CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125554Orig1s022

Trade Name:	OPDIVO
Generic or Proper Name:	nivolumab
Sponsor:	Bristol-Myers Squibb Company
Approval Date:	November 10, 2016
Indication:	Opdivo is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with: • BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent. • BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. • Unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. • 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.

- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy.
- Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554/S-022

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Michael R. Ladd, Pharm.D.
Associate Director, Global Regulatory Strategy – Oncology
Global Regulatory Sciences
5 Research Parkway
Wallingford, CT 06457

Dear Dr. Ladd:

Please refer to your Supplemental Biologics License Application (sBLA), dated May 11, 2016, submitted under section 351(a) of the Public Health Service Act for OPDIVO (nivolumab) Injection for Intravenous Infusion, 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) single-dose vial.

This Prior Approval supplemental biologics application provides for a new indication for nivolumab, as a single agent, 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.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide) and include

the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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 MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this indication because necessary studies are impossible or highly impracticable since the disease/condition does not exist in children.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3137-1	Provide the results of an analytic validation study for the assay used to identify patients with PD-L1 positive and PD-L1 negative SCCHN in Study CA2090141 to inform product labeling for the device and for nivolumab.

The timetable you submitted on October 31, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: January 31, 2017

Submit the analytical validation protocols and results in the final report as a supplement to the Pre-Market Application (PMA) P150027 for the PDL-1 IHC 28-8 pharmDx assay.

In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans

since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 Meredith Libeg, Senior Regulatory Health Project Manager, at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
11/10/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

Indications and Usage (1)	11/2016
Dosage and Administration (2)	11/2016
Warnings and Precautions (5)	10/2016

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

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

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent. (1.1)
- BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- Unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- 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. (1.2)
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.3)
- Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.4)
- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy. (1.5)

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

Administer as an intravenous infusion over 60 minutes.

- Unresectable or metastatic melanoma
  - OPDIVO 240 mg every 2 weeks. (2.1)
  - OPDIVO with ipilimumab: OPDIVO 1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then OPDIVO 240 mg every 2 weeks. (2.1)
- Metastatic non-small cell lung cancer
  - OPDIVO 240 mg every 2 weeks. (2.2)
- Advanced renal cell carcinoma
  - OPDIVO 240 mg every 2 weeks. (2.3)
- Classical Hodgkin lymphoma
  - OPDIVO 3 mg/kg every 2 weeks. (2.4)
- Recurrent or metastatic squamous cell carcinoma of the head and neck
  - OPDIVO 3 mg/kg every 2 weeks. (2.5)

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

Injection: 40 mg/4 mL and 100 mg/10 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 reactions: Discontinue OPDIVO for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. (5.9)
- Complications of allogeneic HSCT after OPDIVO: Monitor for hyperacute graft-versus-host-disease (GVHD), grade 3-4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions. Transplant-related mortality has occurred. (5.10)
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.11, 8.1, 8.3)

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

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

- OPDIVO 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. (6.1)
- OPDIVO with ipilimumab: fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea. (6.1)

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

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

Lactation: Discontinue breastfeeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2016

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 is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*.
- OPDIVO as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*.

  This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- OPDIVO, in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*.

  This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.2 Metastatic Non-Small Cell Lung Cancer

OPDIVO is indicated for the treatment of patients with metastatic non-small cell lung cancer (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 *[see Clinical Studies (14.2)]*.

1.3 Renal Cell Carcinoma

OPDIVO is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy *[see Clinical Studies (14.3)]*.

1.4 Classical Hodgkin Lymphoma

OPDIVO is indicated for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin *[see Clinical Studies (14.4)]*. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials *[see Clinical Studies (14.4)]*.

1.5 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 *[see Clinical Studies (14.5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Melanoma

The recommended dose of OPDIVO as a single agent is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

The recommended dose of OPDIVO is 1 mg/kg administered as an intravenous infusion over 60 minutes, followed by ipilimumab on the same day, every 3 weeks for 4 doses *[see Clinical Studies (14.1)]*. The recommended subsequent dose of OPDIVO, as a single agent, is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. Review the Full Prescribing Information for ipilimumab prior to initiation.

2.2 Recommended Dosage for NSCLC

The recommended dose of OPDIVO is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.3 Recommended Dosage for RCC

The recommended dose of OPDIVO is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.4 Recommended Dosage for cHL

The recommended dose of OPDIVO is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.5 Recommended Dosage for SCCHN

The recommended dose of OPDIVO is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.6 Dose Modifications

Recommendations for OPDIVO modifications are provided in Table 1. When OPDIVO is administered in combination with ipilimumab, if OPDIVO is withheld, ipilimumab should also be withheld.

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

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

Table 1: 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

Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose[a]
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	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 upper limit of normal	Withhold dose[a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	 Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	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 returns to Grade 0 or 1.

2.7 Preparation and Administration

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

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.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.

Storage of Infusion

The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

Administration

Administer the infusion over 60 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).

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

When administered in combination with ipilimumab, infuse OPDIVO first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) 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 (2.6)]*.

OPDIVO as a Single Agent

In patients receiving 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

In patients receiving OPDIVO with ipilimumab, immune-mediated pneumonitis occurred in 6% (25/407) of patients. The median time to onset of immune-mediated pneumonitis was 1.6 months (range: 24 days to 10.1 months). Immune-mediated pneumonitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 2.2% and 3.7% of patients, respectively. Approximately 84% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 30 days (range: 5 days to 11.8 months). Complete resolution occurred in 68% of patients. Approximately 13% of patients had recurrence of pneumonitis after re-initiation of OPDIVO with ipilimumab.

5.2 Immune-Mediated Colitis

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

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

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 (2.6)]*.

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 (2.6)]*.

OPDIVO as a Single Agent

In patients receiving 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

In patients receiving OPDIVO with ipilimumab, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases. The median time to onset of immune-mediated colitis was 1.6 months (range: 3 days to 15.2 months). Immune-mediated colitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 16% and 7% of patients, respectively. Approximately 96% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.1 month (range: 1 day to 12 months). Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 75% of patients. Approximately 28% of patients 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. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.6)]*.

OPDIVO as a Single Agent

In patients receiving 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

In patients receiving OPDIVO with ipilimumab, immune-mediated hepatitis occurred in 13% (51/407) of patients; the median time to onset was 2.1 months (range: 15 days to 11 months). Immune-mediated hepatitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 6% and 5% of patients, respectively. Approximately 92% of patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.1 month (range: 1 day to 13.2 months). Complete resolution occurred in 75% of patients. Approximately 11% of 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 (2.6)]*.

In patients receiving 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).

In patients receiving OPDIVO with ipilimumab, hypophysitis occurred in 9% (36/407) of patients; the median time to onset was 2.7 months (range: 27 days to 5.5 months). Hypophysitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 1.0% and 3.9% of patients, respectively. Approximately 75% of patients with hypophysitis received hormone replacement therapy and 56% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 19 days (range: 1 day to 2.0 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 (2.6)]*.

In patients receiving 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).

In patients receiving OPDIVO with ipilimumab, adrenal insufficiency occurred in 5% (21/407) of patients and the median time to onset was 3.0 months (range: 21 days to 9.4 months). Adrenal insufficiency led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.5% and 1.7% of patients, respectively. Approximately 57% of patients with adrenal insufficiency received hormone replacement therapy and 33% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 9 days (range: 1 day to 2.7 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.

In patients receiving 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 receiving 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.

In patients receiving OPDIVO with ipilimumab, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients; the median time to onset was 2.1 months (range: 1 day to 10.1 months). Approximately 73% of patients with hypothyroidism or thyroiditis received levothyroxine. Resolution occurred in 45% of patients.

Hyperthyroidism occurred in 8% (34/407) of patients receiving OPDIVO with ipilimumab: the median time to onset was 23 days (range: 3 days to 3.7 months). Approximately 29% of patients with hyperthyroidism received methimazole and 24% received carbimazole. Resolution occurred in 94% of patients.

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 (2.6)]*.

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

In patients receiving OPDIVO with ipilimumab, diabetes occurred in 1.5% (6/407) of patients; the 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.

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 (2.6) and Adverse Reactions (6.1)]*.

OPDIVO as a Single Agent

In patients receiving 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

In patients receiving OPDIVO with ipilimumab, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients; the 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.

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 (2.6)]*.

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 receiving 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 days 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

In patients receiving OPDIVO with ipilimumab, immune-mediated rash occurred in 22.6% (92/407) of patients; the median time to onset was 18 days (range: 1 day to 9.7 months). Immune-mediated rash led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.5% and 3.9% of patients, respectively. Approximately 17% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 14 days (range: 2 days to 4.7 months). Complete resolution occurred in 47% of patients. Approximately 6% of patients who resumed OPDIVO and ipilimumab after resolution had recurrence of rash.

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 (2.6)]*.

OPDIVO as a Single Agent

In patients receiving 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

Encephalitis occurred in one patient receiving OPDIVO with ipilimumab (0.2%) after 1.7 months of exposure.

5.8 Other Immune-Mediated Adverse Reactions

OPDIVO can cause other clinically significant 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 (2.6)]*.

Across clinical trials of OPDIVO administered as a single agent or in combination with ipilimumab, the following clinically significant immune-mediated adverse reactions occurred in less than 1.0% of patients receiving OPDIVO: 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), myositis, myocarditis, rhabdomyolysis, motor dysfunction, vasculitis, and myasthenic syndrome.

5.9 Infusion Reactions

OPDIVO can cause severe infusion reactions, which have been reported in less than 1.0% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions *[see Dosage and Administration (2.6)]*.

OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, infusion-related reactions occurred in 6.4% (127/1994) of patients.

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, infusion-related reactions occurred in 2.5% (10/407) of patients.

5.10 Complications of Allogeneic HSCT after OPDIVO

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from Trials 8 and 9 who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, two with myeloablative conditioning). The median age at HSCT was 33 (range: 18 to 56), and a median of 9 doses of OPDIVO had been administered (range: 4 to 16). Six of 17 patients (35%) died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 5/17 patients (29%). Hyperacute GVHD, defined as GVHD occurring within 14 days after stem cell infusion, was reported in 2 patients (20%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (35%) within the first 6 weeks post-transplantation, with five patients responding to steroids. Two cases of encephalitis were reported: one case of Grade 3 lymphocytic encephalitis without an identified infectious cause, which occurred and resolved on steroids, and one case of Grade 3 suspected viral encephalitis which was resolved with antiviral treatment. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure.

Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported.

These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

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 an OPDIVO-containing regimen and for at least 5 months after the last dose of OPDIVO *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of 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 Reactions *[see Warnings and Precautions (5.9)]*
- Complications of Allogeneic HSCT after OPDIVO *[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 the Warnings and Precautions section reflect exposure to OPDIVO, as a single agent, for clinically significant adverse reactions in 1994 patients enrolled in Trials 1 through 8 or a single-arm trial in NSCLC (n=117) administering OPDIVO as a single agent *[see Warnings and Precautions (5.1, 5.8)]*. In addition, clinically significant adverse reactions of OPDIVO administered with ipilimumab were evaluated in 407 patients with melanoma enrolled in Trial 6 (n=313) or a Phase 2 randomized study (n=94), administering OPDIVO with ipilimumab, supplemented by immune-mediated adverse reaction reports in ongoing clinical trials *[see Warnings and Precautions (5.1, 5.8)]*.

The data described below reflect exposure to OPDIVO as a single agent in Trials 1, 4, and 6, and to OPDIVO with ipilimumab in Trial 6, which are randomized, active-controlled trials conducted in patients with unresectable or metastatic melanoma. Also described below are single-agent OPDIVO data from Trials 2 and 3, which are randomized trials in patients with metastatic NSCLC, Trial 5, which is a randomized trial in patients with advanced RCC, Trials 7 and 8, which are open-label, multiple-cohort trials in patients with cHL, and Trial 9, a randomized trial in patients with recurrent or metastatic SCCHN.

Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

The safety of OPDIVO as a single agent was evaluated in Trial 1, a randomized, open-label trial in which 370 patients with unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m^2 every 3 weeks *[see Clinical Studies (14.1)]*. 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 greater than 6 months and 3% of patients received OPDIVO for greater than 1 year.

In Trial 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.

The trial 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 LDH at baseline (51% vs. 38%).

OPDIVO was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving OPDIVO had a drug delay for an adverse reaction. Serious adverse reactions occurred in 41% of patients receiving OPDIVO. 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 less than 5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase.

Table 2 summarizes the adverse reactions that occurred in at least 10% of OPDIVO-treated patients in Trial 1. The most common adverse reaction (reported in at least 20% of patients) was rash.

Table 2: 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]) (Trial 1)

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

Toxicity was graded per NCI CTCAE v4.

[a] Rash is a composite term which includes maculopapular rash, erythematous rash, pruritic rash, follicular rash, macular rash, papular rash, pustular rash, vesicular rash, and acneiform dermatitis.

[b] Upper respiratory tract infection is a composite term which includes rhinitis, pharyngitis, and nasopharyngitis.

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in Trial 1 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 3: Laboratory Abnormalities Worsening from Baseline 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]) (Trial 1)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	OPDIVO		Chemotherapy	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Increased AST	28	2.4	12	1.0
Increased alkaline phosphatase	22	2.4	13	1.1
Hyponatremia	25	5	18	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

Trial 4

The safety of OPDIVO was also evaluated in Trial 4, a randomized, double-blind, active-controlled trial in which 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=206) or dacarbazine 1000 mg/m^2 every 3 weeks (n=205) *[see Clinical Studies (14.1)]*. 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 greater than 6 months and 12% of patients received OPDIVO for greater than 1 year.

The trial excluded patients with autoimmune disease and patients requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications.

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%).

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. Serious adverse reactions occurred in 36% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%).

Table 4 summarizes selected adverse reactions that occurred in at least 10% of OPDIVO-treated patients. The most common adverse reactions (reported in at least 20% of patients and at a higher incidence than in the dacarbazine arm) were fatigue, musculoskeletal pain, rash, and pruritus.

Table 4: 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]) (Trial 4)

Adverse Reaction	OPDIVO (n=206)		Dacarbazine (n=205)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	Percentage (%) of Patients			
General Disorders and Administration Site Conditions				
Fatigue	49	1.9	39	3.4
Edema[a]	12	1.5	4.9	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[b]	32	2.9	25	2.4
Skin and Subcutaneous Tissue Disorders				
Rash[c]	28	1.5	12	0
Pruritus	23	0.5	12	0
Erythema	10	0	2.9	0
Vitiligo	11	0	0.5	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.

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in Trial 4 were:

Nervous System Disorders: peripheral neuropathy

Table 5: Laboratory Abnormalities Worsening from Baseline 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]) (Trial 4)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	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).

Trial 6

The safety of OPDIVO, administered with ipilimumab or as a single agent, was evaluated in Trial 6 *[see Clinical Studies (14.1)]*, a randomized (1:1:1), a double-blind trial in which 937 patients with previously untreated, unresectable or metastatic melanoma received:

- OPDIVO 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by OPDIVO 3 mg/kg as a single agent every 2 weeks (OPDIVO plus ipilimumab arm; n=313),
- OPDIVO 3 mg/kg every 2 weeks (OPDIVO arm; n=313), or
- Ipilimumab 3 mg/kg 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 18.8 months) for the OPDIVO plus ipilimumab arm and 6.6 months (range: 1 day to 17.3 months) for the OPDIVO arm. In the OPDIVO plus ipilimumab arm, 39% were exposed to OPDIVO for ≥6 months and 24% exposed for >1 year. In the OPDIVO arm, 53% were exposed for ≥6 months and 32% for >1 year.

Trial 6 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.

The trial population characteristics were: 65% male, median age 61 years, 97% White, baseline ECOG performance status 0 (73%) or 1 (27%), 93% with 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.

In Trial 6, serious adverse reactions (73% and 37%), adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and Grade 3 or 4 adverse

reactions (72% and 44%) all occurred more frequently in the OPDIVO plus ipilimumab arm relative to the OPDIVO arm.

The most frequent (≥10%) serious adverse reactions in the OPDIVO plus ipilimumab arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). The most frequent adverse reactions leading to discontinuation of both drugs in the OPDIVO plus ipilimumab arm and of OPDIVO in the OPDIVO arm, respectively, were diarrhea (8% and 1.9%), colitis (8% and 0.6%), increased ALT (4.8% and 1.3%), increased AST (4.5% and 0.6%), and pneumonitis (1.9% and 0.3%). The most common (≥20%) adverse reactions in the OPDIVO plus ipilimumab arm were fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea. The most common (≥20%) adverse reactions in the OPDIVO arm were fatigue, rash, diarrhea, and nausea. Table 6 summarizes the incidence of adverse reactions occurring in at least 10% of patients in either OPDIVO-containing arm in Trial 6.

Table 6: Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO plus 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]) (Trial 6)

Adverse Reaction	Percentage (%) of Patients					
	OPDIVO plus 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 Disorders and Administration Site Conditions						
Fatigue[a]	59	6	53	1.9	50	3.9
Pyrexia	37	1.6	14	0	17	0.6
Skin and Subcutaneous Tissue Disorders						
Rash[b]	53	5	40	1.6	42	3.9
Gastrointestinal Disorders						
Diarrhea	52	11	31	3.8	46	8
Nausea	40	3.5	28	0.6	29	1.9
Vomiting	28	3.5	17	1.0	16	1.6
Respiratory, Thoracic and Mediastinal Disorders						
Dyspnea	20	2.2	12	1.3	13	0.6

Toxicity was graded per NCI CTCAE v4.

[a] Fatigue is a composite term which includes asthenia and fatigue.

[b] Rash is a composite term which includes pustular rash, dermatitis, acneiform dermatitis, allergic dermatitis, atopic dermatitis, bullous dermatitis, exfoliative dermatitis, psoriasiform dermatitis, drug eruption, erythema, exfoliative rash, erythematous rash, generalized rash, macular rash, maculopapular rash, morbilliform rash, papular rash, papulosquamous rash, pruritic rash, and seborrheic dermatitis.

Other clinically important adverse reactions in less than 10% of patients treated with either OPDIVO with ipilimumab or single-agent OPDIVO in Trial 6 were:

Gastrointestinal Disorders: stomatitis, intestinal perforation

Skin and Subcutaneous Tissue Disorders: vitiligo

Musculoskeletal and Connective Tissue Disorders: myopathy, Sjogren's syndrome, spondyloarthropathy

Nervous System Disorders: neuritis, peroneal nerve palsy

Table 7: Laboratory Abnormalities Worsening from Baseline 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]) (Trial 6)

Laboratory Abnormality	Percentage (%) of Patients[a]					
	OPDIVO plus Ipilimumab		OPDIVO		Ipilimumab	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Chemistry						
Increased ALT	53	15	23	3.0	28	2.7
Increased AST	47	13	27	3.7	27	1.7
Hyponatremia	42	9	20	3.3	25	7
Increased lipase	41	20	29	9	23	7
Increased alkaline phosphatase	40	6	24	2.0	22	2.0
Hypocalcemia	29	1.1	13	0.7	21	0.7
Increased amylase	25	9.1	15	1.9	14	1.6
Increased creatinine	23	2.7	16	0.3	16	1.3
Hematology						
Anemia	50	2.7	39	2.6	40	6
Lymphopenia	35	4.8	39	4.3	27	3.4

[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 plus ipilimumab (range: 241 to 297); OPDIVO (range: 260 to 306); ipilimumab (range: 253 to 304).

Metastatic Non-Small Cell Lung Cancer

The safety of OPDIVO in metastatic NSCLC was evaluated in Trial 2, 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 Trial 3, 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 (14.2)]*. Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks or docetaxel administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy in OPDIVO-treated patients in Trial 2 was 3.3 months (range: 1 day to 21.7+ months)

and in Trial 3 was 2.6 months (range: 0 to 24.0+ months). In Trial 2, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1 year and in Trial 3, 30% of patients received OPDIVO for greater than 6 months and 20% of patients received OPDIVO for greater than 1 year.

Trial 2 and Trial 3 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease.

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%).

OPDIVO was discontinued in 11% of patients, and was delayed in 28% of patients for an adverse reaction. Serious adverse reactions occurred in 46% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Trial 3, 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. Across both trials, the most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

Table 8 summarizes selected adverse reactions occurring more frequently in at least 10% of OPDIVO-treated patients.

Table 8: 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]) (Trials 2 and 3)

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

Toxicity was graded per NCI CTCAE v4.

Other clinically important adverse reactions observed in patients treated with OPDIVO and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (48% Grade 1-4, 5% Grade 3-4), musculoskeletal pain (33%), pleural effusion (4.5%), pulmonary embolism (3.3%).

Table 9: Laboratory Abnormalities Worsening from Baseline 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]) (Trials 2 and 3)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	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); TSH: OPDIVO group n=314 and docetaxel group n=297.

[b] Not graded per NCI CTCAE v4.

Renal Cell Carcinoma

The safety of OPDIVO was evaluated in Trial 5, a randomized open-label trial in which 803 patients with advanced RCC who had experienced disease progression during or after at least one anti-angiogenic treatment regimens received OPDIVO 3 mg/kg every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.3)]*. 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.

Study therapy was discontinued for adverse reactions in 16% of OPDIVO patients and 19% of everolimus patients. Forty-four percent (44%) of patients receiving OPDIVO had a drug delay for an adverse reaction. Serious adverse reactions occurred in 47% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia.

Rate of death on treatment or within 30 days of the last dose of study drug was 4.7% on the OPDIVO arm versus 8.6% on the everolimus arm.

The most common adverse reactions (reported in at least 20% of patients) were asthenic conditions, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia. Table 10 summarizes adverse reactions that occurred in greater than 15% of OPDIVO-treated patients.

Table 10: Grade 1-4 Adverse Reactions in >15% of Patients Receiving OPDIVO (Trial 5)

	OPDIVO (n=406)		Everolimus (n=397)	
	Percentage (%) of Patients			
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Adverse Reaction	98	56	96	62
General Disorders and Administration Site Conditions				
Asthenic conditions[a]	56	6	57	7
Pyrexia	17	0.7	20	0.8
Respiratory, Thoracic and Mediastinal Disorders				
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 Disorders				
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 Disorders				
Rash[d]	28	1.5	36	1.0
Pruritus/generalized pruritus	19	0	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	23	1.2	30	1.5
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	20	1.0	14	0.5
Back pain	21	3.4	16	2.8

Toxicity was graded per NCI CTCAE v4.

[a] Asthenic conditions covering PTs asthenia, decreased activity, fatigue, and malaise.

[b] Includes nasopharyngitis, pharyngitis, rhinitis, and viral 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 Trial 5 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

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, elevated triglycerides, and hyperkalemia. Table 11 summarizes the laboratory abnormalities that occurred in greater than 15% of OPDIVO-treated patients.

Table 11: Grade 1-4 Laboratory Values Worsening from Baseline Occurring in >15% of Patients on OPDIVO (Trial 5)

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline[a]			
	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).

In addition, among patients with TSH less than ULN at baseline, a greater proportion of patients experienced a treatment-emergent elevation of TSH greater than ULN in the OPDIVO group compared to the everolimus group (26% and 14%, respectively).

Classical Hodgkin Lymphoma

The safety of OPDIVO 3 mg/kg every 2 weeks was evaluated in 263 adult patients with cHL (240 patients in Trial 7 and 23 patients in Trial 8). Treatment could continue 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: 1 to 15). Patients received a median of 10 doses (cycles) of OPDIVO (range: 1 to 48), with a median duration of therapy of 4.8 months (range: 0.3 to 24 months).

OPDIVO was discontinued due to adverse reactions in 4.2% of patients. Twenty-three percent (23%) of patients had a dose delay for an adverse reaction. Serious adverse reactions occurred in 21% of patients. The most frequent serious adverse reactions reported in at least 1% of patients were infusion-related reaction, pneumonia, pleural effusion, pyrexia, rash, and pneumonitis. Ten patients died from causes other than disease progression, including 6 who died from complications of allogeneic HSCT.

The most common adverse reactions (reported in at least 20%) among all patients (safety population), were fatigue, upper respiratory tract infection, pyrexia, diarrhea, and cough.

Among the subset of patients in the efficacy population, the most common adverse reactions also included rash, musculoskeletal pain, pruritus, nausea, arthralgia, and peripheral neuropathy. Serious adverse reactions occurred in 27% of these patients.

Table 12 summarizes both the adverse reactions that occurred in at least 10% of patients in the safety population (n=263) and the efficacy population (n=95). There is a greater incidence of adverse reactions in the subset of patients evaluated for efficacy; these patients received a median of 17 doses of OPDIVO and a median of 5 prior systemic regimens *[see Clinical Studies (14.4)]*.

Table 12: Non-Hematologic Adverse Reactions Occurring in ≥10% of Patients with cHL (Trials 7 and 8)

	OPDIVO cHL Safety Population(n=263)		OPDIVO cHL Efficacy Population (n=95)	
	Percentage (%) of Patients			
Adverse Reaction[a]	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
General Disorders and Administration Site Conditions				
Fatigue[b]	32	1.1	43	1.1
Pyrexia	24	0.8	35	1.1
Gastrointestinal Disorders				
Diarrhea	23	0.8	30	1.1
Nausea	17	0	23	0
Vomiting	15	0.8	16	1.1
Abdominal pain[c]	11	0.8	13	2.1
Constipation	9	0.4	14	0
Infections				
Upper respiratory tract infection[d]	28	0.4	48	1.1
Pneumonia / bronchopneumonia[e]	9	3.0	19	5.3
Respiratory, Thoracic and Mediastinal Disorders				
Cough/productive cough	22	0	35	0
Dyspnea/exertional dyspnea	10	0.8	16	2.1
Skin and Subcutaneous Tissue Disorders				
Rash[f]	19	1.5	31	3.2
Pruritus	17	0	25	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[g]	19	1.1	27	1.1
Arthralgia	11	0	21	0
Endocrine Disorders				
Hypothyroidism/thyroiditis	12	0	17	0
Hyperglycemia/Blood Glucose Increased	9	0.4	14	1.1
Nervous System Disorders				
Headache	12	0.4	12	1.1
Neuropathy peripheral[h]	11	0.4	21	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction	12	0.4	18	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-mediate adverse reaction, reactions following nivolumab rechallenge were included if they occurred up to 30 days after completing the initial nivolumab course.

[b] Includes asthenia.

[c] Includes abdominal discomfort and upper abdominal pain.

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

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

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

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

[h] Includes hyperesthesia, hypoesthesia, paresthesia, dysesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Additional information regarding clinically important adverse reactions:

Immune-mediated pneumonitis: In Trials 7 and 8, pneumonitis, including interstitial lung disease, occurred in 4.9% (13/263) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 3.4% (9/263) of patients receiving OPDIVO (one Grade 3 and eight Grade 2). The median time to onset was 2.2 months (range: 1 day to 10.1 months). All nine patients received systemic corticosteroids, with resolution in seven. One patient permanently discontinued OPDIVO due to Grade 2 pneumonitis. Dose delay occurred in three patients. Five patients resumed OPDIVO, of whom none had recurrence of pneumonitis.

Peripheral neuropathy: In Trials 7 and 8, peripheral neuropathy was observed in 11% (30/263) of all patients receiving OPDIVO. Twenty-two patients (8%) had new-onset peripheral neuropathy, and four patients had worsening from baseline. Four additional patients with peripheral neuropathy at baseline (three Grade 1 and one Grade 2) did not worsen. All events were Grade 1 or 2, except for 1 Grade 3 event (0.4%).

Complications of allogeneic HSCT after OPDIVO: [see Warnings and Precautions (5.10)].

Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated cHL Patients (Trials 7 and 8)

	OPDIVO cHL Safety Population[a]		OPDIVO cHL Efficacy Population[b]	
	Percentage (%) of Patients[c]			
Laboratory Abnormality	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Hematology				
Neutropenia	29	3.6	37	6
Thrombocytopenia	28	2.4	33	3.2
Lymphopenia	24	8	32	7
Anemia	22	2.8	27	2.1
Chemistry				
Increased ALT	24	2.0	25	2.1
Increased AST	23	2.4	32	3.2
Increased alkaline phosphatase	17	1.6	21	2.1
Increased lipase	16	6.5	28	12
Hyponatremia	14	0.8	15	1.1
Hypokalemia	11	1.6	14	3.2
Hypocalcemia	11	0.4	14	1.1
Hypomagnesemia	10	0.4	15	1.3
Increased creatinine	10	0	15	0
Increased bilirubin	9	0.8	10	0

[a] Number of evaluable patients for the safety population ranges from 226 to 253.
[b] Number of evaluable patients for the efficacy population ranges from 80 to 85.
[c] Includes events occurring up to 30 days after last nivolumab dose. After an immune-mediate adverse reaction, reactions following nivolumab rechallenge were included if they occurred within 30 days of completing the initial nivolumab course.

Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

The safety of OPDIVO was evaluated in Trial 9, 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 (14.5)]*. Patients received 3 mg/kg of OPDIVO (n=236) administered intravenously (IV) over 60 minutes every 2 weeks or investigator's choice of either:

- cetuximab (n=13), 400 mg/m^2 loading dose IV followed by 250 mg/m^2 weekly
- or methotrexate (n=46) 40 to 60 mg/m^2 IV weekly, or
- docetaxel (n=52) 30 to 40 mg/m^2 IV 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 greater than 6 months and 2.5% of patients received OPDIVO for greater than 1 year.

Trial 9 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).

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.

OPDIVO was discontinued in 14% of patients and was delayed in 24% of patients for an adverse reaction. Serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis. Adverse reactions and laboratory abnormalities occurring in patients with SCCHN were generally similar to those occurring in patients with melanoma and NSCLC. 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.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Of 1586 patients who were treated with OPDIVO as a single agent 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 157 patients (9.9%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and nine patients (0.6%) had neutralizing antibodies against nivolumab. There was no evidence of altered pharmacokinetic profile or increased incidence of infusion reactions with anti-nivolumab antibody development.

Of 394 patients who were treated with OPDIVO with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, 149 patients (37.8%) tested positive for treatment-emergent anti-nivolumab antibodies by an ECL assay and 18 patients (4.6%) had neutralizing antibodies against nivolumab. Of the 391 patients evaluable for the presence of anti-ipilimumab antibodies, 33 patients (8.4%) tested positive for treatment-emergent anti-ipilimumab antibodies by an ECL assay and one patient (0.3%) had neutralizing antibodies against ipilimumab. There was no

evidence of increased incidence of infusion reactions with anti-nivolumab antibody development.

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.

7 DRUG INTERACTIONS

No formal pharmacokinetic drug-drug interaction studies have been conducted with OPDIVO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. 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 human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, 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 of nivolumab (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

It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment with OPDIVO.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, 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 of OPDIVO.

8.4 Pediatric Use

The safety and effectiveness of OPDIVO have not been established in pediatric patients.

8.5 Geriatric Use

Of the 1359 patients randomized to single-agent OPDIVO in Trials 2 through 6, 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.

Trials 1, 7, 8, and 9 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 Trial 6, 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.

8.6 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild hepatic impairment. OPDIVO has not been studied in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no information on overdosage with OPDIVO.

11 DESCRIPTION

Nivolumab is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous infusion 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. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.

12.2 Pharmacodynamics

Based on dose/exposure efficacy and safety relationships, there are no clinically significant differences in safety and efficacy between a nivolumab dose of 240 mg or 3mg/kg every 2 weeks in patients with melanoma, NSCLC, and RCC.

12.3 Pharmacokinetics

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent OPDIVO and OPDIVO with ipilimumab.

OPDIVO as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-

life ($t_{1/2}$) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

OPDIVO with ipilimumab: The geometric mean (CV%) CL, Vss, and terminal half-life of nivolumab were 10.0 mL/h (50.3%), 7.92 L (30.1%), and 24.8 days (94.3%), respectively. When administered in combination, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab.

When administered in combination, the clearance of nivolumab increased by 42% in the presence of anti-nivolumab antibodies. There was no effect of anti-ipilimumab antibodies on the clearance of ipilimumab.

Specific Populations: The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), gender, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m^2; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m^2; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n=92). No clinically important differences in the clearance of nivolumab were found between patients with mild hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe hepatic impairment (TB greater than 3 times ULN and any AST) *[see Use in Specific Populations (8.7)]*.

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

Trial 1 was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either OPDIVO administered intravenously at 3 mg/kg 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 every 3 weeks plus paclitaxel 175 mg/m^2 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 Trial 1 and in whom the minimum duration of follow-up was 6 months. The major efficacy outcome measures in this population were confirmed objective 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, 33 patients (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 objective responses in patients with and without BRAF V600 mutation-positive melanoma.

Previously Untreated Metastatic Melanoma

Trial 4

Trial 4 was a multicenter, double-blind, randomized (1:1) trial conducted in 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 by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (greater than or equal to 5% of tumor cell membrane staining by immunohistochemistry vs. less than 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 objective response rate (ORR) per RECIST v1.1.

A total of 418 patients were randomized to OPDIVO (n=210) or dacarbazine (n=208). The median age was 65 years (range: 18 to 87), 59% were men, and 99.5% were white. Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (11%), elevated LDH level (37%), PD-L1 greater than or equal to 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%).

Trial 4 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. Table 14 and Figure 1 summarize the efficacy results.

Table 14: Efficacy Results - Trial 4

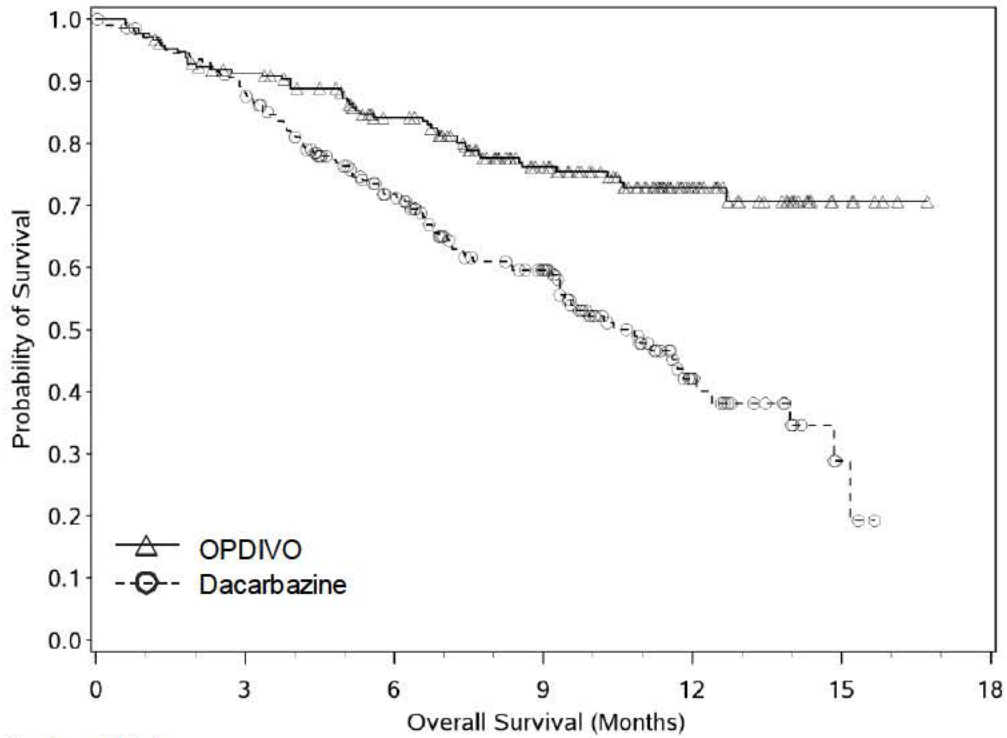
	OPDIVO (n=210)	**Dacarbazine (n=208)**
Overall Survival		
Deaths (%)	50 (24)	96 (46)
Median, months (95% CI)	Not Reached	10.8 (9.3, 12.1)
Hazard ratio (95% CI)[a]	0.42 (0.30, 0.60)	
p-value[b,c]	<0.0001	
Progression-Free Survival		
Disease progression or death (%)	108 (51)	163 (78)
Median, months (95% 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	
Objective 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 1: Kaplan-Meier Curves of Overall Survival - Trial 4



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

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.

Trial 6

Trial 6 was a multicenter, double-blind trial that randomized (1:1:1) patients with previously untreated, unresectable or metastatic melanoma to one of the following arms: OPDIVO plus 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 every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg as a single agent every 2 weeks (OPDIVO plus ipilimumab arm),
- OPDIVO 3 mg/kg every 2 weeks (OPDIVO arm), or

- Ipilimumab 3 mg/kg 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 American Joint Committee on Cancer (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.

A total of 945 patients were randomized, 314 patients to the OPDIVO plus ipilimumab arm, 316 to the OPDIVO arm, and 315 to the ipilimumab arm. 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%).

Trial 6 demonstrated statistically significant improvements in PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. Efficacy results are presented in Table 15 and Figure 2.

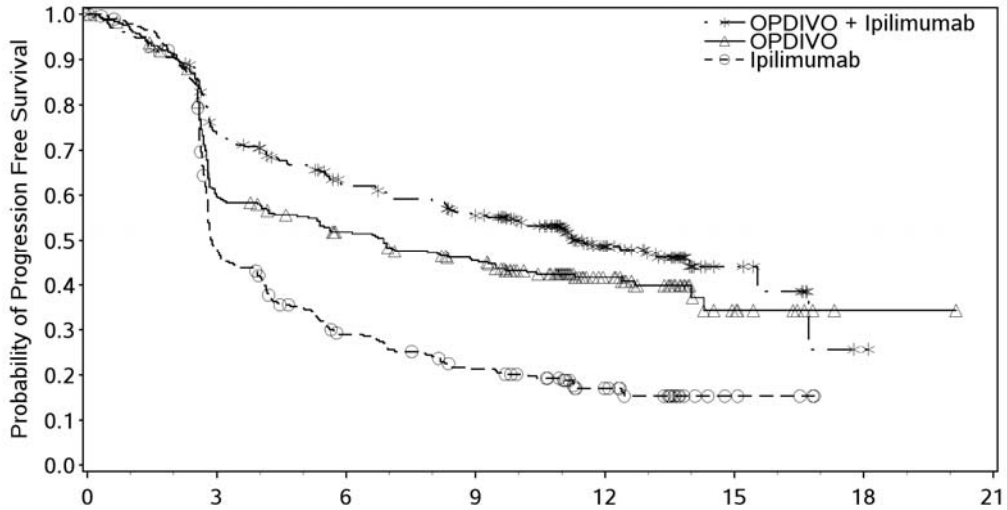
Table 15: Efficacy Results in Trial 6

	OPDIVO plus Ipilimumab (n=314)	**OPDIVO (n=316)**	**Ipilimumab (n=315)**
Progression-free Survival			
Disease progression or death	151	174	234
Median in months (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
Hazard ratio[a] (vs. ipilimumab)	0.42	0.57	
(95% CI)	(0.34, 0.51)	(0.47, 0.69)	
p-value[b,c]	<0.0001	<0.0001	
Confirmed Objective Response Rate	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value[d]	<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] Based on a stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with .005 of the allocated alpha for final PFS treatment comparisons.

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

Figure 2: Progression-free Survival: Unresectable or Metastatic Melanoma - Trial 6

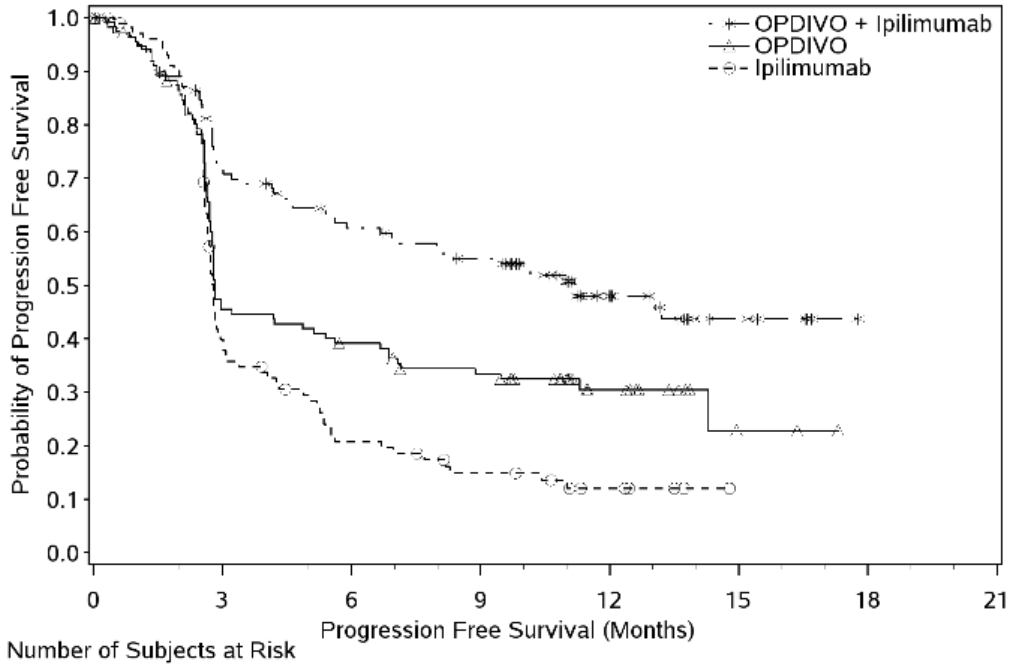


Number of Subjects at Risk

OPDIVO + Ipilimumab							
314	219	173	151	65	11	1	0
OPDIVO							
316	177	147	124	50	9	1	0
Ipilimumab							
315	137	77	54	24	4	0	0

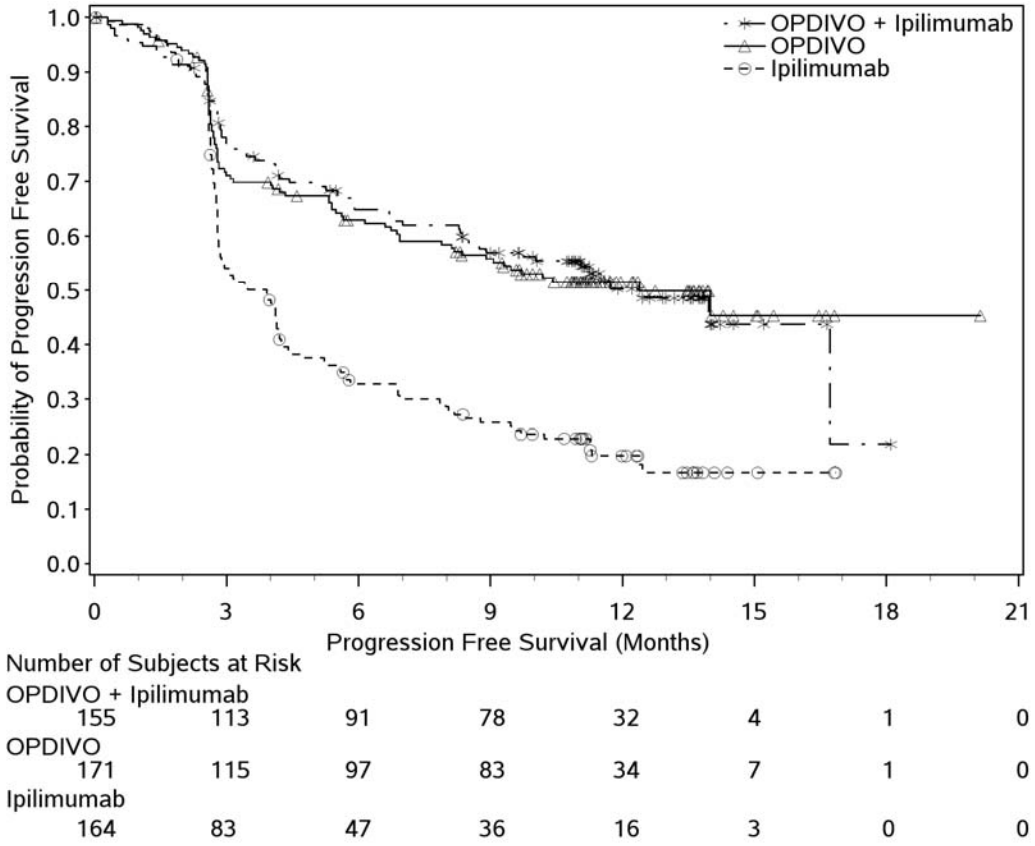
Figures 3 and 4 present exploratory efficacy subgroup analyses of PFS based on defined PD-L1 expression levels determined in archival tumor specimens using the PD-L1 IHC 28-8 pharmDx assay. Tumor samples were available for retrospective assessment for 97% of the study population; PD-L1 expression status was ascertained for 89% of the study population while in 6% of patients, melanin precluded evaluation of PD-L1 expression status. PD-L1 expression status was unknown for 5% of the study population due to consent withdrawal or missing samples.

Figure 3: Progression-free Survival by PD-L1 Expression (<1%) - Trial 6



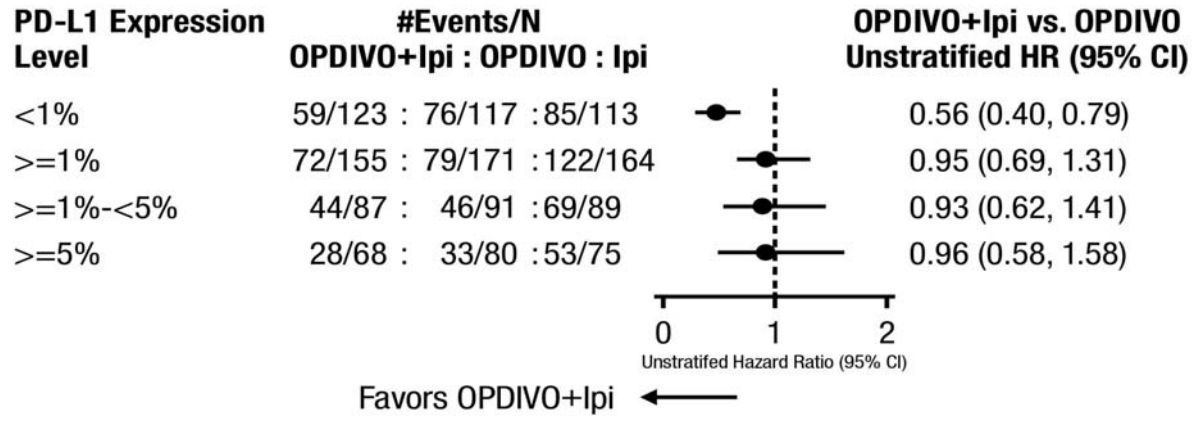
Number of Subjects at Risk							
OPDIVO + Ipilimumab							
123	82	65	57	26	6	0	0
OPDIVO							
117	50	42	34	13	2	0	0
Ipilimumab							
113	39	19	12	5	0	0	0

Figure 4: Progression-free Survival by PD-L1 Expression (≥1%) - Trial 6



The data presented in the figure below summarize the results of exploratory analyses comparing the two OPDIVO-containing arms in subgroups defined by PD-L1 tumor expression.

Figure 5: Forest Plot: PFS Based on PD-L1 Expression Comparing OPDIVO-Containing Arms - Trial 6



14.2 Metastatic Non-Small Cell Lung Cancer (NSCLC)

Second-line Treatment of Metastatic Squamous NSCLC

Trial 2 was a randomized (1:1), open-label study enrolling 272 patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received OPDIVO (n=135) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=137) administered intravenously at 75 mg/m^2 every 3 weeks. Randomization was stratified by prior paclitaxel vs other prior treatment and region (US/Canada vs. Europe vs. Rest of World). This study 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.

In Trial 2, the 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) (Table 16 and Figure 6).

Table 16: Efficacy Results in Trial 2

	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	
Objective 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	

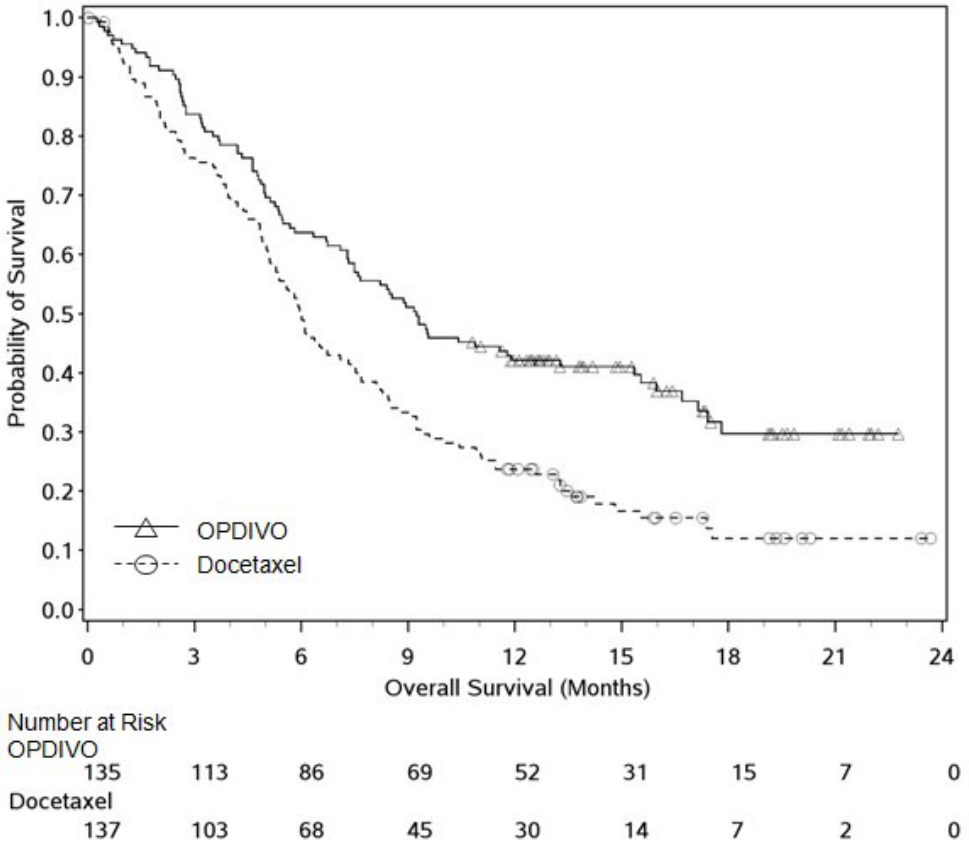
[a] Based on a stratified proportional hazards model.

[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 6: Overall Survival - Trial 2



Archival tumor specimens were retrospectively evaluated for PD-L1 expression. Across the study population, 17% (47/272) of patients had non-quantifiable results. Among the 225 patients with quantifiable results, 47% (106/225) had PD-L1 negative squamous NSCLC, defined as <1% of tumor cells expressing PD-L1, and 53% (119/225) 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 NSCLC subgroup.

Second-line Treatment of Metastatic Non-Squamous NSCLC

Trial 3 was a randomized (1:1), open-label study of 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 (n=292) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=290) administered intravenously at 75 mg/m^2 every 3 weeks. 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.

In Trial 3, the 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%).

Trial 3 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) (Table 17 and Figure 7).

Table 17: Efficacy Results in Trial 3

	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	
Objective 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	

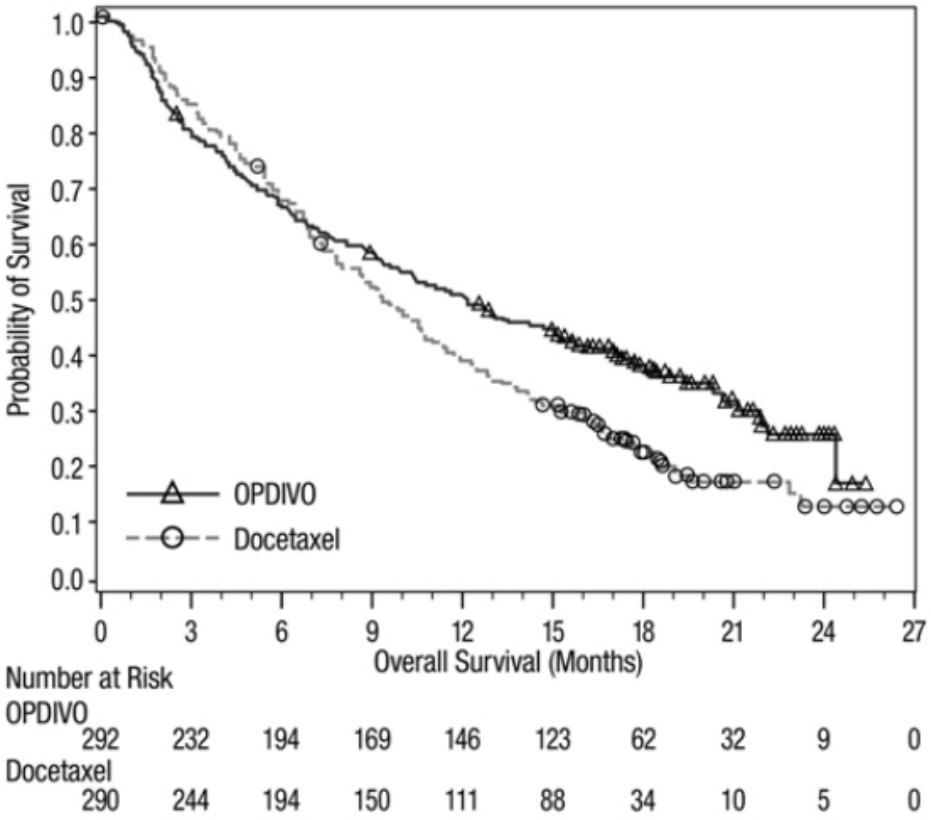
[a] Based on a stratified proportional hazards model.

[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 7: Overall Survival - Trial 3



Archival tumor specimens were evaluated for PD-L1 expression following completion of the trial. Across the study population, 22% (127/582) of 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% (209/455) PD-L1 negative, defined as <1% of tumor cells expressing PD-L1 and 54% (246/455) had PD-L1 expression, defined as ≥1% of tumor cells expressing PD-L1. Among the 246 patients with tumors expressing PD-L1, 26% (65/246) had ≥1%, but <5% tumor cells with positive staining, 7% (16/246) had ≥5% but <10% tumor cells with positive staining, and 67% (165/246) had greater than or equal to 10% tumor cells with positive staining. Figure 8 summarizes the results of prespecified analyses of survival in subgroups determined by percentage of tumor cells expressing PD-L1. Figure 9 summarizes the results of prespecified analyses of progression-free survival in subgroups determined by percentage of tumor cells expressing PD-L1.

Figure 8: Forest Plot: OS Based on PD-L1 Expression - Trial 3

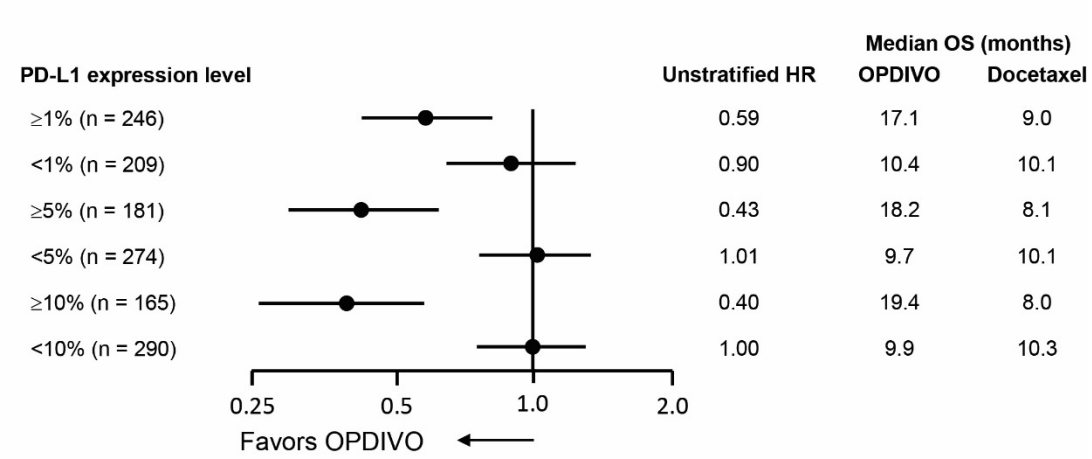
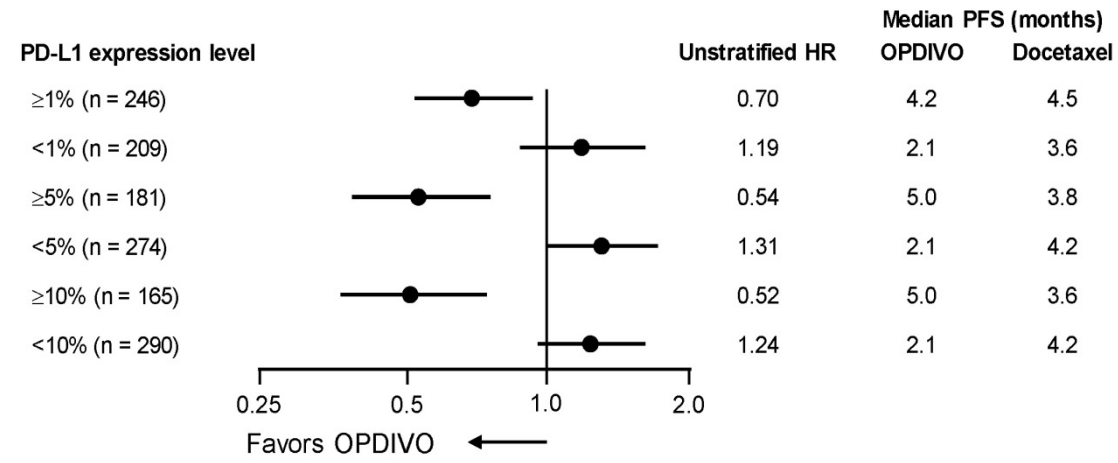


Figure 9: Forest Plot: PFS Based on PD-L1 Expression - Trial 3



14.3 Renal Cell Carcinoma

Trial 5 was a randomized (1:1), open-label study 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. Trial 5 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 to OPDIVO (n=410) administered intravenously at 3 mg/kg every 2 weeks or everolimus (n=411) administered orally 10 mg daily. The 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 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 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) (Table 18 and Figure 10). OS benefit was observed regardless of PD-L1 expression level.

Other endpoints include confirmed objective response rates, which are also presented in Table 18.

Table 18: Efficacy Results - Trial 5

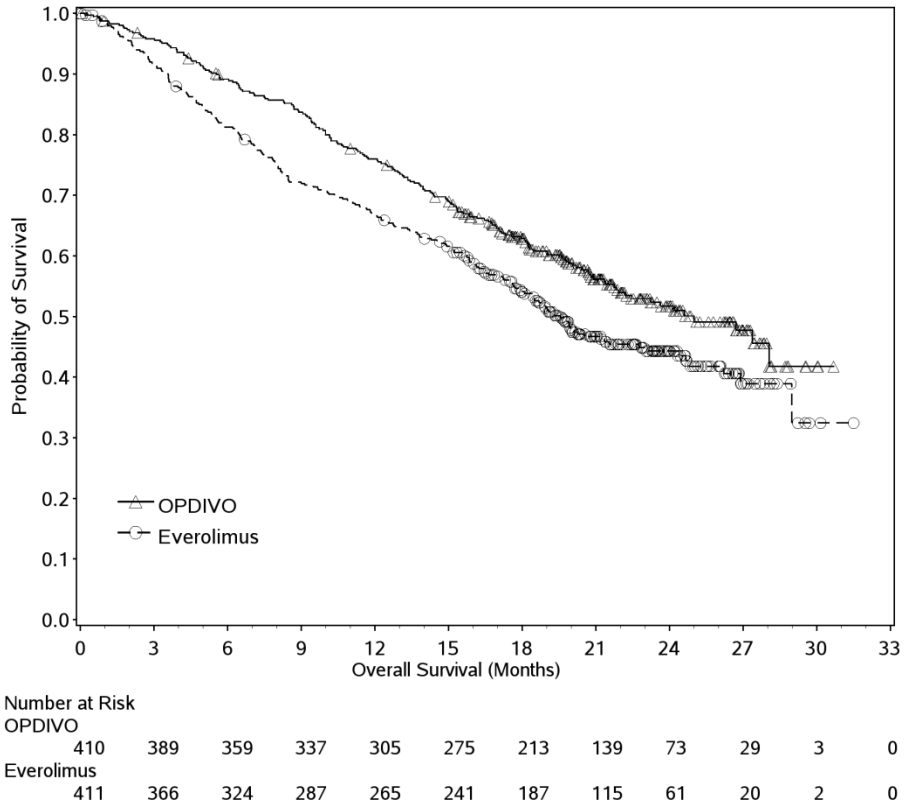
	OPDIVO (n=410)	**Everolimus (n=411)**
Overall Survival		
Deaths (%)	183 (45)	215 (52)
Median survival in months (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0018	
Confirmed Objective Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median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

[a] Based on a stratified proportional hazards model.

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

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

Figure 10: Overall Survival - Trial 5



14.4 Classical Hodgkin Lymphoma

Two studies evaluated the efficacy of OPDIVO as a single agent in patients with cHL after failure of autologous HSCT and post-transplantation brentuximab vedotin.

Trial 7 was a single-arm, open-label, multicenter, multicohort study in cHL. Trial 8 was an open-label, multicenter, dose escalation study 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 less than 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 3 mg/kg of OPDIVO administered intravenously over 60 minutes 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 objective response rate (ORR) as determined by an independent radiographic review committee (IRRC). Additional outcome measures included duration of response. Efficacy was evaluated in 95 patients in Trials 7 and 8 combined who had received brentuximab vedotin after failure of autologous HSCT. 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: 3 to 15).

Results are shown in Table 19. Patients received a median of 17 doses of OPDIVO (range 3 to 48), with a median duration of therapy of 8.3 months (range 1.9 to 24 months).

Table 19: Efficacy in cHL after Autologous HSCT and Brentuximab Vedotin

	Trial 7 and Trial 8 (n=95)
Objective Response Rate, n (%) [a] (95% CI)	62 (65%) (55, 75)
Complete Remission Rate (95% CI)	7 (7%) (3, 15)
Partial Remission Rate (95% CI)	55 (58%) (47, 68)
Median Duration of Response (months) (95% CI) Range	8.7 (6.8, NE) 0.0+, 23.1+
Median Time to Response (months) Range	2.1 0.7, 5.7

[a] Per 2007 revised International Working Group criteria.

14.5 Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Trial 9 was a randomized (2:1), active-controlled, open-label study 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 administered intravenously (IV) at 3 mg/kg every 2 weeks or investigator's choice of:

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

In Trial 9, total of 361 patients were randomized; 240 patients to OPDIVO and 121 patients to investigator's choice (45% received docetaxel, 43% received methotrexate, and 12% received cetuximab). The 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). The survival results are displayed in Table 22 and Figure 11. 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).

Table 22: Overall Survival in Trial 9

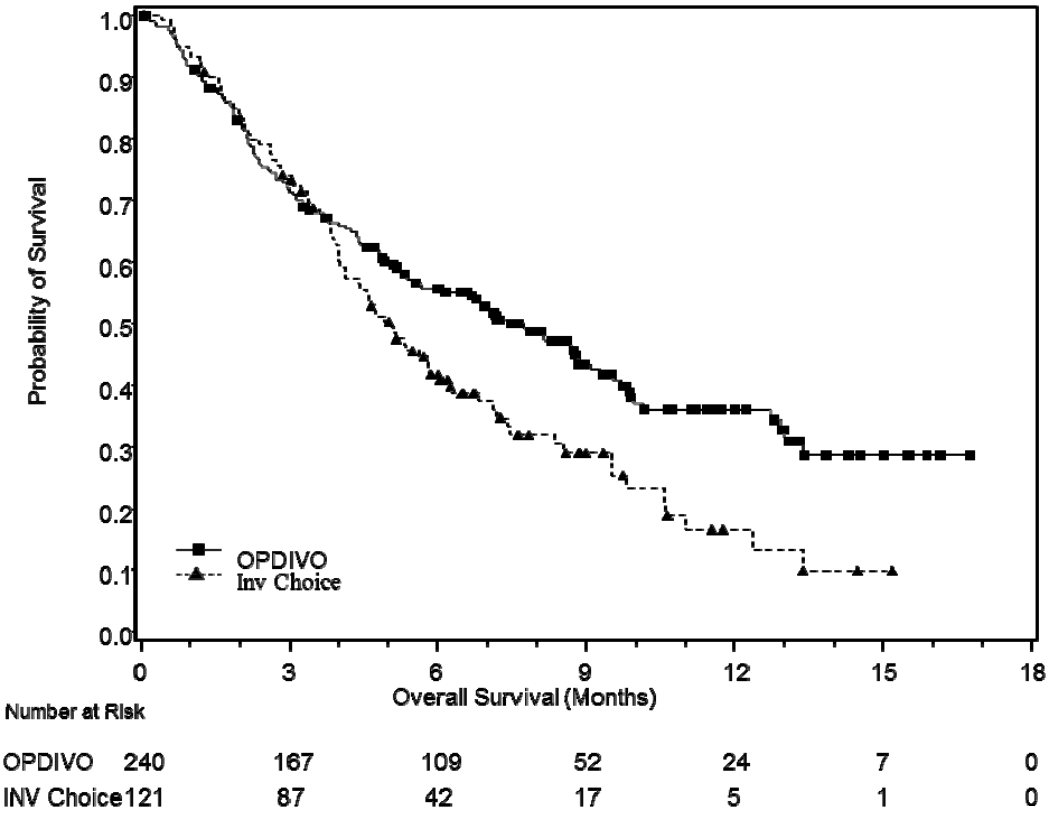
	OPDIVO (n=240)	**Investigator's Choice (n=121)**
Overall Survival		
Deaths (%)	133 (55%)	85 (70%)
Median (months) (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
Hazard ratio (95% CI)[a]	0.70 (0.53, 0.92)	
p-value[b,c]	0.0101	

[a] Based on stratified proportional hazards model.

[b] Based on stratified log-rank test.

[c] p-value is compared with 0.0227 of the allocated alpha for this interim analysis.

Figure 11: Overall Survival - Trial 9



Archival tumor specimens were retrospectively evaluated for PD-L1 expression using the PD-L1 IHC 28-8 pharmDx assay. Across the study 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) 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

Store OPDIVO under refrigeration at 2°C to 8°C (36°F to 46°F). Protect OPDIVO 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).

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 Reactions: Advise patients of the potential risk of infusion reaction *[see Warnings and Precautions (5.9)]*.
- Complications of allogeneic HSCT after OPDIVO: Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.10)]*.
- Females of Reproductive Potential: 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 of OPDIVO *[see Use in Specific Populations (8.3)]*.

- Lactation: Advise women not to breastfeed while taking OPDIVO *[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 your melanoma, lung cancer, kidney cancer, blood cancer, or head and neck cancer by working with your immune system. OPDIVO can cause your immune system to attack normal organs and tissues in many areas 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

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

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:

- **a type of skin cancer called melanoma that has spread or cannot be removed by surgery (advanced melanoma).** You may receive OPDIVO alone or in combination with ipilimumab.
- **a type of advanced stage lung cancer (called non-small cell lung cancer)**
  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.
- **kidney cancer (renal cell carcinoma)**
  - OPDIVO may be used when your cancer has spread or grown after treatment with other cancer medications.
- **a type of blood cancer that affects white blood cells known as lymphocytes (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 (Adcetris®) after your stem cell transplant.
- **head and neck cancer**
  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.

It is not known if OPDIVO is safe and effective in children less than 18 years of age.

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 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 60 minutes.
- OPDIVO is usually given every 2 weeks.
- When used in combination with ipilimumab, OPDIVO is usually given every 3 weeks, for a total of 4 doses. Ipilimumab will be given on the same day. After that, OPDIVO will be given alone every 2 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of OPDIVO?

OPDIVO can cause serious side effects, including:

- **See "What is the most important information I should know about OPDIVO?"**
- **Severe infusion reactions.** Tell your doctor or nurse right away if you get these symptoms during an infusion of OPDIVO:
  - chills or shaking
  - itching or rash
  - flushing
  - difficulty breathing
  - dizziness
  - fever
  - feeling like passing out
- **Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO.** 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
- pain in muscles, bones, and joints
- diarrhea
- cough
- constipation
- back pain
- fever
- rash
- itchy skin
- nausea
- shortness of breath
- decreased appetite
- upper respiratory tract infection
- weakness

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

- feeling tired
- diarrhea
- fever
- shortness of breath
- rash
- nausea
- vomiting

These are not all the possible side effects of OPDIVO. For more information, ask your healthcare provider or pharmacist. 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: November 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s022

SUMMARY REVIEW

Division Director Summary Review

Date	November 10, 2016
From	Patricia Keegan
Subject	Division Director Summary Review
BLA Supplement #	BLA 125554/S-022
Applicant Name	Bristol-Myers Squibb (BMS)
Date of Submission	May 11, 2016
PDUFA Goal Date	November 11, 2016
Proprietary Name / Established (USAN) Name	OPDIVO injection/ nivolumab
Dosage Forms / Strength	Injection/ 40 mg/mL and 100 mg/mL in single-dose vials
Proposed Indication(s)	(b) (4)
Approved Indication	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
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Meredith Libeg
Joint Clinical/Statistical Review	Barbara Scepura & Sirisha L. Mushti
Quality Review	Xianghong Jing
Clinical Pharmacology Review	Brian D. Furmanski & Hongshan Li
OPDP	Nicholas J. Senior
OSI	Lauren Iacono-Connors
Patient Labeling Team	Sharon R. Mills

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

Division Director Summary Review

1. Introduction

This efficacy supplement supports a new indication for nivolumab for the (b) (4) based on the results of a single trial, Study CA209141, also known as CheckMate141. Nivolumab was approved on December 22, 2014 and is currently approved for the following indications:

- The treatment, as a single agent, of patients with BRAF V600 wild-type unresectable or metastatic melanoma and of patients with BRAF V600 mutation-positive, unresectable or metastatic, melanoma;
- The treatment, in combination with ipilimumab, of patients with unresectable or metastatic melanoma;
- The treatment, as a single agent, of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy;
- The treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy; and
- The treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.

This supplement relies on the findings of safety and efficacy observed in Study CA209141, titled "An Open-Label, Randomized Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN)." The study design was an open-label, randomized (2:1), multicenter, clinical trial comparing the efficacy and safety of treatment with nivolumab to investigator's choice of chemotherapy for patients with unresectable or metastatic SCCHN with disease progression within 6 months of receiving platinum-based chemotherapy. Patients were randomized to receive nivolumab 3 mg/kg intravenously every 14 days or the investigator's choice among the following chemotherapy regimens: cetuximab, 400 mg/m^2 loading dose intravenously followed by 250 mg/m^2 intravenously every week; methotrexate 40 to 60 mg/m^2 intravenously every week; or docetaxel 30 to 40 mg/m^2 intravenously every week. Randomization was stratified by prior cetuximab treatment (yes/no). The primary efficacy endpoint was overall survival and the key secondary efficacy endpoints were progression-free survival and overall response rate.

The trial randomized 361 patients; 240 patients to OPDIVO and 121 patients to investigator's choice of chemotherapy (54 patients were to receive docetaxel, 52 patients were to receive methotrexate, and 15 patients were to receive cetuximab). The median age was 60 years; 83% were White, 12% Asian, and 4% were Black, 83% male; 78% had an ECOG performance status of 1 and 20% had an ECOG PS of 0; 76% were former/current smokers; 90% had Stage IV disease; and 55% received two or more prior lines of systemic therapy. For 51% of the

study population, the human papilloma virus (HPV) p16 status was unknown and of those with known status, approximately half were HPV p16 positive.

The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab [HR 0.70 (95% CI: 0.52, 0.92): p=0.0101 as compared with adjusted p-value of 0.0277 for the interim analysis] at the pre-specified interim analysis conducted at 78% of the planned number of events for final analysis. The median survival was 7.5 months for the nivolumab arm as compared with 5.1 months for the chemotherapy arm. There were no statistically significant differences between the two arms for progression-free survival [HR=0.89 (95% CI: 0.70, 1.13)] or ORR which was 13.3% (95% CI: 9.3, 18.3) in the nivolumab arm and 5.8% (95% CI: 2.4, 11.6) in the chemotherapy arm.

The toxicity profile of nivolumab is well-characterized across the cumulative clinical trial experience in 1994 patients receiving nivolumab as a single agent in eight clinical trials previously submitted and reviewed under this BLA or BLA 125527. The median duration of exposure to nivolumab was 1.9 months (range 1 day to 16.1+ months) among these 236 patients, with 42 (18%) patients exposed to nivolumab for > 6 months and 6 (2.5%) patients exposed to nivolumab for > 12 months. The most common adverse reactions of nivolumab observed in Study CA2090141, occurring at a higher incidence than in patients who received chemotherapy, were cough and dyspnea. The most common laboratory abnormalities of nivolumab, occurring at a higher incidence than in patients who received chemotherapy, were increased alkaline phosphatase, increased amylase, hypercalcemia, hyperkalemia, and increased TSH. There were no new serious safety signals identified in this trial.

All reviewers recommended approval of this supplement with agreed upon labeling. The major issue identified during review of this application was interpretation of data in an exploratory analysis of efficacy outcomes based on PD-L1 tumor status. This exploratory analysis was conducted in a convenience sample of 72% of the patients enrolled and the analytical performance of the assay (PD-L1 IHC 28-8 pharmDx assay) used for detection of PD-L1 tumor expression in this tumor has not been submitted to FDA. However, the exploratory results are consistent with the findings in squamous NSCLC, suggesting that PD-L1 tumor expression may be a predictive biomarker. In the exploratory analyses conducted in patients with a quantifiable PD-L1 result in Study CA209141, there was no apparent treatment effect on survival in the 57% of patients with PD-L1 negative SCCHN [HR 0.98, (95% CI: 0.54, 1.45)]. In addition, the data suggest that PD-L1 expression may be an adverse prognostic factor, with a median survival of 4.6 months among patients with PD-L1-positive SCCHN and 5.8 months among patients with PD-L1-negative SCCHN in the chemotherapy arm.

While the exploratory analysis based on PD-L1 expression (none vs. ≥ 1%) has been included in product labeling to inform prescribers, a post-marketing commitment to provide the analytic validation report for the assay used in this trial in support of a potential PMA supplement to identify this assay as a complementary diagnostic for nivolumab for the treatment of patients with SCCHN.

2. Background

Proposed Indication and Available Therapy

(b) (4)

is a serious disease. The American Cancer Society estimates that there will be 48,330 new cases of cancer of the oral cavity and pharynx and 13,430 new cases of cancer of the larynx diagnosed and approximately 9,570 deaths cancer of the oral cavity and pharynx and 3620 deaths due to cancer of the larynx in the United States in 2016.[1] The 5-year survival rates for SCCHN vary by the site of origin; however regardless of the primary site, the 5-year survival rate is less than 50% for all patients with metastatic disease.[2] In the Study CA209141, the median survival in the control arm was 5.1 months, reflecting the poor prognosis of patients within 6 months of receiving platinum-based chemotherapy.

Available therapy for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) previously treated with a platinum-based chemotherapy regimen include the following FDA-approved drugs:

Cetuximab was approved in 2006, as a single agent for the treatment of patients with recurrent or metastatic SCCHN who have progressed after platinum-based therapy. Approval was based on the results from a single-arm, multicenter clinical trial enrolling 103 patients who had documented disease progression within 30 days of a platinum-based chemotherapy regimen. The ORR was 13% (95% CI 7%, 21%) and the median duration of response was 5.8 months (range 1.2 - 5.8 months).[3] The reported median survival was approximately 4 months with a 1 year survival rate of < 5%.[4]

Docetaxel was approved on September 28, 2007, in combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). Approval was based on demonstration of an improvement in overall survival [HR 0.70 (95% CI: 0.54, 0.90): p=0.0058, log-rank test] for the 255 patients randomized to receive docetaxel in combination with cisplatin compared with the 246 patients randomized to receive cisplatin and fluorouracil. The median survival was 70.6 months in the docetaxel-containing arm compared with 30.1 months in the control arm. Docetaxel does not carry an approved indication for the treatment of patients with disease progression following platinum-based chemotherapy but is used off-label for this setting and is listed on the NCCN guidelines for this use.

Methotrexate was approved on August 10, 1959; it is approved for use as a single agent or in combination with other anticancer agents for the treatment of epidermoid cancers of the head

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[1] http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf.
[2] http://www.cancer net/cancer-types/head-and-neck-cancer/overview.
[3] http://www.accessdata fda.gov/drugsatfda_docs/label/2015/125084s262lbl.pdf
[4] Vermorken JB, Trigo J, Hitt R, et al. Open-Label, Uncontrolled, Multicenter Phase II Study to Evaluate the Efficacy and Toxicity of Cetuximab As a Single Agent in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Failed to Respond to Platinum-Based Therapy. JCO 2007:25:2171-77.

and neck. In a recently reported randomized, open-label clinical trial conducted in 483 adults histologically or cytologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, which had recurred or metastasized and were not amenable for salvage surgery or radiotherapy and with documented progression based on investigator assessment following ≥2 cycles of cisplatin or carboplatin for recurrent or metastatic disease, there was minimal treatment effect of methotrexate on overall response rate.[5] Patients were randomized (2:1) to afatinib 40 mg/day orally (n=322) or methotrexate 40 mg/m^2/week intravenously (n=161) until disease progression. Progression-free survival was the primary end point; overall survival (OS) was the key secondary end point. Other end points included: objective response rate (ORR), patient-reported outcomes, tumor shrinkage, and safety.

Progression-free survival, as assessed by independent review, was inferior in the methotrexate arm as compared to afatinib [hazard ratio (HR) 0·80 (95% CI 0·65–0·98); p=0·030], with median PFS of 2·6 months for the afatinib arm and 1.7 months for the methotrexate arm. There was no difference in the overall response rate per independent review between arms with response rates of 10% and 6% for afatinib and methotrexate respectively.

Bleomycin was approved on July 31, 1973 and had the following indication relevant to this application: **"**Bleomycin should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents: Squamous Cell Carcinoma- Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingivae, epiglottis, skin, and larynx), penis, cervix, and vulva. The response to bleomycin is poorer in patients with previously irradiated head and neck cancer."

Pembrolizumab was approved on August 5, 2016 under the provisions of 21 CFR 610.41 (accelerated approval) for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

NCCN Practice Guidelines: The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend treatment with systemic chemotherapy, enrollment in a clinical trial, or supportive care for patients with recurrent, unresectable or metastatic SCCHN. Agents listed in the NCCN guidelines include cisplatin, carboplatin, paclitaxel, docetaxel, 5-fluorouracil, methotrexate, cetuximab, gemcitabine, capecitabine, vinorelbine, and afatinib. Since patients in this clinical trial were required to have progressed within 6 months of a

[5] Machiels JP, Haddad RI, Fayette J, Licitra LF, Tahara M, Vermorken JB, Clement PM, Gauler T, Cupissol D, Grau JJ, Guigay J, Caponigro F, de Castro G Jr., de Souza Viana L, Keilholz U, Del Campo JM, Cong XJ, Ehmrooth E, Cohen EE. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol 2015 May;16(5):583-94. doi: 10.1016/S1470-2045(15)70124-5. Epub 2015 Apr 16.

platinum-containing regimen, such patients would generally considered platinum-insensitive and unlikely to benefit from cisplatin or carboplatin.

Pre-Submission Regulatory History

IND 100052 submitted for the investigation of nivolumab for treatment of advanced cancers

February 14, 2014: New clinical protocol, CA209141, submitted to IND 119382 to support an indication for the treatment of patients with SCCHN. During review of the initial IND, FDA raised concerns on March 20, 2014, regarding the study design, which was powered to detect a small difference in PFS that might not be clinically meaningful, lack of justification for not stratifying randomization based on HPV p-16 status as imbalances in HPV status between treatment arms could confound interpretation of study results; and lack of justification for cetuximab as an adequate control in patients who had previously received cetuximab.

April 3, 2014: FDA issued an Advice/Information Request letter regard Study CA209141, recommending that the primary analysis of progression-free survival (PFS) be assessed by an independent radiologic review committee and that any other analyses of PFS be considered sensitivity analyses. FDA also recommended that the interim analysis of overall survival (OS) and the final PFS analysis be conducted at the same time.

July 10, 2014: BMS modified the protocol for Study 209141 with regard to the interim analysis of survival. The interim analysis was to be performed 2 months after the end of accrual at which time it was projected that 75% of the required number of deaths would have occurred. In the modified protocol, the interim analysis was to be conducted "after 70% of events or 6 months after the end of accrual, whichever occurs earlier."

March 4, 2015: BMS submitted an amended protocol for Study CA209141 to the IND with major revisions, including increase in sample size and change from co-primary endpoints of PFS and OS to a primary endpoint of OS with PFS as a secondary endpoint.

August 18, 2015: Protocol amended with regard to the interim analysis plan for overall survival.

April 8, 2016: Type B, pre-sBLA meeting was held to discuss the content of the planned supplement. FDA requested that

- The supplement contain information for the 38 responders in Study CA209141, regarding DoR, PD-L1 status, HPV status, and site of initial disease for each patient in tabular format; and provide an analysis of interaction between PD-L1 status and HPVp16 status in Study CA209141.
- The safety information should include all adverse events leading to drug discontinuation, all grade laboratory abnormalities (nivolumab versus chemotherapy) and NCI CTCAE Grade 3 and 4 laboratory abnormalities, immunogenicity data, and provide\ patient narratives for all deaths in Study CA209141.

- FDA stated that revisions to the Warnings and Precautions section of the USPI would be required only for a new safety event was identified in the patient population for this proposed indication and that a 120-day safety update would not be required.
- Finally, the sBLA should contain BMS' justification with supporting data for not including E-R analysis in this population and patients with SCCHN treated with nivolumab. BMS noted that the analytic validation of the PD-L1 assay would not be available prior to submission of the sBLA. BMS proposed inclusion of data in Section 14 of the USPI based on these exploratory subgroup analyses based on PD-L1 expression by central testing. FDA stated whether these data could be included in the USPI in advance of the validation data for the complimentary diagnostic would be a review issue. If FDA required a companion diagnostic, than a contemporaneous approval of the assay would be required.

April 20, 2016: A teleconference was held between BMS and FDA. BMS requested the teleconference to inform FDA of inconsistencies between tumor measurement data and the Investigator determined best overall response (BOR), date of response, and date of progressive disease (PD) identified in the database for Study CA209141. The discrepancies affected patients in both treatment arms though the absolute number of such discrepancies was higher in the nivolumab arm due to the 2:1 randomization ratio. Based on resolution of the inconsistencies through data queries and audits, BMS generated a new database for efficacy with a data lock of May 5, 2016 to be provided in the planned sBLA. FDA requested that BMS provide listing of PFS, ORR, and DOR for the 33 patients with the discrepancies and a listing of the 30 sites affected and how many had inconsistencies via email and formally to the IND. Upon receipt of the information, FDA will communicate how best to proceed with the sBLA in response to the BMS proposal. In subsequent emails on April 20, 2016, BMS confirmed that the clinical study report (CSR) and Summary Documents to be provided in the sBLA would contain summaries of PFS, ORR and DoR based on the earlier dataset.

April 22, 2016: A Breakthrough Therapy Designation letter was issued for nivolumab for "for the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).

April 29, 2016: The information provided by email prior to the April 20, 2016 teleconference and requested by FDA during the April 20, 2016, teleconference, were submitted to IND 119382.

3. CMC

BMS' request for categorical exclusion from the environmental assessment, pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, as provided in 21 CFR 25.31(c) for an action on a BLA supplement, is accepted. No other CMC information was included in this supplement.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Pharmacogenomics

I concur with the conclusions reached by the clinical pharmacology/pharmacogenomics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

The supplement contained the results of a population PK (PopPK) analysis characterizing nivolumab exposure when administered at 3 mg/kg every 2 weeks in Study CA209141 and comparing the results to a pooled analysis including 1035 patients enrolled across 6 studies (including CA209141). In Study CA209141, blood samples for PK and immunogenicity assessment were collected pre-dose on Day 1 of Cycles 1 (week 1), 5 (week 9), 13 (week 25) and every 16 weeks (every 8 cycles) until discontinuation of nivolumab. This analysis showed that exposure and clearance of nivolumab in patients with SCCHN were comparable to patients with other primary tumors. Exposure-response analyses were not conducted; BMS' rational is that Study CA209141 evaluated only on dose level. Based on lack of this data, the clinical pharmacology reviewer could not evaluate whether a fixed dose would be appropriate for treatment of patients with SCCHN.

The application also contained an updated, pooled analysis of the incidence and clinical effects of anti-drug antibody (ADA) development in patients with SCCHN and in a pooled analysis across multiple tumors. The incidence of treatment-emergent ADA in nivolumab-treated patients in Study CA209141 was 8.8%, which was similar to that observed in other cancers. Based on assessment of the data, the reviewer concluded that there is no evidence that the development of ADA either leads to clinically important effects on the pharmacokinetic profile of nivolumab or results in increased toxicity.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Clinical Study Design

Title: Protocol CA209141: "An Open-Label, Randomized Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN)"

Design: The trial was a randomized (2:1), multicenter, active-controlled, open-label study.

Key eligibility criteria were adults with metastatic or recurrent SCCHN; 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; and in patients with known CNS metastases, neurologically stable following CNS-directed treatment. Patients with autoimmune disease or medical conditions requiring immunosuppression; recurrent or metastatic carcinoma of the nasopharynx; squamous cell carcinoma of unknown primary; salivary gland or non-squamous histologies (e.g., mucosal melanoma); and untreated brain metastasis were ineligible.

Treatment plan: Patients were randomized to receive nivolumab or chemotherapy according to the following treatment regimens.

- Nivolumab 3 mg/kg intravenously (IV) every 2 weeks
  OR
- Investigator's choice of one of the following chemotherapy regimens:
  - cetuximab 400 mg/m^2 loading dose IV followed by 250 mg/m^2 weekly
  - methotrexate 40 to 60 mg/m^2 IV weekly
  - docetaxel 30 to 40 mg/m^2 IV weekly

Randomization was stratified by prior cetuximab treatment (yes/no).

Tumor assessments were conducted at baseline, week 9 following randomization, then every 6 weeks thereafter.

In the final version of the protocol, the primary efficacy endpoint was overall survival and the key secondary efficacy endpoints were progression-free survival and overall response rate.

Statistical analysis plan: The analysis plan in the final version of the protocol specified a sample size of 360 patients to observe the 278 deaths required to detect a hazard ratio of 0.667 for overall survival, corresponding to median OS of 6 months in the control arm and 9 months in the nivolumab arm, with 90% at a 2-sided alpha level of 0.05. The primary analysis method for both OS and PFS will be the two-sided stratified log-rank test, stratifying by prior cetuximab use. The primary analysis of ORR was to be performed using a Cochran-Mantel Haenszel (CMH) test stratified by prior cetuximab therapy (yes/no) with the results presented as the observed point estimates of ORR and corresponding 95% exact two-sided confidence intervals. Exploratory analyses were to be conducted in subgroups defined by HPV p16 status in oropharyngeal primary cancers and PD-L1 tumor expression (none vs. ≥1% tumor expression).

One formal interim analysis of overall survival was to be conducted after 195 deaths (70% of the events required for the final analysis. The stopping boundaries for the interim and final analyses were planned to be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries, controlling for an experiment wise type-I error at 5%.

The overall alpha level of 0.05, two-sided, for testing of secondary endpoints was to be controlled using a gatekeeping testing approach, with PFS tested first and then ORR.

Data Integrity: Two clinical sites, which randomized 36 and 10 patients, respectively, were selected for BioResearch Monitoring inspections by FDA. During the audit, the results for the primary endpoint (overall survival), the key secondary endpoint (progression-free survival), and adverse events were verified against source records generated at the inspected clinical sites for a subset of those enrolled. No significant deficiencies were identified and the data appear reliable in support of this efficacy supplement.

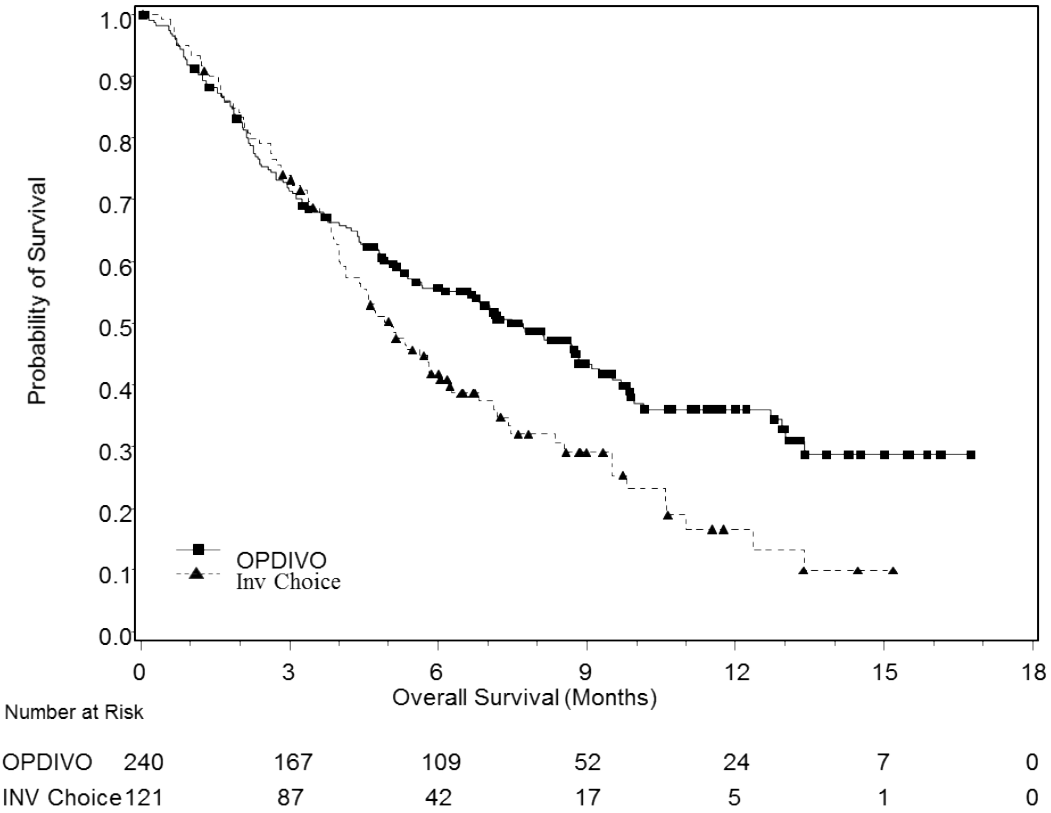
Efficacy Results

Study CA209141 was conducted across 15 countries; 40% of the study population was enrolled in the U.S. The first patient visit occurred on May 29, 2014 and the last patient was randomized on August 28, 2015. On January 29, 2016, the Data Monitoring Committee (DMC) conducted an interim analysis of overall survival that included 218 deaths. The DMC recommended termination of the trial based on evidence of an improvement in survival in this analysis.

There were 361 patients were enrolled and randomized; 240 patients were randomized to nivolumab and 121 patients were randomized to investigator's choice (45% received docetaxel, 43% received methotrexate, and 12% received cetuximab). The 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 nivolumab [HR 0.70 (95% CI: 0.52, 0.92): p=0.0101 as compared with adjusted p-value of 0.0277 for the interim analysis] at the pre-specified interim analysis conducted at 78% of the planned number of events for final analysis. The median survival was 7.5 months for the nivolumab arm as compared with 5.1 months for the chemotherapy arm. There were no statistically significant differences between the two arms for progression-free survival [HR=0.89 (95% CI: 0.70, 1.13)] or ORR which was 13.3% (95% CI: 9.3, 18.3) in the nivolumab arm and 5.8% (95% CI: 2.4, 11.6) in the chemotherapy arm.

Overall Survival

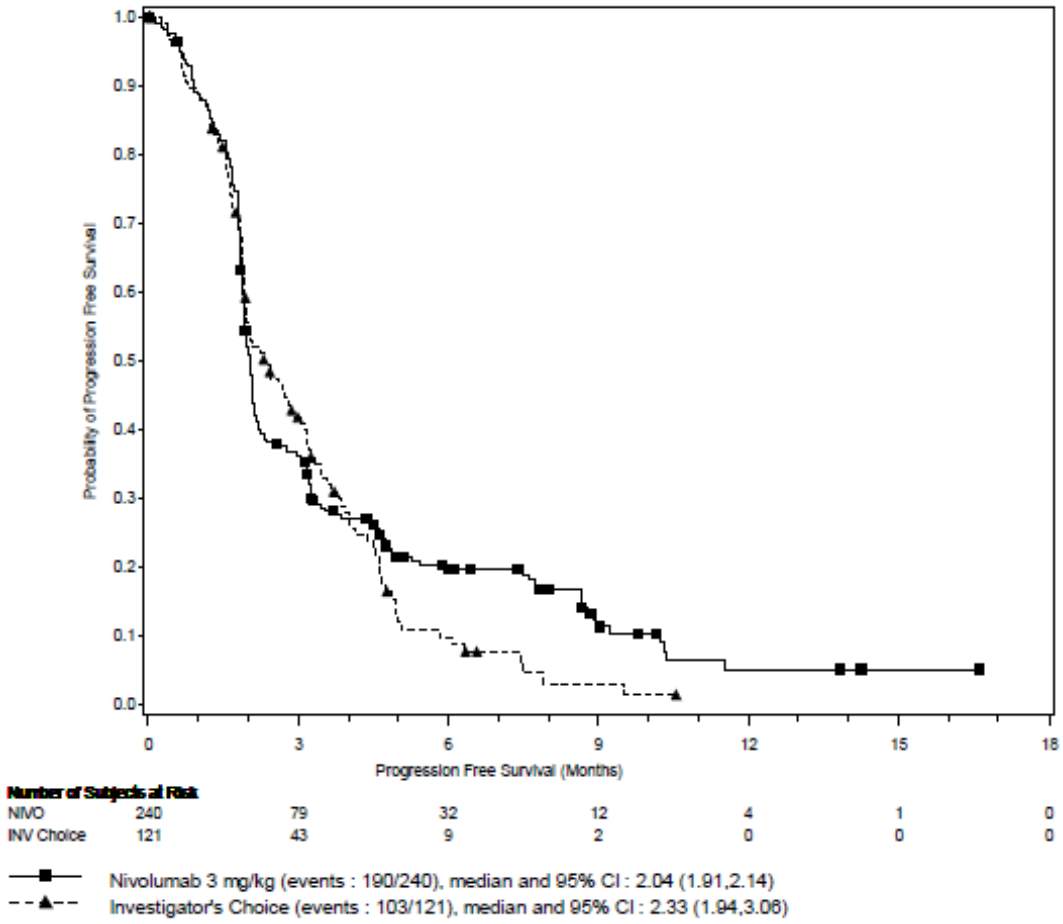


Number at Risk

OPDIVO	240	167	109	52	24	7	0
INV Choice	121	87	42	17	5	1	0

Because the analysis of PFS was not significant, there was no formal comparison of ORR between arms. The Kaplan-Meier curve for PFS, abstracted from the clinical/statistical review, is presented below.

Progression-Free Survival



Approximately 28% (101/361) of the patients randomized in Study CA209141 had non-quantifiable results for PD-L1 tumor expression. Among the 260 patients with quantifiable results as determined by the PD-L1 IHC 28-8 pharmDx assay, 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 one of several pre-specified exploratory subgroup analysis based on PD-L1 tumor status (using cut-points of ≥1%, ≥5%, and ≥10% PD-L1 SCCHN expression, the treatment effect on survival appeared to be greater in those with PD-L1-positive SCCHN as compared to the overall study population and there appeared to be no effect in those with PD-L1-negative SCCHN. 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.

8. Safety

Size of the database
There were no concerns regarding the size of the safety database for this supplement, with 236 nivolumab-treated patients, since safety was well-characterized across the cumulative clinical trial experience in 1994 patients receiving nivolumab as a single agent in eight clinical trials previously submitted and reviewed under this BLA or BLA 125527. Twenty-eight percent of the nivolumab-treated patients were ≥65 years of age. Across the study population, Baseline ECOG performance status was 0 in 20% of patients and ECOG PS was 1 in 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. As with previous trials, Study CA209141 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression. There were no new serious safety signals identified in Study CA209141. Therefore, while the common adverse reactions and laboratory abnormalities were described in Section 6 of product labeling, the Warnings and Precautions section was not updated.

The safety of nivolumab in Study CA209141 was based on adverse events reported in the 236 patients receiving at least one dose of nivolumab, at 3 mg/kg intravenously (IV) over 60 minutes every 2 weeks with patients receiving at least one dose of investigator's choice of cetuximab (n=13), methotrexate (n=46), or docetaxel (n=52) according to the treatment regimens described in Section 7 of this summary review.

The median duration of exposure to nivolumab was 1.9 months (range 1 day to 16.1+ months) among these 236 patients, with 42 (18%) patients exposed to nivolumab for > 6 months and 6 (2.5%) patients exposed to nivolumab for > 12 months. The most common adverse reactions of nivolumab observed in Study CA2090141, occurring at a higher incidence than in patients who received chemotherapy, were cough and dyspnea. The most common laboratory abnormalities of nivolumab, occurring at a higher incidence than in patients who received chemotherapy, were increased alkaline phosphatase, increased amylase, hypercalcemia, hyperkalemia, and increased TSH.

Major safety concerns related to labeling
Nivolumab was discontinued in 14% of patients and was delayed in 24% of patients for an adverse reaction. Serious adverse reactions occurred in 49% of patients receiving nivolumab. The most frequent serious adverse reactions reported in at least 2% of patients receiving nivolumab were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis.

Postmarketing data
The clinical reviewer evaluated the six Periodic Adverse Drug Experience Reports (PADER) for nivolumab generated since the drug was first approved and confirmed that all serious adverse reactions identified in this reports have been previously included in product labeling under earlier supplements.

REMS
I concur with the recommendations of the clinical reviewer that risk evaluation and mitigation strategies (REMS) are not required to ensure safe use of nivolumab for this patient population with a serious, life-threatening disease. Product labeling and the Medication Guide provide sufficient information for prescribers and patients to mitigate the serious risks of nivolumab.

PMRs and PMCs
There were no new serious risks identified in this efficacy supplement; therefore no PMRs were required under the provisions of 505(o).

Based on the exploratory analyses conducted by FDA and BMS, there appears to be correlation between presence of PD-L1 tumor expression and treatment outcomes on survival. To further explore this correlation, FDA requested (and BMS agreed to) a post-marketing commitment to perform analytic validation on the assay used to assess PD-L1 tumor expression in CheckMate-0141 in support of its use as a complementary diagnostic assay.

9. Advisory Committee Meeting

This efficacy supplement was not referred for review to the Oncologic Drugs Advisory Committee because this drug is not the first in its class, the safety profile is acceptable for the proposed indication, the clinical trial design is acceptable, and evaluation of the safety data did not raise significant safety concerns for the intended population. Therefore, outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

On September 28, 2016, the Pediatric Review Committee (PeRC) reviewed Merck's request for waiver of the requirements of the Pediatric Research Equity Act (PREA) submitted under sBLA 125554/S-022 for (b) (4) The PeRC agreed with the recommendation of the clinical review Division (DOP2) to grant a full waiver because the disease/condition does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Physician labeling
  - Indications and Usage: the proposed indication was revised (b) (4)
  - Dosage and Administration: revised to include the dosage regimen of nivolumab investigated in Study CA209141. BMS did not provide the results of exposure-response analyses in this supplement, thus there was insufficient information to support a fixed dosing regimen for this patient population.
  - Warnings and Precautions: There were no new safety signals identified in Study CA209141. Given the large database already evaluated for serious adverse reactions of nivolumab, these general risks have been adequately characterized and this section was not updated to include results from CA209141 which would not have altered the current description of serious adverse reactions in a meaningful way.
  - Adverse Reactions: This section was updated to include the safety results from Study CA209141 based on clinical events and laboratory abnormalities in text and removed BMS' proposed (b) (4) . In addition, the summary of the safety population was amended to describe population based on prior treatment and noted that patients had progressed " (b) (4) or within 6 months of receiving" platinum-based therapy. The Immunogenicity subsection (6.2) was updated to include additional information on the rate and clinical impact of ADA development in patients with SCCHN.
  - Use in Specific Populations: The Geriatrics Use subsection (8.5) was updated to note that there were insufficient numbers of patients aged ≥65 years or older to assess for differences between younger and older patients based on the population studied in CA209141.
  - Clinical Studies: Modified to include results of Study CA209141. BMS agreed to FDA's proposal to include full breakdown of HPV p16 testing, a summary of the secondary efficacy endpoint comparisons and description of exploratory analyses by PD-L1 status using the ≥1% cut-point.

- Medication guide: Revised to include a description of the new indication.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  Squamous cell carcinoma of the head and neck (SCCHN) is a serious and life-threatening disease, with 5-year survival rates of less than 50% for all patients with metastatic disease. In Study CA209141, the median survival in the control arm was 5.1 months. There are no satisfactory therapies for patients with metastatic SCCHN, consisting of single agent

chemotherapy (e.g., docetaxel, methotrexate, cetuximab, and bleomycin) with low response rates and no evidence of effects on overall survival.

Study CA209141 was a randomized, international, active-controlled trial which demonstrated a statistically significant improvement in overall survival among patients randomized to nivolumab [HR 0.70 (95% CI: 0.52, 0.92): p=0.0101 as compared with adjusted p-value of 0.0277 for the interim analysis] at a pre-specified interim analysis. This treatment effect corresponds to a 2.4-month improvement in median survival, with a median survival of 7.5 months for the nivolumab arm and 5.1 months for the chemotherapy arm. There were no statistically significant differences between the two arms for progression-free survival [HR=0.89 (95% CI: 0.70, 1.13)] or ORR which was 13.3% (95% CI: 9.3, 18.3) in the nivolumab arm and 5.8% (95% CI: 2.4, 11.6) in the chemotherapy arm.

The toxicity of nivolumab is due to its mechanism of action with development of autoimmune disease. As with prior approvals in other tumor types, the risks of autoimmune disease with nivolumab the occur in a minority of patients (≤ 10%) is acceptable given the ability to manage these risks in most cases with discontinuation of nivolumab and intensive immunosuppression and the serious and life-threatening nature of the disease with no satisfactory alternatives. While serious adverse reactions occurred in 49% of patients receiving nivolumab, there was no dominant organ site of involvement for autoimmune disease. The most frequent serious adverse reactions reported in at least 2% of patients receiving nivolumab were pneumonia, dyspnea, respiratory failure, respiratory tract infection, and sepsis, which may also represent disease progression and no new safety signals were identified in this clinical trial. Of note, evidence of improved survival is also a measure of safety and indicates that toxicity of the drug did not outweigh its clinical benefit for this population with a serious and life-threatening disease with unmet medical needs.

Based on the demonstrated improvement in survival and in light of the serious nature of the disease, I agree with the review team that the supplement should be approved based on its favorable risk: benefit assessment.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  On August 5, 2015, the Pediatric Review Committee (PeRC) reviewed Merck's request for waiver of the requirements of the Pediatric Research Equity Act (PREA) for non-small cell lung cancer submitted under sBLA 125514/S-005. The PeRC agreed with the recommendation of the clinical review Division (DOP2) to grant a full waiver because the disease/condition does not exist in pediatric patients.

- Recommendation for other Postmarketing Requirements and Commitments
  There were no new serious risks identified in this efficacy supplement; therefore no PMRs were required under the provisions of 505(o).

  Based on the exploratory analyses conducted by FDA and BMS, there appears to be correlation between presence of PD-L1 tumor expression and treatment outcomes on

survival. To further explore this correlation, FDA requested (and BMS agreed to) a post-marketing commitment to perform analytic validation on the assay used to assess PD-L1 tumor expression in CheckMate-0141 in support of its use as a complementary diagnostic assay.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
11/10/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s022

OFFICER/EMPLOYEE LIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 10, 2016

From: Meredith Libeg, B.S., Senior Regulatory Health Project Manager

Subject: ***BLA 125554/S-022 – OPDIVO (nivolumab injection for intravenous infusion)***
Officer / Employee List

The following lists the officers / employees who participated in the decision to approve this application and consented to be identified on this list:

Officer / Employee
Blumenthal, Gideon
Donoghue, Martha
Furmanski, Brian
He, Kun
Hughes, Monica L
Keegan, Patricia
Libeg, Meredith
Mushti, Sirisha
Scepura, Barbara
Senior, Nicholas
Sridhara, Rajeshwari
Summers, Jeff
Thompson, Susan
Yu, Jingyu

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s022

MEDICAL REVIEW(S)

Application Type	sBLA
Application Number(s)	BLA125554
Priority or Standard	Priority
Submit Date(s)	5/11/2016
Received Date(s)	5/11/2016
PDUFA Goal Date	11/11/2016
Division/Office	OHOP/DOP2
Reviewer Name(s)	Barb Scepura, Clinical Sirisha Mushti, Statistical
Review Completion Date	10/17/2016
Established Name	Nivolumab
(Proposed) Trade Name	Opdivo
Applicant	Bristol-Myers Squibb Company
Formulation(s)	BMS-936558 (nivolumab) for intravenous infusion
Dosing Regimen	3 mg/kg IV every 2 weeks
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(b) (4)

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRAF	mutation associated with melanoma
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
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HPV-16	human papilloma virus-16
IC	Investigator's choice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenously
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
NSCLC	non-small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PD	progressive disease
PD-1	programmed death - 1
PD-L1	programmed death ligand -1
PFS	progression free survival
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
SSCHN	squamous cell carcinoma of the head and neck
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

2 Executive Summary

Purpose statement: This streamlined review evaluates the risk and benefit of nivolumab in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) after progression on platinum-based chemotherapy from a clinical and statistical perspective, to justify broadening the indication.

1.1 Product Introduction

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

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.
- BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- Unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- 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 nivolumab.
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy.
- Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. This indication is approved under accelerated approval based on overall response rate. 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

This sBLA is supported by the results of Check Mate 141, an open label, randomized clinical trial of nivolumab versus Investigator's Choice (IC) of chemotherapy (cetuximab, methotrexate, or docetaxel) in patients with metastatic platinum-refractory SCCHN. Check Mate 141 demonstrated a statistically significant and clinically meaningful treatment benefit in overall survival (OS) for nivolumab over IC. For more details, please see sections 1.3, and 6.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The basis for this sBLA was study CA209141, CheckMate 141, which enrolled 361 patients with stage III/IV histologically confirmed SCCHN (oral cavity, pharynx, larynx) with tumor progression or recurrence on or within 6 months of the last dose of platinum therapy in the adjuvant (i.e., with radiation after surgery), primary (i.e., with radiation), recurrent, or metastatic setting. CheckMate 141 was a prospective, multicenter, multinational, randomized (2:1) open-label study comparing nivolumab to Investigator's Choice (IC) therapy (cetuximab, methotrexate, or docetaxel). The only randomization stratification factor was prior cetuximab. The primary endpoint of the study was overall survival (OS). Patients were included regardless of HPV status or PD-L1 status.

The trial demonstrated a statistically significant and clinically meaningful improvement in overall survival in favor of the nivolumab arm with a HR of 0.7 [95% CI: (0.51, 0.96); p=0.0101 based on stratified log-rank test]. Median OS was 7.5 months [95% CI= (5.5, 9.1)] in the nivolumab arm and 5.1 months [95% CI= (4, 6.1)] for IC.

There were fewer deaths on the nivolumab arm (56%) compared to IC (70%). The most common cause of death on both study arms was disease progression. All cause, any grade adverse events (AEs) occurred at similar rates on both study arms, but there were more grade 3-4 AEs on the IC arm (52.3%) compared to nivolumab (41.1%). The grade 3-4 AEs occurring in >5% of the patients on the nivolumab arm were dyspnea (5.5% vs. 1.8%) and anemia (5.9% vs. 8.1%). The only grade 5 event occurring in >1% of patients was malignant neoplasm progression (16.1% vs. 20.7%). There were fewer treatment discontinuations on the nivolumab arm compared to IC (21.6% vs. 24.3%). AEs specific to nivolumab are immune mediated AEs. The incidence of immune mediated AEs were less than 1% on nivolumab, with the exception of rash (5.1% vs. 4.5%), hypothyroidism (8.1% vs. 5.4%) and hyperthyroidism (1.3% vs. 0). There were no cases of immune mediated nephritis, renal dysfunction, encephalitis or diabetes mellitus reported in this study.

The principle strength of this application is the use of a well-designed randomized trial with an objective and clinically meaningful primary endpoint (OS). The weakness of this application is that the study failed to show statistical significance in the secondary endpoint of progression-free survival (PFS). However, PFS may not be a reliable endpoint for testing the efficacy of immune checkpoint inhibitors as has been observed in other diseases (e.g. NSCLC)

Recommendation: Approval of nivolumab for use in the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after progression on platinum-based chemotherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer world-wide[6]. The main risk factors for cancers of the oropharynx are smoking, alcohol consumption, and infection with the human papilloma virus-16 (HPV-p16). Approximately 40% of patients are initially diagnosed with metastatic disease, and a have poor prognosis. The 5- year survival rate is 6.5% despite treatment with chemo and radiation therapies).[1,5]	SSCHN is a prevalent and life threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	The most commonly used second-line treatments for recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) include single-agent methotrexate, cetuximab, and docetaxel. Pembrolizumab received accelerated approval on August 5, for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. Median OS with these treatments ranges from 4 to less than 7 months. Response rates seen with these treatments range from 4-16%.	There are few treatment options for patients with recurrent or metastatic SCCHN. The existing treatments offer limited benefit.
Benefit	The efficacy of nivolumab for the treatment of patients with recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck was demonstrated in one Phase 3 study, CA209141. CA209141 was a prospective, multicenter, multinational, randomized (2:1), open-label, parallel-arm study of nivolumab versus investigator's choice(IC) of therapy. The efficacy analyses of CA209141 were based on the ITT population, which consisted of 361 patients (240 in Nivolumab arm and 121 in IC arm). At the time of the data cutoff date for this analysis done on December 18, 2015, 133 patients (55%) in the nivolumab arm and 85 patients (70%) in the IC arm had died. The primary endpoint of OS from randomization was met. Estimated median OS was 7.5 months in the nivolumab arm and 5.1 months in the IC arm, with a HR of 0.7 [95% CI: 0.51, 0.96; p-value = 0.0101]. The median survival time was increased by 2.4 months in patients randomized to nivolumab. The secondary endpoint of PFS did not demonstrate superiority of nivolumab [HR = 0.89, 95% CI (0.70; 1.13); p-value = 0.3236] compared with IC. The ORR was not tested for significance according to the hierarchical testing strategy. Response rate was 13.3% vs. 5.8% for the nivolumab and IC arms respectively; there were 6 complete responses and 26 partial responses in the nivolumab arm; in the IC arm only one patient experienced a CR and 6	CA 209141 was a well conducted study that demonstrated a modest survival benefit of nivolumab for treating patients with recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck. The study failed to demonstrate superiority in the key secondary endpoint of PFS and the response rates were analyzed descriptively only.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients experienced a PR.	
Risk	The safety analysis was based on the safety population of the CheckMate 141 study (236 patients on the nivolumab arm, and 111 patients on the IC arm). There were fewer deaths on the nivolumab arm (56%) compared to IC (70%). The most common cause of death on both arms was disease progression. There were slightly more deaths within 30 days of the last dose of nivolumab (21%) compared to IC (19%), but fewer deaths within 100 days of last dose on nivolumab (44%) compared to IC (51%). All cause, any grade AE occurred at similar rates on both study arms. On the nivolumab arm, 97% of patients had an AE compared to IC with 98.2% of patients having an AE. All cause, grade 3-4 AEs were higher on the IC arm (52.3%) compared to nivolumab (41.1%). The grade 3-4 AEs occurring in >5% of the patients on the nivolumab arm are: dyspnea (5.5% vs. 1.8%) and anemia (5.9% vs. 8.1%). There were fewer treatment discontinuations on the nivolumab arm (21.6% vs. 24.3%). Nivolumab is labeled as having the potential to cause immune mediated AEs. All grade immune mediated AEs requiring treatment with an immune modulation medication were diarrhea / colitis 0.8% on nivolumab, 0 on IC, hepatitis 0.4% on nivolumab, 0 on IC , pneumonitis 0.8% on nivolumab, 0.9% on IC, rash 5.1% on nivolumab, 4.5% on IC, and hypersensitivity reactions 0.8% on nivolumab, and 0.9% on IC. Nivolumab is labeled as potentially causing immune-mediated endocrinopathies, and these AEs were higher on the nivolumab arm compared to IC. The incidence of immune mediated AEs were less than 1%, with the exception of rash (5.1% vs. 4.5%), hypothyroidism (8.1% vs. 5.4%) and hyperthyroidism (1.3% vs. 0). There were no cases of immune mediated nephritis, renal dysfunction, encephalitis or diabetes mellitus reported in this study.	Overall, there were fewer deaths on the nivolumab arm and fewer adverse events on the nivolumab arm compared to the IC arm, with the exception of immune mediated adverse events and endocrinopathies. The incidence of immune mediated AEs in this study was relatively low, and poses a reasonable risk for patients with SCCHN.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	The risks of nivolumab use in the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) will be communicated through product labeling. Nivolumab will be administered by oncologists who have specialized training in the administration of anti-neoplastic drugs and in the management of toxicities related to these drugs.	The risks of nivolumab can be mitigated via product labeling and administration of the drug in specialized settings where screening for immune mediated adverse events will be performed.

2 Therapeutic Context

2.1 Analysis of Condition

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer world-wide[5.] The main risk factors for cancers of the oropharynx are smoking, alcohol consumption, and infection with the human papilloma virus-16 (HPV-16). Approximately 40% of patients are initially diagnosed with metastatic disease, and a have poor prognosis. The 5-year survival rate for patients with metastatic disease is 6.5% despite treatment with chemo- and radiation therapies[1,4.]

According to the Surveillance, Epidemiology and End Results program (SEER), the number of new cases of oral cavity and pharynx cancer was 11.1 per 100,000 men and women per year. The number of age-adjusted deaths for 2009-2013 was 2.4 per 100,000 men and women per year[8].

2.2 Analysis of Current Treatment Options

The National Comprehensive Cancer Network (NCCN) guidelines state that the preferred treatment for early stage SCCHN is surgical resection. Adjuvant treatment for presumed or known residual disease is either radiation alone or concurrent radiation with cisplatin chemotherapy (chemoRT). Patients who have disease recurrence after completing their first line treatment, or were diagnosed with metastatic SCCHN and were not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) were included in the CheckMate 141 study.

The most commonly used treatments for recurrent or metastatic SCCHN include single-agent methotrexate, cetuximab, docetaxel, and pembrolizumab. Pembrolizumab was granted accelerated approval in August 2016. Please see Table 1 for approved and standard treatments.

Table 1 Approved / standard of care therapies for the treatment of recurrent / metastatic SCCHN

Approved / standard of care therapies	Study Design	Median OS months	ORR (%)	Dosing and Schedule
Methotrexate*	Randomized vs. afatinib[6] vs. gefitinib[10]	 6.0 6.7	 5.6 3.9	Methotrexate 40 mg/m2 IV push weekly, may be increased to 60 mg/m2 if tolerated, treatment until progression
Cetuximab	Single arm 103 patients[a,11]	5.7	13	Cetuximab 400 mg/m2 IV once then 250 mg/m2 weekly, treatment until progression
Docetaxel**	Single arm 20 patients[b, 12] Single arm 23 patients[2]	4.6 6.7	10 13	Docetaxel 30 mg/m2 IV weekly, may be increased to 40 mg/m2 if tolerated, treatment until progression
Pembrolizumab Accelerated Approval August 2016	Single arm 192 patients	Not reached	16	Pembrolizumab 10 mg/kg every 2 weeks in patients enriched for PD ligand 1 (PD-L1) expression

[a] PD within 30 days of platinum-based regimen
[b] PD within 6 months of platinum-based regimen
* Not FDA approved for this indication.
** Not FDA approved as single agent.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The first approval of nivolumab was on Dec 22, 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Subsequent approvals and Breakthrough Therapy Designation for nivolumab are:

•September 30, 2015 Accelerated Approval for a new indication for nivolumab, in combination with ipilumumab, for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma
•Oct 9, 2015 Approval for the treatment of patients with metastatic non-squamous NSCLC with progression on or after platinum based chemotherapy

•Nov 23, 2015 Accelerated Approval for the treatment of patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy
•January 23, 2016 Accelerated Approval for nivolumab to expanding treatment indication to include treatment in combination with ipilumumab of patients with unresectable or metastatic melanoma (removes the restriction for the treatment of only patients with BRAF wild-type melanoma) and the expansion of the indication for OPDIVO (nivolumab) as a single agent for the treatment of patients with BRAF V600 mutation positive, unresectable or metastatic melanoma to remove the restriction that such patients should have disease progression following ipilumumab and a BRAF inhibitor
•April 22, 2016 Breakthrough Therapy Determination granted for nivolumab for the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN)
•May 17, 2016 Accelerated Approval for nivolumab injection for the treatment of patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post transplantation brentuximab vedotin

3.2 Summary of Presubmission/Submission Regulatory Activity

•August 3, 2009 New IND application for nivolumab monotherapy (IND100052)
•February 27, 2014: Submission of protocol CA209141: "An Open-Label, Randomized Phase 3 Clinical Trial of Nivolumab vs. Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN)
•March 28, 2014 FDA "Study may proceed" memo issued for protocol CA209141
•September 24, 2014 Protocol CA209141 Amendment 03 submitted to IND
•December 22, 2014, FDA granted accelerated approval for Opdivo under BLA 125554 for the treatment of unresectable or metastatic melanoma with disease progression following ipilumumab, and if BRAF mutation-positive, a BRAF inhibitor. Approval was based on demonstration of durable objective responses.
•March 4, 2015 Protocol CA209141 Revised Protocol 02, v3.0; Amendment 07, v1.0 submitted with explanation to IND. Amendment included an increase in sample size based on competitor data; PFS changed to secondary endpoint; OS remains sole primary endpoint.
•March 4, 2015, FDA approved Opdivo (nivolumab) under BLA 125527 for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy based on demonstration of overall survival.
•September 30, 2015, FDA granted accelerated approval for Opdivo under BLA 125554 in combination with ipilumumab, for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma.
•October 9, 2015, FDA approved Opdivo (nivolumab) under BLA 125554 for the treatment of patients with metastatic non-squamous non-small cell lung cancer (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 (nivolumab)
•November 23, 2015, FDA approved Opdivo (nivolumab) under BLA 125554 for the treatment of patients with BRAF wild-type unresectable or metastatic melanoma.

•January 23, 2016, FDA granted accelerated approval for Opdivo (nivolumab) under BLA 125554 for the following indications:

- in combination with ipilumumab, for the treatment of patients with unresectable or metastatic melanoma
- for the treatment of patients with BRAF V600 mutation positive, unresectable or metastatic melanoma

•April 20, 2016 BMS and FDA teleconference regarding response-related data inconsistencies and BMS proposal to submit efficacy supplement based on CA209141 survival results and safety data.
•January 23, 2016, FDA approved Opdivo (nivolumab) under BLA 125554 for the treatment of advanced renal cell carcinoma patients who have received prior antiangiogenic therapy based on results from Study CA209025.
•April 22, 2016 Breakthrough Therapy Designation was granted Opdivo (nivolumab) for the indication: treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).
•April 29, 2016 FDA confirmed acceptability of efficacy supplement based on CA 209141 overall survival and safety data.
•May 12, 2016 BMS submitted a request for a Priority Review for the supplemental Biologic License Application (sBLA 125554) for Opdivo (nivolumab) (b) (4)

3.3 Foreign Regulatory Actions and Marketing History

European Medicines Agency (EMA)
On April 24, 2016, the EMA approved Opdivo for indication of the treatment of advanced (unresectable or metastatic) melanoma in adults. Then, on September 24, 2015 the indication for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults was added. On February 25, 2016, a new indication was added for the treatment of advanced renal cell carcinoma after prior therapy in adults and the lung cancer indication was broadened to include non-squamous NSCLC. On April 1, 2016, the EMA broadened the indication of Opdivo as monotherapy or in combination with ipilumumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Health Canada (HC)
On September 25, 2015, Health Canada approved Opdivo (nivolumab) for the treatment of unresectable or metastatic BRAF V600 wild-type melanoma in previously untreated patients. On February 23, 2016, the indication was broadened to include locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. April 25, 2016, the indication was increased again to include advanced or metastatic renal cell carcinoma.

Pharmaceuticals and Medical Devices Agency (PMDA)
In July 2014, PMDA approved nivolumab for the treatment of radical unresectable advanced or recurrent malignant melanoma for patients previously treated with chemotherapy. In December 2015, PMDA added the indication for the treatment of unresectable advanced/relapsed non-small-cell lung cancer. In February 2016, they included a new dosage indicated for the treatment of unresectable melanoma. And, in August 2016, PMDA added the renal cell carcinoma indication for nivolumab.

Therapeutic Goods Administration (TGA)
As of August 2016, the TGA approved nivolumab for the treatment of unresectable (Stage III) or metastatic (Stage IV) melanoma and locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy.

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

No new significant issues from other disciplines are pertinent to the clinical conclusions on efficacy and safety and are adequately managed through the agreed upon product labeling, still under negotiation.

5 Sources of Clinical Data and Review Strategy

5.1 Table of Clinical Studies

The following clinical study was considered to evaluate the efficacy of Nivolumab in patients with recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck.

Table 2: List of the studies analyzed in this report

	Study Design and endpoints	Treatment Period	Follow-up	# of subjects per Arm	Study Population
CA209141	Design: Phase 3, 2:1 randomized, open-label, multi-center, active-controlled Endpoints: Primary: OS Secondary: PFS, ORR	Treatment Cycles: Nivolumab arm : Two weeks Investigator's choice: One week Treatment was discontinued either due to disease progression, unacceptable toxicity, or withdrawal of consent; For nivolumab treatment beyond progression was allowed.	Patients were followed continuously while on study drug and every 3 months after study drug discontinuation	Nivolumab arm : 240 Investigator choice: 121	Patients at least 18 years or older, histologically confirmed stage-III or IV (unresectable or metastatic) SCCHN, and ECOG performance status of 0 or 1, HPV p16-disease status identification and availability of PD-L1 tumor tissue biopsy

5.2 Review Strategy

This application has met the eligibility criteria for a streamlined review based on a statistically significant and clinically meaningful result using an acceptable primary efficacy endpoint. The efficacy result is in the setting of substantial existing clinical experience with the product and a large clinical trial and post-marketing safety database. As such, the review was carried out predominately based on review of the clinical study report and summary data provided by the sponsor. Complete analysis of datasets was not conducted by the FDA review team other than data audits or targeted analyses wherever required.

Clinical Site Inspection
FDA's Office of Scientific Investigations (OSI) performed clinical site inspections of 2 study sites. These sites were chosen because they have previously not been inspected. Site 1, Dr. Nabil Saba and Site 29, Dr. George Blumenschein were inspected for the primary efficacy endpoint and a key secondary endpoint were examined. There were no significant inspectional findings, and are reported as reliable by OSI.

Compliance with Good Clinical Practices
Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP)[1].

Financial Disclosure
Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1 Study CA209141

6.1.1 Data and Analysis Quality.

The application's data (including raw and analysis datasets) based on a primary lock date of Dec 18, 2015 for the study CA209141 were formally submitted to BLA on May 12, 2016; the SAS programs used to derive the analysis datasets are located in the following network links: \\cdsesub1\evsprod\BLA125554\0192\m5\datasets\ca209141\analysis\adam\datasets

[1] See Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance

On April 20, 2016 BMS brought to the attention of the agency that there were inconsistencies noticed in the data between tumor measurement data and the Investigator evaluation of best overall response (BOR), date of response, and date of progressive disease (PD), which affected calculation of progression-free survival (PFS), objective response rate (ORR), time to response (TTR), and duration of response (DoR) in CA209141. These discrepancies occurred on both arms of the study, and at various sites. Sites were queried, inconsistencies resolved and a new database lock was performed on May 5, 2016.
The updated datasets are available at:
\\cdsesub1\evsprod\BLA125554\0212\m5\datasets\ca209141\analysis\adam\datasets

The clinical study report for this study is located in the following link:
\\cdsesub1\evsprod\BLA125554\0192\m5\53-clin-study-rpts\535-rep-effic-safety-stud\head-and-neck\5351-stud-rep-contr\ca209141

With respect to the efficacy analysis, the above stated CSR consists of only the primary endpoint (OS) analysis results. The efficacy analysis pertaining to the secondary endpoints of PFS and ORR were submitted separately on July 22, 2016 as a response to the FDA's information request dated July 5, 2016 using the updated datasets with inconsistencies resolved. Secondary endpoints efficacy analysis results can be found at
\\cdsesub1\evsprod\BLA125554\0212\m1\us.

For each submission mentioned above, the level of documentation provided to understand the submission type and the data, if any, were adequate.

Efficacy and subgroup analyses were included in the sBLA submission as pre-specified in the protocol and SAP.

6.1.2 Evaluation of Efficacy

This section will focus primarily on the study design, statistical methodologies, and efficacy results from the single pivotal study CA209141.

6.1.2.1 Study Design and Endpoints

Study CA209141 was a randomized, open-label phase-3 study designed to evaluate the efficacy and safety of nivolumab monotherapy vs. investigator's choice of chemotherapy (methotrexate, cetuximab, or docetaxel) in patients with recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).

The primary objective of the study was to compare the overall survival (OS) of patients randomized to receive nivolumab with those who were randomized to receive investigator's choice. The target population for this study was patients who satisfied the following inclusion criteria:

- Adult patients (18 years or older) platinum-refractory recurrent or metastatic SCCHN
- Histologically confirmed Stage-III/IV SCCHN (oral cavity, pharynx, larynx) with tumor progression or recurrence on or within 6 months of the last dose of platinum therapy in the adjuvant (i.e., with radiation after surgery), primary (i.e., with radiation), recurrent, or metastatic setting
- Eastern cooperative oncology group performance score of 0 or 1
- Tumor tissue obtained in the metastatic setting or from an unresectable site of disease must be available for PD-L1 expression analysis and other biomarker analysis
- Documentation of p16-positive or p16-negative disease to determine human papillomavirus (HPV) status of tumor for SCCHN of the oropharynx.
- Prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.
- Patients with active brain metastases were not allowed

Eligible subjects after screening were randomized in a 2:1 ratio to either:

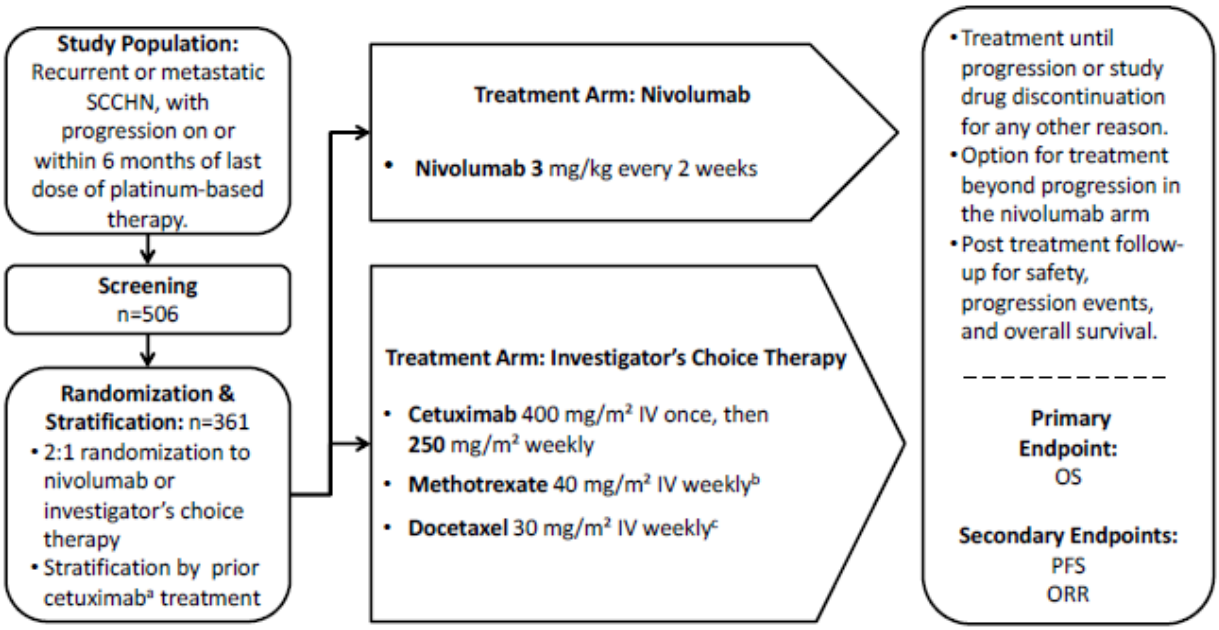
- nivolumab administered at 3 mg/kg as a 60-minute intravenous(IV) infusion every 2 weeks (Q2W) or
- Investigator's choice of either
    - Cetuximab 400 mg/m^2 loading dose IV followed by 250 mg/m2 weekly,
    - Methotrexate 40 to 60 mg/m^2 IV weekly, or
    - Docetaxel 30 to 40 mg/m^2 IV weekly.

Subjects were treated until progression, unacceptable toxicity, or other protocol-defined reasons. Treatment beyond initial investigator-assessed RECIST v1.1-defined progression was permitted for nivolumab if the subject had an investigator-assessed clinical benefit and was tolerating study drug.

Randomization was stratified based on prior cetuximab therapy (yes/no).

Figure 1 presents the schematics of the study design.

Figure 1:Trial design for Study CA209141



[a] Prior cetuximab Yes = 221 (61.2%), No = 140 (38.8%)
[b] Methotrexate could be increased to 60 mg/m2 if tolerated per local practices
[c] Docetaxel could be increased to 40 mg/m2 if tolerated per local practices
[Source: Clinical Study Report Figure 3.1-1]

Dose reductions were not permitted for nivolumab, but were permitted for investigator's choice therapies.

Objectives and Endpoints
The Table 3 summarizes the efficacy related study objectives and the corresponding endpoints used to assess the objectives. In this review the efficacy results for the endpoints of OS, PFS, ORR and DoR will be presented.

Table 3: Study Objectives and Endpoints

Objectives	Endpoints
Primary: To compare OS of nivolumab to investigator's choice	**OS** Definition: Time from randomization to the date of death from any cause.
Secondary: To compare Progression Free Survival (PFS) of Nivolumab to Investigator's Choice	**PFS** Definition: time between the date of randomization and the first date of documented progression, as determined by the investigator (as per RECIST 1.1 criteria), or death due to any cause, whichever occurs first.
To compare Objective Response Rate (ORR) of Nivolumab to Investigator's choice.	**ORR** Definition: proportion of randomized subjects who achieve a best response of complete response (CR) or partial response (PR) using the RECIST1.1 criteria as per investigator assessment.
Exploratory: To estimate Duration of Response (DoR) and Time to Response (TTR) of nivolumab and Investigator's Choice arms	**DoR** Definition: Time since first objective response of CR or PR until date of progression event. **TTR** Definition: time since randomization to the first objective documentation of partial or better response as per investigator assessment using the RECIST 1.1 criteria.

The censoring rules for OS, PFS, DoR, TTR are provided in Table 4.

Changes in tumor measurement, tumor responses and progression will be assessed by the investigator using the RECIST 1.1criteria. Subjects will be evaluated for tumor response every 6 weeks (± 1 week) beginning at Week 9 (+/- 1 week) from randomization, until disease progression is documented or treatment is discontinued (whichever occurs later).

Table 4: Censoring rules for OS, PFS and DoR

Censoring Condition	Date of censoring
OS: Subjects who did not die by the data cutoff date	Date of last contact ("last known alive date")
PFS: Subjects who did not progress or die Subjects who did not have any on study tumor assessments and did not die Subjects who receive subsequent systemic anti-cancer therapy prior to documented progression	Date of their last evaluable tumor assessment Date of randomization Date of the last tumor assessment prior to the initiation of the new therapy
DoR: subject with objective response who does not have a progression event	Censoring date of PFS will be used

6.1.2.2 Statistical Methodologies

Sample size calculations
Assuming that the true OS hazard ratio (HR) was 0.667 corresponding to median OS of 6 months in the control arm and 9 months in the nivolumab arm, and exponential distribution of OS, a total of 278 events were needed to show a statistically significant difference in overall survival between the treatment and control arm based on stratified log-rank test with 90% power at a 2-sided alpha level of 0.05. Approximately 360 patients were to be randomized to observe 278 deaths. With an estimated 26 patients per month accrual rate, it will take 14 months to accrue 360 patients and a follow-up period of 11 months to observe 278 deaths.

Analysis methods for OS and PFS
The analysis of OS and PFS were conducted using a two-sided log-rank test stratified by prior cetuximab therapy (yes/no). The median OS and median PFS were estimated using the Kaplan-Meier method and the corresponding 95% confidence intervals were reported. The hazard ratio for OS and PFS and the corresponding 95% CI were calculated using the stratified cox-proportional hazards model, with treatment arm as a single covariate. The Kaplan-Meyer (KM) plots for OS and PFS were also presented. Additionally, KM plots for OS for the PD-L1 positive and negative/indeterminate and HPV-p16 status were explored.

Analysis methods for ORR
Analysis of ORR was performed using a Cochran-Mantel Haenszel (CMH) test stratified by prior cetuximab therapy (yes/no). The point estimates of ORR and its corresponding 95% exact two-sided confidence intervals were calculated.

Interim analysis
One formal interim analysis of OS was planned to assess the evidence of clinical benefit conducted after 70% (195 deaths) of the expected total number of 278 deaths had occurred. Stopping the study for substantial evidence of nivolumab benefit would have been considered if the OS were significantly better in the nivolumab treatment arm compared to the investigator's choice arm. The stopping boundaries for the interim and final analyses were planned to be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries, controlling for an experiment wise type-I error at 5%; the study could be stopped for efficacy at the interim if a statistical significance was shown based on the interim data. In addition to the formal planned interim analysis for OS, the data monitoring committee (DMC) will have access to periodic interim reports of efficacy and safety to allow a risk/benefit assessment.

If the interim analysis were performed at exactly 195 deaths, the significance level at the interim analysis for declaring superiority would be 0.0148, and if the study continued beyond the interim analysis, the significance level for final analysis, after 278 events, would be 0.0455. An independent statistician external to the applicant will perform these analyses and DMC will review.

Multiplicity adjustment
The experimental-wise type I error rate of 5% was preserved by implementing a gatekeeping testing approach for key secondary endpoints in the order of PFS and ORR, if overall survival benefit in the all randomized population is demonstrated.

Subgroup Analysis
Hazard ratios of OS and their 95% confidence intervals were estimated using the unstratified Cox PH model for each of the subgroups defined in Section-6.1.3. A forest plot of the estimated HRs and their 95% CIs were provided.

6.1.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient population
Study CA 209141 was conducted at 55 sites in 15 countries (Argentina, Brazil, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Netherlands, Spain, Switzerland, Taiwan, United Kingdom, and United States of America). 40% of the patients were enrolled across 13 sites in USA. The table below summarizes the total number of subjects enrolled in the study and the number of subjects in each of the analyses population considered in this study.

The first patient first visit date was May 29, 2014 and the last patient was randomized on Aug 28, 2015. The clinical database lock date was Dec 18, 2015 for the current submission based on interim analysis. The last patient last visit date (based on clinical cut-off) for this clinical study

report (CSR) occurred on Nov 6, 2015. On Jan 26, 2016, the independent Data Monitoring Committee reviewed the data.

Table 5: Analyses populations

Analysis Populations	Nivolumab	Investigator's Choice	Total
Enrolled Subjects: All subjects who signed an ICF and were registered into the IVRS.			506
Randomized subjects*: All enrolled subjects who were randomized.	240	121	361
All Treated Population: All randomized subjects who received at least one dose of study drug.	236	111	347
PD-L1 quantifiable subjects: All randomized subjects with quantifiable PD-L1 expression at baseline	161	99	260

*The baseline demographics and efficacy analyses are performed using the randomized subjects.

Patient Disposition

Of the 506 enrolled patients, 145 were not randomized, and 14 patients from the randomized group were not treated due to the reasons stated in Table 6. The table below also summarizes the number of patients who were continuing the study treatment at the time of database lock date.

Table 6: Disposition of Subjects

Subject Disposition, n	Nivolumab	Investigator's Choice	Total
Enrolled			506
Randomized(ITT)	240	121	361
Investigator's choice:			
Cetuximab		15	
Methotrexate		52	
Docetaxel		54	
Reason for not being randomized:			
Adverse event			5
Subject withdrew consent			18
Death			7
Subject no longer meets study criteria			108
Other			7

Subject Disposition, n	Nivolumab	Investigator's Choice	Total
Treated	236	111	347
Not Treated	4	10	14
Reason for not being treated:			
Disease Progression	1	0	1
Discontinue study treatment	1	2	3
Withdrawal of consent	0	6	6
No longer meets study criteria	2	2	4
Subjects continuing treatment	41	3	44
Subject who discontinued treatment	195	108	303
Reason for discontinuing treatment :			
Disease Progression	162	83	245
Study drug toxicity	9	11	20
Adverse event unrelated to study drug	12	3	15
Discontinue study treatment	4	6	10
Withdrawal of consent	4	1	5
Maximum clinical benefit	1	1	2
Poor/non-compliance	0	1	1
Other	0	2	2
Not reported	3	0	3

Baseline Demographic and disease characteristics

The demographic and baseline characteristics of the subjects are summarized by treatment arm in Table 7. In general, the distribution of the demographic characteristics and baseline disease characteristics appear to be balanced between nivolumab and investigator's choice (IC) arms.

Table 7: Baseline demographic and disease characteristics

n (%)		Nivolumab N=240	IC N=121	Total N=361
Gender	Male	197 (82.1)	103 (85.1)	300 (83.1)
	Female	43 (17.9)	18 (14.9)	61 (16.9)
Race	White	196 (81.7)	104 (86.0)	300 (83.1)
	Black or African American	10 (4.2)	3 (2.5)	13 (3.6)
	Asian	29 (12.1)	14 (11.6)	43 (11.9)
	Other	5(2.1)	0	5(1.4)
Age(in years)	Mean(SD)	59	59.4	59.1
	Median	59	61	60
	Min , Max	29,83	28,78	28,83

n (%)		Nivolumab N=240	IC N=121	Total N=361
Age Group	< 65	172 (71.7)	76 (62.8)	248 (68.7)
	>= 65 AND < 75	56 (23.3)	39 (32.2)	95 (26.3)
	>= 75	12 (5.0)	6 (5.0)	18 (5.0)
Region	US/Canada	101 (42.1)	44 (36.4)	145 (40.2)
	Europe	109 (45.4)	62 (51.2)	171 (47.4)
	Rest of World	30 (12.5)	15 (12.4)	45 (12.5)
ECOG Performance status	0	49 (20.4)	23 (19.0)	72 (19.9)
	1	189 (78.8)	94 (77.7)	283 (78.4)
	>= 2	1 (0.4)	3 (2.5)	4 (1.1)
	Not Reported	1 (0.4)	1 (0.8)	2 (0.6)
Smoking	Never	39 (16.3)	31 (25.6)	70 (19.4)
	Former/Current	191 (79.6)	85 (70.2)	276 (76.5)
	Unknown	10 (4.2)	5 (4.1)	15 (4.2)
Disease stage at study entry	Stage III	25 (10.4)	10 (8.3)	35 (9.7)
	Stage IV	214 (89.2)	111 (91.7)	325 (90.0)
	Not Reported	1 (0.4)	0	1 (0.3)
Prior Lines Of Systemic Cancer Therapy	1	105 (43.8)	58 (47.9)	163 (45.2)
	2	81 (33.8)	45 (37.2)	126 (34.9)
	>= 3	54 (22.5)	18 (14.9)	72 (19.9)

6.1.2.4 Study Results

The study was originally designed to conduct a pre-specified interim analysis for OS when 195 events (70% of the total 278 deaths) were observed. The study began to enroll patient since May 29, 2014 and on Jan 29, 2016 DMC performed a preliminary review of data based on a database lock date of Dec 18, 2015 and concluded a survival benefit in the subjects receiving the nivolumab treatment compared to investigator's choice. These conclusions were derived based on 218 deaths (78.4% of the total 278 expected deaths) and hence the corresponding O'Brien-Fleming boundary based on a Lan-DeMets spending function calculated for 218 deaths would have a significance level of 0.0227 for the first interim analysis.

Primary efficacy results of OS:
The interim results based on Dec 18, 2015 data cutoff demonstrated a significant improvement in overall survival result. A total of 218 deaths were observed by the database lock date. The estimated hazard ratio of 0.7 [95% CI: (0.51, 0.96); p-val=0.0101 based on stratified log-rank test] favors nivolumab arm. The estimated median survival time was 7.5 months [95% CI= (5.5,

9.1)] in the nivolumab arm and for the investigator's choice arm, the estimated median survival time was 5.1 months [95% CI= (4, 6.1)].

The primary OS analysis results are summarized in the Table 8.

Table 8: OS Efficacy Results

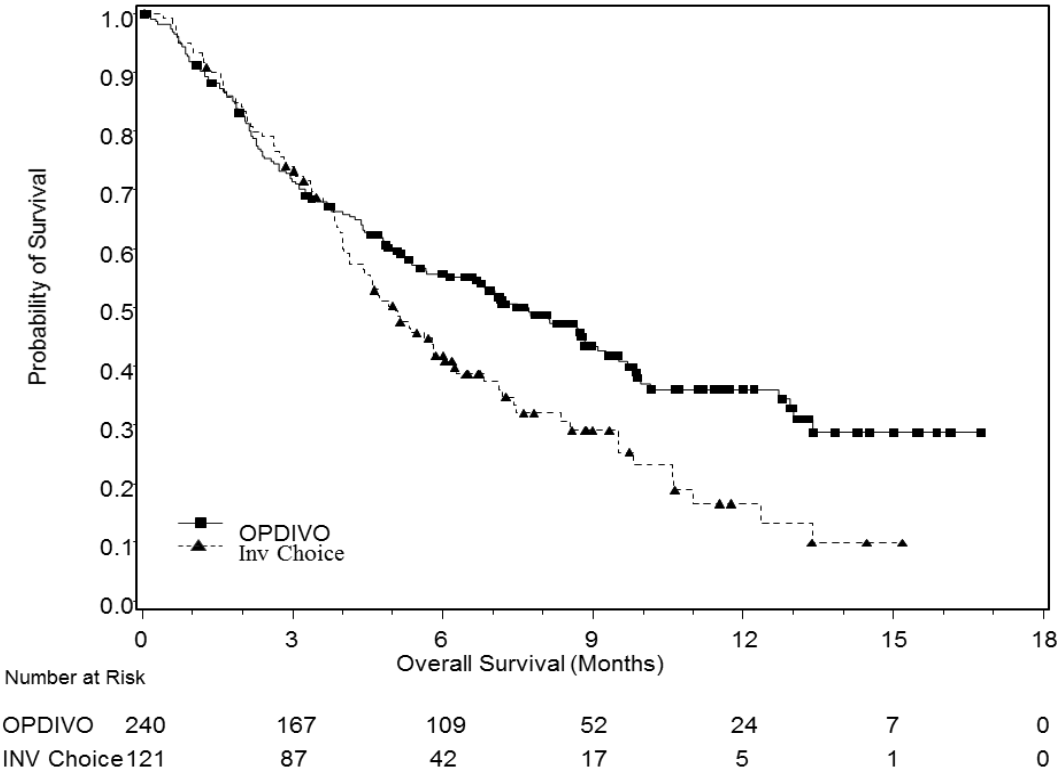
	Nivolumab (n=240)	**IC (n=121)**
Overall Survival:		
Deaths (%)	133 (55.4)	85 (70.2)
Median (mons) (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.1)
HR (95% CI)	0.7 (0.51, 0.96)	
p-value	0.0101*	

*Compared to the OBF boundary of 0.0227

[Source: Clinical Study Report Table 7.1-1]

The Kaplan-Meier plot of survival curves is given in Figure 2.

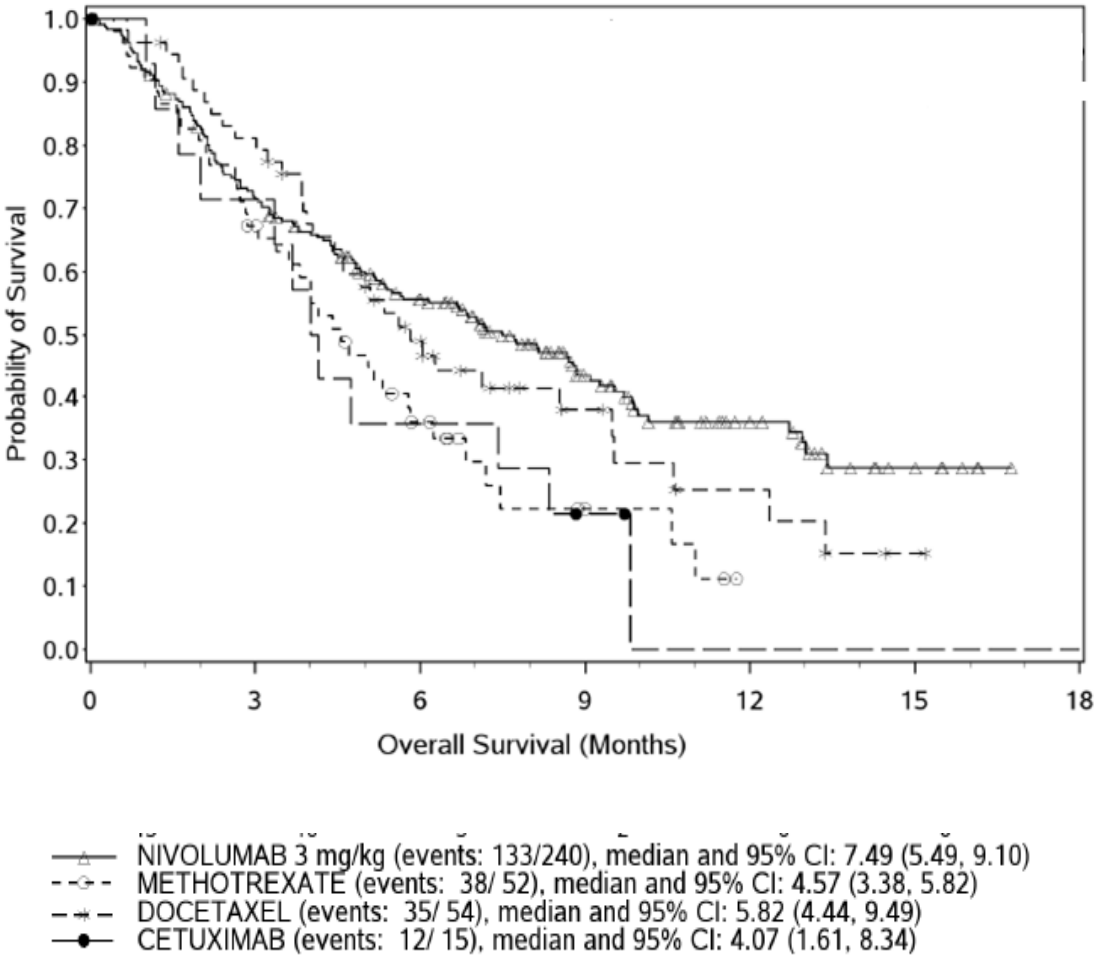
Figure 2: Kaplan-Meier Plot of OS (Nivolumab vs. Investigator's choice)



[Source: Clinical Study Report Figure 7.2-1]

A further breakdown of the median survival times and hazard ratios by investigator's choice are as follows: Estimated median OS was 4.1 months [95%CI= (1.6, 8.3)] in cetuximab treated patients, 4.6 months [95%CI= (3.4, 5.8)] for methotrexate and 5.8 months [95%CI= (4.4, 9.5)] for Docetaxel.

Figure 3: Kaplan-Meier plot of OS (Nivolumab vs. Cetuximab vs. Methotrexate vs. Docetaxel)



[Source: Clinical Study Report Figure 7.2-2]

Efficacy results for the key Secondary endpoints

As discussed in Section-6.1.1, analysis of the key secondary endpoints of progression-free survival (PFS) and objective response rate (ORR) in CA209141 was performed based on a new database lock date of May 5, 2016 due to the inconsistencies noticed in the data between tumor measurement data and the Investigator evaluation of best overall response (BOR), date of response, and date of progressive disease (PD). Since the issues affected only tumor assessments and their interpretation according to RECIST v1.1, the database update was limited

to the tumor assessments, BOR, and progression data. Survival data remained unchanged and hence the survival results presented above are based on the original data base lock-date of Dec 18, 2015. The exploratory endpoints of time to response (TTR), and duration of response (DoR) are also affected. Since the cutoff for tumor response data was May 5, 2016 and since deaths were not updated beyond Dec 18, 2015, DoR was not analyzed and presented in this report. As per applicant's response to the IR dated July 27, 2016, DoR is planned to be analyzed based on a late September, 2016 database lock date and will be completed by December 2016 (Reference: eCTD-0231).

The analysis results for PFS and ORR based on the new database lock date are provided in Table 9 below.

Table 9: PFS and ORR Efficacy Results

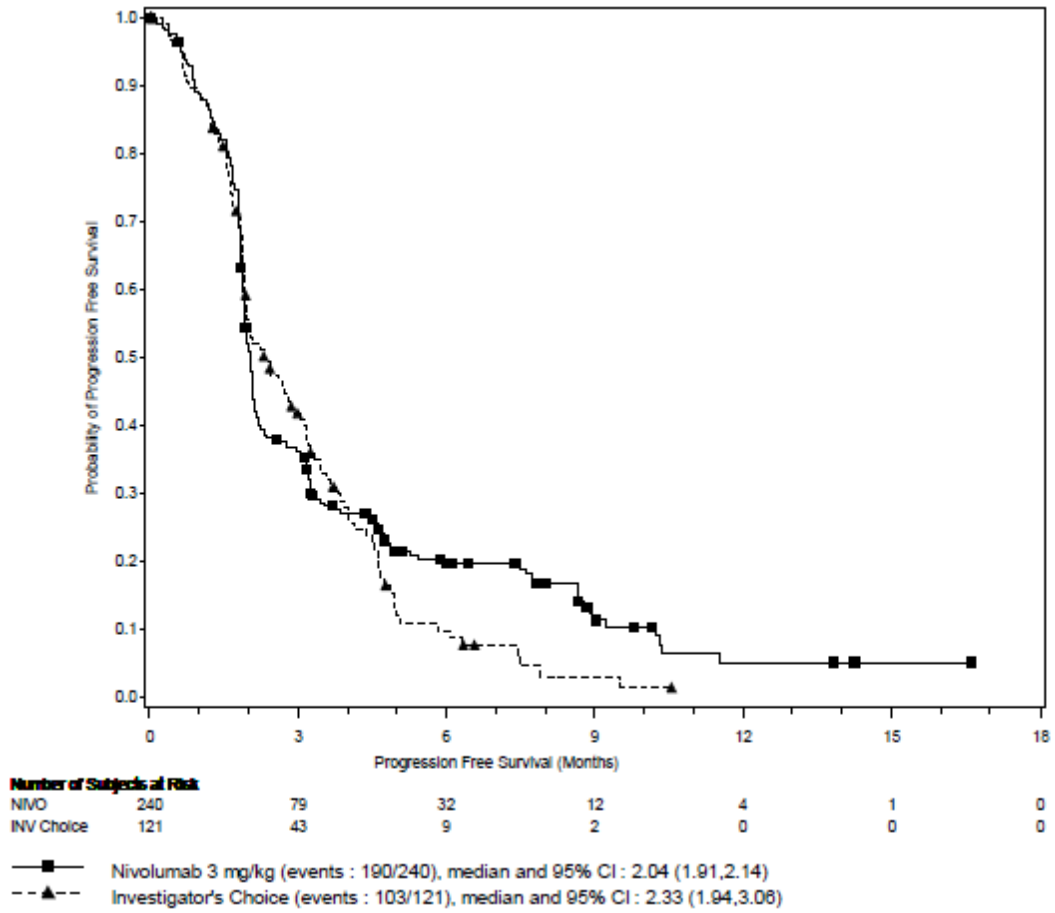
	Nivolumab (n=240)	**IC (n=121)**
Progression-free Survival:		
Disease Progression or Deaths (%)	190 (79.2)	103 (85.1)
Median (mons) (95% CI)	2.04 (1.91, 2.14)	2.33 (1.94, 3.06)
HR (95% CI)	0.89 (0.70, 1.13)	
p-value	0.3236	
Objective Response Rate:		
#Responders	32	5.8
Response Rate (95% CI)	13.3 (9.3, 18.3)	5.8 (2.4, 11.6)

[Source: Reponse to IR sent on 5-July-2016]

Per the analysis plan, PFS was the secondary endpoint to be tested hierarchically when OS benefit is demonstrated. The PFS was not significant (p-value=0.3236) and hence no hypothesis test was conducted for the secondary endpoint of ORR.

The Kaplan-Meier plot of PFS curves comparing nivolumab and investigator's choice is given in Figure 4.

Figure 4: Kaplan-Meier Plot of PFS (Nivolumab vs. Investigator's choice)



[Source: Reponse to IR sent on 5-July-2016]

The best overall investigator assessed response for each treatment arm is summarized by response category in Table 10.

Table 10: Best Overall Response

Best Overall Response n (%)	**Nivolumab (n=240)**	**Inv. Choice (n=121)**
Complete Response	6 (2.5)	1 (0.8)
Partial Response	26 (10.8)	6 (5.0)
Stable Disease	55 (22.9)	43 (35.5)
Progressive Disease	100 (41.7)	42 (34.7)
Unable to Determine	53 (22.1)	29 (24.0)

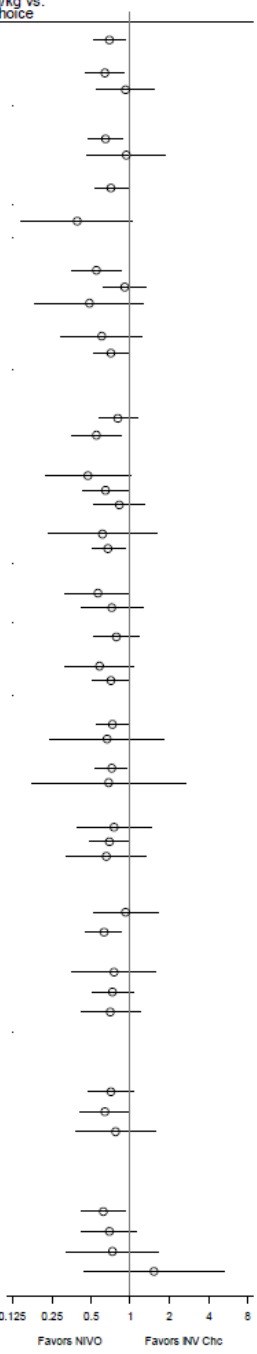
[*Source: Response to IR sent on 5-July-2016*]

6.1.3 Efficacy in Sub-Populations

OS analyses were conducted in the subgroups as provided in Figure 5. All subgroup efficacy analyses were performed using the randomized population and only the subgroups with sample size>20 subjects per subgroup are presented. The hazard ratios (computed using the unstratified cox model) and the corresponding 95% confidence intervals are provided in Figure 5.

Figure 5: Forest plot for subgroup analysis of OS

	N	Nivolumab 3 mg/kg		Investigator's Choice		Unstratified Hazard Ratio (95% CI)
		N of events (N of subjects)	mOS (95% CI)	N of events (N of subjects)	mOS (95% CI)	Nivolumab 3 mg/kg vs. Investigator's Choice
Overall	361	133 (240)	7.5 (5.5-9.1)	85 (121)	5.1 (4.0-6.0)	0.69 (0.53, 0.91)
Age categorization						
< 65	248	90 (172)	8.7 (5.5-9.9)	54 (76)	4.9 (3.9-5.8)	0.64 (0.45, 0.89)
>= 65 AND < 75	95	35 (56)	7.1 (3.7-9.7)	26 (39)	6.2 (4.4-9.8)	0.93 (0.56, 1.54)
>= 75	18	8 (12)	5.0 (2.3-NR)	5 (6)	2.0 (0.7-3.8)	
Gender						
Male	300	106 (197)	8.1 (5.7-9.9)	73 (103)	5.1 (4.0-6.3)	0.65 (0.48, 0.88)
Female	61	27 (43)	5.5 (2.3-7.8)	12 (18)	4.6 (2.2-9.5)	0.93 (0.47, 1.85)
Race						
White	300	115 (196)	6.9 (4.8-8.7)	76 (104)	4.7 (3.9-5.8)	0.72 (0.53, 0.96)
Black	13	5 (10)	7.9 (2.0-NR)	1 (3)	NR (2.7-NR)	
Asian	43	9 (29)	12.7 (9.1-12.7)	8 (14)	5.9 (2.6-NR)	0.39 (0.15, 1.04)
Other	5	4 (5)	4.8 (1.3-NR)			
Region						
North America	145	52 (101)	8.7 (6.8-10.2)	33 (44)	4.6 (3.7-7.2)	0.55 (0.36, 0.85)
EU	171	72 (109)	4.4 (3.1-7.2)	44 (62)	5.2 (4.0-6.3)	0.91 (0.62, 1.33)
ROW	45	9 (30)	9.5 (9.1-NR)	8 (15)	4.7 (2.6-NR)	0.48 (0.19, 1.26)
ECOG performance status						
0	72	18 (49)	10.0 (8.1-NR)	13 (23)	8.3 (3.9-NR)	0.60 (0.30, 1.23)
>= 1	287	114 (190)	6.8 (4.8-8.7)	71 (97)	4.6 (4.0-5.6)	0.71 (0.53, 0.96)
Not Reported	2	1 (1)	4.8 (NR-NR)	1 (1)	1.2 (NR-NR)	
Prior Cetuximab Use (Stratification Factor)						
Yes	221	85 (147)	6.9 (4.9-8.8)	50 (74)	5.2 (4.1-6.8)	0.81 (0.57, 1.15)
No	140	48 (93)	8.1 (5.3-12.7)	35 (47)	4.7 (3.0-7.2)	0.55 (0.35, 0.86)
Intended investigator's choice therapy from IVRS						
Cetuximab	48	17 (33)	8.1 (6.7-10.0)	12 (15)	4.1 (1.6-8.3)	0.47 (0.22, 1.01)
Methotrexate	171	69 (119)	7.2 (4.8-8.8)	38 (52)	4.6 (3.4-5.8)	0.64 (0.43, 0.96)
Docetaxel	142	47 (88)	6.8 (4.4-13.0)	35 (54)	5.8 (4.4-9.5)	0.82 (0.53, 1.28)
Disease stage at study entry						
III	35	15 (25)	6.7 (1.8-7.8)	7 (10)	3.4 (2.1-6.3)	0.61 (0.23, 1.61)
IV	325	117 (214)	8.1 (5.7-9.7)	78 (111)	5.2 (4.1-6.8)	0.68 (0.51, 0.91)
Not Reported	1	1 (1)	3.0 (NR-NR)			
HPV-16 status						
Positive	92	33 (63)	9.1 (7.2-10.0)	20 (29)	4.4 (3.0-9.8)	0.56 (0.32, 0.99)
Negative	86	28 (50)	7.5 (3.0-NR)	25 (36)	5.8 (3.8-9.5)	0.73 (0.42, 1.25)
Unknown	3	1 (2)	NR (6.9-NR)	1 (1)	5.1 (NR-NR)	
Not Reported	180	71 (125)	5.7 (4.4-8.8)	39 (55)	4.9 (4.0-5.8)	0.78 (0.53, 1.16)
Tobacco use						
Never	70	20 (39)	7.2 (4.4-NR)	23 (31)	4.0 (2.0-7.4)	0.58 (0.32, 1.06)
Current/Former	276	106 (191)	8.7 (5.5-9.7)	58 (85)	5.3 (4.4-6.8)	0.71 (0.52, 0.99)
Not Reported	15	7 (10)	1.8 (0.8-NR)	4 (5)	4.0 (1.0-12.4)	
Prior surgery						
Yes	316	122 (207)	7.1 (5.3-8.7)	79 (109)	5.1 (4.0-6.2)	0.73 (0.55, 0.97)
No	45	11 (33)	NR (4.4-NR)	6 (12)	4.7 (3.8-NR)	0.66 (0.24, 1.80)
Prior radiotherapy						
Yes	330	124 (216)	7.0 (5.2-8.7)	82 (114)	4.7 (4.0-5.8)	0.72 (0.54, 0.95)
No	31	9 (24)	12.9 (8.8-NR)	3 (7)	8.3 (2.2-NR)	0.68 (0.18, 2.64)
Best response to the most recent regimen						
Responder	63	26 (44)	7.1 (5.0-12.9)	14 (19)	5.8 (3.9-9.5)	0.76 (0.39, 1.45)
Non-responder	245	88 (159)	7.7 (5.7-9.1)	58 (86)	4.7 (4.0-6.3)	0.69 (0.50, 0.97)
Unknown\Not Reported	53	19 (37)	5.3 (2.7-NR)	13 (16)	3.9 (2.4-6.2)	0.66 (0.32, 1.33)
Time from initial disease diagnosis to randomization						
<1 year	91	36 (62)	8.7 (3.1-10.0)	18 (29)	7.2 (2.4-13.4)	0.92 (0.52, 1.62)
>= 1 year	270	97 (178)	7.5 (5.7-9.3)	67 (92)	5.1 (4.0-5.8)	0.63 (0.46, 0.86)
Site of Primary Tumor						
Larynx	49	22 (34)	5.2 (3.5-12.9)	11 (15)	4.0 (3.0-11.0)	0.75 (0.36, 1.59)
Oral cavity	175	61 (108)	7.0 (4.8-9.5)	51 (67)	4.6 (3.7-5.8)	0.73 (0.51, 1.07)
Pharynx	128	47 (92)	8.8 (6.9-12.7)	21 (36)	6.2 (4.1-9.5)	0.71 (0.42, 1.19)
Other	9	3 (6)	NR (2.1-NR)	2 (3)	7.5 (2.6-7.5)	
Number of prior lines of systemic therapy						
1	163	62 (105)	7.8 (4.4-9.5)	39 (58)	5.3 (3.1-6.8)	0.71 (0.48, 1.07)
2	126	42 (81)	7.2 (5.2-NR)	35 (45)	4.7 (4.0-7.1)	0.64 (0.41, 1.00)
>=3	72	29 (54)	8.7 (4.2-13.0)	11 (18)	5.1 (3.8-NR)	0.77 (0.38, 1.57)
Number of lines of prior chemotherapy in the metastatic setting						
0	190	64 (128)	8.7 (5.4-13.4)	44 (62)	4.6 (3.6-6.3)	0.62 (0.42, 0.91)
1	111	48 (74)	7.2 (4.9-8.8)	27 (37)	4.6 (3.4-5.8)	0.69 (0.43, 1.11)
2	40	14 (27)	8.7 (4.2-NR)	10 (13)	7.1 (3.8-11.0)	0.73 (0.32, 1.65)
>=3	20	7 (11)	4.8 (1.2-NR)	4 (9)	7.5 (1.2-NR)	1.52 (0.44, 5.22)



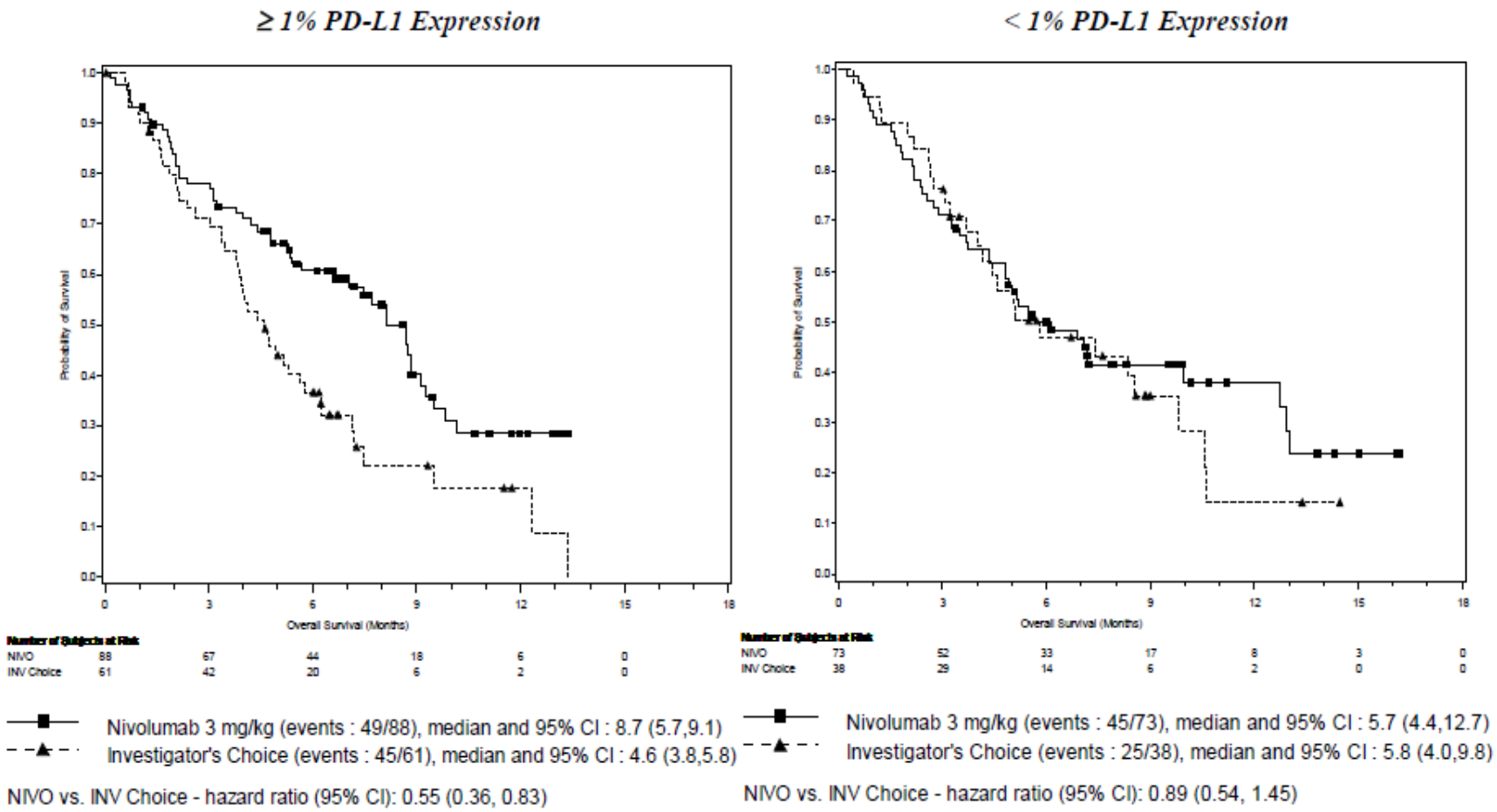
[Source: Clinical Study Report Figure 7.2.1-1]

6.1.3.1 Other Special/Subgroup Population

Survival was further assessed for the subgroups of PD-L1 (1% cutoff) and HPV p-16 status. All the results presented in this section should be considered as exploratory since there were no pre-specified hypotheses and power analyses for these subgroups, and also they are not adjusted for multiplicity.

Figure 6 shows the OS for patients by PD-L1 expression. Of the safety population, 28% (101/361) of patients had non-quantifiable PD-L1 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. For patients with PD-L1 expression ≥1% there is an early separation of the survival curves, starting at the first month of treatment. In patients with PD-L1 positive tumor, the HR was 0.55 (95% CI 0.36, 0.83) with median survival of 8.7 months for patients receiving nivolumab and 4.6 months for patients receiving investigators choice of chemotherapy. Among patients with PDL1 negative tumors, the HR was 0.89 (95% CI 0.54, 1.45) with median survival of 5.7 months for patients receiving nivolumab and 5.8 months for patients receiving investigators choice of chemotherapy.

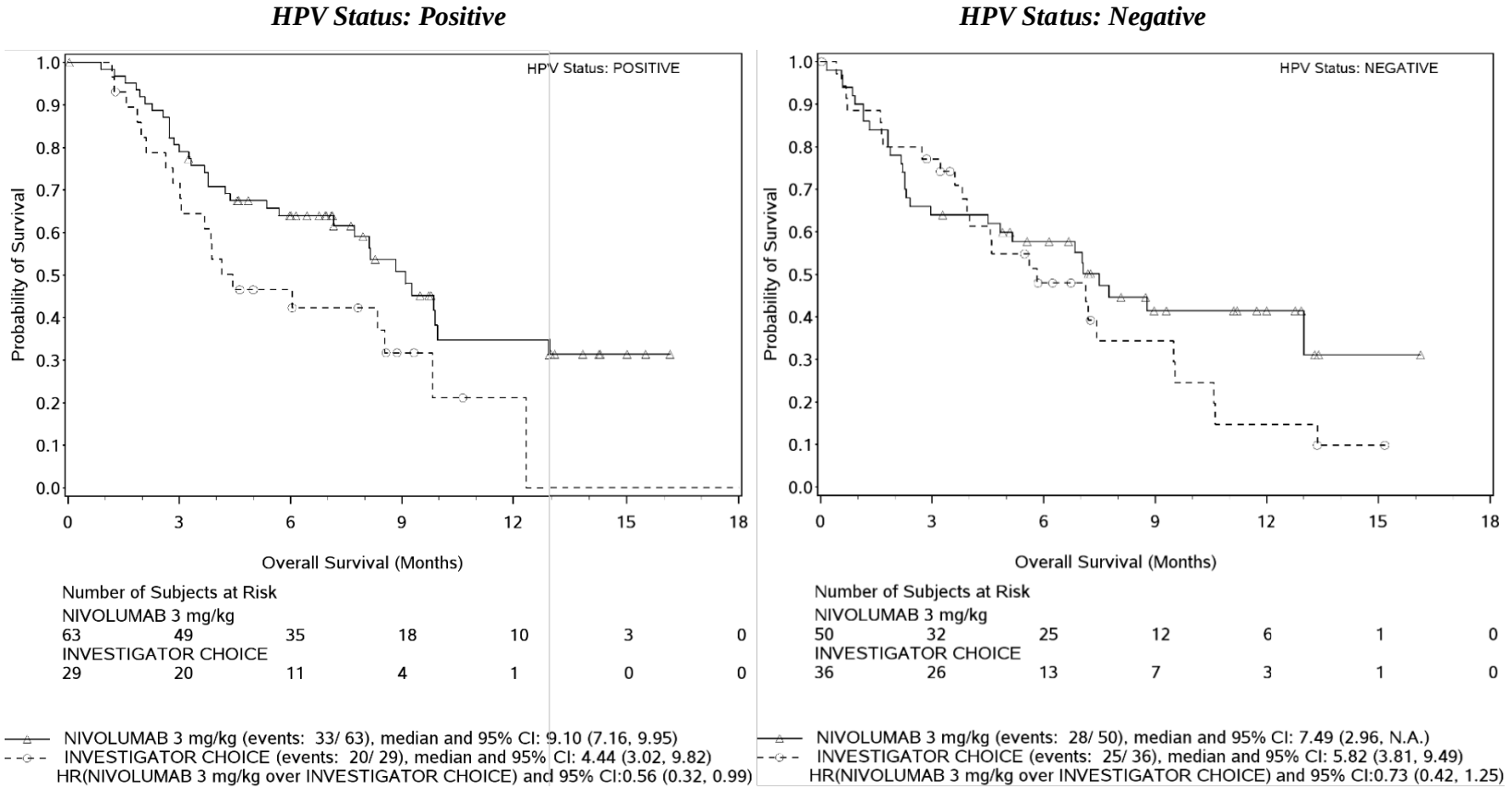
Figure 6: Kaplan-Meier Plot of OS by Baseline PD-L1 Expression (1% Expression Level)



[Source: Clinical Study Report Figure 7.3.2-2]

Of the safety population, 25% (92/361) were HPV positive, 23% (86/361) were HPV negative and 50% (183/361) were status unknown. Consistent with the natural course of disease, patients with HPV positive tumors had better OS than patients with HPV negative disease. Patients with HPV positive tumors on nivolumab had a median OS of 9.1 months [95% CI= (7.2, 10)] compared to IC 4.4 months [95% CI= (3.0, 9.8)]. Patients with HPV negative tumors on nivolumab had median OS of 7.5 months [95% CI= (3.0, NR)] compared with IC 5.8 months [95% CI= (3.8, 9.5) months.

Figure 7: Kaplan-Meier Plot of OS by HPV Status



[Source: Clinical Study Report Figure 7.4.2-1]

6.1.4 Conclusions

In summary, based on study CA209141, the interim analysis results with 361 randomized patients, an improvement of overall survival was observed in the nivolumab arm compared to the investigator's choice arm. The median overall survival was 7.5 months [95% CI= (5.5, 9.1)] in the nivolumab arm and 5.1 months [95% CI= (4, 6.1)] in the investigator's choice arm. The hazard ratio estimate was 0.7 with 95% confidence interval of (0.51, 0.96) obtained from Cox proportional hazards model stratified by prior cetuximab therapy. A significant p-value of 0.0101 (compared to the interim boundary of 0.0227) indicates a significantly higher survival duration for patients received nivolumab compared to those who received the investigator's choice.

The result based on the key secondary endpoints of PFS was not significant [median PFS: 2 vs. 2.3 months for nivolumab and investigator's choice arms, respectively, HR: 0.89 (0.70, 1.13); p-value=0.3236] and hence the objective response rate was not tested further according to the hierarchical testing strategy. The endpoint of ORR was analyzed only descriptively [ORR: 13.3% vs. 5.8% for nivolumab and investigator's choice arms respectively].

7 Integrated Review of Effectiveness

Integrated review of effectiveness is not relevant for this streamlined review.

8 Review of Safety

8.1 Safety Review Approach

This application has met the eligibility criteria for a streamlined review based on a statistically significant and clinically meaningful result using an acceptable primary efficacy endpoint in the setting of a well-established safety profile. The safety results are viewed in the setting of substantial existing clinical experience with the product and a large clinical trial and post-marketing safety database. As such, the review was carried out predominately based on review of the clinical study report and summary data provided by the sponsor. Direct analysis of datasets was not conducted by the FDA other than data audits or targeted analyses where specifically noted.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

The median duration of therapy for nivolumab as 1.9 months, for cetuximab and methotrexate it was 1.6 months and for docetaxel it was 2 months. The median number of infusions was 5 for nivolumab (dosed every 2 weeks), 8 for cetuximab (dosed weekly), 7.5 for methotrexate (dosed weekly) and 9 for docetaxel (dosed weekly). Eighteen percent of patients treated with nivolumab received treatment longer than 6 months and 2.5% received treatment longer than 12 months. The majority of the patients of the nivolumab (82%) and cetuximab (76%) arms received median relative dose intensity from 90-100% of the planned dose, while only 50% on the methotrexate arm and 34% on the docetaxel arm received the 90-100% of the planned dose. Patients on the nivolumab arm stayed on treatment longer compared to the other study arms.

Table 11 Dose Exposure

	Nivolumab N=236	Investigator's Choice N=111		
		Cetuximab N=13	Methotrexate N=46	Docetaxel N=52
Duration of Therapy Median (months)	1.9	1.6	1.6	2.0
Number of Doses Mean (SD)	7.6 (6.71)	10.5 (7.61)	7.8 (5.17)	10.5 (7.11)
Number of Doses Median (Min-Max)	5.0 (1 -34)	8.0 (3.32)	7.5 (1-18)	9 (1.31)
Cumulative Dose Mean (SD)	22.8 (20.15)	2826 (1899.72)	301.3 (194.09)	354.8 (253.82)
Cumulative Dose Median (min-max)	15.0 (3-102)	2246.9 (923-8232)	272.4 (27-725)	279.9 (30-978)
Relative Dose Intensity 90-100%	195 (82.6)	10 (76.9)	23 (50.0)	18 (34.6)
Relative Dose Intensity 70-<90%	35 (14.8)	2 (15.4)	13 (28.3)	11 (21.2)

Source: Clinical Study Report for Study CA209141, page 61.

Dose modifications for nivolumab were not permitted. Dose reductions for the IC drugs were allowed and specified in the protocol. Dose delays were allowed for all treatment arms allowing for toxicity to resolve. Doses were considered delayed if received 4 or more days after the scheduled dose date. Docetaxel (57.7%) and methotrexate (50%) had the most delays and nivolumab (32.7%) and cetuximab (23.1%) had the least delays. Cetuximab had the highest rate of interrupted infusions 23%; the rates of interrupted infusions were low for all other treatment

arms: nivolumab (3%), methotrexate (2%), and docetaxel (4%). Infusion rate reduction was highest for patients on methotrexate (6.5%), and was less than 2% for nivolumab, and docetaxel. Cetuximab did not require any IV rate reductions.

Table 12 Infusion Interruption, Infusion Rate Reductions, and Dose Delays

	Nivolumab N=236	Investigator's Choice N=111		
		Cetuximab N=13	Methotrexate N=46	Docetaxel N=52
Number of Delayed Doses Per Subject (%)				
0	159 (67.4)	10 (76.9)	23 (50.0)	22 (42.3)
1	49 (20.8)	3 (23.1)	9 (19.6)	15 (28.8)
2	18 (7.6)	0	8 (17.4)	7 (13.5)
3	7 (3)	0	1 (2.2)	3 (5.8)
≥4	3 (1.3)	0	5 (10.9)	5 (9.6)
Interrupted Infusions per subject (%)				
0	229 (97)	10 (76.9)	45 (97.8)	50 (96.2)
1	7 (3)	3 (23.1)	1 (2.2)	2 (3.8)
Number of Infusions with IV rate reduction per subject (%)				
0	231 (97.9)	13 (100)	43 (93.5)	51 (98.1)
1	4 (1.7)	0	3 (6.5)	1 (1.9)
2	1 (0.4)	0	0	0

Source: Clinical Study Report for Study CA209141, page 63-65.

In summary, the duration of therapy was similar for all treatment arms. Patients on the nivolumab arm received fewer infusions overall because nivolumab is dosed every 2 weeks, compared to IC (dosed weekly). More patients on nivolumab (83%) and cetuximab (77%) received 90-100% of the planned dose compared to patients on methotrexate (50%) and docetaxel (34%). Dose delays to allow for recovery from toxicity were low for nivolumab (3%), methotrexate (2%), and docetaxel (4%), and relatively higher for cetuximab (23%). Patients on cetuximab (23%) required the most infusion interruptions, while patients on methotrexate (6.5%) required the most IV rate reductions. Some variation between arms is expected, and it is unlikely that these variances affected the primary outcome of this study.

8.2.2 Relevant characteristics of the safety population

A total of 506 patients were enrolled in the CheckMate 141 study, 361 were randomized in the ITT population, 240 to the nivolumab arm and 121 to the IC arm. Of the patients randomized to the nivolumab arm, four patients did not receive treatment, one was due to disease progression, one due to patient's request to discontinue study treatment, and two were because they no longer met study inclusion criteria. Of the 121 patients randomized to the IC arm, ten did not receive treatment, two requested to discontinue study treatment, six

withdrew consent, and two no longer met study criteria. The total safety population was 347 patients, with 236 randomized to the nivolumab arm and 111 randomized to the IC arm.

The baseline demographics were similar between the two study arms. The median age was 60 years (range 28 to 83 years), and the majority of participants were non-Hispanic, white males. Eighty percent of the patients randomized to nivolumab were former smokers, compared to 70% of the patients randomized to IC. Twenty-six percent of patients randomized to nivolumab were HPV positive compared to 24% randomized to IC. Eighty-nine percent of patients randomized to nivolumab had stage 4 disease, while 92% randomized to IC had stage 4 diseases. In general, the study arms were well balanced.

8.3 Safety Results

There were fewer deaths, less serious adverse events, and fewer drug discontinuations due to toxicity on the nivolumab arm compared to IC. There were more immune mediated AEs on the nivolumab arm, but these events occurred with low frequency.

8.3.1 Deaths

There were fewer deaths on the nivolumab arm (56%) compared to IC (70%). The most common cause of death on both arms was disease progression. There were 2 treatment related deaths on the nivolumab arm, and no treatment related deaths on the IC arm. There were slightly more deaths within 30 days of the last dose of nivolumab (21%) compared to IC (19%), but fewer deaths within 100 days of last dose on nivolumab (44%) compared to IC (51%).

Table 13 Deaths

	Nivolumab (N=236)	Investigator's Choice (N=111)
Number of Subjects who died (%)	132 (55.9)	78 (70.3)
Primary Reason for death (%)		
Disease	109 (46.2)	68 (61.3)
Study Drug Toxicity	2(0.8)	0
Unknown	8(3.4)	3 (2.7)
Other	13 (5.5)	7 (6.3)
Number of Subjects who died within 30 days of the last dose (%)	50(21.2)	21 (18.9)
Primary Reason for death (%)		
Disease	40(16.9)	18 (16.2)
Study Drug Toxicity	1(0.4)	0
Unknown	0	1 (0.9)
Other	9 (3.8)	2 (1.8)
Number of Subjects who died within 100 days of the last dose (%)	103 (43.6)	57 (51.4)
Primary Reason for death (%)		
Disease	85 (36)	50 (45)
Study Drug Toxicity	2(0.8)	0
Unknown	3(1.3)	1 (0.9)
Other	13 (5.5)	6 (5.4)

Source: Clinical Study Report for Study CA209141, page 88.

Deaths Attributed to Study Drug Toxicity

There were 2 deaths due to drug toxicity on the nivolumab arm, one patient died due to pneumonitis and atrial fibrillation / flutter (CA209141-(b) (6)) and the other patient died due to hypercalcemia (CA209141-(b) (6)).

Patient CA209141-(b) (6)

This patient was a 55 year old male with stage 4 SCCHN. On study day 21, five days after his second infusion of nivolumab he presented with dyspnea and productive cough requiring hospitalization for treatment of pneumonitis. He was treated with corticosteroids and antibiotics with little improvement, and on day 44 he developed a sudden increase in heart rate, and his ECG showed atrial flutter with marked ST abnormality with possible inferior sub-endocardial injury. He required a 5 days of intensive care to manage his heart rhythm. When the arrhythmia resolved, his care was downgraded to a medical floor for respiratory care. One study day 61, he died due to complications of pneumonitis after 2 doses of nivolumab.

Reviewer's Comment: Pneumonitis and ventricular arrhythmias are labeled toxicities.

CA209141-(b) (6)
This patient was a 61 year old male with stage 4 SCCHN. Seven days after the first infusion, he presented with grade 2 confusion and a serum calcium level of 3.48 mol/L (ref. range 2.20-2.55 mol/L). He was admitted to the hospital and received medical treatment, but died on study day 22, after one dose of nivolumab.

Reviewer's Comment: Hypercalcemia is labeled as a serious adverse reaction of nivolumab.

Deaths Attributed to Other Reasons
There were 13 deaths attributed to "other reasons "on the nivolumab arm. The causes of death were: hemorrhagic shock, pneumonia with pulmonary embolism, euthanasia, disease progression, acute respiratory failure, general status alteration, suspicion of stroke, worsening of general condition, cardiopulmonary insufficiency, pharyngeal stenosis, cardiorespiratory arrest, and 2 cases of pneumonia.

There were 7 deaths attributed to "other reasons" on the IC arm. The cetuximab arm had 2 cases, septic shock with ischemic CVA and cardiac arrest. The docetaxel arm had 2 cases, lung infection and septic shock. The methotrexate arm had three cases: sepsis, respiratory failure, and pneumonia with renal failure, encephalopathy and pharyngocutaneous fistula.

Overall, there were fewer on study deaths in the nivolumab arm compared to IC. There were more deaths within 30 days of the last dose of study drug on the nivolumab arm compared to IC, but there were fewer deaths within 100 days of the last dose of study drug on the nivolumab arm. There were 2 deaths related to nivolumab, and both were determined to be related to known, labeled adverse events. Some deaths due "to other causes" are expected in pre-treated patients with a median age of 60 years.

8.3.2 Nonfatal SAEs

Serious Adverse Events (SAE)
All cause serious adverse events of any grade occurred in 53.8% of patients on nivolumab and 59.5% of patients on IC. The incidence of grade ≥3 SAE was lower on nivolumab (28%) compared with IC (32.4%) The most frequently reported SAE in the nivolumab arm were malignant neoplasm progression (18.2% vs. 22.5%), pneumonia (4.2% vs. 0.9%), dyspnea (3.8% vs. 0.9%), and pneumonia aspiration (3.4% vs. 1.8). In summary, there were more any grade and grade 3-4 AEs on the IC arm compared to nivolumab. The AEs occurring at a higher rate on the nivolumab arm compared to IC are: pneumonia, respiratory tract infection, dyspnea, aspiration pneumonia, respiratory failure, decreased appetite, and dehydration. A possible explanation for the increase in respiratory AEs on nivolumab compared to IC was that there are a higher proportion of smokers on the nivolumab arm compared to IC and nivolumab.

Table 14 SAE Reported in ≥ 1% of all treated Subjects

Preferred Term	Nivolumab 3mg/kg N=236		Investigator's Choice N=111	
	Any Grade	Grade 3-4	Any Grade	Grade 2-4
SAE	127 (53.8)	66 (28)	66 (59.5)	36 (32.4)
Neoplasms, Malignant and Unspecified	47 (19.9)	7 (3)	26 (23.4)	2 (1.8)
Malignant Progression	43 (18.2)	5 (2.1)	25 (22.5)	2 (1.85)
Pneumonia	10 (4.2)	8 (3.4)	1 (0.9)	1 (0.9)
Respiratory Tract Infection	5 (2.1)	3 (1.3)	1 (0.9)	0
Sepsis	5 (2.1)	5 (2.1)	3 (2.7)	3 (2.7)
Lung Infection	4 (1.7)	3 (1.3)	4 (3.6)	3 (2.7)
Urinary Tract Infection	4 (1.7)	3 (1.3)	0	0
Lower Respiratory Tract Infection	3(1.3)	1 (0.4)	3 (2.7)	3 (2.7)
Device Related Infection	0	0	2 (1.8)	1 (0.9)
Dyspnea	9 (3.8)	9 (3.8)	1 (0.9)	1 (0.9)
Pneumonia Aspiration	8 (3.4)	8 (3.4)	2 (1.8)	2 (1.8)
Respiratory Failure	4 (1.7)	4 (1.7)	0	0
Pleural Effusion	2 (0.8)	2 (0.8)	3 (2.7)	3 (2.7)
Respiratory Distress	1 (0.4)	1 (0.4)	2 (1.8)	2 (1.8)
Decreased Appetite	4 (1.7)	2 (0.8)	1 (0.9)	1 (0.9)
Dehydration	3 (1.3)	3 (1.3)	0	0
Hypercalcemia	3 (1.3)	1 (0.4)	1 (0.9)	1 (0.9)
Dysphagia	2 (0.8)	2 (0.8)	3 (2.7)	3 (2.7)
Abdominal Pain	1 (0.4)	1 (0.4)	2 (1.8)	1 (0.9)
Diarrhea	0	0	2 (1.8)	2 (1.8)
Pyrexia	3 (1.3)	1 (0.4)	4 (3.6)	3 (2.7)
Asthenia	1 (0.4)	1 (0.4)	2(1.8)	1(0.9)
Malaise	0	0	2(1.8)	1(0.9)
Dizziness	0	0	2(1.8)	1(0.9)
Anemia	0	0	2(1.8)	2(1.8)

Source: Clinical Study Report for Study CA209141, page 90-92.

Adverse Events

All cause any grade adverse events were more frequent on IC (59.5%) compared to nivolumab (53.8). Also, all cause grade 3-4 events were higher on IC (32.4%) compared to nivolumab (28%). The most frequent drug related AE >15% in either treatment group were fatigue, nausea and anemia. All of these AEs occurred at higher rates on the IC arm compared to nivolumab arm.

Table 15 Adverse Events

Preferred Term	Nivolumab N=236		Investigator's Choice N=111	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All Cause SAE	127 (53.8)	66 (28)	66 (59.5)	36 (32.4)
Drug Related SAEs	16 (6.8)	11 (4.7)	17 (15.3)	12 (10.8)
Drug Related AE >15% on either treatment arm				
Fatigue	33 (14)	5 (2.1)	19 (17.1)	3 (2.7)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)

Source: Clinical Study Report for Study CA209141, page 87.

All cause, any grade AEs were high on both arms of the study (Nivolumab 97% vs. IC 98.2%). The any grade AEs occurring in >5% of patients on the nivolumab arm are: fatigue (26.3% vs. 32.4%), pyrexia (12.7% vs. 14.4%), asthenia (10.2% vs. 21.6%), peripheral edema (7.6% vs. 4.5%), nausea (19.1% vs. 30.6%), constipation (15.3% vs. 18%), diarrhea (14.8% vs. 23.4%), vomiting (11.4% vs. 12.6%), cough (13.6% vs. 9%), dyspnea (13.6% vs. 10.8%), productive cough (5.1% vs. 1.8%), decreased appetite (18.6% vs. 19.8%), hyponatremia (9.3% vs. 12.6%), hypercalcemia (6.8% vs. 7.2%), hyperglycemia (5.5% vs. 8.1%), dehydration (5.1% vs. 4.5%), pneumonia (6.4% vs. 1.8%), weight decreased (13.1% vs. 14.4%), blood alkaline phosphatase increased (7.2% vs. 2.7%), aspartate aminotransferase increased (5.1% vs. 3.6%), back pain (5.9% vs. 0), neck pain 5.1% vs. 7.2%), malignant neoplasm progression (18.2% vs. 22.5%), tumor pain (5.5% vs. 5.4%), pruritus (8.5% vs. 0), rash (8.5% vs. 4.5%), headache (8.9% vs. 3.6%), anemia (18.6%vs. 33.3%), insomnia (5.1% vs. 6.3%), hypertension (5.9% vs. 2.7%), and hypothyroidism (6.4% vs. 5.4%).

All cause, grade 3-4 AEs were higher on the IC arm (52.3%) compared to nivolumab (41.1%). The grade 3-4 AEs occurring in >5% of the patients on the nivolumab arm are: dyspnea (5.5% vs. 1.8%) and anemia (5.9% vs. 8.1%).

Malignant neoplasm progression (16.1% vs. 20.7%) is the only grade 5 event occurring on the nivolumab arm in >1% of patients.

Table 16 Events by Worst CTC Grade with 5% Cutoff for All Treated Subjects

Preferred Term	Nivolumab N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Total Subjects with an Event	229 (97)	97(41.1)	46 (19.5)	109 (98.2)	58 (52.3)	25 (22.5)
General Disorders and Administration Site Conditions	134 (56.8)	17 (7.2)	0	79 (71.2)	16 (14.4)	0
Fatigue	62 (26.3)	8 (3.4)	0	36 (32.4)	7 (6.3)	0
Pyrexia	30 (12.7)	1 (0.4)	0	16 (14.4)	3 (2.7)	0
Asthenia	24 (10.2)	5 (2.1)	0	24 (21.6)	4 (3.6)	0
Peripheral Edema	18 (7.6)	1 (0.4)	0	5 (4.5)	0	0
Face Edema	10 (4.2)	0	0	9 (8.1)	0	0
Mucosal Inflammation	8 (3.4)	0	0	17 (15.3)	2 (1.8)	0
Gastrointestinal Disorders	129 (54.7)	19 (8.1)	0	73 (65.8)	11 (9.9)	0
Nausea	45 (19.1)	1 (0.4)	0	34 (30.6)	1 (0.9)	0
Constipation	36 (15.3)	2 (0.8)	0	20 (18)	0	0
Diarrhea	35 (14.8)	2 (0.8)	0	26(23.4)	3 (2.7)	0
Dysphagia	29 (12.3)	9 (3.8)	0	15 (13.5)	3 (2.7)	0
Vomiting	27 (11.4)	1 (0.4)	0	14 (12.6)	0	0
Dry Mouth	7 (3)	0	0	6 (5.4)	0	0
Stomatitis	7 (3)	3 (1.3)	0	11 (9.9)	3 (2.7)	0
Gastroesophageal Reflux Disease	2 (0.8)	0	0	8 (7.2)	0	0
Respiratory, Thoracic and Mediastinal Disorders	107 (45.3)	38 (16.1)	1 (0.4)	47 (42.3)	12 (10.8)	0
Cough	32 (13.6)	1 (0.4)	0	10 (9)	0	0
Dyspnea	32 (13.6)	13 (5.5)	0	12 (10.8)	2 (1.85)	0
Productive Cough	12 (5.1)	0	0	2 (1.8)	0	0
Hemoptysis	9 (3.8)	2 (0.8)	0	6 (5.4)	1 (0.9)	0
Pleural Effusion	7 (3)	2 (0.8)	0	7 (6.3)	5 (4.5)	0
Epistaxis	4 (1.7)	0	0	11 (9.9)	0	0
Metabolism and Nutrition Disorders	106 (44.9)	34 (14.4)	1 (0.4)	56 (50.5)	21 (18.9)	0
Decreased Appetite	44 (18.6)	3 (1.3)	0	22 (19.8)	4 (3.6)	0
Hyponatremia	22 (9.3)	11 (4.7)	0	14 (12.6)	9 (8.1)	0

Hypercalcemia	16 (6.8)	5 (2.1)	1 (0.4)	8 (7.2)	2 (1.8)	0
Hyperglycemia	13 (5.5)	3 (1.3)	0	9 (8.1)	3 (2.7)	0
Dehydration	12 (5.1)	4 (1.7)	0	05 (4.5)	1 (0.9)	0
Hypokalemia	8 (3.4)	0	0	8(7.2)	2 (1.8)	0
Infections and Infestations	88 (37.3)	29 (12.3)	1 (0.4)	54 (48.6)	19 (17.1)	1 (0.9)
Pneumonia	15 (6.4)	9 (3.8)	0	2 (1.8)	1 (0.9)	0
Lung Infection	10 (4.2)	4 (1.7)	0	7 (6.3)	4 (3.6)	1 (0.9)
Respiratory Tract Infection	7 (3)	3 (1.3)	0	6 (5.4)	0	0
Oral Candidiasis	6 (2.5)	0	0	6 (5.4)	0	0
Investigations	81 (34.3)	18 (7.6)	0	033 (29.7)	9 (8.1)	0
Weight Decreased	31 (13.1)	0	0	16 (14.4)	0	0
Blood Alkaline Phosphatase Increased	17 (7.2)	3 (1.3)	0	3 (2.7)	0	0
Aspartate Aminotransferase Increased	12 (5.1)	3 (1.3)	0	4 (3.6)	0	0
Musculoskeletal and Connective Tissue Disorders	66 (28)	7 (3)	1 (0.4)	29 (26.1)	2 (1.8)	0
Back Pain	14 (5.9)	3 (1.3)	0	0	0	0
Neck Pain	12 (5.1)	1 (0.4)	0	8 (7.2)	1 (0.9)	0
Neoplasms benign, malignant and unspecified	64 (27.1)	8 (3.4)	39 (16.5)	33 (29.7)	2 (1.8)	23 (20.7)
Malignant neoplasm progression	43 (18.2)	5 (2.1)	38(16.1)	25 (22.5)	2 (1.8)	23 (20.7)
Tumor Pain	13 (5.5)	2 (0.8)	0	6 (5.4)	0	0
Skin and Subcutaneous Tissue Disorders	62 (26.3)	1 (0.4)	0	40 (36)	8 (7.2)	0
Pruritis	20 (8.5)	0	0	0	0	0
Rash	20 (8.5)	0	0	5 (4.5)	1 (0.9)	0
Dry Skin	11 (4.7)	0	0	12 (10.8)	0	0
Erythema	3 (1.3)	0	0	6 (5.4)	1 (0.9)	0
Alopecia	2 (0.8)	0	0	14 (12.6)	3 (2.7)	0
Nervous System Disorders	59 (25)	11 (4.7)	1 (0.4)	33 (29.7)	5 (4.5)	0
Headache	21 (8.9)	1 (0.4)	0	4 (3.6)	1 (0.9)	0
Dizziness	8 (3.4)	0	0	6 (5.4)	1 (0.9)	0
Peripheral	4 (1.7)	0	0	8 (7.2)	0	0

Neuropathy						
Blood and Lymphatic System Disorders	58 (24.6)	22 (9.3)	0	44 (39.6)	20 (18)	0
Anemia	44 (18.6)	14 (5.9)	0	37 (33.3)	9 (8.1)	0
Thrombocytopenia	3 (1.3)	0	0	6 (5.4)	1 (0.9)	0
Neutropenia	1 (0.4)	0	0	9 (8.1)	8 (7.2)	0
Psychiatric Disorders	39 (16.5)	2 (0.8)	0	19 (17.1)	0	0
Insomnia	12 (5.1)	0	0	7 (6.3)	0	0
Anxiety	8 (3.4)	0	0	7 (6.3)	0	0
Vascular Disorders	32 (13.6)	6 (2.5)	1 (0.4)	15 (13.5)	3 (2.7)	0
Hypertension	14 (5.9)	3 (1.3)	0	3 (2.7)	0	0
Endocrine Disorders	23 (9.7)	1 (0.4)	0	6 (5.4)	0	0
Hypothryoidism	15 (6.4)	0	0	6 (5.4)	0	0
Cardiac Disorders	17 (7.2)	4 (1.7)	2 (0.8)	14 (12.6)	4 (3.6)	1 (0.9)
Tachycardia	3 (1.3)	0	0	6 (5.4)	0	0
Eye Disorders	14 (5.9)	3 (1.3)	0	12 (10.8)	1 (0.9)	0
Lacrimation Increased	1 (0.4)	0	0	6 (5.4)	0	0

Source: Clinical Study Report for Study CA209141, page 658-661.

8.3.3 Dropouts and/or Discontinuations Due to Adverse Effects

Overall, 21.6% of subjects in the nivolumab arm and 24.3% in the IC arm discontinued treatment due to AEs. Any cause AEs leading to discontinuation in the nivolumab arm that were reported in at least 2 subjects included malignant neoplasm progression (18 subjects, 7.6%), pneumonitis (2 subjects, 0.8%), and pneumonia (2 subjects, 0.8%). For the investigator's choice group, AEs leading to discontinuation reported in at least 2 subjects included malignant neoplasm progression (6 subjects, 5.4%) and ALT increased (2 subjects, 1.8%). There were fewer drug related discontinuations in the nivolumab arm (3.8%) than the IC arm (9.9%).

Table 17 Drug related AE leading to drug discontinuation in the nivolumab arm

Subject Identifier	Adverse Event	Details
CA209141-(b) (6)	AST/ ALT increased	After third infusion, grade 4 AST/ ALT elevation requiring steroid treatment. This case resolved, treatment was discontinued.
CA209141-(b) (6)	Churg-Strauss	After first infusion, developed grade 3 allergic granulomatous angiitis requiring steroid treatment. Treatment was discontinued, no information on outcome.
CA209141-(b) (6)*	Pneumonitis and Arrhythmia	After second infusion, arrhythmia and pneumonitis developed requiring intensive care. Arrhythmia resolved, the patient died due to complications of pneumonitis.
CA209141-(b) (6)	Diarrhea, amylase and lipase increased	After fourth infusion diarrhea started and was treated with steroids and antibiotics. After steroid taper, diarrhea recurred and treatment was discontinued. Final outcome not reported.
CA209141-(b) (6)	Diarrhea	After eighth infusion, diarrhea responded to steroid taper, after 22nd infusion pneumonitis started, treatment was held and re-started after 25th infusion pneumonitis recurred and treatment was discontinued. Final outcome not reported.
CA209141-(b) (6)	AST/ ALT increased	After eighth infusion, hypothyroidism was diagnosed and treated. After ninth infusion AST/ALT increased requiring steroid treatment, patient discontinued nivolumab and was discharged, final outcome not reported.
CA209141-(b) (6)	Hypercalcemia	Seven days after first infusion patient developed hypercalcemia and despite medical management, the patient died.
CA209141-(b) (6)	Myocardial Infarction, hypothyroidism, hypophysitis, and adrenal insufficiency	After third infusion, presented with shortness of breath, diagnosed with grade 2 non-ST elevation myocardial infarction (determined to be not drug related) and he received medical management. Additionally, he was diagnosed with hypothyroidism, hypophysitis and adrenal insufficiency requiring treatment with levothyroxine and steroids. Two days later he died, and the cause of death was listed as disease progression.
CA209141-(b) (6)	Increase in skin mass	After the second infusion, the patient was diagnosed with "skin nodule increased" and nivolumab was discontinued. The patient died due to disease progression 253 days later.

Source: Clinical Study Report for Study CA209141, page 306-313
*Grade 5

Reviewer's Comment: The cause of death for subject # CA209141-(b) (6) is not listed as drug-related. This patient died within 2 days of diagnosis of hypothyroidism, hypophysitis, and adrenal insufficiency, which are labeled toxicities.

8.3.4 Significant Adverse Events

Immune mediated AEs

The adverse events specific to nivolumab are immune mediated AEs. Typically, immune mediated AEs are not associated with traditional chemotherapies. All grade immune mediated AEs requiring treatment with an immune modulation medication were diarrhea / colitis 0.8% on nivolumab, 0 on IC, hepatitis 0.4% on nivolumab, 0 on IC , pneumonitis 0.8% on nivolumab, 0.9% on IC, rash 5.1% on nivolumab, 4.5% on IC, and hypersensitivity reactions 0.8% on nivolumab, and 0.9% on IC. Additionally, immune-mediated endocrine AE were higher on the nivolumab arm. There was 1 (0.4%) case of adrenal insufficiency on the nivolumab arm, and no cases on IC. There were 2 (0.8%) cases of hypophysitis on nivolumab, and no cases on IC. There were 19 (8.1%) cases of hypothyroidism / thyroiditis on nivolumab and 6 (5.4%) on IC. Finally, there were 3 (1.3%) cases of hyperthyroidism on nivolumab and no cases on IC. There were no cases of immune mediated nephritis, renal dysfunction, encephalitis or diabetes mellitus reported in this study. Overall, the incidence of immune mediated AEs on nivolumab were less than 1%, with the exception of rash (5.1% vs. 4.5%), hypothyroidism (8.1% vs. 5.4%) and hyperthyroidism (1.3% vs. 0). Nivolumab is labeled as having the potential to cause immune mediated AEs.

Table 18 Immune Mediated AEs

Preferred Term	Nivolumab 3 mg / kg N=236		Investigator's Choice N=111	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Immune Mediated AE treated with Immune Modulating Medication				
Diarrhea / Colitis	2(0.8)	0	0	0
Hepatitis	1(0.4)	1(0.4)	0	0
Pneumonitis	2(0.8)	2(0.8)	1(0.9)	0
Nephritis / Renal Dysfunction	0	0	0	0
Rash	12(5.1)	0	5(4.5)	1(0.9)
Hypersensitivity / Infusion Reactions	2(0.8)	1(0.4)	1(0.9)	0
Immune Mediated Endocrine AE treated with or without Immune Modulating Medications				
Adrenal Insufficiency	1(0.4)	1(0.4)	0	0
Hypophysitis	2(0.8)	1(0.4)	0	0
Hypothyroidism/ Thyroiditis	19(8.1)	0	6(5.4)	0
Hyperthyroidism	3(1.3)	0	0	0
Diabetes Mellitus	0	0	0	0

Source: Clinical Study Report for Study CA209141, page 87.

Hepatic Adverse Events

Overall, there were more all cause grade 3-4 hepatic events on the nivolumab arm, compared to the Investigator's Choice arm, but there was a slightly higher percentage of any grade hepatic AE on the Investigator's Choice arm (10.8%) compared to nivolumab (9.7%). Two patients on the nivolumab arm had investigator determined "drug-related" hepatic adverse events, and both were treated with high dose corticosteroids for a median duration of four weeks. One of the two patients had resolution of the event by the time of the data lock. The median time to onset of drug-related hepatic events was 93 days. Overall, the majority of hepatic events were grades 1 and 2, there was a low incidence of grade 3-4 hepatic events and no grade 5 events. Nivolumab is labeled as having the potential to cause immune mediated hepatitis.

Table 19 Hepatic Adverse Events

Preferred Term	Nivolumab N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Blood Alkaline Phosphatase Increased	17 (7.2)	3 (1.3)	0	3 (2.7)	0	0
Aspartate Aminotransferase Increased	12 (5.1)	3 (1.3)	0	4 (3.6)	0	0
Alanine Aminotransferase Increased	8 (3.4)	1 (0.4)	0	5 (4.5)	3 (2.7)	0
Transaminases Increased	3 (1.3)	1 (0.4)	0	0	0	0
Bilirubin Increased	2 (0.8)	1 (0.4)	0	1 (0.9)	0	0
Gamma-Glutamyltransferase Increased	2 (0.8)	3 (0.8)	0	1 (0.9)	1 (0.9)	0
Liver Function Test Abnormal	2 (0.8)	1 (0.4)	0	1 (0.9)	0	0
Hepatic Enzyme Increased	0	0	0	1 (0.9)	0	0

Source: Clinical Study Report for Study CA209141, page 779.

8.3.5 Laboratory Findings

The frequency of laboratory abnormalities measured on treatment and within 30 days of the last dose was lower on the nivolumab arm than the investigator's choice arm. Laboratory abnormalities occurring at a rate of 5% or higher on the nivolumab arm compared with

investigator's choice are hemoglobin (8.4% vs. 11.5%), lymphocytes (33.6% vs. 50%) and hyponatremia (11.6% vs. 15.4%). Overall, there were fewer laboratory abnormalities on nivolumab compared to IC.

Table 20 On treatment Laboratory AE by Treatment, Grade 3-4

Laboratory Test	Nivolumab N=236		Investigator's Choice N=111	
	Grade 3-4	# Subjects with Result	Grade 3-4	# Subjects with Result
Hemoglobin	19 (8.4)	N=227	12 (11.5)	N=104
Leukocytosis	3 (1.3)	N=227	7 (6.7)	N=105
Lymphocytes (Absolute)	75 (33.6)	N=223	52 (50)	N=104
Neutrophils	1(0.4)	N=223	8 (7.7)	N=104
Platelet Count	1 (0.4)	N=225	2 (1.9)	N=104
Alanine Aminotransferase	2 (0.9)	N=221	2 (1.9)	N=104
Alkaline Phosphatase	4(1.8)	N=221	1(1)	N=104
Aspartate Aminotransferase	4 (1.9)	N=221	0	N=103
Bilirubin	1 (0.5)	N=221	1(1)	N=103
Hypernatremia	1(0.4)	N=224	1(1)	N=104
Hyponatremia	26 (11.6)	N=224	16(15.4)	N=104
Magnesium Serum High	1 (0.4)	N=223	0	N=103
Magnesium Serum Low	2(0.8)	N=223	0	N=103
Hypercalcemia	5 (2.2)	N=226	1 (1)	N=104
Hypocalcemia	1 (0.4)	N=226	0	N=104
Hyperkalemia	1 (0.4)	N=225	0	N=104
Hypokalemia	2 (0.8)	N=225	3 (2.9)	N=104

Source: Clinical Study Report for Study CA209141, page 1940-1944.

Hematologic

On the nivolumab arm, the hematologic laboratory parameters with a ≥2 grade shift from baseline are: hemoglobin, leukocytes, lymphocytes, neutrophils, and platelet count. For hemoglobin, there were 13 patients on the nivolumab arm with a shift from grade 1 to grade 3. For leukocytes, 2 patients on nivolumab shifted from grade 0 to grade 3, and 1 patient shifted from grade 0 to grade 4. For lymphocytes, 4 patients shifted from grade 0 to grade 3, 7 patients shifted from grade 1 to grade 3, 2 patients shifted from grade 1 to grade 4 and 4 patients shifted from grade 2 to grade 4. For neutrophils, one patient on nivolumab shifted from grade

1 to grade 3. In summary, there were fewer laboratory abnormalities on nivolumab compared to IC.

Table 21 Subjects who experienced a ≥2 grade shift from baseline to a grade 3 or 4 hematologic abnormality.

Laboratory Test	Nivolumab N=236			Investigator's Choice N=111		
	Baseline	Grade 3	Grade 4	Baseline	Grade 3	Grade 4
Hemoglobin	Grade 0	0	NA	Grade 0	0	NA
	Grade 1	13 (5.5)	NA	Grade 1	7 (6.3)	NA
	Grade 2	--	NA	Grade 2	--	NA
Leukocytes	Grade 0	2 (0.8)	1 (0.4)	Grade 0	7 (6.3)	0
	Grade 1	0	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Lymphocytes	Grade 0	4 (1.7)	0	Grade 0	0	0
	Grade 1	7 (3.0)	2 (0.8)	Grade 1	11 (9.9)	0
	Grade 2	--	4 (1.7)	Grade 2	--	5 (4.5)
Neutrophils	Grade 0	1 (0.4)	0	Grade 0	6 (5.4)	2 (1.8)
	Grade 1	0	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Platelet Count	Grade 0	0	0	Grade 0	0	2 (1.8)
	Grade 1	0	1 (0.4)	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0

Source: Clinical Study Report for Study CA209141, page 139.

Hepatic Laboratory Testing

There was one case of hepatitis reported for the nivolumab arm, and one case of laboratory shift of AST from baseline grade 0 to grade 4. On the nivolumab arm, there were 2 patients with increased ALT, shifted from grade 0 at baseline to grade 3. For alkaline phosphatase, 2 patients on nivolumab shifted from baseline grade 0 to grade 3, and one patient shifted from baseline grade 1 to grade 3. For AST, one patient shifted from baseline 0 to grade 3, one shifted from baseline grade 1 to grade 4, and two patients shifted from baseline grade 1 to grade elevation. For bilirubin, one patient on nivolumab shifted from grade 0 to grade 3. The hepatic laboratory shift from baseline on both arms of the study occurred in less than 1% of patients.

Table 22 Subjects who experienced a ≥2 grade shift from baseline to a grade 3 or 4 liver test abnormality

Laboratory Test	Nivolumab N=236			Investigator's Choice N=111		
	Baseline	Grade 3	Grade 4	Baseline	Grade 3	Grade 4
ALT	Grade 0	2 (0.8)	0	Grade 0	0	0
	Grade 1	0	0	Grade 1	1 (0.9)	0
	Grade 2	--	0	Grade 2	--	0
Alkaline Phosphatase	Grade 0	2 (0.8)	0	Grade 0	0	0
	Grade 1	1 (0.4)	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
AST	Grade 0	1 (0.4)	1 (0.4)	Grade 0	0	0
	Grade 1	2 (0.8)	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Bilirubin	Grade 0	1 (0.4)	0	Grade 0	0	1 (0.9)
	Grade 1	0	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0

Source: Clinical Study Report for Study CA209141, page 140.

Patient Identifier: CA209141-(b) (6)
This patient was a 62 year old female with stage 4 SCCHN. After her eighth infusion, she was diagnosed with grade 2 hypothyroidism. After her tenth infusion, she was found to have grade 3 increased AST and ALT. She was treated with methylprednisolone 100 mg IV daily and was discontinued from study. The methylprednisolone was tapered to 50 mg daily and abdominal MRI showed dilation of the common bile duct and intrahepatic gall ducts due to compression of a previously known liver metastasis.

Reviewer Comment: This case of hepatitis is likely disease related, and unrelated to nivolumab.

Renal
In both the nivolumab arm and the investigator's choice arm, the increases in creatinine were grade 1 or 2. There were no 2 grade shifts from baseline in either study arm for creatinine.

Thryoid
There were more subjects with changes in thyroid function tests on the nivolumab arm compared to the Investigator's Choice arm. On the nivolumab arm, 18% of patients had thyroid stimulating hormone levels that were normal at baseline and above the upper limit of normal on study, compared to 12% on the Investigator's choice arm. Immune mediated endocrinopathies are labeled toxicity associated with nivolumab.

Table 23 Thyroid Stimulating Hormone laboratory value – On Treatment

Thyroid Stimulating Hormone	Nivolumab N=236	Investigator's Choice N=111
TSH > ULN	107 (45.3)	39 (35.1)
TSH > ULN with TSH ≤ at baseline	43 (18.2)	14 (12.6)
TSH > ULN With at least one FT3/FT4 test value < LLN With all other FT3/FT4 test values ≥ LLN With FT3/FT4 test missing	 67 (28.4) 33 (14) 7 (3)	 16 (14.4) 16 (14.4) 7 (6.3)
TSH < LLN	39 (16.5)	
TSH < LLN with TSH ≥ LLN at baseline	32 (13.6)	
TSH < LLN With at least one FT# / FT4 test value > ULN With all other FT3/FT4 test values ≤ULN With FT3 / FT4 test missing	 16 (6.8) 20 (8.5) 3 (1.3)	 4 (2.7) 5 9 (8.1) 6 1 (0.9)

Source: Clinical Study Report for Study CA209141, page 2008.

8.4 Analysis of Submission-Specific Safety Issues

AE related to SCCHN
Safety issues specific to the SCCHN population are related to problems with the face, mouth, throat, airway and esophagus. The overall incidences of adverse events specific to SCCHN were low, and there were no grade 5 events specific to these selected preferred terms. "Face edema" occurred at a lower rate on nivolumab (4.2%) compared to IC (8.1%). "Swelling face" occurred at similar rates on both arms.

Table 24 Selected Adverse Events specific to SCCHN

Preferred Term	Nivolumab N=236	Investigator's Choice N=111
Face Edema	10 (4.2)	9 (8.1)
Swelling Face	1 (0.4)	1 (0.9)
Oral pain	3 (1.3)	4 (3.6)
Oral dysaesthesia	3 (1.3)	0
Dry Mouth	7 (3)	6 (5.4)
Stridor	2 (0.8)	1 (0.9)
Trismus	4 (1.7)	2 (1.8)
Tracheal Irritation	1 (0.4)	1 (0.9)
Esophageal Stenosis	1 (0.4)	0
Tracheoesophageal Fistula	0	1 (0.9)

Source: Clinical Study Report for Study CA209141, page 589-621.

AE related to Age
The majority of patients in this study were age 75 years or younger. There were 239 participants less than 65 years old, there were 92 participants aged 65 to 74 years and 16 participants over aged 75 years or older. The number of patients over age 75 is very small, causing the percentage of adverse event appear large in this age group. The adverse events that occurred at the highest rates in the age over 75 group were decreased appetite (25%), dehydration, lung infection (25%), constipation (25%), diarrhea (25%), productive cough (16.7%), and pyrexia (16.7%). The following adverse events all occurred in one patient over age 75, with a rate of 8.3%: abdominal pain, breast tenderness, catheter site infection, chest pain, deafness, dysgeusia, face edema, performance status decreased, hypertension, hypothyroidism, ischemic stroke, leukocytosis, lymphopenia, malignant pleural effusion, mouth hemorrhage, neck pain, neck injury, pleuritic pain, subdural hematoma, tachycardia, thrombosis, tumor hemorrhage, tumor ulceration, and wheezing. Overall, there are no clinically significant increases in AEs related to advanced age.

Table 25 Adverse Events occurring ≥5% on the Nivolumab arm, by age.

Preferred Term	Nivolumab Age <65 years N=168			Investigator's Choice Age <65 years N=71			Nivolumab Age 65 - <75 N=56			Investigator's Choice Age 65 - <75 N=36			Nivolumab Age 75 - <85 N=12			Investigator's Choice Age 75 - <85 N=4		
	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	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Total Subjects with an event	165 (98.2)	68 (40.5)	32 (19)	71 (100)	38 (53.5)	14 (19.7)	54 (96.4)	25 (44.6)	13 (23.2)	34 (94.4)	17 (47.2)	10 (27.8)	10 (83.3)	4 (33.3)	1 (8.3)	4 (100)	3 (75)	1 (25)
Fatigue	41 (24.4)	6 (3.6)	0	25 (35.2)	5 (7)	0	20 (35.7)	2 (3.6)	0	11 (30.6)	2 (5.6)	0	1 (8.3)	0	0	0	0	0
Pyrexia	19 (11.3)	1 (0.6)	0	11 (15.5)	1 (1.4)	0	9 (16.1)	0	0	4 (11.1)	1 (2.8)	0	2 (16.7)	0	0	1 (25)	1 (25)	0
Asthenia	17 (10.1)	3 (1.8)	0	16 (22.5)	3 (4.2)	0	6 (10.7)	2 (3.6)	0	7 (19.4)	0	0	1 (8.3)	0	0	1 (25)	2 (25)	0
Peripheral Edema	12 (7.1)	0	0	4 (5.6)	0	0	5 (8.9)	1 (1.8)	0	1 (2.8)	0	0	1 (8.3)	0	0	0	0	0
Performance Status Decreased	1 (0.6)	0	0	0	0	0	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Face Edema	8 (4.8)	0	0	6 (8.5)	0	0	1 (1.8)	0	0	3 (8.3)	0	0	1 (8.3)	0	0	0	0	0
Nausea	33 (19.6)	1 (0.6)	0	24 (33.8)	1 (1.4)	0	11 (19.6)	0	0	10 (27.8)	0	0	1 (8.3)	0	0	0	0	0
Constipation	23 (13.7)	1 (0.6)	0	16 (22.5)	0	0	10 (17.9)	1 (1.8)	0	4 (11.1)	0	0	3 (25)	0	0	0	0	0
Diarrhea	22 (13.1)	2 (1.2)	0	13 (18.3)	1 (1.4)	0	10 (17.9)	0	0	12 (33.3)	2 (5.6)	0	3 (25)	0	0	1 (25)	0	0
Vomiting	20 (11.9)	1 (0.6)	0	9 (12.7)	0	0	6 (10.7)	0	0	5 (13.9)	0	0	1 (8.3)	0	0	0	0	0
Stomatitis	*	*	*	*	*	*	4 (7.1)	1 (1.8)	0	3 (8.3)	1 (2.8)	0	*	*	*	*	*	*
Abdominal Pain	*	*	*	*	*	*	3 (5.4)	1 (1.8)	0	3 (8.3)	1 (2.8)	0	1 (8.3)	0	0	0	0	0
Chest Pain	3 (1.8)	0	0	2 (2.8)	0	0	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Pleuritic Pain	1 (0.6)	0	0	1 (1.4)	0	0	1 (1.8)	0	0	0	0	0	1 (8.3)	0	0	0	0	0

Preferred Term	Nivolumab Age <65 years N=168			Investigator's Choice Age <65 years N=71			Nivolumab Age 65 - <75 N=56			Investigator's Choice Age 65 - <75 N=36			Nivolumab Age 75 - <85 N=12			Investigator's Choice Age 75 - <85 N=4		
	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	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Dysphagia	19 (11.3)	8 (4.8)	0	11 (15.5)	2 (2.8)	0	9 (16.1)	1 (1.8)	0	3 (8.3)	1 (2.8)	0	1 (8.3)	0	0	1 (25)	0	0
Dyspnea	23 (13.7)	10 (6)	0	8 (11.3)	2 (2.8)	0	8 (14.3)	3 (5.4)	0	4 (11.1)	0	0	1 (8.3)	0	0	0	0	0
Dysgeusia	2 (1.2)	0	0	3 (4.2)	0	0	1 (1.8)	0	0	0	0	0	1 (8.3)	0	0	0	0	0
Productive Cough or Cough	21 (12.5)	0	0	6 (8.5)	0	0	9 (16.1)	0	0	4 (11.1)	0	0	2 (16.7)	1 (8.3)	0	0	0	0
Wheezing	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Hemoptysis	*	*	*	*	*	*	4 (7.1)	1 (1.8)	0	1 (2.8)	1 (2.8)	0	*	*	*	*	*	*
Mouth Hemorrhage	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Aspiration pneumonia	9 (5.4)	8 (4.8)	0	2 (2.8)	2 (2.8)	0	*	*	*	*	*	*	*	*	*	*	*	*
Decreased Appetite	23 (13.7)	0	0	16 (22.5)	2 (2.8)	0	18 (32.1)	2 (3.6)	0	5 (13.9)	1 (2.8)	0	3 (25)	1 (8.3)	0	1 (25)	1 (25)	0
Dehydration	*	*	*	*	*	*	3 (5.4)	0	0	1 (2.8)	1 (2.8)	0	1 (8.3)	0	0	1 (25)	0	0
Hyponatremia	17 (10.1)	8 (4.8)	0	7 (9.9)	4 (5.6)	0	4 (7.1)	2 (3.6)	0	6 (16.7)	4 (11.1)	0	1 (8.3)	1 (8.3)	0	1 (25)	1 (25)	0
Hypercalcemia	12 (7.1)	2 (1.2)	1 (0.6)	5 (7)	2 (2.8)	0	4 (7.1)	3 (5.4)	0	3 (8.3)	0	0	*	*	*	*	*	*
Hypoalbuminemia	4 (5.9)	1 (1.5)	0	0	0	0	4 (7.1)	1 (1.8)	0	0	0	0	*	*	*	*	*	*
Hyperglycemia	10 (6)	2 (1.2)	0	6 (8.5)	2 (2.8)	0	3 (5.4)	1 (1.8)	0	2 (5.6)	1 (2.8)	0	*	*	*	*	*	*
Hyperkalemia	*	*	*	*	*	*	3 (5.4)	0	0	1 (2.8)	0	0	*	*	*	*	*	*
Pneumonia	10 (6)	6 (3.6)	0	1 (1.4)	1 (1.4)	0	5 (8.9)	3 (5.4)	0	1 (2.8)	0	0	*	*	*	*	*	*

Preferred Term	Nivolumab Age <65 years N=168			Investigator's Choice Age <65 years N=71			Nivolumab Age 65 - <75 N=56			Investigator's Choice Age 65 - <75 N=36			Nivolumab Age 75 - <85 N=12			Investigator's Choice Age 75 - <85 N=4		
	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	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Lung Infection	*	*	*	*	*	*	4 (7.1)	1 (1.8)	0	2 (5.6)	1 (2.8)	1 (2.8)	3 (25)	2 (16.7)	0	0	0	0
Catheter Site Infection	0	0	0	1 (1.4)	1 (1.4)	0	1 (1.8)	0	0	1 (2.8)	1 (2.8)	0	1 (8.3)	0	0	0	0	0
Infected Skin Ulcer	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Malignant Pleural Effusion	7 (4.2)	2 (1.2)	0	4 (5.6)	4 (5.6)	0	0	0	0	3 (8.3)	1 (2.8)	0	1 (8.3)	1 (8.3)	0	0	0	0
Headache	17 (10.1)	1 (0.6)	0	3 (4.2)	1 (1.4)	0	3 (5.4)	0	0	1 (2.8)	0	0	1 (8.3)	0	0	0	0	0
Pruritis	15 (8.9)	0	0	0	0	0	3 (5.4)	0	0	0	0	0	2 (16.7)	1 (8.3)	0	1 (25)	0	0
Rash	15 (8.9)	0	0	1 (1.4)	0	0	4 (7.1)	0	0	3 (8.3)	1 (2.8)	0	1 (8.3)	0	0	1 (25)	0	0
Dry Skin	9 (5.4)	0	0	8 (11.3)	0	0	*	*	*	*	*	*	*	*	*	*	*	*
Malignant Neoplasm Progression	30 (17.9)	4 (2.4)	26 (15.5)	16 (22.5)	2 (2.8)	14 (19.7)	12 (21.4)	1 (1.8)	11 (19.6)	8 (22.2)	0	0	1 (8.3)	0	1 (8.3)	1 (25)	0	1 (25)
Tumor Pain	10 (6)	2 (1.2)	0	4 (5.6)	0	0	3 (5.4)	0	0	2 (5.6)	0	0	*	*	*	*	*	*
Tumor Hemorrhage	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Tumor Ulceration	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Anemia	31 (18.5)	9 (5.4)	0	26 (36.6)	5 (7)	0	11 (19.6)	5 (8.9)	0	11 (30.6)	4 (11.1)	0	2 (16.7)	0	0	0	0	0
Leukocytosis	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Lymphopenia	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Insomnia	10 (6)	0	0	4 (5.6)	0	0	*	*	*	*	*	*	*	*	*	*	*	*

Preferred Term	Nivolumab Age <65 years N=168			Investigator's Choice Age <65 years N=71			Nivolumab Age 65 - <75 N=56			Investigator's Choice Age 65 - <75 N=36			Nivolumab Age 75 - <85 N=12			Investigator's Choice Age 75 - <85 N=4		
	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	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Hypertension	9 (5.4)	0	0	3 (4.2)	0	0	4 (7.1)	2 (3.6)	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0	0
Hypothyroidism	10 (6)	1 (0.6)	0	2 (2.8)	0	0	4 (7.1)	0	0	3 (8.3)	0	0	1 (8.3)	0	0	1 (25)	0	0
Back Pain	*	*	*	*	*	*	5 (8.9)	1 (1.8)	0	0	0	0	1 (8.3)	0	0	0	0	0
Arthralgia	*	*	*	*	*	*	3 (5.4)	0	0	2 (5.6)	0	0	*	*	*	*	*	*
Neck Pain	*	*	*	*	*	*	3 (5.4)	0	0	2 (5.6)	0	0	1 (8.3)	0	0	0	0	0
Depression	6 (3.6)	0	0	1 (1.4)	0	0	3 (5.4)	0	0	1 (2.8)	0	0	*	*	*	*	*	*
Balance Disorder	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0	1 (8.3)	0	0	0	0	0
Ischemia Stroke	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	1 (8.3)	0	0	0	0
Neck Injury	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Subdural Hematoma	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Thrombosis	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	1 (8.3)	0	0	0	0
Tachycardia	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Deafness	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Breast Tenderness	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0

Source: Clinical Study Report for Study CA209141, pages 1017 -1327.

The incidence of adverse events in the investigations category were low and similar between arms. The incidence of hepatic AE was higher on nivolumab, and is a labeled toxicity. The incidence of hepatic AEs did not increase with advanced age.

Table 26: Adverse Events – Investigations occurring ≥5% on the Nivolumab Arm by Age

Preferred Term	N <65			IC <65			N 65-<75 N=56			IC 65-<75 N=36			N			IC		
Weight Decreased	24 (14.3)	0	0	13 (18.3)	0	0	6 (10.7)	0	0	2 (5.6)	0	0	1 (8.3)	0	0	1 (25)	0	0
Amylase Increased	9 (5.4)	4 (2.4)	0	1 (1.4)	1 (1.4)	0	*	*	*	*	*	*	*	*	*	*	*	*
Blood Alkaline Phosphatase Increased	9 (5.4)	1 (0.6)	0	3 (4.2)	0	0	7 (12.5)	1 (1.8)	0	0	0	0	1 (8.3)	1 (8.3)	0	0	0	0
Amylase Increased	9 (5.4)	4 (2.4)	0	1 (1.4)	1 (1.4)	0	*	*	*	*	*	*	1 (8.3)	0	0	0	0	0
Aspartate Aminotransferase Increased	*	*	*	*	*	*	5 (8.9)	1 (1.8)	0	1 (2.8)	0	0	2 (16.7)	1 (8.3)	0	0	0	0
Alanine Aminotransferase increased	*	*	*	*	*	*	4 (7.1)	0	0	1 (2.8)	0	0	1 (8.3)	0	0	0	0	0
Gamma-Glutamyltransferase Increased	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	1 (8.3)	0	0	0	0
Lipase Increased	*	*	*	*	*	*	*	*	*	*	*	*	1 (8.3)	1 (8.3)	0	0	0	0

Source: Clinical Study Report for Study CA209141, pages 1017 -1327.

*No reported cases for this age group.

8.5 Safety in the Postmarket Settings

8.5.1 Safety Concerns Identified Through Postmarket Experience

There have been a total of six Periodic Adverse Drug Experience Reports (PADER) submitted regarding nivolumab. Brief statements about these reports are listed here in reverse chronologic order.

The PADER covering the time period of March 22, 2016 through June 21, 2016 reports that myocarditis, myositis, and rhabdomyolysis were considered adverse drug reactions for nivolumab, nivolumab in combination with ipilumumab, and nivolumab in combination with other agents. The USPI will be updated to include myocarditis, myositis, and rhabdomyolysis. Additionally, there is a Post Marketing Requirement (PMR) for (sBLA) BLA 125554/S-019 to further characterize the complications of allogeneic Hematopoietic Stem Cell Transplant (HSCT) after PD1 immunotherapy. BMS agreed to the proposal in May 2016, and the expected FDA receipt date for the final protocol submission is December 2016.

The PADER covering December 22, 2015 through March 21, 2016 does not report any new safety issues.

The PADER covering September 22, 2015 through December 21, 2015 does not report any new safety issues. (b) (6) [redacted]

The PADER covering June 22, 2015 through September 21, 2015 (b) (6) [redacted]. On 21-Sep-2015, the DHCP letter regarding toxic epidermal necrolysis and encephalitis was distributed in the US to oncologists, oncology nurses and pharmacists.

The PADER covering the dates March 22, 2015 through June 21, 2015 reports that “new important ADRs of TEN and encephalitis” have been identified. The appropriate risk minimization strategy is being actively evaluated including potential change to the nivolumab USPI. These life threatening events occurred in low frequency and do not alter the benefit/risk of nivolumab in the context of established efficacy and advanced cancer population.

Continuous Company safety monitoring will ensure that updated safety information is available as needed.

The first PADER covered the dates December 22, 2014 through March 21, 2015. New important ADRs of toxic epidermal necrolysis (TEN) and encephalitis were identified during this reporting period and appropriate risk minimization strategy is being actively evaluated including potential change to the nivolumab USPI.

8.6 Integrated Assessment of Safety

Integrated review of safety is not relevant for this streamlined review.

9 Advisory Committee Meeting and Other External Consultations

This application provides a clear favorable risk: benefit and an advisory committee was not required.

10 Labeling Recommendations

10.1 Prescribing Information

The prescribing information was updated with the new indication of recurrent or metastatic squamous cell carcinoma of the head and neck. The clinical trials experience section now includes information on CheckMate 141, here named Trial 10, stating that 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.

The clinical studies section was updated with the Kaplan-Meier curve for overall survival from Trial 10, and states that 28% (101/361) of patients had non-quantifiable PD-L1 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. And, states that in an exploratory subgroup analysis of survival, patients with PD-L1 positive tumor, the HR was 0.55 (95% CI 0.36, 0.83) with median survival of 8.7 months for patients receiving nivolumab and 4.6 months for patients receiving investigators choice of chemotherapy. Among patients with PDL1 negative tumors, the HR was 0.89 (95% CI 0.54, 1.45) with median survival of 5.7 months for patients receiving nivolumab and 5.8 months for patients receiving investigators choice of chemotherapy.

11 Risk Evaluation and Mitigation Strategies (REMS)

No new concerning safety signals were noted and the existing safety issues are adequately managed through the agreed upon product labeling, still under negotiation.

12 Postmarketing Requirements and Commitment

The clinical team is recommending one postmarketing commitment. The commitment is to analytically validate and establish performance characteristics of the Dako PD-L1 IHC 28-8 pharmDx assay for HNSCC that was used to assess PD-L1 expression in tumor samples in this study.

The Proposed Postmarketing Commitment:

1. To provide the results of an analytic validation study for an assay identification, and possible selection of, patients with PD-L1 positive and PD-L1 negative SCCHN to inform product labeling.

13 Appendices

13.1 References

1. Agulnick, M. New approaches to EGFR inhibition for locally advanced or metastatic squamous cell carcinoma of the head and neck (SCCHN). Med Oncol. 2012; 29: 2481-2491.
2. Cho et al, Weekly docetaxel in patients with platinum-refractory metastatic or recurrent squamous cell carcinoma of the head and neck. Cancer Chemother Pharmacol, 2009, 65:27-32.
3. FDA Grants Genentech's Cancer Immunotherapy Atezolizumab Priority Review for Advanced Bladder Cancer. (2016, March 14). Retrieved August 12, 2016.
4. Lefebvre, J. Current clinical outcomes demand new treatment options for SCCHN. Annals of Oncology. 2005; 16 (suppl 6) vi7-vi12.
5. Machiels, J. et al. Advances in the management of squamous cell carcinoma of the head and neck. F1000 Prime Reports 2014, 6:44.
6. Machiels et al, Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomized phase 3 trial. Lancet Oncol, 2015, 16:583-594.

7. NCCN Guidelines. Head and Neck Cancers, Version 2.2013. Retrieved March 9, 2016, from http://oralcancerfoundation.org/treatment/pdf/head-and-neck.pdf.
8. SEER Stat Fact Sheets: Oral Cavity and Pharynx Cancer. (n.d.). Retrieved August 12, 2016, from http://seer.cancer.gov/statfacts/html/oralcav.html.
9. Starr, P. (2015, August 8). Encouraging Results for Pembrolizumab in Head and Neck Cancer. American Health and Drug Benefits, 8(16). Retrieved August 12, 2016, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4570057/.
10. Stewart et al, Phase III Study of Gefitinib Compared With Intravenous Methotrexate for Recurrent Squamous Cell Carcinoma of the Head and Neck J Clin Oncol, 2009, 27:1864-1871.
11. Vermorken et al, Open-Label, Uncontrolled, Multicenter Phase II Study to Evaluate the Efficacy and Toxicity of Cetuximab As a Single Agent in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Failed to Respond to Platinum-Based Therapy J Clin Oncol, 2007, 25:2171-2177.
12. Zenda et al, Single-agent docetaxel in patients with platinum refractory metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN) Jpn J Clin Oncol, 2007, 37:477-481.

13.2 Financial Disclosure

Covered Clinical Study: CheckMate 141 / CA209141

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 487		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none. Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: none. Significant equity interest held by investigator in S Sponsor of covered study: none.		

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 ☒ Not applicable.	No ☐ (Request explanation from Applicant)

14.0 Appendix

Study Schedule, Clinical Protocol CA 209141

Table 5.1-2: Short-term Procedural Outline (Nivolumab)

Procedure	During Treatment Visit[a]	Notes
Safety Assessments		
Targeted Physical Examination	X	Focused exam (at a minimum skin, GI, endocrine, and pulmonary) and history on AEs stemming from immune MOA described in IB Appendix.
Vital Signs and Oxygen Saturation	X	Including BP, HR, temperature, and oxygen saturation by pulse oximetry.
Physical Measurements (including performance status)	X	To include weight and performance status.
Adverse Events Assessment	X	
Review of Concomitant Medication	X	
Laboratory Tests	X	On-study local laboratory assessments should be done within 72 hours prior to each dose through Week 24 and every alternate dose thereafter and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3.
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Efficacy Assessments		
Tumor Assessment	X	• Tumor assessments should continue every 6 weeks (± 7 days) beginning at Week 9 (± 7 days) until disease progression or treatment is discontinued (whichever occurs later). • CT or MRI of head and neck, chest, and abdomen, and all known sites of disease. Use same imaging method as was used at screening/baseline. • Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

Table 5.1-2: Short-term Procedural Outline (Nivolumab)		
Procedure	**During Treatment Visit[a]**	**Notes**
Outcomes Research Assessment		
QLQ-C30	X	Assessed before dosing (starting at Week 1, then every 6 weeks as of week 9).
QLQ-H&N 35	X	Assessed before dosing (starting at Week 1, then every 6 weeks as of week 9).
EQ-5D	X	Assessed before dosing (starting at Week 1, then every 6 weeks as of week 9).
Health Related Resource Utilization	X	Assessed before dosing (first assessment at Week 1, then every 6 weeks as of Week 9).
Pharmacokinetic Assessments		
PK samples (Serum)	X	See separate Table 5.6-1
Exploratory Biomarker Testing		
Immunogenicity samples (Serum)	X	See separate Table 5.6-1
Soluble Biomarkers (Serum)	X	See separate Table 5.7-1
Immunophenotyping (PBMC)	X	See separate Table 5.7-1
Ex vivo functional assay (PBMC)	X	See separate Table 5.7-1
SNP (Whole Blood)	X	See separate Table 5.7-1
Tumor Biopsy (Gene Expression)	X	See separate Table 5.7-1
Saliva Sample	X	See separate Table 5.7-1

Table 5.1-2: Short-term Procedural Outline (Nivolumab)		
Procedure	**During Treatment Visit[a]**	**Notes**
Study Drug		
Randomize	X	
IVRS Drug Vial Assignment	X	
Dispense Study Drug	X	Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 12 days between doses.

[a] Week1, Day 1; Week 3, Day 1; Week 5, Day 1; and Every Other Week Thereafter

Table 5.1-3: Short-term Procedural Outline (Investigator's Choice)		
Procedure	**During Treatment Visit[a]**	**Notes**
Safety Assessments		
Targeted Physical Examination	X	Focused exam (at a minimum skin, GI, endocrine, and pulmonary) and history on AEs stemming from immune MOA described in IB Appendix. Week 1, Day 1, then every 2 weeks
Vital Signs and Oxygen Saturation	X	Including BP, HR, temperature, and oxygen saturation by pulse oximetry. Week 1, Day 1, then every 2 weeks
Physical Measurements (including performance status)	X	Weight and ECOG status. Week 1, Day 1, then every 2 weeks The dosing calculations should be based on body surface area (BSA).
Adverse Events Assessment	X	
Review of Concomitant Medication	X	
Laboratory Tests	X	On-study local laboratory assessments should be done within 72 hours prior to every other dose through Week 24 and every four doses thereafter and include: CBC w/differential; LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to first dose and then every 4 weeks (± 1 week) regardless of dosing schedule.
Efficacy Assessments		
Tumor Assessment	X	Tumor assessments should continue every 6 weeks (± 7 days) beginning at Week 9 (± 7 days) until disease progression or treatment is discontinued (whichever occurs later). CT or MRI of head and neck, chest, abdomen, and all known sites of disease. Use same imaging method as was used at screening/baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

Table 5.1-3: Short-term Procedural Outline (Investigator's Choice)		
Procedure	**During Treatment Visit[a]**	**Notes**
Outcomes Research Assessment		
QLQ-C30	X	Assessed before dosing (first assessment at Week 1, then every 6 weeks as of Week 9).
QLQ-H&N 35	X	Assessed before dosing (first assessment at Week 1, then every 6 weeks as of Week 9).
EQ-5D	X	Assessed before dosing (first assessment at Week 1, then every 6 weeks as of Week 9).
Health Related Resource Utilization	X	Assessed before dosing (first assessment at Week 1, then every 6 weeks as of Week 9).
Exploratory Biomarker Testing		
Soluble Biomarkers (Serum)	X	See separate Table 5.7-1 for detailed sample collection timing.
Immunophenotyping (PBMC)	X	See separate Table 5.7-1 for detailed sample collection timing;
Ex vivo functional assay (PBMC)	X	See separate Table 5.7-1 for detailed sample collection timing.
SNP (Whole Blood)	X	See separate Table 5.7-1 for detailed sample collection timing.
Tumor Biopsy	X	See separate Table 5.7-1 for detailed sample collection timing.
Saliva Sample	X	See separate Table 5.7-1 for detailed sample collection timing.
Study Drug		
Randomize	X	
IVRS Drug (Vial) Assignment	X	Not applicable if study drug is managed without IVRS.
Dispense Study Drug	X	Within 3 days from vial allocation, the subject must receive the first dose of study medication. Subjects may be dosed no less than 7 days between doses.

[a] Week 1, Day 1; Week 2, Day 1; etc. for Weekly Dosing of chemotherapy of investigator's choice.

Table 5.1-4: Follow-up Period (All Treatment Arms)			
Procedure	**Follow-Up Visits 1 and 2[a]**	**Survival Follow-up Visits[b]**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues.
Vital Signs	X		
Adverse Events Assessment	X	X	In survival period only to include toxicities from study therapy.
Review of Concomitant Medication	X	X	
Laboratory Tests	X		CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (+ reflex Free T4 and Free T3). To be done at FU1, to be repeated at FU2, if study related toxicity persists.
Pregnancy Test (WOCBP only)	X		Serum or urine.
Efficacy Assessments			
Tumor Assessment	X	X	For subjects without previous disease progression ONLY. • Tumor assessments should occur every 6 weeks (± 1 wk) until disease progression. • CT or MRI of head and neck, chest, abdomen, and all known sites of disease. Use same imaging method as was used at screening/baseline. • Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated

Table 5.1-4: Follow-up Period (All Treatment Arms)			
Procedure	**Follow-Up Visits 1 and 2[a]**	**Survival Follow-up Visits[b]**	**Notes**
Outcomes Research Assessment			
QLQ-C30	X		
QLQ-H&N 35	X		
EQ-5D	X	X[c]	
Health Related Resource Utilization	X		
Pharmacokinetic Assessments			
PK samples (Serum)	X	NA	FU1 and FU2 only; not in investigator's choice arm
Exploratory Biomarker Testing			
Immunogenicity Samples (Serum)	X	NA	FU1 and FU2 only; not in investigator's choice arm
Subject Status			
Survival Status	X	X	Every 3 months after FU2; may be accomplished by visit or phone contact to assess subsequent anti-cancer therapy.

[a] Follow-up Visit (FU1) = 35 Days from the Last Dose ± 7 Days or Coincides with the Date of Discontinuation (± 7 Days) if Date of Discontinuation is Greater Than 35 Days After Last dose, Follow-up Visit 2 (FU2) = 80 Days (± 7 Days) from Follow-up Visit 1

[b] Every 3 Months (± 7 Days) from FU2

[c] EQ-5D data can be collected over the phone.

Table 5.1-1: Screening Procedural Outline (CA209141)		
Procedure	**Screening Visit**	**Notes**
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History	X	
Tumor Tissue Sample	X	Sufficient evaluable tumor tissue obtained before start of study drug treatment in the metastatic setting or from an unresectable site (block or minimum of 10 slides containing a minimum of 100 evaluable tumor cells obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen; a fine needle biopsy is not sufficient). Biopsy procedures requiring general anesthesia should in general not be performed, see also Section 5.7.3. For subjects where a fresh biopsy is not feasible, archival tumor material that meets Section 5.7.3 criteria must be made available.
Saliva Sample	X	For oral microbiome sequencing, see Section 5.7.7
Human Papillomavirus Status (p-16 expression)	X	As results are used in a preplanned analysis they must be made available. (Option 1: test results are available at site. Option 2: a sample is sent to the Central Laboratory for analysis).
Safety Assessments		
Physical Examination	X	
Physical Measurements	X	Height & weight; Body Surface Area (in case of randomization to investigator's choice treatment arm).

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/s/

BARBARA A SCEPURA
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10/24/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s022

ENVIRONMENTAL ASSESSMENT

US Food & Drug Administration
Center for Drug Evaluation & Research
Office of Biotechnology Products

MEMORANDUM

DATE:	May 20, 2016
BLA:	**125554**
SUPPLEMENT:	**022**
FROM:	Xianghong Jing, Ph.D., Product Quality Reviewer CDER/OPQ/OBP/DBRR II
THROUGH:	Joel Welch, Ph.D., Product Quality Team Leader CDER/OPQ/OBP/DBRR II
PRODUCT:	OPDIVO (Nivolumab/BMS-936558/MDX-1106) fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) target to the programmed death-1 (PD-1) receptor
ROUTE OF ADMIN:	Intravenous infusion
INDICATION:	Recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck
DOSE REGIMEN:	3 mg/kg every two weeks
STRENGTHS:	40mg/4ml (10mg/ml) vial, 100mg/10ml (10mg/ml) vial
SPONSOR:	Bristol-Myers Squibb
CLINICAL DIVSION:	CDER/OHOP/DOP II
REVIEW TEAM:	Product Quality: Xianghong Jing RPM: Meredith Libeg

BACKGROUND:

On May 11, 2016, the sponsor submitted s-022 supplement to request regular approval of Opdivo for the treatment of patients with recurrent or metastatic SCCHN after platinum-based therapy. This request is based on the clinically and statistically significant results from CA209141, a global, randomized, open-label, Phase 3 study evaluating nivolumab versus investigator's choice (cetuximab, methotrexate, or docetaxel) in adults with recurrent or metastatic SCCHN who had progressed on or within 6 months of the last dose of a platinum-based therapy.

This review is about the environmental assessment the sponsor submitted in the supplement (sequence #0172).

ADMINISTRATIVE INFORMATION

Environmental Assessment [21 CFR 312.23(a)(7)(iv)(e)]

Bristol-Myers Squibb Company is requesting a categorical exclusion from the preparation of an environmental assessment (EA) for nivolumab according to section 505(b) of the Federal Food, Drug, and Cosmetic Act. The subject of the proposed action (sBLA for nivolumab) will not significantly affect the quality of the environment and meets the requirements for a categorical exclusion from submitting an environmental assessment under 21 CFR 25.31(c). In addition, to Bristol-Myers Squibb Company's knowledge, no extraordinary circumstances exist, as referenced in 21 CFR 25.15(d). This drug is a protein which is expected to rapidly degrade to amino acids and mineralize to carbon dioxide. It is not derived from any wild-sourced plant and/or animal material 21 CFR 25.21(b).

This is considered appropriate.

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/s/

KIM E ROBINSON
03/08/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s022

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
BLA (supplement)	125554 (S-22)
Submission Date:	May 11, 2016
PDUFA Date:	November 11th 2016
Brand Name:	Opdivo ®
Generic Name:	Nivolumab (BMS-936558)
Formulation/Strength:	40 mg/4 mL and 100 mg/10 mL solution in a single-dose vial
Sponsor:	Bristol-Myers Squibb
Submission Type; Code:	Efficacy Supplement
Dosing regimen:	3 mg/kg as a 60 minute intravenous (IV) infusion once every 2 weeks (Q2W)
Proposed Indication:	(b) (4)
Pharmacometrics Reviewer:	Hongshan Li, Ph.D.
Pharmacometrics Team Leader:	Jingyu Yu, Ph.D.
OCP Reviewer:	Brian D. Furmanski, Ph.D.
OCP Team Leader:	Hong Zhao, Ph.D.
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Oncology Products 2 (DOP2)

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2.2.3. What is the incidence (rate) of the formation of the anti-drug antibodies (ADA)? Do the ADAs have neutralizing activity?

2.2.4. What bioanalytical methods are used to assess nivolumab concentrations?

2.2.5. What methods are used to assess nivolumab ADA incidence in SCCHN patients?

3. Detailed Labeling Recommendations

1. EXCUTIVE SUMMARY

Nivolumab (OPDIVO®) was granted accelerated approval on December 22, 2014 for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab and, for BRAF V600 positive patients that have received treatment with ipilimumab and a BRAF inhibitor. It was later received approval for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. In the current efficacy supplement, Bristol-Myers Squibb (BMS) is requesting full approval for nivolumab in patients with recurrent or metastatic platinum-refractory SCCHN.

In support of approval of the SCCHN indication, BMS submitted results from a randomized (2:1) multicenter study (CA209141), which compared nivolumab monotherapy (N=236) to investigator's choice therapy consisting of cetuximab, methotrexate, or docetaxel (N=111). Randomization was stratified based on prior treatment with cetuximab vs. no prior cetuximab treatment. Study CA209141 demonstrated an improvement in overall survival (OS) vs investigator's choice therapy in patients with recurrent or metastatic platinum-refractory SCCHN (HR = 0.70 [97.73% CI: 0.51, 0.96]; stratified log-rank test p-value = 0.0101), with a median OS of 7.49 months for nivolumab and 5.06 months for investigator's choice. The following clinical pharmacology pertinent information was submitted to support the use of nivolumab at a dose 3 mg/kg Q2W in patients with recurrent or metastatic platinum-refractory SCCHN:

- Population PK (PopPK) analysis characterizing the concentration-time data of nivolumab in patients with SCCHN and comparing the results to patients with NSCLC and other tumor types. Nivolumab plasma exposure and clearance in the SCCHN population was comparable to patients with other tumors.
- Updated immunogenicity profile of nivolumab alone and pooled analyses across multiple tumor types. The rate of anti-drug antibody (ADA) formation in the SCCHN population was 8.8% ADA positive and similar to the studied populations for nivolumab. The effect of ADA formation on nivolumab safety and pharmacokinetic profile is minimal and is not clinically meaningful.

1.1. Recommendations

The Office of Clinical Pharmacology (Division of Pharmacometrics and Division of Clinical Pharmacology V) has reviewed the information contained in Supplement 22 of BLA125554 and concludes that nivolumab at 3 mg/kg Q2W for use in patients with recurrent or metastatic platinum-refractory SCCHN is supported by the clinical pharmacology data.

There are no clinical pharmacology pertinent labeling changes proposed in this submission.

1.2. Post Marketing Requirements or Commitments

There are no postmarketing requirements (PMR) or postmarketing commitment (PMC) studies requested by the Office of Clinical Pharmacology.

Signatures:

Hongshan Li, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Jingyu Yu, Ph.D. Pharmacometrics Team Leader Division of Pharmacometrics
Brian D. Furmanski, Ph.D. Reviewer Division of Clinical Pharmacology V	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V

Cc: DOP2: RPM – M Lidbeg; DD – P Keegan; MTL – G Blumenthal; MO – B Scepura
DCPV: DDD - B Booth; DD - A Rahman

2.1. Introduction

Nivolumab (OPDIVO, BMS-936558) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody that targets the programmed death–1 (PD-1, CD279) cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes.

2.1.1. Clinical pharmacology study design to support labeling claims

Study CA209141 was a randomized (2:1) multicenter trial, which compared nivolumab monotherapy (N=236) to investigator's choice therapy consisting of cetuximab, methotrexate, or docetaxel (N=111) in patients with recurrent or metastatic platinum-refractory SCCHN. Randomization was stratified based on prior treatment with cetuximab vs. no prior cetuximab treatment.

Group 1) Nivolumab 3 mg/kg was administered as a 60-minute intravenous (IV) infusion Q2W

Group 2) Investigator's choice

- Cetuximab 400 mg/m^2 IV once, then 250 mg/m^2 weekly (where approved for use as monotherapy for recurrent SCCHN)
- Methotrexate 40 mg/m^2 IV weekly (could be increased to 60 mg/m^2 if tolerated as per local\ practices)
- Docetaxel 30 mg/m^2 IV weekly (could be increased to 40 mg/m^2 if tolerated as per local practices)

The Primary objective of study CA209141 was the comparison of OS of nivolumab to investigator's choice therapy.

PK and immunogenicity schedules for study CA209141

Blood samples for PK and immunogenicity assessment were collected predose on Day 1 of Cycles 1, 5, 13 and on every 16th week until discontinuation of study treatment.

2.1.2. Formulation and Dose Regimen

Sterile solution available as a 40 mg/ 4 mL and 100 mg/ 10 mL single use vial

3 mg/kg administered as an intravenous (IV) infusion over 60 minutes Q2W

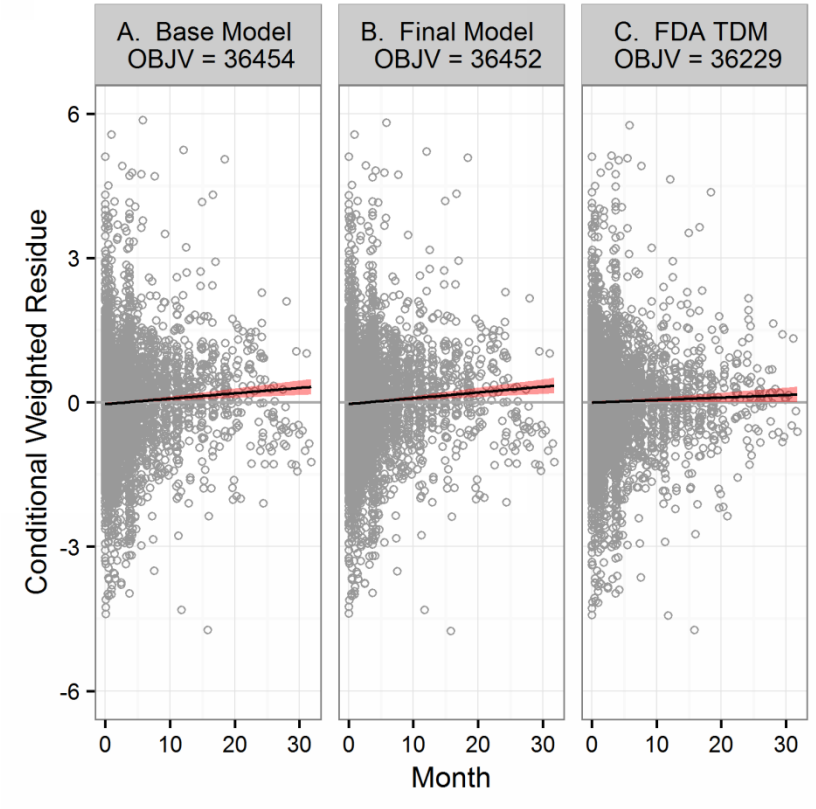
2.2. Key Review Questions

2.2.1. What are the findings in the population pharmacokinetics (PopPK) report of this efficacy supplement due to the addition of Trial CA209141, the registration trial in patients with SCCHN?

There are no new findings from the PopPK analysis utilizing data from 1035 patients in multiple Phase 1, 2 and 3 studies (MDX1106-01, MDX1106-03, CA209063, CA209017, CA209057, and CA209141). A static clearance PK model was applied to the dataset and resulted in biased conditional weighted residue over time (Figure 1A for base model and Figure 1B for final

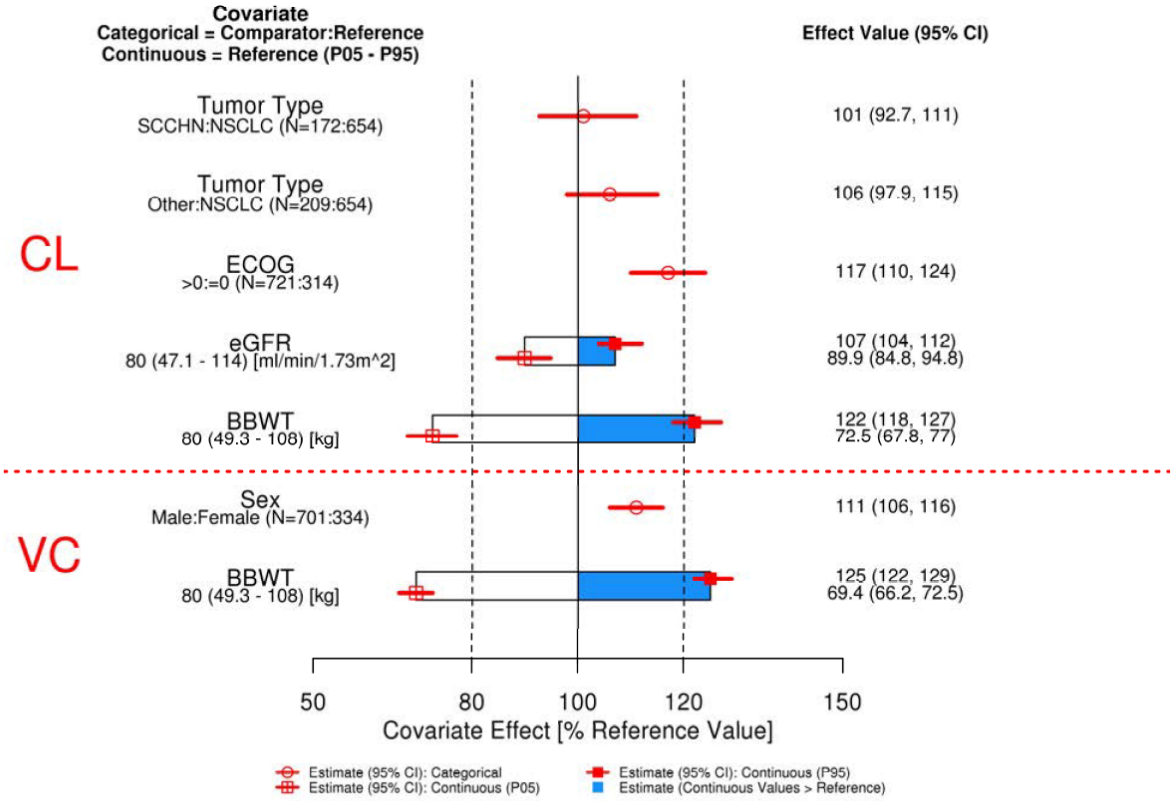
model). Time-varying clearance is added to the final model and resulted in better diagnostic plot (Figure 1C). Therefore, the time-varying clearance model is considered more robust for the data in this submission. In addition, the labeling for previous submissions (i.e., BLA125554 S-17 and S-18) provides sufficient information about time-varying PK characteristics (Clinical Pharmacology Review authored by Yuan Xu and Jingyu (Jerry) Yu and documents on 08/03/2016), hence there is no need to update the current label in this regard.

Figure 1. Diagnostic Comparison of the CWRES-Time Plots of Nivolumab between the Time-Static Pharmacokinetics Models and the Time Dependent Pharmacokinetics Model



Based on previous experience with nivolumab in other tumor types, the effects of the following covariates were included in the current popPK model for the SCCHN population: clearance (CL) including tumor type, baseline body weight, baseline Eastern Cooperative Oncology Group (ECOG) and baseline estimated glomerular filtration rate (eGFR); and volume of the central compartment (VC) including baseline body weight and sex. The magnitude of effect of the tested covariates on CL and VC, accounting for uncertainty, was within the ≤ 20% boundaries for all covariates with the exception of body weight, see figure 2 below. These findings from PopPK analysis in this submission are consistent with those in previous submissions.

Figure 2) Covariate effects on PopPK model parameters (Full PopPK Model)



Analysis-Directory: /global/pkms/data/CA/209/C15/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/cov-eff-plot-fullmodel.r
Source: Analysis-Directory/R/plots/full-ppk-cov-eff-plot.png

Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal red lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal red lines). Open/Blue area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is female, ECOG=0, eGFR=80 m>/min/1.73m^2, body weight=80kg, NSCLC tumor type. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

2.2.2. Does the dose/exposure relationship for efficacy and safety from related studies support the dose regimen of 3 mg/kg Q2W for the proposed indication in SCCHN?

Exposure-response (ER) analyses were not included in this application. Rationale for not conducting ER analyses provided by BMS includes that data is only from one dose level and that the effect of nivolumab CL and Cavgss will be confounded, thus E-R analysis will not provide interpretable conclusions.

Additionally, E-R analysis of safety was not conducted for SCCHN patients from Study CA209141. Rationale for not conducting ER analysis for safety provided by BMS includes that nivolumab 3 mg/kg Q2W has been shown to be safe and well-tolerated in several tumor types and the rate of adverse events leading to discontinuation or death in Study CA209141 was similar to that seen in previous studies.

2.2.3. What is the incidence (rate) of the formation of the anti-drug antibodies (ADA), including the rate of pre-existing antibodies, the rate of ADA formation during and after the treatment, time profiles and adequacy of the sampling schedule? Do the ADAs have neutralizing activity?

In study CA209141, 148 of 236 patients who were treated with nivolumab 3 mg/kg Q2W were evaluated for the presence of the formation of ADA against nivolumab. Thirteen patients (8.8%) were ADA positive following administration of nivolumab, 9 patients (6.1%) were positive only at the last sample, 1 patient was positive of neutralizing ADA, none of the patients were considered persistent positive. Additionally, none of the patients who were ADA positive had hypersensitivity/ infusion related reactions. Pooled ADA analysis comparing CA209141 and previous studies indicates a similar rate of ADA formation in other tumor types, see Table 1 below. Per BMS, the effect of neutralizing ADA on efficacy and safety of nivolumab is inconclusive due to limited clinical data. An assessment of ADA formation and its relationship with clearance was not provide in the current submission; however BMS states that effect of immunogenicity on nivolumab clearance has been assessed as part of previous PPK analyses as a time-varying covariate, and was associated with a 13% to 25% increase in CL, which was not considered clinically relevant. The nivolumab labeling states that there was no evidence of altered pharmacokinetic profile or toxicity profile with anti-product binding antibody development based on the population pharmacokinetic and exposure-response analyses.

Table 1) Summary of ADA assessments following nivolumab 3 mg/kg every 2 weeks

	Number of Subjects (%)		
Study Number	Summary of Previous Studies[a] (N=1586)	CA209141 (N=148)	Pooled Summary (N=1734)
Baseline ADA Positive	79 (4.98)	13 (8.8)	92 (5.3)
ADA Positive	157 (9.9)	13 (8.8)	170 (9.8)
Persistent Positive[b]	2 (0.1)	0	2 (0.1)
Only Last Sample Positive	54 (3.4)	9 (6.1)	63 (3.6)
Other Positive	101 (6.4)	4 (2.7)	105 (6.1)
Neutralizing ADA Positive	9 (0.6)	1 (0.7)	10 (0.6)
ADA Negative	1429 (90.1)	135 (91.2)	1564 (90.2)

Source: See note a and Table 8.13.1-1 of the CA209141 CSR[6]

[a] Previous studies includes studies CA209-063, -037, -066, -017, -057, -067, -025, -039, -205 summarized in Module 2.7.2 Summary of Clinical Pharmacology for Classical Hodgkin Lymphoma[17]

[b] Persistent positive subject defined as a subject with ADA-positive samples at 2 or more consecutive time points, where the first and last ADA positive samples were at least 16 weeks apart.

2.2.4. What bioanalytical methods are used to assess nivolumab concentrations?

In study CA209141, PK samples were analyzed at [redacted] (b) (4) via validated sandwich enzyme-linked immunosorbent (ELISA) assay with an electrochemiluminescence (ECL) reporter (ICD416). The ICD 416 assay was also used to analyze PK samples collected in

Studies CA209063, CA209017, and CA209057. The PK samples collected in study MDX1106-01 and before protocol Amendment 4 for Study MDX1106-03 were analyzed using a validated sandwich ligand binding enzyme-linked immunosorbent (ELISA) assay with a pNPP substrate used for a colorimetric readout (ICD 316). The methods were cross validated and reported in the methods comparison section in the validation report for ICD416, see Table 2 below.

Table 2. Summary of cross validation for ICD 316 and ICD 416

Validated Method	ELISA (ICD 316)	ECL (ICD 416)
Species and Matrix	Human Sera	Human Sera
Analyte	Nivolumab	Nivolumab
Cross Validated to	Method ICD 416	Not applicable
Standard Curve		
LLOQ	1 µg/mL	0.2 µg/mL
ULOQ	10 µg/mL	6.5 µg/mL
QC Precision (%CV)		
Intra Assay	≤ 14.6%	≤ 3.87%
Inter Assay	≤ 15.5%	≤ 10.1%
QC Accuracy (% Deviation)	Within ± 21%	Within ± 12%
Studies in Which Method Was Used	MDX-1106-01 (CA209001) and MDX-1106-03 (CA209003) (cohorts prior to Protocol Amendment 4)	MDX-1106-03 (CA209003) (cohorts enrolled under Protocol Amendment 4), CA209063, CA209017, CA209057 and CA209141

Cross Validation is reported in the "Method Comparison" section of the ECL (ICD 416) validation report.
ELISA: enzyme-linked immunosorbent assay; ECL: electrochemiluminescence; LLOQ: lower limit of quantification; ULOQ: Upper limit of quantification; QC: quality control; %CV: coefficient of variation expressed as a percentage

2.2.5. What methods are used to assess nivolumab ADA incidence in SCCHN patients?

In study CA209141, the rate of ADA formation was assessed at [redacted] (b) (4) via a validated ECL assay using magnetic bead extraction with acid dissociation (ICDIM 140 V2.02). The pooled immunogenicity analysis for nivolumab utilized either ICDIM 140 V1.00 or V2.02. A 3 tier approached was used in determining an ADA positive finding. Briefly, during Tier 1 sample analysis samples with raw responses at or above the assay cut point (1.52*Mean NC Response) are considered potentially positive for anti-BMS-936558 antibodies. In Tier 2 samples that are confirmed positive have suppression in signal ≥ 77.2% when spiked with BMS-936558. Tier 3 determines the reportable titer result as the reciprocal of that dilution used to produce a signal below the sample titration cut point; 2.11*Mean NC Response.

3. Detailed Labeling Recommendations

There are no proposed clinical pharmacology pertinent labeling changes in this submission.

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/s/

BRIAN D FURMANSKI
10/12/2016

HONG ZHAO
10/12/2016
I concur.

JINGYU YU
10/12/2016

HONGSHAN LI
10/12/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s022

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: October 11, 2016

To: Meredith Libeg
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

From: Nick Senior, PharmD, JD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Comments on BLA 125554
OPDIVO (nivolumab) injection, for intravenous use

OPDP has reviewed the proposed product labeling (PI) for OPDIVO (nivolumab) injection, for intravenous use (Opdivo) as requested in the consult dated May 16, 2016. The following comments, using the proposed substantially complete, marked-up version of the PI emailed to OPDP by Meredith Libeg on September 26, 2016, are provided below.

If you have any questions, please feel free to contact me (contact information: 240-402-4256; Nicholas.Senior@fda.hhs.gov)

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NICHOLAS J SENIOR
10/11/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	September 27, 2016
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, 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)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	OPDIVO (nivolumab)
Dosage Form and Route:	injection for intravenous infusion
Application Type/Number:	BLA 125554
Supplement Number:	S-022
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On May 11, 2016, Bristol-Myers Squibb Company submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved Biologics License Application (BLA) 125554/S-022 for OPDIVO (nivolumab) injection. In this supplement, the Applicant proposes a new indication (b) (4)

On December 22, 2014, OPDIVO (nivolumab) injection received Accelerated Approval for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. OPDIVO (nivolumab) injection is currently indicated:

- as a single agent for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.
- as a single agent for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.
- in combination with ipilimumab for the treatment of patients with unresectable or metastatic melanoma.
- for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.
- for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
- for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Oncology Products 2 (DOP2) on May 16, 2016, for DMPP to review the Applicant's proposed Medication Guide (MG) for OPDIVO (nivolumab) injection.

2 MATERIAL REVIEWED

- Draft OPDIVO (nivolumab) injection MG received on May 11, 2016 and further revised on May 27, 2016.
- Draft OPDIVO (nivolumab) injection Prescribing Information (PI) received on May 11, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on September 26, 2016.
- Approved OPDIVO (nivolumab) injection labeling dated September 13, 2016.

3 REVIEW METHODS

In our focused review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
09/28/2016

BARBARA A FULLER
09/29/2016

LASHAWN M GRIFFITHS
09/29/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s022

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119382

MEETING MINUTES

Bristol-Myers Squibb
Attention: Michael Ladd, Pharm.D.
Associate Director, Global Regulatory, Safety, and Biometrics, US Oncology
5 Research Parkway, Mailstop 2DW-213
Wallingford, CT 06492

Dear Dr. Ladd:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Nivolumab."

We also refer to the meeting between representatives of your firm and the FDA on April 8, 2016. The purpose of the meeting was to discuss the proposed content of a planned supplemental BLA (sBLA) seeking approval for the proposed indication of nivolumab, as a single agent, for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) after platinum chemotherapy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	Friday, April 8, 2016; 9:00 to 10:00 AM (ET)
Meeting Location:	White Oak Building 22, Conference Room: 1313
Application Number:	IND 119382
Product Name:	Nivolumab
Indication:	(b) (4) [redacted]
Sponsor/Applicant Name:	Bristol-Myers Squibb (BMS)
Meeting Chair:	Gideon Blumenthal, M.D.
Meeting Recorder:	Meredith Libeg

FDA ATTENDEES

Patricia Keegan, M.D.	Division Director, DOP2
Gideon Blumenthal, M.D.	Clinical Team Leader, DOP2
Barbara Scepura, M.D.	Medical Officer, DOP2
Kun He, Ph.D.	Statistical Reviewer, Team Leader, DBV
Sirisha Mushti, Ph.D.	Statistical Reviewer, DBV
Brian Furmanski, Ph. D.	Clinical Pharmacology Reviewer, DCP5
Prakash Jha, M.D.,M.P.H.	Medical Officer, Division of Molecular Genetics and Pathology, CDRH
Reena Philip, Ph.D.	Director, Division of Molecular Genetics and Pathology, CDRH
Janaki Veeraraghavan, Ph.D.	Scientific Reviewer, CDRH/OIR
Meredith Libeg, B.S.	Regulatory Health Project Manager, DOP2

SPONSOR ATTENDEES

Nick Botwood, M.D.	Vice President Opdivo/Yervoy Lung, Head, & Neck Development Lead
Jean Viallet, M.D.	Vice President, Global Clinical Research, Oncology

Matthew Robson, M.B.,Ch.B.	Vice President Global Clinical Research, Immuno-Oncology
Sabine Maier, M.D.	Group Medical Director, Global Clinical Research
Manish Monga, M.D.	Director, Global Clinical Research, Oncology
Mark Lynch, Ph.D.	Study Director, Global Clinical Research, Oncology
Ramachandran Suresh, Ph.D.	Vice President, Global Biometric Sciences, Oncology
Aparna Anderson, Ph.D.	Group Director, Global Biometric Sciences, Oncology
Justin Kopit, Ph.D.	Associate Director, Global Biometric Sciences, Oncology
Shruti Agrawal, MS, Ph.D.	Director, Clinical Pharmacology and Pharacometrics
Steven Averbuch, M.D.	Vice President, Development, Oncology & Pharmacodiagnostics
James Novotny, Ph.D.	Group Director, Pharmacodiagnostics
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences, Oncology
Kathleen O'Donnell	Group Director, U.S. Regulatory
Eric Richards, M.S., M.P.H.	Executive Director, Global Regulatory Sciences, Solid Tumors
Michael Ladd, Pharm.D.	Associate Director, Global Regulatory Sciences

BACKGROUND

Nivolumab is a monoclonal antibody directed against the Programmed Cell Death-1 (PD-1) molecule. Programmed Death-ligand 1 (PD-L1) expression has been documented in multiple solid tumor histologies including: non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, gastric cancer, and breast cancer.

BMS is planning to submit a supplemental Biologics License Application (sBLA) for nivolumab for the treatment of (b) (4) The sBLA will be supported primarily by efficacy and safety data from a single clinical trial, Study CA209141, titled "An Open Label, Randomized Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN) (CheckMate 141: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 141)."

Regulatory History

- On February 27, 2014, a new IND was submitted which contained a new clinical protocol, Protocol CA209141 entitled "An Open Label, Randomized Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN)."
- On March 28, 2014, IND 119382 was allowed to proceed.

- On April 3, 2014, an Advice Information providing comments regarding the potential use of Protocol CA209141 an indication for the treatment of patients with SCCHN.
- [redacted] (b) (4)
- On February 23, 2016, BMS submitted request for Breakthrough Therapy designation for the treatment of recurrent or metastatic platinum-refractory SCCHN after platinum therapy. The assessment of this BTDR is under review.

Trial CA209141

Design:

Study CA209141 is an open-label, randomized, study of nivolumab conducted in patients with recurrent or metastatic platinum-refractory SCCHN, defined as tumor progression on or within 6 months of last dose of platinum therapy. Other eligibility criteria were age ≥ 18 years, measurable disease, documentation of HPV p16 status, and availability of tumor for biomarker analysis. Patients with prior exposure to an anti-PD-1, PD-L1, PD-2, or CTLA-4 antibody were ineligible. The protocol has been revised multiple times; the current version of the protocol is dated February 11, 2016 (version 11). The primary objective of the study was to compare the overall survival (OS) between the two treatment arms. The secondary objectives were to compare the progression-free survival (PFS) and the objective response rate (ORR). Key exploratory endpoints were to assess the safety of nivolumab in subjects with SCCHN, estimate duration of response (DOR) and time to response (TTR) of nivolumab and investigator's choice groups, and investigate the association between biomarkers in the peripheral blood and tumor tissue, such as PD-L1 expression, and safety or efficacy.

Patients were randomized (2:1) to nivolumab 3 mg/g IV every 2 weeks or to investigator's choice of therapy (Arm IC), comprising one of the following single agents administered until progression or unacceptable toxicity:

- cetuximab 400 mg/m^2 IV once then 250 mg/m^2 weekly
- methotrexate 40 mg/m^2 IV push weekly, may be increased to 60 mg/m^2 if tolerated as per local practices
- docetaxel 30 mg/m^2 IV weekly, may be increased to 40 mg/m^2 if tolerated as per local practice.

Randomization was stratified by prior cetuximab (yes vs. no).

The analysis plan in the most recent version of the protocol states that the sample size of 360 patients was based on the assumed accrual rate of 26 patients per month and requirement for 278 OS events (deaths) to detect a statistically significant difference in OS at an overall two-sided error rate of 0.05 (adjusted for the single planned interim analysis) at 90% power assuming the true hazard ratio was 0.6667 and the median OS was 9 months in the nivolumab and 6 months in the IC arm.

A single interim analysis of OS was to be performed 2 months after the end of accrual at which time it was projected that 75% of the required number of deaths would have occurred, assuming an accrual rate of 20 subjects per month. The protocol was modified on July 10, 2014, to specify that the interim analysis would be conducted "after 70% of events or 6 months after the end of accrual, whichever occurs earlier." As stated in the protocol, "the boundaries for declaring superiority will be derived based on the actual number of deaths using Lan-DeMets spending function with O'Brien and Fleming type of boundary in EAST v5.4. If the analysis is performed exactly at 105 deaths, the boundary in terms of statistical significance at the interim analysis for declaring superiority would be 0.0059."

The protocol further states that "if a statistically significant improvement of OS is demonstrated for the nivolumab arm randomized subjects, a hierarchical testing procedure will be used to test for the secondary endpoints preserving the study-wise type I error rate at 0.05. The detail of the testing procedure will be specified in the statistical analysis plan. The key secondary endpoints will be tested in the following hierarchical order:

1) PFS as per investigator among randomized subjects
2) ORR as per investigator among randomized subjects"

The timing (or number of events) in the primary analysis of PFS is not specified in the clinical protocol.

Efficacy Results:

As stated in the most recent version of the clinical protocol, "the DMC for the CA209141 study convened on 26-Jan-2016 to evaluate data from a planned formal Interim Analysis of OS. The DMC declared superiority for OS in subjects receiving nivolumab as compared to Arm IC. As a result of the DMC assessment, this protocol amendment is being implemented to provide a mechanism for eligible subjects originally randomized to the treatment Arm IC to receive subsequent nivolumab therapy as part of a nivolumab extension phase."

A total of 361 patients were enrolled, of whom 240 were randomized to nivolumab and 121 were randomized to investigator's choice of therapy. In the analysis conducted after 218 deaths, the median OS for nivolumab was 7.5 months, compared to IC median survival of 5.1 months, (hazard ratio [HR]: 0.70, 97.73% confidence interval [CI]; 0.51, 0.96, stratified log-rank test: $p = 0.0101$). The stopping boundary using the O'Brien Fleming method for this interim analysis based on the observed number of deaths (218) was 0.0227. There was no statistically significant difference in PFS between nivolumab and IC (HR: 0.88 [95% CI: 0.69, 1.13]; stratified log-rank test p-value = 0.3028). The investigator-assessed confirmed ORR using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria was 12.1% in the nivolumab group vs 7.4% in the investigator's choice group; stratified CMH odds ratio of 1.70.

Subgroups - PD-L1 Status and HPV-pV16 Status:

Per BMS, PD-L1 expression was generally balanced between the 2 treatment groups within the 3 predefined subgroups based on PD-L1 expression levels (≥1%, ≥5%, and ≥10%). In exploratory subgroups analyses, the subgroup of patients enrolled with quantifiable PD-L1 expression had an expression level ≥ 1% (constituting 57% in the intent-to-treat [ITT] population), the treatment effect of nivolumab on OS appeared larger (HR = 0.56) than in the 43% of patients with < 1% PD-L1 expression (HR = 0.88). The effect of nivolumab on OS as assessment by the HR appeared similar regardless of the cut-point used for PD-L1 positivity. The treatment effect of nivolumab also appeared to be larger in patients with HPV-p16 positive SCCHN (HR = 0.57; HPV negative OS HR = 0.72).

Safety Results:

Per BMS, no new safety signals arose during the CA209141 study. In Study CA209141, 56% of patients treated with nivolumab and 70% of patients on the IC arm died within 30 days of the last dose of study drug. Across the study, 30% of patients treated with nivolumab and 37% of patients treated on the IC arm had a grade 3-4 adverse event (AE); 40% of patients treated with nivolumab and 51% of patients treated on the IC arm had a grade 5 AE, with the majority of these patients dying as a result of disease progression. One patient on each arm was reported by BMS as having died from a drug related AE.

Proposed content of the planned sBLA

The sBLA will be supported by solely by the efficacy results from Study CA209141 (b) (4) [redacted]

BMS states that majority of the Summary of Clinical Safety (SCS) will focus on the CA209141 study for updated characterization of immune-mediated adverse events (IMAEs) intended to update the Warning and Precautions section of the United States Package Insert (USPI) and supportive datasets. In addition, BMS will present tables that allow for comparison of the safety in the SCCHN population compared to safety data in indications.

Table 9: Safety of Nivolumab Monotherapy Across Approved or Submitted Indications (cHL, RCC, Melanoma, and NSCLC)

	cHL N = 263	RCC N = 406	Melanoma N = 787	NSCLC N = 535
Outputs will be generated for:				
- Deaths (within 30 days and within 100 days) - AEs (all-causality and drug-related within 30 days of last dose) - SAEs (all-causality and drug-related within 30 days of last dose) - AEs leading to discontinuation (all-causality and drug-related within 30 days of last dose) - IMAEs (within 100 days of last dose)				
For adverse events, outputs will be provided for any grade events and Grade 3-4 events.				

DISCUSSION

Clinical:

1. *Background: The efficacy data in this SCCHN sBLA is based on a single, well-controlled survival study (CA209141) to support the overall risk/benefit assessment and labeling of nivolumab in SCCHN. The efficacy data from CA209141 will not be pooled with any other studies. BMS will describe all data and any high level interpretation in support of the labeling objectives within the Clinical Study Report (CSR) and/or the clinical overview. See Pages 6 to 20 and Appendix 1 of the Briefing Document.*

Does FDA agree that (b) (4) **?**

FDA Response: No. (b) (4) Given the apparent treatment effect in that is present in patients with both PD-L1 negative and PD-L1 positive HNSCC, the sBLA should contain available data on ORR and DoR from patients with HNSCC enrolled in other studies. Also, in the SCE, provide a table of the 38responders in Study CA209141, including information on the DoR, PD-L1 status, HPV status, and site of initial disease. In addition, provide an analysis of interaction between PD-L1 status and HPV status in Study CA209141. Also, provide an analysis of HPV status by site of initial diagnosis.

Please see: Integrated Summary of Effectiveness Guidance for Industry, found at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079803.pdf.

Discussion During Meeting of 4/8/16: BMS acknowledged FDA's response and agreed to also include in the sBLA that efficacy data observed in HNSCC in clinical trials other than Study CA209141. BMS noted that there were no other trials that limited enrollment to patients with HNSCC.

BMS clarified that the site of disease was captured on Case Report Forms (CFRs) as oral cavity, pharynx, larynx, and other. HPV testing was required for all patients with oropharyngeal tumors, which included a subset of oral cavity tumors.

2. *Background: See Pages 20 to 21 and Appendix 2 of the Briefing Document.*

Does FDA agree with the proposed plans for the safety presentation?

FDA Response: No. In addition to the proposed plans for presentation of safety data in the sBLA, BMS should include in the CSR and SCS all AEs leading to drug discontinuation, all grade laboratory abnormalities (nivolumab versus chemotherapy) and NCI CTCAE Grade 3 and 4 laboratory abnormalities, immunogenicity data, and provide patient narratives for all deaths.

Discussion During Meeting of 4/8/16: BMS acknowledged FDA's response and will provide this information in the sBLA. FDA noted that it might not be necessary to revise the Warnings and Precautions section of the USPI to include this new information unless an unusual safety event was identified in the patient population for this proposed indication. FDA clarified that patient narratives should be submitted for all deaths on study except for those attributed to progressive disease; however, FDA stated that they may request additional narratives during the review of the sBLA.

3. *Background: BMS proposes to submit a 60-day safety update report for CA209141 (mid-April database lock) that consists of safety narratives for events reported within 100 days of last dose that meet the following criteria:*

- *Deaths (other than those due to disease progression)*
- *Drug-related SAEs by worst CTC grade*
- *Drug-related IMAEs by worst CTC grade*

This scope is consistent with previous agreements with FDA at the pre-sBLA meetings for studies CA209017 (IND 100,052, 29-Apr-2015) and CA209057 (IND 100,052, 23-Jun-2015).

A new subject narrative or updated subject narrative (if a narrative already exists) will be provided for each subject from CA209141 who experiences an event of worse CTC grade since the initial database lock (18-Dec-2015) that falls under the narrative scope specified above

Does FDA agree with this proposal for the Safety Update Report?

FDA Response: No. FDA does not agree that submission of a Safety Update Report is necessary for the planned sBLA, given the large safety database across advanced malignancies.

Discussion During Meeting of 4/8/16: BMS acknowledged FDA's response. No further discussion occurred during the meeting.

4. *Background: See Pages 21 to 22 and Table 10 of the Briefing Document.*

Does FDA agree with this proposal for the clinical pharmacology presentation?

FDA Response: The proposed clinical pharmacology package appears reasonable to support the filing of the sBLA; however, its adequacy will be determined upon the sBLA review. In the sBLA submission provide justification with supporting data for not including E-R analysis in patients with SCCHN treated with nivolumab.

Discussion during the meeting: BMS acknowledged FDA's response and will provide the requested justification for not conducting an E-R analysis.

5. *Background: See Pages 22 to 24 of the Briefing Document.*

a) **Does the Agency agree that the analytical validation of the assay should not delay the review and approval of nivolumab for SCCHN, even if inclusion of PDL1 status is required for the clinical studies section of the label?**

FDA Response: If BMS/Dako intends to market PD-L1 IHC 28-8 pharmDx as a companion or a complementary diagnostic, the analytic validation and reproducibility studies should be provided during the review.

Discussion during meeting: BMS stated that the analytic validation and reproducibility studies could not be completed and provided at the time of submission of the proposed supplement. BMS will propose inclusion of data in Section 14 of the USPI based on these exploratory subgroup analyses based on PD-L1 expression by central testing. FDA stated whether these data could be included in the USPI in advance of the validation data for the complimentary diagnostic would be a review issue.

b) **Should the Agency foresee potential issues with the review and approval timing of nivolumab and Dako's PD-L1 IHC 28-8 pharmDx test for SCCHN, would the Agency support updating the nivolumab label in Section 14: clinical studies post approval and upon completion of the analytical validation for Dako's PD-L1 IHC 28-8 pharmDx test in SCCHN?**

FDA Response: Based on available data, a companion diagnostic will not be required. If FDA required a companion diagnostic, than a contemporaneous approval would be required. If BMS/Dako intends to market PD-L1 IHC 28-8 pharmDx as a complementary diagnostic, a post marketing commitment for full analytic validation and reproducibility may be indicated.

In the sBLA submission, BMS may submit proposed language in Section 14 to physician labeling to describe the apparent differential treatment effects in terms of ORR, PFS, and OS by PD-L1 status or by HPV status. However, please note that these are exploratory post-hoc subgroup analyses, where randomization did not stratify for PD-L1 status or HPV status. Inclusion of this language in final labeling would be determined during sBLA review.

Discussion during meeting: See discussion during meeting under response to 5a above.

PREA REQUIREMENTS

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.

FDA acknowledges receipt of BMS' Agreed Initial Pediatric Study Plan submitted on January 28, 2015, and also refers to the February 27, 2015, letter confirming FDA's agreement to the Agreed iPSP for the proposed indication of treatment of squamous cell cancers of the oropharynx. This fulfills BMS' requirements at this stage of development to reach an Agreed Initial Pediatric Study Plan with the Agency.

Discussion During Meeting of 4/8/16: BMS acknowledged FDA's response. No further discussion occurred during the meeting.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Discussion During Meeting of 4/8/16: BMS acknowledged FDA's response. No further discussion occurred during the meeting.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

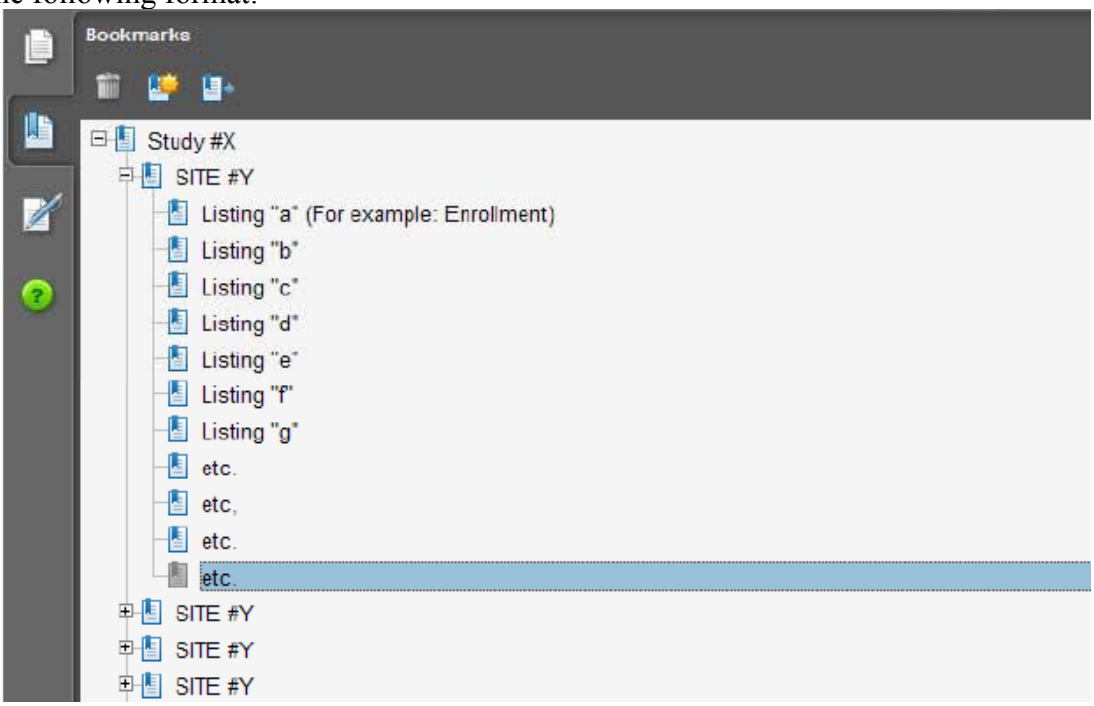
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Discussion During Meeting of 4/8/16: BMS acknowledged FDA's response. No further discussion occurred during the meeting.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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