OPDIVO 1 mg/kg with Ipilimumab 3 mg/kg

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

OPDIVO 3 mg/kg with Ipilimumab 1 mg/kg

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

5.10 Complications of Allogeneic Hematopoietic Stem Cell Transplantation

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

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

5.11 Embryo-Fetal Toxicity

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

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

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

6 ADVERSE REACTIONS

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

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

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

6.1 Clinical Trials Experience

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

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

Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

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

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

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

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

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

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

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes rhinitis, pharyngitis, and nasopharyngitis.

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

Cardiac Disorders: ventricular arrhythmia

Eye Disorders: iridocyclitis

General Disorders and Administration Site Conditions: infusion-related reactions

Investigations: increased amylase, increased lipase

Nervous System Disorders: dizziness, peripheral and sensory neuropathy

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

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

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

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

Previously Untreated Metastatic Melanoma

CHECKMATE-066

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

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

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

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

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

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

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

Toxicity was graded per NCI CTCAE v4.

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

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

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

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

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

Nervous System Disorders: peripheral neuropathy

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

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

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

CHECKMATE-067

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

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

Patients were randomized to receive:

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

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

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

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

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

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

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

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

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

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia and fatigue.

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

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

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

[e] Includes hypertension and blood pressure increased.

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

Gastrointestinal Disorders: stomatitis, intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

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

Nervous System Disorders: neuritis, peroneal nerve palsy

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

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

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

Adjuvant Treatment of Melanoma

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

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

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

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

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

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

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

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

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

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

[e] Includes postural dizziness and vertigo.

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

[g] Includes secondary hypothyroidism and autoimmune hypothyroidism.

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

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

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

Metastatic Non-Small Cell Lung Cancer

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

The safety of OPDIVO in combination with ipilimumab was evaluated in CHECKMATE-227, a randomized, multicenter, multi-cohort, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.3)]*. The trial excluded patients with untreated brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients received OPDIVO 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks and ipilimumab 1 mg/kg by intravenous infusion over 30 minutes every 6 weeks or platinum-doublet chemotherapy every 3 weeks for 4 cycles. The median duration of therapy in OPDIVO and ipilimumab-treated patients was 4.2 months (range: 1 day to 25.5 months): 39% of patients received OPDIVO and ipilimumab for >6 months and 23% of patients received OPDIVO and ipilimumab for >1 year. The population characteristics were: median age 64 years (range: 26 to 87); 48% were ≥65 years of age, 76% White, and 67% male. Baseline ECOG performance status was 0 (35%) or 1 (65%), 85% were former/current smokers, 11% had brain metastases, 28% had squamous histology and 72% had non-squamous histology.

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

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

Tables 12 and 13 summarize selected adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-227.

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

Adverse Reaction	OPDIVO and Ipilimumab (n=576)		Platinum-doublet Chemotherapy (n=570)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	44	6	42	4.4
Pyrexia	18	0.5	11	0.4
Edema[b]	14	0.2	12	0.5
Skin and Subcutaneous Tissue				
Rash[c]	34	4.7	10	0.4
Pruritus[d]	21	0.5	3.3	0
Metabolism and Nutrition				
Decreased appetite	31	2.3	26	1.4
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[e]	27	1.9	16	0.7
Arthralgia	13	0.9	2.5	0.2
Gastrointestinal				
Diarrhea/colitis[f]	26	3.6	16	0.9
Nausea	21	1.0	42	2.5
Constipation	18	0.3	27	0.5
Vomiting	13	1.0	18	2.3
Abdominal pain[g]	10	0.2	9	0.7
Respiratory, Thoracic, and Mediastinal				
Dyspnea[h]	26	4.3	16	2.1
Cough[i]	23	0.2	13	0
Hepatobiliary				
Hepatitis[j]	21	9	10	1.2
Endocrine				
Hypothyroidism[k]	16	0.5	1.2	0
Hyperthyroidism[l]	10	0	0.5	0
Infections and Infestations				
Pneumonia[m]	13	7	8	4.0
Nervous System				
Headache	11	0.5	6	0

[a] Includes fatigue and asthenia.

[b] Includes eyelid edema, face edema, generalized edema, localized edema, edema, edema peripheral, and periorbital edema.

[c] Includes autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption.

[d] Includes pruritus and pruritus generalized.

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

Other clinically important adverse reactions in CHECKMATE-227 were:

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

Gastrointestinal: stomatitis, pancreatitis, gastritis

Musculoskeletal and Connective Tissue: arthritis, polymyalgia rheumatica, rhabdomyolysis

Nervous System: peripheral neuropathy, autoimmune encephalitis

Blood and Lymphatic System: eosinophilia

Eye Disorders: blurred vision, uveitis

Cardiac: atrial fibrillation, myocarditis

Table 13: Laboratory Values Worsening from Baseline[a] Occurring in ≥20% of Patients on OPDIVO and Ipilimumab - CHECKMATE-227

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

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

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

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

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

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

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

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

Adverse Reaction	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy (n=358)		Platinum-Doublet Chemotherapy (n=349)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue[a]	49	5	40	4.9
Pyrexia	14	0.6	10	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	39	4.5	27	2.0
Gastrointestinal				
Nausea	32	1.7	41	0.9
Diarrhea[c]	31	6	18	1.7
Constipation	21	0.6	23	0.6
Vomiting	18	2.0	17	1.4
Abdominal pain[d]	12	0.6	11	0.9
Skin and Subcutaneous Tissue				
Rash[e]	30	4.7	10	0.3
Pruritus[f]	21	0.8	2.9	0

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

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

Toxicity was graded per NCI CTCAE v4.

[a] Includes fatigue and asthenia

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

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

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

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

[f] Includes pruritus and generalized pruritus

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

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

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

[j] Includes dizziness, vertigo and positional vertigo

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

Laboratory Abnormality	OPDIVO and Ipilimumab and Platinum-Doublet Chemotherapy		Platinum-Doublet Chemotherapy	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	70	9	74	16
Lymphopenia	41	6	40	11
Neutropenia	40	15	42	15
Leukopenia	36	10	40	9

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

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

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

Second-line Treatment of Metastatic NSCLC

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

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

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

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

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

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

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

Toxicity was graded per NCI CTCAE v4.

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

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

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

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

[b] Not graded per NCI CTCAE v4.

Small Cell Lung Cancer

The safety of OPDIVO was evaluated in CHECKMATE-032, a multicenter, multi-cohort, open-label, ongoing trial that enrolled 245 patients with SCLC with disease progression after platinum-

based chemotherapy *[see Clinical Studies (14.4)]*. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Patients received OPDIVO 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks. The median duration of therapy in OPDIVO-treated patients was 1 month (range: 0 to 44.2+ months): 17% of patients received OPDIVO for >6 months and 9% of patients received OPDIVO for >1 year.

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

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

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

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

Advanced Renal Cell Carcinoma

Previously Treated Renal Cell Carcinoma

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

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

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

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

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

Adverse Reaction	OPDIVO (n=406)		Everolimus (n=397)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Adverse Reaction	98	56	96	62
General				
Fatigue[a]	56	6	57	7
Pyrexia	17	0.7	20	0.8
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	34	0	38	0.5
Dyspnea/exertional dyspnea	27	3.0	31	2.0
Upper respiratory infection[b]	18	0	11	0
Gastrointestinal				
Nausea	28	0.5	29	1
Diarrhea[c]	25	2.2	32	1.8
Constipation	23	0.5	18	0.5
Vomiting	16	0.5	16	0.5
Skin and Subcutaneous Tissue				
Rash[d]	28	1.5	36	1.0
Pruritus/generalized pruritus	19	0	14	0
Metabolism and Nutrition				
Decreased appetite	23	1.2	30	1.5
Musculoskeletal and Connective Tissue				
Arthralgia	20	1.0	14	0.5
Back pain	21	3.4	16	2.8

Toxicity was graded per NCI CTCAE v4.

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

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

[c] Includes colitis, enterocolitis, and gastroenteritis.

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

Other clinically important adverse reactions in CHECKMATE-025 were:

General Disorders and Administration Site Conditions: peripheral edema/edema

Gastrointestinal Disorders: abdominal pain/discomfort

Musculoskeletal and Connective Tissue Disorders: extremity pain, musculoskeletal pain

Nervous System Disorders: headache/migraine, peripheral neuropathy

Investigations: weight decreased

Skin Disorders: palmar-plantar erythrodysesthesia

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

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

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

Previously Untreated Renal Cell Carcinoma

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

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

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

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

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

Adverse Reaction	OPDIVO and Ipilimumab (n=547)		Sunitinib (n=535)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Adverse Reaction	99	65	99	76
General				
Fatigue[a]	58	8	69	13
Pyrexia	25	0.7	17	0.6
Edema[b]	16	0.5	17	0.6
Skin and Subcutaneous Tissue				
Rash[c]	39	3.7	25	1.1
Pruritus/generalized pruritus	33	0.5	11	0
Gastrointestinal				
Diarrhea	38	4.6	58	6
Nausea	30	2.0	43	1.5
Vomiting	20	0.9	28	2.1
Abdominal pain	19	1.6	24	1.9
Constipation	17	0.4	18	0
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	37	4.0	40	2.6
Arthralgia	23	1.3	16	0
Respiratory, Thoracic and Mediastinal				
Cough/productive cough	28	0.2	25	0.4
Dyspnea/exertional dyspnea	20	2.4	21	2.1
Metabolism and Nutrition				
Decreased appetite	21	1.8	29	0.9
Nervous System				
Headache	19	0.9	23	0.9
Endocrine				
Hypothyroidism	18	0.4	27	0.2

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema, peripheral swelling.

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

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

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

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

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

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

Classical Hodgkin Lymphoma

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

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

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

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

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

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

Adverse Reaction[a]	OPDIVO (n=266)	
	All Grades (%)	Grades 3-4 (%)
Infections		
Upper respiratory tract infection[b]	44	0.8
Pneumonia/bronchopneumonia[c]	13	3.8
Nasal congestion	11	0
General		
Fatigue[d]	39	1.9
Pyrexia	29	<1
Respiratory, Thoracic and Mediastinal		
Cough/productive cough	36	0
Dyspnea/exertional dyspnea	15	1.5
Gastrointestinal		
Diarrhea[e]	33	1.5
Nausea	20	0
Vomiting	19	<1
Abdominal pain[f]	16	<1
Constipation	14	0.4
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[g]	26	1.1
Arthralgia	16	<1
Skin and Subcutaneous Tissue		
Rash[h]	24	1.5
Pruritus	20	0
Nervous System		
Headache	17	<1
Neuropathy peripheral[i]	12	<1
Injury, Poisoning and Procedural Complications		
Infusion-related reaction	14	<1
Endocrine		
Hypothyroidism/thyroiditis	12	0

Toxicity was graded per NCI CTCAE v4.

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

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

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

[d] Includes asthenia.

[e] Includes colitis.

[f] Includes abdominal discomfort and upper abdominal pain.

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

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

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

Additional information regarding clinically important adverse reactions:

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

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

Complications of allogeneic HSCT after OPDIVO: Of 17 patients with cHL from the CHECKMATE-205 and CHECKMATE-039 trials who underwent allogeneic HSCT after treatment with OPDIVO, 6 patients (35%) died from transplant-related complications. Five deaths occurred in the setting of severe (Grade 3 to 4) or refractory GVHD. Hyperacute GVHD occurred in 2 patients (12%) and Grade 3 or higher GVHD was reported in 5 patients (29%). Hepatic VOD occurred in 1 patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure.

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

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

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

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

Laboratory Abnormality	OPDIVO[a] (n=266)	
	All Grades (%)[b]	Grades 3-4 (%)[b]
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 24 and 25 summarize adverse reactions and laboratory abnormalities, respectively, in CHECKMATE-275.

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

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

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

Adverse Reaction	OPDIVO (n=270)	
	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue		
Rash[c]	16	1.5
Pruritus	12	0
Endocrine		
Thyroid disorders[d]	15	0

Toxicity was graded per NCI CTCAE v4.

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

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

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

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

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

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

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: range: 84 to 256 patients.

MSI-H or dMMR Metastatic Colorectal Cancer

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

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

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

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

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

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

Adverse Reaction	OPDIVO (n=74)		OPDIVO and Ipilimumab (n=119)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Psychiatric				
Insomnia	9	0	13	0.8
Investigations				
Weight decreased	8	0	10	0

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

[b] Includes peripheral edema and peripheral swelling.

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

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

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

[f] Includes nasopharyngitis and rhinitis.

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

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

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

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

Hepatocellular Carcinoma

The safety of OPDIVO 3 mg/kg every 2 weeks as a single agent was evaluated in a 154-patient subgroup of patients with HCC and Child-Pugh Class A cirrhosis who progressed on or were intolerant to sorafenib. These patients enrolled in Cohorts 1 and 2 of CHECKMATE-040, a

multicenter, multiple cohort, open-label trial *[see Clinical Studies (14.10)]*. Patients were required to have an AST and ALT ≤5 x ULN and total bilirubin <3 mg/dL. The median duration of exposure to OPDIVO was 5 months (range: 0 to 22+ months). Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, pneumonia, and anemia.

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

The safety of OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg was evaluated in a subgroup comprising 49 patients with HCC and Child-Pugh Class A cirrhosis enrolled in Cohort 4 of the CHECKMATE-040 trial who progressed on or were intolerant to sorafenib. OPDIVO and ipilimumab were administered every 3 weeks for 4 doses, followed by single-agent OPDIVO 240 mg every 2 weeks until disease progression or unacceptable toxicity. During the OPDIVO and ipilimumab combination period, 33 of 49 (67%) patients received all 4 planned doses of OPDIVO and ipilimumab. During the entire treatment period, the median duration of exposure to OPDIVO was 5.1 months (range: 0 to 35+ months) and to ipilimumab was 2.1 months (range: 0 to 4.5 months). Forty-seven percent of patients were exposed to treatment for >6 months, and 35% of patients were exposed to treatment for >1 year. Serious adverse reactions occurred in 59% of patients. Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction.

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

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

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

Adverse Reaction	OPDIVO and Ipilimumab (n=49)		OPDIVO (n=154)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Rash	53	8	26	0.6
Pruritus	53	4	27	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain	41	2	36	1.9
Arthralgia	10	0	8	0.6
Gastrointestinal				
Diarrhea	39	4	27	1.3

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

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

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

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

Laboratory Abnormality	OPDIVO and Ipilimumab (n=47)		OPDIVO*	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	53	13	59	15
Anemia	43	4.3	49	4.6
Neutropenia	43	9	19	1.3
Leukopenia	40	2.1	26	3.3
Thrombocytopenia	34	4.3	36	7
Chemistry				
Increased AST	66	40	58	18
Increased ALT	66	21	48	11
Increased bilirubin	55	11	36	7
Increased lipase	51	26	37	14
Hyponatremia	49	32	40	11
Hypocalcemia	47	0	28	0
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 30 and 31 summarize the adverse reactions and laboratory abnormalities, respectively, in ATTRACTION-3.

Table 30: 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 31: 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).

6.2 Immunogenicity

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

Of the 2085 patients who were treated with OPDIVO as a single agent at dose of 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 11% tested positive for

treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 0.7% had neutralizing antibodies against nivolumab. There was no evidence of altered pharmacokinetic profile or increased incidence of infusion-related reactions with anti-nivolumab antibody development.

Of the patients with melanoma, advanced renal cell carcinoma, metastatic colorectal cancer, and metastatic or recurrent non-small cell lung cancer who were treated with OPDIVO and ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26% (132/516) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks, 36.7% (180/491) with OPDIVO 3 mg/kg every 2 weeks and ipilimumab 1 mg every 6 weeks, and 38% (149/394) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralizing antibodies against nivolumab was 0.8% (4/516) with OPDIVO 3 mg/kg followed by ipilimumab 1 mg/kg every 3 weeks, 1.4% (7/491) with OPDIVO 3 mg/kg every 2 weeks and ipilimumab 1 mg every 6 weeks, and 4.6% (18/394) with OPDIVO 1 mg/kg followed by ipilimumab 3 mg/kg every 3 weeks.

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

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

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

6.3 Postmarketing Experience

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

Eye: Vogt-Koyanagi-Harada (VKH) syndrome

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of

organogenesis through delivery resulted in increased abortion and premature infant death *(see Data)*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available data on OPDIVO use in pregnant women to evaluate a drug-associated risk. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

OPDIVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose.

8.4 Pediatric Use

The safety and effectiveness of OPDIVO as a single agent and in combination with ipilimumab have been established in pediatric patients age 12 years and older with microsatellite instability-

high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for this indication is supported by evidence from adequate and well-controlled studies of OPDIVO in adults with MSI-H or dMMR mCRC with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady-state exposure of nivolumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MSI-H or dMMR mCRC is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.9)]*.

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

8.5 Geriatric Use

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

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

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

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

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

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

Of the 49 patients who received OPDIVO 1 mg/kg in combination with ipilimumab 3 mg/kg in CHECKMATE-040 (hepatocellular carcinoma), 29% were between 65 years and 74 years of age and 8% were 75 years or older. Clinical studies of OPDIVO in combination with ipilimumab did

not include sufficient numbers of patients with hepatocellular carcinoma aged 65 and over to determine whether they respond differently from younger patients.

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

Of the 361 patients randomized to OPDIVO 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and platinum-doublet chemotherapy every 3 weeks (for 2 cycles) in CHECKMATE-9LA (NSCLC), 51% were 65 years or older and 10% were 75 years or older. No overall difference in safety was reported between older patients and younger patients; however, there was a higher discontinuation rate due to adverse reactions in patients aged 75 years or older (43%) relative to all patients who received OPDIVO with ipilimumab and chemotherapy (24%). For patients aged 75 years or older who received chemotherapy only, the discontinuation rate due to adverse reactions was 16% relative to all patients who had a discontinuation rate of 13%. Based on an updated analysis for overall survival, of the 361 patients randomized to OPDIVO in combination with ipilimumab and platinum-doublet chemotherapy in CHECKMATE-9LA, the hazard ratio for overall survival was 0.61 (95% CI: 0.47, 0.80) in the 176 patients younger than 65 years compared to 0.73 (95% CI: 0.56, 0.95) in the 185 patients 65 years or older.

11 DESCRIPTION

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

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

12.3 Pharmacokinetics

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

Distribution

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

Elimination

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

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

Specific Populations

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

Drug Interaction Studies

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

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

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

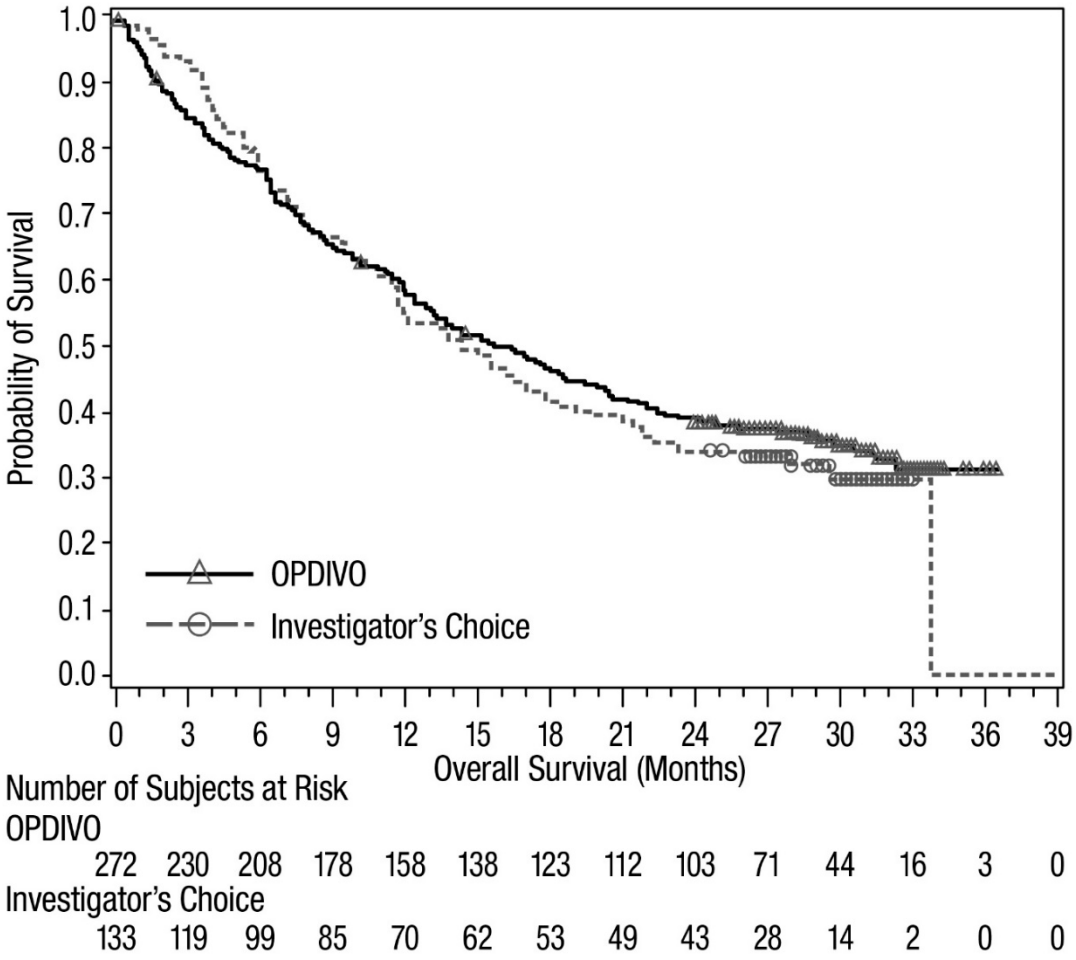
Efficacy was evaluated in a single-arm, non-comparative, planned interim analysis of the first 120 patients who received OPDIVO in CHECKMATE-037 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed overall response rate (ORR)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

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

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

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

Figure 1: Overall Survival - CHECKMATE-037*



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

Previously Untreated Metastatic Melanoma

CHECKMATE-066

CHECKMATE-066 (NCT01721772) was a multicenter, double-blind, randomized (1:1) trial in 418 patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m^2 intravenously every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (≥5% of tumor cell membrane staining by immunohistochemistry vs. <5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). Key eligibility criteria included histologically confirmed, unresectable or metastatic, cutaneous, mucosal, or acral melanoma; no prior therapy for metastatic disease; completion of prior adjuvant or neoadjuvant therapy at least 6 weeks prior to randomization; ECOG performance status 0 or 1; absence of autoimmune disease; and absence of active brain or leptomeningeal metastases. The trial excluded patients with ocular melanoma. Tumor assessments were conducted 9 weeks after

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

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

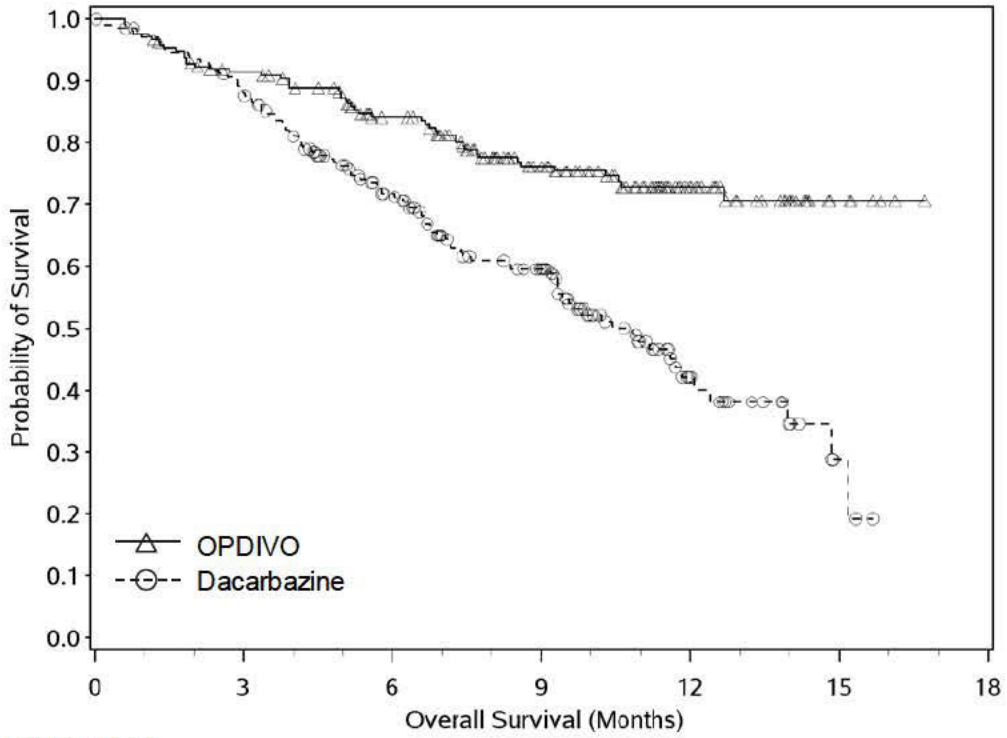
CHECKMATE-066 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. At the time of analysis, 88% (63/72) of OPDIVO-treated patients had ongoing responses, which included 43 patients with ongoing response of 6 months or longer. Efficacy results are shown in Table 32 and Figure 2.

Table 32: Efficacy Results - CHECKMATE-066

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

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

Figure 2: Overall Survival - CHECKMATE-066



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

CHECKMATE-067

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

Patients were randomized to receive:

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

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

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

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

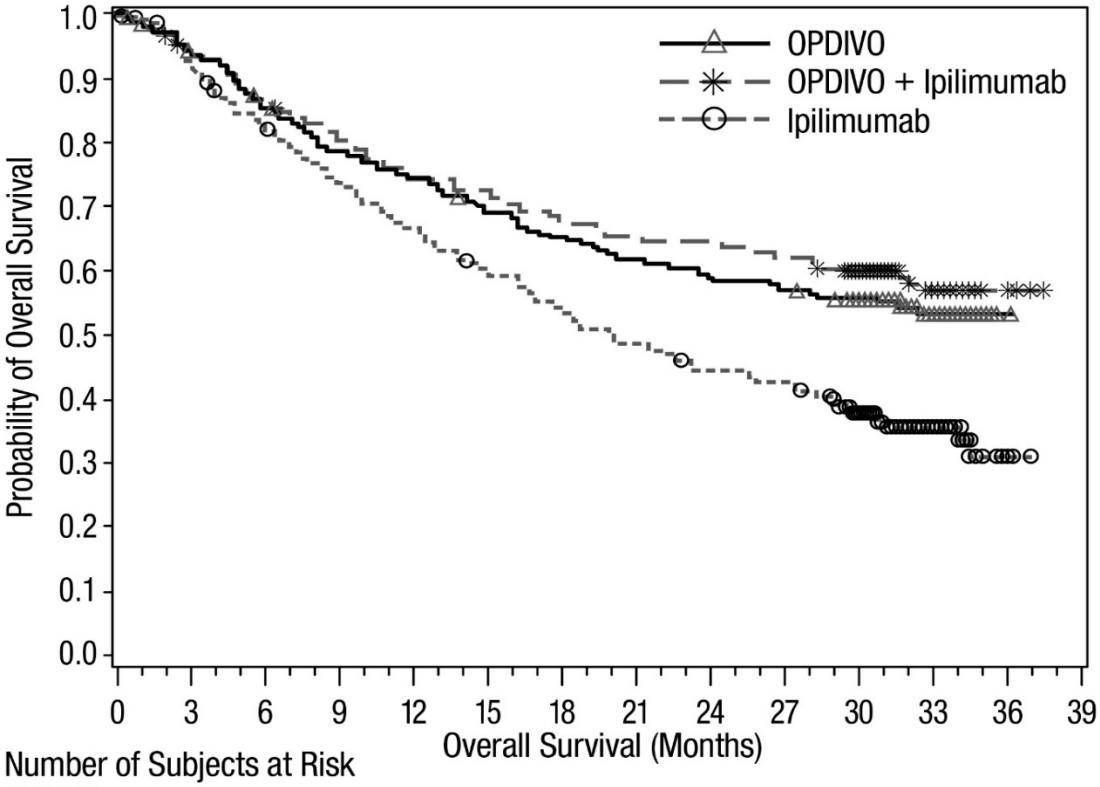
CHECKMATE-067 demonstrated statistically significant improvements in OS and PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. The trial was not designed to assess whether adding ipilimumab to OPDIVO improves PFS or OS compared to OPDIVO as a single agent. Efficacy results are shown in Table 33 and Figure 3.

Table 33: 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%).

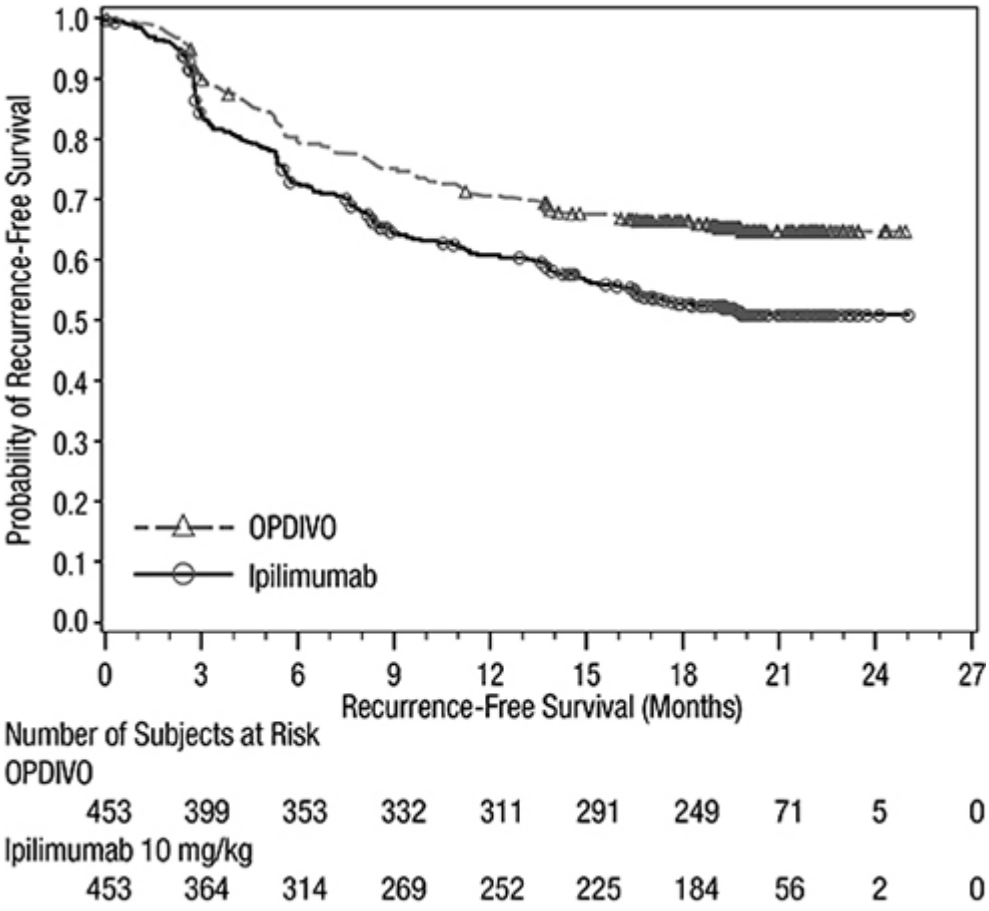
CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the ipilimumab 10 mg/kg arm. Efficacy results are shown in Table 34 and Figure 4.

Table 34: 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 35 and Figure 5.

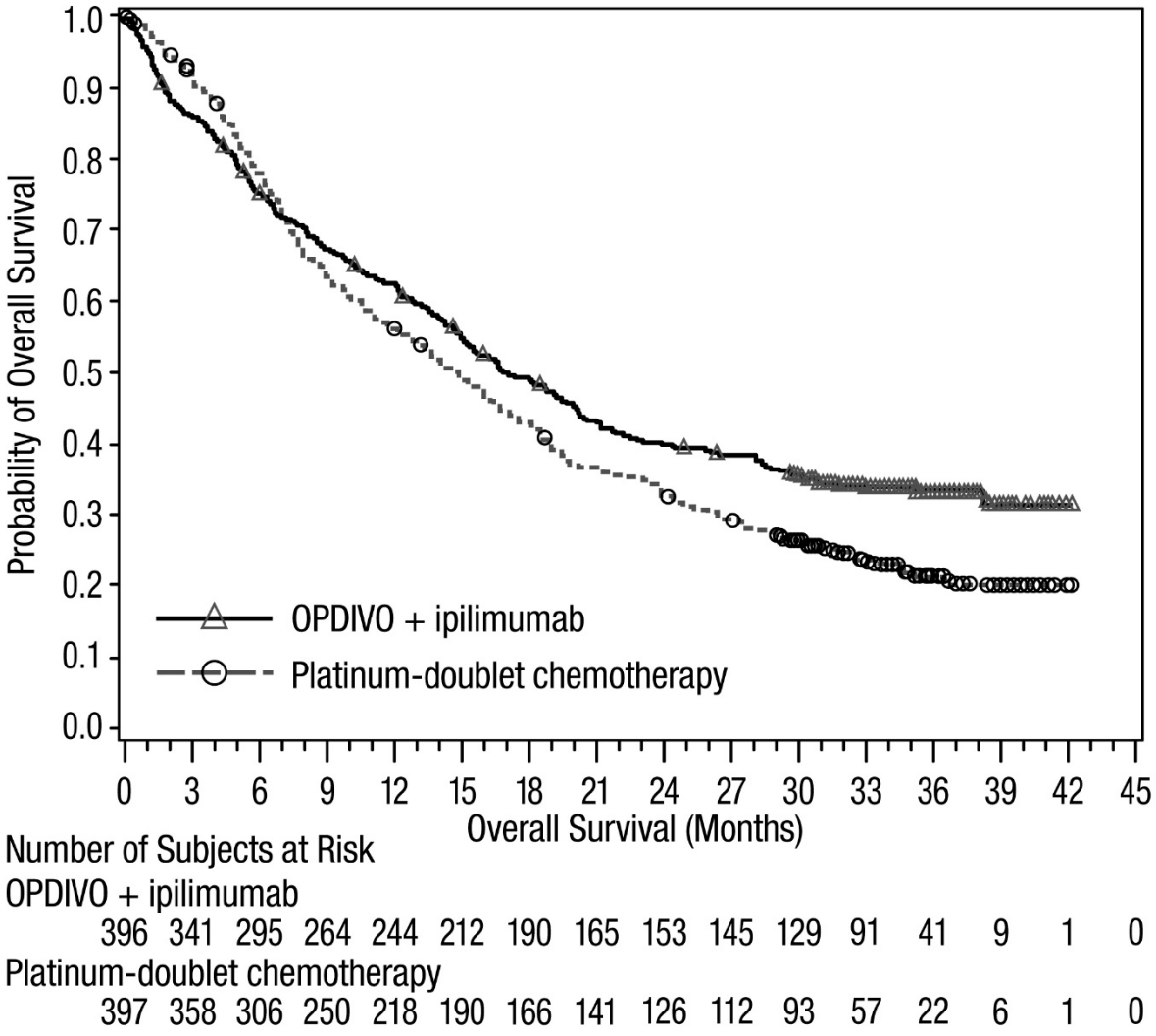
Table 35: Efficacy Results (PD-L1 ≥1%) - CHECKMATE-227 Part 1a

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

[a] Kaplan-Meier estimate.

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

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



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

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

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

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

Patients were randomized 1:1 to receive either:

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

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

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

The study demonstrated a statistically significant benefit in OS, PFS, and ORR. Efficacy results from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis) are presented in Table 36.

Table 36: 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.

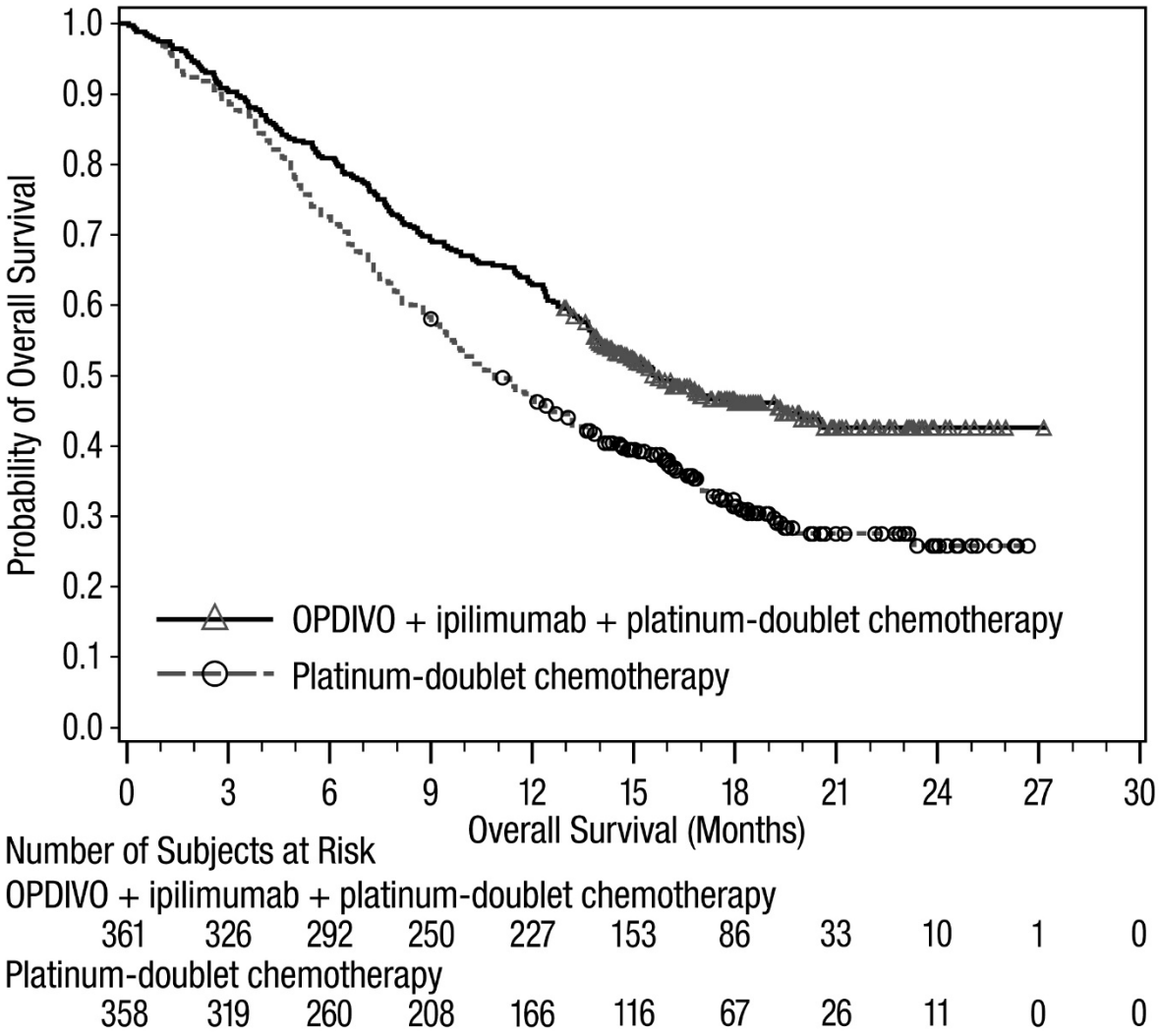
[d] Kaplan-Meier estimate.

[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 37 and Figure 7.

Table 37: Efficacy Results - CHECKMATE-017

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

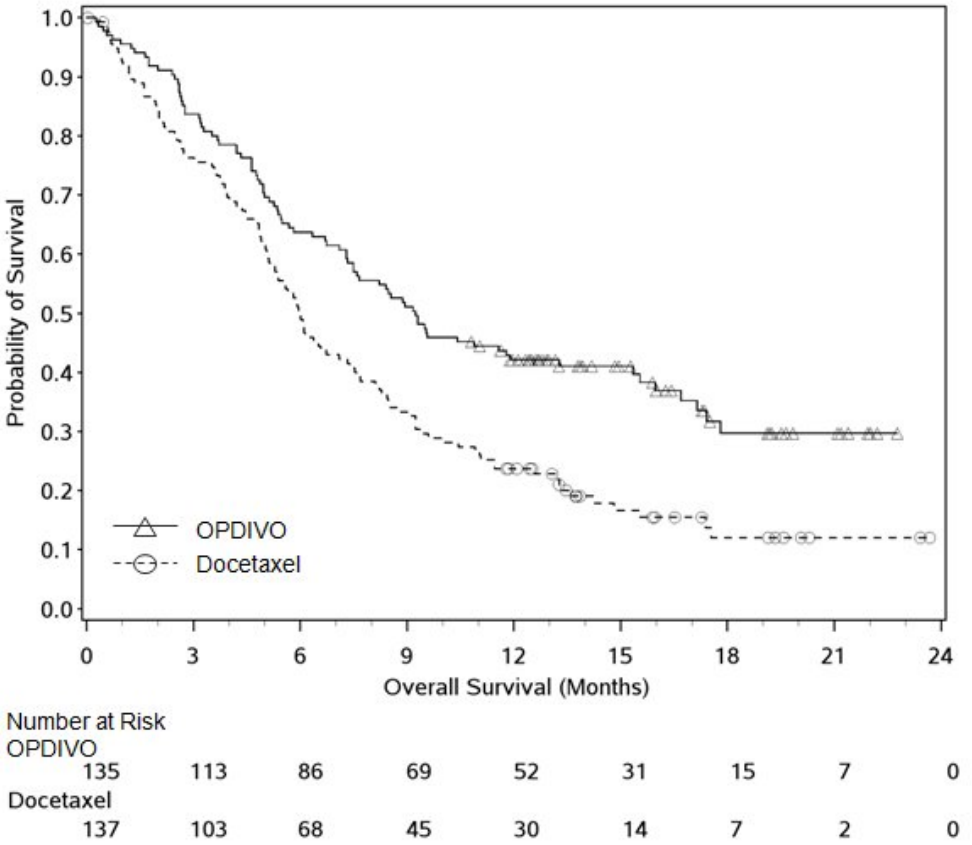
[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

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

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

Figure 7: Overall Survival - CHECKMATE-017



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

Second-line Treatment of Metastatic Non-Squamous NSCLC

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

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

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

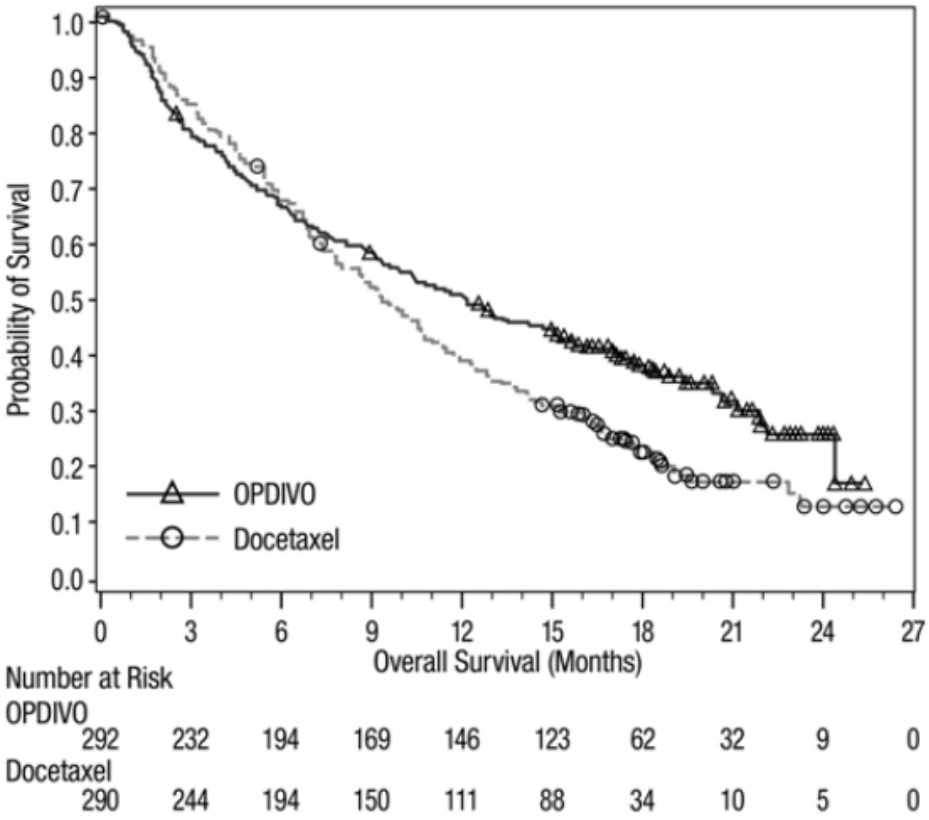
CHECKMATE-057 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis). Efficacy results are shown in Table 38 and Figure 8.

Table 38: Efficacy Results - CHECKMATE-057

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

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

Figure 8: Overall Survival - CHECKMATE-057



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

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

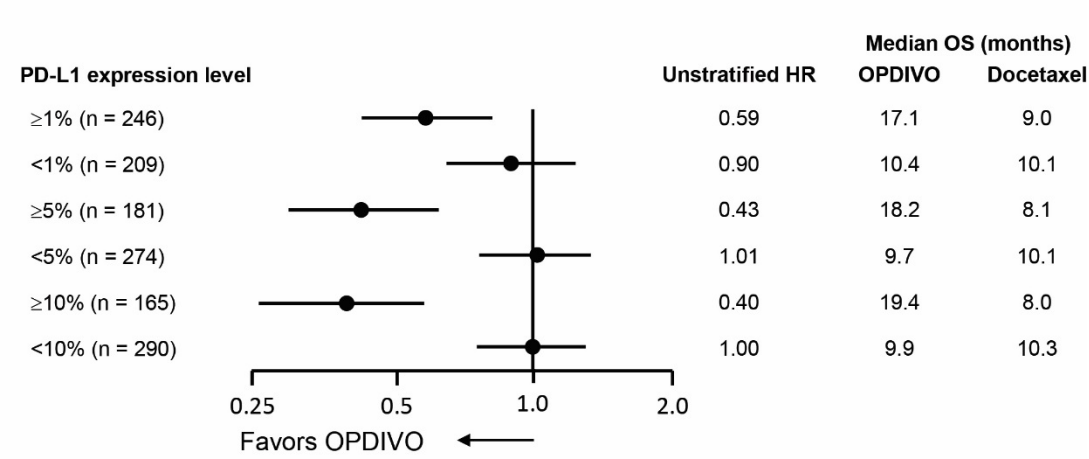
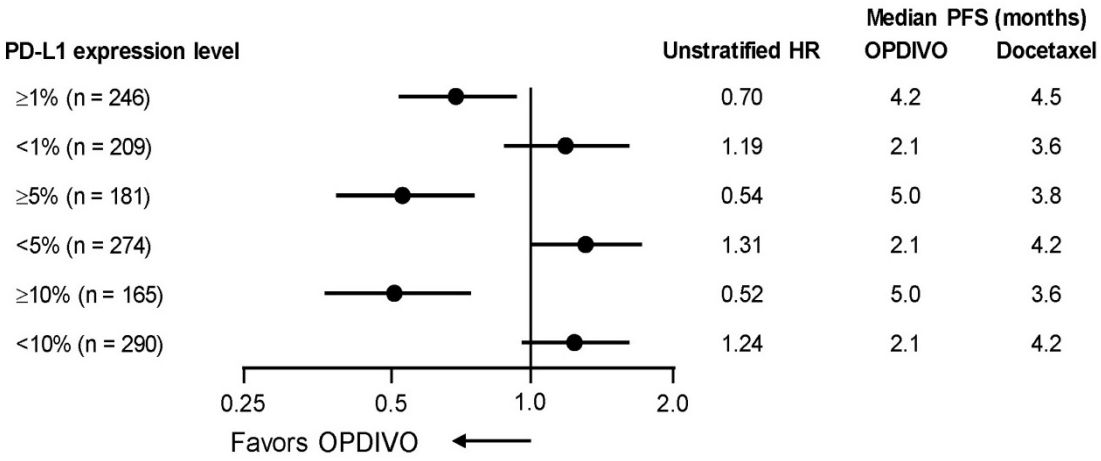


Figure 10: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



14.4 Small Cell Lung Cancer

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

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

Efficacy results are shown in Table 39.

Table 39: Efficacy Results - CHECKMATE-032

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

14.5 Advanced Renal Cell Carcinoma

Previously Treated Renal Cell Carcinoma

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

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

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

observed (70% of the planned number of events for final analysis). OS benefit was observed regardless of PD-L1 expression level. Efficacy results are shown in Table 40 and Figure 11.

Table 40: Efficacy Results - CHECKMATE-025

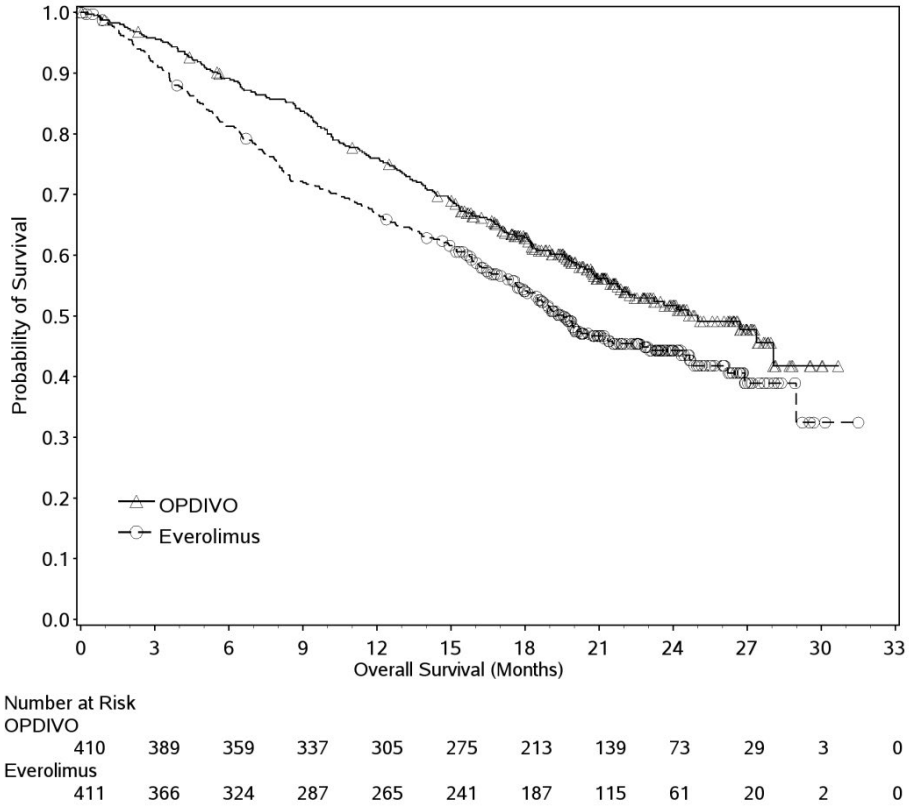
	OPDIVO (n=410)	**Everolimus (n=411)**
Overall Survival		
Deaths (%)	183 (45)	215 (52)
Median survival (months) (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0018	
Confirmed Overall Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median duration of response (months) (95% CI)	23.0 (12.0, NE)	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] Based on a stratified proportional hazards model.

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

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

Figure 11: Overall Survival - CHECKMATE-025



Previously Untreated Renal Cell Carcinoma

CHECKMATE-214 (NCT02231749) was a randomized (1:1), open-label trial in patients with previously untreated advanced RCC. Patients were included regardless of their PD-L1 status. CHECKMATE-214 excluded patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients were stratified by International Metastatic RCC Database Consortium (IMDC) prognostic score and region.

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

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

The trial population characteristics were: median age was 61 years (range: 21 to 85) with 38% ≥65 years of age and 8% ≥75 years of age. The majority of patients were male (73%) and White (87%) and 26% and 74% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively.

The major efficacy outcome measures were OS, PFS (independent radiographic review committee [IRRC]-assessed) and confirmed ORR (IRRC-assessed) in intermediate/poor risk patients. In this population, the trial demonstrated statistically significant improvement in OS and ORR for patients randomized to OPDIVO and ipilimumab as compared with sunitinib (Table 41 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 41 and Figure 12.

Table 41: Efficacy Results - CHECKMATE-214

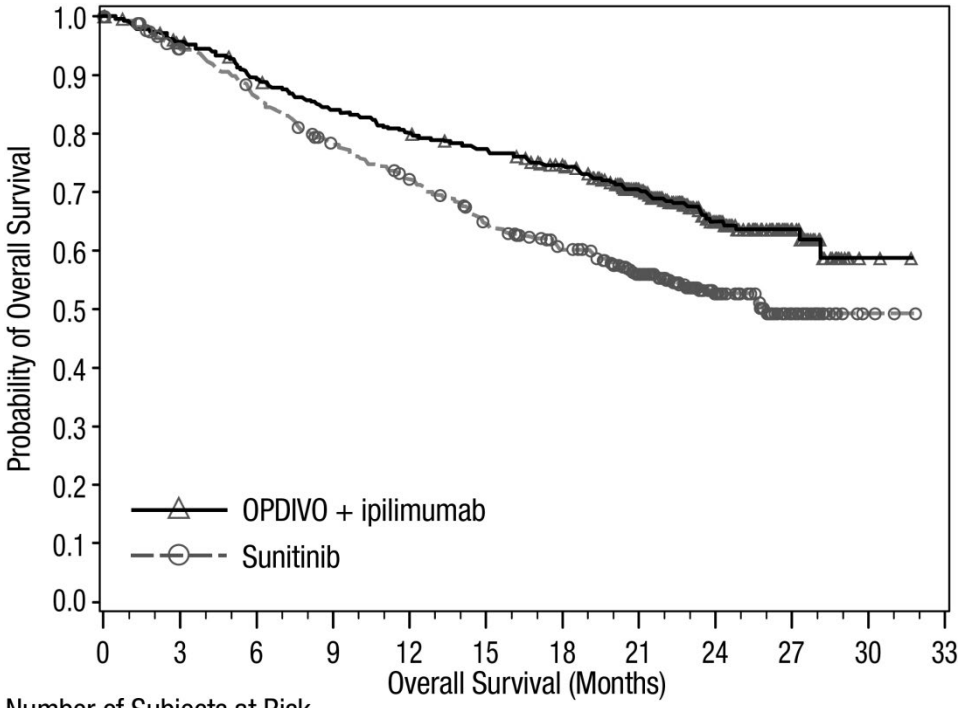
	Intermediate/Poor-Risk	
	OPDIVO and Ipilimumab (n=425)	**Sunitinib (n=422)**
Overall Survival		
Deaths (%)	140 (32.9)	188 (44.5)
Median survival (months)	NE	25.9
Hazard ratio (99.8% CI)[a]	0.63 (0.44, 0.89)	
p-value[b,c]	<0.0001	
Confirmed Overall Response Rate (95% CI)	41.6% (36.9, 46.5)	26.5% (22.4,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

Table 41: Efficacy Results - CHECKMATE-214

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

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

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



Number of Subjects at Risk

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

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

14.6 Classical Hodgkin Lymphoma

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

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

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

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

Efficacy was evaluated in 95 patients in CHECKMATE-205 and CHECKMATE-039 combined who had failure of autologous HSCT and post-transplantation brentuximab vedotin. The median age was 37 years (range: 18 to 72). The majority were male (64%) and White (87%). Patients had received a median of 5 prior systemic regimens (range: 2 to 15). They received a median of 27 doses of OPDIVO (range: 3 to 48), with a median duration of therapy of 14 months (range: 1 to 23 months). Efficacy results are shown in Table 42.

Table 42: Efficacy in cHL after Autologous HSCT and Post-transplantation Brentuximab Vedotin

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

[a] Per 2007 revised International Working Group criteria.

[b] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 9.9 months.

[c] A + sign indicates a censored value.

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

78% received it only after HSCT, and 5% received it both before and after HSCT. Patients received a median of 21 doses of OPDIVO (range: 1 to 48), with a median duration of therapy of 10 months (range: 0 to 23 months). Efficacy results are shown in Table 43.

Table 43: Efficacy in cHL after Autologous HSCT

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

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

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

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

CHECKMATE-141 (NCT02105636) was a randomized (2:1), active-controlled, open-label trial enrolling patients with metastatic or recurrent SCCHN who had experienced disease progression during or within 6 months of receiving platinum-based therapy administered in either the adjuvant, neo-adjuvant, primary (unresectable locally advanced) or metastatic setting. The trial excluded patients with autoimmune disease, medical conditions requiring immunosuppression, recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology, salivary gland or non-squamous histologies (e.g., mucosal melanoma), or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. Patients were randomized to receive OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or investigator's choice of cetuximab (400 mg/m^2 initial dose intravenously followed by 250 mg/m^2 weekly), or methotrexate (40 to 60 mg/m^2 intravenously weekly), or docetaxel (30 to 40 mg/m^2 intravenously weekly).

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

A total of 361 patients were randomized; 240 patients to 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.

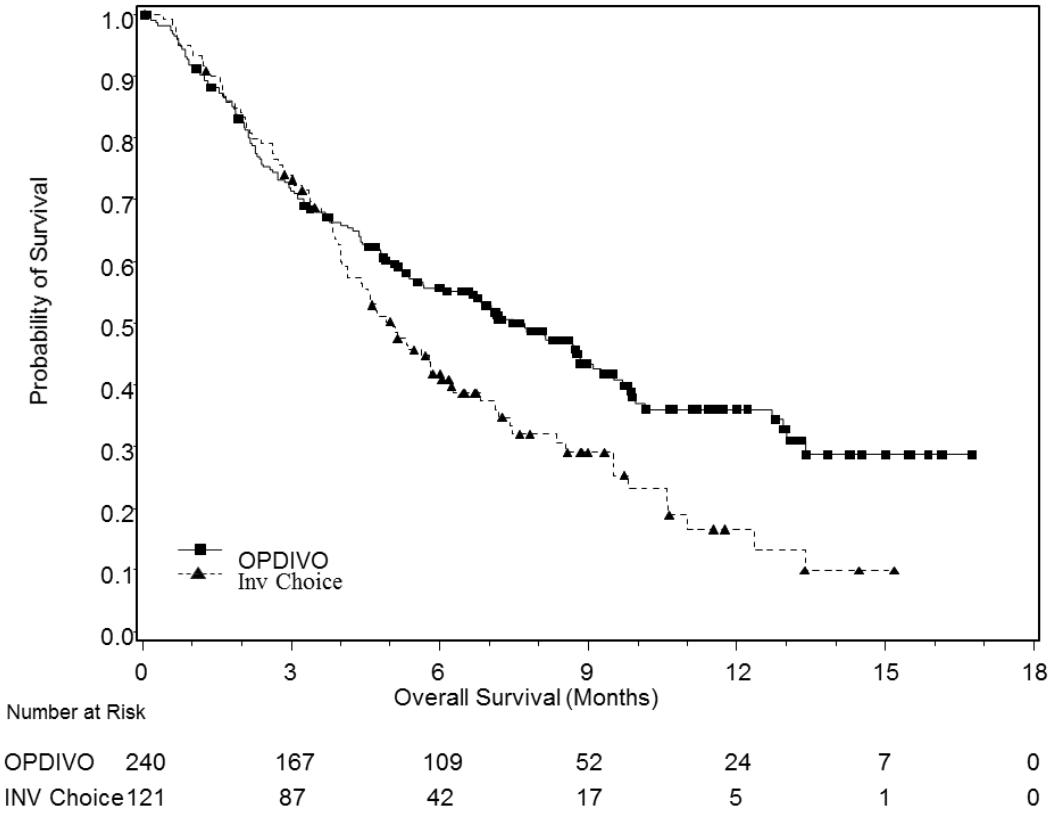
The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice at a pre-specified interim analysis (78% of the planned number of events for final analysis). There were no statistically significant differences between the two 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 44 and Figure 13.

Table 44: 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 13: Overall Survival - CHECKMATE-141



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

14.8 Urothelial Carcinoma

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

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

Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are shown in Table 45. 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 45: Efficacy Results - CHECKMATE-275

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

[a] Estimated from the Kaplan-Meier Curve

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

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

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

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

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

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

Efficacy results for each of these single-arm cohorts are shown in Table 46.

Table 46: Efficacy Results - CHECKMATE-142

	OPDIVO MSI-H/dMMR Cohort		**OPDIVO and Ipilimumab MSI-H/dMMR Cohort**	
	All Patients (n=74)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)**	**All Patients (n=119)**	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
IRRC Overall Response Rate; n (%)	24 (32%)	15 (28%)	58 (49%)	38 (46%)
(95% CI)[a]	(22, 44)	(17, 42)	(39, 58)	(35, 58)
Complete response (%)	2 (2.7%)	1 (1.9%)	5 (4.2%)	3 (3.7%)
Partial response (%)	22 (30%)	14 (26%)	53 (45%)	35 (43%)
Duration of Response				
Proportion with ≥6 months response duration	63%	67%	83%	89%
Proportion with ≥12[b] months response duration	38%	40%	19%	21%

[a] Estimated using the Clopper-Pearson method.

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

14.10 Hepatocellular Carcinoma

CHECKMATE-040 (NCT01658878) was a multicenter, multiple cohort, open-label trial that evaluated the efficacy of OPDIVO as a single agent and in combination with ipilimumab in patients with hepatocellular carcinoma (HCC) who progressed on or were intolerant to sorafenib.

Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible.

Tumor assessments were conducted every 6 weeks for 48 weeks and then every 12 weeks thereafter. The major efficacy outcome measure was confirmed overall response rate as assessed by BICR using RECIST v1.1 and modified RECIST (mRECIST) for HCC. Duration of response was also assessed.

The efficacy of OPDIVO as a single agent was evaluated in a pooled subgroup of 154 patients across Cohorts 1 and 2 who received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until disease progression or unacceptable toxicity. The median age was 63 years (range: 19 to 81), 77% were male, and 46% were White. Baseline ECOG performance status was 0 (65%) or 1 (35%). Thirty-one percent (31%) of patients had active HBV infection, 21% had active HCV infection, and 49% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 18% and non-alcoholic fatty liver disease in 6.5% of patients. Child-Pugh class and score was A5 for 68%, A6 for 31%, and B7 for 1% of patients. Seventy-one percent (71%) of patients had extrahepatic spread, 29% had macrovascular invasion, and 37% had alfa-fetoprotein (AFP) levels ≥400 µg/L. Prior treatment history included surgical resection (66%), radiotherapy (24%), or locoregional treatment (58%). All patients had received prior sorafenib, of whom 36 (23%) were unable to tolerate sorafenib; 19% of patients had received 2 or more prior systemic therapies.

The efficacy of OPDIVO in combination with ipilimumab was evaluated in 49 patients (Cohort 4) who received OPDIVO 1 mg/kg and ipilimumab 3 mg/kg administered every 3 weeks for 4 doses, followed by single-agent OPDIVO at 240 mg every 2 weeks until disease progression or unacceptable toxicity. The median age was 60 years (range: 18 to 80), 88% were male, 74% were Asian, and 25% were White. Baseline ECOG performance status was 0 (61%) or 1 (39%). Fifty-seven (57%) percent of patients had active HBV infection, 8% had active HCV infection, and 35% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 16% and non-alcoholic fatty liver disease in 6% of patients. Child-Pugh class and score was A5 for 82% and A6 for 18%; 80% of patients had extrahepatic spread; 35% had vascular invasion; and 51% had AFP levels ≥400 µg/L. Prior cancer treatment history included surgery (74%), radiotherapy (29%), or local treatment (59%). All patients had received prior sorafenib, of whom 10% were unable to tolerate sorafenib; 29% of patients had received 2 or more prior systemic therapies.

Efficacy results are shown in Table 47. 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 47: 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%).

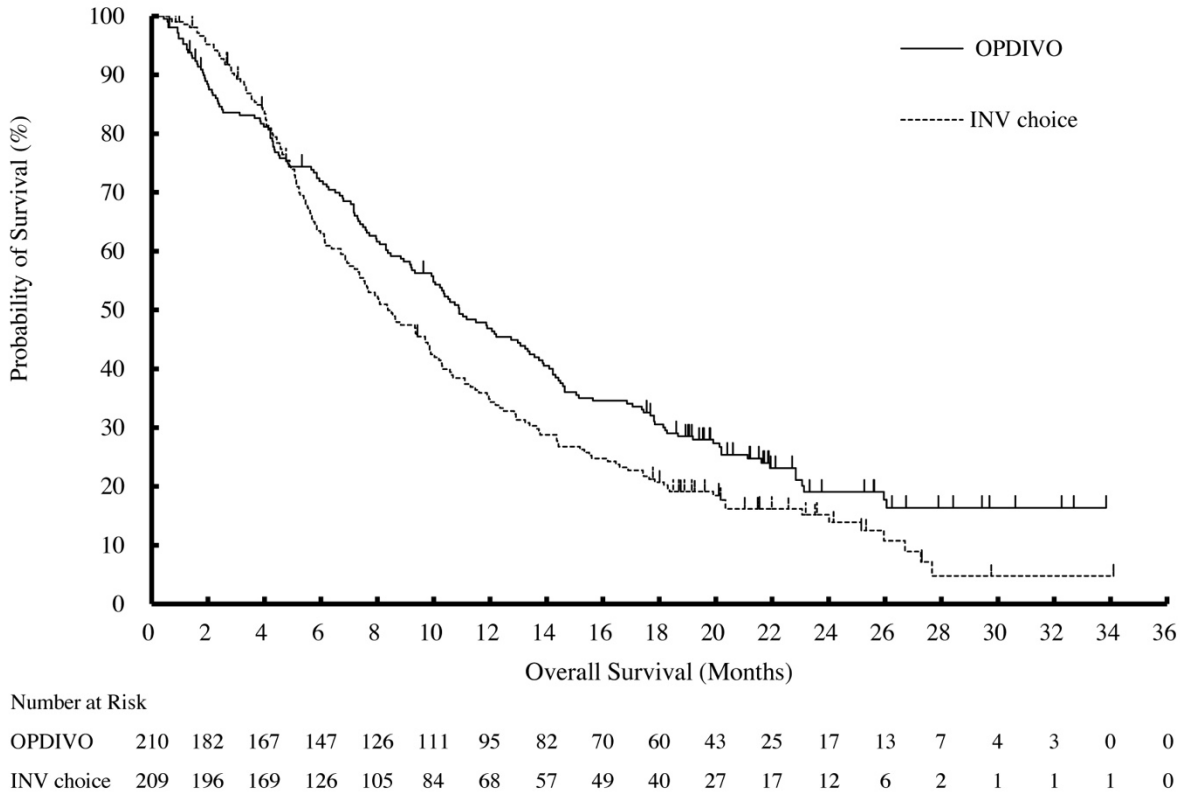
ATTRACTION-3 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with investigator's choice of taxane chemotherapy. OS benefit was observed regardless of PD-L1 expression level. The minimum follow-up was 17.6 months. Efficacy results are shown in Table 48 and Figure 14.

Table 48: 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 14: Overall Survival - ATTRACTION-3



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.

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) Injection is available as follows:

Carton Contents	NDC
40 mg/4 mL single-dose vial	0003-3772-11
100 mg/10 mL single-dose vial	0003-3774-12
240 mg/24 mL single-dose vial	0003-3734-13

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

17 PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

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

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

Infusion-Related Reactions

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

Complications of Allogeneic HSCT

- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.10)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with OPDIVO and for 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

U.S. License No. 1713

MEDICATION GUIDE
OPDIVO® (op-DEE-voh)
(nivolumab)
Injection

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

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

OPDIVO is a medicine that may treat certain cancers by working with your immune system. OPDIVO can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death. These problems may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when OPDIVO is used in combination with ipilimumab.

Call or see your healthcare provider right away if you develop any symptoms of the following problems or these symptoms get worse:

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

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

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood in your stools or dark, tarry, sticky stools
- severe stomach-area (abdomen) pain or tenderness

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

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

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

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- hair loss
- feeling cold
- constipation
- voice gets deeper
- excessive thirst or lots of urine
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

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

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

Skin Problems. Signs of these problems may include:

- rash
- itching
- skin blistering
- ulcers in mouth or other mucous membranes

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

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

Problems in other organs. Signs of these problems may include:

- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness
- chest pain

Getting medical treatment right away may keep these problems from becoming more serious.

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

What is OPDIVO?

OPDIVO is a prescription medicine used to treat:

- **people with a type of skin cancer called melanoma:**
  - OPDIVO may be used alone or in combination with ipilimumab to treat melanoma that has spread or cannot be removed by surgery (advanced melanoma), **or**
  - OPDIVO may be used alone to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.
- **people with a type of advanced stage lung cancer called non-small cell lung cancer (NSCLC).**
  - OPDIVO may be used in combination with ipilimumab as your first treatment for NSCLC:
    - when your lung cancer has spread to other parts of your body (metastatic), and
    - your tumors are positive for PD-L1, but do not have an abnormal EGFR or ALK gene.
  - OPDIVO may be used in combination with ipilimumab and 2 cycles of chemotherapy that contains platinum and another chemotherapy medicine, as the first treatment of your NSCLC when your lung cancer:
    - has spread or grown, or comes back, **and**
    - your tumor does not have an abnormal EGFR or ALK gene.
  - OPDIVO may be used when your lung cancer:
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

    If your tumor has an abnormal EGFR or ALK gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, **and** it did not work or is no longer working.
- **people with a type of lung cancer called small cell lung cancer.**
  - OPDIVO may be used when your lung cancer:
    - has spread or grown, **and**
    - you have tried at least two different types of chemotherapy, including one that contains platinum, and it did not work or is no longer working.
- **people with kidney cancer (renal cell carcinoma).**
  - OPDIVO may be used alone when your cancer has spread or grown after treatment with other cancer medicines.
  - OPDIVO may be used in combination with ipilimumab in certain people when their cancer has spread.
- **adults with a type of blood cancer called classical Hodgkin lymphoma.**
  - **OPDIVO may be used if:**
    - your cancer has come back or spread after a type of stem cell transplant that uses your own stem cells (autologous), **and**
    - you used the drug brentuximab vedotin before or after your stem cell transplant, **or**
    - you received at least 3 kinds of treatment including a stem cell transplant that uses your own stem cells (autologous).
- **people with head and neck cancer (squamous cell carcinoma).**
  - **OPDIVO may be used when your head and neck cancer:**
    - has come back or spread, **and**
    - you have tried chemotherapy that contains platinum and it did not work or is no longer working.
- **people with bladder cancer (urothelial carcinoma).**
  - **OPDIVO may be used when your bladder cancer:**
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- **adults and children 12 years of age and older, with a type of colon or rectal cancer (colorectal cancer).**
  - OPDIVO may be used alone or in combination with ipilimumab when your colon or rectal cancer:
    - has spread to other parts of the body (metastatic),

- is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), **and**
- you have tried treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, and it did not work or is no longer working.

- **people with liver cancer (hepatocellular carcinoma).**
  - OPDIVO may be used alone or in combination with ipilimumab if you have previously received treatment with sorafenib.
- **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.

It is not known if OPDIVO is safe and effective when used:
- in children younger than 12 years of age with MSI-H or dMMR metastatic colorectal cancer, or
- in children younger than 18 years of age for the treatment of any other cancers.

What should I tell my healthcare provider before receiving OPDIVO?

Before you receive OPDIVO, tell your healthcare provider if you:
- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. OPDIVO can harm your unborn baby.

  Females who are able to become pregnant:

  Your healthcare provider should do a pregnancy test before you start receiving OPDIVO.
  - You should use an effective method of birth control during and for at least 5 months after the last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant during treatment with OPDIVO.
- are breastfeeding or plan to breastfeed. It is not known if OPDIVO passes into your breast milk. Do not breastfeed during treatment with OPDIVO.

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

Know the medicines you take. Keep a list of them to show your healthcare providers and pharmacist when you get a new medicine.

How will I receive OPDIVO?
- Your healthcare provider will give you OPDIVO into your vein through an intravenous (IV) line over 30 minutes.
- When OPDIVO is used alone, it is usually given every 2 weeks or 4 weeks depending on the dose you are receiving.
- When OPDIVO is used in combination with ipilimumab (except for treating NSCLC), OPDIVO is usually given every 3 weeks, for a total of 4 doses. Ipilimumab will be given on the same day. After that, OPDIVO will be given alone every 2 weeks or 4 weeks depending on the dose you are receiving.
- For NSCLC that has spread to other parts of your body, when OPDIVO is used in combination with ipilimumab, OPDIVO is given either every 2 weeks or every 3 weeks, and ipilimumab is given every 6 weeks for up to 2 years. Your healthcare provider will determine if you will also need to receive chemotherapy every 3 weeks for 2 cycles.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of OPDIVO?

OPDIVO can cause serious side effects, including:
- **See "What is the most important information I should know about OPDIVO?"**
- **Severe infusion reactions.** Tell your doctor or nurse right away if you get these symptoms during an infusion of OPDIVO:
  - chills or shaking
  - itching or rash
  - dizziness
  - fever

- flushing
- difficulty breathing
- feeling like passing out

- **Complications of stem cell transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

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

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

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

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

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

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

These are not all the possible side effects of OPDIVO.

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

General information about the safe and effective use of OPDIVO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about OPDIVO, talk with your healthcare provider. You can ask your healthcare provider for information about OPDIVO that is written for health professionals.

What are the ingredients in OPDIVO?

Active ingredient: nivolumab

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

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

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s081

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Supplemental BLA (sBLA)
Application Number(s)	125554/S-81
Priority or Standard	Priority
Submit Date(s)	December 11, 2019
Received Date(s)	December 11, 2019
PDUFA Goal Date	June 11, 2020
Division/Office	DO3/OOD/OND/CDER
Review Completion Date	June 10, 2020
Established Name	Nivolumab
(Proposed) Trade Name	OPDIVO
Pharmacologic Class	Anti-PD-1 antibody
Code name	BMS 936558, MDX 1106, ONO 4538
Applicant	Bristol-Myers Squibb
Formulation(s)	Injection; 100 mg/10 mL solution
Dosing Regimen	Nivolumab 240 mg intravenously every 2 weeks or until disease progression or unacceptable toxicity
Applicant Proposed Indication(s)/Population(s)	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
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	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

Version date: July 24, 2019 (ALL NDA/ BLA reviews)

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.

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Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Maryam Khazraee
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Microbiology	N/A
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DMPP	Sharon Mills
OSI	Zana Handy Marks
OSE/DEPI	N/A
OSE/DMEPA	Max Straka

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Glossary

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

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
USPI	U.S. Package Insert

1 Executive Summary

1.1. Product Introduction

Nivolumab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with its ligands PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

Nivolumab is approved for the treatment of:

- patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
- patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.
- 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.
- 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.
- 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.
- patients with metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy.[a]
- patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.
- patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab.
- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after[a]:
    - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
    - 3 or more lines of systemic therapy that includes autologous HSCT.
- patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
- 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.

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

[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.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Esophageal cancer is a serious and life-threatening disease that is projected to cause approximately 16,000 deaths in the U.S. in 2020 (Siegel 2020). Although esophageal squamous cell carcinoma (ESCC) accounts for less than a third of esophageal cancer cases in the U.S. (Siegel 2020), it is an aggressive disease with a particularly poor prognosis. Standard first-line systemic therapy for advanced, metastatic disease consists of a fluoropyrimidine- and platinum-based regimen and single-agent taxanes such as docetaxel or paclitaxel are typically used in the second-line setting.

The FDA review team recommends regular approval of nivolumab for the treatment of patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy. The submitted data provide substantial evidence of the safety and effectiveness of nivolumab for this indication. This conclusion is based on demonstration of a clinically meaningful improvement in overall survival (OS) in patients randomized to receive nivolumab compared to those randomized to receive the investigator's choice of either paclitaxel or docetaxel for the treatment of ESCC in the second-line setting in Study ONO-4538-24 (CA209473; ATTRACTION-3), a single adequate and well controlled trial.

Study ONO-4538-24 is a multicenter, randomized, open-label, active-controlled trial conducted 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 (1:1) to receive nivolumab 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 as assessed by the investigator per RECIST v1.1, or unacceptable toxicity. Tumor assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures were overall response rate (ORR) and progression-free survival (PFS) as assessed by the investigator using RECIST v1.1 and duration of response (DOR).

A total of 419 patients were randomized, 210 patients to the nivolumab arm and 209 patients to the investigator's choice arm (docetaxel: 31%, paclitaxel: 69%). Study ONO-4538-24 demonstrated a clinically meaningful, statistically significant improvement in OS favoring the nivolumab arm. The hazard ratio (HR) for OS was 0.77 (95% confidence interval [CI]: 0.62, 0.96; p-value=0.0189). Median OS in the nivolumab arm was 10.91 months (95% confidence interval [CI]: 9.23, 13.34) and 8.38 months [95% CI: 7.20, 9.86] in the taxane chemotherapy arm.

There was no statistically significant difference in ORR or PFS between the two arms. The hazard ratio for PFS was 1.1 (95% CI: 0.9, 1.13), corresponding to a median PFS of 1.7 months (95% CI: 1.5, 2.7) and 3.4 months (95% CI: 3.0, 4.2) in the nivolumab and investigator's choice arms, respectively. The ORR was 19% in the nivolumab arm and 22% in the investigator's choice arm, although responses in the nivolumab arm appeared more durable; the median duration of response was 6.9 months (95% CI: 5.4, 11.1) and 3.9 months (95% CI: 2.8, 4.2) in the response-evaluable set (RES) nivolumab and investigator's choice arms, respectively.

Given the mechanism of action of nivolumab and biologic plausibility for increased efficacy in tumors with higher levels of PD-L1 expression, an important issue considered by the review team was whether the improvement in OS was restricted to patients with ESCC with PD-L1 positive tumors. In Study ONO-4538-24, an improvement in OS was observed irrespective of PD-L1 status, although there was a trend for improved OS outcomes in patients with PD-L1 positive ESCC, defined as ≥1% of tumor cells expressing PD-L1. Of the 419 patients randomized in Study ONO-4538-24, 48% had PD-L1 positive ESCC. 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 nivolumab 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 nivolumab and investigator's choice arms, respectively.

The statistical and clinical review teams also noted that the observed OS curves crossed around 5 months (Figure 2), indicating that the hazards were not proportional. Furthermore, a pre-specified analysis to examine the assumption of proportional hazards of the Cox model indicated a violation of such assumption (p= 0.0682). At the request of the FDA, the Applicant conducted a post-hoc analysis to assess the treatment difference in OS using a weighted log-rank test, which were supportive of the primary analysis. The FDA statistical review team concluded that despite the observed non-proportional hazards, the statistical test used for the primary OS analysis was valid.

Finally, the review team considered whether the results of Study ONO-4538-24 were applicable to U.S. patients with ESCC. Most of the patients in Study ONO-4538-24 were enrolled in Japan and only 18 patients (9 in the nivolumab arm and 9 in the control arm) were enrolled in Western clinical sites. Of these 18 patients, only 1 patient was from the U.S. (and was randomized to the nivolumab arm). Thus, subgroup analyses comparing the effectiveness of nivolumab in Western patients with ESCC compared to patients with ESCC enrolled in Asia are of limited value. Nevertheless, within a small subset of Western subjects representing 4.3% of the overall trial population, a similar HR for OS was observed compared to the overall study population (HR=0.53 [95% CI: 0.17, 1.65]). Additionally, published literature in ESCC, including those described by the Applicant in Section 8.1.5 (“Integrated Assessment of Effectiveness”), report similarities across regions regarding disease features and treatment approaches for ESCC. Data from studies of nivolumab with a broader representation of U.S. and Western Patients in other disease settings (such as CHECKMATE-141 in patients with squamous cell carcinoma of the head and neck and CHECKMATE-067 in patients with melanoma) reviewed by FDA also support the effectiveness of nivolumab in Western patients (refer to the Opdivo product labeling). The review team concluded that the totality of information supports a conclusion that Western patients with ESCC derive an OS benefit from nivolumab and are not at increased risk of toxicities compared to patients with ESCC from Asia.

The FDA review teams concluded that nivolumab, at the dose and schedule proposed by the Applicant, is safe and effective in patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Esophageal cancer is a serious and life-threatening disease that is projected to cause approximately 16,000 deaths in the U.S. in 2020 (Siegel 2020). The 5-year survival rate of advanced unresectable or metastatic esophageal cancer is 3.4% (Zhang 2013). Although esophageal squamous cell carcinoma (ESCC) accounts for less than a third of esophageal cancer cases in the U.S. (Siegel 2020), it is an aggressive disease with a particularly poor prognosis. This poor prognosis highlights the need for new therapies to improve long-term outcomes after standard first-line therapies. The incidence and histological type of esophageal cancer varies with geographic location. While the rate of ESCC exceeds esophageal adenocarcinoma (EAC) in more than 90% of all countries (Arnold M 2015), EAC predominates in the US, accounting for 63.5% of all EC cases (National Cancer Institute (2018).

Standard first-line systemic therapy for advanced, metastatic ESCC generally consists of a fluoropyrimidine- and platinum-based regimen, which confers modest benefit. Single-agent taxanes such as docetaxel or paclitaxel are typically used in the second-line setting. Pembrolizumab is approved for the treatment of refractory microsatellite-high/mismatch repair-deficient (MSI-H/dMMR) solid tumors including ESCC, and in the second line setting for the treatment of patients with ESCC whose tumors express PD-L1 (CPS≥10). There are no randomized, well-controlled trials demonstrating an overall survival benefit for any drug or combination of drugs in the second-line setting for patients with microsatellite stable/mismatch repair-proficient ESCC with low levels of PD-L1 expression.

The safety and effectiveness of nivolumab for the treatment of patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy was established by a single adequate and well controlled trial, Study ONO-4538-24 (CA209473; ATTRACTION-3). Study ONO-4538-24 is a multicenter, randomized, open-label, active-controlled trial conducted 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 (1:1)

to receive nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks or investigator's choice of taxane chemotherapy consisting of docetaxel (75 mg/m2 intravenously every 3 weeks) or paclitaxel (100 mg/m2 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. Tumor assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures were overall response rate (ORR) and progression-free survival (PFS) as assessed by the investigator using RECIST v1.1 and duration of response (DOR).

A total of 419 patients were randomized, 210 patients to the nivolumab arm and 209 patients were randomized to the investigator's choice arm (docetaxel: 31%, paclitaxel: 69%). Study ONO-4538-24 demonstrated a clinically meaningful, statistically significant improvement in OS favoring the nivolumab arm. The hazard ratio (HR) for OS was 0.77 (95% confidence interval [CI]: 0.62, 0.96; p-value=0.0189). Median OS in the nivolumab arm was 10.91 months (95% confidence interval [CI]: 9.23, 13.34) and 8.38 months [95% CI: 7.20, 9.86] in the taxane chemotherapy arm.

There was no statistically significant difference in ORR or PFS between the two arms. The hazard ratio for PFS was 1.1 (95% CI: 0.9, 1.13), corresponding to a median progression free survival of 1.7 months (95% CI: 1.5, 2.7) and 3.4 months (95% CI: 3.0, 4.2) in the nivolumab and investigator's choice arms, respectively. The ORR in the nivolumab arm was 19% and the ORR in the investigator's choice arm was 22%, although responses in the nivolumab arm appeared more durable; the median duration of response was 6.9 months (95% CI: 5.4, 11.1) and 3.9 months (95% CI: 2.8, 4.2) in the response-evaluable set (RES) nivolumab and investigator's choice arms, respectively.
There was no statistically significant difference in ORR or PFS between the two arms. The hazard ratio for PFS was 1.1 (95% CI: 0.9, 1.13), corresponding to a median progression free survival of 1.7 months (95% CI: 1.5, 2.7) and 3.4 months (95% CI: 3.0, 4.2) in the nivolumab and investigator's choice arms, respectively. The ORR was 19% in the nivolumab arm and 22% in the investigator's choice arm, although responses in the nivolumab arm appeared more durable; the median duration of response was 6.9 months (95% CI: 5.4, 11.1) and 3.9 months (95% CI: 2.8, 4.2) in the response-evaluable set (RES) nivolumab and investigator's choice arms, respectively.

In Study ONO-4538-24, an improvement in OS was observed irrespective of PD-L1 status, although there was a trend for improved OS outcomes in patients with PD-L1 positive ESCC, defined as ≥1% of tumor cells expressing PD-L1. Of the 419 patients randomized in Study ONO-4538-24, 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 nivolumab 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 nivolumab and investigator's choice arms, respectively.

The safety profile of nivolumab observed in Study ONO-4538-24 was generally consistent with the established safety profile of nivolumab and compared favorably to the safety profile of docetaxel and paclitaxel. The median duration of exposure was 2.6 months (range: 0 to 29.2 months) in nivolumab-treated patients and 2.6 months (range: 0 to 21.4 months) in patients treated with docetaxel- or paclitaxel. In this trial, 26% of patients received nivolumab for >6 months and 10% of patients received nivolumab for >1 year.

The most common adverse reactions to nivolumab of any severity were rash (22%) and decreased appetite (21%), and the most common severe (Grade 3 or 4) adverse reactions were anemia (8%), pneumonia (5%). rash (2%), decreased appetite (2%), and diarrhea (2%). The most common laboratory abnormalities were increased creatinine (78%), lymphopenia (46%), anemia (42%), hyponatremia (42%), increased aspartate aminotransferase (40%), increased alkaline phosphatase (33%), and increased alanine aminotransferase (31%). Serious adverse reactions occurred in 38% of patients receiving nivolumab and the most common serious adverse reactions (in ≥2% of patients who received nivolumab) were pneumonia, esophageal fistula, interstitial lung disease and pyrexia. The frequency of treatment-emergent adverse events leading to death was low and similar in both arms (5.3% in the nivolumab arm and 4.3% in the chemotherapy arm). The following fatal adverse reactions occurred in patients who received nivolumab: 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%). Nivolumab was discontinued in 13% of patients and was delayed in 27% of patients for an adverse reaction.

Immune-mediated adverse reactions generally occurred at similar frequencies in patients with ESCC who received nivolumab compared to incidences observed with other tumor types, with the exception of pneumonitis, which was reported more frequently in patients with ESCC. Using the composite Preferred Terms for pneumonitis (which includes interstitial lung disease, and radiation pneumonitis), the incidence of pneumonitis was lower in a pooled population of patients who received single-agent nivolumab for treatment of other tumor types (3.3%)

compared to patients with ESCC (8.6%, n=18). Of the patients in the nivolumab group who developed pneumonitis, 77.8% (n=14 of 18) had prior radiation therapy for ESCC, which may account for the increased incidence of immune-mediated pneumonitis in this trial.

The review team concluded that the overall risk:benefit assessment favored approval of nivolumab for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy. The demonstrated improvement in OS for patients randomized to the nivolumab arm compared to patients randomized to receive either paclitaxel or docetaxel is clinically meaningful and statistically significant. The adverse reaction profile observed in patients receiving nivolumab is consistent with the established safety profile for this biologic, and the demonstrated OS benefit further supports the safety of nivolumab in patients with ESCC. The most important risks are immune-mediated adverse reactions, which are largely manageable with patient surveillance, dose interruption and supportive care . The risks of nivolumab are acceptable considering the life-threatening nature of unresectable, recurrent, or metastatic ESCC in the second-line setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Esophageal cancer is a serious and life-threatening disease and is the sixth most fatal cancer worldwide (Bray F 2018) • In the US, esophageal cancer is considered an orphan disease and is projected to cause approximately 16,000 deaths in the U.S. in 2020 (Siegel 2020). • The 5-year survival rate of advanced unresectable or metastatic esophageal cancer is 3.4% (Zhang 2013). • The incidence and histological type of esophageal cancer varies with geographic location. While the rate of esophageal squamous cell carcinoma (ESCC) exceeds esophageal adenocarcinoma (EAC) in more than 90% of all countries (Arnold M 2015), EAC predominates in the US, accounting for 63.5% of all EC cases (National Cancer	Esophageal cancer is a serious and life threatening illness with a 5-year survival rate of 3.4%.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Institute (2018).	
Current Treatment Options	• Cytotoxic chemotherapy is the mainstay of treatment for advanced esophageal cancer. • For initial treatment of unresectable locally advanced or metastatic ESCC,NCCN guidelines recommend the combination of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin), which confer moderate benefit. • In the refractory setting, pembrolizumab is approved for the treatment of refractory microsatellite-high/mismatch repair-deficient (MSI-H/dMMR) solid tumors including ESCC based on demonstration of durable overall responses. • Pembrolizumab is also approved in the second line setting for the treatment of patients with ESCC whose tumors express PD-L1 (combined positive score [CPS]≥10) based on an exploratory analysis conducted in the subset of patients with PD-L1 positive tumors demonstration of an improvement in overall survival (OS) over an active comparator consisting of paclitaxel or docetaxel (Hazard Ratio [HR]=0.64 [95% CI:0.46,0.69]). • There are no approved treatments for patients with unresectable advanced, recurrent, or metastatic esophageal microsatellite stable/mismatch repair proficient ESCC following receipt of	There is an unmet medical for new effective therapies that improve survival in patients with unresectable or metastatic EC who are refractory to first-line cytotoxic chemotherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	fluoropyrimidine- and platinum-based chemotherapy with tumors that have a CPS < 10.	
Benefit	• Study ONO-4538-24 demonstrated an improvement in OS favoring the nivolumab arm compared to an active comparator (docetaxel or paclitaxel) in patients with unresectable, recurrent or metastatic ESCC in the second-line setting. The hazard ratio (HR) for OS was 0.77 (95% confidence interval [CI]: 0.62, 0.96; p-value=0.0189). Median OS in the nivolumab arm was 10.91 months (95% confidence interval [CI]: 9.23, 13.34) and 8.38 months [95% CI: 7.20, 9.86] in the taxane chemotherapy arm. • There was no statistically significant difference in overall response rate (ORR) or PFS between the two arms. The ORR in the investigator's choice arm was 22%, although responses in the nivolumab arm appeared more durable; the median duration of response was 6.9 months (95% CI: 5.4, 11.1) and 3.9 months (95% CI: 2.8, 4.2) in the response-evaluable set (RES) nivolumab and investigator's choice arms, respectively. • Patients appeared to derive an OS benefit irrespective of tumor PD-L1 status. 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 nivolumab and investigator's choice arms, respectively, in the PD-L1 positive subgroup. In the PD-L1	Study ONO-4538-24 demonstrated a statistically significant, clinically meaningful improvement in OS for nivolumab compared to the investigator's choice of either docetaxel or paclitaxel in patients with unresectable, recurrent or metastatic ESCC in the second-line setting, irrespective of tumor PD-L1 status. These results were supported by an observation of responses that were more durable in the nivolumab arm compared to the chemotherapy arm.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 nivolumab and investigator's choice arms, respectively.	
Risk and Risk Management	• The safety of nivolumab has been previously established for the treatment of patients with a variety of advanced solid tumors, including non-small cell lung cancer, small-cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, MSI-H/dMMR colorectal cancer and other refractory MSI-H/dMMR solid tumors, and hepatocellular carcinoma. • The observed safety profile of nivolumab in patients with ESCC enrolled in Study ONO-4538 is generally consistent with the known safety profile of nivolumab. Additionally, this trial showed an OS benefit for patients with ESCC, which further supports the safety of nivolumab in this patient population. • Adverse reactions occurring in in ≥ 20% of patients with ESCC treated with nivolumab were rash (22%) and decreased appetite (21%), and the most common severe (Grade 3 or 4) adverse reactions were anemia (8%), pneumonia (5%). rash (2%), decreased appetite (2%), and diarrhea (2%). • Serious adverse reactions occurred in 38% of patients receiving nivolumab and the most common serious adverse reactions (in ≥2% of patients who received nivolumab) were pneumonia, esophageal fistula, interstitial lung disease and pyrexia. The frequency of	The toxicity profile of nivolumab is acceptable when assessed in the context of the life-threatening nature of refractory ESCC and considering the demonstrated improvement in OS, which also reflects the safety of use of nivolumab in this patient population. No new significant safety concerned 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. Significant and serious adverse reactions to nivolumab, including immune-mediated adverse reactions, are largely manageable through surveillance and timely dose interruption or discontinuation with supportive care. Additionally, oncologists who treat patients with ESCC are well trained in monitoring and treatment of the adverse reactions to nivolumab. The review team determined that standard postmarketing surveillance would be sufficient for continued assessment of the safety of nivolumab in patients with ESCC, and that a postmarketing

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment-emergent adverse events leading to death was low and similar in both arms (5.3% in the nivolumab arm and 4.3% in the chemotherapy arm). The following fatal adverse reactions occurred in patients who received nivolumab: 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%). • Nivolumab was discontinued in 13% of patients and was delayed in 27% of patients for an adverse reaction. • Aside from esophageal fistula, which may be at least in part related to the underlying ESCC, no new or unexpected adverse reactions were observed in patients who received nivolumab in Study ONO-4538. With the exception of pneumonitis, which occurred at a higher incidence in patients with ESCC, the overall incidence immune-mediated adverse reactions was similar to that seen in other patients with advanced solid tumors treated with nivolumab as a single agent. The increased incidence in pneumonitis appeared to be associated with prior receipt of radiation therapy for ESCC.	requirement (PMR) under the Food and Drug Administration Amendments Act of 2007 (FDAAA) was not needed.

1.4. Patient Experience Data

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

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Section 8.1.2 Efficacy Results – Secondary or exploratory COA (PRO) endpoints
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	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

Martha Donoghue, MD

Cross-Disciplinary Team Leader

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.

2 Therapeutic Context

2.1. Analysis of Condition

Esophageal cancer (EC) is the seventh most common cancer worldwide and the sixth most common cause of death from cancer in 2018, with an estimated 572,034 new cases (3.2% of all cancers) and 508,585 cancer deaths (5.3% of all cancer deaths).[1] Although EC is relatively uncommon in the US, it remains a major global health threat. According to the GLOBOCAN 2018 estimates, the age-standardized rate of EC per 100,000 among men was 5.6 and 1.2 among females.[1]

EC consists of two major histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Approximately three quarters of all EACs are found in the distal esophagus, from columnar-lined metaplastic epithelium (Barrett's esophagus), whereas ESCC are more evenly distributed between the middle and upper third. ESCC accounts for 88% of ECs worldwide and is more common in the regions with the highest incidence rates for EC, while EAC is more common in the regions with the lowest EC incidence rates. High-risk areas for ESCC include South America and the "Asian Esophageal Cancer Belt," which extends from eastern Turkey, through Iraq, Iran, and the southern part of the former Soviet Union (Kazakhstan, Turkmenistan, Uzbekistan, Tajikistan) to Mongolia and Western/Northern China.[2] The incidence of ESCC is decreasing in US and other Western countries, where it is considered to be a rare disease.[3,4,5]

The etiology of ESCC is multifactorial and strongly population-dependent.[6] Overall, poor socioeconomic status, alcohol consumption, and smoking are common major risk factors for ESCC in Western countries and Asia. Some risk factors such as betel quid chewing or consuming hot beverages appear to be region specific. Differences in exposure to well-established common risk factors such as smoking and alcohol, genetic polymorphism in alcohol metabolism genes, and different levels of exposure to suspected risk factors such as polycyclic aromatic hydrocarbons may contribute to the observed regional differences in ESCC. The decreasing incidence of ESCC in Western countries such as the US is likely to reflect the decreasing rates of smoking.[7]

The recent Cancer Genome Atlas (TCGA) study enhanced the molecular characterization of ESCC and EAC fueling debate on the utility of histology to guide treatment choice management of the disease. The comprehensive molecular analyses by TCGA of EAC and ESCC from both Asian and Western populations have shown that ESCC is molecularly distinct from EAC. Based on these analyses, ESCC has stronger resemblance to other squamous tumors like SCCHN than to EAC, and consequently, EAC resembles gastric cancers more than ESCC.

Furthermore, based on integrated clustering of somatic copy-number alterations (SCNA), DNA methylation, mRNA, and microRNA expression data, the TCGA classified ESCC into 3 molecular subtypes (n subjects in the TCGA dataset): ESCC1 (n=50), ESCC2 (n=36) and ESCC3 (n=4).[8] Other than ESCC3 which only had 4 subjects in the TCGA dataset, subjects from Brazil, Vietnam, Eastern Europe, and North America are present in both the ESCC1 and ESCC2 subtypes. The limited number of subjects precluded statistically meaningful analysis of patient distribution between the subtypes. However, these data

suggest that similar molecular biology exists among different ethnic groups.[8] The disease and molecular biology of ESCC is not yet fully understood. The currently available literature and data suggest that there are more similarities than differences between races and ethnic groups. In particular, despite small differences, the molecular subtypes, genome-wide somatic mutations, methylation, and gene expression are generally similar between Asian and Caucasian subjects.[9]

The global profiles of somatic mutations are consistent between Asian and Caucasian subjects in ESCC.[9] The majority of significantly mutated driver genes including TP53, NOTCH1 and PIK3CA had similar mutational frequencies between Asian and Caucasian subjects. The top significantly mutated driver genes were enriched in cell cycle, p53, JAK-STAT, and Notch signaling pathways. Although some genes belonging to the same signaling pathway may have differences between Asian and Caucasian subjects, the net outcomes on signaling pathway alterations were consistent between Asian and Caucasian subjects.[9] Thus, current evidence indicates that ESCC is molecularly distinct from EAC. The similarities in various molecular aspects of ESCC between Asian and Caucasian subjects suggest that they have similar underlying disease biology. Such similarities are not expected to introduce differences in response to nivolumab therapy in ESCC subjects in Asian and Western countries.

PD-L1 expression is enriched in ESCC, which might increase tumor susceptibility in these patients to elimination following immune-checkpoint inhibition. The reported prevalence of PD-L1 expression in ESCC ranges from 15% to 83% in tumour cells.[10,11,12,13] Nivolumab, a human monoclonal anti-PD-1 antibody, has been approved for the treatment of several solid tumors, and showed promising antitumour activity and a manageable safety profile in a Phase 2 study (ONO-4538-24/ATTRACTION-1) of patients with advanced ESCC who were refractory or intolerant to fluoropyrimidine-based, platinum-based, and taxane-based chemotherapies.[14]

The FDA's Assessment:

FDA agrees that esophageal cancer is a serious and life-threatening illness and acknowledges the differences discussed by the Applicant with respect to EAC and ESCC and esophageal cancer in high-risk regions of the world compared to in lower-risk regions of the world (including the U.S). In the U.S., esophageal cancer is estimated to be the 11th leading cause of cancer-related death in 2020 (American Cancer Society). Approximately 18,400 new cases of esophageal cancer are expected to be diagnosed and approximately 16,000 deaths are expected in 2020. The estimated 5-year survival rate for U.S. patients with esophageal cancer is only approximately 20% (Siegel 2020). EAC is more common in Western populations (Torre 2016) and ESCC accounts for less than 30% of all esophageal cancers in the U.S. (American Cancer Society).

Regarding the Applicant's presentation of data from The Cancer Genome Atlas (TCGA) Research Network publication (Kim 2017), it is difficult to draw conclusions given the small numbers of patients with the different subtypes (50 with ESCC1, 36 with ESCC2, and 4 with ESCC3). Additionally, only Vietnam was represented among Asian nations in this study. Thus, extrapolating these TCGA findings to the larger issue of differences between Asian and Western patients with ESCC is difficult. Regarding PD-L1 status, FDA agrees that reports in the literature suggest that ESCC may express PD-L1 at a higher

incidence compared to other tumor types but the estimated prevalence varies widely across studies, as noted by the Applicant, and appears to be influenced by the cells sampled and the assay used.

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2.2. Analysis of Current Treatment Options

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product(s) Name	Relevant Indication	Year of Approval Type of Approval	Dosing/ Admin-istration	Efficacy Information	Important Safety and Tolerability Issues	Other Comment
FDA Approved Treatments						
KEYTRUDA[15] (pembrolizumab)	Treatment of patients with recurrent, locally advanced or metastatic, squamous cell carcinoma of the esophagus (ESCC) whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10).	2019 Full approval	200 mg IV Q3W	KEYNOTE-181 Pembrolizumab vs chemotherapy in patients with ESCC and PD-L1 CPS ≥10: mOS (mos): 10.3 vs 6.7 HR (95% CI): 0.64 (0.46, 0.9) mPFS (mos): 3.2 vs 2.3 HR (95% CI): 0.66 (0.48, 0.92) ORR: 22% vs 7% CR: 4% vs 1% PR: 15% vs 5% mDOR (mos): 9.3 vs 7.7 KEYNOTE-180 In patients with ESCC and PD-L1 CPS ≥10: ORR: 20% mDOR (mos) (7 responders): 4.2 to 25.1+	IMARs, refer to W&P/ AEs (USPI)	

Product(s) Name	Relevant Indication	Year of Approval Type of Approval	Dosing/ Admin-istration	Efficacy Information	Important Safety and Tolerability Issues	Other Comment
Other Treatments						
Taxane (Paclitaxel, Docetaxel)	For the treatment of patients with unresectable locally advanced, recurrent or metastatic disease (≥2L).	N/A	Refer to NCCN guideline for detail	Efficacy has not been confirmed in any comparative study in ESCC	Refer to NCCN Guideline	As monotherapy, category 1.* (Docetaxel only) In combination with irinotecan, Category 2B.*
Irinotecan						As monotherapy, Category 1.* In combination with fluorouracil or cisplatin, Category 2A.* In combination with docetaxel, Category 2B.*
Fluorouracil						In combination with irinotecan, Category 2A.*
Cisplatin						In combination with irinotecan, Category 2A.*

*Per NCCN Guideline[16]

Table 2: Outcomes with Standard of Care in Advanced ESCC

Line of Treatment	Dataset	N	Regimen	ORR (%)	mPFS (mo)	mOS (mo)
1L	**Kato 2014**[17]	42 (Japanese)	5-FU + nedaplatin	40	2.5	8.8
	Iizuka 1992[18]	39 (Japanese)	5-FU + cis	36	Pts with response: 3.5	Pts with response: 9.5 Pts without response: 5.6
	Bleiberg 1997[19]	44 (European)	5-FU + cis	35	6.2	7.6
	Lorenzen 2009[20]	30 (German)	5-FU + cis	13	3.6	5.5
	Moehler 2017[21]	73 (German)	5-FU + cis	43	5.8	10.2
2L	**Muro 2004**[26]	SCC: 46, other: 3 (Japanese**)**	Docetaxel	20	2.3[a]	8.1[a]
	Kato 2011	52 (Japanese)	Paclitaxel	44	3.9	10.4

[a] Including 1L subjects (n=14)

Abbreviations: 1L: first-line; 2L: second-line; 5-FU: 5-fluorouracil; cis: cisplatin; ESCC: esophageal squamous cell carcinoma; mo: months; mOS: median overall survival; mPFS: median progression-free survival; ORR: overall response rate; pts: patients

The Applicant's Position:

Advanced/metastatic or recurrent ESCC, regardless of region or ethnicity, is an aggressive disease and is associated with poor prognosis. Palliative options depend on the clinical situation and may include chemotherapy, radiotherapy, or best supportive care. Prognosis is dismal in subjects with advanced disease, and conventional chemotherapy beyond standard therapy with platinum- and fluoropyrimidine- combination therapy offers limited survival benefit.

Patients with advanced (metastatic or disseminated) and recurrent ESCC are treated with palliative intent with chemotherapy to extend survival, and with localized treatments, such as radiotherapy (including external radiation or brachytherapy), or endoscopic therapies, such as stents, for the symptomatic treatment of obstruction and dysphagia.[16,22] Generally, chemotherapy is offered to selected patients with good performance status (PS), and prognosis of ESCC is considered to be poorer compared to EAC. Since the value of palliative chemotherapy is less proven, best supportive care (BSC) could be considered for unfit patients. Advanced EAC is managed mostly according to recommendations for gastric cancer.

There are scarce survival data from clinical trials with standard of care (SOC chemotherapy) in advanced ESCC, but overall outcomes are comparable across regions suggesting limited benefit in metastatic disease (Table 2). Approaches to systemic palliative therapy are similar across regions. Advanced ESCC is typically treated in the US,[16] Europe,[23] and Japan[24] with front-line platinum and fluoropyrimidine doublet chemotherapy. Alternatively, a triplet platinum, fluoropyrimidine, and taxane combination regimen could be considered for very fit patients under selected circumstances in the US.

The selection of a 2L therapy regimen is dependent on prior therapy and performance status. Taxanes (either docetaxel or paclitaxel) are typically administered as 2L treatment for ESCC and both compounds hold Category 1 recommendation in the NCCN guidelines (Table 1). Irinotecan as monotherapy

(Category 1) and in combination with fluorouracil (Category 2a) are listed as preferred regimens. Recommended yet not indicated as preferred regimens by the NCCN include irinotecan in combination with either cisplatin (Category 2A) or docetaxel (category 2B).

Although taxanes (docetaxel and paclitaxel) are commonly used in this setting,[25] survival prolongation with these agents has not been confirmed in comparative ESCC studies. Results of two small Asian Phase 2 studies suggested median OS of 8.1-10.4 months with docetaxel and paclitaxel.[26,27] Furthermore in 5 observational studies which evaluated taxane monotherapy use in 2L for subjects with advanced/metastatic EC the median OS ranged from 5.1 to 8.6 months.[28,29,30,31,32] Three of these studies included subjects with ESCC only,[30,31,32] and 2 studies included predominantly ESCC and a small percentage of subjects with esophageal adenocarcinoma (5 and 11%).[28,29] In the three studies which only included ESCC subjects, the median OS ranged from 5.5 to 7.3 months.[30,31,32]

The modest benefits with chemotherapy in the 2L setting are associated with significant toxicities. The use of taxanes is often complicated by hematological, gastrointestinal, and neurological side effects leading to frequent treatment interruptions, delays, and dose reductions. Docetaxel is linked to severe (Grade 3 and 4) hematological toxicity including leukopenia (73%), neutropenia (88%), febrile neutropenia (18%), and anemia (12%) as well as non-hematological toxicity including Grade 3 anorexia (18%), fatigue (12%), and diarrhea (6%). Likewise, commonly reported Grade 3 or 4 adverse events (AEs) with paclitaxel are neutropenia (52.8%), leukopenia (45.3%), anorexia (9.4%), fatigue (9.4%), constipation (7.5%), pneumonia (7.5%), and sensory neuropathy (5.7%). Sensory neuropathy of any grade can be observed in 81.1% of subjects treated with paclitaxel and often can be bothersome and debilitating.[26,27]

In Jul-2019, US FDA approved pembrolizumab for the treatment of patients with recurrent, locally advanced or metastatic ESCC whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10), with disease progression after one or more prior lines of systemic therapy,[15] based on 2 clinical studies, KEYNOTE-180 (single-arm, open-label) and KEYNOTE-181 (randomized, open-label, active-controlled trial). The final analysis of KEYNOTE-181 (N=628) demonstrated a directionally favorable, yet not statistically significant by pre-defined criteria, difference in OS with pembrolizumab versus chemotherapy in previously treated subjects with advanced ESCC (HR=0.78 [95% CI: 0.63, 0.96]; p=0.0095).[33] In the current NCCN guidelines, pembrolizumab is recommended for the treatment of EC (including ESCC) with tumor PD-L1 expression (CPS $\geq$ 10) (Category 1).[16]

Irrespective of the recent pembrolizumab approval in 2L+ ESCC subjects with PD L1 expressing tumors (CPS ≥ 10), an unmet medical need still exists in the broader patient population, and effective new treatment options are needed regardless of tumor cell PD L1 expression status.

The FDA's Assessment:

FDA generally agrees with the Applicant's analysis of current treatment options for unresectable, advanced ESCC that are presented above. The approval of pembrolizumab for the treatment of patients with recurrent, locally advanced or metastatic ESCC whose tumors express PD-L1 (Combined Positive

Score [CPS] ≥ 10), *with disease progression after one or more prior lines of systemic therapy with disease* (the line of therapy was omitted from the indication in the Applicant's Table 1, above) was primarily based upon results of the KEYNOTE-181 trial. KEYNOTE-181 was a multicenter, randomized, open-label, active-controlled study in 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. Patients were randomized (1:1) to receive either pembrolizumab 200 mg every 3 weeks or investigator's choice of any of the following chemotherapy regimens: paclitaxel 80-100 mg/m^2 on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m^2 every 3 weeks, or irinotecan 180 mg/m^2 every 2 weeks. Randomization was stratified by tumor histology (ESCC vs. esophageal EAC/Siewert type I EAC of the gastroesophageal junction [GEJ]), and geographic region (Asia vs. ex-Asia). Of the 628 enrolled patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS ≥10 and 85 of these patients were randomized to receive pembrolizumab. KEYNOTE-180 was a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced o metastatic esophageal cancer who progressed on or after at least 2 prior systemic treatments for advanced disease. Of these 121 patients, 35 (29%) had ESCC that expressed PD-L1 CPS ≥10. The ORR in the 35 patients was 20% with a 95% confidence interval (CI) of 8, 37 (the CI was omitted from the Applicant's Table 1, above).

FDA agrees with the Standard of Care (SOC) data presented in Table 2 by the Applicant. Of note, the Kato et al. 2014 study is the JCOG9905-DI study (not JCOG9901-DI study as written in the references). Also, the appropriate reference for "Kato 2011" is Kato K et al. Cancer Chemother Pharmacol. 2011 Jun;67(6):1265-72.

Regarding therapies approved under the accelerated approval pathway, pembrolizumab is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Based on literature reports, the incidence of MSI-H/dMMR ESCC is estimated to range from 3-14% (Hayashi 2003, Kubo 2005, Matsumoto 2007, Campanella 2018).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Nivolumab monotherapy was first approved in melanoma by FDA on 22-Dec-2014 and is currently approved for numerous additional tumor types, including NSCLC, SCLC, RCC, cHL, SCCHN, mUC, MSI-H/dMMR CRC and HCC. 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 and MSI-H/dMMR CRC. The approved dosage for nivolumab monotherapy is the same as the dosage proposed for ESCC in this application (240 mg Q2W or 480 mg Q4W).

The FDA's Assessment:

FDA agrees with the Applicant's summary above. Additionally:

- On March 10, 2020, the combination of nivolumab and ipilimumab was approved for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; 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.
- On May 15, 2020, nivolumab was approved for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer (NSCLC) whose tumors express PD-L1(≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, in combination with ipilimumab.
- On May 26, 2020, nivolumab was approved in combination with ipilimumab and 2 cycles of platinum-based chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 3 Key Regulatory Milestones

Date	Regulatory Milestones
01-Dec-2015 (SN 0055)	Submission of Protocol 3 for ONO-4538-24 (CA209473) to IND 126406.
12-May-2016	FDA issued an Advice/Information letter informing BMS to submit an End of Phase 2 (EOP2) meeting and a detailed description of the overall development program for 2L esophageal cancer.
06-Jun-2016 (SN 0106)	BMS submitted the response to FDA Advice/Information letter dated 12-May-2016.
28-Jun-2016 (SN 0108)	Submission of revised Protocol 6 for ONO-4538-24 (CA209473) to IND 126406 based on FDA 12-May-2016 letter.
22-Aug-2016 (SN 0122)	Orphan designation granted for nivolumab for the treatment of Esophageal Cancer (16-5310). Courtesy copy of ODD granted letter was submitted to IND 126406 on 31-Aug-2016.
24-Oct-2016 (Preliminary Comments)	Type C meeting with FDA to review the global development program for nivolumab as monotherapy and in combination with ipilimumab for the treatment of upper GI malignancies, including esophageal cancer. • FDA agreed that Study ONO-4538-24 (CA209473) could potentially support the approval of nivolumab for the treatment of (b) (4) provided that the results of the single trial demonstrate a highly statistically significant effect on survival that is internally consistent across relevant subgroups (including patients enrolled outside of Asia). • FDA stated that the results should also be applicable to the U.S. population according to the ICH E5 The meeting scheduled on 25-Oct-2016 was subsequently cancelled.
24-Aug-2018 (SN 0250)	BMS submitted the Statistical Analysis Plan for Study ONO- 4538-24 (CA209473).
15-May-2019 (SN 0304)	BMS submitted Revised Protocol 10 for ONO-4538-24 (CA209473).
06-Aug-2019 (Preliminary Comments)	Type B pre-sBLA meeting to discuss the adequacy of data from study ONO-4538-24 (CA209473) to support a sBLA submission for the proposed indication of "nivolumab for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination therapy". • FDA agreed that the efficacy results from Study ONO-4538-24 (CA209473) are likely to support the filing of a marketing application seeking the proposed indication.

	• FDA requested the inclusion of sufficient data and information in the sBLA to support the comparability of the Ono and BMS drug products in order for FDA to file the application. Additional advice on this topic would be provided in a separate communication. • FDA did not agree that the proposed (b) (4) FDA requested the submission of all relevant information summarized in the meeting package and the final determination would be a review issue. • FDA agreed that the proposed plan for the clinical pharmacology presentation appears acceptable for the sBLA. • FDA agreed that the proposed dossier content in Module 5.3.5.1 regarding the datasets and program files are acceptable. • FDA commented that BMS should ensure that all the required elements for an ISE described in the Integrated Summary of Effectiveness: Guidance for Industry (October 2015) are contained in the SCE. • FDA requested BMS to: o provide the primary and key secondary efficacy results for the ITT population that includes the 31 patients (b) (4) who were affected by (b) (4), and o provide a sensitivity analysis that excludes all patients enrolled at any clinical site at which (b) (4) • FDA requested a justification in the sBLA to support why lack of MSI/MMR status is not relevant to a determination regarding the safety and effectiveness of nivolumab for the proposed indication. • FDA requested the submission of serious adverse events and deaths that occur during or within 30 days of nivolumab treatment for patients treated in the control arm (in addition to those treated with nivolumab) and narratives for all patients that discontinue from study therapy prior to disease progression. • FDA requested the submission (in the integrated summary of safety) of analyses and supportive side-by-side tabular summaries comparing the safety profile of nivolumab observed in the ONO-4538-24 trial with the safety profile observed in an pooled population of patients with esophageal cancer treated with nivolumab and in a current safety database across the nivolumab development program. • FDA requested the submission of datasets that are appropriately flagged and organized and the rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs. • FDA agreed with BMS' proposal not to submit a 120-day Safety Update Report for the proposed supplement. • FDA additional comment #5: FDA requested additional information concerning (b) (4) • FDA additional comment #6: FDA requested a summary of all completed, ongoing and planned trials conducted in patients with esophageal cancer. • FDA requested additional post-hoc analyses for the analysis of OS in the presence of non-proportional hazards as observed in this trial. • FDA agreed that the granted orphan drug designation exempts BMS from requirements under PREA for the proposed indication. The meeting scheduled on 08-Aug-2019 was subsequently cancelled.
14-Aug-2019 (SN 0315)	BMS submitted the response to FDA additional comment #6.
18-Oct-2019	FDA emailed BMS with additional advice regarding the product quality information that will be needed to support comparability of the two products.
22-Nov-2019 (SN 0329)	BMS submitted the response to FDA additional comment #5.

The FDA's Assessment:

FDA agrees with the Applicant's summary of presubmission/submission key regulatory milestones presented above. Additional pertinent regulatory history that is not described above is summarized below:

- In the Advice/Information letter issued by FDA on May 12, 2016, FDA stated: "The safety and efficacy of nivolumab may differ between patients who are unable to tolerate fluoropyrimidine and platinum-based chemotherapy and those with disease progression following such therapy. Therefore, such patients should be identified prior to randomization, the basis for "intolerance" captured on case report forms, and consideration be given to stratification of randomization based on intolerance to prior chemotherapy (yes vs. no)" and also recommended that the Applicant: "Revise the protocol to provide the order in which the key secondary endpoints of PFS and ORR will be tested if you plan to use a gate-keeping procedure (at a 2-sided significance level of 5%) to adjust for multiplicity in the testing of secondary endpoints. The details provided in Section-10.3.1 lack the information regarding the order of precedence among the secondary endpoints".

- In the responses issues by BMS on June 6, 2016, BMS stated that the current case report forms capture the information necessary to determine those patients who are "intolerant" to prior therapy. BMS also stated that: " The protocol is currently ongoing in Japan, Taiwan, and Korea making the insertion of an additional stratification factor based on "intolerance of prior chemotherapy" impractical to implement. However, exploratory analysis will be conducted to assess the potential safety and efficacy differences based on intolerance to prior pharmacotherapy". Regarding a gate-keeping procedure, BMS stated that: "if superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints will be tested in the following hierarchical order: 1. ORR 2. PFS".

- Regarding the proposed [redacted] (b) (4), in the August 6, 2019 pre-sBLA preliminary meeting comments, FDA stated that: "No FDA does not agree [redacted] (b) (4). BMS should submit all of the information summarized in the meeting package, including a description of disease biology based on The Cancer Genome Atlas (TCGA), identification of possible disease risk factors known to be population-dependent, and differences in medical practice patterns including outcomes with standard of care treatment based on published literature A final determination of the justification for extrapolation of the data to the U.S. population will be made at the time of sBLA review".

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct inspections of the study sponsor (ONO Pharmaceutical Co, Ltd.) and the contract research organization (CRO: (b) (4)) for Study ONO-4538-24 (CA209473). Physical inspections were not possible due to COVID-19-related travel restrictions. However, OSI reviewed the inspection report of the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, monitoring visit reports for (b) (4), the Applicant's audit summaries, and the Applicant's responses to several FDA inquiries regarding violations of Good Clinical Practice (GCP) guidelines reported for (b) (4). OSI concluded that "the efficacy and safety data as submitted by the Applicant to this supplemental BLA appear reliable in support of the application. The sponsor's oversight of the study as reported by PMDA appear adequate". Please refer to the subsection entitled "Compliance with Good Clinical Practices" in Section 8.1.2 of this review for information regarding FDA's evaluation of violations of GCP guidelines reported by the trial sponsor.

4.2. Product Quality

The Office of Biotechnology Products (OBP) reviewers recommended approval of this supplemental application. Study ONO-4538-24 included use of non-US licensed nivolumab drug product (DP) manufactured by Ono Pharmaceuticals, Co. (Ono) using drug substance (DS) batches manufactured by the Applicant in accordance with the US-licensed DS process. To support the use of non-US licensed nivolumab DP materials produced by Ono pharmaceuticals Study ONO-4538-24, the Applicant provided the following data and information: 1) manufacturing process comparison between BMS and Ono DP processes, 2) batch release data of BMS and Ono clinical DP batches used in ONO-4538-24 study and batch release data of source DS batches for assays that were not tested for Ono DP, 3) information of methods used for BMS and Ono DP release, 4) stability data of BMS and Ono DP batches.

Both the BMS and Ono clinical DP batches were manufactured using DS batches produced at the same approved manufacturing site (b) (4)), using the commercial (b) (4) as approved in BLA 125554 Module 3. The liquid dosage form, formulation, and primary packaging of BMS and Ono DP are the same. Differences in the DP manufacturing processes between BMS and Ono are minor and pose low risk to impact product quality. The nivolumab DP process consists of simple dilution and filling operations that do not impact most critical quality attributes (CQAs) of the DS. Therefore, the OBP review team concluded that the DS release results for the clinical batches support comparability as the risk for differences in potency or purity attributes intrinsic to the DS due to the Ono DP process is negligible.

In their review, the OBP reviewers noted that DP release data of BMS and Ono clinical DP batches further support product comparability and mitigate residual uncertainty for potential differences in relevant CQAs. Notably, 2 of the clinical DP lots, including 1 of the 4 Ono clinical DP lots, were tested using BMS commercial DP release methods (except for cell-based bioassay) and met commercial

acceptance criteria. For the other 3 Ono clinical DP lots, BMS provided information to support methods used for DP release testing at BMS and Ono are comparable and Ono methods use the same or similar procedures as the commercial BMS methods with minor differences. The Ono DP release testing program uses the same reference material as BMS, and includes relevant attributes that may be impacted by the DP process such as protein concentration, high molecular weight species, and particulate matter. Stability data of BMS and Ono DP batches support comparable product stability under long-term condition (2oC to 8oC).

In summary, the OBP reviewers determined that data and information provided in the application support analytical comparability between the BMS and Ono DP lots used in clinical study ONO-4538-24. The results were considered comprehensive and sufficient to justify the use of clinical data from patients treated with the nivolumab DP batches produced by Ono Pharmaceuticals.

OBP also determined that the anti-drug antibody (ADA) assay in Study ONO-4838-24 was valid and enabled appropriate interpretation of the ADA test results, and granted the Applicant's request for categorical exclusion from an environmental assessment.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees that no new nonclinical pharmacology/toxicology information was submitted with this application.

X X

Primary Reviewer
Emily Place

Nonclinical Team Leader
Matthew Thompson

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

In this supplemental BLA submission, the Applicant seeks FDA approval of nivolumab for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy. The clinical data to support the proposed indication are from a randomized open-label Study ONO-4538-24 (CA209473), in which nivolumab was administered at a fixed dose of 240 mg by intravenous (IV) infusion every two weeks (Q2W) as a monotherapy. Based on results from Study ONO-4538-24 (CA209473), and the well characterized nivolumab pharmacokinetics (PK) and exposure-response (E-R) relationships, the Applicant proposed two alternate recommended dosing regimens: 240 mg Q2W or 480 mg every 4 weeks (Q4W). These two dosing regimens are the same as the dosing regimens recommended for previously approved indications for nivolumab as a monotherapy. Per FDA's previous analyses, nivolumab AUC (Cavg) and Ctrough at steady state with the 480 mg Q4W dosing regimen are expected to be comparable to the 240 mg Q2W dosing regimen in patients with ESCC. In addition, nivolumab Cmax at steady state with the 240 mg Q2W and 480 Q4W dosing regimens are also expected to be within the tolerated range of exposures with 10 mg/kg Q2W dosing (see the Clinical Pharmacology review for BLA 125554 Supplement-48-52, 61-62 and 64-66). The anti-drug antibody (ADA) incidence for nivolumab in patients with 2L ESCC in ONO-4538-24 (CA209473) was 4.9%, which is similar to the incidence of ADA previously observed across various tumor types and ADA do not appear to have clinically meaningful effect on the efficacy or safety of nivolumab.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Pharmacology

Nivolumab is a human 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.

Clinical Pharmacokinetics

The PPK analysis included in this submission was performed to characterize nivolumab PK in ESCC patients and to determine the magnitude of effect of intrinsic and extrinsic covariates on nivolumab PK. Consistent with the previous analyses, the results of the analysis demonstrated that nivolumab PK was well characterized by a linear, 2-compartment, zero-order IV infusion model with time varying CL described using a sigmoid-maximum effect (Emax) function. Nivolumab CL decreases over time with approximately 30 % maximal reduction from baseline values. Among the covariates included in the full model, CL and VC were higher in subjects with higher body weight and CL was higher in subjects with lower albumin. These results are similar to those in a previously conducted PPK analysis. The magnitude

of the effect of other covariates on CL and VC was less than 20%, indicating that these are not clinically significant.

The full model included tumor type as a covariate on CL. The difference in CL between ESCC and, for example, 2L+ NSCLC was as small as 2%, indicating that nivolumab PK does not substantially differ between esophageal cancer and other tumor types.

The magnitude of the effect of race, which was included in the full model as a covariate for CL, was found to be less than 20%, indicating that nivolumab PK does not substantially differ between Asians and other races. Comparisons of exposures in Study ONO-4538-24/CA209473 following treatment with nivolumab 240 mg Q2W in patients with ESCC with different ethnicities (Japanese, non-Japanese Asian, or non-Asian) showed that the difference in Cavgss among the ethnic groups was ~20% and the distribution of exposures for each ethnicity was overlapped, indicating that there were no clinically meaningful difference in exposures among the ethnic groups.

Predictions of the exposures for nivolumab 240 mg Q2W and 480 mg Q4W in subjects with esophageal cancer showed that Cmax1 was 100% higher for 480 mg Q4W than 240 mg Q2W and Cmaxss with 480 mg Q4W was approximately 37% higher than that with 240 mg Q2W. However, neither dosing regimen provides exposures exceeding those at 10 mg/kg Q2W, indicating that exposures with these regimens are all expected to be within the well tolerated range previously confirmed in cancer patients. The magnitudes of the exposure differences for Cavgd28, Cavgss and trough concentrations are comparable to those that can be explained by inter-individual variability, indicating that the differences would have no clinically significant effects.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:
The recommended nivolumab dose of 240 mg Q2W or 480 mg Q4W was selected based on the clinical data and subsequent analysis from Study ONO-4538-24/CA209473 and the collective clinical experience of nivolumab monotherapy from other tumor types. Based on the PPK analysis, there were no clinically meaningful differences in predicted exposures in ESCC patients between 240 mg Q2W and 480 Q4W. Although the Cmax1 and Cmaxss were 100% and 37% higher respectively for 480 mg Q4W, they were within the well-tolerated range that was previously observed for cancer patients who received 10 mg/kg Q2W.[34] Cmind28 and Cminss for 480 mg Q4W were approximately 25% and 18% lower, respectively compared to 240 mg Q2W, however, the magnitudes of the exposure differences are comparable to those that can be explained by inter-individual variability indicating that the differences have no clinically significant effects. In addition, there were no significant differences in predicted exposures of Cavgss between 480 mg Q4W and 240 mg Q2W dosing regimens.

Furthermore, the E-R analysis in ESCC from Study ONO-4538-24/CA209473 demonstrated that nivolumab exposure was not a significant predictor of safety and the risk of death was not higher in subjects with lower nivolumab exposure. While the E-R analysis was limited by the confounding effect of clearance and exposures assessed at one dose level, exposures were not correlated with reduced efficacy or increased safety risk. In addition, results from ONO-4538-24/CA209473 demonstrated that nivolumab 240 mg Q2W had an acceptable safety profile and a clinically meaningful OS in patients with ESCC refractory to or intolerant of fluoropyrimidine and platinum-based combination therapy. E-R analysis was not performed on the predicted exposures from 480 mg Q4W due to the confounding effects between exposure (Cavg1) and CL observed in the current E-R analysis from single-dose data as this would lead to inconclusive results.

Previously, quantitative systems pharmacology (QSP) approach was used to predict the intratumoral PD-1 receptor occupancy (RO) of nivolumab representing a variety of tumor types and it has shown that the day 28 pre-dose intratumoral RO was predicted to be maintained when comparing the 480 mg Q4W and 240 mg Q2W regimens to 3 mg/kg Q2W regardless of the tumor biology scenario. The intratumoral PD-1 RO predictions provide the confidence that inhibition of PD-1 checkpoint will be maintained similarly at high levels for both the regimen across different tumor types.[35] This data further supports that lower Ctrough concentrations with 480-mg Q4W may not affect efficacy.

Collectively, the clinically meaningful OS observed in the Study ONO-4538-24/CA209473, along with PK similarity across the ethnic groups and relatively flat E-R safety and efficacy relationships support the recommended dose and schedule of nivolumab 240 mg Q2W or 480 Q4W in the treatment of patients with ESCC refractory to or intolerant of fluoropyrimidine and platinum-based combination therapy.

The FDA's Assessment:

FDA agrees with the Applicant's proposed dosage regimens. Nivolumab Cavg and Cmin at steady state with the 240 mg Q2W and 480 Q4W dosage regimens are not expected to have clinically meaningful differences in patients with ESCC. Nivolumab Cmax at steady state with the 240 mg Q2W and 480 Q4W dosage regimens are also within the tolerated range of exposures from 10 mg/kg Q2W dosing. Please refer to the Clinical Pharmacology review for BLA 125554 Supplement-48-52, 61-62 and 64-66 for details on FDA's evaluation of the 240 mg Q2W and 480 Q4W dosing regimens.

The Applicant's E-R analyses of the efficacy and safety of nivolumab in patients with ESCC are acceptable but have limitations. For example, only one dosing regimen (i.e., 240 mg Q2W) was tested in the clinical trial and nivolumab exposure was confounded by baseline disease severity and treatment response. The Applicant's QSP model appears reasonable. However, results of QSP analyses can only serve as supportive evidence given the limited experience and lack of appropriate data/methods to validate these models. The main evidence supporting the approval of the proposed dosing regimens is based on the comparability of exposures with the 480 mg Q4W and 240 mg Q2W dosing regimens estimated by modeling and simulation, the flat dose-response relationships, and similar predicted efficacy outcomes based on the E-R relationship.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:
There were no clinically relevant differences in nivolumab PK parameters or exposures identified for the intrinsic and extrinsic factors tested and described below; therefore, therapeutic individualization of nivolumab is not recommended.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.2.2.3. Outstanding Issues

The Applicant's Position:
There are no outstanding clinical pharmacology issues or omissions related to this submission.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

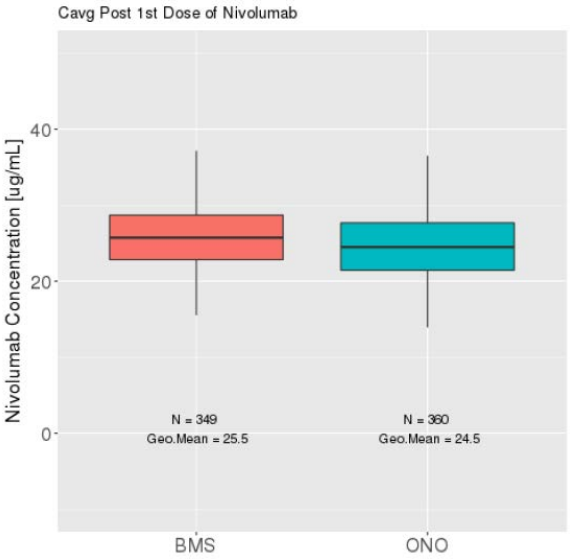
The Applicant's Position:
The nivolumab clinical pharmacology profiles, including single- and multiple-dose PK, pharmacodynamics (PD), pharmacogenomics, drug-drug interaction (DDI) potential, and E-R relationships with safety and efficacy across multiple tumor types have been previously characterized. This information was described in the various clinical pharmacology packages that supported the approvals for melanoma, NSCLC, SCLC, RCC, SCCHN, cHL, UC, CRC, and HCC. Clinical pharmacology information are included in the approved product label.

The PPK analysis was updated for nivolumab for this 2L ESCC submission to include subjects receiving nivolumab monotherapy for 2L ESCC and other solid tumors, including NSCLC. The results from the updated analysis are consistent with the previous PPK analysis across tumor types.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

- The clinical trial product used in Study ONO-4538-24(CA209473) consists of nivolumab injection manufactured by both the Ono facility and the approved BMS facility (Manati, Puerto Rico, USA). The Applicant's PPK analysis showed that the PK parameter (i.e., CL) of nivolumab was not affected by the use of the BMS or Ono product, as the estimate of the PK effect is small and the 90% CI includes 1. The covariate effect (i.e., ratio) of the Ono product to the reference product on CL has a point estimate of nearly 1, and the 90% CI is within the 80% to 125% limit. A comparison of nivolumab Cavg post first dose following administration of the BMS or Ono drug product in Asian patients demonstrated that the exposure estimates for the two drug products are similar (
- Figure **1**), indicating that there are no clinically meaningful differences between the two products.

Figure 1. Comparison of Nivolumab PK in Asian Patients Administered BMS and Ono Drug Products



Source: Figure 2.3.4-2 of the Quality Overall Summary.

- The PK assay used to measure nivolumab concentrations in Study ONO-4538-24 (CA209473) was performed by the same laboratory ((b) (4)) using the validated method (ICD 416) described in the original BLA 125554 application.

- The Applicant's PPK analysis reported that nivolumab average plasma concentration (Cave) at steady state is 23% higher in patients with ESCC compared to other tumor types (e.g., NSCLC); the difference in exposure may be attributed to the difference in body weight between the patients with ESCC (median body weight, 55.2 kg) and NSCLC 2L+ (median body weight, 72.4 kg), and is not likely to result in a clinically meaningful difference in either efficacy or safety.

6.3.2. Clinical Pharmacology Questions

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

The Applicant's Position:

Results from ONO-4538-24 (CA209473) demonstrated statistically significant improvement in overall survival with a PD-1 inhibitor (nivolumab) vs. chemotherapy in previously treated advanced ESCC unselected for PD-L1. The study met its primary endpoint of OS and demonstrated significant improvement in OS in the nivolumab group vs. chemotherapy control group (docetaxel or paclitaxel) (HR=0.77, p=0.0189), in ESCC subjects, refractory or intolerant to fluoropyrimidine and platinum-based combination therapy. In addition, results from ONO-4538-24/CA209473 demonstrated that nivolumab 240 mg Q2W had an acceptable safety profile and a clinically meaningful OS in patients with ESCC refractory to or intolerant of fluoropyrimidine and platinum-based combination therapy.

The E-R analysis in ESCC from Study ONO-4538-24/CA209473 demonstrated that nivolumab exposure was not a significant predictor of safety and the risk of death was not higher in subjects with lower nivolumab exposure. While the E-R analysis was limited by the confounding effect of clearance and exposures assessed at one dose level, exposures were not correlated with reduced efficacy or increased safety risk. E-R analysis was not performed on the predicted exposures from 480 mg Q4W due to the confounding effects between exposure (Cavg1) and CL observed in the current E-R analysis from single-dose data as this would lead to inconclusive results.

Collectively, the clinically meaningful OS observed in the Study ONO-4538-24/CA209473, along with relatively flat E-R efficacy relationships provides evidence of clinical effectiveness of nivolumab in patients with ESCC refractory to or intolerant of fluoropyrimidine and platinum-based combination therapy.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. The Applicant's E-R analyses indicated that nivolumab exposure was not a significant predictor of safety or efficacy (i.e., the risk of death was not higher in patients with lower nivolumab exposure) of nivolumab in patients with ESCC. Although these analyses have limitations, including evaluation of a single dosing regimen (i.e., 240 mg Q2W) in the clinical trial and confounding of nivolumab exposure by baseline disease severity and treatment response, the Applicant's E-R analyses support the proposed dosing regimens.

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

The Applicant's Position:
The recommended nivolumab dose of 240 mg Q2W or 480 mg Q4W was selected based on the clinical data and subsequent analysis from Study ONO-4538-24/CA209473 and the collective clinical experience of nivolumab monotherapy from other tumor types.

The full E-R efficacy model showed that nivolumab Cavg1 and baseline CL were both significant predictors of OS (95% CI of hazard ratio did not include 1). The risk of death was lower in subjects with lower Cavg1 and lower baseline nivolumab CL over the range of exposure achieved by nivolumab 240 mg Q2W dosing regimen. This unexpected E-R relationship is likely attributed to confounding effect of CL as the parameter estimates of nivolumab Cavg1 and baseline CL were highly correlated (R=0.84), suggesting that the effect of Cavg1 and CL on OS is not independent. Age, baseline body weight, baseline tumor size, baseline albumin, baseline LDH, sex, performance status, and PD-L1 status were not significant covariates of OS in the full model.

The E-R safety analysis in the full model showed that nivolumab exposure Cavg1 was not significantly associated with the risk of GR. 2+ IMAE. The risk of GR. 2+ IMAE was higher in subjects with higher baseline LDH. Nivolumab CL, Body weight, age, sex, baseline PS, and baseline albumin did not have significant effects on the risk of Gr. 2+ IMAE.

E-R analysis was not performed on the predicted exposures from 480 mg Q4W due to the confounding effects between exposure (Cavg1) and CL observed in the current E-R analysis from single-dose data, as this would lead to inconclusive results.

Based on the PPK analysis, there were no clinically meaningful differences in predicted exposures in ESCC patients between 240 mg Q2W and 480 Q4W. Although the Cmax1 and Cmaxss were 100% and 37% higher respectively for 480 mg Q4W, they were within the well-tolerated range that was previously observed for cancer patients who received 10 mg/kg Q2W. Cmind28 and Cminss for 480 mg Q4W were approximately 25% and 18% lower, respectively compared to 240 mg Q2W, however, the magnitudes of the exposure differences are comparable to those that can be explained by inter-individual variability indicating that the differences have no clinically significant effects. In addition, there were no significant differences in predicted exposures of Cavgss between 480 mg Q4W and 240 mg Q2W dosing regimens.

Being a monoclonal antibody, nivolumab is not sensitive to ethnic factors that typically impact a small molecule (e.g., CYP450 polymorphism, dietary variations, etc.). In addition, comparisons of exposures in Study ONO-4538-24 (CA209473) following treatment with nivolumab 240 mg Q2W in patients with 2L ESCC with different ethnicities (Japanese, non-Japanese Asian, or non-Asian) showed that the difference in Cavgss among the ethnic groups was ~20% and the distribution of exposures for each ethnicity overlapped, indicating that there were no clinically meaningful differences in exposures among the ethnic groups.

Previously, QSP approach was used to predict the intratumoral PD-1 RO of nivolumab representing a variety of tumor types and it has shown that the day 28 pre-dose intratumoral RO was predicted to be maintained when comparing the 480 mg Q4W and 240 mg Q2W regimens to 3 mg/kg Q2W regardless of the tumor biology scenario. The intratumoral PD-1 RO predictions provide the confidence that inhibition of PD-1 checkpoint will be maintained similarly at high levels for both the regimen across different tumor types. This data further supports that lower Ctrough concentrations with 480-mg Q4W may not affect efficacy.

Collectively, the clinically meaningful OS observed in the Study ONO-4538-24/CA209473, along with PK similarity across the ethnic groups and relatively flat E-R safety and efficacy relationships support the recommended dose and schedule of nivolumab 240 mg Q2W or 480 Q4W in the treatment of patients with ESCC refractory to or intolerant of fluoropyrimidine and platinum-based combination therapy.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The Applicant's E-R analyses of the efficacy and safety of nivolumab in ESCC patients are acceptable and support the proposed dosage regimens, despite their limitations as previously described above. The Applicant's QSP model also appears reasonable. However, results of QSP analyses can only serve as supportive evidence given the limited experience and lack of appropriate data/methods to validate these models. The main evidence supporting the approval of the proposed dosing regimens is based on comparable exposures with the 480 mg Q4W and 240 mg Q2W dosing regimens estimated by modeling and simulation, flat dose-response relationships, and similar predicted efficacy outcomes based on the E-R relationship.

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

The Applicant's Position:
An alternative nivolumab dosing regimen or management strategy is not required for subpopulations based on intrinsic patient factors evaluated on the PK of nivolumab.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Please refer to Clinical Pharmacology Review of the original BLA. The ADA testing used in Study ONO-4538-24 (CA209473) was performed by the same laboratory ([redacted] (b) (4)) using a validated method (ICDIM 140) described in the original BLA 125554 application. Of the 184 patients treated with nivolumab 240 mg Q2W and evaluable for immunogenicity in Study ONO-4538-24, 9 (4.9%) were ADA positive, which is comparable to the incidence of ADA previously observed across various tumor types. ADA do not appear to have a clinically meaningful effect on the efficacy and safety of nivolumab.

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

The Applicant's Position:
There are no clinically relevant food-drug or drug-drug interactions with nivolumab in subjects with ESCC.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. A food-drug interaction is not expected for nivolumab because it is administrated as IV infusion. The risk of drug-drug interactions for nivolumab is low as it is a monoclonal antibody and its metabolism does not involve CYP enzymes.

X X

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 4: Listing of Clinical Trials Relevant to this sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
ONO-4538-024/ CA209-473	NCT 02569242	A global, Phase 3 study in subjects with unresectable advanced, recurrent or metastatic ESCC refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs	Subjects were randomized in a 1:1 ratio to the nivolumab group or control group (docetaxel or paclitaxel) and stratified by region (Japan vs. the rest of the world), number of organs with metastases (≤1 vs ≥2), and expression of PD-L1 (≥1% vs <1% or indeterminate). After randomization, the nivolumab group received nivolumab (240 mg at 2-week intervals) IV, and the control group received docetaxel (75 mg/m^2 at 3-week intervals) or paclitaxel (100 mg/m^2 weekly for 6 weeks followed by 1 week off).	In patients with ESCC refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs: -To compare overall survival (OS) between the nivolumab group and control group (docetaxel or paclitaxel). -To compare progression-free survival (PFS) between the nivolumab group and control group (docetaxel or paclitaxel). -To compare objective response rates between the nivolumab group and control group (docetaxel or paclitaxel).	Treatment was continued until progressive disease was assessed by the investigator or subinvestigator according to the RECIST Guideline Version 1.1. The 3 treatment arms had a minimum follow-up of approximately 17.6 months. The median duration of therapy for the treatment period was 2.56 and 2.56 (2.10 and 2.79) months in the nivolumab and control (docetaxel and paclitaxel) groups, respectively. Study duration was ~34.2 months as of the 12-Nov-2018 data cutoff date.	590 subjects provided informed consent and were enrolled in the study.	Subjects with histologically confirmed advanced ESCC refractory to or intolerant of combination therapy with fluoropyrimidine- and platinum-based drugs. Subjects were not indicated for a radical resection and had at least 1 measurable or non-measurable lesion per the RECIST Guideline Version 1.1 as confirmed by imaging within 28 days before randomization.	90 study sites in 8 countries (Japan, Korea, Taiwan, UK, US, Germany, Italy, and Denmark)

Source: Refer to Synopsis of ONO-4538-24/CA209473 Final CSR.

The Applicant's Position:

Results from ONO-4538-24/CA209473 are used in this submission to provide evidence of efficacy to support the proposed indication of nivolumab for the treatment of patients with unresectable, advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy (Table 4).

The FDA's Assessment:

FDA agrees with Applicant's description of the clinical trials considered in this review. For clarification, the dosing of paclitaxel is worded differently in different parts of the submission (e.g. " 100 mg/m2 weekly for 6 weeks followed by 1 week off" in Table 4 above "100 mg/m^2 weekly for 6 weeks in succession followed by a 2-week washout period" in the clinical study report (CSR)) but these are the equivalent in that patients received 6 doses of paclitaxel and then had 13 days off before the next dose.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. ONO-4538-24/CA209473

Trial Design

The Applicant's Description:

Study ONO-4538-24 (CA209473) is a Phase 3, global, multicenter, randomized open-label study in subjects with esophageal squamous cell carcinoma refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs. Results from this study are provided in this supplement.

Table 5: ONO-Sponsored Study ONO-4538-24/CA209473

Study Number	ONO-4538-24 (CA209473)
Study Title	A Phase 3, multicenter, randomized, open-label study in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs
Study Design	Phase 3, global, multicenter, open-label, controlled, randomized study
Treatment (1)	Nivolumab 240 mg IV Q2W, docetaxel 75 mg/m^2 IV Q3W, or paclitaxel 100 mg/m^2 IV every week for 6 weeks followed by 1 week off
Study Population	Subjects with histologically confirmed advanced ESCC refractory to or intolerant of combination therapy with fluoropyrimidine- and platinum-based regimen. Subjects were not indicated for a radical resection and had at least 1 measurable or non-measurable lesion per the RECIST Guideline Version 1.1 as confirmed by imaging within 28 days before randomization.
IND No.	126406

Geographic Location	90 study sites in 8 countries: Japan, Korea, Taiwan, UK, US, Germany, Italy, and Denmark
Primary Endpoint	OS
Additional Efficacy Endpoints	Secondary Endpoints Investigator-assessed PFS, ORR, DoR, TTR, DCR, maximum percent change from baseline in the sum of diameters of target lesions
Number of Subjects	Enrolled: 590 subjects Randomized (1:1): N=419 Nivolumab monotherapy: N=210 Control (docetaxel or paclitaxel): N=209 Treated: N=417 Nivolumab monotherapy: N=209 Control (docetaxel or paclitaxel): N=208
Study Status	Data cut-off date: 12-Nov-2018 Database lock for the ONO-4538-24 (CA209473) Final CSR: 28-Dec-2018

(1) In the protocol and CSR for ONO-4538-24 (CA209473), nivolumab treatment is referred to as ONO-4538
Abbreviations: CSR: clinical study report; DCR: disease control rate; DOR: duration of response; EAC: Esophageal adenocarcinoma; EC: Esophageal cancer; ESCC: Esophageal squamous cell carcinoma; EU: European Union; IND: Investigational New Drug; IV: intravenous; ORR: overall response rate; OS: overall survival; PD-L1: programmed cell death ligand-1; PFS: progression-free survival; Q2W: every 2 weeks; Q3W: every 3 weeks; Q6W: every 6 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; TTR: time to response.
Source: Refer to Table 1.3.1-2 in Module 2.5 Clinical Overview

Enrollment/Assignment to Treatment:

Patients were randomly assigned (1:1) to either nivolumab or investigator's choice of chemotherapy (paclitaxel or docetaxel). Randomisation was done using an interactive web response system with a block size of four and stratified according to geographical region (Japan vs the rest of the world), number of organs with metastases (≤1 vs ≥2), and expression of PD-L1 (≥1% vs <1% or indeterminate). Investigators registered patients at each site via the web registration system. An authorised vendor used their original internal system to generate the sequentially numbered containers to ensure random allocation, and to assign patients to study treatments. The web registration system ensured that the container sequence was concealed until the treatment allocation was completed. Patients and investigators were not masked to treatment allocation. Subjects who met all inclusion criteria were assigned to the nivolumab group or control group (docetaxel group or paclitaxel group) in a 1:1 ratio.

Trial Location: 90 study sites in 8 countries (Japan, Korea, Taiwan, UK, US, Germany, Italy, and Denmark) enrolled 590 subjects.

Key Inclusion/Exclusion Criteria: The study population included adult subjects with histologically confirmed advanced ESCC, refractory or intolerant to 1 prior fluoropyrimidine and platinum-based combination therapy and not indicated for radical resection. Refractory disease included progressive disease/recurrence during initial chemotherapy (including chemoradiation) within 8 weeks after the last dose; within 24 weeks after the last dose (if 2 or more consecutive complete responses were confirmed

during initial chemotherapy); or within 24 weeks after the last dose of neoadjuvant/adjuvant therapy associated with radical resection.

Subjects were required to have an ECOG performance status (PS) of 0-1, a life expectancy of at least 3 months, and age of at least 20 years. Furthermore, subjects were required to have at least 1 measurable or non-measurable lesion per the RECIST 1.1 guideline as confirmed by imaging within 28 days before randomization, and to provide tumor tissue for analysis of programmed death ligand-1 (PD-L1) expression.

Subjects who were refractory or intolerant to taxane therapy, had brain metastases or autoimmune disease, or used systemic corticosteroids or immunosuppressants were excluded. Also, patients were excluded if they were receiving stent therapy in the esophagus or respiratory tract

Study Treatments

- Nivolumab group: nivolumab 240 mg intravenously (IV) over 30 minutes every 2 weeks (Q2W). Each cycle was 6 weeks.
- Control group: Paclitaxel and docetaxel were administered IV for at least 60 minutes.
    - Docetaxel group: docetaxel 75 mg/m^2 Q3W. Each cycle was 3 weeks.
    - Paclitaxel group: paclitaxel 100 mg/m^2 once per week for 6 weeks followed by 1 week off. Each cycle was 7 weeks.

Treatment cycles were repeated until disease progression assessed by the investigator per RECIST version 1.1, or unacceptable toxicity. Patients were permitted to continue treatment beyond initial disease progression in both treatment groups based on the investigators' judgement.

Dose Selection: See Section 6.2.2 for details of Dose Selection and Section 9.4.4 (Selection of Doses in the Study) of the ONO-4538-24/CA209473 Final CSR for details and rationale for nivolumab dose selection.

Dose Modification, Dose Discontinuation: Treatment was interrupted or delayed in case of adverse event occurrence and resumed if protocol-defined criteria for treatment resumption were met. Dose reductions were allowed for paclitaxel and docetaxel for toxicities prespecified in the protocol under dose reduction criteria. Dose reductions were not permitted in the nivolumab group.

Administrative Structure: This study was conducted in accordance with the ethical principles that are consistent with the Good Clinical Practice (GCP) guidelines developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local regulations. This study was conducted in compliance with the protocol. Prior to initiation of the study, the protocol and any amendments, as well as the patient ICF, received approval/a favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC). The Department of Clinical Quality Assurance, Ono Pharmaceutical Co. Ltd., independent of the unit implementing the study, audited the study according to its standard operating procedure for quality assurance of clinical studies.

Table 6: Study Schedule for the Nivolumab Group (ONO-4538-24/CA209473)

Item	Screening phase[1]	Treatment phase									Post-treatment observation period	
		Cycle 1						Cycle ≥2				
Study day		1		8	15	29	43	1	15, 29	43	End (or discontinuation) of the treatment phase[3]	Examination 28 days after the end of treatment phase[2, 3]	Follow-up investigation
		Predose	Postdose										
Allowable window (day/days)	-7 to -1	±0		-3 to +3	-3 to +7	-6 to +7	-6 to +7	±0	-6 to +7	-6 to +7	±3	±7	—
Written informed consent	○[4]												
Demographic data, Eligibility check	○												
Administration of the investigational product[5]		○			○	○		○[6]	○				
Viral tests	○												
Pregnancy testing[7]	○	○						○[8]			○	○	
Performance Status	○			○	○[8]	○[8]	○	○[6, 8]	○[8]	○	○	○	
Vital signs and body weight measurement	○	○[2]	○[9]	○[9]	○[8, 9]	○[8, 9]	○	○[6, 8]	○[8, 9]	○	○	○	
Chest X-ray[10]	○						○			○	○	○	
12-lead ECG	○		○				○	○[8, 11]		○[11]	○	○	
Hematology, biochemistry, and urinalysis	○			○	○[8]	○[8]	○	○[6, 8]		○	○	○	
Immunological and hormone tests[12]	○						○			○	○	○	
Serum drug concentration		○				○[8]		○[8, 13]				○[14]	●[15]
Anti-ONO-4538 antibody		○				○[8]		○[8, 13]				○[14]	●[15]
Exploratory biomarkers[16] (other blood tests)	○						○				○[17]		
Blood cell subset analysis	●						●				●[17]		
Genetic testing (blood)	●												
Tumor tissue examination (PD-L1)	○[18]										●[19]		
Tumor tissue examination (optional)	●												
Imaging (e.g., CT, MRI)[20]	○[21]	○[22]									○	○[23]	○[23]
Tumor markers[24]	As needed												
Concomitant treatment and AE monitoring	←										→		○[23, 25]
Outcome investigation													○[26]
Patient Reported Outcomes / Healthcare Resource Utilization	○						○			○[27]	○		○[27]

○ indicates mandatory items; ● indicates optional items.

Source: Refer to Table 6-1 in the ONO-4538-24/CA209473 Protocol Revision 09 for footnotes.

Table 7: Study Schedule for the Docetaxel Group (ONO-4538-24/CA209473)

Item	Screening phase[1]	Treatment phase							Post-treatment observation period	
		Cycle 1				Cycle ≥2		End (or discontinuation) of the treatment phase[2]	Examination 28 days after the end of treatment phase[2, 3]	Follow-up investigation
Study day		1		8	22	1	22			
		Pre dose	Post dose							
Allowable window (day/days)	-7 to -1	±0		-3 to +3	-6 to +7	±0	-6 to +7	±3	±7	—
Written informed consent	○[4]									
Demographic data, Eligibility check	○									
Administration of the investigational product		○				○[5]				
Serological tests	○									
Pregnancy testing[6]	○	○				○[7]		○	○	
Performance Status	○			○	○	○[5, 7]	○	○	○	
Vital signs and body weight	○	○[2]	○[8]	○[8]	○	○[5, 7]	○	○	○	
Chest X-ray [9]	○				○		○	○	○	
12-lead ECG	○		○		○	○[7, 10]	○[10]	○	○	
Hematology, biochemistry, and urinalysis	○			○	○	○[5, 7]	○	○	○	
Immunological and hormone tests[11]	○				○		○	○	○	
Exploratory biomarkers[12] (other blood tests)	○						○[13]	○[14]		
Blood cell subset analysis	●						●[13]	●[14]		
Genetic testing (blood)	●									
Tumor tissue examination (PD-L1)	○[15]							●[16]		
Tumor tissue examination (optional)	●									
Imaging (e.g., CT, MRI)[17]	○[18]	○[19]						○	○[20]	○[20]
Tumor markers[21]	As needed									
Concomitant treatment and AE monitoring			⟷							○[20, 22]
Outcome investigation										○[23]
Patient Reported Outcomes / Healthcare Resource Utilization	○	○[24]						○		○[24]

○ indicates mandatory items; ● indicates optional items.

Source: Refer to Table 6-2 in the ONO-4538-24/CA209473 Protocol Revision 09 for footnotes.

Table 8: Study Schedule for the Paclitaxel Group (ONO-4538-24/CA209473)

Item	Screening phase[1]	Treatment phase									Follow-up phase	
		Cycle 1						Cycle ≥2			End (or discontinuation) of the treatment phase[2]	Examination 28 days after the end of treatment phase[2, 3]	Follow-up investigation
Study day		1		8	15, 22, 29, 36	43	50	1	8, 15, 22, 29, 36	50			
		Pre dose	Post dose										
Allowable window (day/days)	-7 to -1	±0		-1 to +3	-2 to +3	-2 to +3	-6 to +7	±0	-2 to +3	-6 to +7	±3	±7	—
Written informed consent	○[4]												
Demographic data, Eligibility check	○												
Administration of the investigational product[5]		○		○	○			○[6]	○				
Serological tests	○												
Pregnancy testing[7]	○	○						○[8]			○	○	
Performance Status	○			○[8]			○	○[6, 8]		○	○	○	
Vital signs and body weight	○	○[2]	○[9]	○[8, 9]	○[8, 9, 10]		○	○[6, 8]	○[8, 9, 10]	○	○	○	
Chest X-ray[11]	○						○			○	○	○	
12-lead ECG	○		○				○	○[8, 12]		○[12]	○	○	
Hematology, biochemistry, and urinalysis	○			○[8, 10]	○[8, 10]		○	○[6, 8]	○[8, 10]	○	○	○	
Immunological and hormone tests[13]	○						○			○	○	○	
Exploratory biomarkers[14] (other blood tests)	○					○					○[15]		
Blood cell subset analysis	●					●					●[15]		
Genetic testing (blood)	●												
Tumor tissue examination (PD-L1)	○[16]										●[17]		
Tumor tissue examination (optional)	●												
Imaging (e.g., CT, MRI)[18]	○[19]	○[20]									○	○[21]	○[21]
Tumor markers[22]		As needed											
Concomitant treatment and AE monitoring		←								→			○[21, 23]
Outcome investigation													○[24]
Patient Reported Outcomes / and Healthcare Resource Utilization	○	○[25]									○		○[25]

○ indicates mandatory items; ● indicates optional items.

Source: Refer to Table 6-3 in the ONO-4538-24/CA209473 Protocol Revision 09 for footnotes.

Concurrent Medications: The following treatments were prohibited throughout the study period in the nivolumab and control groups: immunosuppressants and corticosteroids (except topically or temporarily); any antitumor therapies; surgical treatment for malignant tumors; (chemo)radiotherapy; radiopharmaceuticals (except for examination/diagnostic use); bisphosphonates and anti-receptor activator of NF-κB ligand (RANKL) antibody products (could be continued only if there were no changes made to the dosage and mode of administration); and unapproved drugs. For the paclitaxel group only, disulfiram, cyanamide, carmofur, and procarbazide hydrochloride were also prohibited.

Treatment Compliance: Treatment compliance was monitored by drug accountability as well as the subject's medical record and electronic Case Report Form (eCRF).

Subject Completion, Discontinuation, or Withdrawal: Treatment was continued until progressive disease (PD) was assessed by the investigator or subinvestigator according to the RECIST Guideline Version 1.1, as described in Section 9.4.1 (Treatments Administered) of the ONO-4538-24/CA209473 Final CSR. Patients were permitted to continue treatment beyond initial disease progression in both treatment groups based on the investigators' judgement.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the main trial design features, as described above. Additional inclusion criteria not summarized above include adequate organ function and adequate contraception (further specified in the protocol). Additional exclusion criteria not summarized above include peripheral neuropathy Grade ≥2 and patients who had received antineoplastic drugs within 28 days before randomization. In Section 9.4.4 ("Selection of Doses in the Study"), the Applicant provided justification for the nivolumab dose of 240 mg Q2W. Briefly, the dose of 3 mg/kg every 2 weeks was chosen as the clinically recommended dose for treating esophageal cancer based on various studies throughout the world, including in Japan. Based on the safety, efficacy, and PPK data, the 240 mg dose appears to be comparable to the 3 mg/kg dose. Thus, the dose of 240 mg Q2W was selected for this study. Regarding administrative structure, the CSR contains a GCP compliance statement, amended in the addended CSR (see Section 8.1.2 ["Study Results"] below for additional details). Regarding PD-L1 testing, the diagnostic device used for this study was the Agilent/Dako PD-L1 IHC 28-8 pharmDx kit.

FDA additionally notes that the trial was designed to randomize 390 patients in a 1:1 ratio to observe a total of 331 OS events. The assumptions for the sample size were as follows:

- an OS hazard ratio of 1.0 for the first 3 months and 0.65 thereafter, with an average hazard ratio of 0.70
- an exponential distribution for OS in the control group with median OS of 7.2 months and a piecewise mixture model for the nivolumab group with an overall median of 10 months
- long term survival rate of 5% in the nivolumab group
- two-sided significance level of 5%
- 90% power
- 16-month accrual period followed by 18 months' of follow-up.

No formal interim analysis was planned for this study.

Study Endpoints

The Applicant's Description:
The primary endpoint of ONO-4538-24/CA209473 was overall survival (OS). Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), disease control rate (DCR), duration of response, time to response, best overall response (BOR), and maximum percent change from baseline in the sum of diameters of the target lesion. These endpoints are all accepted and well-recognized for oncology trials. For endpoint definitions, refer to Sections 10.5.4.3 and 10.5.5.2 of the ONO-4538-24 (CA209473) Protocol and Sections 9.3 and 10.2 of the ONO-4538-24 (CA209473) Statistical Analysis Plan (Ver 3.0).

The FDA's Assessment:
FDA agrees with Applicant's description of study endpoints. For the list of key secondary endpoints, refer to the section below. Tumor based endpoints are assessed by investigator using RECIST v1.1.

Statistical Analysis Plan and Amendments

The Applicant's Description:
OS and PFS data were compared between the two treatment groups using the stratified log-rank test with the location (Japan vs Rest of the world), the number of organs with metastases (1 organ or less vs 2 organs or more), and PD-L1 expression (≥ 1% vs < 1% or indeterminate) which were the randomization factors from IWRS as the stratification factors. ORR data were compared between the two treatment groups using the Cochran-Mantel-Haenszel (CMH) test with the randomization factors as the stratification factors (IWRS).

The primary endpoint (OS) was analyzed with a two-sided log-rank test stratified by the 3 stratification factors (based on IWRS data) at the 5.0% significance level. If superiority in OS was determined, a hierarchical hypothesis testing approach for the key secondary endpoints was used to preserve a study-wise type I error rate at 5%. The key secondary endpoints were tested in the following hierarchical order, ORR and PFS, respectively.

For more detail on statistical methods, refer to Section 9.7.1 of the ONO-4538-24 (CA209473) Final CSR.

There were 2 SAP amendments during the study. For details about the SAP amendment, refer to Section 9.8.2 of the ONO-4538-24 (CA209473) Final CSR.

The FDA's Assessment:
FDA notes that the Applicant did not provide definitions for the analysis populations that are referred to in later sections of this assessment aid. They are as follows:

- All efficacy analysis are based on intent-to-treat (ITT) population, that consisted of all randomized subjects.

- The Safety Analysis Set (SAF) consisted of all subjects given at least one dose of the investigational product
- The Response Evaluable Set (RES) excluded subjects in the ITT population who met one of the following criteria:
    i. GCP-noncompliant subjects, defined as those who were enrolled on the basis of materials not reviewed by the IRB/IEC, who were enrolled at a medical institution where no study contract had been signed, or who did not provide informed consent appropriately.
    ii. Target lesion measurements were missing at baseline.

The ITT analysis set was used for analyzing the OS and PFS endpoints, and the RES analysis population was used for analyzing ORR.

Protocol Amendments

The Applicant's Description:
There were 10 protocol amendments during the study. The first protocol sent to the IEC/IRB authorities was version 1.0 dated 27-Jul-2015. The changes in methodology described in the amendments have been incorporated into the appropriate sections of the CSR and are summarized below (Table 9). Protocol amendments through Revised Protocol 09 can be found in Appendix 16.1.1 of the ONO-4538-24 (CA209473) Final CSR.

Table 9: Amendments to Study Protocol ONO-4538-24 (BMS-209473)

Document	Date of Issue	Summary of Change
Revised Protocol 11	18-Oct-2019	• Added live/attenuated vaccine as a prohibited therapy during the study period
Revised Protocol 10	05-Apr-2019	• Addition of a protocol ONO-4538 extension phase to allow subjects in the chemotherapy arm to shift to treatment with Nivolumab
Revised Protocol 09	07-Nov-2017	• Due to cancellation of interim analysis, the two-sided significance level for the final analysis was changed, and the roles of the Independent Data Monitoring Committee were updated. • Descriptions which say that appropriate treatment should be performed for prophylactic premedication in the docetaxel group following the recommendations per the local SmPC/Package Insert and treatment guidelines were added.
Revised Protocol 08	12-Jul-2017	• In consideration of the latest results of clinical trial ONO-4538, required events for the interim analysis of OS and two-sided significance levels for the interim analysis and the final analysis were changed. Due to the above change, " Rationale for the Sample Size" was also updated.
Revised Protocol 07	30-Nov-2016	• The description regarding the duration for contraception and the prohibited period of breast feeding in Inclusion Criteria 10 and 11 were updated in accordance with the latest Investigator's Brochure.

Document	Date of Issue	Summary of Change
		• The details of the analytical method for efficacy were specified.
Revised Protocol 06	30-Aug-2016	• Based on the data collected so far, including the data from other studies, the duration of contraception and the prohibited period of breastfeeding were revised.
Revised Protocol 05	09-May-2016	• The definition of the final date of chemoradiation was specified in the Inclusion Criteria. • The rules for the prohibited therapies for the nivolumab group and the control group during the study period were clarified. • The study procedures for viral tests, SP-D and KL-6, Patient Reported Outcomes and Healthcare Resource Utilization were specified in the footnotes of the Study Schedule tables for each investigational product. • A description of post-study access to the investigational product was added. • Study procedures were specified under Items Related to Safety (Sections 8.2.4.1.1, 8.2.4.1.2, 8.2.4.2, 8.2.4.3.1, 8.2.4.3.2, 8.2.4.4, 8.2.4.6, 8.2.8, 8.2.9.1, 8.2.9.2, 8.2.9.3, 8.2.9.4, 8.2.9.5). • Analytical methods were specified in the sections on "Distribution of Patient Background Factors" (10.5.3.1, 10.5.3.2, 10.5.3.3, 10.5.3.4).
Revised Protocol 04	22-Jan-2016	• The study procedure was modified to change the rules for the timing of administration of the investigational product after informed consent was obtained. • As part of the definition of IMAEs, the language "Irrespective of being treated with immunosuppressive medications or not" was added.
Revised Protocol 03	26-Oct-2015	• Since this study is to be conducted in collaboration with the co-development partner Bristol-Myers Squibb (BMS), the BMS IND Number, EUDRACT Number and BMS Protocol Number were added. • The classification of PD-L1 expression was changed from "intensity of expression of PD-L1 (positive vs. negative and indeterminate)" to "expression of PD-L1 (≥1% vs. <1% or indeterminate)". • A definition of adenosquamous cancer was added to Inclusion Criteria 3. • The wording in Exclusion Criteria 30 was changed from "Patients who are contraindicated to docetaxel or paclitaxel" to "Patients who are contraindicated to docetaxel and paclitaxel". • Wording regarding the administration time for nivolumab was changed from "ONO-4538 240 mg will be administered intravenously over at least 30 minutes" to "ONO-4538 240 mg will be administered intravenously over 30 minutes". • The contents of the control to be used in US/EU (DTX/PTX) were clarified in Table 6-1. In addition, the wording in the section "Handling and Supply of Investigational Product" was changed. • The criteria for discontinuation of ONO-4538 (nivolumab) was updated to reflect the latest criteria. • Rules for lost to follow-up and withdrawal of consent were specified. • Regarding the Anti-drug Antibody Set (ADA), detailed descriptions for the appropriate analytical methods and analysis set were added. • Appropriate analytical methods were specified for the following parameters: - OS - Progression-free survival

Document	Date of Issue	Summary of Change
		- Duration of response - Time to response - Best overall response • Wordings for analytical methods for progression-free survival and duration of response were also changed.
Revised Protocol 02	25-Aug-2015	• The following criteria were reconsidered based on the opinions of specialists: - Criteria for laboratory test values in Inclusion Criteria 9 - Exclusion Criteria 1 and 2 - Criteria for administration and dose reduction of docetaxel and paclitaxel • Healthcare Resource Utilization was added to Other Test Variables. Wording was changed due to the addition. • Description in the Introduction was changed in accordance with the latest situation. • The wording of Note #2 in Inclusion Criteria 11 was changed. • Due to a revision of the Investigator's Brochure, sections of "Summary of Non-clinical Data" and "Summary of Clinical Data and Summary of Known and Potential Risks and Benefits to Subject" were changed. • The definition of "other medically important events" was clarified. • "Drug interrupted" and "Dose reduced" were added to actions taken with the investigational product by the investigator/subinvestigator for AEs.
Revised Protocol 01	27-Jul-2015	N/A

Source: Section 9.8.1 of the ONO-4538-24 (BMS-209473) Final CSR.

The FDA's Assessment:

FDA agrees with the Applicant's summary of protocol amendments. Additional key changes are included below:

- In version 07 (issue date 30-Nov-2016), the hierarchical testing procedure for key secondary endpoints in the order of ORR and PFS, and significance level considered for interaction tests were added to the protocol.

- In version 05 (issue date 09-May-2016), the IND number was updated from 127494 to 126406 (Study ONO-4538-24/BMS CA209473 was withdrawn from IND 127494 and submitted to IND 126406).

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

The ONO-4538-24 (CA209473) trial is sponsored and conducted by ONO in collaboration with BMS, according to GCP guidelines developed by the ICH and in compliance with the study protocol and all applicable local regulations. Essential documents were archived according to ICH-GCP. Prior to study

initiation, the protocol and any amendments, as well as the patient informed consent form (ICF), received approval/ a favorable opinion from the IRB/IEC. The ONO-4538-24 (CA209473) CSR was written in accordance with the ICH E3 guidelines.

An incident occurred in (b) (4) which was discovered by the Sponsor after the database lock (DBL) and following the finalization of the ONO-4538-24 (CA209473) Final CSR. (b) (4), which is contracted to execute monitoring activities (b) (4) For more details, refer to BMS's response to FDA pre-sBLA Meeting Comment 5 submitted to IND 126406 on 22-Nov-2019 (Seq 0329).

BMS acknowledges that these actions constitute a GCP non-compliant activity; however, following an internal assessment of the impact of these actions, it has been concluded that neither patient safety nor the interpretation or scientific value of the reported trial results were adversely impacted by this matter. In total, 29 subjects were randomized (b) (4) .

As a result of these actions, additional analyses based on modified ITT populations were performed:

- ITT population excluding 29 subjects randomized (b) (4)
- ITT population excluding 31 subjects randomized (b) (4)

The FDA's Assessment:

Additional information not detailed above include specifics about a SUSAR of allergic shock [anaphylactic shock] occurring in a patient enrolled at (b) (4) that was not reported to the local IRB in a timely manner per protocol. (b) (4) Additional details were provided in the November 22, 2019 (IND 126406), February 5, 2020 (BLA 125554-S81), February 14, 2020 (BLA 125554-S81), February 28, 2020 (BLA 125554-S81), March 16, 2020 (BLA 125554-S81), April 7, 2020 (BLA 125554-S81), and May 4, 2020 (BLA 125554-S81) submissions by the Applicant.

FDA agrees with the Applicant's assessment of the impact of the GCP-non-compliant activity on the final analysis results. FDA reviewed the Applicant's responses and the audit reports related to this issue and also assessed whether excluding results from patients enrolled in the non-GCP-compliant sites would alter the conclusions regarding the safety and effectiveness of nivolumab in this supplemental application; results of a sensitivity analysis excluding data from patients enrolled in the affected sites were consistent with the results based on the inclusion of data from these sites. (b) (4) constitute a material violation of GCP guidelines, the FDA review team concluded that the Applicant, clinical trial sponsor (ONO) and the contract research organization for Study ONO-4538-24 ((b) (4)) took appropriate measures to investigate these violations and mitigate the impact of these violations on human subject protections. Additionally, these violations did not appear to adversely impact patient safety or the efficacy results of the trial. The review team also concluded, in conjunction with the FDA OSI, that the observed violations did not compromise the data integrity of the study at these sites and therefore decided not to exclude the study data obtained from these sites from the overall efficacy analysis.

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 ONO-4538-24 (BMS-209473) clinical study as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators.

The FDA's Assessment:

In accordance with 21 CFR 54, the Applicant submitted information for all 889 Principal Investigators and Subinvestigators who participated in Study CA209-473/ONO-4538-24. Of note, not all investigators/sites ultimately enrolled patients. Of these 889 investigators, 884 investigators did not have financial information to disclose (as documented in sBLA module 1.3.4, Table 1) and five investigators had interests to disclose (as documented in sBLA module 1.3.4, Table 2). Each of these five investigators disclosed that they (or their sites) were going to be receiving speaking honoraria, consulting fees, endowed chair fees, or lecture fees valued between $28,000 and $140,000 annually during the time period of this study and continuing through the year after the study was conducted. These five investigators randomized between (b) (4) and (b) (4) patients each at their respective sites. Upon review of the information provided about these five investigators and in the context of this study that randomized 419 patients and had a primary endpoint of overall survival, FDA concluded that these disclosed financial interests are not likely to have had a material impact on the conduct of Study ONO-4538-24 and conclusions derived from this clinical study.

Patient Disposition

Data:

Table 10: Subject Disposition - ONO-4538-24 (CA209473)

Subjects enrolled	590	
Subjects randomized (%)	419 (71.0%)	
Non-randomized subjects (%)	171 (29.0%)	
Subjects treated	417 (70.7%)	
Subjects treated - nivolumab	209	
Subjects treated - control group	208	
Subjects randomized and not treated	2	
	Nivolumab N = 209	**Control N = 208**
Subjects continuing in the treatment period (%)	16 (7.7%)	3 (1.4%)
Subjects not continuing in the treatment period (%)	193 (92.3%)	205 (98.6%)
Reason for not continuing in the treatment period due to disease progression according to the RECIST Guideline Version 1.1 (%)	133 (63.6%)	137 (65.9%)
Subjects continuing to be followed/N ITT (%)	46/210 (21.9%)	31/209 (14.8%)

Abbreviation: ITT=intention-to-treat; RECIST=Response Evaluation Criteria in Solid Tumors
Note: The numbers do not always add up to the total because some subjects had more than one reason for exclusion from randomization or for discontinuation from treatment.
Source: Table 3.1.1-1 of the Summary of Clinical Efficacy (Module 2.7.3); ADaM dataset: ADSL.xpt, ADTTE.xpt

The Applicant's Position:

The enrollment period lasted approximately 18 months (Dec-2015 to May-2017). The data cut-off date for the ONO-4538-24 (CA209473) Final CSR was 12-Nov-2018 and the database was locked on 28-Dec-2018. The last patient's first treatment (LPFT) occurred on 03-May-2017. The minimum follow-up (time from randomization of the last patient to data cut-off) was 17.6 months.

There were a total of 90 study sites in 8 countries (Japan, Korea, Taiwan, UK, US, Germany, Italy, and Denmark). 417 subjects (209 subjects in the nivolumab group and 208 subjects in the control group [Table 10] [65 docetaxel; 143 paclitaxel]) received at least 1 dose of the study treatment. Per IWRS and eCRF, 64.8% (136/210) and 66.0% (138/209) of subjects randomized to the nivolumab and control groups, respectively, were located in Japan, and 35.2% (74/210) and 34.0% (71/209) of randomized subjects in the nivolumab and control groups, respectively, were located in Rest of World. Of all randomized subjects, 4.3% (18/419) were non-Asian and from Western countries, and were equally distributed between the nivolumab and control groups.

The FDA's Assessment:

FDA agrees with Applicant's patient disposition results provided above.

Protocol Violations/Deviations

Data:

Table 11: Relevant Protocol Deviations

Analysis Set: ITT	Nivolumab	Control group		
		Total	Docetaxel	Paclitaxel
N:	210	209	65	144
Subjects with at least one deviation	2 (1.0)	0	0	0
Eligibility				
Subjects who failed to fulfill inclusion criteria #3	0	0	0	0
Subjects who failed to fulfill inclusion criteria #4	1 (0.5)	0	0	0
Subjects who failed to fulfill inclusion criteria #6	0	0	0	0
On-study				
Subjects receiving any concurrent anti-cancer therapy (ie, chemotherapy,hormonal therapy, immunotherapy, surgery, or radiation therapy) while on study therapy	1 (0.5)	0	0	0
Subjects treated differently as randomized (ie, subjects who received the wrong treatment excluding the never treated)	0	0	0	0

Source: Table 14.1.1-1 of the ONO-4538-24 (BMS CA209473) Final CSR; ADaM dataset: ADSL.xpt

The Applicant's Position:

As of the data cut-off date for this CSR, at least 1 relevant deviation from the protocol was reported in 1.0% (2 subjects) in the nivolumab group and 0% (0 subject) in the control group (Table 11). Two additional protocol deviations were reported for 2 subjects while on study treatment. These protocol deviations were added to Appendix 16.2.2 (List_0005) of the ONO-4538-25 (CA209473) Final CSR:

- 1 deviation for a subject receiving prohibited concomitant medication which was not reported but the CRA indicated as completed on the MVR
- Failure to report all SAEs in accordance with the time required by GCP, the protocol, BMS and applicable regulation for 1 subject with an SAE of diabetic ketoacidosis (nivolumab group; expected; Grade 4; related; date of onset: 11-Apr-2017)

The FDA's Assessment:

The Applicant reported two patients as having relevant protocol deviations, both in the nivolumab arm. One of these events was a patient who did not fulfill inclusion criteria #4 ["If a CR (≥2 consecutive CRs confirmed by imaging after an interval of ≥4 weeks) was assessed as a result of the initial chemotherapy (including chemoradiation), patients whose recurrence was confirmed by imaging during the initial chemotherapy (including chemoradiation) or within 24 weeks after the last dose#1 of chemotherapy were determined to be "Refractory"] in that this patient did not have a second radiological (CT) confirmation of his/her complete response after initial chemotherapy. The second event was a patient who received a concurrent off-label (anti-cancer) therapy by receiving an intravitreal injection of Avastin for ocular metastasis.

Regarding the additional two protocol deviations discussed by the Applicant in the bulleted list, above, the patient described in the second bullet does not appear to be listed in Appendix 16.2.2 but was the subject of an FDA clinical information request (IR) and subsequent BMS response on March 16, 2020.

Protocol deviations listed in Appendix 16.2.2 as "relevant" but not included in the Applicant's Table 11, above, include events of:

- several instances of patients initiating a bisphosphonate to treat hypercalcemia (initiation of or dose changes to baseline bisphosphonate use was not allowed per protocol)
- certain screening labs (e.g. HIV testing) not performed prior to first treatment
- enrollment of a patient with Grade 2 peripheral neuropathy at baseline (baseline neuropathy was supposed to be Grade 0-1 per protocol)
- enrollment of a patient with baseline hemoglobin of 8.5 (supposed to be 9 or higher per protocol)
- certain labs and ECGs not being performed due to patient consent issues (i.e. patients in Denmark did not consent to genetic testing)
- a dose reduction of docetaxel to 75 mg/m^2 instead of the protocol-mandated 60 mg/m^2
- reportable events being reported outside the allowed reporting window

Regardless, however, because of the nature of these protocol deviations, they are unlikely to have had an impact on the observed efficacy outcomes or assessment of the safety of nivolumab for the proposed indication.

Table of Demographic Characteristics

Data:

Table 12: Key Demographic Characteristics - All Randomized Subjects (ITT) - ONO-4538-24 (CA209473)

Parameters	Nivolumab Group (N=210) n (%)	Control Chemotherapy Group			Total (N=419) n (%)
		Total (N=209) n (%)	Docetaxel (N=65) n (%)	Paclitaxel (N=144) n (%)	
Sex					
Male	179 (85.2)	185 (88.5)	56 (86.2)	129 (89.6)	364 (86.9)
Female	31 (14.8)	24 (11.5)	9 (13.8)	15 (10.4)	55 (13.1)
Age					
Mean (SD) (years)	62.8 (8.90)	64.9 (9.33)	65.5 (8.61)	64.6 (9.65)	63.8 (9.17)
Median (min, max) (years)	64.0 (37, 82)	67.0 (33, 87)	67.0 (48, 81)	67.0 (33, 87)	65.0 (33, 87)
Age Group					
< 65 years	112 (53.3)	85 (40.7)	21 (32.3)	64 (44.4)	197 (47.0)
≥ 65 years	98 (46.7)	124 (59.3)	44 (67.7)	80 (55.6)	222 (53.0)
≥ 75 years	14 (6.7)	28 (13.4)	7 (10.8)	21 (14.6)	42 (10.0)
Race					
White	9 (4.3)	9 (4.3)	4 (6.2)	5 (3.5)	18 (4.3)
Asian	201 (95.7)	200 (95.7)	61 (93.8)	139 (96.5)	401 (95.7)
Ethnicity					
Hispanic or Latino	0	3 (1.4)	0	3 (2.1)	3 (0.7)
Not Hispanic or Latino	210 (100.0)	205 (98.1)	65 (100.0)	140 (97.2)	415 (99.1)
Not reported	0	1 (0.5)	0	1 (0.7)	1 (0.2)

Parameters	Nivolumab Group (N=210) n (%)	Control Chemotherapy Group			Total (N=419) n (%)
		Total (N=209) n (%)	Docetaxel (N=65) n (%)	Paclitaxel (N=144) n (%)	
Geographic Region (ECRF Source)					
Japan	136 (64.8)	138 (66.0)	44 (67.7)	94 (65.3)	274 (65.4)
Rest of the World	74 (35.2)	71 (34.0)	21 (32.3)	50 (34.7)	145 (34.6)
Body Mass Index					
Median (min, max) (kg/m^2)	19.49 (13.1, 27.9)	20.21 (12.9, 32.9)	20.22 (12.9, 30.9)	20.20 (13.9, 32.9)	19.93 (12.9, 32.9)

Source: Table 2 of Appendix 1 of the Summary of Clinical Efficacy (SCE) (Module 2.7.3); ADaM dataset: SCS ADSL.xpt, ADAE.xpt

The Applicant's Position:

The distribution of demographic characteristics in ONO-4538-24 (CA209473) reflects the general population of patients with advanced ESCC. The majority of enrolled subjects were Asian and male (Table 12). Among all randomized subjects, demographics were generally well balanced between the treatment groups, and any differences did not appear to unilaterally favor one group versus the other. Although the chemotherapy group had a higher percentage of subjects older than 65 years, an OS subgroup analysis (Figure 4) suggested benefit with nivolumab irrespective of age group (<65 and ≥65). Also refer to Section 11.4.2.1 and Table 11.4-10 in the ONO-4538-24 (CA209473) Final CSR for results of a baseline factor interaction analysis.

The FDA's Assessment:

FDA agrees with Applicant's results and position provided above.

The exploratory subgroup analysis for older patients are discussed later in the review.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 13: Key Baseline Characteristics - All Randomized Subjects (ITT) -ONO-4538-24 (CA209473)

	Nivolumab N = 210	Control			Total N = 419
		Total N = 209	Docetaxel N = 65	Paclitaxel N = 144	
Time from the date of diagnosis of the primary disease to randomization (Months)					
≤12.0	170 (81.0)	174 (83.3)	60 (92.3)	114 (79.2)	344 (82.1)
>12.0 - 24.0	29 (13.8)	31 (14.8)	5 (7.7)	26 (18.1)	60 (14.3)
>24.0	11 (5.2)	4 (1.9)	0	4 (2.8)	15 (3.6)
Mean (SD)	8.70 (12.20)	7.28 (5.70)	6.27 (4.50)	7.73 (6.13)	7.99 (9.54)
Median	6.31	5.65	5.36	5.78	6.01
Min - Max	0.1 - 150.2	0.1 - 38.7	0.7 - 23.1	0.1 - 38.7	0.1 - 150.2
Lesion site (TNM classification)					
Cervical Esophagus	5 (2.4)	7 (3.3)	3 (4.6)	4 (2.8)	12 (2.9)
Thoracic Esophagus	84 (40.0)	93 (44.5)	30 (46.2)	63 (43.8)	177 (42.2)
Upper Thorax	20 (9.5)	24 (11.5)	10 (15.4)	14 (9.7)	44 (10.5)

	Nivolumab N = 210	Control			Total N = 419
		Total N = 209	Docetaxel N = 65	Paclitaxel N = 144	
Middle Thorax	43 (20.5)	54 (25.8)	14 (21.5)	40 (27.8)	97 (23.2)
Lower Thorax	34 (16.2)	34 (16.3)	10 (15.4)	24 (16.7)	68 (16.2)
Cervical Esophagus and Thoracic Esophagus	3 (1.4)	7 (3.3)	1 (1.5)	6 (4.2)	10 (2.4)
Unknown	118 (56.2)	102 (48.8)	31 (47.7)	71 (49.3)	220 (52.5)
Recurrent					
No	107 (51.0)	120 (57.4)	34 (52.3)	86 (59.7)	227 (54.2)
Yes	103 (49.0)	89 (42.6)	31 (47.7)	58 (40.3)	192 (45.8)
Disease stage (TNM classification)[a]					
I-III	11 (5.2)	18 (8.6)	7 (10.8)	11 (7.6)	29 (6.9)
IV	172 (81.9)	168 (80.4)	49 (75.4)	119 (82.6)	340 (81.1)
Unknown	27 (12.9)	23 (11.0)	9 (13.8)	14 (9.7)	50 (11.9)
Number of organs with metastases (IWRS source)					
≤1	89 (42.4)	91 (43.5)	30 (46.2)	61 (42.4)	180 (43.0)
≥2	121 (57.6)	118 (56.5)	35 (53.8)	83 (57.6)	239 (57.0)
PD-L1 expression (CRF results)[b]					
<1%	109 (51.9)	107 (51.2)	30 (46.2)	77 (53.5)	216 (51.6)
≥1%	101 (48.1)	102 (48.8)	35 (53.8)	67 (46.5)	203 (48.4)
<5%	136 (64.8)	137 (65.6)	41 (63.1)	96 (66.7)	273 (65.2)
≥5%	74 (35.2)	72 (34.4)	24 (36.9)	48 (33.3)	146 (34.8)
<10%	146 (69.5)	152 (72.7)	47 (72.3)	105 (72.9)	298 (71.1)
≥10%	64 (30.5)	57 (27.3)	18 (27.7)	39 (27.1)	121 (28.9)
Not Quantifiable	0	0	0	0	0

Abbreviations: CRF=case report form; ECOG=Eastern Cooperative Oncology Group; IWRS=interactive web response system; SD=standard deviation; PD-L1=programmed death ligand 1; TNM=tumor node metastasis.

a Summarized for subjects at randomization

b Note: CRF results=test results. A discrepancy in the tumor cell PD-L1 expression results between IWRS and the CRF results was observed due to 1 subject who was randomized in absence of PD-L1 test results. There was a delay in processing the sample and reporting the test results by the central lab; therefore, the subject was randomized as 'indeterminate' (which is grouped along with PD-L1 <1%) and assigned to the control group. The PD-L1 test result, which was received after the randomization, suggested that the subject had tumor cell PD L1 expression level ≥ 1%, and subsequently had data entered in the CRF.

Source: Table 3.1.2-1 of the Summary of Clinical Efficacy (Module 2.7.3); ADaM dataset: SCS ADSL.xpt, ADAE.xpt

The Applicant's Position:

The distribution of baseline disease characteristics in ONO-4538-24 (CA209473) reflects the general population of patients with advanced ESCC. Among all randomized subjects, baseline disease characteristics were generally well balanced between the treatment groups with the following exceptions, which nevertheless do not appear to unilaterally favor one group versus the other: median time from diagnosis to randomization, previous surgery, previous radiotherapy, R0 resection, and recurrent disease. A higher proportion of subjects in the nivolumab group had previous tumor surgery (52.9% in nivolumab vs 45.0% in control), previous radiotherapy (72.9% vs 67.9%), R0 resection (93.2% vs 84.3%), and recurrent disease (49.0% vs 42.6%) than in the control group. The median time from diagnosis to randomization was longer in the nivolumab group (6.31 months) than in the control group (5.65 months) (see Table 13).

The FDA's Assessment:

FDA agrees with Applicant's results and position provided above. Additional baseline characteristics are presented below.

Table 14: Additional Baseline Characteristics - All Randomized Subjects (ITT) in Study ONO-4538-24 (CA209473) (FDA analysis)

	Trial Arm			
		Chemotherapy Control		
	Nivolumab (n=210)	Chemotherapy Pooled (n=209)	Docetaxel (n=65)	Paclitaxel (n=144)
Histological classification				
Squamous cell carcinoma	210 (100)	209 (100)	65 (100)	144 (100)
ECOG status				
0	101 (48.10)	107 (51.20)	38 (58.46)	69 (47.92)
1	109 (51.90)	102 (48.80)	27 (41.54)	75 (52.08)
Cancer stage				
IB	1 (0.48)	0	0	0
IIA	1 (0.48)	4 (1.91)	1 (1.54)	3 (2.08)
IIB	1 (0.48)	1 (0.48)	1 (1.54)	0
IIIA	4 (1.90)	7 (3.35)	4 (6.15)	3 (2.08)
IIIB	1 (0.48)	2 (0.96)	0	2 (1.39)
IIIC	3 (1.43)	4 (1.91)	1 (1.54)	3 (2.08)
IV	172 (81.90)	168 (80.38)	49 (75.38)	119 (82.64)
Unknown	27 (12.86)	23 (11.0)	9 (13.85)	14 (9.72)
Previous therapies				
Surgery	111 (52.86)	94 (44.98)	29 (44.62)	65 (45.14)
Radiotherapy	153 (72.86)	142 (67.94)	46 (70.77)	96 (66.67)
Any chemotherapy	210 (100)	209 (100)	65 (100)	144 (100)
Fluoropyrimidine chemotherapy	210 (100)	209 (100)	65 (100)	144 (100)

	Trial Arm			
	Nivolumab (n=210)	Chemotherapy Control		
		Chemotherapy Pooled (n=209)	Docetaxel (n=65)	Paclitaxel (n=144)
Platinum chemotherapy	208 (99.05)	209 (100)	65 (100)	144 (100)
Residual tumor[1]				
Had R0 resection	96 (45.71)	75 (35.89)	24 (36.92)	51 (35.42)
Unknown	1 (0.48)	3 (1.44)	1 (1.54)	2 (1.39)
History of Alcohol				
Current	60 (28.57)	40 (19.14)	13 (20.0)	27 (18.75)
Former	135 (64.29)	147 (70.33)	44 (67.69)	103 (71.53)
Never	15 (7.14)	22 (10.53)	8 (12.31)	14 (9.72)
History of Smoking				
Current	21 (10.0)	30 (14.35)	10 (15.38)	20 (13.89)
Former	159 (75.71)	147 (70.33)	48 (73.85)	99 (68.75)
Never	30 (14.29)	32 (15.31)	7 (10.77)	25 (17.36)

1 - Dataset only reported R0 and "unknown" resection status.
Source: ADaM dataset from Module 5.3.5.1 - adsl.xpt, adcm.xpt

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Measurements of Treatment Compliance: Study drugs were administered intravenously by trained medical personnel at each study site. Treatment compliance was monitored by routine monitoring of clinical course documentation and drug accountability and by the subject's medical record and eCRF. The start date, start and end time of infusion, and total dose (mg) infused were recorded on the eCRF.

Concomitant Medications: Immune-modulating medications (IMMs) were used for management of AEs in 40.2% (84 subjects) in the nivolumab group, 72.3% (47 subjects) in the docetaxel group, and 44.8% (64 subjects) in the paclitaxel group. The most common type of IMM used in the nivolumab group was systemic hormonal preparations excluding sex hormones and insulins (23.9%), followed by dermatologicals (22.0%). The most common type of IMM used in the docetaxel group was antineoplastic and immunomodulating agents (56.9%), followed by dermatologicals (20.0%). The most common type of IMM used in the paclitaxel group was dermatologicals (21.7%), followed by systemic hormonal preparations excluding sex hormones and insulins (17.5%).

Subsequent Anti-Cancer Therapy: Any subsequent anti-cancer therapy was given to 56.7% (119 subjects) in the nivolumab group and 55.0% (115 subjects) in the control group (docetaxel group: 55.4% [36 subjects]; paclitaxel group: 54.9% [79 subjects]). Subsequent systemic therapy (pharmacotherapy) was given to 53.3% (112 subjects) in the nivolumab group and 47.4% (99 subjects) in the control group (docetaxel group: 52.3% [34 subjects]; paclitaxel group: 45.1% [65 subjects]): taxanes to 47.6% (100 subjects) in the nivolumab group and 20.6% (43 subjects) in the control group; fluoropyrimidine-based chemotherapy to 11.4% (24 subjects) in the nivolumab group and 18.7% (39 subjects) in the control group; platinum-based chemotherapy to 9.5% (20 subjects) of the nivolumab group and 10.5% (22 subjects) in the control group; and immunotherapy to 0.5% (1 subject) in the nivolumab group and 6.2% (13 subjects) in the control group.

The FDA's Assessment:

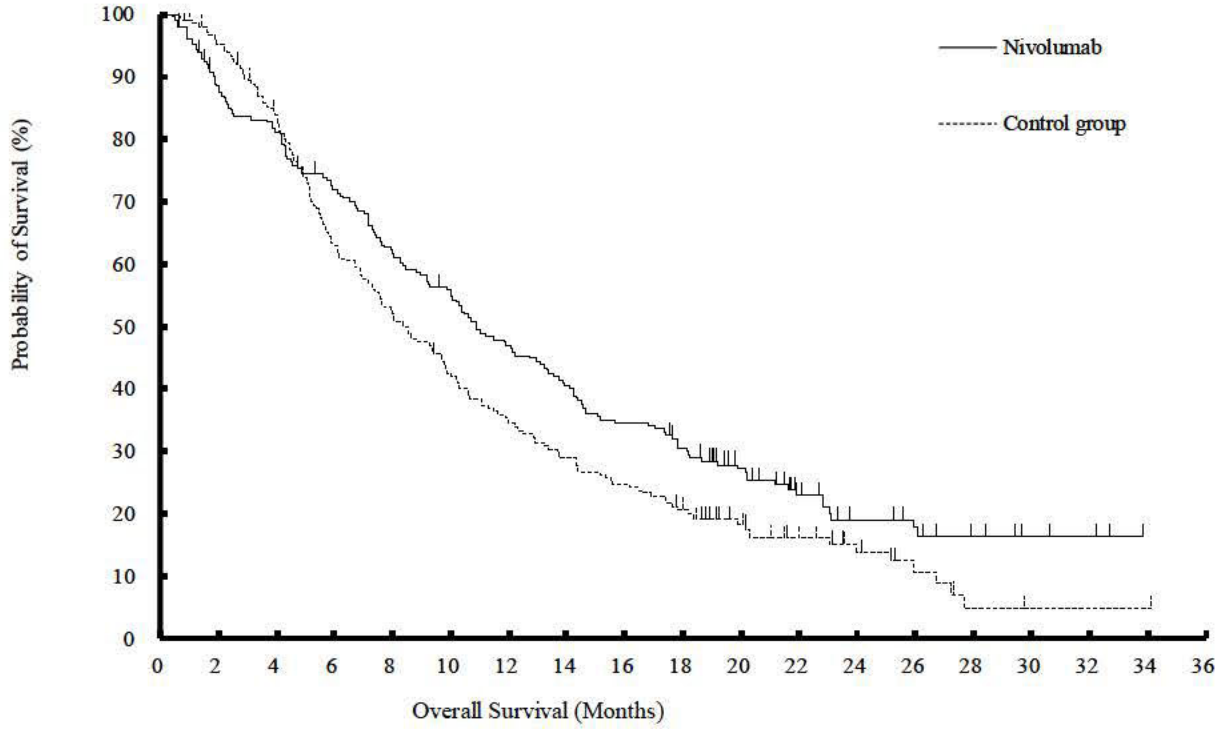
FDA agrees with the information presented above by the Applicant. The nivolumab arm and the control arm were generally balanced with regard to baseline characteristics but there were differences noted including a lower percentage of ECOG performance status 0 patients in the nivolumab arm compared to the control arm (48.1% compared to 51.2%) which could favor the control arm and a higher percentage of patients who underwent an R0 resection in the nivolumab arm compared to the control arm (45.7% compared to 35.9%) which could favor the nivolumab arm. Overall, these differences were not felt to impact the overall conclusions of this study. Regarding subsequent anticancer therapy, a little more than half of all patients received subsequent anti-cancer therapy, including approximately 6% of patients in the control arm who received nivolumab after discontinuing taxane chemotherapy due to disease progression.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

APPEARS THIS WAY ON ORIGINAL

Data:

Figure 2: Kaplan-Meier Plot of Overall Survival (Nivolumab vs Control) - All Randomized Subjects (ITT)

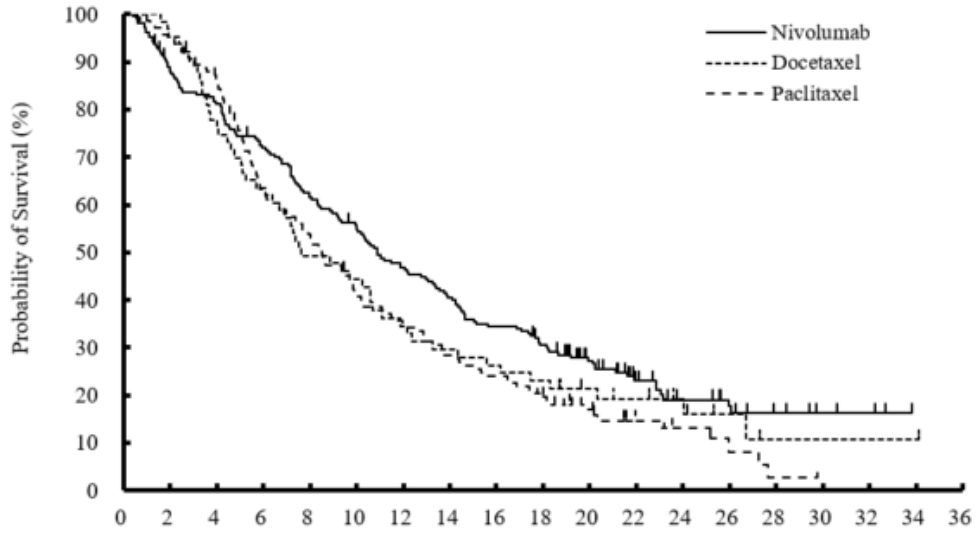


Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
Control group	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

Source: Figure 11.4-1 of the ONO-4538-24 (CA209473) Final CSR; ADaM dataset: ADSL.xpt, ADTTE.xpt

Figure 3: Kaplan-Meier Plot of Overall Survival (Nivolumab vs Docetaxel and Paclitaxel) - All Randomized Subjects (ITT)



At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
Docetaxel	65	61	49	40	31	27	21	18	16	14	10	8	6	3	1	1	1	1	0
Paclitaxel	144	135	120	86	74	57	47	39	33	26	17	9	6	3	1	0	0	0	0

Source: Figure 14.2.1.1-2 of the ONO-4538-24 (CA209473) Final CSR; ADaM dataset: ADSL.xpt, ADTTE.xpt

Table 15: Overall Survival - All Randomized Subjects and Western Subjects

Efficacy Parameter	All Subjects (ITT Population)				Western Subjects	
	Nivolumab	Control			Nivolumab	Control (Total)
		Total	Docetaxel	Paclitaxel		
N	**210**	**209**	**65**	**144**	**9**	**9**
Overall Survival (OS)						
Events, n (%)	160 (76.2)	173 (82.8)	52 (80.0)	121 (84.0)	7 (77.8)	8 (88.9)
Median, months	10.91	8.38	7.62	8.51	6.21	6.11
95% CI[a]	(9.23, 13.34)	(7.20, 9.86)	(6.11, 10.68)	(6.87, 9.89)	(1.41, 20.14)	(2.60, 13.24)
HR (95% CI)[b]		0.77 (0.62, 0.96)	0.78 (0.56, 1.07)	0.76 (0.60, 0.97)	0.53 (0.17, 1.65)	
p-value[c]		p=0.0189*	--	--	--	

[a] This estimation was conducted by using the Kaplan-Meier method.

[b] HR and the corresponding two-sided 95% CI for the nivolumab group relative to the each column group was calculated using the stratified Cox proportional-hazards model adjusted by the 3 stratification factors as mentioned in footnote 'c'. For western subjects column, hazard ratio and the corresponding two-sided 95% CI for the nivolumab group relative to each column group was calculated by using the unstratified Cox proportional-hazards model.

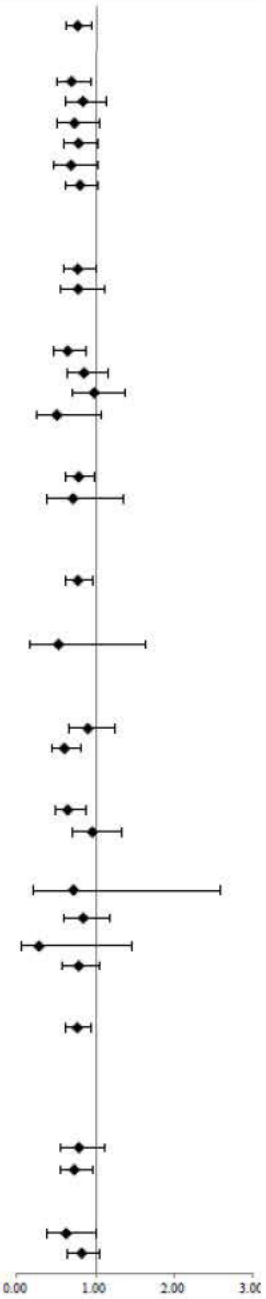
[c] Nivolumab group and total of control group were used for the calculation of p-value. The calculation of p-value was conducted by using the two-sided stratified log-rank test adjusted by the following 3 factors (IWRS source): 1) location (Japan vs Rest of World); 2) the number of organs with metastases (≤ 1 vs ≥ 2); 3) PD-L1 expression (≥ 1% vs < 1% or indeterminate)

*: p<0.05; N.S.: p>=0.05

Source: Table 14.2.1-1 of ONO-4538-24 (CA209473) Final CSR; Table 3.1.5-1 of the SCE; ; ADaM dataset: ADSL.xpt, ADTTE.xpt

Figure 4: Forest Plot of Subgroup Analyses for Overall Survival - All Randomized Subjects (ITT)

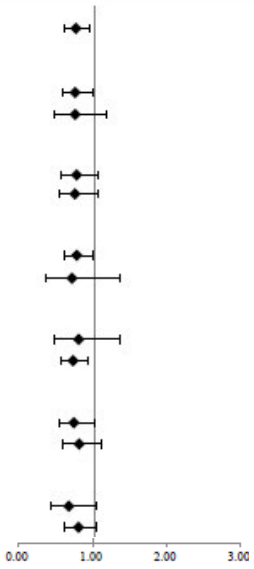
	N	Nivolumab		Control group		Hazard Ratio*) (95% CI)
		N of Events (N of subjects)	median(95% CI)	N of Events (N of subjects)	median(95% CI)	
ALL	419	160(210)	10.91 [9.23, 13.34]	173(209)	8.38 [7.20, 9.86]	0.77 [0.62, 0.95]
PD-L1 Expression (eCRF)						
>=1%	203	77(101)	10.91 [7.98, 14.23]	89(102)	8.05 [5.98, 9.86]	0.69 [0.51, 0.94]
<1%	216	83(109)	10.91 [8.38, 13.90]	84(107)	9.33 [7.20, 11.96]	0.84 [0.62, 1.14]
>=5%	146	56(74)	10.74 [7.33, 13.86]	61(72)	7.62 [5.68, 10.18]	0.73 [0.51, 1.06]
<5%	273	104(136)	11.04 [8.94, 14.09]	112(137)	9.33 [7.29, 10.32]	0.78 [0.60, 1.03]
>=10%	121	48(64)	11.50 [7.59, 14.23]	48(57)	7.62 [5.45, 10.25]	0.69 [0.46, 1.04]
<10%	298	112(146)	10.87 [8.84, 13.73]	125(152)	8.64 [7.29, 10.32]	0.80 [0.62, 1.04]
Not Quantifiable	0	-	-	-	-	-
Location (IWRS)						
Japan	274	101(136)	13.40 [10.35, 15.05]	109(138)	9.36 [7.39, 10.58]	0.77 [0.59, 1.01]
Rest of world	145	59(74)	8.31 [6.08, 10.87]	64(71)	7.29 [5.22, 10.18]	0.78 [0.55, 1.12]
Age						
<65	197	86(112)	10.74 [8.84, 13.40]	73(85)	8.08 [6.11, 10.02]	0.65 [0.47, 0.89]
>=65	222	74(98)	11.86 [7.39, 14.09]	100(124)	8.54 [6.70, 10.58]	0.86 [0.63, 1.16]
65 - <75	180	64(84)	11.17 [7.20, 14.23]	74(96)	9.86 [7.00, 12.85]	0.99 [0.71, 1.38]
>=75	42	10(14)	11.89 [4.27, 18.14]	26(28)	5.88 [4.60, 9.36]	0.51 [0.25, 1.07]
Sex						
Male	364	139(179)	10.74 [8.84, 13.24]	156(185)	8.08 [6.93, 9.86]	0.79 [0.63, 0.99]
Female	55	21(31)	14.09 [8.31, 17.81]	17(24)	9.36 [5.06, 13.24]	0.72 [0.38, 1.36]
Race						
American Indian or Alaska Native	0	-	-	-	-	-
Asian	401	153(201)	10.91 [9.33, 13.34]	165(200)	8.54 [7.29, 10.02]	0.78 [0.62, 0.97]
Black or African American	0	-	-	-	-	-
Native Hawaiian or Other Pacific Islander	0	-	-	-	-	-
White	18	7(9)	6.21 [1.41, 20.14]	8(9)	6.11 [2.60, 13.24]	0.53 [0.17, 1.65]
Other	0	-	-	-	-	-
ECOG Performance Status score at baseline						
0	208	73(101)	13.57 [10.38, 16.85]	81(107)	11.30 [8.64, 13.73]	0.90 [0.66, 1.24]
1	211	87(109)	9.20 [6.67, 11.50]	92(102)	6.11 [5.16, 7.92]	0.61 [0.45, 0.82]
Recurrent						
No	227	79(107)	10.35 [8.08, 14.23]	103(120)	7.36 [5.85, 8.54]	0.65 [0.48, 0.87]
Yes	192	81(103)	11.50 [9.20, 13.73]	70(89)	10.68 [8.38, 13.40]	0.96 [0.70, 1.32]
Lesion sites (TNM classification)						
Cervical Esophagus	12	4(5)	9.99 [5.95, N.A.]	6(7)	7.52 [1.15, 12.19]	0.72 [0.20, 2.59]
Thoracic Esophagus (Upper Thorax, Middle Thorax, Lower Thorax)	177	65(84)	8.48 [7.16, 10.91]	78(93)	7.36 [5.75, 9.79]	0.84 [0.61, 1.18]
Cervical Esophagus and Thoracic Esophagus	10	2(3)	10.87 [10.51, N.A.]	6(7)	5.54 [3.29, 15.51]	0.28 [0.05, 1.47]
Unknown	220	89(118)	13.34 [10.38, 14.65]	83(102)	9.86 [7.66, 11.99]	0.79 [0.58, 1.06]
Histological classification						
Squamous Cell Carcinoma	419	160(210)	10.91 [9.23, 13.34]	173(209)	8.38 [7.20, 9.86]	0.77 [0.62, 0.95]
Adenosquamous Cell Carcinoma	0	-	-	-	-	-
Other	0	-	-	-	-	-
Unknown	0	-	-	-	-	-
Number of organs with metastases (IWRS)						
<=1	180	63(89)	14.59 [11.17, 18.66]	67(91)	11.96 [9.89, 15.18]	0.79 [0.56, 1.12]
>=2	239	97(121)	8.84 [7.16, 10.74]	106(118)	5.78 [5.16, 7.39]	0.73 [0.55, 0.97]
Lymph Node metastasis						
No	97	33(51)	17.05 [9.17, 20.14]	36(46)	10.68 [7.56, 14.36]	0.63 [0.39, 1.01]
Yes	322	127(159)	10.35 [8.31, 12.06]	137(163)	7.92 [6.18, 9.69]	0.83 [0.65, 1.05]



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.

Figure 3: Forest Plot of Subgroup Analyses for Overall Survival - All Randomized Subjects (ITT)

	N	Nivolumab N of Events (N of subjects)	Nivolumab median(95% CI)	Control group N of Events (N of subjects)	Control group median(95% CI)	Hazard Ratio[a] (95% CI)
ALL	419	160(210)	10.91 [9.23, 13.34]	173(209)	8.38 [7.20, 9.86]	0.77 [0.62, 0.95]
Liver metastasis						
No	308	114(153)	13.08 [10.74, 14.59]	126(155)	9.89 [8.51, 11.47]	0.76 [0.59, 0.98]
Yes	111	46(57)	5.65 [3.88, 9.17]	47(54)	5.13 [4.24, 6.70]	0.76 [0.50, 1.15]
Lung metastasis						
No	229	87(112)	10.58 [8.31, 13.40]	95(117)	8.34 [6.87, 9.89]	0.78 [0.58, 1.04]
Yes	190	73(98)	11.86 [8.38, 14.65]	78(92)	8.51 [6.14, 11.10]	0.76 [0.55, 1.04]
Bone metastasis						
No	371	141(187)	11.04 [9.92, 13.57]	151(184)	9.36 [7.52, 10.32]	0.78 [0.62, 0.98]
Yes	48	19(23)	7.33 [4.34, 14.09]	22(25)	5.13 [3.91, 7.92]	0.72 [0.38, 1.33]
Target lesion						
No	88	26(38)	11.56 [7.95, 21.13]	36(50)	11.99 [7.56, 16.16]	0.80 [0.48, 1.34]
Yes	331	134(172)	10.87 [8.84, 13.24]	137(159)	7.69 [6.18, 9.40]	0.73 [0.57, 0.93]
Past treatments for cancer (surgery)						
No	214	72(99)	10.22 [7.39, 12.22]	96(115)	7.52 [5.85, 9.69]	0.74 [0.55, 1.01]
Yes	205	88(111)	12.75 [9.23, 14.49]	77(94)	9.69 [7.56, 11.60]	0.81 [0.59, 1.10]
Past treatments for cancer (radiotherapy)						
No	124	40(57)	11.50 [9.23, 17.45]	52(67)	7.20 [5.75, 9.69]	0.68 [0.45, 1.03]
Yes	295	120(153)	10.74 [8.31, 13.24]	121(142)	9.33 [7.39, 10.68]	0.80 [0.62, 1.04]



a) Hazards ratio was estimated by using unstratified Cox proportional hazards model
Note: PD-L1 Expression (test results) refers to CRF results
Source: Figure 11.4-8 and Figure 11.4-9 of the ONO-4538-24 (CA209473) Final CSR; ADaM dataset: ADSL.xpt, ADTTE.xpt

Table 16: Overall Survival Rate at Selected Landmark Times - All Randomized Subjects (ITT)

Survival Rate % (95% CI)	**Nivolumab (N=210)**	**Control**		
		Total (N=209)	**Docetaxel (N=65)**	**Paclitaxel (N=144)**
6 months	71.9 (65.3, 77.5)	63.0 (55.9, 69.2)	63.6 (50.5, 74.1)	62.6 (54.0, 70.1)
12 months	46.9 (39.9, 53.5)	34.4 (27.8, 40.9)	34.6 (23.1, 46.3)	34.2 (26.4, 42.1)
18 months	30.5 (24.4, 36.9)	20.7 (15.4, 26.6)	23.0 (13.5, 34.1)	19.6 (13.5, 26.7)
24 months	19.1 (13.3, 25.6)	15.1 (10.3, 20.9)	19.3 (10.4, 30.1)	13.1 (7.5, 20.1)
30 months	16.3 (10.6, 23.2)	4.8 (1.2, 12.1)	10.7 (2.9, 24.3)	NA (NA, NA)

The estimation was derived from the Kaplan-Meier estimate and corresponding CI was derived based on Greenwood formula for variance and on log-log transformation.
Source: Table 14.2.1-5 of the ONO-4538-24 (CA209473) Final CSR; ADaM dataset: ADSL.xpt, ADTTE.xpt

The Applicant's Position:

Nivolumab demonstrated superior OS in the all randomized (ITT) population, with a statistically significant and clinically meaningful reduction in the risk of death versus the control group (HR= 0.77 [95% CI: 0.62, 0.96; p=0.0189]) (Figure 2; Table 15). Nivolumab also demonstrated an improved OS and clinically meaningful risk reduction of death compared to docetaxel (HR=0.78 [95% CI: 0.56, 1.07]) and paclitaxel (HR=0.76 [95% CI: 0.60, 0.97]) (Figure 3; Table 15). The KM estimate of median OS was greater in the nivolumab group than in the control group. Improved 12- and 18-month OS rates were likewise observed in the nivolumab group vs the control group (Table 16). In pre-planned OS analyses of subgroups, the observed treatment effect (HR) of nivolumab over control was < 1 across all subgroups (Figure 4), although the 95% CIs for the HRs included 1 in some subgroups.

Within the small subset of Western subjects, a similar HR for OS was observed compared to the overall study population (HR=0.53 [95% CI: 0.17, 1.65]), with median OS of 6.21 months (95% CI: 1.41, 20.14) in the nivolumab group and 6.11 months (95% CI: 2.60, 13.24) in the control group (Table 15).

The observed OS curves crossed around 5 months (Figure 2), indicating that the hazard was not proportional. Furthermore, a pre-specified analysis to examine the assumption of proportional hazards of the Cox model indicated a violation of such assumption (p= 0.0682). Following FDA's request (pre-sBLA meeting Comment 7), the treatment difference in OS was assessed in a post-hoc analysis using a weighted log-rank test from the Fleming-Harrington G(ρ–γ) family with a ρ value of 1 and γ value of 1.[36] The p value based on the weighted log-rank test results of OS (ITT population) for nivolumab vs control was 0.0019, favoring nivolumab over chemotherapy.

Results of post-hoc survival analyses for modified ITT populations, using both modified ITT-31 (N=388) and modified ITT-29 (N=390) methods, were consistent with those for the overall ITT population (N=419) (see 'Compliance with Good Clinical Practices' section for rationale for these analyses).

The FDA's Assessment:

FDA agrees with the results of the Applicant's primary and subgroup analyses of OS. FDA also agrees with the results of the Applicant's additional analysis conducted in the presence of non-proportional hazards based on weighted log-rank test, as pre-specified. Note that even though subgroup analyses were pre-planned, there was no alpha allocated to any subgroup analyses and results should be considered exploratory. In general, if the 95% confidence interval for HR includes 1 then it is interpreted that there is no difference in treatment effect with respect to OS between the treatment groups even if the point estimate of HR is <1. However, since the study was not designed to formally assess OS in any of these subgroups, no such conclusions can be drawn.

Data Quality and Integrity

The Applicant's Position:

Data cleaning and quality control checks were implemented by ONO and consisted of site monitoring visits guided by the SMP to review source documents against the eCRF and data validation checks of the eCRF and external data (data collected through non-CRF) as per the established Data Management Plan. In addition, a review of the database was performed by ONO planning and data management following the pre-defined criteria of subject-level analysis dataset to enhance the quality and ensure completeness of the data. When the database was declared complete and accurate, the database was locked.

The FDA's Assessment:

FDA agrees that Applicant has provided all the datasets and supporting metadata documentation required to validate the results. No issues were found when performing a data quality check.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 17: Secondary Efficacy Results - All Subjects and Western Subjects

Efficacy Parameter	All Subjects (ITT)		Western Subjects	
	Nivolumab	Control	Nivolumab	Control
RES Population (N) [a]	**171**	**158**	**7**	**8**
Investigator-assessed Objective Response Rate (ORR)				
Responders, n (%)	33 (19.3)	34 (21.5)	1 (14.3)	1 (12.5)
95% CI[b]	(13.7, 26.0)	(15.4, 28.8)	(0.4, 57.9)	(0.3, 52.7)
Odds ratio (95% CI)[c]	0.88 (0.51, 1.50)		1.00 (0.06, 15.99)	
Difference (95% CI)[d]	-2.13 (-10.87, 6.61)		0.00 (-40.17, 40.17)	
p-value[e]	p=0.6323*		--	
Investigator-assessed Time to Response (TTR)				
Subjects with CR or PR, n (%)	33 (19.3)	34 (21.5)	1 (14.3)	1 (12.5)
Median (months)	2.60	1.48	2.99	1.35
Min - Max (months)	1.2 - 6.5	1.2 - 5.6	3.0 - 3.0	1.3 - 1.3
Investigator-assessed Duration of Response (DOR)				
Median, months (95% CI)[f]	6.93 (5.39, 11.14)	3.91 (2.79, 4.17)	5.55 (N.A, N.A)	5.13 (N.A, N.A)
Min - Max (months)[g]	2.1 - 18.0+	2.5+- 18.0+	5.6 - 5.6	5.1 - 5.1
ITT Population (N)	**210**	**209**	**9**	**9**
Investigator-assessed Progression-free Survival (PFS)				
Events, n (%)	187 (89.0)	176 (84.2)	8 (88.9)	8 (88.9)
Progression	167 (79.5)	162 (77.5)	6 (66.7)	6 (66.7)
Death	20 (9.5)	14 (6.7)	2 (22.2)	2 (22.2)
Median, months (95% CI)[f]	1.68 (1.51, 2.73)	3.35 (2.99, 4.21)	1.45 (1.05, 6.21)	4.24 (1.51, 5.22)
HR (95% CI)[h]	1.08 (0.87, 1.34)		1.42 (0.50, 4.06)	
12-month PFS rate (95% CI) %[i]	11.9 (7.8, 16.8)	7.2 (3.8, 12.0)	N.A	N.A
18-month PFS rate (95% CI) %[i]	9.0 (5.5, 13.6)	4.0 (1.6, 8.2)	N.A	N.A

[a] RES population consisted of the ITT subjects with target lesion measurements at baseline.

[b] Exact 95% CI was calculated by using Clopper-Pearson method.

[c] Odds ratio and the corresponding CI for the nivolumab group relative to the control group was calculated using Cochran-Mantel-Haenszel methodology with the following 3 stratification factors: (IWRS source): 1) location (Japan vs Rest of World); 2) the number of organs with metastases (≤1 vs ≥2); 3) PD-L1 expression (≥1% vs <1% or indeterminate).

[d] Difference and the corresponding CI for the nivolumab group relative to the control group was calculated using Cochran-Mantel-Haenszel methodology with the 3 stratification factors as mentioned in footnote 'c'.

[e] Nivolumab group and control group were used for the calculation of p-value. The calculation of p-value was conducted by using the Cochran-Mantel-Haenszel test stratified with the 3 stratification factors as mentioned in footnote 'c';*: p<0.05; N.S.: p>=0.05

[f] This estimation was conducted by using the Kaplan-Meier method.

[g] Censored value was indicated as "+"

[h] HR and the corresponding two-sided 95% CI for the nivolumab group relative to the control group was calculated using the stratified Cox proportional-hazards model adjusted by the 3 stratification factors as mentioned in footnote 'c'. For Western

subjects column, hazard ratio and the corresponding two-sided 95% CI for the nivolumab group relative to the control group was calculated by using the unstratified Cox proportional-hazards model.

[i] The estimation was derived from the Kaplan-Meier estimate and corresponding CI was derived based on Greenwood formula for variance and on log-log transformation.

Source: For all subjects, refer to Table 11.4-4 (PFS, ITT), Table 11.4-6 (Rates for PFS, ITT), Table 11.4-3 (ORR, RES), Table 11.4-8 (TTR, RES), and Table 11.4-7 (DOR,RES), in the ONO-4538-24 (CA209473) Final CSR. For Western subjects, refer to Table 16.2.2-1 (PFS, ITT), Table 16.2.2-2 (Rates for PFS, ITT), Table 16.2.2-5-2 (ORR, RES), Table 16.2.2-7-2-1 (TTR, RES), and Table 16.2.2 6 2 (DOR, RES) of the Summary of Clinical Efficacy (Module 2.7.3) Appendix 2; ADaM dataset: ADSL.xpt, ADTTE.xpt, ADRS.xpt

Table 18: Best Overall Response, Objective Response Rate, and Disease Control Rate - RES Population

	Nivolumab N = 171	**Control N = 158**
Best overall response		
CR, n (%) (95% CI)[a]	1 (0.6) (95% CI: 0.0, 3.2)	2 (1.3) (95% CI: 0.2, 4.5)
PR, n (%) (95% CI)[a]	32 (18.7) (95% CI: 13.2, 25.4)	32 (20.3) (95% CI: 14.3, 27.4)
SD, n (%) (95% CI)[a]	31 (18.1) (95% CI: 12.7, 24.7)	65 (41.1) (95% CI: 33.4, 49.2)
PD, n (%)	94 (55.0)	51 (32.3)
NE, n (%)	13 (7.6)	8 (5.1)
Objective response rate		
ORR (CR+PR) , n (%)	33 (19.3)	34 (21.5)
(95% CI)[a]	(13.7, 26.0)	(15.4, 28.8)
Odds ratio (95% CI) [b]	0.88 (0.51, 1.50)	
Difference (95% CI) [c]	-2.13 (-10.87, 6.61)	
p-value[d]	p=0.6323	
Disease control rate		
DCR (CR+PR+SD) , n (%)	64 (37.4)	99 (62.7)
(95% CI)[a]	(30.2, 45.1)	(54.6, 70.2)
Odds ratio (95% CI)[b]	0.33 (0.21, 0.53)	
Difference (95% CI)[c]	-25.41 (-35.64, -15.19)	

Abbreviations: CR=complete response; DCR=disease control rate; NE=not evaluable; PD=progressive disease; PR=partial response; RES=response evaluable set; SD=stable disease.

Best overall response was determined solely by imaging assessment according to the RECIST Guideline Version 1.1

[a] Exact 95% confidence interval was calculated by using Clopper-Pearson method.

[b] Odds ratio and the corresponding confidence interval for the nivolumab group relative to the control group was calculated using Cochran-Mantel-Haenszel methodology with the three stratification factors (IWRS source) mentioned in footnote 'd'.

[c] Difference and the corresponding confidence interval was calculated by using Cochran-Mantel-Haenszel methodology with the three stratification factors (IWRS source) mentioned in footnote 'd'.

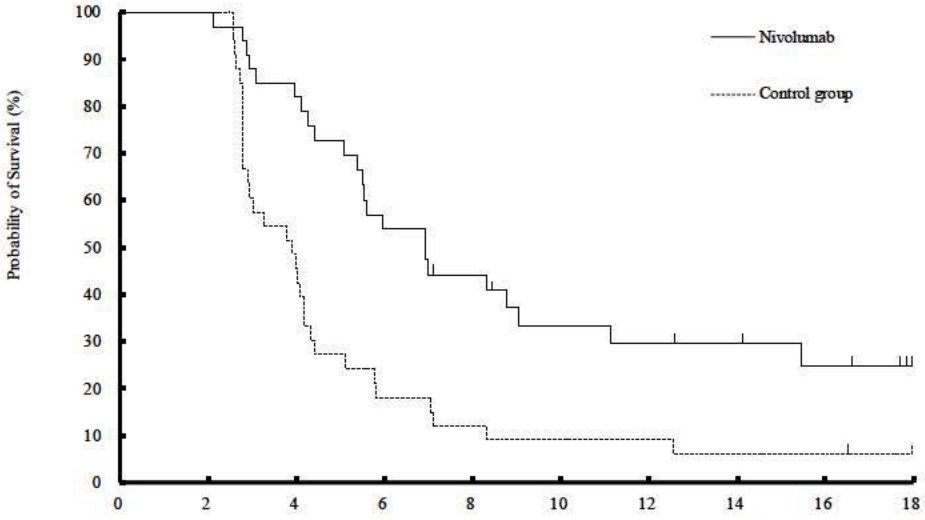
[d] Nivolumab group and control group were used for the calculation of p-value. The calculation of p-value was conducted by using Cochran-Mantel-Haenszel test stratified by the following three factors (IWRS source):

1) Location (Japan vs Rest of the world)
2) The number of organs with metastases (≤1 vs ≥2)
3) PD-L1 expression (≥1% vs <1% or indeterminate)

*: p<0.05, N.S.: p≥0.05

Source: Table 11.4-3 of the ONO-4538-24 (CA209473) Final CSR; ADaM dataset: ADSL.xpt, ADRS.xpt, ADTTE.xpt

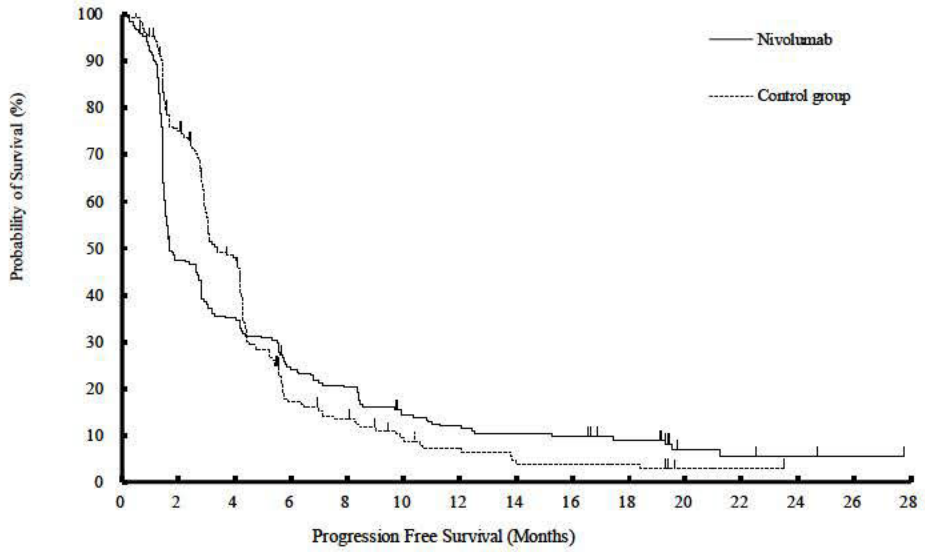
Figure 5: Kaplan-Meier Plot of Duration of Response - RES Population



At risk	0	2	4	6	8	10	12	14	16	18
Nivolumab	33	33	27	17	13	9	8	7	5	0
Control group	34	34	16	6	4	3	3	2	2	0

Note: RES (Subjects whose BOR was assessed as either CR or PR)
Source: Figure 11.4-3 of the ONO-4538-24 (CA209473) Final CSR; ADaM dataset: ADSL.xpt, ADTTE.xpt

Figure 6: Kaplan-Meier Plot of Progression-Free Survival (Primary Definition) - ITT Population



At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Nivolumab	210	96	71	48	40	27	22	19	18	13	5	4	3	1	0
Control group	209	147	89	29	22	12	9	5	5	5	1	1	0	0	0

Abbreviation: ITT=intention-to-treat.
Source: Figure 11.4-2 of the ONO-4538-24 (CA209473) Final CSR; ADaM dataset: ADSL.xpt, ADTTE.xpt

Table 19: Tumor Cell PD-L1 Expression Level (1% Cut-Off) Based on CRF Results and Efficacy

Efficacy Endpoint	Nivolumab	Control
Subjects with ≥ 1% PD-L1 Expression		
ITT Population (N)	**101**	**102**
Overall Survival		
Events, n	77	89
Median, months (95% CI)	10.91 (7.98, 14.23)	8.05 (5.98, 9.86)
HR (95% CI)[a]	0.69 (0.51, 0.94)	
RES Population (N)	**87**	**80**
Investigator-assessed Objective Response Rate		
Events, n	21	20
ORR (95% CI) [b]	24.14 (15.60, 34.50)	25.00 (15.99, 35.94)
Odds Ratio (95% CI)[c]	0.95 (0.47, 1.93)	
ITT Population (N)	**101**	**102**
Investigator-assessed Progression-free Survival		
Events, n	88	86
Median, months (95% CI)	2.73 (1.51, 3.25)	3.06 (2.89, 4.17)
HR (95% CI)[a]	0.90 (0.67, 1.23)	
Subjects with < 1% PD-L1 Expression		
ITT Population (N)	**109**	**107**
Overall Survival		
Events, n	83	84
Median, months (95% CI)	10.91 (8.38, 13.90)	9.33 (7.20, 11.96)
HR (95% CI)[a]	0.84 (0.62, 1.14)	
RES Population (N)	**84**	**78**
Investigator-assessed Objective Response Rate		
Events, n	12	14
ORR (95% CI)[b]	14.29 (7.61, 23.62)	17.95 (10.17, 28.28)
Odds Ratio (95% CI)[c]	0.76 (0.33, 1.77)	
ITT Population (N)	**109**	**107**
Investigator-assessed Progression-free Survival		
Events, n	99	90
Median, months (95% CI)	1.61 (1.48, 2.63)	4.11 (3.02, 4.27)
HR (95% CI)[a]	1.30 (0.97, 1.73)	

Abbreviations: CI=confidence interval; HR=hazard ratio; ITT=Intention-to-treat; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; RES=response evaluable set.

a HR was estimated by using unstratified Cox proportional hazards model.

b Exact 95% CI was calculated by using Clopper-Pearson method. Items whose estimated value exceeded 10.00 were not plotted.

c Odds ratio was estimated by using the logistic regression model with the treatment group as the single covariate.

Note: CRF results=test results.

Source: Refer to Figure 11.4-8 (OS Forest Plot), Figure 11.4-10 (PFS Forest Plot), Figure 11.4 12 (ORR Forest Plot), Table 14.2.6.2-1 (RES ORR ≥ 1%), and Table 14.2.6.2-2 (RES ORR <1%) of the ONO-4538-24 (CA209473) Final CSR; ADaM dataset: ADSL.xpt, ADTTE.xpt, ADRS.xpt

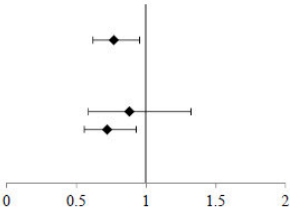
Table 20: Microsatellite Instability Results - All Randomized Subjects (ITT)

	Nivolumab N = 210 (%)	Control N = 209 (%)
-Microsatellite Instability Result		
MSI-H	0 (0.0)	0 (0.0)
MSS	64 (30.5)	63 (30.1)
MSI-L	0 (0.0)	0 (0.0)
MSI unknown due to QC failure	4 (1.9)	5 (2.4)
MSI N/A due to pre-analysis failure	12 (5.7)	14 (6.7)
No sample available	130 (61.9)	127 (60.8)
Microsatellite Instability Result Analysis Category		
MSI-H	0 (0.0)	0 (0.0)
NON MSI-H	64 (30.5)	63 (30.1)
Unknown/ Not reported	146 (69.5)	146 (69.9)

Abbreviations: MSI-H=microsatellite instability high; MSI-L=microsatellite instability low; MSS=microsatellite instability stable; QC=quality control
Source: Table 3.1.5.8-1 of the Summary of Clinical Efficacy (Module 2.7.3); ADaM dataset: ADSL.xpt, ADMSI.xpt

Figure 7: Forest Plot of Subgroup Analyses of OS by MSI Status - All Randomized Subjects (ITT)

	N	Nivolumab N of Events (N of subjects)	Nivolumab median(95% CI)	Control group N of Events (N of subjects)	Control group median(95% CI)	Hazard ratio[a] (95% CI)
ALL	419	160(210)	10.91 [9.23, 13.34]	173(209)	8.38 [7.20, 9.86]	0.77 [0.62, 0.95]
MSI Status						
MSI-H	0	0(0)	- [-, -]	0(0)	- [-, -]	- [-, -]
NON MSI-H	127	47(64)	14.23 [10.05, 17.81]	46(63)	10.02 [5.68, 13.67]	0.88 [0.59, 1.32]
UNKNOWN/NOT REPORTED	292	113(146)	10.28 [8.08, 12.06]	127(146)	8.05 [6.87, 9.69]	0.72 [0.56, 0.93]
Analysis Set : ITT						



Abbreviations: ITT=intention to treat; MSI-H=microsatellite instability high
[a] Hazards ratio was estimated by using unstratified Cox proportional hazards model
Source: Figure 3.1.5.8-1 of the Summary of Clinical Efficacy (Module 2.7.3); ADaM dataset: ADSL.xpt, ADMSI.xpt, ADTTE.xpt

The Applicant's Position:

Objective Response Rate: In ONO-4538-24 (CA209473), investigator-assessed ORR was a key secondary endpoint and was planned to be tested in a hierarchical order if superiority in OS was determined. Results are provided for the RES. The ORR for the RES in the nivolumab group had 33/171 responders (19.3%; 95% CI: 13.7, 26.0) and 34/158 responders (21.5%; 95% CI: 15.4, 28.8) in the control group (Table 17). The odds ratio of responses in the nivolumab group relative to the control group was 0.88 (95% CI: 0.51, 1.50). The p value for the odds ratio (p=0.6323) did not meet the pre-specified boundary for significance (p<0.05). DCR for the RES was 37.4% (95% CI: 30.2, 45.1) in the nivolumab group and 62.7% (95% CI: 54.6, 70.2) in the control group (Table 18). Seven subjects (21.2%) in the nivolumab group and 2 subjects (5.9%) in the control group for the RES had a continued response to the treatment at the time of data cut-off.

Duration of Response: The median TTR (BOR of CR or PR) for RES was 2.60 months (range: 1.2 to 6.5) in the nivolumab group and 1.48 months (range: 1.2 to 5.6) in the control group. The median DOR for RES

in the nivolumab group was 6.93 months (95% CI: 5.39, 11.14) which was longer than the 3.91 months (95% CI: 2.79, 4.17) median DOR for RES in the control group (Table 17; Figure 5).

Progression-free Survival: Median PFS was 1.68 months (95% CI: 1.51, 2.73) in the nivolumab group vs 3.35 months (95% CI: 2.99, 4.21) in the control group, with a HR of 1.08 (95% CI: 0.87, 1.34) (Table 17). PFS was not formally tested as ORR did not pass the statistical boundary for significance. Nevertheless, PFS KM curves showed late crossing favoring nivolumab (Figure 6); consequently, the 12-month and 18-month PFS rates were 11.9% (95% CI: 7.8, 16.8) and 9.0% (95% CI: 5.5, 13.6) with nivolumab, and 7.2% (95% CI: 3.8, 12.0) and 4.0% (95% CI: 1.6, 8.2) with the control group, respectively. PFS events (disease progression or death) occurred in 187 (89.0%) subjects in the nivolumab group and 176 (84.2%) subjects in the control group by the data cut-off date.

Efficacy among Western Subjects: Among Western subjects, ORR (RES) was comparable in the nivolumab (14.3% [95% CI: 0.4, 57.9]) and control (12.5% [95% CI: 0.3, 52.7]) groups. DCR (RES) was higher in the control vs nivolumab group. The 1 (14.3%) responder in the nivolumab group (RES) had a TTR of 2.99 months and DOR of 5.55 months. Median PFS (primary definition) was 1.45 months (95% CI: 1.05, 6.21) in the nivolumab group vs 4.24 months (95% CI: 1.51, 5.22) in the control group with HR=1.42 (95% CI: 0.50, 4.06).

Efficacy by PD-L1 Status: The data suggest improved efficacy with nivolumab vs control regardless of tumor cell PD L1 expression, although subjects with PD L1 ≥ 1% expression derived numerically greater benefit than those with PD-L1 < 1%. HRs of OS favored nivolumab over control across tumor cell PD-L1 expression levels: 0.69 (95% CI: 0.51, 0.94) for subjects with PD-L1 ≥ 1%, and 0.84 (95% CI: 0.62, 1.14) for subjects with PD-L1 < 1% (Table 19). OS results from additional exploratory analyses performed at higher tumor cell PD-L1 expression levels (5% and 10%) were consistent with those at the 1% expression level (Figure 4).

Efficacy by MSI Status: Microsatellite instability (MSI) status was evaluated using the Foundation Medicine FoundationOne CDx™ (F1CDx) assay.[37] In this dataset there were no subjects with MSI-H tumors (Table 20), which is consistent with findings from other studies suggesting that MSI-H is very rare or nonexistent in ESCC. Survival benefit from nivolumab treatment was seen in the non-MSI-H subjects, with a HR of 0.88 (95% CI: 0.59, 1.32). In addition, the OS HR of the MSI unknown/not reported subjects, 0.72 (95% CI: 0.56, 0.93), is similar to OS HR for the overall population (0.77 [95% CI: 0.62, 0.95]) (Figure 7). Based on these data as well as available literature pointing to the rarity of MSI-H in ESCC, it is extremely unlikely that MSI-H was driving the clinical benefit observed with nivolumab in this study. Hence, MSI might not be a relevant biomarker for this indication.

The FDA's Assessment:

FDA agrees with the results of the Applicant's secondary endpoint analyses. FDA notes that there was no statistically significant improvement in ORR or PFS.

The ORR was lower in the nivolumab arm compared to the control arm. Note that, as defined

previously, ORR was analyzed using RES analysis set which was a subset of ITT population that excluded subjects who were GCP-noncompliant and subjects who had incomplete target lesion measurements at baseline. Based on the data, there were 329 patients included in the RES population (171 in the nivolumab arm and 158 in the control arm). There were no GCP-noncompliant subjects noted in this study; all subjects excluded from the RES had incomplete target lesion measurements. FDA notes that there were no clear imbalances in demographics or baseline characteristics between arms within this subset of patients making up the RES.

The median PFS was lower in the nivolumab arm compared to the control arm; however, the medians should not be considered representative of treatment effect in this case as the PFS curves cross at a later time.

FDA also notes that the analyses of efficacy among Western subjects, efficacy by PD-L1 status, and efficacy by MSI status are all considered exploratory. Due to the small number of randomized patients enrolled in Western clinical sites (n=18), exploratory analyses of this subset of patients are very difficult to interpret.

Dose/Dose Response

The Applicant's Position:
E-R analyses support the clinical efficacy results. Refer to Section 6 for details.

The FDA's Assessment:
Refer to Section 6, above.

Durability of Response

The Applicant's Position:
The proportions of subjects alive at 12 and 18 months were higher in the nivolumab group vs the chemotherapy control group; suggesting a durable OS benefit with nivolumab: 46.9% (95% CI: 39.9, 53.5) vs 34.4% (95% CI: 27.8, 40.9) at 12 months, and 30.5% (95% CI: 24.4, 36.9) vs 20.7% (95% CI: 15.4, 26.6) at 18 months, respectively. At data cut-off, 12-month PFS rates were numerically higher in the nivolumab group (11.9%) compared with the chemotherapy control group (7.2%). Responses were more durable in the nivolumab group compared with the chemotherapy control group, with median DOR of 6.93 months (95% CI: 5.39, 11.14) vs 3.91 months (95% CI: 2.79, 4.17), respectively.

The FDA's Assessment:
FDA agree with Applicant's interpretation of longer durability of responses.

Persistence of Effect

The Applicant's Position:
The persistence of effect is supported by the observed OS benefit based on mature data and a minimum follow-up of approximately 17.6 months.

The FDA's Assessment:

FDA agree with Applicant's interpretation of persistence of effect.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:
As an exploratory endpoint, health-related quality of life (HRQoL) was assessed using the three-level version of the EQ-5D (EQ-5D-3L). EQ-5D UI scores were calculated based on the UK value set.[38] Changes from baseline and differences between treatment groups in HRQoL were assessed using a longitudinal mixed model repeated measures (MMRM) approach. For time-to-event analyses, a stratified Cox regression model was used to estimate hazard ratios, and an un-stratified Kaplan-Meier method was used to estimate median times to event and the proportion of subjects who were event-free.

Compliance rates were high, with >85% of expected EQ-5D assessments completed through Week 42.[39]

For the EQ-5D VAS, the difference between treatment groups nominally favored nivolumab at all time points as well as for the overall time-averaged least squares (LS) mean estimate (least squares means difference [LSMD]: 6.9; 95% CI: 3.0, 10.9). The estimated difference between treatment groups exceeded the threshhold for meaningful change (≥ 7 points)[40] at Weeks 18, 24, and 30.[39]

For EQ-5D UI, the difference between treatment groups nominally favored nivolumab at all time points and for the overall time-averaged LS mean estimate (LSMD: 0.076; 95% CI: 0.011, 0.142). The estimated difference between treatment groups exceeded the threshhold for meaningful change (≥ 0.08 points) at Weeks 24, 30, 36, and 42.[39]

Subjects treated in nivolumab group had a decreased risk of deterioration in patient reported outcomes compared with subjects treated in the control group as measured by the EQ-5D VAS (HR=0.65 [95% CI: 0.49, 0.86]) and EQ-5D UI (HR=0.73 [95% CI: 0.55, 0.97]).[39]

The FDA's Assessment:
FDA generally agrees with the Applicant's description of their descriptive analyses of PROs using the EQ-5D-3L. However, FDA notes that the EQ-5D-3L is a composite that incorporates self-reported ability to function, pain, and general health status as filled out by the patient. This instrument is a generic preference-based measure intended to provide a health utility index value for use in economic analyses and lacks content validity for use in estimating clinical benefit for the purposes of labeling claims; FDA does acknowledge that this instrument is often used by other regulatory authorities and payers.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:
Not applicable.

The FDA's Assessment:
No additional analyses were conducted by FDA. The subgroups of interest, PDL1 status and Western versus Asian region, were presented above in the efficacy results sections.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Study ONO-4538-24 (CA209473) was designed compare the OS in patients with ESCC that is refractory (or the patient is intolerant) to one prior line of systemic fluoropyrimidine- and platinum-based therapy who receive nivolumab to those who receive docetaxel or paclitaxel. Study ONO-4538-24 demonstrated a statistically significant, clinically meaningful improvement in OS for patients randomized to nivolumab compared with investigator's choice of taxane chemotherapy. The median OS of patients in the nivolumab arm was 10.91 months [95% CI: 9.23, 13.34] and the median OS of patients in the control arm was 8.38 [95% CI: 7.20, 9.86] with an OS HR of 0.77 [95% CI: 0.62, 0.96; p=0.0189]. Additionally, the OS benefit in the ITT population appears to be durable based on survival estimates at landmark timepoints. Study ONO-4538-24 did not demonstrate a statistically significant improvement in PFS or ORR with nivolumab compared to chemotherapy. Although the point estimate for ORR was marginally lower in the nivolumab arm compared to the control arm (19% versus 22%), the confidence intervals for ORR overlapped; additionally, responses appeared more durable on the nivolumab arm with a median DoR of 6.93 months (95% CI: 5.39, 11.14) versus 3.91 months (95% CI: 2.79, 4.17) in the RES population randomized to the nivolumab and control arms, respectively. Several pre-planned subgroup analyses of the ITT population showed generally consistent treatment effects with nivolumab, including in patients with PD-L1 positive (as ≥1% of tumor cells expressing PD-L1) and PD-L1 negative (as <1% of tumor cells expressing PD-L1) tumors, supporting an OS advantage for nivolumab in these subgroups. However, although pre-planned, no alpha was allocated for these subgroup analyses and, thus, these are considered exploratory.

In summary, the data submitted to this application provide substantial evidence of the effectiveness of nivolumab based on an OS benefit.

8.1.4. Assessment of Efficacy Across Trials

Data and the Applicant's position of "Assessment of Efficacy Across Trials" are provided in Section 8.1.5: Integrated Assessment of Effectiveness.

The FDA's Assessment:
See the FDA's Assessment in Section 8.1.5.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

ONO-4538-24 (CA209473) met its primary endpoint of OS and demonstrated significant improvement in OS in the nivolumab group vs chemotherapy control group (docetaxel or paclitaxel) (HR=0.77; p=0.0189), in ESCC subjects refractory or intolerant to fluoropyrimidine- and platinum-based combination therapy. The median OS was 10.91 months (95% CI: 9.23, 13.34) with nivolumab vs 8.38 months (95% CI: 7.20, 9.86) with chemotherapy, resulting in a clinically meaningful improvement of 2.53 months in median OS. The proportions of subjects alive at 12 and 18 months were higher in the nivolumab group vs the chemotherapy control group, suggesting a durable OS benefit with nivolumab.

The hazard ratio for OS consistently favored nivolumab across baseline demographic and disease characteristics; in particular, survival benefit in ONO-4538-24 (CA209473) was observed regardless of tumor PD-L1 expression level. Within a small subset of Western subjects representing 4.3% of the overall trial population, a similar HR for OS was observed compared to the overall study population (HR=0.53 [95% CI: 0.17, 1.65]).

The PFS observed in subjects randomized to nivolumab vs the chemotherapy control group was similar, as measured by HR=1.08 (95% CI: 0.87, 1.34). However, analysis of PFS showed late crossing of the KM curves, favoring nivolumab over control. Consequently, at data cut-off, 12-month PFS rates were numerically higher in the nivolumab group (11.9%) compared with the chemotherapy control group (7.2%). This phenomenon has also been observed with nivolumab in other solid tumors.[41,42,43]

Investigator-determined ORR was comparable between the nivolumab (19.3%) and chemotherapy control (21.5%) groups. Comparison between groups was not statistically significant. Nevertheless, responses were more durable with nivolumab vs chemotherapy (median DOR of 6.93 vs 3.91 months),which is consistent with the accumulating evidence suggesting that time to response with immunotherapy is longer but responses are more durable than with chemotherapy.[44]

Patient-reported outcomes for subjects treated in the nivolumab group demonstrated improvements in health status and HRQoL as compared with subjects in the control group.

Based on the clinical data of nivolumab, it is not expected that exposures in safety or efficacy profiles would be different across ethnic groups. As demonstrated in nivolumab PPK analysis across different tumor types, race did not have a clinically relevant effect on CL, and exposures were similar between Asian and Non-Asian subjects (see Section 6.2.1). These observations indicate that results from ONO-4538-24 (CA209473) are applicable to the US population and medical practice.

Support for Applicability of Findings from ONO-4538-24/CA209473 to the US Population: To elucidate similarities and differences in disease between Asian and Western countries, BMS conducted a real-world retrospective global treatment patterns study using patient charts among subjects treated in 2L ESCC.[25] This study compared Western subjects (US, Canada, England, Italy, France, Germany, and Spain; N=195) to Asian subjects (Japan, South Korea, Taiwan, and China; N=192) for a total of 387 subjects.

Over 70 baseline variables were evaluated, with the majority showing no differences between Western and Asian subjects, including no differences in age, gender, history of smoking/drinking, or baseline ECOG PS scores. On the other hand, a higher proportion of Western subjects were diagnosed with metastatic disease and received systemic treatment than Asian subjects.

Notably, the rate of advanced or metastatic disease varies by country, potentially impacting both treatment options and survival. Incidence of EC with distant metastases in the US is 40% and in Japan is 19.2%. 5-year survival rate of metastatic EC in the US is 4.8% and in Japan is 7.9%.[45] The implementation of early screening programs for gastric cancer in Japan and Korea may explain the larger proportion of subjects diagnosed with earlier stage disease in these countries compared to Western countries.[46]

In the US, survival disparities by race and ethnicity (White vs non-White) exist among subjects with ESCC. However, differences in mortality risk by race and ethnicity appear to be largely explained by additional factors, including surgery and tumor stage. These disparities do not persist after controlling for key demographic and clinical characteristics and treatment received, as a recent Surveillance, Epidemiology, and End Results (SEER)-Medicare study suggested.[47]

Another US study used the SEER and Shanghai Cancer Registries databases to compare clinicopathological features of ESCC and found that ESCC was diagnosed at an earlier age and stage in Chinese than in Caucasian patients.[2] Adjusting for these differences, the study showed similar OS between Chinese and Caucasian patients (15.3 vs 14.2 months, p=0.40) with no statistical difference in 1-year, 3-year and 5-year survival rates. In contrast, a separate US study using the SEER database found that Chinese patients with ESCC had better OS compared with Caucasian patients (HR =1.330; 95% CI: 1.159–1.527, $p < 0.001$).[48] However, this study did not control for cancer staging or treatment regimens, both of which are associated with treatment outcomes. Furthermore, the Chinese patient population in this study was derived from patients living in the US, and the reported differences may be associated with differences in socioeconomic factors rather than with underlying differences between Asian and Western patients.

Support for Findings from ONO-4538-24/CA209473 from Analyses of Real-World Data (RWD) in 2L ESCC:
Results from RWD analyses conducted by BMS and other observational studies suggest OS in advanced stages of 2L ESCC is comparable across regions.

To explore the OS outcome of 2L therapy in subjects with advanced or metastatic ESCC, BMS conducted 2 retrospective studies using 2 US databases: US SEER[49] and Flatiron electronic health record (EHR)[50]. In the first retrospective study (CA209-7E7), using the US SEER–Medicare population to evaluate 2L ESCC subjects, the median duration of treatment was 1.5 months, and median OS was 5.7 months (95% CI: 5.0-8.5), with 6-month, 1-year and 2-year survival rates of 48.0%, 29.2%, and 17.6%, respectively.

The other retrospective study (CA209-8LY) used a Flatiron EHR database and included 86 advanced ESCC subjects who received 2L treatment.[50] Consistent with results observed from SEER data, median duration of treatment of 1.7 months, and the median OS was 6.7 months (95% CI: 5.1, 8.3) with 6-month, 1-year

and 2-year survival rates of 51%, 28%, and 19%, respectively.[50] In the Cox model, only 2 variables were statistically significant: gender and ECOG PS.[50]

Three observational studies evaluated taxane monotherapy use among Japanese subjects with advanced/metastatic 2L ESCC.[28,29,30] The median OS ranged from 5.5 to 8.6 months, which aligns with the results from both the SEER[49] and Flatiron EHR[50] analyses, and suggests OS is comparable across regions in advanced stages of disease in the observational setting.

Similar molecular features suggest similar underlying disease biology in Asians and non-Asians (see Section 2.1). Differences in risk factors may contribute to the observed regional differences in the prevalence of the disease (see Section 2.1); however there are similarities in the management and survival outcomes appear comparable across regions in both the experimental (Table 2) and observational settings for subjects in advanced stages of disease. Overall there is limited benefit with standard of care (SOC chemotherapy) in advanced ESCC irrespective of region.

In summary, in this randomized active-controlled study, nivolumab demonstrated statistically significant and meaningful clinical benefit compared to chemotherapy in unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy, providing evidence for a potential new treatment option in this patient population.

The FDA's Assessment:

Data from the real-world retrospective global treatment patterns study and the RWD analyses referred to by the Applicant, above, were not submitted with this application. Thus, FDA is unable to comment specifically on these conclusions. However, FDA notes the similarities in treatment strategies across populations with ESCC and the consistencies of results across different populations described in the above studies above which suggest a broader benefit in the treatment of second-line ESCC beyond the specific demographic make-up of Study ONO-4538-24 (CA209473).

Regarding the patient-reported outcomes (PRO) data presented by the Applicant, the EQ-5D-3L is a generic preference-based measure intended to provide a health utility index value for use in economic analyses and lacks content validity for use in estimating clinical benefit for the purposes of labeling claims. FDA does generally agree with the descriptive analysis provided by the Applicant but these do not support labeling claims.

8.2. Review of Safety

The Applicant's Position:

The safety data from ONO-4538-24 (CA209473) demonstrate an acceptable safety profile in subjects with advanced ESCC who were refractory to or intolerant of fluoropyrimidine and platinum-based combination therapy. Nivolumab was well tolerated and provided an improved safety profile versus

chemotherapy. The overall safety profile was consistent with expectations based on the known safety profile of nivolumab, and there were no new safety concerns with nivolumab monotherapy.

The FDA's Assessment:

Nivolumab was generally better tolerated than chemotherapy and had less treatment delays and discontinuations, but esophageal fistula was a new clinically significant safety signal associated with this patient population. In addition, in an exploratory analysis, patients with ESCC had a higher rate of pneumonitis compared patients with other tumor types treated with nivolumab, perhaps due to previous radiation therapy to the thorax.

8.2.1. Safety Review Approach

The Applicant's Position:

The Safety Set (SAF) consisted of all subjects given at least one dose of the investigational product. Data from the Safety Set (SAF) of the overall population in study ONO-4538-24 (CA209473) will be presented. This will be followed by data from a subgroup of Western subjects in ONO-4538-24 (CA209473), presented separately for key analyses.

The characterization of the safety profile of nivolumab monotherapy is derived from 209 nivolumab monotherapy-treated subjects in the Phase 3 study ONO-4538-24 (CA209473). Additional safety data are provided for 9 nivolumab monotherapy treated Western subjects (not located in Japan, Korea, or Taiwan) in ONO-4538-24 (CA209473). All nivolumab-treated subjects were treated with 240 mg nivolumab Q2W.

Based on the design of ONO-4538-24 (CA209473), the primary presentation of AEs, SAEs, AEs leading to treatment discontinuation, and other events of special interest (OESIs) are based on those occurring within either 28 days after the end of the treatment period or the start date of post study treatment after the end of the treatment period, whichever was earlier. Additionally, SAEs occurring within 100 days after the end of the treatment period or the start date of post-study treatment after the end of the treatment period, whichever was earlier, are presented in Section 12.2 of the ONO-4538-24 (CA209473) Final CSR.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) according to the most recent version of the dictionary at the time of the CSR analyses (v21.1 for ONO-4538-24 [CA209473]). Analyses conducted specifically for inclusion also utilize MedDRA v21.1. In both the ONO-4538-24 (CA209473) final CSR and SCS, AE results were graded for severity using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 criteria. Note that Grade 5 AEs (death related to adverse event) are included in AE summary tables in compliance with ONO reporting practice.

Subjects with at least 1 AE were summarized by treatment group using individual standardized MedDRA query (SMQ) narrow and broad scopes. The windows used for these AEs were either up to 28 days after last dose or the start date of post-study treatment after the end of the treatment period, whichever was earlier.

The FDA's Assessment:

Treatment-emergent IMAEs occurring within 100 days after the last dose of study treatment or the start date of post-study treatment, whichever was earlier, should also be included in the safety analysis. The protocol for Study ONO-4538-24 (CA209473) also required monitoring for treatment-emergent SAEs that occurred within 100 days after the last dose of study treatment or the start date of post-study treatment, whichever was earlier, and thus these SAEs should also be included in the safety analysis. The FDA did not do an additional analysis of AEs that the Applicant flagged as "drug-related," except for Grade 5 treatment-emergent AEs (TEAEs), due to the subjectivity of this assessment. The FDA's assessment of the safety of nivolumab for the proposed indication is based on the overall safety data submitted in this Application. Thus, the FDA will not comment on the Applicant's analysis of "drug-related" TEAEs, except for Grade 5 TEAEs. Otherwise, the FDA agrees with the Applicant's description of the safety review approach.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 21: Safety Population, Size, and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N=417			
Clinical Trial Groups	Nivolumab (n=209)	Docetaxel (n=65)	Paclitaxel (n=143)
Controlled trials conducted for this indication[2]	209	65	143

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling
Source: Refer to Table 14.1.1-2 from the ONO-4538-24 (CA209473) final CSR; ADaM dataset: ADSL.xpt

The Applicant's Position:

A total of 209 subjects in the nivolumab group and 208 subjects in the control group (65 subjects in the docetaxel group and 143 subjects in the paclitaxel group) were administered at least one dose of the investigational product (Table 21).

The median duration of treatment was 2.56 months (range: 0.0 to 29.2 months) in the nivolumab group and 2.56 months (range: 0.0 to 21.4 months) in the control group. The median number of doses received was 6.0 (range: 1 to 60 doses) in the nivolumab group. The median number of doses received was 3.0 (range: 1 to 22 doses) in the docetaxel group and 10.0 doses (range: 1 to 75 doses) in the paclitaxel group. The median cumulative dose was 1440.00 mg (range: 240.00 to 14400.00 mg) and the median relative dose intensity was 100% (range: 63.8% to 112.0%) in the nivolumab group (refer to Section 12.1 in the ONO-4538-24 [CA209473] final CSR).

The FDA's Assessment:

The FDA agrees with the size of the safety population for each treatment arm, and the Applicant's description of the patients' study treatment exposure time. Further FDA analysis of cumulative dose and relative dose intensity is in Table 22.

Table 22: Cumulative dose and relative dose intensity summary for Study ONO-4538-24 (CA209473) – All treated subjects (FDA analysis)

	Trial Arm			
	Nivolumab (n=209)	Chemotherapy Control		
		Chemotherapy Pooled (n=208)	Docetaxel (n=65)	Paclitaxel (n=143)
Duration of Therapy (months)				
Mean (SD)	4.89 (5.90)	3.33 (3.31)	2.92 (3.32)	3.51 (3.31)
Median (Min – Max)	2.56 (0.0 – 29.24)	2.56 (0.0 – 21.36)	2.10 (0.0 – 18.89)	2.79 (0.0 – 21.36)
Off Treatment, n (%)	193 (92.34)	205 (98.56)	64 (98.46)	141 (98.60)
>3 Months, n (%)	93 (44.50)	83 (39.90)	20 (30.77)	63 (44.06)
>6 Months, n (%)	54 (25.84)	24 (11.54)	6 (9.23)	18 (12.59)
>9 Months, n (%)	32 (15.31)	13 (6.25)	4 (6.15)	9 (6.29)
>12 Months, n (%)	21 (10.05)	7 (3.37)	3 (4.62)	4 (2.80)
Number of Doses Received				
Mean (SD)	10.78 (11.73)	9.75 (9.54)	4.78 (4.09)	12 (10.43)
Median (Min – Max)	6 (1 – 60)	7 (1 – 75)	3 (1 – 22)	10 (1 – 75)
1 dose, n (%)	14 (6.70)	8 (3.85)	5 (7.69)	3 (2.10)
2 doses, n (%)	16 (7.66)	21 (10.10)	14 (21.54)	7 (4.90)
3 doses, n (%)	37 (17.70)	20 (9.62)	14 (21.54)	6 (4.20)
4 doses, n (%)	10 (4.78)	19 (9.13)	9 (13.85)	10 (6.99)
>4 doses, n (%)	132 (63.16)	140 (67.31)	23 (35.38)	117 (81.82)
Cumulative Dose (mg)				
Mean (SD)	2585.15 (2816.07)	1304.32 (1302.62)	486.40 (390.78)	1676.11 (1399.74)
Median (Min – Max)	1440.0 (240.0 – 14400.0)	918.54 (104.80 – 10561.79)	365.98 (104.80 – 2022.16)	1349.37 (136.40 – 10561.79)
Cumulative Dose (mg/kg for nivolumab and mg/m2 for chemotherapies)				
Mean (SD)	47.91 (52.60)	810.97 (793.54)	304.32 (238.85)	1041.26 (849.32)
Median (Min – Max)	29.17 (3.0 – 264.49)	577.5 (75 – 6380)	225 (75 – 1215)	860 (100 – 6380)

	Trial Arm			
	Nivolumab (n=209)	Chemotherapy Control		
		Chemotherapy Pooled (n=208)	Docetaxel (n=65)	Paclitaxel (n=143)
Relative Dose Intensity (%)				
Mean (SD)	95.42 (7.78)	81.42 (15.65)	85.11 (13.75)	79.74 (16.21)
Median (Min – Max)	100 (63.81 – 112)	83.18 (43.33 – 107.69)	86.67 (51.43 – 104.13)	80 (43.33 – 107.69)
≥110%, n (%)	1 (0.48)	0	0	0
90% to <110%, n (%)	173 (82.78)	75 (36.06)	27 (41.54)	48 (33.57)
70% to <90%, n (%)	33 (15.79)	84 (40.38)	28 (43.08)	56 (39.16)
50% to <70%, n (%)	2 (0.96)	47 (22.60)	10 (15.38)	37 (25.87)
<50%, n (%)	0	2 (0.96)	0	2 (1.40)

SD=standard deviation, Min=minimum, Max=maximum
Source: ADaM dataset from Module 5.3.5.3 - adexs.xpt, adsl.xpt

Relevant characteristics of the safety population:

The Applicant's Position:
The baseline demographics and disease characteristics between the nivolumab group and the control (total) group were generally well balanced, with the following exceptions which, nevertheless, do not appear to unilaterally favor one group versus the other: age, median time from diagnosis to randomization, previous surgery, previous radiotherapy, R0 resection, and recurrent disease (Table 12, Table 13). Characteristics were consistent with what was expected in a population with advanced ESCC.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment that the baseline demographics and disease characteristics are generally well-balanced, with exceptions as highlighted by the Applicant as well as the smoking and alcohol intake status (Table 12, Table 13, Table 14). In the nivolumab group compared to the chemotherapy control group, less patients were ≥65 years old and ≥75 years old and more patients had prior R0 resections, both of which would generally favor the nivolumab group (Table 12, Table 14). On the other hand, patients in the nivolumab group had a longer median time from diagnosis to randomization, more recurrent disease, more previous surgery, and more previous radiotherapy, all of which suggest that the patients in the nivolumab group had more advanced or aggressive disease (Table 13, Table 14). However, the cancer stage was well-balanced between the nivolumab group and the chemotherapy control group (Table 14). Thus, the FDA agrees with the Applicant's conclusion that these slight imbalances do not appear to unilaterally favor one study treatment group versus the other.

Adequacy of the safety database:

The Applicant's Position:
The patients with advanced ESCC recruited in Study ONO-4538-24 (CA209473) adequately represent the target population, including demographic, disease, and other baseline characteristics. The exposure to study treatment in ONO-4538-24 (CA209473) allowed for sufficient characterization of the safety of nivolumab monotherapy in the proposed indication. The routine clinical and laboratory evaluations performed in ONO-4538-24 (CA209473) were appropriate, and the safety profile of nivolumab was manageable with no new safety signals identified. Building on the extensive safety experience of nivolumab monotherapy, the safety of nivolumab monotherapy from ONO-4538-24 (CA209473) was further compared to a nivolumab monotherapy pool of 3503 patients with multiple tumor types (see Section 8.2.5). Overall, the safety profile of nivolumab monotherapy in ESCC was consistent with the safety profile of nivolumab monotherapy in other tumor types.

The FDA's Assessment:
The FDA agrees with the Applicant that the exposure is adequate to assess the safety of nivolumab for patients with squamous cell carcinoma of the esophagus or esophagogastric junction who meet the eligibility criteria Study ONO-4538-24 (CA209473) and that the study population adequately represents the target population for the proposed indication. All treated patients had unresectable squamous cell carcinoma of the esophagus or esophagogastric junction, and all but two patients had prior treatment with both fluoropyrimidine and platinum-based combination chemotherapy; these two patients were in the nivolumab treatment arm, and only had prior fluoropyrimidine chemotherapy, and no prior platinum chemotherapy (Table 14). Nivolumab was generally better tolerated than chemotherapy, but esophageal fistula was a new clinically significant safety signal associated with this patient population. See the section entitled "All causality treatment-emergent SAEs" of Section 8.2.4 for a discussion regarding esophageal fistulas and hematemesis. Blood creatine phosphokinase (CPK) increase was another new safety signal, but after a thorough review of the patient narratives and dataset, the FDA has determined that its clinical significance was inconclusive in this study (see the section entitled "Dose Interruption/Reduction Due to Adverse Effects" in Section 8.2.4). Compared to patients with other tumor types who also received nivolumab, patients with ESCC had a higher rate of pneumonitis, perhaps due to previous radiation therapy to the thorax.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
This study was conducted in accordance with the ethical principles that are consistent with the Good Clinical Practice (GCP) guidelines developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local regulations. This study was conducted in compliance with the protocol. Prior to initiation of the study, the protocol and any amendments, as well as the patient informed consent form (ICF), received approval/a favorable opinion from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

An Independent Data Monitoring Committee (IDMC) was established to independently monitor safety data as well as operation of the study. The IDMC had periodic meetings to ensure careful monitoring of subject safety. Ad hoc meetings were also held as required. After each meeting, the IDMC was to provide advice on whether the study should be continued, modified, or discontinued on the basis of the toxicities observed.

Representatives of the sponsor were allowed to visit all study site locations periodically to assess the data quality and study integrity. Onsite monitoring and/or auditing were performed according to the sponsor's (Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb Company) standard operating procedures. The quality of data collected and analyzed was monitored according to the sponsor's standard operating procedures.

During the course of investigations of a GCP non-compliant activity in (b) (4) (see Section 8.1.2 "Compliance with Good Clinical Practices"), the Sponsor identified one SAE of diabetic ketoacidosis (nivolumab group; Grade 4; related; date of onset: (b) (6)) that occurred prior to the clinical cut-off date ((b) (6)) but was not reported by the DBL date of 28-Dec-2018). A brief narrative of the SAE is included below:

- On (b) (6), the patient initiated study treatment with nivolumab at a dose of 240 mg IV. The patient received a total of 4 cycles of nivolumab, and the last dose was on (b) (6) prior to the event. On (b) (6), the patient was admitted to the hospital for hyperglycemia, with suspicion of diabetic ketoacidosis. After admission, there was consultation with the endocrinology and metabolism division for hyperglycemia control. Laboratory results showed glucose 968 mg/dL (normal range: 70-100 mg/dL). The patient received human insulin on (b) (6) for diabetic ketoacidosis; glucose decreased to normal after treatment and the event diabetic ketoacidosis was considered resolved on (b) (6), with sequelae. Subsequent laboratory results on (b) (6) showed glucose 399 mg/dL. The patient received human insulin from (b) (6) to (b) (6) and glimepiride and metformin on (b) (6) for diabetic ketoacidosis. Laboratory results on (b) (6) showed glucose 180 mg/dL. After consultation with a social worker and hospice team due to disease progression and terminal stage illness, the patient's family agreed to palliative care only. The case was diagnosed as Type 2 diabetes mellitus. The patient was kept hospitalized to monitor until stable, and was discharged on (b) (6).

Since diabetic ketoacidosis is a known side effect of nivolumab[51] and this occurrence represented the only such event in study ONO-4538-24 (CA209473), the Sponsor concluded that this does not alter the safety evaluation of the study results and the subsequent risk and benefit assessment.

The FDA's Assessment:

Section 11.1 of the last version of the clinical protocol submitted in this Application (version 9, v9, dated November 7, 2017) indicated that the study would be conducted in accordance with the ethical principles that are consistent with the GCP guidelines developed by the ICH, and Section 5.2 in the Clinical Study Report (CSR) stated that the study was indeed conducted in accordance with these ethical principles. Section 5.2 of the CSR also reported the non-GCP-compliant activity that occurred in sites in

(b) (4) (please see Section 8.1.2 of this review for further details regarding the FDA assessment of the non-GCP complaint activity). Section 10.2 of clinical protocol v9 outlined the role of the IDMC as described above by the Applicant.

The Applicant submitted the names and addresses of the IECs/IRBs and the protocol approval dates in Section 16.1.3 of the CSR. In a response to an FDA Information Request, the Applicant adequately explained why some versions of the protocol were not reviewed by the IEC/IRBs (i.e., a more updated version of the protocol was available at the time of site initiation or the site was closed at the time an updated version of the protocol was available).

The FDA concurs with the Applicant's statement that diabetic ketoacidosis (DKA) is a known side effect of nivolumab. The nivolumab product labeling states that 0.9% (17/1994) patients who received single agent nivolumab developed diabetes, of which there were two cases of DKA. The time of onset for the case of DKA in Study ONO-4538-24 (CA209473) was 3.5 months, which was also consistent with the time to onset of DKA reported in the nivolumab product labeling (median: 4.4 months, range: 15 days to 22 months).

Categorization of Adverse Event

The Applicant's Position:
Adverse events (AEs) were coded by using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. Adverse events and drug-related AEs in each treatment group were summarized by System Organ Class (SOC), Preferred Term (PT), Grade, etc. For laboratory parameters for which Grades were defined in CTCAE version 4.0, the baseline Grade and the worst CTC Grade after treatment in each treatment group were evaluated in the shift table.

The FDA's Assessment:
National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0 was used to assess the severity of all TEAEs. The MedDRA version 21.1 dictionary was used to code TEAE data. TEAEs were assessed from the time of study treatment initiation and for 28 days after the last dose of study treatment (referred to as the "28-day window"). Because of the long half-life of monoclonal antibodies and the potential for late-onset treatment-emergent IMAEs beyond the 28-day period following the last dose of nivolumab, treatment-emergent SAEs and IMAEs were also followed for 100 days after the last dose of study treatment per the study protocol (the "100-day window"). The Preferred Terms "lymphangiosis carcinomatosa," "malignant neoplasm progression," and "disease progression" were cases of disease progression that were in the AE dataset (n=3 nivolumab, n=1 paclitaxel), and these cases were not included in the FDA's TEAE analysis. The FDA reviewed the narratives of the events associated with these Preferred Terms and the Applicant's responses to FDA Information Requests regarding these events, and determined that these four events were indeed disease progression. One of the four events was reported as a Grade 5 event (patient ID (b) (6) in the nivolumab group, Preferred Term "disease progression"), where the patient developed concurrent Grade 3 Stevens-Johnson syndrome (SJS) and rapidly progressing metastatic retroperitoneal lymph

nodes that caused obstruction of the inferior vena cava (IVC), and subsequent lower extremity and scrotal swelling. The patient also developed disseminated intravascular coagulation (DIC) and required renal replacement therapy, and ultimately died during the same hospitalization. The Investigator attributed the patient's DIC to stasis caused by the IVC obstruction, and attributed the patient's death to disease progression. The Investigator stated that SJS leading to DIC, coagulopathy, and renal failure could not be ruled out, but the Investigator ultimately determined that SJS was not the direct cause of the patient's death because the Investigator considered the SJS to be "early stage." Although the cause of death in this case is hard to determine, the event of SJS does not change the risk profile of nivolumab where SJS and Toxic epidermal necrolysis, some with fatal outcomes, are listed under Warnings and Precautions in the product labeling for nivolumab.

Routine Clinical Tests

Data:

Table 23: Safety Laboratory Assessments

Safety Laboratory Assessments	Screening	Study Visits as Outlined in Study Protocol
Hematology: red blood cell count, MCV, MCH, MCHC, hemoglobin, hematocrit, white blood cell count, white blood cell differential count (neutrophils, lymphocytes, eosinophils, basophils, monocytes), platelet count	X	X
Biochemistry: albumin, ALP, AST (GOT), ALT (GPT), total bilirubin, direct bilirubin, gamma-GTP, total protein, creatinine, blood glucose, LDH, BUN, uric acid, CK (CPK), P, Ca, Na, K, Cl, C-reactive protein (CRP)	X	X
Urinalysis: specific gravity, protein, glucose, occult blood, sediment (white blood cells, red blood cells)	X	X
Immunological Tests: rheumatoid factor (RA), antinuclear antibody (ANA), surfactant protein D (SP-D), Krebs von den Lungen-6 (KL-6)	X	X
Hormone Tests: thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), free thyroxine (free T4)	X	X
Pregnancy Test: urine or serum pregnancy (WOCBP only)	X	X
Viral Tests: HIV-1 antibody, HIV-2 antibody, HTLV-1 antibody, HBs antigen, HBs antibody, HBc antibody, HCV antibody	X	

Source: Refer to protocol synopsis Tables 6-1, 6-2, 6-3 and protocol Sections 8.2.4.3 (Laboratory Tests), 8.2.4.4 (Pregnancy Testing), and 8.2.4.5 (Viral Tests) from the ONO-4538-24 (CA209473) final CSR.

The Applicant's Position:

Clinical laboratory parameters (hematology and serum chemistry) were graded using the NCI Common Toxicity Criteria (CTC), version 4.0, and are reported using International System (SI) units and US units. In ONO-4538-24 (CA209473), summaries of on-treatment worst CTC grade (Grade 1-4 and Grade 3-4) laboratory parameters that worsened relative to baseline were tabulated. By-subject listings of abnormal laboratory values are provided in the CSR. The baseline grade and the worst CTC grade after treatment in each treatment group were evaluated in shift tables. Numbers of subjects with abnormal hepatic function and thyroid dysfunction in each treatment group were summarized. The number and

percentage of subjects with ALT or AST level > 3 x, 5 x, 10 x, and 20 x upper limit of normal (ULN), and the bilirubin level (measured within 30 days before or after ALT or AST measurement) > 2 x ULN were tabulated. The number and percentage of subjects with elevated (> ULN) or low (< LLN) TSH, T3 and T4 levels, and those subjects who had shifted between the categories were also summarized.

Overall, the routine clinical laboratory tests performed in ONO-4538-24 (CA209473) are considered adequate for the evaluation of safety of nivolumab in the target patients population.

The FDA's Assessment:

Error! Not a valid bookmark self-reference. provides the schedule for laboratory tests performed during study treatment as outlined in clinical protocol v9. These tests were also performed at screening, the end of treatment, and 28 days after the end of treatment. The FDA agrees with the Applicant's assessment that the clinical laboratory tests performed in Study ONO-4538-24 (CA209473) are adequate for the evaluation of the safety of nivolumab in the target patient population.

Table 24: Laboratory test schedules for Study ONO-4538-24 (CA209473) – All treated patients (FDA analysis)

Schedule	Nivolumab	Docetaxel	Paclitaxel
Treatment schedule	administered every 2 weeks, each cycle is 6 weeks long	administered every 3 weeks, each cycle is 3 weeks long	administered once a week for 6 weeks, followed by a 2-week holiday
Laboratory schedule			
Hematology, biochemistry, and urinalysis	Cycle 1: Days 8, 15, 29, 43 Cycle ≥2: Days 1, 15, 29, 43	Cycle 1: Days 8, 22 Cycle ≥2: Days 1, 22	Cycle 1: Days 8, 15, 22, 29, 36, 50 Cycle ≥2: Days 1, 8, 15, 22, 29, 36, 50
Immunological tests and hormone tests	Cycle ≥1: Day 43	Cycle ≥1: Day 22	Cycle ≥1: Day 50
Pregnancy test	prior to dose on Day 1 of each cycle (Cycle ≥1: Day 1)		

Source: Tables 6-1, 6-2, and 6-3 in Section 6.4 of clinical protocol version 9.

8.2.4. Safety Results

Table 25: Summary of Safety Results - ONO-4538-24 (CA209473) - All Treated Subjects

	No. of Subjects (%)											
	Nivolumab (N= 209)			Control								
				Total (N=208)			Docetaxel (N=65)			Paclitaxel (N =143)		
DEATHS												
No. of Subjects who died	159 (76.1)			173 (83.2)			52 (80.0)			121 (84.6)		
Initial Disease	141 (67.5)			151 (72.6)			47 (72.3)			104 (72.7)		
Drug Toxicity[a,b]	2 (1.0)			3 (1.4)			0			3 (2.1)		
Other Cancer	1 (0.5)			0			0			0		
Other	15 (7.2)			19 (9.1)			5 (7.7)			14 (9.8)		
Subjects who died within 28 days of last dose or start of subsequent anticancer therapy, whichever was first	18 (8.6)			9 (4.3)			1 (1.5)			8 (5.6)		
Initial Disease	11 (5.3)			3 (1.4)			0			3 (2.1)		
Drug Toxicity[a]	0			2 (1.0)			0			2 (1.4)		
Other Cancer	0			0			0			0		
Other	7 (3.3)			4 (1.9)			1 (1.5)			3 (2.1)		
Subjects who died within 100 days of last dose	60 (28.7)			65 (31.3)			23 (35.4)			42 (29.4)		
Initial Disease	46 (22.0)			50 (24.0)			19 (29.2)			31 (21.7)		
Drug Toxicity[a]	2 (1.0)			2 (1.0)			0			2 (1.4)		
Other Cancer	0			0			0			0		
Other	12 (5.7)			13 (6.3)			4 (6.2)			9 (6.3)		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
SAEs[c,d]												
All causality	68 (32.5)	43 (20.6)	7 (3.3)	77 (37.0)	63 (30.3)	5 (2.4)	27 (41.5)	27 (41.5)	0	50 (35.0)	36 (25.2)	5 (3.5)
Drug-related	33 (15.8)	20 (9.6)	0	47 (22.6)	39 (18.8)	2 (1.0)	17 (26.2)	17 (26.2)	0	30 (21.0)	22 (15.4)	2 (1.4)
AEs LEADING TO DISCONTINUATION[d]												
All causality	29 (13.9)	11 (5.3)	5 (2.4)	33 (15.9)	22 (10.6)	4 (1.9)	9 (13.8)	7 (10.8)	0	24 (16.8)	15 (10.5)	4 (2.8)
Drug-related	18 (8.6)	8 (3.8)	0	19 (9.1)	12 (5.8)	1 (0.5)	6 (9.2)	4 (6.2)	0	13 (9.1)	8 (5.6)	1 (0.7)
ALL CAUSALITY AEs[d]	189 (90.4)	80 (38.3)	7 (3.3)	205 (98.6)	147 (70.7)	5 (2.4)	63 (96.9)	49 (75.4)	0	142 (99.3)	98 (68.5)	5 (3.5)
DRUG-RELATED AEs[d,e]	137 (65.6)	38 (18.2)	0	198 (95.2)	131 (63.0)	2 (1.0)	60 (92.3)	47 (72.3)	0	138 (96.5)	84 (58.7)	2 (1.4)

Table 25: Summary of Safety Results - ONO-4538-24 (CA209473) - All Treated Subjects

	No. of Subjects (%)											
	Nivolumab (N= 209)			Control								
				Total (N=208)			Docetaxel (N=65)			Paclitaxel (N =143)		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL CAUSALITY IMAEs WITHIN 28 DAYS OF LAST DOSE												
IMAEs treated with Immune-modulating medication[f,g]												
Diarrhea/colitis	4 (1.9)	1 (0.5)	0	0	0	0	0	0	0	0	0	0
Hepatitis	1 (0.5)	0	0	0	0	0	0	0	0	0	0	0
Pneumonitis	9 (4.3)	2 (1.0)	0	6 (2.9)	3 (1.4)	0	1 (1.5)	0	0	5 (3.5)	3 (2.1)	0
Nephritis and renal dysfunction	0	0	0	0	0	0	0	0	0	0	0	0
Rash	23 (11.0)	3 (1.4)	0	23 (11.1)	1 (0.5)	0	7 (10.8)	0	0	16 (11.2)	1 (0.7)	0
Hypersensitivity/Infusion reaction	1 (0.5)	1 (0.5)	0	1 (0.5)	0	0	0	0	0	1 (0.7)	0	0
ALL CAUSALITY IMAEs WITHIN 28 DAYS OF LAST DOSE												
Endocrine IMAEs treated with or without Immune-modulating medications[f,g]												
Adrenal Insufficiency	0	0	0	0	0	0	0	0	0	0	0	0
Hypothyroidism/Thyroiditis	21 (10.0)	0	0	3 (1.4)	0	0	0	0	0	3 (2.1)	0	0
Hyperthyroidism	3 (1.4)	0	0	0	0	0	0	0	0	0	0	0
Diabetes mellitus	1 (0.5)	0	0	2 (1.0)	1 (0.5)	0	0	0	0	2 (1.4)	1 (0.7)	0
Hypophysitis	1 (0.5)	0	0	0	0	0	0	0	0	0	0	0

MedDRA Version 21.1; CTACAE version 4.0

[a] Deaths which result from drug-related AEs were counted.

[b] The deaths in the nivolumab arm were due to interstitial lung disease and pneumonitis. The deaths in the chemotherapy arm were due to pneumonia, spinal cord abscess, and interstitial lung disease.

[c] One case of Grade 4 SAE of diabetic ketoacidosis was reported after the DBL date and therefore is not captured here.

[d] AEs, drug-related AEs, SAEs, and drug-related SAEs occurring between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequent anti-cancer therapy after the last dose, whichever comes first, were tabulated.

[e] Drug-related AEs were defined as any AEs with causal relationship with the product is "Related" or missing.

[f] Events occurring between the start date of the first administration of the product and the earlier date between 28 days after the end of the treatment period and the start date of the post-treatment observation period.

[g] Immune-mediated AEs are defined per BMS nivolumab standard (Table E.51-SCS in SCS Appendix 2).

Source: Refer to Table 14.3.1.1-2 (deaths), Table 14.3.1.1.8-2 through -3 and Table 14.3.1.1.9-1 through -6 (all-causality and drug-related AEs), Table 14.3.1.1.13-1 through -3 (all-causality and drug-related AEs leading to discontinuation), and Table 14.3.1.1.19-1 through -3 (all-causality and drug-related SAEs) in the ONO-4538-24 (CA209473) Final CSR. See SCS Appendix 2 for Table E.28.a-SCS (all-causality IMAEs) and Table E.30.a-SCS (all-causality endocrine IMAEs); ADaM dataset: ADSL.xpt, ADAE.xpt

Deaths

Data:
Please see death data included in Table 25.

The Applicant's Position:
As of the CSR data cutoff date (12-Nov-2018), deaths from any cause during the study were reported in 159 subjects (76.1%) in the nivolumab group and 173 subjects (83.2%) in the control group (Table 25). Progression of initial disease was the most common reason for death in each group (141 nivolumab subjects [67.5%] and 151 control subjects [72.6%]).

Two deaths (1.0%) were attributed to study drug toxicity with nivolumab; these occurred after 28 and within 100 days of permanent drug discontinuation. With chemotherapy, 3 deaths (1.4%) were attributed to study drug toxicity; all related to paclitaxel. Two of these deaths occurred within 28 days of last dose and 1 occurred beyond 100 days of last dose; these included the following:

- Nivolumab group: pneumonitis and interstitial lung disease (1 subject each)
- Control group: pneumonia, spinal cord abscess, and interstitial lung disease (1 subject each)

Details regarding the 2 subjects who died in the nivolumab group due to drug toxicity are included in Section 14.3.3 in the ONO-4538-24 (CA209473) final CSR, and Section 2.2 of the Summary of Clinical Safety.

The FDA's Assessment:

The FDA has the following comments regarding the Applicant's Table 25:

To better characterize the causes of deaths reported as "other cancer" and "other" in the Applicant's Table 25, the FDA analysis in Pneumonitis is a known adverse reaction for nivolumab and does not raise new safety concerns relative to the safety profile of nivolumab described in the current product labeling. Non-DRAEs, as assessed by Investigator or Applicant, leading to death of note were deaths due to esophageal fistulas (n=2) and hematemesis (n=1) in the nivolumab group and the hematemesis (n=1) in the paclitaxel group. Although these AEs are expected in patients with ESCC, it is notable that three patients (1.4%) in the nivolumab group versus one (0.5%) patient in the chemotherapy group experienced these events. See the section entitled "All causality treatment-emergent SAEs" of Section 8.2.4 for a discussion regarding esophageal fistulas and hematemesis. An exploratory analysis performed by the FDA indicated that the esophageal fistulas tended to develop in patients whose ESCC progressed later during the course of study treatment (i.e., late progressors). This suggests that although nivolumab was associated with more deaths due to these two TEAEs which may signify ESCC progression, early progressors did not experience these TEAEs at a higher rate than late progressors (see Section 8.2.9 for this exploratory FDA analysis). Given that the FDA cannot conclusively determine that these esophageal fistulas and hematemesis occurred due to disease progression and because their corresponding narratives did not describe disease progression or disease-related issues as the cause of death, these Grade 5 events were included in the list of fatal reactions in the nivolumab product labeling.

Table 26 categorizes the causes of deaths as related to initial disease, TEAEs (within which drug-related TEAEs [DRAE] as assessed by the Investigator or Applicant is a subcategory) and not related to initial disease or TEAEs. Note, in contrast to the Applicant's Table 25, which reports the *deaths* that occurred within the indicated timeframe (i.e., 28 days from last dose or 100 days from last dose), Pneumonitis is a known adverse reaction for nivolumab and does not raise new safety concerns relative to the safety profile of nivolumab described in the current product labeling. Non-DRAEs, as assessed by Investigator or Applicant, leading to death of note were deaths due to esophageal fistulas (n=2) and hematemesis (n=1) in the nivolumab group and the hematemesis (n=1) in the paclitaxel group. Although these AEs are expected in patients with ESCC, it is notable that three patients (1.4%) in the nivolumab group versus one (0.5%) patient in the chemotherapy group experienced these events. See the section entitled "All causality treatment-emergent SAEs" of Section 8.2.4 for a discussion regarding esophageal fistulas and hematemesis. An exploratory analysis performed by the FDA indicated that the esophageal fistulas tended to develop in patients whose ESCC progressed later during the course of study treatment (i.e., late progressors). This suggests that although nivolumab was associated with more deaths due to these two TEAEs which may signify ESCC progression, early progressors did not experience these TEAEs at a higher rate than late progressors (see Section 8.2.9 for this exploratory FDA analysis). Given that the FDA cannot conclusively determine that these esophageal fistulas and hematemesis occurred due to disease progression and because their corresponding narratives did not describe disease progression or disease-related issues as the cause of death, these Grade 5 events were included in the list of fatal reactions in the nivolumab product labeling.

- **Table 26** reports *TEAEs* that occurred within the indicated timeframe that led to deaths which may have occurred beyond the respective timeframe.
- One patient in the nivolumab group (patient ID (b) (6)) was reported to have died from disease progression 14 days after the last dose of nivolumab (see the patient narrative summary in the "Categorization of Adverse Event" section of this review), and thus deaths from initial disease in the nivolumab group prior to the data cutoff date should be 142 (67.9%) instead of 141 (67.5%).
- Three patients died from DRAEs as assessed by the Investigator or Applicant in the nivolumab group prior to the DBL (all due to pneumonitis/interstitial lung disease [ILD]), not two as indicated in the Applicant's Table 25. One case of pneumonitis (patient ID (b) (6)) was reported as "not related" to nivolumab, but the FDA disagrees with this assessment. The patient received 2 doses of nivolumab and died 13 days after the last dose of nivolumab.
- Five patients died due to DRAEs as assessed by the Investigator or Applicant in the chemotherapy group prior to the DBL (n=1 docetaxel, 4=paclitaxel) instead of three as indicated in the Applicant's Table 25. The FDA determined that one additional patient died in each chemotherapy arm. A patient in the docetaxel arm (patient ID (b) (6)) was reported as having an "unknown" cause of death because the patient refused further assessments eight days prior to death during a hospitalization for Grade 3 febrile neutropenia and Grade 4 septic shock in the setting of pneumonia. A patient in the paclitaxel arm (patient ID (b) (6)) was reported as having died from "pneumonia" not related to paclitaxel, but the patient died from PJP pneumonia 15 days after the last dose of paclitaxel. The

> FDA considers both of these patients to have died from a TEAE possibly related to docetaxel and paclitaxel, respectively, given the temporal relationship between the TEAE, death and study drug exposure, and because chemotherapies increase the risk of infections. Thus in addition to the three causes of death listed by the Applicant attributable the chemotherapy group (i.e., pneumonia, spinal cord abscess, and ILD), there were two additional causes of death attributable to this treatment group: one case of febrile neutropenia and one case of pneumonia.

The FDA agrees with the Applicant's statement that the most common cause of death in both treatment groups was disease progression. Slightly more patients in the chemotherapy treatment group died over the course of the study, both from initial disease and TEAEs including DRAEs as assessed by the Investigator or Applicant. Although formal comparisons cannot be made between the treatment groups, numerically more patients died from initial disease within 28 days from the last dose of study treatment in the nivolumab group compared to the chemotherapy group (5.7% versus 1.4%), but by 100 days from the last dose of study treatment, the number of patients who died from initial disease were similar between the two groups (22.5% versus 24.0%). Deaths due to TEAEs and DRAEs as assessed by the Investigator or Applicant are numerically higher in the chemotherapy group compared to the nivolumab group using both timeframes (28-day and 100-day windows), except for TEAEs that occurred within 28 days of last dose that led to death (nivolumab 5.3% versus chemotherapy 4.3%). TEAEs that occurred within the 28-day window that led to death in the nivolumab group were: pneumonitis or ILD (n=3), pneumonia (n=2), sepsis or septic shock (n=2), esophageal fistula (n=1), gastrointestinal hemorrhage (n=1), sudden death (n=1), and pulmonary embolism (n=1). The additional TEAE that occurred in the nivolumab group within the 100-day window that led to death was esophageal fistula (n=1), but the narrative for this event stated that "the patient developed a rupture of the aorta due to progressive esophageal tumor with progressive infiltration of the aortic arch," so this TEAE was due to disease progression. The Grade 5 TEAEs that occurred within the 28-day window, except for one case of sepsis potentially attributable to subsequent cytotoxic chemotherapy, were included in the list of fatal reactions in the product labeling for nivolumab because their corresponding narratives did not describe disease progression or disease-related issues as a potential cause of death.

TEAEs that occurred within the 28-day window that led to death in the chemotherapy control group were the following in the paclitaxel arm: pneumonia (n=2), sepsis (n=1), spinal abscess (n=1), ILD (n=1), tumor hemorrhage (n=1), sudden death (n=1), and hypercalcemia (n=1); and in the docetaxel arm: unknown (n=1, narrative reported that the patient died during a hospitalization for Grade 3 febrile neutropenia and Grade 4 septic shock due to pneumonia). The additional TEAEs that occurred in the chemotherapy control group within the 100-day window that led to death were pneumonia (n=3) and dyspnea (n=1) in the paclitaxel arm; and pneumonia (n=2) and unknown (n=1, narrative did not provide details regarding the cause of death) in the docetaxel arm.

Pneumonitis is a known adverse reaction for nivolumab and does not raise new safety concerns relative to the safety profile of nivolumab described in the current product labeling. Non-DRAEs, as assessed by Investigator or Applicant, leading to death of note were deaths due to esophageal fistulas (n=2) and hematemesis (n=1) in the nivolumab group and the hematemesis (n=1) in the paclitaxel group. Although

these AEs are expected in patients with ESCC, it is notable that three patients (1.4%) in the nivolumab group versus one (0.5%) patient in the chemotherapy group experienced these events. See the section entitled "All causality treatment-emergent SAEs" of Section 8.2.4 for a discussion regarding esophageal fistulas and hematemesis. An exploratory analysis performed by the FDA indicated that the esophageal fistulas tended to develop in patients whose ESCC progressed later during the course of study treatment (i.e., late progressors). This suggests that although nivolumab was associated with more deaths due to these two TEAEs which may signify ESCC progression, early progressors did not experience these TEAEs at a higher rate than late progressors (see Section 8.2.9 for this exploratory FDA analysis). Given that the FDA cannot conclusively determine that these esophageal fistulas and hematemesis occurred due to disease progression and because their corresponding narratives did not describe disease progression or disease-related issues as the cause of death, these Grade 5 events were included in the list of fatal reactions in the nivolumab product labeling.

Table 26: Summary of deaths in Study ONO-4538-24 (CA209473) – All treated patients (FDA analysis)

	Trial Arm			
	Nivolumab (n=209)	Chemotherapy Control		
		Chemotherapy Pooled (n=208)	Docetaxel (n=65)	Paclitaxel (n=143)
Deaths until data cutoff (November 12, 2018), n (%)				
Total deaths	159 (76.1)	173 (83.2)	52 (80.0)	121 (84.6)
Progressive Disease	142 (67.9)	151 (72.6)	47 (72.3)	104 (72.7)
Related to TEAEs (regardless of causality)	14 (6.7)	20 (9.6)	5 (7.7)[a]	15 (10.5)
Drug-related TEAEs (DRAEs) as assessed by the Investigator or Applicant	3 (1.4)	5 (2.4)	1 (1.5)	4 (2.8)
Not related to initial disease or TEAEs	3 (1.4)[b]	3 (1.4)	1 (1.5)[c]	2 (1.4)[c]
Deaths due to initial disease, n (%)				
Within 28 days of last dose or start of subsequent anticancer therapy, whichever was first	12 (5.7)	3 (1.4)	0	3 (2.1)
Within 100 days of last dose	47 (22.5)	50 (24.0)	19 (29.2)	31 (21.7)

	Trial Arm			
	Nivolumab (n=209)	Chemotherapy Control		
		Chemotherapy Pooled (n=208)	Docetaxel (n=65)	Paclitaxel (n=143)
Deaths related to TEAEs, n (%)				
TEAE occurred within 28 days of last dose or start of subsequent anticancer therapy, whichever was first	11 (5.3)[d]	9 (4.3)	1 (1.5)[e]	8 (5.6)[f]
TEAE occurred within 100 days of last dose	12 (5.7)[g]	16 (7.7)	4 (6.2)[h]	12 (8.4)[i]
Deaths related to DRAEs as assessed by the Investigator or Applicant, n (%)				
DRAE occurred within 28 days of last dose or start of subsequent anticancer therapy, whichever was first	3 (1.4)[j]	5 (2.4)	1 (1.5)[e]	4 (2.8)[k]
DRAE occurred within 100 days of last dose	3 (1.4)[l]	5 (2.4)	1 (1.5)[e]	4 (2.8)[k]

a. One patient (ID (b) (6)) developed a TEAE within the 28-day window, but died beyond the 100-day window; the patient developed interstitial lung disease (ILD) 4 days after the last dose of docetaxel, but died 142 days after the last dose of paclitaxel due to a multitude of reasons, including "aggravated ILD." However, it is unclear if the cause of death was related to ILD as a DRAE, so this patient's TEAE was excluded from DRAE.
b. Causes of death "unknown" (n=2) and "other cancer" (n=1).
c. Causes of death "unknown."
d. Seven patients died within the 28-day window.
e. This one patient died within the 28-day window. Cause of death was reported as "unknown," but the narrative reported that the patient was hospitalized for Grade 3 febrile neutropenia and Grade 4 septic shock due to pneumonia, and died during that hospitalization.
f. Five patients died within the 28-day window.
g. All twelve patients died within the 100-day window.
h. All four patients died within the 100-day window.
i. Eleven patients died within the 100-day window.
j. One patient died within the 28-day window. Cause of death was pneumonitis.
k. Three patients died within the 28-day window. Causes of death were pneumonia (n=2), spinal abscess (n=1), ILD (n=1).
l. All three patients died within the 100-day window. Cause of death was pneumonitis for all three patients.

Source: ADaM dataset from Module 5.3.5.3 - adsl.xpt

Serious Adverse Events

Data:

Table 27: Summary of Serious Adverse Events by Worst CTC Grade with 2% Cutoff - All Treated ONO-4538-24 (CA209473) Subjects

SOC PT	AEs (n [%])					
	Nivolumab			Control group		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
N	209	209	209	208	208	208
All Causality SAEs	68 (32.5)	43 (20.6)	7 (3.3)	77 (37.0)	63 (30.3)	5 (2.4)
Blood and lymphatic system disorders	2 (1.0)	2 (1.0)	0	17 (8.2)	17 (8.2)	0
Febrile neutropenia	0	0	0	16 (7.7)	16 (7.7)	0
General disorders and administration site conditions	9 (4.3)	2 (1.0)	1 (0.5)	7 (3.4)	5 (2.4)	1 (0.5)
Pyrexia	6 (2.9)	1 (0.5)	0	1 (0.5)	1 (0.5)	0
Infections and infestations	20 (9.6)	15 (7.2)	2 (1.0)	28 (13.5)	22 (10.6)	3 (1.4)
Pneumonia	10 (4.8)	5 (2.4)	2 (1.0)	13 (6.3)	9 (4.3)	2 (1.0)
Lung infection	1 (0.5)	1 (0.5)	0	5 (2.4)	4 (1.9)	0
Metabolism and nutrition disorders	12 (5.7)	10 (4.8)	0	8 (3.8)	8 (3.8)	0
Decreased appetite	3 (1.4)	0	0	6 (2.9)	6 (2.9)	0
Drug-related SAEs	33 (15.8)	20 (9.6)	0	47 (22.6)	39 (18.8)	2 (1.0)
Blood and lymphatic system disorders	1 (0.5)	1 (0.5)	0	17 (8.2)	17 (8.2)	0
Febrile neutropenia	0	0	0	16 (7.7)	16 (7.7)	0
General disorders and administration site conditions	6 (2.9)	1 (0.5)	0	3 (1.4)	2 (1.0)	0
Pyrexia	5 (2.4)	1 (0.5)	0	0	0	0
Infections and infestations	4 (1.9)	3 (1.4)	0	13 (6.3)	9 (4.3)	2 (1.0)
Lung infection	0	0	0	5 (2.4)	4 (1.9)	0
Metabolism and nutrition disorders	2 (1.0)	1 (0.5)	0	7 (3.4)	7 (3.4)	0
Decreased appetite	1 (0.5)	0	0	6 (2.9)	6 (2.9)	0

Any AEs were coded using MedDRA version 21.1.
CTCAE version 4.0.
AEs occurring between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequent anti-cancer therapy after the last dose, whichever comes first, were tabulated.
Source: refer to Table 14.3.1.1.19-1 from the ONO-4538-24 (CA209473) final CSR; ADaM dataset: ADSL.xpt, ADAE.xpt

The Applicant's Position:

All Causality SAEs

Any Grade: SAEs of any grade were reported in 32.5% of subjects in the nivolumab group and 37.0% of subjects in the control group (Table 27Table 27). Common SAEs (incidence ≥ 2%) included:

- Nivolumab group: pneumonia (10 subjects, 4.8%) and pyrexia (6 subjects, 2.9%)
- Control group: febrile neutropenia (16 subjects, 7.7%), pneumonia (13 subjects, 6.3%), decreased appetite (6 subjects, 2.9%), and lung infection (5 subjects, 2.4%)

Grade 3-4: Grade 3 to 4 SAEs were reported in 20.6% and 30.3% of subjects in the nivolumab and control groups, respectively (Table 27). The most common Grade 3-4 SAEs were as follows:

- Nivolumab group: pneumonia (5 subjects, 2.4%) and hypercalcaemia (4 subjects, 1.9%)

- Control group: febrile neutropenia (16 subjects, 7.7%), pneumonia (9 subjects, 4.3%), and decreased appetite (6 subjects, 2.9%)

Drug-related SAEs

Any Grade: Drug-related SAEs were reported in 15.8% of nivolumab-treated subjects and 22.6% of chemotherapy treated subjects, respectively (Table 27, Table 14.3.1.1-19-1 of the ONO-4538-24 (CA209473) Final CSR). Drug-related SAEs reported in ≥2 subjects were as follows:

- Nivolumab group: pyrexia (5 subjects, 2.4%), ILD (4 subjects, 1.9%), tumour haemorrhage (3 subjects, 1.4%), pneumonia and pneumonitis (each 2 subjects, 1.0%)
- Control group: febrile neutropenia (16 subjects, 7.7%), decreased appetite (6 subjects, 2.9%), lung infection (5 subjects, 2.4%), pneumonia, neutrophil count decreased, and ILD (each 3 subjects, 1.4%), and diarrhoea, nausea, vomiting, pneumonia aspiration, and pneumonitis (each 2 subjects, 1.0%)

Grade 3-4: Drug-related Grade 3-4 SAEs were reported in 9.6% and 18.8% of subjects in the nivolumab and control groups, respectively. Drug-related Grade 3-4 SAE reported in ≥2 subjects were as follows:

- Nivolumab group: tumor haemorrhage (3 subjects, 1.4%)
- Control group: febrile neutropenia (16 subjects, 7.7%), decreased appetite (6 subjects, 2.9%), lung infection (4 subjects, 1.9%), decreased neutrophil count (3 subjects, 1.4%), aspiration pneumonia and pneumonitis (each 2 subjects, 1.0%)
- The docetaxel group had more Grade 3-4 drug-related SAEs (26.2% of subjects) compared to the paclitaxel group (15.4% of subjects) (Table 25)

The FDA's Assessment:

Summary of safety results

Numerically more patients experienced TEAEs, Grade 3-4 TEAEs, and treatment-emergent serious AEs (SAEs) in the pooled chemotherapy group compared to the nivolumab group within both the 28-day window and the 100-day window (**Error! Not a valid bookmark self-reference.**). **Error! Not a valid bookmark self-reference.Error! Not a valid bookmark self-reference.** includes the patient in the nivolumab group who experienced a nivolumab-related SAE of Grade 4 DKA 97 days after the last dose of nivolumab. This SAE was not included in the Applicant's Table 25 (although the SAE is mentioned as a footnote in Table 25) because the SAE was not reported prior to the DBL due to GCP non-compliant activity in (b) (4)

Table 28: Summary of major safety results in Study ONO-4538-24 (CA209473) – All treated patients (FDA analysis)

	Trial Arm			
	Nivolumab (n=209)	Chemotherapy Control		
		Chemotherapy Pooled (n=208)	Docetaxel (n=65)	Paclitaxel (n=143)
Patients who experienced a TEAE, n (%)				
28-day window	189 (90.4)	205 (98.6)	63 (96.9)	142 (99.3)
100-day window	190 (90.9)	206 (99.0)	64 (98.5)	142 (99.3)
Patients who experienced a Grade 3-4 TEAE, n (%)				
28-day window	80 (38.3)[b]	148 (71.2)	49 (75.4)	99 (69.2)[c]
100-day window	88 (42.1)[a,b]	143 (68.8)	47 (72.3)	96 (67.1)[c]
Patients who experienced a treatment-emergent SAE, n (%)				
28-day window	67 (32.1)[b]	76 (36.5)	27 (41.5)	49 (34.3)[c]
100-day window	80 (38.3)[a,b]	87 (41.8)	31 (47.7)	56 (39.2)[c]
Patients who permanently discontinued study treatment due to a TEAE, n (%)				
28-day window	28 (13.4)[d,e,f]	32 (15.4)[g]	9 (13.8)[g]	23 (16.1)[c,g]
100-day window	30 (14.4)[d,e,f]	32 (15.4)[g]	9 (13.8)[g]	23 (16.1)[c,g]
Patients who delayed study treatment due to a TEAE, n (%)				
28-day window	57 (27.3)	120 (57.7)	13 (20.0)	107 (74.8)
Patients who dose-reduced study treatment due to a TEAE, n (%)				
28-day window	0	77 (37.0)	36 (55.4)	41 (28.7)

a. This number includes the patient in the nivolumab group who experienced a treatment-emergent SAE of Grade 4 DKA 97 days after the last dose of nivolumab, but this SAE was not reported prior to the DBL due to GCP non-compliant activity in (b) (4). The SAE was considered a DRAE as assessed by the Investigator or Applicant.

b. Grade 3 "Lymphangiosis carcinomatosa" was excluded from this analysis since this is not a TEAE, but disease progression (patient ID (b) (6) in the nivolumab group).

c. Grade 4 and 5 "disease progression" was excluded from this analysis since this is not a TEAE, but disease progression (patient ID (b) (6) in the paclitaxel treatment arm).

d. Grade 5 "malignant neoplasm progression" was excluded from this analysis since this is not a TEAE, but disease progression (patient ID (b) (6) in the nivolumab group).

e. Two patients (in the nivolumab group) received their last dose of study treatment before the occurrence of the TEAEs, which occurred in the 100-day window, that led to treatment discontinuation. Because "treatment discontinuation flags" are marked on the day of treatment discontinuation, there is a discrepancy between the 28-day window and 100-day window for the number of patients who permanently discontinued nivolumab due to a TEAE due to these 2 patients. The day of treatment discontinuation does not necessarily align with the day of the last dose of study treatment administration.

f. This table does not include the four patients who the Applicant did not flag as having discontinued nivolumab due to a TEAE. However, the FDA review of the narratives for these patients suggests that nivolumab was discontinued due to

TEAEs that occurred within the 28-day window:

- Patient ID (b) (6) – treatment discontinuation reason stated, "starting post study treatment is more effective than waiting for AE resolution" (AE was Grade 1 extraocular myositis that progressed to Grade 2 extraocular myositis).
- Patient ID (b) (6) – treatment discontinuation reason stated, "onset of penumonia [*sic*] with a causal relationship to ONO-4528."
- Patient ID (b) (6) – narrative stated, "The patient discontinued the treatment on 16-May-2017 due to lung dysfunction and investigator's judgement that the patient's activities of daily living (ADL) were getting worse for continuing nivolumab treatment;" the only lung-associated TEAE reported was Grade 2 bronchitis that the investigator did not think was related to nivolumab.
- Patient ID (b) (6) – treatment discontinuation reason stated "intolerant;" the patient's TEAEs were Grade 2 ascites, Grade 1 cough, and Grade 1 productive cough.

g. This table does not include the three patients who the Applicant did not flag as having discontinued chemotherapy due to a TEAE. However, the FDA review of the narratives for these patients suggests that chemotherapy was discontinued due to TEAEs that occurred within the 28-day window:

- Patient ID (b) (6) – paclitaxel was discontinued while the patient was hospitalized for pneumonia.
- Patient ID (b) (6) – paclitaxel treatment discontinuation reason stated, "subject's family informed to site staff via cell phone that subject had been in the ER due to dyspnea. subject withdrew all procedures related with this study."
- Patient ID (b) (6) – narrative reported that docetaxel was discontinued during a hospitalization for Grade 4 febrile neutropenia and Grade 4 septic shock, and the patient died during the hospitalization with cause of death as "unknown." Note, the FDA included this patient's death as death due to DRAE (i.e., pneumonia) and not "unknown."

Source: ADaM dataset from Module 5.3.5.3 - adae.xpt

All causality treatment-emergent SAEs

The FDA excluded the two events due to disease progression that were reported as SAEs from the treatment-emergent SAE safety analysis, both of which occurred during the 28-day window: patient ID (b) (6) in the nivolumab group who had Grade 3 "lymphangiosis carcinomatosa" and patient ID (b) (6) in the paclitaxel arm who had Grade 4 and 5 "disease progression." As such, the FDA analysis in Numerically more patients experienced TEAEs, Grade 3-4 TEAEs, and treatment-emergent serious AEs (SAEs) in the pooled chemotherapy group compared to the nivolumab group within both the 28-day window and the 100-day window (**Error! Not a valid bookmark self-reference.**). **Error! Not a valid bookmark self-reference.Error! Not a valid bookmark self-reference.** includes the patient in the nivolumab group who experienced a nivolumab-related SAE of Grade 4 DKA 97 days after the last dose of nivolumab. This SAE was not included in the Applicant's Table 25 (although the SAE is mentioned as a footnote in Table 25) because the SAE was not reported prior to the DBL due to GCP non-compliant activity in (b) (4)

Table 28 had one less patient in each of the following groups: nivolumab, chemotherapy pooled and paclitaxel, compared to the Applicant. The FDA does not agree with the list of common treatment-emergent SAEs provided by the Applicant. After pooling of the Preferred Terms as indicated in Table 29, the FDA determined that the following are the most common treatment-emergent SAEs with an incidence rate ≥2% (for both the 28-day and 100-day windows):

- Nivolumab group: pneumonia, pneumonitis, esophageal fistula, and pyrexia
- Control group: pneumonia, febrile neutropenia, pneumonitis, and decreased appetite

Of the treatment-emergent SAEs that occurred in ≥1% of the patients who received nivolumab, the following SAEs occurred numerically more often in the nivolumab group than the chemotherapy group during both the 28-day and 100-day windows: pneumonitis, esophageal fistula, pyrexia, hemorrhage,

hepatobiliary disorders, and hypercalcemia. The composite term "hepatobiliary disorders" includes the Preferred Terms alanine aminotransferase increased, bile duct obstruction, hepatic function abnormal, and liver function test increased. These aforementioned treatment-emergent SAEs also occurred in the paclitaxel arm, but not in the docetaxel arm, except for hepatobiliary disorders, which did not occur in either chemotherapy arm. Among these treatment-emergent SAEs, the incidence of esophageal fistulas and pyrexia were ≥2% higher in the nivolumab group compared to the chemotherapy group during the 28-day window. During the 100-day window, the incidence of pneumonitis and esophageal fistulas were ≥2% higher in the nivolumab group compared to the chemotherapy group.

Thus, although some of the treatment-emergent SAEs that occurred more frequently in the nivolumab group were well-characterized adverse reactions of nivolumab (pneumonitis, pyrexia, and hepatobiliary disorders), there were three treatment-emergent SAEs that warrant further discussion: esophageal fistula, hemorrhage, and hypercalcemia. These treatment-emergent SAEs may represent disease progression that nivolumab was unable to control, rather than an adverse reaction to nivolumab. Thus, the FDA performed an exploratory analysis to investigate if patients whose ESCC progressed earlier in the study treatment course (i.e., early progressors) experienced these three TEAEs more frequently than those who progressed later (see Section 8.2.9). The analysis indicated that in the nivolumab group, a higher proportion of early progressors experienced hypercalcemia and Grade 3-4 and serious hemorrhages compared to late progressors, but the inverse was true for esophageal fistulas. The inconsistent pattern between these three TEAEs and the small number of patients who experienced these TEAEs preclude any conclusive observations.

All esophageal fistula events in both the nivolumab and chemotherapy groups were reported as Grade 3 to 5 in severity, except for one patient (patient ID (b) (6)) in the nivolumab arm who was reported to have a Grade 2 "oesophageal disorder." However, the patient's narrative describes a serious medical condition of perforation of the posterior wall of the esophagus to the vertebral body and "obvious air inside the vertebral body" on CT and the MRI, demonstrating infective spondylitis. The patient was hospitalized to receive intravenous antibiotics. The two Grade 5 esophageal fistula TEAEs that occurred in the study were both in the nivolumab group. One patient (ID (b) (6)) developed an esophagobronchial fistula 14 days after the last dose of nivolumab, which led to a fatal respiratory tract hemorrhage 45 days after the last dose of nivolumab. The other patient (ID (b) (6)) died 49 days after the last dose of nivolumab due an aortic rupture secondary to ESCC tumor progression.

The hemorrhages were all due to upper gastrointestinal (n=2) or esophageal tumor bleeding (n=5), and were all Grade 3 to 5 in severity. One of the upper gastrointestinal bleeding (UGIB) events occurred two months after the patient started taking aspirin 100 mg daily and one month after the patient started paclitaxel (patient ID (b) (6)); the patient was found to have gastric ulcers. The other patient with the UGIB was in the nivolumab group, and had two episodes of hematemesis on two consecutive days, of which the second episode was fatal (patient ID (b) (6)); the patient died 13 days following the last dose of nivolumab. One patient died in each treatment group (nivolumab and paclitaxel) from hemorrhages that occurred within the 28-day window, and both were not considered related to the study drug. The narrative for the patient who died from hemorrhage in the nivolumab group was described above (patient ID (b) (6)). The fatal hemorrhage that occurred in the paclitaxel arm was in a patient who developed hematemesis, but could not be resuscitated in the emergency department 8

days following the last dose of paclitaxel (patient ID (b) (6)).

SAEs of hypercalcemia were Grade 3 to 4 severity in the nivolumab group and Grade 5 severity in the paclitaxel arm; none were considered related to the study treatment by the Investigator or the Applicant. The Investigator stated that the patient died from "increasing adynamia" related to hypercalcemia in the narrative for the fatal case in the paclitaxel arm (patient ID (b) (6)).

Table 29: Treatment-emergent SAEs in ≥1% of patients receiving any study treatment (FDA analysis)

SAE	All grades SAE occurred within 28 days of last of study treatment		All grades SAE occurred within 100 days of last of study treatment	
	Nivolumab (n=209) n (%)	Chemotherapy Pooled (n=208) n (%)	Nivolumab (n=209) n (%)	Chemotherapy Pooled (n=208) n (%)
Pneumonia[a]	14 (6.7)	21 (10.1)	17 (8.1)	31 (14.9)
Interstitial lung disease[b]	8 (3.8)	6 (2.9)[j]	11 (5.3)	6 (2.9)[j]
Esophageal fistula[c]	7 (3.4)	1 (0.5)[j]	9 (4.3)	1 (0.5)[j]
Pyrexia	6 (2.9)	1 (0.5)[j]	6 (2.9)	2 (1.0)[j]
Hemorrhage[d]	4 (1.9)	2 (1.0)[j]	4 (1.9)	3 (1.4)[j]
Hypercalcemia	4 (1.9)[k]	1 (0.5)[j]	4 (1.9)[k]	1 (0.5)[j]
Hepatobiliary[e]	3 (1.4)	0	4 (1.9)	0
Decreased appetite[f]	3 (1.4)	6 (2.9)	3 (1.4)	7 (3.4)
Dyspnea	3 (1.4)	1 (0.5)	3 (1.4)	4 (1.9)
Diarrhea[g]	2 (1.0)	2 (1.0)	4 (1.9)	3 (1.4)
Pneumothorax[h]	2 (1.0)	3 (1.4)	2 (1.0)	3 (1.4)
Pleural effusion[i]	1 (0.5)	5 (2.4)	3 (1.4)	6 (2.9)
Febrile neutropenia	0	16 (7.7)	2 (1.0)	17 (8.2)
Neutrophil count decreased	0	3 (1.4)	0	3 (1.4)

Toxicity was graded per NCI CTCAE v4.

a. Includes pneumonia aspiration, pneumonia bacterial, and lung infection.
b. Includes pneumonitis, and radiation pneumonitis.
c. Includes tracheal fistula, oesophagobronchial fistula, oesophageal fistula, aorta-oesophageal fistula, fistula*, oesophageal perforation*, oesophageal disorder*, and aortic rupture*. Two patients whose Preferred Terms (PTs) were not in the composite PTs were added into this analysis after FDA review of the narratives; both patients were in the nivolumab group and had the treatment-emergent SAEs within 28 days of the last of nivolumab. Patient ID (b) (6) had an "unassigned" AEDECOD, and the narrative stated that the patient developed a Grade 3 esophagobronchial fistula that caused fatal respiratory tract hemorrhage. Patient ID (b) (6) had a Grade 2 "oesophageal disorder," which the patient's narrative described as perforation of the posterior wall of the esophagus to the vertebral body and associated infective spondylitis and hospitalization. *The narratives for the events associated with these PTs were reviewed to confirm that these events occurred due to an esophageal fistula.
d. Includes tumor-haemorrhage, upper gastrointestinal haemorrhage, and gastrointestinal haemorrhage.
e. Includes alanine aminotransferase increased, bile duct obstruction, hepatic function abnormal, and liver function test increased.
f. Includes hypophagia.
g. Includes colitis, and enterocolitis.
h. Includes spontaneous pneumothorax.

i. Includes infectious pleural effusion.
j. The SAE only occurred in the paclitaxel treatment arm.
k. This includes a patient (ID (b) (6)) whose narrative described a hospitalization due to Grade 2 blood creatinine increase (creatinine was 1.96 mg/dL) and hypercalcaemia (calcium was 12.6 mg/dL). However, the AETERM was reported as "hypercalemia," which coded to AEDECOD "hyperkalaemia." The narrative did not report hyperkalemia, nor elevated blood potassium level.

Source: ADaM dataset from Module 5.3.5.3 - adae.xpt

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 30: All Causality AEs and Drug-related AEs Leading to Discontinuation of Study Treatment by Worst CTCAE Grade in ≥ 2 Subjects - All Treated ONO-4538-24 (CA209473) Subjects

SOC		AEs (n [%])					
		Nivolumab			Control group		
PT		Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
	N	209	209	209	208	208	208
All Causality							
Total		29 (13.9)	11 (5.3)	5 (2.4)	33 (15.9)	22 (10.6)	4 (1.9)
Endocrine disorders		3 (1.4)	1 (0.5)	0	0	0	0
Hypothyroidism		2 (1.0)	0	0	0	0	0
Gastrointestinal disorders		4 (1.9)	3 (1.4)	1 (0.5)	3 (1.4)	3 (1.4)	0
Dysphagia		2 (1.0)	2 (1.0)	0	0	0	0
Infections and infestations		2 (1.0)	1 (0.5)	1 (0.5)	8 (3.8)	6 (2.9)	2 (1.0)
Pneumonia		1 (0.5)	0	1 (0.5)	4 (1.9)	2 (1.0)	2 (1.0)
Infectious pleural effusion		0	0	0	2 (1.0)	2 (1.0)	0
Investigations		0	0	0	3 (1.4)	3 (1.4)	0
Neutrophil count decreased		0	0	0	2 (1.0)	2 (1.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps		2 (1.0)	0	0	2 (1.0)	1 (0.5)	1 (0.5)
Malignant neoplasm progression		2 (1.0)	0	0	0	0	0
Nervous system disorders		0	0	0	5 (2.4)	3 (1.4)	0
Neuropathy peripheral		0	0	0	2 (1.0)	1 (0.5)	0
Respiratory, thoracic mediatinal disorders		14 (6.7)	4 (1.9)	2 (1.0)	7 (3.4)	4 (1.9)	0
Interstitial lung disease		5 (2.4)	1 (0.5)	0	3 (1.4)	1 (0.5)	0
Pneumonitis		5 (2.4)	1 (0.5)	1 (0.5)	2 (1.0)	2 (1.0)	0
Drug-related							
Total		18 (8.6)	8 (3.8)	0	19 (9.1)	12 (5.8)	1 (0.5)
Endocrine disorders		3 (1.4)	1 (0.5)	0	0	0	0
Hypothyroidism		2 (1.0)	0	0	0	0	0
Investigations		0	0	0	2 (1.0)	2 (1.0)	0
Neutrophil count decreased		0	0	0	2 (1.0)	2 (1.0)	0
Nervous system disorders		0	0	0	5 (2.4)	3 (1.4)	0
Neuropathy peripheral		0	0	0	2 (1.0)	1 (0.5)	0
Respiratory, thoracic mediatinal disorders		11 (5.3)	3 (1.4)	0	7 (3.4)	4 (1.9)	0
Interstitial lung disease		5 (2.4)	1 (0.5)	0	3 (1.4)	1 (0.5)	0
Pneumonitis		4 (1.9)	1 (0.5)	0	2 (1.0)	2 (1.0)	0

Any AEs were coded using MedDRA version 21.1. CTCAE version 4.0.
AEs of any grade occurred in ≥ 2 subjects in any group are included. AEs and drug-related AEs occurring between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequence anti-cancer therapy

after the last dose whichever comes first were tabulated. Drug-related AEs were defined as any AEs with causal relationship with the product is "Related" or missing.
Source: refer to Table 14.3.1.1.13-1 from the ONO-4538-24 (CA209473) final CSR; ADaM dataset: ADSL.xpt, ADAE.xpt

The Applicant's Position:

All Causality AEs Leading to Discontinuation

Any Grade: AEs leading to discontinuation of study treatment were reported in 13.9% of subjects in the nivolumab group and 15.9% of subjects in the control group (Table 30). No meaningful differences in the incidence of AEs leading to discontinuation were observed between the docetaxel and paclitaxel groups (see Table 25). AEs leading to discontinuation of study treatment, excluding disease progression, at an incidence of ≥2% included:

- Nivolumab group: interstitial lung disease and pneumonitis (each 5 subjects, 2.4%)
- Control group: none reported at an incidence of ≥2%.

Grade 3-4: Grade 3-4 AEs leading to treatment discontinuation were reported in 5.3% and 10.6% of subjects in the nivolumab and control groups, respectively (Table 30). Grade 3-4 AE leading to discontinuation reported in >1 subject included:

- Nivolumab group: dysphagia (2 subjects).
- Control group: pneumonia, infectious pleural effusion, decreased neutrophil count, and pneumonitis (each 2 subjects).

Drug-related AEs Leading to Discontinuation

Any Grade: Drug-related AEs leading to discontinuation of study treatment were reported in 8.6% (nivolumab) and 9.1% (control) of subjects (Table 30). Drug-related AEs leading to discontinuation of study treatment, excluding disease progression, at an incidence of ≥2% included:

- Nivolumab: interstitial lung disease (5 subjects, 2.4%). Drug-related AEs leading to discontinuation in >1 subject were pneumonitis (4 subjects, 1.9%) and hypothyroidism (2 subjects, 1.0%).
- Control: none reported at an incidence of ≥2%. Drug-related AEs leading to discontinuation in >1 subject were interstitial lung disease (3 subjects, 1.4%), neutrophil count decreased, neuropathy peripheral, and pneumonitis (each 2 subjects, 1.0%).

Grade 3-4 : Drug-related Grade 3-4 AEs leading to discontinuation of study treatment were reported in 3.8% and 5.8% of nivolumab and chemotherapy-treated subjects, respectively (Table 30). Drug-related Grade 3-4 AEs leading to discontinuation in > 1 patient included:

- Nivolumab: none
- Control: neutrophil count decreased and pneumonitis (1.0%, 2 subjects each)

The FDA's Assessment:

The FDA does not agree with the discontinuation rate due to TEAEs provided by the Applicant because the Applicant included the patients who discontinued study treatment due "AEs" that were actually disease progression events (see FDA's analysis tabulated in Numerically more patients experienced TEAEs, Grade 3-4 TEAEs, and treatment-emergent serious AEs (SAEs) in the pooled chemotherapy group

compared to the nivolumab group within both the 28-day window and the 100-day window (**Error! Not a valid bookmark self-reference.**). **Error! Not a valid bookmark self-reference.Error! Not a valid bookmark self-reference.** includes the patient in the nivolumab group who experienced a nivolumab-related SAE of Grade 4 DKA 97 days after the last dose of nivolumab. This SAE was not included in the Applicant's Table 25 (although the SAE is mentioned as a footnote in Table 25) because the SAE was not reported prior to the DBL due to GCP non-compliant activity in (b) (4).
Table 28). After excluding discontinuation of study treatment due to disease progression, 13.4% in the nivolumab group and 15.4% in the chemotherapy control group discontinued treatment due to TEAEs during the 28-day window (Numerically more patients experienced TEAEs, Grade 3-4 TEAEs, and treatment-emergent serious AEs (SAEs) in the pooled chemotherapy group compared to the nivolumab group within both the 28-day window and the 100-day window (**Error! Not a valid bookmark self-reference.**). **Error! Not a valid bookmark self-reference.Error! Not a valid bookmark self-reference.** includes the patient in the nivolumab group who experienced a nivolumab-related SAE of Grade 4 DKA 97 days after the last dose of nivolumab. This SAE was not included in the Applicant's Table 25 (although the SAE is mentioned as a footnote in Table 25) because the SAE was not reported prior to the DBL due to GCP non-compliant activity in (b) (4).
Table 28). Within the 100-day window, the proportion of patients who discontinued treatment due to AEs increased slightly to 14.4% in the nivolumab group and did not change in the chemotherapy group (Numerically more patients experienced TEAEs, Grade 3-4 TEAEs, and treatment-emergent serious AEs (SAEs) in the pooled chemotherapy group compared to the nivolumab group within both the 28-day window and the 100-day window (**Error! Not a valid bookmark self-reference.**). **Error! Not a valid bookmark self-reference.Error! Not a valid bookmark self-reference.** includes the patient in the nivolumab group who experienced a nivolumab-related SAE of Grade 4 DKA 97 days after the last dose of nivolumab. This SAE was not included in the Applicant's Table 25 (although the SAE is mentioned as a footnote in Table 25) because the SAE was not reported prior to the DBL due to GCP non-compliant activity in (b) (4)
Table 28, see footnote e for the reason why there is a difference in treatment discontinuation rates between the 28-day window and the 100-day window). It should be noted that the Applicant and Investigators did not flag all treatment discontinuation events that could have been due to TEAEs (see footnotes f and g of Table 28: Summary of major safety results in Study ONO-4538-24 (CA209473) – All treated patients (FDA analysis)the addition of addition of four and three patients into the number of patients who discontinued nivolumab and chemotherapy due to TEAEs, respectively, the difference in treatment discontinuation rates due to TEAEs between the two arms becomes even smaller (nivolumab group – 15.3% during the 28-day window and 16.3% during the 100-day window, and pooled chemotherapy group – 16.8%) (Table 28).

The FDA agrees with the all-grade incidence of TEAEs leading to dose delay or dose reduction in the Applicant's Table 30 except for those TEAEs listed in Table 31 due to the use of composite Preferred Terms in the FDA analysis. In addition, disease progression is not included in the FDA analysis of the safety data. Using the composite Preferred Terms, the TEAEs leading to discontinuation of study treatment at an incidence of ≥2% were pneumonitis in the nivolumab group, and pneumonitis and pneumonia in the chemotherapy control group.

Table 31: TEAEs that leading to study treatment discontinuation for which the FDA analysis results are different from the Applicant's (FDA analysis)

AE	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All grades, n (%)	Grade 3-4, n (%)	All grades, n (%)	Grade 3-4, n (%)
Pneumonitis[a]	11 (5.3)[e]	0	5 (2.4)[f]	2 (1.0)
Pneumonia[b]	2 (1.0)[g]	1 (0.5)	6 (2.9)[h]	4 (1.9)
Neuropathy peripheral[c]	0	0	4 (1.9)	3 (1.44)
Esophageal fistula[d]	2 (1.0)[i]	1 (0.5)	2 (1.0)	2 (1.0)

Toxicity was graded per NCI CTCAE v4.
a. Includes interstitial lung disease.
b. Includes pneumonia aspiration, and lung infection.
c. Includes peripheral motor neuropathy, and periphery sensory neuropathy.
d. Includes tracheal fistula, oesophagobronchial fistula, and fistula. See footnote c in Table 29 for further details.
e. Three patients (1.4%) in the nivolumab group died of pneumonitis.
f. One patient (0.5%) in the pooled chemotherapy group died of pneumonitis; the patient was in the paclitaxel arm.
g. One patient (0.5%) in the nivolumab group died of pneumonia.
h. Two patients (1.0%) in the pooled chemotherapy group died of pneumonia; the patients were in the paclitaxel arm.
i. One patient (0.5%) died of an esophageal fistula (Preferred Term was oesophagobronchial fistula).
Source: ADaM dataset from Module 5.3.5.1 - adae.xpt

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 32: Adverse Events Leading to Dose Delay and Dose Reduction - All Treated ONO-4538-24 (CA209473) Subjects

	Nivolumab			Control group		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
N	209	209	209	208	208	208
All-causality						
No. of subjects (%) with AEs leading to dose delay	57 (27.3)	33 (15.8)	0	120 (57.7)	90 (43.3)	0
No. of subjects (%) with AEs leading to dose reduction	0	0	0	77 (37.0)	38 (18.3)	0
Drug-related						
No. of subjects (%) with drug-related AEs leading to dose delay[a]	34 (16.3)	15 (7.2)	0	104 (50.0)	81 (38.9)	0
No. of subjects (%) with drug-related AEs leading to dose reduction[a]	0	0	0	75 (36.1)	37 (17.8)	0

AEs, drug-related AEs occurring between the start date of the first administration of the investigational product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.
[a] Drug-related AEs were defined as any AEs with causal relationship with the investigational product is "Related" or missing.
Source: refer to Table 14.3.1.1.1-1 from the ONO-4538-24 (CA209473) final CSR; ADaM dataset: ADSL.xpt, ADAE.xpt

The Applicant's Position:

No dose reductions were allowed for nivolumab in the study. A numerically lower incidence of AEs (all causality or drug-related) leading to dose delay of study treatment was reported in the nivolumab group vs the control group (Table 32Table 32).

The FDA's Assessment:

The FDA agrees with the results presented by the Applicant in Table 32Table 32 and the Applicant's position regarding dose delays. TEAEs that led to dose delay in ≥2% of patients in the nivolumab group were pneumonia, upper respiratory tract infection (URI) and rash, of which pneumonia and URI of all grades occurred more frequently in the pooled chemotherapy group compared to the nivolumab group, and rash of all grades occurred at the same frequency between the nivolumab group and the pooled chemotherapy group (Table 33). In addition, these TEAEs leading to dose delays in ≥2% of patients in nivolumab are expected. Among the TEAEs listed in Table 33, only esophageal fistula and increased blood creatine phosphokinase (CPK) were not previously reported as adverse reactions in the nivolumab product labeling, but their incidence rate was low (<2%) in this study. See the section entitled "All causality treatment-emergent SAEs" of Section 8.2.4 for a discussion regarding esophageal fistulas.

Eight patients had treatment-emergent increased blood CPK in this study, all of whom were in the nivolumab group. None of these patients discontinued nivolumab due to blood CPK increase, but nivolumab dosing was delayed in four patients due to increases in blood CPK (n=1 Grade 2 [patient ID (b) (6)], n=2 Grade 3 [patient ID (b) (6) and (b) (6)], and n=1 Grade 4 [patient ID (b) (6)]). To investigate if the blood CPK increase was clinically significant, the FDA analyzed the safety dataset for patients who experienced both blood CPK increase and a musculoskeletal TEAE or a cardiac TEAE, and only one patient was retrieved (patient ID (b) (6) in the nivolumab group). However, this patient's musculoskeletal TEAE was spondylolisthesis, which is not a medical condition known to be associated with blood CPK increase, and the two TEAEs occurred 7.5 months apart. In addition, nivolumab dosing was not delayed due to the increased blood CPK in this patient. To determine if the blood CPK increase was associated with any other TEAEs, the FDA reviewed the safety dataset for the other TEAEs that occurred around the same time as the blood CPK increase. Four of the patients had no other TEAEs reported around the time of blood CPK increase, and four did. One patient (patient ID (b) (6)) had Grade 3 transaminitis and Grade 2 hypothyroidism at the same time as Grade 3 blood CPK increase; the drug was discontinued due to the Grade 2 hypothyroidism. One patient (patient ID (b) (6)) had only Grade 1 events (dry skin, skin exfoliation and angular cheilitis) around the time of Grade 3 blood CPK increase; nivolumab was delayed for the Grade 3 CPK increase and the patient discontinued treatment due to disease progression 57 days after Grade 3 CPK increase started. One patient in the nivolumab group (patient ID (b) (6)) had Grade 3 anemia, Grade 3 diarrhea, Grade 2 pneumonia, Grade 2 cancer pain, Grade 2 decreased appetite, Grade 2 dysgeusia, Grade 2 nausea, and Grade 1 pyrexia around the time of Grade 4 blood CPK increase; these TEAE did not lead to dose delay and the patient discontinued treatment due to disease progression 68 days after the Grade 4 CPK increase started. One patient (patient ID (b) (6)) had Grade 1 increased aspartate aminotransferase and Grade 1 hypothyroidism at the same time as Grade 3 blood CPK increase; the drug was delayed for the Grade 1 aspartate aminotransferase increase and Grade 3 blood CPK increase and the patient remained on study

treatment at the time of the DBL. Thus, of the four patients who required a delay in nivolumab dosing due to increased CPK, only two had other TEAEs occur around the same time (patient IDs (b) (6) and (b) (6), who had Grade 3 blood CPK increases), and the other two patients had isolated increases in blood CPK that led to nivolumab dose delay (patient ID (b) (6) with Grade 2 and patient ID (b) (6) with Grade 4 blood CPK increases). Of the four patients who had other TEAEs at the time of blood CPK increase, only two of them had nivolumab dose delayed due to the blood CPK increase. Transaminitis (Grades 1 and 3) and hypothyroidism (Grades 1 to 2) were the only TEAEs that occurred around the time of blood CPK increase in more than one patient (occurred in only two of four patients). However, the small sample size precludes the ability to draw definitive conclusions regarding the clinical significance of the blood CPK increase. It is reassuring that the change in nivolumab dosing due to blood CPK increase was temporary and relatively rare (occurring in 1.9% of patients; all of which required nivolumab dose delays, not permanent discontinuation).

Table 33: TEAEs leading to dose delay in ≥2 patients receiving nivolumab within 28 days of last dose of study treatment, includes dose reduction for pooled chemotherapy group (FDA analysis)

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades[h] n (%)	Grades 3-4 n (%)	All Grades[h] n (%)	Grades 3-4 n (%)
Pneumonia[a]	9 (4.3)	5 (2.4)	15 (7.2)	6 (2.9)
Upper respiratory tract infection[b]	6 (2.9)	1 (0.5)	13 (6.3)	0
Rash[c]	5 (2.4)	2 (1.0)	5 (2.4)	2 (1.0)
Anemia	4 (1.9)	3 (1.4)	11 (5.3)	9 (4.3)
Hepatobiliary	4 (1.9)	1 (0.5)	4 (1.9)	2 (1.0)
Aspartate aminotransferase increased	2 (1.0)	0	0	0
Alanine aminotransferase increased	1 (0.5)	0	0	0
Bile duct obstruction	1 (0.5)	1 (0.5)	0	0
Gamma-glutamyltransferase increased	0	0	2 (1.0)	2 (1.0)
Hepatic function abnormal	0	0	2 (1.0)	0
Diarrhea	4 (1.9)	0	3 (1.4)	1 (0.5)
Pneumonitis[d]	4 (1.9)	1 (0.5)	3 (1.4)	1 (0.5)
Blood creatine phosphokinase increased	4 (1.9)	3 (1.4)	0	0
Pyrexia[e]	3 (1.4)	0	6 (2.9)	1 (0.5)
Esophageal fistula[f]	3 (1.4)	3 (1.4)	0	0
Blood creatinine increased	3 (1.4)	0	0	0
C-reactive protein increased	2 (1.0)	2 (1.0)	4 (1.9)	0
Herpes zoster	2 (1.0)	0	3 (1.4)	0
Hemorrhage[g]	2 (1.0)	2 (1.0)	2 (1.0)	1 (0.5)

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades[h] n (%)	Grades 3-4 n (%)	All Grades[h] n (%)	Grades 3-4 n (%)
Bacteremia	2 (1.0)	2 (1.0)	0	0

Toxicity was graded per NCI CTCAE v4.
a. Includes pneumonia aspiration, pneumonia bacterial, and lung infection.
b. Includes pharyngitis, nasopharyngitis, tracheitis, bronchitis, and upper respiratory infection with bronchitis. .
c. Includes drug eruption, palmar-plantar erythrodysaesthesia syndrome, blister, and pustular rash.
d. Includes interstitial lung disease, and radiation pneumonitis.
e. Includes tumor-associated fever.
f. Includes oesophagobronchial fistula, aorta-oesophageal fistula, and tracheo-oesophageal fistula.
g. Includes tumor-haemorrhage, upper gastrointestinal haemorrhage, and epistaxis.
h. There were no Grade 5 events.
Source: ADaM dataset from Module 5.3.5.1 - adae.xpt

Significant Adverse Events

Data:
See IMAE data presented in Table 25.

The Applicant's Position:

IMAEs
In the ONO-4538-24 (CA209473) nivolumab monotherapy population:

- The frequencies of IMAEs were low (Table 25).
- The most frequently reported IMAEs (≥ 5% of subjects) were in the rash (23 subjects; 11.0%) and hypothyroidism (21 subjects; 10.0%) categories.
- The majority of IMAEs were Grade 1-2.

IMAEs were generally considered manageable using the recommended treatment guidelines for early work-up and intervention. Some endocrine IMAEs, although well-controlled with hormone replacement therapy, were not considered resolved due to the continuing need for hormone replacement therapy.

Other Events of Special Interest (OESIs)
In ONO-4538-24 (CA209473), OESIs are events that do not fulfill all criteria to qualify as IMAEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management, but do not benefit from pooling of multiple AE terms for full characterization and are therefore presented as unique events rather than using IMAE methodology. OESI included the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis, pancreatitis, rhabdomyolysis, uveitis, autoimmune neuropathy, and graft vs host disease. No OESIs were reported in ONO-4538-24 (CA209473).

The FDA's Assessment:
IMAEs
Table 34 provides FDA's analysis of TEAEs that were flagged by the Applicant as immune-mediated. The FDA has different results for the incidence of IMAEs from those provided by the Applicant in Table 25 for

the following reasons:

a. Because of the potential for IMAEs to be delayed, the FDA analysis includes IMAEs that occurred up to 100 days after the last dose of study treatment. The Applicant's Table 25: Summary of Safety Results - ONO-4538-24 (CA209473) - All Treated SubjectsTable 25 includes IMAEs that occurred up to 28 days after the last dose of study treatment.
b. The FDA analysis uses composite Preferred Terms (see footnotes in Table 34).
c. The FDA's Table 34 is an analysis of the TEAEs that the Applicant flagged as immune-mediated. The Applicant's Table 25: Summary of Safety Results - ONO-4538-24 (CA209473) - All Treated SubjectsTable 25 did not use this flag.

Eighty-five patients (40.7%) in the nivolumab group and 112 patients (53.8%) in the control chemotherapy group experienced TEAEs that the Applicant determined were IMAEs (Table 34). However, excluding the Preferred Terms in the "Blood and Lymphatic System Disorder" System Organ Class (SOC), the incidence of each IMAE was higher in the nivolumab group compared to the pooled chemotherapy group. SOC "Blood and Lymphatic System Disorders" classified as IMAEs by the Investigator or Applicant were unlikely to be IMAEs, and more likely to be cytotoxic bone-marrow suppression characteristic of chemotherapeutic agents. For example, this FDA clinical reviewer does not consider febrile neutropenia and neutrophil count decrease as IMAEs. As expected, febrile neutropenia and neutrophil count decrease were more frequent in the pooled chemotherapy group compared to the nivolumab group.

All patients who experienced TEAEs that the Applicant flagged as IMAEs received immunomodulating agents for the IMAEs. The immunomodulating agents used to treat these IMAEs were corticosteroid preparations and colony-stimulating factors, except for one patient who received picibanil (a mixture of group A Streptococcus pyogenes with anti-neoplastic activity) for ILD.

The FDA noted that there were TEAEs that were not flagged as IMAEs by the Applicant, but were likely immune-mediated. For instance, the FDA determined that 23 patients (11%) developed treatment-emergent hypothyroidism in the nivolumab arm within the 100-day window (Table 38), but only 2 patients (1%) were assessed to have immune-mediated hypothyroidism by the Applicant (Table 34). A similar argument can be made for treatment-emergent diarrhea. Table 35 provides the FDA analysis of TEAEs that were not flagged by the Applicant as immune-mediated, but have the potential to be immune-mediated. In addition, the Applicant flagged TEAEs as immune-mediated that may not have been immune-mediated (e.g., febrile neutropenia, entropion, urinary tract infection, TEAEs in the chemotherapy group, etc.). The IMAEs (including all TEAEs that may be immune-mediated, regardless of whether the Applicant flagged them as such) that occurred within 100 days of the last dose study treatment in ≥5% of patients in the nivolumab group were (all grades, Table 38): rash (n=48, 23.0%), diarrhea (n=43, 20.6%), hepatobiliary disorders (n=30, 14.4%), pruritus (n=25, 12.0%), hypothyroidism (n=23, 11%), and pneumonitis (n=22, 10.5%). The composite term "hepatobiliary disorders" includes the Preferred Terms alanine aminotransferase increased, aspartate aminotransferase increased, bile duct obstruction, blood bilirubin increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal, hepatitis, acute hepatitis, hyperbilirubinaemia, liver function test abnormal, and liver function test increased (see footnote d in Table 37).

Pneumonitis and rash occurred at a numerically higher rate than reported for single-agent nivolumab in the Warnings and Precautions section of nivolumab product labeling (rates reported in the Warnings and Precautions section of product labeling: pneumonitis – 3.1%, 61/1994 and rash – 9%, 171/1994). Pneumonitis also occurred at a higher frequency in patients with ESCC compared to patients with other tumor types; see Section 8.2.5.1 (Safety of Nivolumab Monotherapy in Ono-4538-24 (CA209473) Compared with Other Tumor Types) for a discussion of this finding. Hepatitis occurred at a slightly numerically higher rate than reported for single-agent nivolumab in product labeling (labeled incidence: 1.8%, 35/1994). However, the rates of pneumonitis, rash, and hepatitis were consistent with rates for individual trials investigating single-agent nivolumab in described in nivolumab product labeling. Otherwise, the following IMAEs occurred at a similar or lower incidence rate than described in the Warnings and Precautions section of nivolumab product labeling: endocrinopathies, colitis, and nephritis.

The IMAEs (including TEAEs that were flagged by the Applicant as immune-mediated, and TEAEs that were likely IMAEs but not flagged as immune-mediated, such as treatment-emergent hyperthyroidism) that led to death were pneumonitis, pneumonia, and sepsis in the nivolumab group, and pneumonitis and pneumonia in the pooled chemotherapy group. More patients died of pneumonitis in the nivolumab group (n=2, 1%) compared to the pooled chemotherapy group (n=1, 0.5%), and more patients died of pneumonia in the pooled chemotherapy group (n=5, 2.4%) compared to the nivolumab group (n=2, 1.0%). However, these observed differences are small and given the mechanism of action of nivolumab and chemotherapy, these causes of deaths are not unexpected.

Despite the differences in interpretation of whether a TEAE is immune-mediated or not between the Applicant's and the FDA's analyses, the overall safety profile is consistent with the well-characterized safety profile of nivolumab except for the higher incidence of pneumonitis and rash in this study. The increased incidence of pneumonitis may be due to the increase rate of prior radiotherapy to the thorax in patients with ESCC compared to the pooled cancer population in the product labeling who received nivolumab (see Section 8.2.5.1 of this review). However, the rate of nivolumab discontinuation due to pneumonitis was relatively low (5.3%), and Grade 3-4 pneumonitis rate was also low (2.4%) in the nivolumab group. As for the higher incidence of rash in this study, when the same composite Preferred Terms were used to analyze the incidence of rash in patients with ESCC in Study ONO-4538-24 (CA209473) that were used to analyze the incidence of rash in the pooled cancer population in the product labeling who received single-agent nivolumab, the incidence of rash in the ESCC patient population was comparable to that in the pooled cancer population (see Section 8.2.5.1 of this review).

Table 34: TEAEs that occurred in ≥1 patient in the nivolumab group within 100 days of last dose of study treatment flagged by the Applicant as immune-mediated (FDA analysis)

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Total immune-mediated AEs	85 (40.7)	60 (28.7)	112 (53.8)	21 (10.1)

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Skin and Subcutaneous Tissue Disorders				
Rash[a]	35 (16.8)	3 (1.4)	33 (15.9)	1 (0.5)
Pruritus	14 (6.7)	0	4 (1.9)	0
Dry skin[b]	2 (1.0)	0	1 (0.5)	0
Catheter site erythema	1 (0.5)	0	0	0
Angular cheilitis	1 (0.5)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Pneumonitis[c]	14 (6.7)[n]	2 (1.0)	6 (2.9)[n]	2 (1.0)
Pneumonia[d]	5 (2.4)[o]	1 (0.5)	9 (4.3)[o]	3 (1.4)
Dyspnea[e]	4 (1.9)	2 (1.0)	1 (0.5)	0
Cough[f]	2 (1.0)	0	1 (0.5)	0
Tachypnea	1 (0.5)	1 (0.5)	0	0
Esophageal fistula[g]	1 (0.5)	1 (0.5)	0	0
Gastrointestinal Disorders				
Hepatobiliary[h]	5 (2.4)	4 (1.9)	0	0
Diarrhea[i]	5 (2.4)	1 (0.5)	0	0
Stomatitis[j]	3 (1.4)	1 (0.5)	11 (5.3)	0
Nausea	2 (1.0)	0	0	0
Dysphagia	1 (0.5)	1 (0.5)	0	0
Anal fistula	1 (0.5)	0	0	0
General Disorders				
Pyrexia[k]	3 (1.4)	0	2 (1.0)	0
Peripheral swelling	1 (0.5)	0	0	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain or swelling[l]	3 (1.4)	0	0	0
Endocrine Disorders				
Hypothyroidism	2 (1.0)	0	0	0
Hyperthyroidism	1 (0.5)	0	0	0
Hypopituitarism	1 (0.5)	0	0	0
Adrenocorticotropic hormone deficiency	1 (0.5)	1 (0.5)	0	0
Immune System Disorders				
Drug hypersensitivity	2 (1.0)	1 (0.5)	0	0
Anaphylactic shock	1 (0.5)	1 (0.5)	0	0
Blood and Lymphatic System Disorders				
Febrile neutropenia	2 (1.0)	2 (1.0)	18 (8.7)	18 (8.7)
Neutrophil count decreased	1 (0.5)	1 (0.5)	32 (15.4)	30 (14.4)
Eye disorders				

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Conjunctival deposit	1 (0.5)	0	0	0
Corneal oedema	1 (0.5)	0	0	0
Entropion	1 (0.5)	0	0	0
Extraocular muscle disorder	1 (0.5)	0	0	0
Renal and Urinary disorders				
Urinary tract infection[m]	1 (0.5)	0	0	0
Nephritis	1 (0.5)	0	0	0
Infections and Investigations				
Sepsis	1 (0.5)[p]	0	0	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, Stevens-Johnson syndrome, toxic skin eruption, dermatitis, dermatitis described as acneiform, or bullous, and rash described as maculo-papular, pruritic, or pustular.
b. Includes xeroderma.
c. Includes interstitial lung disease, and radiation pneumonitis.
d. Includes pneumonia aspiration, and lung infection.
e. Includes dyspnoea exertional.
f. Includes productive cough.
g. Includes aorta-oesophageal fistula.
h. Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, hepatitis, acute hepatitis, and liver function test increased.
i. Includes colitis.
j. Includes mucosal inflammation.
k. Includes tumor-associated fever.
l. Includes arthralgia, pain in extremity, periarthritis calcarea, and joint swelling.
m. Includes cystitis.
n. Two patients (1.0%) in the nivolumab group, and one patient (0.5%) in the paclitaxel arm died of pneumonitis.
o. Two patients (1.0%) in the nivolumab group, and five patients (2.4%) the pooled chemotherapy group died of pneumonia. Within the chemotherapy group, three patients were in the paclitaxel arm and two patients were in the docetaxel arm.
p. One patient (0.5%) in the nivolumab group died of sepsis.

Source: ADaM dataset from Module 5.3.5.1 - adae.xpt

Table 35: TEAEs that occurred in ≥1 patient in the nivolumab group within 100 days of last dose of study treatment that may have been immune-mediated AEs but were not flagged by the Applicant as immune-mediated (FDA analysis)

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Endocrine Disorders				
Diabetes mellitus[a]	1 (0.5)[b]	1 (0.5)	0	0
Hyperthyroidism	3 (1.4)	0	0	0
Renal and Urinary disorders				
Acute kidney injury[c]	2 (1.0)	1 (0.5)	2 (1.0)	0

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Immune System Disorders				
Hypersensitivity	1 (0.5)	0	1 (0.5)	0
Infusion-related reaction	1 (0.5)[d]	0	1 (0.5)[d]	0
Anaphylactic shock	1 (0.5)	1 (0.5)	0	0

Toxicity was graded per NCI CTCAE v4.

a. Excludes type 2 diabetes mellitus and the following AELLTs: Worsening of diabetes, Diabetes mellitus aggravated.
b. Includes the case of Grade 4 SAE of diabetic ketoacidosis was reported after the DBL date.
c. Includes azotaemia.
d. The FDA noticed a discrepancy regarding the AEDECOD "Infusion related reaction" between the ADAE dataset submitted to module 5.3.5.1 and the ADAE dataset submitted to module 5.3.5.3. In the ADAE dataset submitted to module 5.3.5.1, the following patients in the Safety Population (SAFFL – Y) were reported to have experienced an infusion-related reaction: patient ID (b) (6) (grade 2) and patient ID (b) (6) (grade 1), and both patients were reported to be in the paclitaxel arm. In the ADAE dataset submitted into module 5.3.5.3, the following patients in the Safety Population (SAFFL – Y) were reported to have experienced an infusion-related reaction: patient (b) (6) (grade 2) in the paclitaxel arm, and patient ID (b) (6) in the nivolumab arm (grade 2). The FDA sent an Information Request to BMS regarding this discrepancy. BMS responded that "BMS acknowledges the discrepancies regarding the AEDECOD "Infusion related reaction" (for PID (b) (6) and PID (b) (6)) between the CSR ADAE dataset submitted into Module 5.3.5.1 and the integrated ADAE dataset submitted into Module 5.3.5.3. BMS would like to clarify that the differences in the AEDECOD between these 2 ADAE datasets are due to different MedDRA Lowest Level Terms (LLTs) that were selected for the term by BMS and ONO, even though the same version (v21.1) of MedDRA was used." Upon reviewing BMS' reasons for their LLT choice, the FDA determined that BMS coded the AETERM to the appropriate AEDECOD and ONO did not, and thus used BMS' dataset to determine the incidence rate of the infusion-related reaction

Source: ADaM dataset from Module 5.3.5.1 - adae.xpt (this dataset was generated by ONO) for all AEs except for infusion-related reaction (IRR). IRR data is from ADaM dataset from Module 5.3.5.3 – adae.expt (this dataset was generated by BMS).

OESIs

As for the OESIs listed by the Applicant, there was one patient who experienced extraocular myositis (patient ID (b) (6)) that the Investigator determined was related to nivolumab. The patient developed Grade 1 extraocular myositis 224 days after starting nivolumab. Nivolumab was continued, and the patient received the next dose of nivolumab 28 days after the myositis started. However, the myositis increased to Grade 2 36 days after it started, and nivolumab was discontinued with the treatment discontinuation reason reported as, "starting post study treatment is more effective than waiting for AE resolution". There were no other cases of OESIs listed by the Applicant upon review of the Preferred Terms in the ADAE dataset and review of the narrow SMQ terms. The FDA also searched for the OESIs listed by the Applicant in the broad SMQ terms and found the following in the nivolumab group: encephalitis (n=2), Guillain-Barré syndrome (n=4), pancreatitis (n=2), and rhabdomyolysis (n=4). However, none of these patients experienced these OESIs based on the FDA's review of the narratives of the patients when narratives were available, and review of the Preferred Terms and Investigator terms (AETERM) reported for these patients.

Based on the review of the FDA's Algorithmic SMQ and the adverse events associated with the SMQs, the FDA found that there was one case of anaphylactic shock (reported as Grade 4 anaphylactic shock, patient ID (b) (6)) and one case of tumor lysis syndrome (TLS, reported as Grade 3 acute renal failure,

patient ID (b) (6)). Both patients were in the nivolumab group. There were no other reports of anaphylactic shock (or similar terms) as Preferred Terms or AETERMs in the ADAE dataset. There were no cases of TLS in the chemotherapy group based on the Algorithmic SMQ. The patient who experienced anaphylactic shock developed dizziness, hypotension (blood pressure 69/43 with heart rate 98 beats per minute), and hypoxia (oxygen saturation 80-85%) about 7 minutes following initiation of the infusion of the first dose of nivolumab (Cycle 1 Day 1). The patient recovered following treatment with intravenous normal saline, hydrocortisone, and chlopheniramine. Nivolumab was not discontinued due to this event. The patient who experienced TLS had chronic kidney disease and Stage IIIc (T2BN2Mb) ESCC status-post concurrent chemoradiotherapy and total esophagectomy (ypTNo) prior to study enrollment. Twenty-eight days after initiation of nivolumab and 14 days after his most recent nivolumab dose, the patient's blood creatinine increased to 6.47 mg/dL, accompanied by a blood potassium level of 5.0 mmol/L and hyperuricemia (at least up to 16 mg/dL). The patient was treated with intravenous hydration and rasburicase, after which his blood creatinine, potassium and uric acid improved.

Nivolumab product labeling reports that <1% of patients who received nivolumab experienced myositis, which is consistent with the incidence of myositis in this study (n=1, 0.5%). Nivolumab product labeling also reports that <1% of patients who receive nivolumab experienced severe infusion-related reactions, which is consistent with the incidence of anaphylactic shock in this study (n=1, 0.5%). TLS is not reported as an adverse reaction to nivolumab in product labeling, but it is an AE associated with the treatment of cancer, and not necessarily specific to nivolumab. Given that there was only one case of TLS, more cases are needed prior to determining that this is a new safety signal.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

APPEARS THIS WAY ON ORIGINAL

Table 36 Summary of Drug-related AEs by Worst CTC Grade with 10% Cutoff - All Treated ONO 4538-24 (CA209473) Subjects

SOC		Nivolumab (n [%])			Control group (n [%])		
PT		Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
	N	209	209	209	208	208	208
All Subjects with Drug-related AEs		**137 (65.6)**	**38 (18.2)**	**0**	**198 (95.2)**	**131 (63.0)**	**2 (1.0)**
Skin and subcutaneous tissue disorders		**37 (17.7)**	**1 (0.5)**	**0**	**112 (53.8)**	**2 (1.0)**	**0**
Rash		23 (11.0)	1 (0.5)	0	31 (14.9)	2 (1.0)	0
Alopecia		3 (1.4)	0	0	98 (47.1)	0	0
Gastrointestinal disorders		**33 (15.8)**	**3 (1.4)**	**0**	**76 (36.5)**	**4 (1.9)**	**0**
Diarrhoea		22 (10.5)	2 (1.0)	0	20 (9.6)	2 (1.0)	0
Stomatitis		5 (2.4)	1 (0.5)	0	25 (12.0)	1 (0.5)	0
Nausea		4 (1.9)	0	0	34 (16.3)	1 (0.5)	0
General disorders and administration site conditions		**33 (15.8)**	**2 (1.0)**	**0**	**94 (45.2)**	**9 (4.3)**	**0**
Fatigue		15 (7.2)	1 (0.5)	0	43 (20.7)	9 (4.3)	0
Malaise		9 (4.3)	0	0	45 (21.6)	0	0
Metabolism and nutrition disorders		**16 (7.7)**	**2 (1.0)**	**0**	**56 (26.9)**	**10 (4.8)**	**0**
Decreased appetite		16 (7.7)	2 (1.0)	0	56 (26.9)	10 (4.8)	0
Investigations		**8 (3.8)**	**4 (1.9)**	**0**	**101 (48.6)**	**70 (33.7)**	**0**
Neutrophil count decreased		3 (1.4)	1 (0.5)	0	76 (36.5)	59 (28.4)	0
White blood cell count decreased		2 (1.0)	1 (0.5)	0	72 (34.6)	46 (22.1)	0
Blood and lymphatic system disorders		**6 (2.9)**	**4 (1.9)**	**0**	**88 (42.3)**	**61 (29.3)**	**0**
Anaemia		5 (2.4)	4 (1.9)	0	49 (23.6)	19 (9.1)	0
Neutropenia		1 (0.5)	0	0	40 (19.2)	29 (13.9)	0
Febrile neutropenia		0	0	0	22 (10.6)	22 (10.6)	0
Musculoskeletal and connective tissue disorders		**5 (2.4)**	**0**	**0**	**34 (16.3)**	**2 (1.0)**	**0**
Arthralgia		3 (1.4)	0	0	21 (10.1)	1 (0.5)	0
Nervous system disorders		**4 (1.9)**	**0**	**0**	**78 (37.5)**	**2 (1.0)**	**0**
Peripheral sensory neuropathy		1 (0.5)	0	0	47 (22.6)	1 (0.5)	0
Neuropathy peripheral		0	0	0	22 (10.6)	1 (0.5)	0

MedDRA version 21.1. CTCAE version 4.0.
AEs and drug-related AEs occurring between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.
Drug-related AEs were defined as any AEs with causal relationship with the product "Related" or missing.
Source: Table 14.3.1.1-1-1 (total) and Table 14.3.1.1.9-4 (5% cut-off) in the ONO-4538-24 (CA209473) final CSR; ADaM dataset: ADSL.xpt, ADAE.xpt

The Applicant's Position:
Nivolumab was well tolerated in ONO-4538-24 (CA209473), with an improved safety profile versus chemotherapy (docetaxel or paclitaxel). Frequencies of any-grade and Grade 3-4 all causality AEs and SAEs, as well as any-grade and Grade 3-4 drug-related AEs and SAEs with nivolumab were generally lower in comparison to chemotherapy (either docetaxel or paclitaxel). Any grade and Grade 3-4 AEs (both all causality and drug-related) leading to dose delay were reported less frequently in the nivolumab than in the control group.

Drug-related AEs

Any Grade: Overall, a lower frequency of drug-related AEs was observed in the nivolumab group than in the control group (Table 36). The most common (≥ 10% subjects) drug-related AEs by PT included:

- Nivolumab group: rash (23 subjects, 11.0%), and diarrhoea (22 subjects, 10.5%)
- Control group: alopecia (98 subjects, 47.1%), neutrophil count decreased (76 subjects, 36.5%), white blood cell count decreased (72 subjects, 34.6%), decreased appetite (56 subjects, 26.9%), anaemia (49 subjects, 23.6%), peripheral sensory neuropathy (47 subjects, 22.6%), malaise (45 subjects, 21.6%), fatigue (43 subjects, 20.7%), neutropenia (40 subjects, 19.2%), nausea (34 subjects, 16.3%), rash (31 subjects, 14.9%), stomatitis (25 subjects, 12.0%), febrile neutropenia (22 subjects, 10.6%), neuropathy peripheral (22 subjects, 10.6%), arthralgia (21 subjects, 10.1%)

Among commonly observed drug-related AEs (>10% of any grade in the nivolumab or total chemotherapy arm), the following were reported at a higher frequency (≥10% difference) in either the docetaxel or paclitaxel arm compared to the other chemotherapy arm:

- Reported more frequently with docetaxel vs paclitaxel: decreased appetite (33.8% vs 23.8%), malaise (29.2% vs 18.2%), nausea (27.7% vs 11.2%), febrile neutropenia (27.7% vs 2.8%), and stomatitis (20.0% vs 8.4%)
- Reported more frequently with paclitaxel vs docetaxel: alopecia (51.0% vs 38.5%), neuropathy peripheral (14.0% vs 3.1%), and peripheral sensory neuropathy (27.3% vs 12.3%)

Grade 3-4: Fewer drug-related Grade 3-4 AEs were reported in the nivolumab group than in the control group (Table 36Table 36). The most common Grade 3-4 drug-related AEs included:

- Nivolumab group: anaemia (4 subjects, 1.9%), diarrhoea and decreased appetite (2 subjects each, 1.0%)
- Control group (incidence ≥10%): neutrophil count decreased (59 subjects, 28.4%), white blood cell count decreased (46 subjects, 22.1%), and neutropenia (29 subjects, 13.9%)

Among commonly observed drug-related Grade 3-4 AEs (>10% of any grade in the nivolumab or total chemotherapy arm), the following were reported at a higher frequency (≥10% difference) with docetaxel vs paclitaxel: neutrophil count decreased (36.9% vs 24.5%), white blood cell count decreased (35.4% vs 16.1%), and febrile neutropenia (27.7% vs 2.8%).

The FDA's Assessment:
All causality treatment-emergent AEs (all grades)
Table 37 summarizes the FDA analysis of the TEAEs that occurred in ≥10% of patients receiving

nivolumab within 28 days of last dose of study treatment in Study ONO-4538-24 (CA209473). Among these TEAEs, only pneumonia was associated with death (n=1 each for nivolumab and paclitaxel treatment groups). The most common TEAEs occurring in ≥20% of nivolumab-treated patients were rash and decreased appetite. Of the TEAEs that occurred ≥10% of patients who received nivolumab, the following TEAEs occurred at a higher incidence in the nivolumab group than in the chemotherapy group during the 28-day window: pruritus, diarrhea, hepatobiliary disorder, URIs, cough, and hypothyroidism. Of these TEAEs, the per-patient incidence of pruritus, hepatobiliary disorder, URIs, and hypothyroidism was higher by at least 2% in the nivolumab group compared to the chemotherapy group. The only Grade 3-4 events that occurred more frequently in the nivolumab group among the TEAEs (all grades) that occurred in ≥10% of patients who received nivolumab were rash, diarrhea, hepatobiliary disorder, and URIs, all of which occurred in ≤1.9% of the patients except for hepatobiliary disorders. The Preferred Terms for that hepatobiliary TEAEs that occurred in >2% of the patients in the nivolumab group were aspartate aminotransferase increased (n=13, 6.2%), alanine aminotransferase increased (n=11, 5.3%), and gamma-glutamyltransferase increased (n=9, 4.3%). Among the TEAEs (all grades) that occurred ≥10% of patients who received nivolumab, only pneumonia led to deaths in both treatment groups (n=3, 1.4% in the nivolumab group and n=2, 1% in the paclitaxel arm).

The TEAEs increased in incidence between the 28-day and 100-day window in the nivolumab group for all TEAEs in Table 37 except for URI, pruritus, and hypothyroidism; the increase was ≤1% for each common TEAE except for diarrhea, hepatobiliary disorders, and pneumonia. In addition, pneumonitis increased in incidence in the nivolumab group between the 28-day and 100-day window (n=18, 8.6% to n=22, 10.5%, respectively), so it is included in Table 38 (but not Table 37). The incidence of pneumonitis did not change in the pooled chemotherapy group between the 28-day and 100-day window. The following Grade 3-4 TEAEs increased in incidence between the 28-day and 100-day window in the nivolumab group: decreased appetite, diarrhea, hepatobiliary disorder, musculoskeletal pain, pneumonia, pneumonitis (n=4, 1.9% to n=5, 2.4%, respectively), and anemia; the increase was ≤1% except for hepatobiliary disorder and pneumonia.

Overall, the TEAEs occurring in ≥10% of patients receiving nivolumab are consistent with the known safety profile of nivolumab and analyses of these TEAEs did not raise new safety concerns. The FDA agrees with the Applicant's assessment that the observed safety profile of nivolumab was acceptable in Study ONO-4538-24 (CA209473), and was more favorable overall compared to the safety profile of the chemotherapies (docetaxel or paclitaxel) comprising the control arm.

Table 37: Treatment-emergent AEs in ≥10% of patients receiving nivolumab within 28 days of last dose of study treatment (FDA analysis)

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Skin and Subcutaneous Tissue Disorders				
Rash[a]	46 (22.0)	4 (1.9)	58 (27.9)	2 (1.0)
Pruritus	25 (12.0)	0	15 (7.2)	0

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Gastrointestinal Disorders				
Decreased appetite[b]	44 (21.1)	4 (1.9)	73 (35.1)	11 (5.3)
Diarrhea[c]	38 (18.2)	4 (1.9)	36 (17.3)	3 (1.4)
Constipation	35 (16.8)	0	40 (19.2)	0
Hepatobiliary disorder[d]	25 (12.0)	11 (5.3)	12 (5.8)	5 (2.4)
Nausea	23 (11.0)	0	41 (19.7)	1 (0.5)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[e]	35 (16.8)	0	54 (26.0)	3 (1.4)
Respiratory, Thoracic and Mediastinal Disorders				
Upper respiratory tract infection[f]	36 (17.2)	2 (1.0)	29 (13.9)	0
Cough[g]	33 (15.8)	0	30 (14.4)	1 (0.5)
Pneumonia[h]	27 (12.9)[m]	13 (6.2)	40 (19.2)[n]	21 (10.1)
General Disorders				
Pyrexia[i]	34 (16.3)	1 (0.5)	40 (19.2)	1 (0.5)
Fatigue[j]	25 (12.0)	3 (1.4)	56 (26.9)	10 (4.8)
Blood and Lymphatic System Disorders				
Anemia[k]	27 (12.9)	17 (8.1)	63 (30.3)	26 (12.5)
Endocrine Disorders				
Hypothyroidism[l]	23 (11.0)	0	3 (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, generalised, or pustular.
b. Includes hypophagia, and food aversion.
c. Includes colitis.
d. Includes alanine aminotransferase increased, aspartate aminotransferase increased, bile duct obstruction, blood bilirubin increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal, hepatitis, acute hepatitis, hyperbilirubinaemia, liver function test abnormal, and liver function test increased.
e. Includes spondylolisthesis, periarthritis, musculoskeletal chest pain, neck pain, arthralgia, back pain, myalgia, pain in extremity, arthritis, bone pain, and periarthritis calcarea.
f. Includes influenza, influenza-like illness, pharyngitis, nasopharyngitis, tracheitis, bronchitis, and upper respiratory infection with bronchitis.
g. Includes productive cough.
h. Includes pneumonia aspiration, pneumonia bacterial, and lung infection.
i. Includes tumor-associated fever.
j. Includes asthenia.
k. Includes hemoglobin decreased, and iron deficiency anemia.
l. Includes blood thyroid stimulating hormone increased.
m. Three patients (1.4%) died of pneumonia in the nivolumab group.
n. Two patients (1%) died of pneumonia in the chemotherapy group; these deaths occurred with paclitaxel only.

Source: ADaM dataset from Module 5.3.5.3 - adae.xpt

Table 38: Treatment-emergent AEs in ≥10% of patients receiving nivolumab within 100 days of last dose of study treatment (FDA analysis)

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Skin and Subcutaneous Tissue Disorders				
Rash[o]	48 (23.0)	4 (1.9)	58 (27.9)	2 (1.0)
Pruritus	25 (12.0)	0	15 (7.2)	0
Gastrointestinal Disorders				
Decreased appetite[b]	45 (21.5)	5 (2.4)	74 (35.6)	12 (5.8)
Diarrhea[p]	43 (20.6)	5 (2.4)	38 (18.3)	4 (1.9)
Constipation	37 (17.7)	0	40 (19.2)	0
Hepatobiliary[d]	30 (14.4)	15 (7.2)	14 (6.7)	6 (2.9)
Nausea	23 (11.0)	0	41 (19.7)	1 (0.5)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[q]	36 (17.2)	1 (0.5)	55 (26.4)	3 (1.4)
Respiratory, Thoracic and Mediastinal Disorders				
Upper respiratory tract infection[f]	36 (17.2)	2 (1.0)	29 (13.9)	0
Cough[g]	35 (16.8)	0	31 (14.9)	1 (0.5)
Pneumonia[r]	33 (15.3)[m]	16 (7.7)	49 (23.6)[t]	30 (14.4)
Pneumonitis[s]	22 (10.5)[u]	5 (2.4)	13 (6.3)[v]	5 (2.4)
General Disorders				
Pyrexia[i]	35 (16.8)	1 (0.5)	42 (20.2)	1 (0.5)
Fatigue[j]	26 (12.4)	3 (1.4)	57 (27.4)	10 (4.8)
Blood and Lymphatic System Disorders				
Anemia[k]	29 (13.9)	19 (9.1)	63 (30.3)	26 (12.5)
Endocrine Disorders				
Hypothyroidism[l]	23 (11.0)	0	3 (1.4)	0

Toxicity was graded per NCI CTCAE v4.

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

p. Includes colitis, and enterocolitis.

q. Includes spondylolisthesis, periarthritis, musculoskeletal chest pain, neck pain, arthralgia, back pain, myalgia, pain in extremity, arthritis, bone pain, periarthritis calcarean, and sciatica.

r. Includes pneumonia aspiration, pneumonia bacterial, lung infection, and pneumocystis jirovecii.

s. Includes interstitial lung disease, and radiation pneumonitis.

t. Seven deaths (3.4%) died of pneumonia in the chemotherapy group during the 100-day window, which is an increase from the number of patients who died of pneumonia in the chemotherapy group during the 28-day window. Five of the deaths were in the paclitaxel arm, and two deaths were in the docetaxel arm.

u. Three patients (1.4%) died of pneumonitis in the nivolumab group during the 100-day window, which is not an increase from the number of patients who died of pneumonitis in the nivolumab group during the 28-day window.

v. One patient (0.5%) died of pneumonitis in the chemotherapy group during the 100-day window, which is not an increase from the number of patients who died of pneumonitis in the chemotherapy group during the 28-day window. This death occurred in the paclitaxel arm.

Refer to Table 1 for the other footnotes.
Source: ADaM dataset from Module 5.3.5.3 - adae.xpt

Grade 3 and 4 AEs

Table 39 summarizes the FDA analysis of the Grade 3 and 4 (severe) TEAEs that occurred in ≥1% of patients receiving nivolumab within 28 days of the last dose of study treatment in Study ONO-4538-24 (CA209473). The most common Grade 3-4 TEAEs occurring in ≥2% of patients receiving nivolumab were anemia, pneumonia, hepatobiliary disorder, hypercalcemia, esophageal fistula, dysphagia, and increased blood CPK. Of the Grade 3-4 TEAEs occurring in ≥2% of patients who received nivolumab, the following TEAEs occurred more often in the nivolumab group than the chemotherapy group during the 28-day window: hepatobiliary disorders, hypercalcemia, esophageal fistula, dysphagia, and increased blood CPK. Of these TEAEs, at least a 2% higher incidence of hepatobiliary disorders, hypercalcemia, and increased blood CPK occurred in the nivolumab group compared to the chemotherapy group.

Anemia, pneumonia, hepatobiliary disorders, and hypercalcemia are labeled adverse reactions to nivolumab. Hypercalcemia, esophageal fistula, and dysphagia may be caused by disease progression, rather than an adverse reaction to nivolumab (see the section entitled “All causality treatment-emergent SAEs” of Section 8.2.4 for a discussion of these TEAEs), but in some cases it was difficult to rule out a causal role for nivolumab. In addition, all three severe TEAEs occurred more frequently overall in the nivolumab group compared to the chemotherapy group (6.2% versus 4.3%, 3.4% versus 1.0%, and 7.2% versus 2.4%, respectively). Increased blood CPK and esophageal fistula are AEs that have not been previously described in nivolumab product labeling. See the section entitled “Dose Interruption/Reduction Due to Adverse Effects” of Section 8.2.4 for a discussion regarding the incidence and clinical significance of blood CPK increase in this study.

Of the Grade 3-4 TEAEs included in Table 39 that were not in Table 37 and Table 38 (i.e., dyspnea, hypercalcemia, esophageal fistula, dysphagia, increased blood CPK, decreased lymphocyte count, hyperuricemia, hyponatremia, hypokalemia, hemorrhage, hypertension, and abnormal hepatic function), the following Grade 3-4 TEAEs in the nivolumab group had a slightly higher incidence when evaluated using the 100-day window compared to the 28-day window: esophageal fistula (n=6, 2.9% to n=7, 3.4%), lymphocyte count decreased (n=3, 1.4% to n=5, 2.4%), hypouricemia (n=4, 1.9% to n=5, 2.5%), hypokalemia (n=3, 1.4% to n=5, 2.4%), and hepatic function abnormal (n=3, 1.4% to n=4, 1.9%). Only one additional death, due to esophageal fistula, occurred in the 100-day window.

Table 39: Grade 3 or 4 TEAEs in ≥1% of patients receiving nivolumab within 28 days of last dose of study treatment (FDA analysis)

Adverse Event	Nivolumab (n=209)		Chemotherapy pooled (n=208)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Blood and Lymphatic System Disorders				
Anemia[a]	27 (12.9)	17 (8.1)	63 (30.3)	26 (12.5)
Respiratory, Thoracic and Mediastinal Disorders				
Pneumonia[b]	27 (12.9)[l]	13 (6.2)	40 (19.2)[l,p]	21 (10.1)
Pneumonitis[c]	18 (8.6)[m]	4 (1.9)	13 (6.3)[m,p]	5 (2.4)
Dyspnea	17 (8.1)	4 (1.9)	14 (6.7)	0
Gastrointestinal Disorders				
Hepatobiliary disorder[d]	25 (12.0)	11 (5.3)	12 (5.8)	5 (2.4)
Esophageal fistula[e]	7 (3.4)[n]	6 (2.9)	2 (1.0)	2 (1.0)
Dysphagia	15 (7.2)	5 (2.4)	5 (2.4)	3 (1.4)
Diarrhea[f]	38 (18.2)	4 (1.9)	36 (17.3)	3 (1.4)
Endocrine Disorders				
Hypercalcemia	14 (6.7)[q]	9 (4.3)[q]	9 (4.3)	3 (1.4)
Investigations				
Blood creatine phosphokinase increased	8 (3.8)	5 (2.4)	0	0
Lymphocyte count decreased	6 (2.9)	3 (1.4)	21 (10.1)	15 (7.2)
Metabolism and Nutrition Disorders				
Decreased appetite[g]	44 (21.1)	4 (1.9)	73 (35.1)	11 (5.3)
Hyperuricemia	8 (3.8)	4 (1.9)	1 (0.5)	0
Hyponatremia	5 (2.4)	3 (1.4)	11 (5.3)	10 (4.8)
Hypokalemia	8 (3.8)	3 (1.4)	5 (2.4)	4 (1.9)
Vascular Disorders				
Hemorrhage[h]	14 (6.7)[o]	4 (1.9)	11 (5.3)[o,p]	1 (0.5)
Hypertension[i]	4 (1.9)	3 (1.4)	4 (1.9)	3 (1.4)
Skin and Subcutaneous Tissue Disorders				
Rash[j]	46 (22.0)	4 (1.9)	58 (27.9)	2 (1.0)
Hepatobiliary Disorders				
Hepatic function abnormal	3 (1.4)	3 (1.4)	2 (1.0)	0
General Disorders				
Fatigue[k]	25 (12.0)	3 (1.4)	56 (26.9)	10 (4.8)

Toxicity was graded per NCI CTCAE v4.

a. Includes hemoglobin decreased, and iron deficiency anemia.
b. Includes pneumonia aspiration, pneumonia bacterial, and lung infection.
c. Includes interstitial lung disease, and radiation pneumonitis.

d. Includes alanine aminotransferase increased, aspartate aminotransferase increased, bile duct obstruction, blood bilirubin increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal, hepatitis, acute hepatitis, hyperbilirubinaemia, liver function test abnormal, and liver function test increased.
e. Includes tracheal fistula, oesophagobronchial fistula, oesophageal fistula, aorta-oesophageal fistula, fistula, oesophageal perforation, oesophageal disorder, and aortic rupture. See footnote c in Table 29 for further details.
f. Includes colitis.
g. Includes hypophagia, and food aversion.
h. Includes haemoptysis, pharyngeal haemorrhage, tumour haemorrhage, upper gastrointestinal haemorrhage, stoma site haemorrhage, gastrointestinal haemorrhage, conjunctival haemorrhage, epistaxis, and haematuria.
i. Includes blood pressure increased.
j. 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, generalised, or pustular.
k. Includes asthenia.
l. Two patients each (each 1%) died of pneumonia in each of the treatment arms (nivolumab and chemotherapy).
m. Three patients (1.4%) in the nivolumab group, and one patient (0.5%) in the chemotherapy group died of pneumonitis.
n. Only one patient (0.5%) died due to an esophageal fistula, and the patient was in the nivolumab group.
o. One patient each (each 0.5%) died of hemorrhage in each of the treatment arms (nivolumab and chemotherapy).
p. The deaths in the chemotherapy treatment arm occurred with paclitaxel only.
q. This includes a patient (ID (b) (6)) whose narrative described a hospitalization due to Grade 2 blood creatinine increase (creatinine was 1.96 mg/dL) and hypercalcaemia (calcium was 12.6 mg/dL). However, the AETERM was reported as "hypercalemia," which coded to AEDECOD "hyperkalaemia." The narrative did not report hyperkalemia, nor elevated blood potassium level.

Source: ADaM dataset from Module 5.3.5.3 - adae.xpt

Laboratory Findings

Data:

Table 40 Summary of Laboratory Parameter Changes from Baseline Grade, US Conventional Units - All Treated ONO-4538-24 (CA209473) Subjects

	Nivolumab		Control group	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
	n (%)	n (%)	n (%)	n (%)
N	209	209	208	208
Hemoglobin	88 (42.1)	18 (8.6)	147 (70.7)	35 (16.8)
White blood cell count	23 (11.0)	1 (0.5)	164 (78.8)	93 (44.7)
Neutrophils count	8 (3.8)	2 (1.0)	142 (68.3)	104 (50.0)
Lymphocytes count	97 (46.4)	39 (18.7)	148 (71.2)	90 (43.3)
Platelet count	19 (9.1)	0	23 (11.1)	0
ALP	68 (32.5)	10 (4.8)	49 (23.6)	2 (1.0)
AST (GOT)	83 (39.7)	13 (6.2)	64 (30.8)	2 (1.0)
ALT (GPT)	64 (30.6)	11 (5.3)	46 (22.1)	4 (1.9)
Total bilirubin	18 (8.6)	4 (1.9)	8 (3.8)	2 (1.0)
Creatinine	164 (78.5)	1 (0.5)	143 (68.8)	1 (0.5)
Hyperglycemia	108 (51.7)	11 (5.3)	128 (61.5)	11 (5.3)
Hypoglycemia	29 (13.9)	3 (1.4)	29 (13.9)	1 (0.5)
Hypercalcemia	46 (22.0)	13 (6.2)	29 (13.9)	6 (2.9)
Hypocalcemia	13 (6.2)	1 (0.5)	21 (10.1)	2 (1.0)
Hypernatremia	4 (1.9)	0	4 (1.9)	0
Hyponatremia	87 (41.6)	22 (10.5)	103 (49.5)	25 (12.0)
Hyperkalemia	46 (22.0)	1 (0.5)	64 (30.8)	2 (1.0)
Hypokalemia	23 (11.0)	6 (2.9)	27 (13.0)	7 (3.4)

Laboratory tests occurring between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.
Source: Refer to Table 14.3.1.2.2.2-1 in the ONO-4538-24 (CA209473) final CSR; ADaM dataset: ADSL.xpt, ADZL.xpt

The Applicant's Position:

A summary of laboratory parameter changes from baseline in ONO-4538-24 (CA209473) is presented in Table 40Table 40. Any-grade laboratory parameters that worsened relative to baseline in ≥ 10% of subjects in the nivolumab group and more frequently than in the control group were ALP, AST, ALT, creatinine, and hypercalcemia.

The majority of abnormal laboratory values in ONO-4538-24 (CA209473) were Grade 1 or 2 in the nivolumab and chemotherapy groups. There were no clear differences in the frequencies of worsening of laboratory parameters observed between groups except for hematology parameters, wherein higher rates of worsening were seen with chemotherapy, and for thyroid function, wherein higher rates of worsening were seen with nivolumab.

The FDA's Assessment:

In addition to the labs listed by the Applicant, total bilirubin also worsened relative to baseline more frequently in in the nivolumab group compared to the chemotherapy group. Table 41: Laboratory abnormalities for which the calculated per-patient incidence differed between the Applicant's analysis and the FDA analysis (FDA analysis)Table 41 provides the per-patient incidence of laboratory abnormalities calculated by FDA for which there were differences between the FDA and Applicant's analyses (i.e., Grade 1-4 lymphocytopenia in the nivolumab group, and Grade 1-4 AST increase, creatinine increase and platelet increase in the chemotherapy group). Otherwise, the FDA agrees with the Applicant's position.

There were no Hy's Law cases identified by FDA. There was one case of concurrent transaminitis >3x ULN with total bilirubin ≥2x ULN and alkaline phosphatase <2x ULN, but review of the patient narrative indicated that these laboratory abnormalities occurred in the setting of progression of liver metastasis (confirmed by imaging).

Table 41: Laboratory abnormalities for which the calculated per-patient incidence differed between the Applicant's analysis and the FDA analysis (FDA analysis)

Adverse Event	Nivolumab (n=209)	Chemotherapy pooled (n=208)
	All Grades n (%)	All Grades n (%)
Lymphocytopenia worsening	96 (45.9)	
AST increase		63 (30.3)
Creatinine increase		142 (68.3)
Platelet count decrease		22 (10.6)

Source: ADaM dataset from Module 5.3.5.1 - adzl.xpt

Table 42 provides the per-patient incidence of laboratory abnormalities in the thyroid function tests (TFTs). As expected, there were more abnormalities in the TFTs in the nivolumab group compared to the pooled chemotherapy group.

Table 42: Thyroid laboratory parameters of the safety population (FDA analysis)

Thyroid laboratory parameter	Nivolumab (n=209)	Chemotherapy pooled (n=208)
	All Grades n (%)	All Grades n (%)
TSH ≤ULN at baseline and post-baseline TSH increase to >ULN	39 (18.7)	28 (13.5)
TSH ≤ULN at baseline and a post-baseline TSH increase to >ULN accompanied by a decrease at least once in free T3 or free T4 to <LLN within 2 weeks after abnormal TSH test	26 (12.4)	14 (6.7)
TSH ≥LLN at baseline and a post-baseline TSH decrease to <LLN	25 (12.0)	7 (3.4)
TSH ≥LLN at baseline and a post-baseline TSH decrease to <LLN accompanied by an increase at least once in free T3 or free T4 to >ULN within 2 weeks after abnormal TSH test	7 (3.3)	2 (1.0)

Source: ADaM dataset from Module 5.3.5.1 - adzl.xpt

Vital Signs

The Applicant's Position:
Vital signs and oxygen saturation by pulse oximetry were monitored and recorded at the site, per institutional standard of care during screening and treatment visits. In ONO-4538-24 (CA209473), 12-lead electrocardiograms (ECGs) were also collected. These assessments were intended to be used as safety monitoring by the treating physician.

The FDA's Assessment:
The FDA concurs with the Applicant's statement. The FDA did not review vital signs in this Application given that nivolumab has a well-characterized safety profile and any clinically significant changes in vital signs would be captured in the adverse event dataset.

Electrocardiograms (ECGs)

The Applicant's Position:
Not applicable

The FDA's Assessment:
ECG data was submitted for all the patients in the safety population; ECGs were performed prior to initiation of study treatment and prior to the first day of subsequent anti-cancer therapy or within 28

days after the last dose, whichever occurred first.

The FDA analysis of the submitted ECG data focused on the heart rate and QT interval, and the FDA was able to reproduce the heart rate and QT interval data in Table 14.3.1.4-1 of the CSR submitted by the Applicant. The FDA determined that one patient (0.5%) had a heart rate of ≤50 beats/minutes (bpm) in the nivolumab group and no patients in the chemotherapy group had a heart rate ≤50 bpm in at least one ECG assessment. A total of 35 patients (16.7%) and 37 patients (17.8%) had heart rates >100 beats/minutes in the nivolumab group and the pooled chemotherapy group, respectively, in at least one ECG assessment.

The number of patients with heart rates ≤50 and >100 bpm were similar between the treatment groups, and raises no safety concerns.

QT

The Applicant's Position:
Not applicable

The FDA's Assessment:
The FDA reviewed the QTcF in the submitted ECG dataset. Only 1 patient (patient ID (b) (6)), in the nivolumab group, had a QTcF >500 ms, and it was present at screening and did not increase following treatment with nivolumab. As expected because nivolumab is a monoclonal antibody, review of the ECG data submitted with this application did not uncover any safety concerns regarding QTcF interval prolongation with nivolumab.

Immunogenicity

Data:

Table 43: Summary of Anti-Drug Antibody Analysis (ADA Analysis Set)

n (%)	Nivolumab (N=184)
Baseline-positive subject[a]	3 (1.6)
Baseline-negative subject[b]	181 (98.4)
Anti-ONO-4538 antibody-positive subject[c]	9 (4.9)
Persistent Positive (PP)[d]	1 (0.5)
Not PP - Last Sample Positive[e]	3 (1.6)
Other Positive[f]	5 (2.7)
Anti-ONO-4538 antibody-positive subject[g]	175 (95.1)

a) Baseline-positive subject was defined as the subject who has baseline-positive sample.
b) Baseline-negative subject was defined as the subject who has baseline-negative sample.
c) Anti-ONO-4538 antibody-positive subject was defined as the subject who has at least one anti-ONO-4538 antibody-positive sample after the first administration of the investigational product.
d) Persistent positive was defined as the subject who has the anti-ONO-4538 antibody-positive samples on greater than or equal to two consecutive sampling time points after the first administration of the investigational product, provided that the time interval should leave at least 16 weeks (including 1 week as the defined allowable window)
e) Last sample positive was defined as the subject who is not PP with the anti-ONO-4538 antibody-positive sample at the last sampling time point.

f) Other positive was defined as the subject who is not PP but some the anti-ONO-4538 antibody-positive samples after the first administration with last sample being negative.
g) Anti-ONO-4538 antibody-negative subject was defined as the subject who has no anti-ONO-4538 antibody-positive sample despite of the administrations of the investigational product.
Source: Table 14.4.1-1 of ONO-4538-24 (CA209473) Final CSR; ADaM dataset: ADSL.xpt, ADIMA.xpt.

The Applicant's Position:

Of the 184 subjects from Study ONO-4538-24 (CA209473) treated with nivolumab 240 mg Q2W and evaluable for immunogenicity, 3 (1.6%) were anti-drug antibody (ADA) baseline-positive (Table 43Table 43). None of the ADA-positive subjects were nivolumab neutralizing ADA (NAb) positive. Of subjects who were ADA positive, none had a hypersensitivity/infusion reaction category event after nivolumab treatment, suggesting an absence of effect of ADA on safety.

The FDA's Assessment:

The results in Table 43 (Applicant's ADA analysis) and Table 44 (FDA's ADA analysis) are slightly different because the Applicant performed their immunogenicity analysis in the study drug antibody population, and the FDA analysis was based on patients who had an antibody status available for the parameter that was being analyzed. The Applicant's study drug antibody population excluded patients who did not have an anti-nivolumab antibody value available prior to the administration first dose of nivolumab (n=2) or did not have anti-nivolumab antibody values available after initiation of treatment with nivolumab (n=23). Otherwise, the FDA agrees with the Applicant's analysis of patients who had a positive anti-nivolumab antibody status after the first dose of nivolumab.

Of the four patients who had a positive test for anti-nivolumab antibodies at baseline, only one tested positive for anti-nivolumab antibodies status after receipt of the first dose of nivolumab.

Anti-nivolumab antibodies were detected in eight patients following receipt of the first dose of nivolumab. No patient had more than 2 positive anti-nivolumab antibody results, and only three patients had 2 positive anti-nivolumab results during the study, two of whom developed the antibody after the first dose of nivolumab (the third had anti-nivolumab antibodies at baseline). The FDA agrees with the Applicant that only one patient had two positive antibody test results that were obtained at least 16 weeks apart. Three patients had a positive antibody test at the last sampling time-point and none of these patients were "persistent positive" (as defined by the Applicant in footnote d of Table 43) prior to this time point.

The proportion of ADA-positive patients in Study ONO-4538-24 is consistent with prior clinical experience with nivolumab. None of the patients who had a positive anti-nivolumab antibody status at baseline (n=4) or after the first dose of nivolumab (n=9) had an infusion-related reaction or drug-related hypersensitivity. The patient who had anaphylactic shock was negative for anti-nivolumab antibody prior to the first dose of nivolumab and throughout the study.

The FDA would like to note that there is a typographical error in the Applicant's Table 43. The last row of this table states, "Anti-ONO-4538 antibody-positive subject," but it should state, "Anti-ONO-4538 antibody-negative subject."

Table 44: Summary of anti-drug antibody analysis for all patients who have ADA data available (FDA analysis)

Anti-nivolumab status	Nivolumab, n (%)
Baseline anti-nivolumab antibody status (n=207)	
Positive	4 (1.9)
Negative	203 (98.0)
Anti-nivolumab antibody status after first dose of nivolumab (n=191)	
Positive	9 (4.7)
Negative	182 (95.3)

Source: ADaM dataset from Module 5.3.5.1 - adsl.xpt, adima.xpt

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Safety of Nivolumab Monotherapy in Ono-4538-24 (CA209473) Compared with Other Tumor Types

Data:

APPEARS THIS WAY ON ORIGINAL

Table 45 Cumulative Dose and Relative Dose Intensity and Duration of Study Therapy - All Treated Subjects with Nivolumab - ESCC and Monotherapy Pooled Data

	ONO-4538-24 Nivolumab 240 mg N = 209	Monotherapy Pooled Nivolumab 3 mg/kg or 240 mg N = 3503
RELATIVE DOSE INTENSITY		
>= 110%	1 (0.5)	5 (0.1)
90% TO < 110%	173 (82.8)	2916 (83.2)
70% TO < 90%	33 (15.8)	513 (14.6)
50% TO < 70%	2 (1.0)	58 (1.7)
< 50%	0	11 (0.3)
NUMBER OF DOSES RECEIVED		
MEAN (SD)	10.8 (11.7)	16.8 (16.0)
MEDIAN	6.0	11.0
MIN - MAX	1 - 60	1 - 91
NUMBER OF DOSES RECEIVED		
1	14 (6.7)	174 (5.0)
2	16 (7.7)	209 (6.0)
3	37 (17.7)	240 (6.9)
4	10 (4.8)	241 (6.9)
>4	132 (63.2)	2639 (75.3)
CUMULATIVE DOSE (MG)		
MEAN (SD)	2585.15 (2816.07)	3792.81 (4214.73)
MEDIAN	1440.00	2200.00
MIN - MAX	240.0 - 14400.0	18.8 - 26074.8
DURATION OF THERAPY (MONTHS)		
MIN, MAX (A)	0.0, 29.2+	0.0, 44.2+
MEDIAN (95% CI) (B)	2.56 (2.33, 3.48)	5.09 (4.63, 5.36)
MEAN (SD)	4.89 (5.90)	7.70 (7.69)
N OFF TRT/N TREATED (%)	193/209 (92.3)	2860/3503 (81.6)
> 3 MONTHS (%)	93 (44.5)	2176 (62.1)
> 6 MONTHS (%)	54 (25.8)	1586 (45.3)
> 9 MONTHS (%)	32 (15.3)	1236 (35.3)
> 12 MONTHS (%)	21 (10.0)	696 (19.9)

(A) Symbol + indicates a censored value.

(B) Median computed using Kaplan-Meier method.

Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209017, CA209025, CA209032 (UC subjects and SCLC cohort), CA209037, CA209039 (cHL subjects from monotherapy nivo arm), CA209040 (cohorts 1 and 2), CA209057, CA209063, CA209066, CA209067 (monotherapy arm), CA209141, CA209142 (mono cohort), CA209205 (cohort A+B+C) CA209238, CA209275.

Source: Table 4 (cumulative dose and relative dose intensity) and Table 5 (duration of study therapy) in SCS Appendix 4; ADaM dataset: SCS.ADSL.xpt, SCS.ADEXS.xpt

Table 46 Summary of Safety of Nivolumab Monotherapy across Tumor Types - ESCC and Monotherapy Pooled Data

	ONO-4538-24 Nivolumab 240 mg N = 209			Monotherapy Pooled Nivolumab 3 mg/kg or 240 mg N = 3503		
DEATH (%)	159 (76.1)			1562 (44.6)		
PRIMARY REASON FOR DEATH (%)						
DISEASE PREOGRESSION	141 (67.5)			1382 (39.5)		
STUDY DRUG TOXICITY	2 (1.0)			11 (0.3)		
UNKNOWN	0			41 (1.2)		
OTHER	16 (7.7)			128 (3.7)		
WITHIN 30 DAYS OF LAST DOSE (%) (1)	19 (9.1)			313 (8.9)		
WITHIN 100 DAYS OF LAST DOSE (%)	60 (28.7)			826 (23.6)		
	Any Grade	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
ALL-CAUSALITY SAEs	68 (32.5)	43 (20.6)	7 (3.3)	1511 (43.1)	1009 (28.8)	229 (6.5)
DRUG-RELATED SAEs	33 (15.8)	20 (9.6)	0	307 (8.8)	209 (6.0)	7 (0.2)
ALL-CAUSALITY AEs LEADING TO DC	29 (13.9)	11 (5.3)	5 (2.4)	532 (15.2)	343 (9.8)	72 (2.1)
DRUG-RELATED AEs LEADING TO DC	18 (8.6)	8 (3.8)	0	211 (6.0)	140 (4.0)	3 (<0.1)
ALL-CAUSALITY AEs	189 (90.4)	80 (38.3)	7 (3.3)	3433 (98.0)	1550 (44.2)	229 (6.5)
Most frequent AEs(≥ 15% of Any Grade in either group)						
Decreased appetite	43 (20.6)	4 (1.9)	0	680 (19.4)	31 (0.9)	0
Diarrhoea	37 (17.7)	3 (1.4)	0	916 (26.1)	67 (1.9)	0
Constipation	35 (16.7)	0	0	634 (18.1)	13 (0.4)	0
Pyrexia	33 (15.8)	1 (0.5)	0	535 (15.3)	13 (0.4)	0
Cough	32 (15.3)	0	0	829 (23.7)	9 (0.3)	0
Pruritus	25 (12.0)	0	0	680 (19.4)	5 (0.1)	0
Rash	25 (12.0)	1 (0.5)	0	592 (16.9)	21 (0.6)	0
Nausea	23 (11.0)	0	0	857 (24.5)	24 (0.7)	0
Fatigue	20 (9.6)	2 (1.0)	0	1386 (39.6)	89 (2.5)	0
Dyspnoea	15 (7.2)	3 (1.4)	0	593 (16.9)	98 (2.8)	1 (<0.1)
Arthralgia	10 (4.8)	0	0	555 (15.8)	19 (0.5)	0

	ONO-4538-24 Nivolumab 240 mg N = 209			Monotherapy Pooled Nivolumab 3 mg/kg or 240 mg N = 3503		
	Any Grade	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
DRUG-RELATED AEs	137 (65.6)	38 (18.2)	0	2588 (73.9)	555 (15.8)	7 (0.2)
Most Frequent Drug-related AEs (≥ 5% of Any Grade in either group)						
Diarrhoea	22 (10.5)	2 (1.0)	0	489 (14.0)	39 (1.1)	0
Rash	22 (10.5)	1 (0.5)	0	431 (12.3)	19 (0.5)	0
Hypothyroidism	17 (8.1)	0	0	239 (6.8)	2 (<0.1)	0
Decreased appetite	16 (7.7)	2 (1.0)	0	270 (7.7)	5 (0.1)	0
Pruritus	16 (7.7)	0	0	515 (14.7)	4 (0.1)	0
Fatigue	15 (7.2)	1 (0.5)	0	876 (25.0)	46 (1.3)	0
Pyrexia	15 (7.2)	1 (0.5)	0	168 (4.8)	0	0
Nausea	4 (1.9)	0	0	410 (11.7)	6 (0.2)	0
Arthralgia	3 (1.4)	0	0	239 (6.8)	3 (<0.1)	0
Asthenia	1 (0.5)	0	0	241 (6.9)	9 (0.3)	0
ALL-CAUSALITY IMMUNE MEDIATED ADVERSE EVENTS, BY CATEGORY						
Immune-mediated AEs treated with Immune-modulating medications						
PNEUMONITIS	9 (4.3)	2 (1.0)	0	89 (2.5)	28 (0.8)	1 (<0.1)
DIARRHEA/COLITIS	4 (1.9)	1 (0.5)	0	101 (2.9)	41 (1.2)	0
HEPATITIS	1 (0.5)	0	0	67 (1.9)	51 (1.5)	0
NEPHRITIS AND RENAL DYSFUNCTION	0	0	0	28 (0.8)	16 (0.5)	0
RASH	23 (11.0)	3 (1.4)	0	317 (9.0)	30 (0.9)	0
HYPERSENSITIVITY/INFUSION REACTIONS	1 (0.5)	1 (0.5)	0	49 (1.4)	6 (0.2)	0
Immune-mediated Endocrine AEs Treated with or without Immune-Modulating Medications						
ADRENAL INSUFFICIENCY	0	0	0	34 (1.0)	11 (0.3)	0
HYPOPHYSITIS	1 (0.5)	0	0	24 (0.7)	9 (0.3)	0
HYPOTHYROIDISM/THYROIDITIS	21 (10.0)	0	0	315 (9.0)	2 (<0.1)	0
HYPERTHYROIDISM	3 (1.4)	0	0	124 (3.5)	2 (<0.1)	0
DIABETES MELLITUS	1 (0.5)	0	0	19 (0.5)	7 (0.2)	0

MedDRA Version: 21.1; CTC Version 4.0

Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209017, CA209025, CA209032 (UC subjects and SCLC cohort), CA209037, CA209039 (cHL subjects from monotherapy nivo arm), CA209040 (cohorts 1 and 2), CA209057, CA209063, CA209066, CA209067 (monotherapy arm), CA209141, CA209142 (mono cohort), CA209205 (cohort A+B+C) CA209238, CA209275.

(1) For deaths within 30 days of last dose, includes events reported between first dose and 30 days after last dose of study therapy, except for ONO-4538-24. For ONO-4538-24, includes events reported between first dose and 28 days after last dose of study therapy.

For AEs (including IMAEs), includes events reported between first dose and 30 days after last dose of study therapy, except for ONO-4538-24. For ONO-4538-24, includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.

Source: Table 1.1.1 (all AEs), Table 1.1.2 (drug-related AEs), Table 1.1.3 (all SAEs), Table 1.1.4 (drug-related SAEs), Table 1.1.5 (AEs leading to discontinuation), Table 1.1.6 (drug-related AEs leading to discontinuation), Table 2.1 (IMAEs with immune modulating medication), Table 2.2 (endocrine IMAEs with or without immune-modulating medication), and Table 6 (death) in SCS Appendix 4; ADaM dataset: SCS.ADSL.xpt, SCS.ADAE.xpt, SCS.ADAEIMM.xpt

The Applicant's Position:

Safety data from nivolumab monotherapy in patients with ESCC (ONO-4538-24 [CA209473]) are presented side-by-side with safety data integrated across completed studies in multiple indications with nivolumab monotherapy (NSCLC, SCCHN, melanoma, RCC, cHL, UC, SCLC, HCC, CRC, and adjuvant melanoma). See Section 1.1.1.4 of the SCS for a list of studies included in the nivolumab monotherapy integrated dataset.

In ESCC, the median number of doses received and median cumulative dose were lower than those of the monotherapy pooled data of other tumor types (Table 45Table 45). A high proportion of subjects received ≥90% of the relative dose intensity, similar to that of the pooled data of other tumor types. Median duration of therapy was shorter than that of the pooled data of other tumor types. Lower proportions of subjects were treated for more than 3, 6, 9, and 12 months than with the other tumor types.

Overall, the safety profile of nivolumab monotherapy in ESCC was consistent with the safety profile of nivolumab monotherapy in other tumor types. No new safety concerns with nivolumab monotherapy treatment were identified in ESCC.

- Disease progression was the most common cause of death in ESCC and other tumor types, including deaths occurring within 30 days of last dose (within 28 days of last dose for ONO 4538-24 [CA209473]) and deaths occurring within 100 days of last dose (Table 46Table 46).
  - Death attributed to study drug toxicity was reported at 1.0% in ESCC subjects, and 0.3% in other tumor types.
- In general, the type, frequency, and severity of AEs were consistent between ESCC and other tumor types, as shown in Table 46.
  - All-causality AEs were reported less frequently in ESCC (90.4%) compared to other tumor types (98.0%). Decreased appetite was the most frequently reported AE in ESCC and fatigue was the most frequently reported AE in other tumor types.
  - Drug-related AEs were reported less frequently in ESCC (65.6%) compared with other tumor types (73.9%).
  - Drug-related Grade 3-4 AEs were reported more frequently in ESCC (18.2%) compared with other tumor types (15.8%). These included events such as tumor hemorrhage which were reported more frequently with nivolumab in ONO-4538-24 (CA209473) compared to other tumor types (3 cases [1.4%] vs 0) or fistulas (oesophagobrochial fistula, 1 case [0.5%] vs 0; tracheal fistula, 1 case [0.5%] vs 0) that might be specific to the anatomic location of the underlying malignancy.
- IMAEs treated with IMM were reported at similar frequencies in ESCC compared with other tumor types, with the exception of the pneumonitis IMAE category, which was reported more frequently (> 1% difference) in ESCC. Nine (4.3%) patients in the nivolumab arm experienced a pneumonitis IMAE as compared to 6 (2.9%) patients in the control chemotherapy arm.
- Endocrine IMAEs with or without IMM treatment were reported at similar or lower frequency in ESCC compared with other tumor types.

The FDA's Assessment:

Despite the slight differences between the FDA and the Applicant's analyses of the primary reason of death (See Pneumonitis is a known adverse reaction for nivolumab and does not raise new safety concerns relative to the safety profile of nivolumab described in the current product labeling. Non-DRAEs, as assessed by Investigator or Applicant, leading to death of note were deaths due to esophageal fistulas (n=2) and hematemesis (n=1) in the nivolumab group and the hematemesis (n=1) in the paclitaxel group. Although these AEs are expected in patients with ESCC, it is notable that three patients (1.4%) in the nivolumab group versus one (0.5%) patient in the chemotherapy group experienced these events. See the section entitled "All causality treatment-emergent SAEs" of Section 8.2.4 for a discussion regarding esophageal fistulas and hematemesis. An exploratory analysis performed by the FDA indicated that the esophageal fistulas tended to develop in patients whose ESCC progressed later during the course of study treatment (i.e., late progressors). This suggests that although nivolumab was associated with more deaths due to these two TEAEs which may signify ESCC progression, early progressors did not experience these TEAEs at a higher rate than late progressors (see Section 8.2.9 for this exploratory FDA analysis). Given that the FDA cannot conclusively determine that these esophageal fistulas and hematemesis occurred due to disease progression and because their corresponding narratives did not describe disease progression or disease-related issues as the cause of death, these Grade 5 events were included in the list of fatal reactions in the nivolumab product labeling.

Table 26 for the FDA analysis), the FDA agrees with the Applicant's statement that more patients with ESCC died of disease progression compared to other tumor types and that the number of doses received, cumulative dose, and duration of therapy were lower in patients with ESCC compared to other diseases. The FDA also agrees with the Applicant's statement that a high proportion of patients with ESCC received ≥90% of the planned dose intensity, similar to that of the pooled data of other tumor types. This exposure analysis suggests that patients with ESCC permanently discontinue nivolumab earlier in the treatment course compared to patients with other tumor types, with a higher proportion of them discontinuing due to disease progression compared to patients with other tumor types, but prior to discontinuation of nivolumab, patients with ESCC have similar exposure to nivolumab compared to patients with other tumor types.

The FDA agrees with the Applicant's statement that the overall safety profile of nivolumab was consistent with the safety profile observed in other tumor types, but the FDA noted that there was a higher incidence of pneumonitis within 28 days of the last dose of treatment in the safety population of patients with ESCC compared to patients with other tumors in the Applicant's Table 46. Using the composite Preferred Terms for pneumonitis (which includes interstitial lung disease, and radiation pneumonitis), the incidence of pneumonitis of any causality and any grade was lower in the pooled population of patients with other tumor types (3.3%, n=117) compared to patients with ESCC (8.6%, n=18 in Table 39). Of the patients who developed pneumonitis during this study, 77.8% (n=14 of 18) patients in the nivolumab group and 61.5% (n=8 of 13) patients in the pooled chemotherapy group had prior radiation therapy for ESCC (site of radiation not specified). Of the patients who had prior radiation therapy in the safety population, 9.2% (n=14 of 152) patients in the nivolumab group and 5.6% (n=8 of 142) patients in the pooled chemotherapy group developed TEAE pneumonitis. Of the patients who did

not have a prior radiotherapy for ESCC, 7.0% (n=4 of 57) patients in the nivolumab group and 7.6% (n=5 of 66) patients in the pooled chemotherapy group developed TEAE pneumonitis. Thus, the data suggest that patients with ESCC have an increased risk of pneumonitis compared to other tumor types, and the risk of pneumonitis appears to be increased in patients who received prior radiation therapy, and the risk of pneumonitis may be increased with nivolumab compared to taxane chemotherapy. However, a more rigorous analysis adjusting for possible confounding factors is needed before a definitive conclusive can be made.

The FDA agrees with the Applicant's assessment that the anatomic location of ESCC is likely responsible for the increased incidence of certain Grade 3-4 TEAEs (such as tumor hemorrhage and esophageal fistulas) compared to the other tumor types.

Note, the Applicant's Table 46 has an error: there were no cases of hypophysitis in Study ONO-4538-24 (CA209473).

8.2.5.2 Safety of Nivolumab in Western Subjects in ONO-4538-24 [CA209473]

Data:

Table 47 Summary of Adverse Events - All Treated Western Subjects in ONO-4538-24 (CA209473)

	Nivolumab			Control group		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
N	9	9	9	8	8	8
No. of subjects with AEs (%)	9 (100.0)	4 (44.4)	0	8 (100.0)	7 (87.5)	0
No. of subjects with SAEs (%)	4 (44.4)	3 (33.3)	0	6 (75.0)	6 (75.0)	0
No. of subjects with AEs leading to discontinuation of study treatment (%)	3 (33.3)	1 (11.1)	0	1 (12.5)	1 (12.5)	0
No. of subjects with AEs leading to dose delay (%)	1 (11.1)	1 (11.1)	0	3 (37.5)	2 (25.0)	0
No. of subjects with AEs leading to dose reduction (%)	0	0	0	2 (25.0)	1 (12.5)	0
No. of subjects with drug-related AEs (%)[a]	5 (55.6)	1 (11.1)	0	8 (100.0)	5 (62.5)	0
No. of subjects with drug-related SAEs (%)[a]	1 (11.1)	0	0	2 (25.0)	2 (25.0)	0
No. of subjects with drug-related AEs leading to discontinuation of study treatment (%)[a]	1 (11.1)	0	0	0	0	0
No. of subjects with drug-related AEs leading to dose delay (%)[a]	0	0	0	1 (12.5)	1 (12.5)	0
No. of subjects with drug-related AEs leading to dose reduction (%)[a]	0	0	0	2 (25.0)	1 (12.5)	0

a) Drug-related AEs were defined as any AEs with causal relationship with the investigational product is "Related" or missing. AEs, drug-related AEs occurring between the start date of the first administration of the investigational product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.

Source: Table 16.3.1.1-1-1 in SCS Appendix 3; ADaM dataset: ADSL.xpt, ADAE.xpt

The Applicant's Position:

The safety profile of the subgroup of Western subjects was comparable to that of the overall treated population in ONO-4538-24 (CA209473). The safety profile in Western subjects was manageable and consistent with previously reported safety findings for nivolumab in other tumor types. A summary of the analysis populations within the subgroup of Western subjects is presented in Table 47.

The FDA's Assessment:
The safety population of Study ONO-4538-24 (CA209473) consisted of patients who enrolled in four Western countries (Germany, Denmark, Italy, and U.S.) and three Asian countries/regions (Japan, Korea, and Taiwan). Seventeen patients (4.1%) enrolled into sites in Western countries, and 400 patients (95.9%) enrolled into sites in Asian countries/regions. All patients who enrolled in Asian countries/regions were Asian, and all patients enrolled in Western countries were White. Nine of the Western patients were in the nivolumab group and eight were in the pooled chemotherapy group.

The FDA agrees with the Applicant's Table 47 but has the following comments:
- There was a Grade 5 TEAE among the Western patients, and this TEAE was also reported as a Grade 5 SAE: one patient developed worsening hypercalcemia in the paclitaxel arm and had the study treatment permanently discontinued the same day the hypercalcemia worsened. Thus, the TEAE started within 28 days of the last dose of the study treatment, but because the patient died of this TEAE 33 days after the last dose, it was not in the Applicant's Table 47.
- As stated in Section 8.2.1, the FDA did not perform a separate analysis of TEAEs based on what the Applicant or Investigators assessed as "drug-related AEs," and has no comments regarding the "drug-related AE" results in Table 47.

The proportions of Western patients who experienced TEAEs of any grade, Grade 5 TEAEs, and treatment-emergent SAEs of any grade were similar to the overall study population of Study ONO-4538-24 (CA209473). A higher percentage of Western patients discontinued nivolumab due to TEAEs (n=3/9, 33.3%) compared to Asian patients (n=25/200, 12.5%), but a lower percentage of Western patients required a nivolumab dose delay due to TEAEs that occurred in the 28-day window (n=1/9, 11.1%) compared to the Asian patients (n=56/200, 28%). Given the small number of Western patients in this study, it is not possible to conclusively determine whether the safety profile of nivolumab in Western patients with ESCC differs from the safety profile observed in Asian patients with ESCC. However, based upon the vast clinical experience with nivolumab in the U.S. and globally, it is unlikely that the safety profile of nivolumab in Western patients with ESCC would differ from that of Asian patients.

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

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees that the PRO data collected in Study ONO-4538-24 did not provide meaningful information

to augment the understanding of the safety and tolerability of nivolumab in patients with ESCC. Patient Reported Outcome (PRO) information was measured using the EuroQoL 5-dimension (EQ-5D) questionnaire, which was collected at screening, every 6 weeks during the treatment phase, and every 12 weeks during the follow-up phase according to the protocol (see Efficacy Results – Secondary or exploratory COA [PRO] endpoints in Section 8.1.2 for the FDA assessment of the PRO data).

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Table 48: Drug-related AEs Classified by the Worst CTCAE Grade and by Age, Gender, Race, and Region - All Treated ONO-4538-24 (CA209473) Subjects

	Drug-related AEs (n/N [%])					
	Nivolumab			Control group		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Total	137/209 (65.6)	38/209 (18.2)	0	198/208 (95.2)	131/208 (63.0)	2/208 (1.0)
By Age						
< 65 yrs	75/112 (67.0)	18/112 (16.1)	0	81/85 (95.3)	43/85 (50.6)	0
≥ 65 yrs	62/97 (63.9)	20/97 (20.6)	0	117/123 (95.1)	88/123 (71.5)	2/123 (1.6)
By Gender						
Male	117/178 (65.7)	33/178 (18.5)	0	174/184 (94.6)	113/184 (61.4)	2/184 (1.1)
Female	20/31 (64.5)	5/31 (16.1)	0	24/24 (100.0)	18/24 (75.0)	0
By Race						
Asian	132/200 (66.0)	37/200 (18.5)	0	190/200 (95.0)	126/200 (63.0)	2/200 (1.0)
Other	5/9 (55.6)	1/9 (11.1)	0	8/8 (100.0)	5/8 (62.5)	0
By Region						
Japan	92/135 (68.1)	23/135 (17.0)	0	135/138 (97.8)	100/138 (72.5)	2/138 (1.4)
Rest of the World	45/74 (60.8)	15/74 (20.3)	0	63/70 (90.0)	31/70 (44.3)	0

Any AEs were coded using MedDRA version 21.1. CTCAE version 4.0.
AEs occurring between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.
Drug-related AEs were defined as any AEs with causal relationship with the product is "Related" or missing.
Source: Table 14.3.1.1-1-1 (all drug-related AEs), Table 14.3.1.5-2-3-1 (age < 65), Table 14.3.1.5-2-3-2 (age ≥ 65), Table 14.3.1.5-2-4-1 (male), Table 14.3.1.5-2-4-2 (female), Table 14.3.1.5-2-5-1 (race: Asian), Table 14.3.1.5-2-5-2 (race: other), Table 14.3.1.5-2-1-1 (Japan), and Table 14.3.1.5-2-1-2 (rest of world) from the ONO-4538-24 (CA209473) final CSR; ADaM dataset: ADSL.xpt, ADAE.xpt

The Applicant's Position:

The overall incidences of AEs in subgroups were generally similar to those in the all treated subject population, suggesting no effects of the examined demographic and other baseline factors (Table 48).

Analyses were also performed for serious all-causality and drug-related AEs. Any differences observed are of limited interpretability due to small sample sizes and low event rates and do not alter the overall safety profile of nivolumab in these subgroups.

The FDA's Assessment:

Table 49: All causality AEs classified by the worst CTCAE Grade and by age, gender, race, and region - All treated ONO-4538-24 (CA209473) patients (FDA analysis)

Adverse Event	Nivolumab (n=209)			Chemotherapy pooled (n=208)		
	All Grades n (%)	Grades 3-4 n (%)	Grade 5 n (%)	All Grades n (%)	Grades 3-4 n (%)	Grade 5 n (%)
By Age						
<65 years old	100/112 (89.3)	43/112 (38.4)	7/112 (6.3)	84/85 (98.8)	50/85 (58.8)	2/85 (2.4)
≥65 years old	89/97 (91.8)	35/97 (36.1)	3/97 (3.1)	121/123 (98.4)	95/123 (77.2)	6/123 (4.9)
By Gender						
Male	161/178 (90.4)	65/178 (36.5)	9/178 (5.1)	181/184 (98.4)	126/184 (68.5)	8/184 (4.3)
Female	28/31 (90.3)	13/31 (41.9)	1/31 (3.2)	24/24 (100)	19/24 (79.2)	0
By Race						
Asian	180/200 (90.0)	74/200 (37.0)	10/200 (5.0)	197/200 (98.5)	139/200 (69.5)	7/200 (3.5)
Other	9/9 (100)	4/9 (44.4)	0	8/8 (100)	6/8 (75.0)	1/8 (12.5)
By Region						
Japan	119/135 (88.1)	42/135 (31.1)	3/135 (2.2)	137/138 (99.3)	106/138 (76.8)	3/138 (2.2)
Rest of the World	70/74 (94.6)	36/74 (48.6)	7/74 (9.5)	68/70 (97.1)	39/70 (55.7)	5/70 (7.1)

Source: ADaM dataset from Module 5.3.5.3 - adsl.xpt, adae.xpt

TEAEs of any grade were well-balanced across the subgroups presented in Table 48, but Grade 3-4 events occurred at a slightly higher rate in the non-Asian and Rest of the World subgroups (see Section 8.2.5.2 for the discussion regarding Grade 3-4 events among Western patients compared to Asian patients). There are imbalances in the Grade 5 TEAEs among the subgroups, but the small number of Grade 5 TEAEs in general precludes the ability to draw conclusions. In summary, nivolumab did not appear to be more toxic for one subgroup compared to another.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable. BMS has not conducted a specific study or clinical trial to evaluate a specific safety concern for nivolumab in ESCC.

The FDA's Assessment:

There were no special safety studies/clinical trials conducted for this sBLA.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:
There were no new findings related to human carcinogenicity or tumor development for nivolumab in study ONO-4538-24 (CA209473). No secondary primary malignancies were reported.

The FDA's Assessment:
Carcinogenicity studies were not conducted for this drug based on its intended mechanism of action. The Applicant did not report any occurrences of new malignancies among patients enrolled in Study ONO-4538-24 (CA209473).

Human Reproduction and Pregnancy

The Applicant's Position:
There were no new findings related to human reproduction and pregnancy for nivolumab in study ONO-4538-24 (CA209473). Although one female subject had a positive pregnancy test result during the treatment period, the investigator confirmed that the test result was false positive and the subject was not pregnant.

The FDA's Assessment:
The FDA acknowledges the Applicant's position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable. The youngest patient in this study was 33 years old.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
There were no new findings related to overdose, or drug abuse potential for nivolumab in study ONO-4538-24 (CA209473). No cases of withdrawal symptoms related to nivolumab were reported during human clinical trials.

The FDA's Assessment:
Based on its pharmacological properties, there are no concerns regarding the potential for abuse, withdrawal, or rebound with nivolumab. Only 22 patients received a relative dose intensity >100% with a median of 102.0% (minimum 100.5%, maximum 112.0%), and these excursions do not constitute an overdose.

TEAEs among patients who were early progressors in Study ONO-4538-24 (CA209473) (FDA analysis)

Given the non-proportionate hazard ratios for OS and PFS, the FDA performed an exploratory safety analysis of the patients who progressed prior to the crossing of the PFS curves, to determine if 1) early progressors had more TEAEs compared to the patients who progressed later, and 2) if the TEAEs experienced by the early progressors could be due to inability of nivolumab to control the ESCC. Because the PFS curves for the nivolumab and the pooled chemotherapy groups crossed approximately 4.5 months following randomization, early progressors were defined as those patients had a progression event prior to 4.5 months, and late progressors were the remainder of the patients.

Not surprisingly, there was a higher proportion of total deaths among the early progressors compared to the late progressors in both the nivolumab group and the pooled chemotherapy group (Table 50). Compared to late progressors, a higher percentage of early progressors died due to ESCC in both the nivolumab group and the pooled chemotherapy group and there was a slightly higher proportion of early progressors whose death was attributed to a TEAE in the nivolumab group (Table 50).

Table 50: Summary of deaths in early progressors among the safety population in Study ONO-4538-24 (CA209473) (FDA analysis)

	Nivolumab (n=146)		Chemotherapy Control					
			Early progressors			Late progressors		
	Early progressors (n=146)	Late progressors (n=63)	Chemotherapy Pooled (n=154)	Docetaxel (n=49)	Paclitaxel (n=105)	Chemotherapy Pooled (n=54)	Docetaxel (n=16)	Paclitaxel (n=38)
Deaths until data cutoff (November 12, 2018), n (%)								
Total deaths	126 (86.3)	33 (52.4)	137 (89.0)	41 (83.7)	96 (91.4)	36 (66.7)	11 (68.8)	25 (65.8)
Initial disease	111 (76.0)	31 (49.2)	120 (77.9)	36 (73.5)	84 (80.0)	31 (57.4)	11 (68.8)	20 (52.6)
Related to TEAEs (regardless of causality)	12 (8.2)	2 (3.2)	15 (9.7)	4 (8.2)[a]	11 (10.5)	5 (9.3)	1 (6.3)	4 (10.5)
Drug-related TEAEs (DRAEs) as assessed by the Investigator or Applicant	3 (2.1)	0	4 (2.6)	1 (2.0)	3 (2.9)	1 (1.9)	0	1 (2.6)
Not related to initial disease or TEAEs	3 (2.1)[b]	0	2 (1.3)	1 (2.0)[c]	1 (1.0)[c]	1 (1.9)	0	1 (2.6)[c]

a. One patient (ID (b) (6)) died beyond the 100-day window; the patient developed interstitial lung disease (ILD) 4 days after the last dose of paclitaxel but died 142 days after the last dose of paclitaxel due to a multitude of reasons, included "aggravated ILD."
b. Cause of death "unknown" (n=2) and "other cancer" (n=1).
c. Cause of death "unknown."

Source: ADaM dataset from Module 5.3.5.3 - adsl.xpt

A lower proportion of early progressors experienced TEAEs (any grade and Grade 3-4) and TEAEs that led to treatment discontinuation or delay compared to late progressors in the nivolumab group (Table 51). The trend is similar for the chemotherapy group. Early progressors experienced treatment-emergent SAEs only at a slightly lower rate than late progressors in the nivolumab group, and there was no consistent pattern for treatment-emergent SAEs in the chemotherapy group. These results suggest that early progressors experienced less TEAEs compared to late progressors, likely because they had less exposure to the study treatment compared to the late progressors.

Table 51: Summary of major safety results in early progressors among the safety population in Study ONO-4538-24 (CA209473) (FDA analysis)

	Nivolumab		**Chemotherapy Control**					
			Early progressors			Late progressors		
	Early progressors (n=146)	Late progressors (n=63)	Chemotherapy Pooled (n=154)	Docetaxel (n=49)	Paclitaxel (n=105)	Chemotherapy Pooled (n=54)	Docetaxel (n=16)	Paclitaxel (n=38)
Patients who experienced a TEAE, n (%)								
28-day window	127 (87.0)	62 (98.4)	151 (98.1)	47 (95.9)	104 (99.0)	54 (100)	16 (100)	38 (100)
100-day window	128 (87.7)	62 (98.4)	152 (98.7)	48 (98)	104 (99.0)	54 (100)	16 (100)	38 (100)
Patients who experienced a Grade 3-4 TEAE, n (%)								
28-day window	50 (34.2)[a]	30 (47.6)[a]	104 (67.5)	33 (67.3)	71 (67.6)[b]	44 (81.5)	16 (100)	28 (73.7)[b]
100-day window	55 (37.7)[a]	33 (52.4)[a,c]	103 (66.9)	32 (65.3)	71 (67.6)[b]	40 (74.1)	15 (93.8)	25 (65.8)[b]
Patients who experienced a treatment-emergent SAE, n (%)								
28-day window	45 (30.8)[a]	22 (34.9)[a]	56 (36.4)	17 (34.7)	39 (37.1)[b]	20 (37.0)	10 (62.5)	10 (26.3)[b]
100-day window	55 (37.7)[a]	25 (39.7)[a,c]	66 (42.9)	21 (42.9)	45 (42.9)[b]	21 (38.9)	10 (62.5)	11 (28.9)[b]
Patients who permanently discontinued study treatment due to a TEAE, n (%)								
28-day window	17 (11.6)[d]	11 (17.5)[d,e]	20 (13.0)	5 (10.2)	15 (14.3)[b]	12 (22.2)	4 (25.0)	8 (21.1)[b]
100-day window	17 (11.6)[d]	13 (20.6)[d,e]	20 (13.0)	5 (10.2)	15 (14.3)[b]	12 (22.2)	4 (25.0)	8 (21.1)[b]
Patients who delayed study treatment due to a TEAE, n (%)								
28-day window	28 (19.2)	29 (46.0)	82 (53.2)	6 (12.2)	76 (72.4)	38 (70.4)	7 (43.8)	31 (81.6)
Patients who dose-reduced study treatment due to a TEAE, n (%)								

	Nivolumab		Chemotherapy Control					
			Early progressors			Late progressors		
	Early progressors (n=146)	Late progressors (n=63)	Chemotherapy Pooled (n=154)	Docetaxel (n=49)	Paclitaxel (n=105)	Chemotherapy Pooled (n=54)	Docetaxel (n=16)	Paclitaxel (n=38)
28-day window	0	0	52 (33.8)	23 (46.9)	29 (27.6)	25 (46.3)	13 (81.3)	12 (31.6)

a. Grade 3 "Lymphangiosis carcinomatosa" was excluded from this analysis since this is not a TEAE, but disease progression (patient ID (b) (6) in the nivolumab group).
b. Grade 4 and 5 "disease progression" was excluded from this analysis since this is not a TEAE, but disease progression (patient ID (b) (6) in the paclitaxel treatment arm).
c. This number includes the patient in the nivolumab group who experienced a treatment-emergent SAE of Grade 4 DKA 97 days after the last dose of nivolumab, but this SAE was not reported prior to the DBL due to GCP non-compliant activity in (b) (4). The SAE was considered a DRAE as assessed by the Investigator or Applicant.
d. Grade 5 "malignant neoplasm progression" was excluded from this analysis since this is not a TEAE, but disease progression (patient ID (b) (6) in the nivolumab group).
e. Two patients (in the nivolumab group) received their last dose of study treatment before the occurrence of the TEAEs, which occurred in the 100-day window, that led to treatment discontinuation. Because "treatment discontinuation flags" are marked on the day of treatment discontinuation, there is a discrepancy between the 28-day window and 100-day window for the number of patients who permanently discontinued nivolumab due to a TEAE due to these 2 patients. The day of treatment discontinuation does not necessarily align with the day of the last dose of study treatment administration.

Source: ADaM dataset adae.xpt from Module 5.3.5.3 and adtte.xpt from Module 5.3.5.1

The following TEAEs that occurred in ≥10% of the overall safety population receiving nivolumab within the 28-day window (Table 37) occurred in <10% of the early progressors in the nivolumab group: pruritus, hepatobiliary disorders, nausea, and hypothyroidism. Thus these TEAEs were excluded from Table 52. A similar pattern was observed for the TEAEs that occurred within the 100-day window. Nonetheless, there was no consistent pattern suggesting differences in the common TEAEs among early and late progressors in the nivolumab nor chemotherapy treatment groups (Table 52).

Table 52: TEAEs in ≥10% of patients receiving nivolumab within 28 days of last dose of study treatment among early progressors (FDA analysis)

Adverse Event	Nivolumab				Chemotherapy pooled			
	Early progressors (n=146)		Late progressors (n=63)		Early progressors (n=154)		Late progressors (n=54)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Gastrointestinal Disorders								
Decreased appetite[a]	34 (23.3)	3 (2.1)	10 (15.9)	1 (1.6)	60 (39.0)	9 (5.8)	13 (24.1)	2 (3.7)
Constipation	27 (18.5)	0	8 (12.7)	0	32 (20.8)	0	8 (14.8)	0
Diarrhea[b]	24 (16.4)	3 (2.1)	14 (22.2)	1 (1.6)	27 (17.5)	3 (2.0)	9 (16.7)	0
Skin and Subcutaneous Tissue Disorders								
Rash[c]	28 (19.2)	3 (2.1)	18 (28.6)	1 (1.6)	33 (21.4)	0	25 (46.3)	2 (3.7)
General Disorders								
Pyrexia[d]	24 (16.4)	1 (0.7)	10 (15.9)	0	30 (19.5)	1 (0.7)	10 (18.5)	0
Fatigue[e]	15 (10.3)	3 (2.1)	10 (15.9)	0	40 (26.0)	8 (5.2)	16 (29.6)	2 (3.7)

Adverse Event	Nivolumab				Chemotherapy pooled			
	Early progressors (n=146)		Late progressors (n=63)		Early progressors (n=154)		Late progressors (n=54)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Musculoskeletal and Connective Tissue Disorders								
Musculoskeletal pain[f]	18 (12.3)	0	17 (27.0)	0	37 (24.0)	2 (1.3)	17 (31.5)	1 (1.9)
Blood and Lymphatic System Disorders								
Anemia[g]	18 (12.3)	11 (7.5)	9 (14.3)	6 (9.5)	43 (27.9)	19 (12.3)	20 (37.0)	7 (13.0)
Respiratory, Thoracic and Mediastinal Disorders								
Upper respiratory tract infection[h]	17 (11.6)	2 (1.4)	19 (30.2)	0	14 (9.1)	0	15 (27.8)	0
Cough[i]	17 (11.6)	0	16 (25.4)	0	19 (12.3)	0	11 (20.4)	1 (1.9)
Pneumonia[j]	15 (10.3)[k]	7 (4.8)	12 (19.2)[l]	6 (9.5)	27 (17.5)[m]	14 (9.1)	13 (24.1)	7 (13.0)

Toxicity was graded per NCI CTCAE v4.

a. Includes hypophagia, and food aversion.
b. Includes colitis.
c. Includes urticaria, drug eruption, eczema, eczema asteatotic, eczema nummular, palmar-plantar erythrodysaesthesia syndrome, erythema, blister, skin exfoliation, Stevens-Johnson syndrome, dermatitis, dermatitis described as acneiform, or contact, and rash described as maculo-papular, generalised, or pustular.
d. Includes tumor-associated fever.
e. Includes asthenia.
f. Includes periarthritis, arthralgia, back pain, myalgia, pain in extremity, arthritis, and bone pain.
g. Includes hemoglobin decreased, and iron deficiency anemia.
h. Includes influenza, influenza-like illness, pharyngitis, nasopharyngitis, tracheitis, bronchitis, and upper respiratory infection with bronchitis.
i. Includes productive cough.
j. Includes pneumonia aspiration, pneumonia bacterial, and lung infection.
k. One patient (0.7%) died of pneumonia in the nivolumab group among the early progressors.
l. Two patients (3.2%) died of pneumonia in the nivolumab group among the late progressors.
m. Two patients (1.3%) died of pneumonia in the chemotherapy group; these deaths occurred with paclitaxel only.

Source: ADaM dataset adae.xpt from Module 5.3.5.3 and adtte.xpt from Module 5.3.5.1

During the 28-day window, there was no consistent pattern for SAEs (all-grade) among early and late progressors in the nivolumab or chemotherapy treatment groups (Table 53). However, during the 100-day window, there tended to be more SAEs among early progressors compared to the late progressors in the nivolumab group compared to the pooled chemotherapy group (exceptions: pneumonia, esophageal fistula, diarrhea, and pleural effusion), and more SAEs among the late progressors compared to the pooled chemotherapy group (exceptions: pneumonia, dyspnea, hypercalcemia, and neutropenia). Still, given the inconsistent pattern and small sample size, the clinical significance of this finding is uncertain.

Table 53: SAEs in ≥1% of patients receiving any study treatment among early progressors (FDA analysis)

SAE	All grades SAE occurred within 28 days of last of study treatment				All grades SAE occurred within 100 days of last of study treatment			
	Nivolumab n (%)		Chemotherapy Pooled n (%)		Nivolumab n (%)		Chemotherapy Pooled n (%)	
	Early progressors (n=146)	Late progressors (n=63)	Early progressors (n=154)	Late progressors (n=54)	Early progressors (n=146)	Late progressors (n=63)	Early progressors (n=154)	Late progressors (n=54)
Pneumonia[a]	7 (5.0)	7 (11.1)	15 (9.7)	6 (11.1)	8 (5.5)	9 (14.3)	23 (14.9)	8 (14.8)
Pneumonitis[b]	5 (3.4)	3 (4.8)	4 (2.6)[j]	2 (3.7)[j]	8 (5.5)	3 (4.8)	4 (2.6)[j]	2 (3.7)[j]
Pyrexia[c]	5 (3.4)	1 (1.6)	1 (0.7)[j]	0	5 (3.4)	1 (1.6)	1 (0.7)[j]	1 (1.9)[j]
Hypercalcemia	4 (2.7)[k]	0	1 (0.7)[j]	0	4 (2.7)[k]	0	1 (0.7)[j]	0
Decreased appetite	3 (2.1)	0	4 (2.6)	2 (3.7)	3 (2.1)	0	5 (3.3)	2 (3.7)
Hemorrhage[d]	3 (2.1)	1 (1.6)	2 (1.3)[j]	0	3 (2.1)	1 (1.6)	2 (1.3)[j]	1 (1.9)[j]
Dyspnea	3 (2.1)	0	1 (0.7)	0	3 (2.1)	0	3 (2.0)	1 (1.9)
Esophageal fistula[e]	2 (1.4)	5 (7.9)	0	1 (1.9)[j]	4 (2.7)	5 (7.9)	0	1 (1.9)[j]
Hepatobiliary[f]	2 (1.4)	1 (1.6)	0	0	3 (2.1)	1 (1.6)	0	0
Anemia	2 (1.4)	0	0	0	2 (1.4)	0	0	0
Upper respiratory tract infection[g]	2 (1.4)	0	0	0	2 (1.4)	0	0	0
Diarrhea[h]	1 (0.7)	1 (1.6)	2 (1.3)	0	2 (1.4)	2 (3.2)	2 (1.3)	1 (1.9)
Febrile neutropenia	0	0	10 (6.5)	6 (11.1)	2 (1.4)	0	11 (7.1)	6 (11.1)
Pleural effusion[i]	0	1 (1.6)	3 (2.1)	2 (3.7)	2 (1.4)	1 (1.6)	3 (2.1)	3 (5.6)
Neutrophil count decreased	0	0	3 (2.0)	0	0	0	3 (2.0)	0

Toxicity was graded per NCI CTCAE v4.

a. Includes pneumonia aspiration, pneumonia bacterial, and lung infection.
b. Includes interstitial lung disease, and radiation pneumonitis.
c. Includes tumor-associated fever.
d. Includes tumor-haemorrhage, upper gastrointestinal haemorrhage, and gastrointestinal haemorrhage.
e. Includes tracheal fistula, oesophagobronchial fistula, oesophageal fistula, aorta-oesophageal fistula, fistula*, oesophageal perforation*, oesophageal disorder*, and aortic rupture*. One patient whose Preferred Term (PT) was not in the composite PTs was added into this analysis after FDA review of the narratives; the patient was in the nivolumab group and had the AE within 28 days of the last of nivolumab: patient ID (b) (6) had an "unassigned" AEDECOD, and the narrative stated that the patient developed a Grade 3 esophagobronchial fistula that caused fatal respiratory tract hemorrhage. *The narratives for the events associated with these PTs were reviewed to confirm that these events occurred due to an esophageal fistula.
f. Includes alanine aminotransferase increased, hepatic function abnormal, and liver function test increased.
g. Includes bronchitis.
h. Includes colitis.
i. Includes infectious pleural effusion.
j. The SAE only occurred in the paclitaxel treatment arm.
k. This includes a patient (ID (b) (6)) whose narrative described a hospitalization due to Grade 2 blood creatinine increase (creatinine was 1.96 mg/dL) and hypercalcaemia (calcium was 12.6 mg/dL). However, the AETERM was reported as "hypercalemia," which coded to AEDECOD "hyperkalaemia." The narrative did not report hyperkalemia, nor elevated blood potassium level.

Source: ADaM dataset adae.xpt from Module 5.3.5.3 and adtte.xpt from Module 5.3.5.1

Given that the TEAEs hypercalcemia, gastrointestinal or tumor hemorrhages, and esophageal fistulas, may occur due to ESCC progression, the FDA compared the incidence of these TEAEs among the early progressors and the late progressors (Table 54). A higher proportion of the early progressors had hypercalcemia, Grade 3-4 and serious hemorrhages compared to late progressors in the nivolumab group. A higher proportion of the late progressors developed esophageal fistulas compared to the early progressors in the nivolumab group. The inconsistent pattern between these three TEAEs and the small number of patients who experienced these TEAEs preclude formulation of any conclusive observations.

Overall, early progressors in Study ONO-4538-24 (CA209473) did not experience more TEAEs compared to late progressors, and the incidence of TEAEs that suggest disease progression (such as esophageal fistulas, gastrointestinal or tumor hemorrhage, and hypercalcemia) was too low to allow for any definitive observations to be made. As expected, a higher proportion of early progressors died during the study compared to late progressors, with ESCC as the most common cause of death.

Table 54: All causality treatment-emergent hypercalcemia, hemorrhage and esophageal fistula that occurred among early progressors and late progressors in Study ONO-4538-24 (CA209473) (FDA analysis)

Adverse Event	Nivolumab		Chemotherapy pooled	
	Early progressors (n=146) n (%)	Late progressors (n=63) n (%)	Early progressors (n=154) n (%)	Late progressors (n=54) n (%)
Hypercalcemia				
28-day window TEAE, all grade	12 (8.2)[g]	2 (3.2)	8 (5.2)	1 (1.9)
28-day window TEAE, Grade 3-4	7 (4.8)	2 (3.2)	2 (1.3)	1 (1.9)
100-day window TEAE, all grade	12 (8.2)	3 (4.8)	8 (5.2)	1 (1.9)
28-day window SAE, all grade	4 (2.7)	0	1 (0.7)[a]	0
100-day window SAE, all grade	4 (2.7)	0	1 (0.7)[a]	0
Upper gastrointestinal or tumor-associated hemorrhage[b]				
28-day window TEAE, all grade	8 (5.5)[c]	3 (4.8)[c]	4 (2.6)[c]	1 (1.9)[c,d]
28-day window TEAE, Grade 3-4	3 (2.1)	1 (1.6)	1 (0.7)	0
100-day window TEAE, all grade	8 (5.5)[c]	4 (6.3)	4 (2.6)[c]	2 (3.7)
28-day window SAE, all grade	3 (2.1)	1 (1.6)	2 (1.3)[a]	0
100-day window SAE, all grade	3 (2.1)	1 (1.6)	2 (1.3)[a]	1 (1.9)[a]
Esophageal fistula[e]				
28-day window TEAE, all grade	2 (1.4)	5 (7.9)[f]	1 (0.7)	1 (1.9)
28-day window TEAE, Grade 3-4	2 (1.4)	4 (6.3)	1 (0.7)	1 (1.9)
100-day window TEAE, all grade	4 (2.7)	4 (6.3)	1 (0.7)	1 (1.9)
28-day window SAE, all grade	2 (1.4)	5 (7.9)	0	1 (1.9)[a]
100-day window SAE, all grade	4 (2.7)	5 (7.9)	0	1 (1.9)[a]

Toxicity was graded per NCI CTCAE v4.

a. The SAE only occurred in the paclitaxel treatment arm.

b. Includes hemoptysis, pharyngeal haemorrhage, tumour haemorrhage, upper gastrointestinal haemorrhage, stoma site haemorrhage, and gastrointestinal haemorrhage.
c. One patient each (each 0.5%) died of hemorrhage in each of the treatment arms (nivolumab and chemotherapy).
d. The deaths in the chemotherapy treatment arm occurred with paclitaxel only.
e. Includes tracheal fistula, oesophagobronchial fistula, oesophageal fistula, aorta-oesophageal fistula, fistula, oesophageal perforation, oesophageal disorder, and aortic rupture.
f. Only 1 patient (0.5%) died due to an esophageal fistula, and the patient was in the nivolumab group.
g. This includes a patient (ID (b) (6)) whose narrative described a hospitalization due to Grade 2 blood creatinine increase (creatinine was 1.96 mg/dL) and hypercalcaemia (calcium was 12.6 mg/dL). However, the AETERM was reported as "hypercalemia," which coded to AEDECOD "hyperkalaemia." The narrative did not report hyperkalemia, nor elevated blood potassium level.

Source: ADaM dataset adae.xpt from Module 5.3.5.3 and adtte.xpt from Module 5.3.5.1

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:
Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved across multiple countries, including the US and the EU, and for other indications (e.g., metastatic NSCLC, metastatic SCLC, advanced RCC, cHL, SCCHN, urothelial carcinoma, MSI-H dMMR CRC, and advanced HCC). Based on routine pharmacovigilance activities conducted by BMS Global Pharmacovigilance and Epidemiology, review of postmarketing safety data confirms the clinical trial safety data for nivolumab. The established positive benefit-risk profile of nivolumab in the postmarketing setting remains consistent. Postmarketing data for nivolumab are subject to continued active pharmacovigilance monitoring and evaluation, and are reported as per applicable post-marketing safety reporting requirements, as well as periodically to global health authorities.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Nivolumab has a well-characterized safety profile, and it is expected that the safety of nivolumab in patients with ESCC in the postmarket setting will not differ from the known safety profile of nivolumab, as described in product labeling.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:
Safety data from ONO-4538-24 (CA209473) demonstrate an acceptable safety profile in subjects with unresectable advanced, recurrent, or metastatic ESCC, refractory or intolerant to 1 prior fluoropyrimidine- and platinum-based combination therapy. The overall profile was consistent with

expectations based on the known safety profile of nivolumab and there were no new safety concerns with nivolumab monotherapy.

Frequencies of any-grade all causality and drug-related AEs and SAEs were generally lower with nivolumab than with chemotherapy (either docetaxel or paclitaxel). Any grade and Grade 3-4 AEs (both all-causality and drug-related) leading to dose delay were reported less frequently with nivolumab than in the chemotherapy control group. Grade 3-4 AEs (all-causality and drug-related) were reported slightly less frequently with nivolumab than in the chemotherapy group.

The safety profiles of docetaxel and paclitaxel in ONO-4538-24 (CA209473) were comparable to what has been reported in previous studies, with comparatively more hematological toxicities reported in the docetaxel group and more neurotoxicities in the paclitaxel group. The docetaxel regimen (75 mg/m^2 IV for at least 60 minutes Q3W) is within the range recommended by NCCN (75-100 mg/m^2 Q3W), and the paclitaxel regimen (100 mg/m^2 IV for at least 60 minutes weekly for 6 weeks followed by 1 week off) is not dissimilar to the paclitaxel regimens recommended by NCCN (paclitaxel 80 mg/m^2 weekly Q3W, or paclitaxel 80 mg/m^2 on days 1, 8 and 15 cycled every 4 weeks). Despite a higher dose of paclitaxel used in this study compared to regimens used in the US, the safety profile was comparable to previous reports.

The majority of AEs were Grade 1 or 2 and considered manageable, with few discontinuations due to AEs. As of the clinical cut-off date, 159 (76.1%) subjects in the nivolumab group and 173 (83.2%) subjects in the chemotherapy group had died. 2 deaths (ILD and pneumonitis [1 subject each]) in the nivolumab group and 3 deaths (ILD, pneumonitis, and spinal cord abscess [1 subject each]) in the chemotherapy group (paclitaxel) were considered due to study drug toxicity.

IMAEs, including pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine abnormalities, were analyzed. Most IMAEs were Grade 1-2. IMAEs were generally considered manageable using the recommended treatment guidelines for early work-up and intervention. With regard to IMAEs, the safety profile of nivolumab was shown to be acceptable and not different than that seen previously with nivolumab; thus, it is proposed that nivolumab could be given to patients with advanced or recurrent esophageal cancer without any major safety concern.

The majority of abnormal laboratory values in ONO-4538-24 (CA209473) were Grade 1 or 2 in the nivolumab and chemotherapy groups. There were no clear differences in the frequencies of worsening of laboratory parameters observed between groups except for hematology parameters, wherein higher rates of worsening were seen with chemotherapy, and for thyroid function, wherein higher rates of worsening were seen with nivolumab.

The safety profile of nivolumab monotherapy observed in Western subjects, although limited by small sample size, was generally comparable to that reported in the overall nivolumab group of ONO-4538-24 (CA209473), suggesting no clinically significant correlation of race/ethnicity with safety.

Additionally, based on PPK analysis, there were no clinically meaningful differences in predicted exposures in ESCC patients between nivolumab 240 mg Q2W (dose studied in ONO-4538-24

[CA209473]) and nivolumab 480 mg Q4W (dose also proposed for the ESCC indication). The predicted exposures for 480 mg Q4W were within the well tolerated range that was previously observed for patients with cancer who received 10 mg/kg Q2W, supporting the safety and tolerability of the dose of 480 mg Q4W.

In summary, safety data from ONO-4538-24 (CA209473) support the use of nivolumab monotherapy for the treatment of patients with advanced ESCC previously treated with platinum and fluoropyrimidine, in the context of observed clinical efficacy in this study. Standard of care chemotherapy in 2L ESCC is associated with significant toxicities, with use of taxanes often complicated by hematological, gastrointestinal, and neurological side effects, leading to frequent treatment interruptions, delays, and dose reductions. The safety profile of nivolumab in ONO-4538-24 (CA209473) was consistent with that demonstrated in previous studies in solid tumors, and no new safety signals were identified.

The FDA's Assessment:

The FDA agrees that in Study ONO-4538-24 (CA209473), the majority of the patients in the nivolumab group experienced Grade 1 and 2 as the maximum severity for TEAEs (49.3% within the 28-day window) compared to the pooled chemotherapy group (25.5% within the 28-day window), and that fewer patients experienced TEAEs of any grade (90.4% versus 98.6% within the 28-day window), Grade 3-4 TEAEs (38.3% versus 71.2% within the 28-day window), and treatment-emergent SAEs (32.1% versus 36.5% within the 28-day window) in the nivolumab group compared to the pooled chemotherapy group, respectively. However, the FDA did find two new safety signals, esophageal fistula and blood CPK increase, of which only the former is of likely clinical significance. The FDA also determined that the incidence of pneumonitis (of which 3 cases led to death) was higher in the ESCC population than patients with other types of tumors who were treated with nivolumab; this observation may be related to prior receipt of thoracic radiation in patients with ESCC.

The most common TEAEs occurring in ≥20% of nivolumab-treated patients were rash and decreased appetite. The most common TEAEs occurring in ≥10% of nivolumab-treated patients within the 100-day window (in order of decreasing incidence) were rash, decreased appetite, diarrhea, constipation, musculoskeletal pain, upper respiratory tract infection, cough, pyrexia, pneumonia, hepatobiliary disorders, anemia, fatigue, pruritus, hypothyroidism, nausea, and pneumonitis (see Table 38's footnotes for the Preferred Terms included in the composite terms). The most frequent SAEs reported in ≥2% of patients receiving nivolumab were pneumonia, esophageal fistula, pneumonitis and pyrexia. The most common Grade 3 to 4 TEAEs occurring in ≥2% of patients receiving nivolumab were anemia, pneumonia, hypercalcemia, esophageal fistula, dysphagia, and blood CPK increase.

Using the composite term for pneumonitis (consisting of the Preferred Terms of interstitial lung disease, and radiation pneumonitis), 3 patients died from a DRAE as assessed by the Investigator or Applicant, pneumonitis, in the nivolumab group. In addition, the following additional TEAEs were included as adverse reactions that led to death in the nivolumab product label: pneumonia (n=2), septic shock (n=1), esophageal fistula (n=1), gastrointestinal hemorrhage (n=1), sudden death (n=1), and pulmonary embolism (n=1). After review of the narratives, the FDA determined that 5 patients died from DRAEs in

the pooled chemotherapy group: pneumonia (n=2), spinal cord abscess (n=1), febrile neutropenia (n=1), and ILD (n=1).

The FDA agrees with the Applicant that most treatment-emergent IMAEs were Grade 1-2, and that most occurred at a similar or lower rate than reported in product labeling for nivolumab, except for pneumonitis. As described above, the incidence of pneumonitis was higher in patients with ESCC compared patients with other types of tumors, which may be due to the higher incidence of prior radiation therapy to the thorax in patients with ESCC compared to patients with other types of tumors treated with nivolumab.

The abnormal laboratory values were consistent with the known safety profile of nivolumab except for the increased incidence of hypercalcemia and increased blood CPK as discussed above.

In conclusion, nivolumab was generally better tolerated than chemotherapy in patients with advanced ESCC who have been previously treated with or intolerant to platinum and fluoropyrimidine chemotherapy, with no conclusive differential safety profile in the analyzed subgroups, including Western versus Asian patients. However, because of the anatomic location of ESCC, the patients in this study experienced a certain set of TEAEs during treatment with nivolumab that are worth noting. The patients experienced a slightly higher rate of pneumonitis compared to patients with other tumor types, which may be secondary to prior receipt of radiotherapy for ESCC. Patients with ESCC also experienced more esophageal fistulas, gastrointestinal or tumor hemorrhages, and hypercalcemia compared to patients in the chemotherapy group, of which esophageal fistula is a new clinically significant safety signal. Overall, patients in the nivolumab group experienced a lower rate of TEAE (any grade and Grade 3-4) in general, TEAE that led to dose delay or treatment discontinuation, and a lower rate of treatment-emergent SAE compared to chemotherapy. An exploratory analysis indicated that patients with ESCC had a similar relative dose intensity of nivolumab to patients with other tumor types who were treated with nivolumab.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

No statistical issues were found while reviewing this submission. For the OS analysis, although the effect of nivolumab was observed later, as depicted by the crossing of survival curves after around 4.5 months, the statistical test used for OS analysis is still considered valid.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the totality of evidence, the clinical pharmacology, clinical, and statistical review teams recommend granting approval of nivolumab (OPDIVO) for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy. The recommended dosage regimen for this

indication is nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks until unacceptable toxicity or disease progression. The data presented in this sBLA demonstrated a clinically meaningful statistically significant improvement in OS in patients with ESCC randomized to receive nivolumab compared those randomized to receive the investigator's choice of taxane chemotherapy (paclitaxel or docetaxel). The median OS was 10.91 months [95% CI: 9.23, 13.34] in the nivolumab arm compared to 8.38 months [95% CI: 7.20, 9.86] in the control arm with a hazard ratio of 0.77 [95% CI: 0.62,0.96, p = 0.189]. Nivolumab was generally better tolerated than chemotherapy, but esophageal fistula is a new clinically significant safety signal observed in this patient population.

Although no definitive conclusions could be drawn regarding the safety profile of nivolumab in early progressors (i.e., those who progressed prior to 4.5 months) compared to late progressors, it is important to note the presence of non-proportional hazards evident in the Kaplan-Meier OS curve (Figure 1). This same trend has also been observed in other disease settings in which immune-checkpoint inhibitors (ICIs) are compared to chemotherapy. Because of their mechanism of action, ICIs may not be able to impact disease burden quickly enough compared to cytotoxic chemotherapy. Thus, in patients with extensive disease burden or disease in particularly critical locations, ICI therapy may not be an optimal choice.

A review issue considered during the review of this application is the applicability to the U.S. population. Of note, randomization was stratified by location (Japan versus the rest of the world). Most of the patients in Study ONO-4538-24 (CA209473) were enrolled in Japan and only 18 Western patients (9 in the nivolumab arm and 9 in the control arm) were enrolled. Of these 18 patients, only 1 patient from the U.S. was enrolled (randomized to the nivolumab arm). Thus, subgroup analyses comparing the safety and effectiveness of nivolumab in Western and/or U.S. with ESCC compared to patients with ESCC enrolled in Asia are of limited value. As discussed in FDA's comments in Section 2.1 ("Analysis of Condition"), above, the Applicant presented TCGA data comparing patients in Asia and Western patients with ESCC. Given the small numbers, however, it is also difficult to draw conclusions from these data. Nevertheless, published literature in ESCC, including those described by the Applicant in Section 8.1.5 ("Integrated Assessment of Effectiveness"), do demonstrate similarities across regions regarding disease features and treatment approaches for ESCC . Additionally, data from studies of nivolumab with a broader representation of U.S. and Western Patients in other disease settings (such as CHECKMATE-141 in patients with squamous cell carcinoma of the head and neck and CHECKMATE-066 in patients with melanoma) reviewed by FDA support the effectiveness of nivolumab in Western patients. Finally, data from Study ONO-4538-24 (CA209473) do not suggest that Western patients do not benefit from nivolumab or are at increased risk of toxicity with in this setting.

Another review issue is whether a subpopulation of patients is driving the efficacy results. Specifically, MSI-H status and PD-L1 expression are important factors in response to immunotherapy in other settings. Regarding MSI status, in Study ONO-4538-24 (CA209473), data was only available for approximately 30% of the ITT patients (30.5% in the nivolumab arm and 30.1% in the control arm) and all of these patients' tumors were MSS. Thus, based on this study, the role that MSI status may have on the efficacy of nivolumab in this setting is unclear but the percentage of MSI-H patients in this study overall is likely very low (and is not likely to have driven the results) given that no tumors tested were

MSI-H. Regarding PD-L1 expression, randomization was stratified by PD-L1 expression (≥ 1% versus < 1% or indeterminate). Based on subgroup analyses, which were pre-planned but without alpha allocation, there is a suggestion of lower HRs for death in patients with higher PD-L1 expression ≥ 1% but this is considered an exploratory analysis only.

X	X
	Sirisha Mushti, PhD
Joyce Cheng, PhD	
Sirisha Mushti, PhD Primary Statistical Reviewer	Joyce Cheng, PhD Statistical Team Leader

X	X
Lorraine Pelosof, MD PhD May Tun Saung, MD Primary Clinical Reviewer	Martha Donoghue, MD Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

There was no advisory committee meeting for this application because the application did not raise significant public health questions regarding the role of nivolumab for this indication, and outside expertise was not necessary as there were no controversial issues that could benefit from an Advisory Committee discussion.

10 Pediatrics

The Applicant's Position:

This application is exempt from the requirements under the Pediatric Research Equity Act (PREA). Nivolumab was granted orphan drug designation on 22-Aug-2016 for the treatment of esophageal cancer.

The FDA's Assessment:

FDA agrees with the Applicant's position.

APPEARS THIS WAY ON ORIGINAL

11 Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
	Added indication for the treatment of patients with esophageal squamous cell carcinoma	Added age groups based on recommendations found in the labeling guidance for Indications and Usage.
Recommended Dosage (b) (4)	Added recommended dosage for the treatment of patients with esophageal squamous cell carcinoma	Agreed with inclusion of the recommended dosage in Table 1.
Adverse Reactions (6.1)	Clinical safety data from CA209473 added: • Study design • Fatal and Serious Adverse Reactions • Adverse Reactions leading to discontinuation and dose delay • Most common serious Adverse reactions and Adverse Reactions	Added two tables to summarize the adverse reactions and laboratory abnormalities observed in ATTRACTION. Revised the list of adverse reactions that occurred up to 30 days after the last dose and of serious adverse reactions that occurred up to 100 days after the last dose.
Geriatric Use (8.5)	Include recommendation for the use in patients 65 years and older and 75 years and older	Agreed with inclusion of geriatric use statement for ATTRACTION.
Clinical Studies (14.11)	Information from CA209473: • Study design • Key eligibility criteria • Tumor assessments • Demographics and baseline disease characteristics • Efficacy Data (Overall Survival, Progression Free Survival, Overall Response Rate, Duration of Response)	Revised the presentation of the summary of the study design, eligibility criteria and tumor assessment. Included randomization stratification factors. Included p value for overall response rate in efficacy table because the ORR was tested according to hierarchical testing strategy. Reordered presentation of PFS and ORR in the table based on hierarchical testing.

Other Prescription Drug Labeling for Opdivo:

The Medication Guide was updated to include the following proposed changes in patient-friendly language:

- Addition of indication for Opdivo alone for people with (b) (4) cancer that is a type called "squamous" that has come back or spread, and patient has received treatment with platinum and fluoropyrimidine (b) (4)

The Applicant's Position:
The clinical data in the submitted supplemental BLA demonstrate the clinical benefit and safety of the use of nivolumab for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine and platinum-based combination therapy.

The FDA's Assessment:
Please refer to FDA's Risk:Benefit assessment in Section 1 of this review.

APPEARS THIS WAY ON ORIGINAL

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

There are no safety issues identified at this time requiring Risk Evaluation and Mitigations Strategies.

APPEARS THIS WAY
ON ORIGINAL

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

There are no postmarketing requirements or commitments for this application.

APPEARS THIS WAY ON ORIGINAL

14 Division Director (DHOT) (NME ONLY)

X _____

APPEARS THIS WAY
ON ORIGINAL

15 Division Director (OCP)

X

APPEARS THIS WAY ON ORIGINAL

16 Division Director (OB)

X

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical)

X

Lola A.Fashoyin-aje, MD, MPH

APPEARS THIS WAY ON ORIGINAL

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

APPEARS THIS WAY ON ORIGINAL

19 Appendices

19.1. References

See Section 19.6 for references cited in text.

The FDA's References:
Please see "Additional FDA References" in Section 19.6 below.

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 Subinvestigators) participating in the ONO-4538-24 (CA209473) 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. See also "Financial Disclosure" in Section 8.1.2, above.

Covered Clinical Study (Name and/or Number):* ONO-4538-24 (CA209473)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 889		
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: 5 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: ONO (global); BMS (US)		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:
Not applicable.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
Not applicable.

19.6. References Cited in Text

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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Emily Place	OOD/DHOT	Sections: 5	Select one: X Authored ___ Approved
	Signature: Emily J. Place -S Digitally signed by Emily J. Place -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Emily J. Place -S, 0.9.2342.19200300.100.1.1=2001028525 Date: 2020.06.04 10:11:13 -04'00'			
Nonclinical Team Leader	Matthew Thompson	OOD/DHOT	Sections: 5	Select one: ___ Authored X Approved
	Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001270689, cn=Matthew D. Thompson -S Date: 2020.06.04 07:48:17 -04'00'			
Clinical Pharmacology Reviewer	Xiling Jiang	OCP/DCPI	Sections: 6	Select one: X Authored ___ Approved
	Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiling Jiang -S, 0.9.2342.19200300.100.1.1=2001167656 Date: 2020.06.03 15:43:23 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	OCP/DCPII	Sections: 6	Select one: ___ Authored X Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Zhao -S, 0.9.2342.19200300.100.1.1=1300136450 Date: 2020.06.03 16:07:22 -04'00'			

Pharmacometrics Team Leader	Jiang Liu	OCP/DPM	Sections: 6	Select one: ___ Authored X Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.06.03 15:50:04 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Lorraine Pelosof (Efficacy)	OOD/DO3	Sections: 1.1 and 1.2 (excluding safety statement in Section 1.2); 2; 3.1 and 3.2 (with STATS); 7; 8.1 (with STATS); 8.4 (excluding safety statement); 9; 10; 12; 19.2	Select one: X Authored ___ Approved
	Signature: Lorraine Pelosof -S Digitally signed by Lorraine Pelosof -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001855909, cn=Lorraine Pelosof -S Date: 2020.06.03 17:57:46 -04'00'			
Clinical Reviewer	May Tun Saung (Safety)	OOD/DO3	Sections: 8.2; 1.2 and 8.4. (statement regarding safety)	Select one: X Authored ___ Approved
	Signature: May Tun Saung -S Digitally signed by May Tun Saung -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=May Tun Saung -S, 0.9.2342.19200300.100.1.1=2002799116 Date: 2020.06.03 16:28:30 -04'00'			
Clinical Team Leader	Martha Donoghue	OOD/DO3	Sections: 1.1 and 1.2; 2; 3.1 and 3.2; 7; 8.1; 8.2; 8.4; 9; 10; 12; 19.2	Select one: ___ Authored X Approved
	Signature: Martha Donoghue -S Digitally signed by Martha Donoghue -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000339007, cn=Martha Donoghue -S Date: 2020.06.05 16:43 42 -04'00'			
Statistical Reviewer	Sirisha Mushti	OB/DBV	Sections: 1, 7, 8.1, 8.3	Select one: X Authored X Approved
	Signature: Sirisha Mushti -S Digitally signed by Sirisha Mushti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sirisha Mushti -S, 0.9.2342.19200300.100.1.1=2001315241 Date: 2020.06.03 18:23:06 -04'00'			
Statistical Team Leader	Joyce Cheng	OB/DBV	Sections: 1, 7, 8.1, 8.3	Select one: ___ Authored X Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joyce Cheng -S, 0.9.2342.19200300.100.1.1=2001702039 Date: 2020.06.03 18:03:57 -04'00'			
Division Director (OB)	Yuan-Li Shen	OB/DBV	Sections: 1, 7, 8.1, 8.3	Select one: ___ Authored X Approved
	Signature: Yuan-li Shen -S Digitally signed by Yuan li Shen -S DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, cn=Yuan li Shen -S, 0.9.2342.19200300.100.1.1=1300142755 Date: 2020.06.03 16:35:44 -04'00'			

Associate Director for Labeling (ADL)	Stacy Shord	OOD	Sections: 11	**Select one:** X Authored ___ Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Shord -S, 0.9.2342.19200300.100.1.1=2000356537 Date: 2020.06.04 10:49:39 -04'00'			
DISCIPLINE	**REVIEWER**	**OFFICE/DIVISION**	**SECTIONS AUTHORED/ APPROVED**	**AUTHORED/ APPROVED**
Cross-Disciplinary Team Leader (CDTL)	Martha Donoghue	OOD/DO3	Sections: All	**Select one:** ___ Authored X Approved
	Signature: Martha Donoghue -S Digitally signed by Martha Donoghue -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000339007, cn=Martha Donoghue -S Date: 2020.06.05 16:44:21 -04'00'			
Deputy Division Director (Clinical)	'Lola Fashoyin-Aje	OOD/DO3	Sections: All	**Select one:** ___ Authored X Approved
	Signature: Ibilola Fashoyin-aje -S Digitally signed by Ibilola Fashoyin-aje -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014067124, cn=Ibilola Fashoyin-aje -S Date: 2020.06.03 17:54:31 -04'00'			

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

/s/

MARYAM M KHAZRAEE
06/10/2020 03:43:35 PM

MARTHA B DONOGHUE
06/10/2020 03:45:59 PM

IBILOLA A FASHOYIN-AJE
06/10/2020 03:46:53 PM

MEMORANDUM

Date: May 14, 2020
From:
Emily Place, PhD
Nonclinical Reviewer
Division of Hematology Oncology Toxicology (DHOT)
Through:
Matthew Thompson, PhD, MPH
Nonclinical Team Lead (Acting)
Division of Hematology Oncology Toxicology (DHOT)
To: sBLA 125554 / Efficacy Supplement – S81
Re: Nonclinical Review

Application Type	Supplemental BLA (sBLA)
Application Number(s)	125554/S-81
Priority or Standard	Priority
PDUFA Goal Date	June 11, 2020
Division/Office	DO3/OOD/OND/CDER
Established Name	Nivolumab
Trade Name	OPDIVO
Pharmacologic Class	Anti-PD-1 antibody
Applicant	Bristol-Myers Squibb
Formulation(s)	Injection; 100 mg/10 mL solution
Dosing Regimen	Nivolumab 240 mg intravenously every 2 weeks or until disease progression or unacceptable toxicity
Applicant Proposed Indication(s)/Population(s)	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

No new nonclinical information was provided in the submission. There were no labeling changes requiring pharmacology/toxicology input. No nonclinical review was conducted. From a pharmacology/toxicology perspective, there are no issues that would prevent approval of this efficacy supplement. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

EMILY J PLACE
05/15/2020 11:15:37 AM

MATTHEW D THOMPSON
05/15/2020 11:18:08 AM
I concur.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	125554
Supplement #:	81
Drug Name:	Nivolumab (OPDIVO)
Indication(s):	Treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy
Applicant:	Bristol-Myers Squibb
Date(s):	Received Date: December 11, 2019
	PDUFA Date: June 11, 2020
Review Priority:	Priority
Biometrics Division:	V
Statistical Reviewer:	Sirisha Mushti
Concurring Reviewers:	Joyce Cheng, Statistical Team Leader
	Yuan Li Shen, Associate Division Director
Medical Division:	Division of Oncology 3
Clinical Team:	Lorraine Pelosof (Clinical reviewer for efficacy)
	May Tun Saung (Clinical reviewer for safety)
	Martha Donoghue (CDTL)
	Lola Fashoyin-Aje (Acting DDD, OOD/DO3)
Project Manager:	Maryam Khazraee
	Norma Griffin

The statistical review is complete and has been added to the sBLA Assessment Aid. Refer to the Assessment Aid for additional details. The statisitcal review team supports the decision of approval for the proposed indication that was primarily based on efficacy and safety results from a single trial, ONO-4538-024/CA209-473. Efficacy results were based on the primary efficay endpoint of overall survival and supported by overall response rate and progression-free survival.

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/s/

SIRISHA L MUSHTI
06/05/2020 10:12:05 AM

JOYCE H CHENG
06/05/2020 10:14:08 AM

YUAN L SHEN
06/05/2020 10:15:24 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s081

CHEMISTRY REVIEW(S)

Memorandum of Assessment:

Submission Tracking Number (STN):	BLA125554/3580 (eCTD 0677, eCTD 0729)
Subject:	Prior approval efficacy supplement to BLA 125554 to expand label claims for the treatment of patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.
Date Received:	December 13, 2019
Assessment/Revision Date:	April 24, 2020
Primary Assessor:	Lei Zhang, Ph.D.
Secondary Assessor:	Patrick Lynch, Ph.D.
Tertiary Assessor:	Emily Jing, Ph.D.
RPM:	Maryam Khazraee
Consults:	NA
Applicant:	Bristol-Myers Squibb Company (BMS)
Product:	Opdivo (nivolumab)
Mechanism of Action:	Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor on T-cells and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway mediated inhibition of the immune response, including the anti-tumor immune response
Indication:	Esophageal Squamous Cell Carcinoma (ESCC)
Filing Action Date:	February 11, 2020
Action Due Date:	June 11, 2020

1. Summary Basis of Recommendation:

a. Recommendation:

I recommend approval of this supplement.

2. Assessment

This memo provides the Office of Biotechnology Product's assessment of the anti-drug antibody (ADA) assays used to evaluate immunogenicity results for the non-US clinical study ONO-4538-24. In this supplement, the Applicant (BMS) submitted data from the clinical study ONO-4538-24 (CA209473) to support expanding label claims for Opdivo (nivolumab) to include the treatment of patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine-

and platinum-based chemotherapy. The following IR was sent to the Applicant on March 13, 2020 with regards to the assays used for anti-drug antibody (ADA) testing in clinical samples:

You provided anti-drug antibody (ADA) test results from clinical samples taken from patients in clinical study Ono-4538-24. Clarify whether the assays used for the ADA testing are the same as approved in BLA 125554 Module 5. If different procedures were used, provide method validation or qualification reports to support that the ADA assays were appropriate for evaluation of ADA in clinical samples from the patient population.
Include in your response information to support the in-study cut-point(s) used for evaluating clinical samples from study Ono-4538-24, such as verification of the cut-points using treatment naïve samples from the study.

In the IR response on March 20, 2020, the Applicant clarified that the ADA testing for ONO-4538-24 study was performed by the same laboratory using the same validated method (ICDIM 140) as presented in the original BLA 125554 application. According to the validation report of method ICDIM 140 located in section 5.3.1.4 of the approved dossier, the ICDIM 140 ADA analysis is an electrochemiluminescent immunoassay that includes a 3-tier testing approach (screening, confirmatory, and titer). The assay cut-points were statistically determined from analyses of disease state human serum samples. The assay sensitivity was determined to be 6.29 ng/mL and the assay tolerates up to 800 µg/mL of free nivolumab. In the IR response the Applicant states that a False Positive Rate (FPR) of 8.8% (18/204) was obtained based on treatment naïve samples from the ONO-453824 clinical study.

Assessor Comment: The Applicant clarifies that the validated ADA assay (ICDIM 140) was used for ADA testing for ONO-4538-24 study. The false positive rate using treatment naïve samples from the Ono-4538-24 study (8.8%) is close to the targeted false-positive rate of approximately 5% established for the assay validation cut-point based on statistical analysis of treatment naïve samples, as recommended by the Guidance (Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection, January 2019). Consistency between the defined and actual false positive rate verifies that the established in-study cut-points are appropriate for evaluating clinical samples from study Ono-4538-24. The false positive rate supports suitability of the screening cut-point to ensure detection of potential low positive ADA results. Therefore, the ADA assay in the ONO-4838-24 study is considered valid in supportive of the appropriate interpretation of the testing results.

Lei Zhang

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Patrick Lynch

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Date: 4/24/2020 04:31:14PM
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Xianghong Jing

Digitally signed by Xianghong Jing
Date: 4/24/2020 06:06:31PM
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Memorandum of Assessment:

Submission Tracking Number (STN):	BLA125554/3580 (eCTD 0677)
Subject:	Prior approval efficacy supplement to BLA 125554 to expand label claims for the treatment of patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy.
Date Received:	December 13, 2019
Assessment/Revision Date:	March 5, 2020
Primary Assessor:	Lei Zhang, Ph.D.
Secondary Assessor:	Patrick Lynch, Ph.D.
Tertiary Assessor:	Emily Jing, Ph.D.
RPM:	Maryam Khazraee
Consults:	NA
Applicant:	Bristol-Myers Squibb Company (BMS)
Product:	Opdivo (nivolumab)
Mechanism of Action	Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor on T-cells and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway mediated inhibition of the immune response, including the anti-tumor immune response
Indication:	Esophageal Squamous Cell Carcinoma (ESCC)
Filing Action Date:	February 11, 2020
Action Due Date:	June 11, 2020

1. Summary Basis of Recommendation:

a. Recommendation:

From protein product quality perspective, I recommend approval of this supplement.

b. Justification:

In this supplement, the Applicant (BMS) submitted data from the clinical study ONO-4538-24 (CA209473) to support expanding label claims for Opdivo (nivolumab) to include the treatment of patients with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy. The clinical study included use of non-US licensed nivolumab

drug product (DP) manufactured by Ono Pharmaceuticals, Co. (Ono) using drug substance (DS) batches manufactured by BMS in accordance with the US-licensed DS process.

To support the use of non-US licensed nivolumab DP materials produced by Ono pharmaceuticals in clinical trials supporting this application, the Applicant provided the following data and information: 1) manufacturing process comparison between BMS and Ono DP processes, 2) batch release data of BMS and Ono clinical DP batches used in ONO-4538-24 study and batch release data of source DS batches for assays that were not tested for Ono DP, 3) information of methods used for BMS and Ono DP release, 4) stability data of BMS and Ono DP batches. Both the BMS and Ono clinical DP batches were manufactured using DS batches produced at the same approved manufacturing site ((b) (4)), using the commercial (b) (4) as approved in BLA 125554 Module 3. The liquid dosage form, formulation, and primary packaging of BMS and Ono DP are the same. Differences in the DP manufacturing processes between BMS and Ono are minor and pose low risk to impact product quality. The nivolumab DP process consists of simple dilution and filling operations that do not impact most critical quality attributes (CQAs) of the DS. Therefore, the DS release results for the clinical batches support comparability as the risk for differences in potency or purity attributes intrinsic to the DS due to the Ono DP process is negligible.

DP release data of BMS and Ono clinical DP batches further support product comparability and mitigate residual uncertainty for potential differences in relevant CQAs. Notably, 2 of the clinical DP lots, including 1 of the 4 Ono clinical DP lots, were tested using BMS commercial DP release methods (except for cell-based bioassay) and met commercial acceptance criteria. For the other 3 Ono clinical DP lots, BMS provided information to support methods used for DP release testing at BMS and Ono are comparable and Ono methods use the same or similar procedures as the commercial BMS methods with minor differences. The Ono DP release testing program uses the same reference material as BMS, and includes relevant attributes that may be impacted by the DP process such as protein concentration, high molecular weight species, and particulate matter. Stability data of BMS and Ono DP batches support comparable product stability under long-term condition (2^{o}C to 8^{o}C). In summary, data and information provided in the application support analytical comparability between BMS and Ono DP lots used in clinical study ONO-4538-24. The results are comprehensive and sufficient to justify the use of clinical data from patients treated with the nivolumab DP batches produced by Ono Pharmaceuticals.

2. Assessment:

The Applicant submitted a pre-supplemental Biologics Licensing Application (pre-sBLA) meeting request under IND 126406 to gain FDA feedback and reach agreement on the adequacy of Study ONO-4538-24 to serve as the major efficacy study in support of the supplement submission. In the premeeting package, the Applicant indicated that nivolumab product manufactured at Ono Pharmaceutical, Co. (Ono) were used in the clinical study ONO-4538-24. In the preliminary

comments FDA stated that the sBLA needs to include sufficient data and information to support the comparability of the Ono and BMS drug products (DP) in order for FDA to file the application. In a following separate advice letter, FDA explained that "the data and information to support such comparability should include a detailed description of any differences in the manufacturing processes and data from a direct analytical comparison of relevant quality attributes between the ONO-4538 clinical lots and U.S.-licensed nivolumab".

In the ONO-4538-24 (CA209473) study, ONO-4538 (clinical trial product) is given at 240 mg IV Q2W. As shown in the table below (prepared by reviewer), the clinical trial products used in the ONO-4538-24 study consist of one batch manufactured at the approved BMS facility (Manati, Puerto Rico, USA) and four batches manufactured at the Ono facility (Japan). Both BMS and Ono drug products (DP) are manufactured using (b) (4) drug substance (DS) of the same composition, made from the same cell line by the same approved commercial manufacturing site at (b) (4). The Applicant states that the dosage form, formulation, and primary packaging of BMS and Ono drug products are the same.

	Clinical DP Batches		**DS Batches Used**	
	Batch # (Secondary Packaging #)	**Site of DP Manufacture**	**DS Batch # (Process Designation)**	**Site of DS Manufacture**
BMS Product	AAA3322 (AAF9220)	BMS-Manati	349289, 349701A (b) (4)	BMS- (b) (4)
Ono Product	X522 (X573P/X5Y1P/X672P/X661P)	Ono Fujiyama Plant	353854 (b) (4)	
	X5Z2 (X712P)		458788 (b) (4)	
	X641 (X751P)		458788 (b) (4)	
	X664 (X851P)		507781 (b) (4)	

The Applicant's evaluation of DP comparability focuses on 1) DP manufacturing process, 2) analytical testing data between the BMS and Ono DP and DS batches used to manufacture DP, 3) stability comparability, 4) an assessment of clinical pharmacokinetic (PK) data.

To better evaluate the materials used in the clinical study ONO-4538-24, the following information request was sent to the Applicant on February 10, 2020.

1. *You provided batch release data of BMS and Ono drug product lots used in clinical study ONO-4538-24. You state that "other non-compendial methods used to release the Ono clinical batches were essentially the same as the BMS methods with some minor revisions, which are not expected to significantly impact the results obtained." Provide more detailed information on the differences between the non-compendial methods used in BMS and Ono for release testing of the clinical drug product batches used in ONO-4538-24. Include in your response any available information and data to support comparability between the Binding Activity*

ELISA, Potency ELISA, SE-HPLC, and Protein Concentration assays used at both BMS and at Ono.

2. *Clarify whether the drug substance batches 353854, 458788, 507781, 349289, and 349701A used to manufacture drug product lots used in clinical study ONO-4538-24 were manufactured using the* (b) (4) *as approved in BLA 125554 Module 3.*

Reviewer Comment: IR response was received on February 14, 2020. In the IR response, the Applicant confirms that DS batches 353854, 458788, 507781, 349289, and 349701A used to manufacture DP lots used in clinical study ONO-4538-24 were manufactured using the (b) (4) *as approved in BLA 125554 Module 3. Data and information in the IR response regarding method comparability are discussed in the following section.*

DP Manufacturing Process

(b) (4)

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(b) (4)

3. Assessment Conclusions:

Data and information provided (manufacturing process comparison, batch release data, release methods, stability data) support the analytical comparability of BMS and Ono drug product batches used in ONO-4538-24 clinical study.

4. Future Inspection Items:

N/A

Lei Zhang

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Patrick Lynch

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Xianghong Jing

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s081

OTHER REVIEW(S)

Memorandum to File

Date	4/30/2020
From	Zana Marks, MD, MPH Yang-Min (Max) Ning, MD, PhD Kassa Ayalew, MD., MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Lola Fashoyin-Aje, MD, MPH Martha Donoghue, MD Maryam Khazraee, RPM Division of Oncology 3 (DO3) Office of Oncologic Diseases (OOD)
BLA #	125554 S-81
Applicant	Bristol-Myers Squibb (BMS)
Drug	Nivolumab (Opdivo®)
NME (Yes/No)	No
Drug Classification	Human monoclonal antibody directed against programmed death receptor-1 (PD-1)
Proposed Indication	Treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine and platinum-based chemotherapy
Consultation Date	February 13, 2020
Review Priority	Priority
Summary Goal Date	June 1, 2020
PDUFA Date	June 11, 2020

RECOMMENDATION:

The review division DO3 issued an OSI consult, requesting clinical inspections of the study sponsor (ONO Pharmaceutical Co, Ltd.) and a contract research organization (CRO: (b) (4)) for Study ONO-4538-24 (CA209473) which was conducted to support a labeling claim for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine and platinum-based chemotherapy. (b) (4)

As a result of the COVID-19 related travel restrictions and to protect the health, safety, and welfare of FDA employees and study staff, the need for the planned inspections were reevaluated. Following discussions between OSI and the review division, a decision was made that assessments of this application could proceed without the planned clinical inspections (b) (4) To help the review of the application, OSI and the review division agreed to evaluate the sponsor inspection report obtained from Pharmaceuticals and Medical Devices Agency

(PMDA) of Japan and the Applicant's response to OSI's inquiry.

Based on OSI's review of the PMDA's sponsor inspection report and the Applicant's response, non-compliance with Good Clinical Practice (GCP) was noted during the conduct of this study (b) (4), and the efficacy and safety data as submitted by the Applicant to this supplemental BLA appear reliable in support of the application. The sponsor's oversight of the study as reported by PMDA appear adequate.

BACKGROUND:

This supplemental BLA relies solely upon clinical data of a single pivotal trial [ONO-4538-24 (CA209473)] conducted by ONO Pharmaceutical in collaboration with BMS. Study ONO-4538-24 (CA209473) was a Phase 3, global, multicenter, randomized, open-label, docetaxel- or paclitaxel-controlled trial of nivolumab in subjects with histologically confirmed squamous cell carcinoma, refractory or intolerant to one prior fluoropyrimidine and platinum-based combination therapy and not indicated for radical resection. The primary endpoint was overall survival. From 12/14/2015 through 11/12/2018 (data cutoff date for the submitted analysis), the trial enrolled 419 subjects. Sixty-five percent of the subjects were recruited from Japan, 16% from Taiwan, 14% from South Korea, and 4% from other countries (Germany, Denmark, Italy and the United States). One subject of the trial was from the U.S.

The Applicant BMS reported to FDA that a Clinical Research Associate (CRA) at the CRO (b) (4) was found to have conducted GCP non-compliance activities. Specifically, (b) (4), which was contracted to (b) (4) reported that (b) (4) The CRA also was involved in (b) (4) Taiwan FDA conducted a for-cause inspection at the (b) (4) on (b) (4) to determine the possible extent of GCP non-compliance by the CRA to other projects and to review the implementation status of the CAPA that (b) (4) provided to Taiwan FDA.

BMS acknowledged that the actions by the CRA constituted a GCP non-compliant activity and concluded that neither patient safety nor the interpretation of the reported trial results were adversely impacted by this activity.

Based on the aforementioned information, the DO3 review team initially determined that the sponsor and CRO inspections were necessary for this application in an attempt to discern if the noncompliance issue might have compromised the data integrity of this study. With the above described change and discussions secondary to the ongoing COVID-19 pandemic, the review division requested that OSI review PMDA's sponsor inspection report and the Applicant's response to OSI's inquiry to assess data reliability.

Review of PMDA's Sponsor Inspection Report:

Given that ORA could not conduct the two scheduled inspections during the COVID-19 pandemic, OSI contacted PMDA and obtained its sponsor inspection report. The report was obtained to assess the adequacy of sponsor's oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality of the clinical trial data from Study ONO-4538-24 submitted to FDA in support of BLA 125554 S-81. On March 19, 2020, OSI received the PMDA Inspection report titled "Report on Results of Pharmaceutical GCP Field Inspection Clinical Trial Applicant". The content of this report was translated from Japanese to English at the Immediate Office of Compliance at CDER.

Based on the translated report, PMDA inspected the study sponsor ONO Pharmaceutical on October 24-25, 2019 as a routine inspection for the same nivolumab application submitted to PMDA on May 30, 2019. The inspection, performed by PMDA's Quality Assurance Unit, covered Study ONO-4538-24. Based on the report, the primary focus was to evaluate the sponsor's oversight of the study conduct in support of the marketing application in Japan. The inspection reportedly reviewed the informed consents obtained from a total of 544 subjects. Of them, 273 subjects from Japan and 113 from other regions (listed as "Overseas" in the report) received study treatment (described as "Administered" in the report). The inspection also reviewed data collected by the cut-off date of November 12, 2018, which was used to create the inspection report. The inspection found no GCP deficiencies.

The PMDA inspection concluded that the sponsor's oversight of the study conduct was compliant with GCP. The inspection result was supportive of the PMDA approval of nivolumab for the proposed indication in Japan.

Reviewer's Note: *Based on the confidential information received from PMDA on March 19, 2020, the CRA's non-compliance activity as described in the above Background was reported to PMDA by ONO Pharmaceuticals and CRO* (b) (4) *before the application was submitted to PMDA. The details of the issue were examined by PMDA and the submitted corrective and o\preventive action (CAPA) plans were considered appropriate. In addition, PMDA stated that ONO pharmaceuticals excluded the data of the cases in which the CRA was involved from the analysis in the application submitted to PMDA.)*

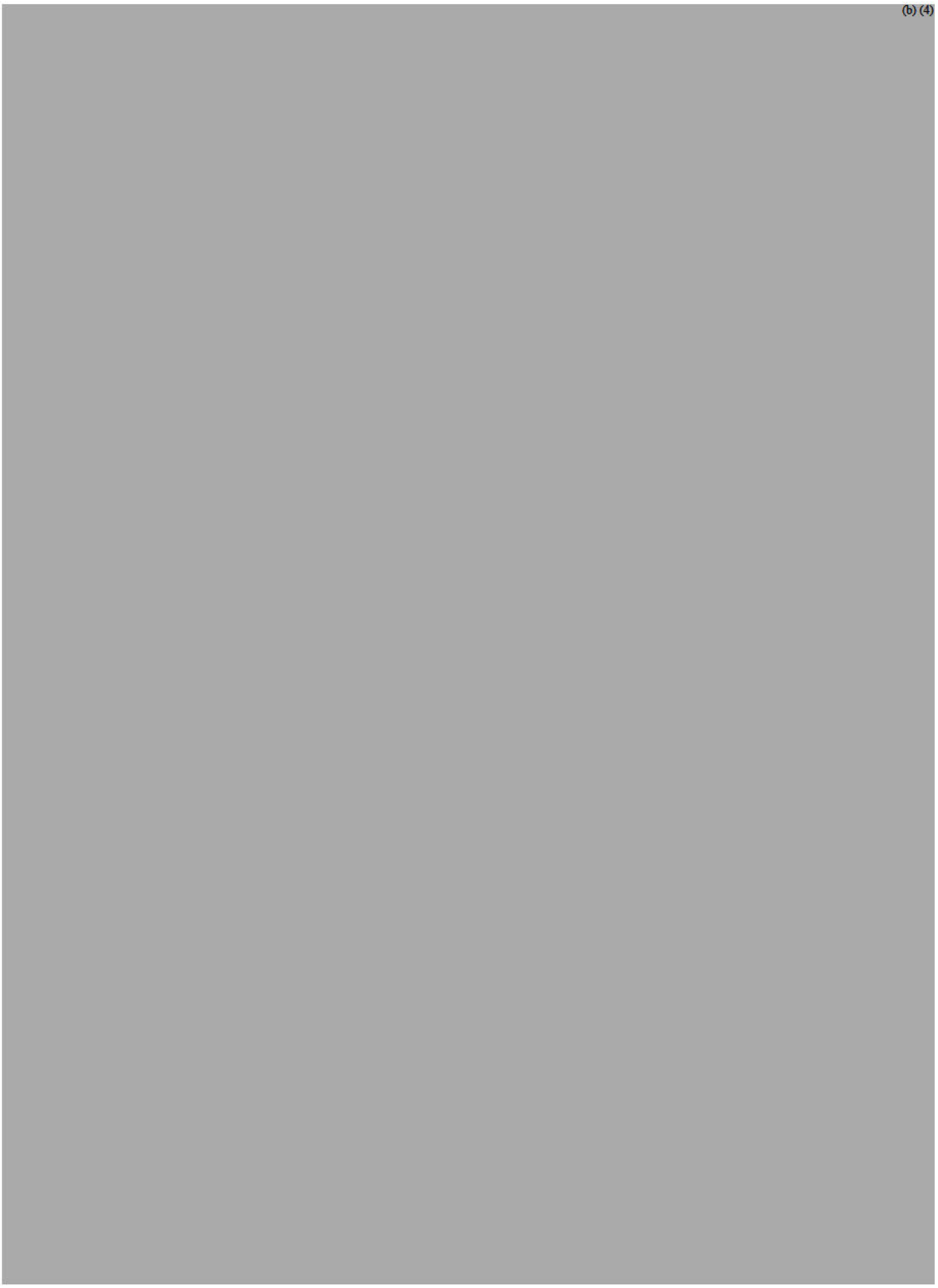
Review of Monitoring Visit Reports and Audit Summary:

On April 6, 2020, OSI received response from the Applicant BMS to its inquiry regarding the GCP non-compliance reported by the sponsor to FDA. The purpose of the information request was to further understand the GCP non-compliance reported by the sponsor to FDA and assess the adequacy of sponsor's oversight on Study ONO-4538-24 . OSI requested the Applicant to submit reports and summary of the internal audit of (b) (4) and (b) (4) as well as the Monitoring Visit Reports (b) (4)

The OSI review of the Applicant's response to its inquiry covers the monitoring and internal audit report for Study ONO-4538-24. Relevant review findings are discussed below.

1) Monitoring Visit Reports:

(b) (4)



(b) (4)

Reviewer's Comments: *No other objectionable issues were observed* (b) (4) *by that CRA. The monitoring reports appears to be adequately complete.*

2) Applicant's Audit Summary:

Audit Summary Report- (b) (4) Service Provider Audit-for BMS-23 October 2019 (DOC101-01) was submitted in response to an information request from OSI through the review division dated March 30, 2020. The audit summary focuses only on Study ONO-4538-24/CA209-473.

The audit was conducted by BMS and ONO Pharmaceutical jointly in June-July 2019, to determine whether the CRO (b) (4) performed contract service in compliance with ICH E6 (R2), Japan and Taiwan local GCP and regulations, clinical study protocols, applicable Standard Operating Procedures (SOPs)/working procedures, and requirements in contractual agreements. Additionally, the audit included assessment of the service regarding the protection of the rights, safety, and well-being of human subjects and the integrity of clinical study data.

The audit resulted in (b) (4) The three major findings are listed as follows.

Major findings

(b) (4)

As indicated in the report, appropriate Corrections and Corrective Actions were put in place by (b) (4).

(b) (4)

(b) (4) committed to (b) (4)

(b) (4)

(b) (4) responded that (b) (4)

They also referred to the Taiwan FDA inspection (b) (4) where the actions taken by (b) (4) for the recent quality issue were considered appropriate.

The audit report concluded that (b) (4) demonstrated that the services were provided in line with the regulations, investigational plans, applicable SOPs/procedures and contracts. The findings discussed above indicated opportunities for enhancements of the Quality Management System as well as study management. The findings do not appear to directly affect the data reliability of Study ONO-4538-24/CA209473.

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Zana Marks, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Yang-Min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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

cc:

Central Doc. Rm. BLA 125554 S-81
Review Division /Division Director/L Fashoyin-Aje
Review Division /Medical Team Leader/M Donoghue
Review Division /Medical Officer/L Pelosof
Review Division/Project Manager/M Khazraee
OSI/Office Director/D Burrow
OSI/DCCE/ Division Director/N Khin
OSI/DCCE/GCPAB Branch Chief/K Ayalew
OSI/DCCE/GCPAB Medical Officer/ZH Marks
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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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: April 17, 2020

To: Maryam Khazraee, PharmD, BCPS, Regulatory Project Manager
Division of Oncology 3 (DO3)

William Pierce, PharmD, Associate Director for Labeling, (DO3)

From: Adesola Adejuwon, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for OPDIVO® (nivolumab) injection, for intravenous use

BLA: 125554/Supplement 81

In response to DO3 consult request dated January 29, 2020, OPDP has reviewed the proposed product labeling (PI)and Medication Guide for OPDIVO® (nivolumab) injection, for intravenous use (Opdivo). This supplement (S 081) proposes a new indication for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DO3 (Maryam Khazraee) on April 6, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on April 16, 2020.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at (240) 402-5773 or Adesola.Adejuwon@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 16, 2020
To:	Maryam Khazraee, PharmD, BCPS Regulatory Project Manager **Division of Oncology 3**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	OPDIVO (nivolumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 125554
Supplement Number:	S-081
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On December 11, 2019, Bristol-Myers Squibb Company submitted for the Agency's review a Prior Approval Supplment (PAS)- Efficacy to their approved Biologic License Application (BLA) 125554/S-081 for OPDIVO (nivolumab) injection. With this supplement, the Applicant proposes a new indication for the treatment of unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after fluoropyrimidine- and platinum-based chemotherapy.

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 January 29, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPDIVO (nivolumab) injection.

2 MATERIAL REVIEWED

- Draft OPDIVO (nivolumab) injection MG received on December 11, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 6, 2020.
- Draft OPDIVO (nivolumab) injection Prescribing Information (PI) received on December 11, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 6, 2020.
- Approved OPDIVO (nivolumab) injection labeling dated September 18, 2019.

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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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:	March 31, 2020
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 125554/S-081
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:	December 11, 2019 and March 17, 2020
OSE RCM #:	2020-191
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

1 REASON FOR REVIEW

Bristol-Myers Squibb submitted BLA 125554/S-081 on December 11, 2019 to update Section 1 Indications of BLA 125554 to include Esophageal Squamous Cell Carcinoma and Section 2 Dosage and Administration to include the dosing for Esophageal Squamous Cell Carcinoma. The Medication guide was updated to include information on when Opdivo is indicated to include patients with Esophageal Squamous Cell Carcinoma.

This review responds to a DO3 consult for DMEPA to review the proposed changes to the Opdivo Prescribing Information (PI) and Medication Guide from a medication error perspective.

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 Label and Labeling 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 1 Indications and Section 2 Dosage and Administration of the Opdivo PI and noted that the recommended Opdivo dosage and duration of therapy for the new indication is the same as seven other indications included in the PI. We find the Prescribing Information and Medication Guide acceptable 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 December 11, 2019 from Bristol-Myers Squibb.

Table 2. Relevant Product Information for Opdivo	
Initial Approval Date	December 22, 2014
Active Ingredient	Nivolumab
Indication	• 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) • patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. (1.3) • patients with metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy.a (1.4) • patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy. (1.5) • patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab. (1.5) • adult patients with classical Hodgkin lymphoma that has relapsed or progressed after[a]: (1.6) o autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or o 3 or more lines of systemic therapy that includes autologous HSCT. • patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy. (1.7) • patients with locally advanced or metastatic urothelial carcinoma who[a]: o have disease progression during or following platinum-containing chemotherapy o have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.8) • adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab.[a] (1.9) • patients with hepatocellular carcinoma who have been previously treated with sorafenib.[a] (1.10) • patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy. (1.11)

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

Table 2: Recommended Dosages of OPDIVO in Combination with Ipilimumab

Indication	Recommended OPDIVO Dosage	Duration of Therapy
Unresectable or metastatic melanoma	1 mg/kg every 3 weeks (30-minute intravenous infusion) with ipilimumab 3 mg/kg intravenously over 90 minutes on the same day	In combination with ipilimumab for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier
	240 mg every 2 weeks (30-minute intravenous infusion) or 480 mg every 4 weeks (30-minute intravenous infusion)	After completing 4 doses of combination therapy, administer as single agent until disease progression or unacceptable toxicity
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)	

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-cc (b) (4) glass vials. • Nivolumab Injection, 240 mg/24 mL (10 mg/mL) is packaged in (b) (4) glass vials. Vials for all three presentations are stoppered with a (b) (4) and sealed with a (b) (4) seal with (b) (4) seal.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 11, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, "Opdivo" and "nivolumab". Our search identified five previous reviews[a,b,c,d,e] and we confirmed that our previous recommendations were implemented.

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,[f] along with postmarket medication error data, we reviewed the following Opdivo labels and labeling submitted by Bristol-Myers Squibb.

- Prescribing Information and Medication Guide (Image not shown) received on March 17, 2020, available from \\cdsesub1\evsprod\bla125554\0725\m1\us\13mar2020-2l-esoph-carcinoma-nivol-ann.pdf

[a] 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.

[b] 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.

[c] 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.

[d] 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.

[e] 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.

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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