CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125554Origs052

Trade Name: OPDIVO

Generic or Proper Name: nivolumab

Sponsor: Bristol-Myers Squibb Company

Approval Date: March 05, 2018

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. (1.1)
- patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent.[a] (1.1)
- patients with unresectable or metastatic melanoma, in combination with ipilimumab.[a] (1.1)
- patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting. (1.2)
- patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFT or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. (1.3)
- patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.4)
- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after[b]: (1.5)

    - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
    - 3 or more lines of systemic therapy that includes autologous HSCT.
- patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy (1.6)
- patients with locally advanced or metastatic urothelial carcinoma who[b]:
    - have disease progression during or following platinum-containing chemotherapy
    - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.7)
- adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[b] (1.8)
- patients with hepatocellular carcinoma who have been previously treated with sorafenib.[b] (1.9)

[a] 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.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554/S-048, S-049, S-050, S-051,
S-052, S-061, S-062, S-064, S-065, and S-066

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Kathleen O'Donnell
Group Director, US Liaison – Oncology
Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. O'Donnell:

Please refer to your Supplemental Biologics License Applications (sBLAs) and to the amendments, submitted under section 351(a) of the Public Health Service Act for OPDIVO (nivolumab) injection, 40 mg/4 mL, 100 mg/10 mL, and 240 mg/24 mL, dated and received:

- May 5, 2017, for supplements S-048, S-049, S-050, S-051, and S-052;
- January 5, 2018, for supplements S-061 and S-062; and,
- February 13, 2018, for supplements S-064, S-065, and S-066.

These Prior Approval supplemental biologic applications provide for the following updates to the prescribing information:

- For supplements S-048, S-049, S-050, S-051, and S-052: a new dosage regimen of Opdivo 480 mg as an intravenous infusion over 30 minutes every 4 weeks for the following approved indications (S-048):
  - metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy (S-048);
  - BRAF V600 wild-type unresectable or metastatic melanoma; patients with BRAF V600 mutation-positive unresectable or metastatic melanoma metastatic melanoma; and, in combination with ipilimumab, for unresectable or metastatic melanoma (S-048);
  - advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy (S-049);
  - adult patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or 3 or more lines of systemic therapy that includes autologous HSCT(S-050);
  - recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy (S-051); and

- locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (S-052).

- For supplements S-061 and S-062: a new dosage regimen of Opdivo 480 mg as an intravenous infusion over 30 minutes every 4 weeks for the following approved indications:
  - adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease following complete resection (S-061); and
  - hepatocellular carcinoma following progression on sorafenib (S-062).

- For supplements S-064, S-065, and S-066: modification of the approved dosage regimens of Opdivo 240 mg every two weeks, to reduce to the infusion time from 60 minutes to 30 minutes, for the following approved indications:
  - adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease following complete resection (S-064);
  - microsatellite instability-high or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (S-065); and
  - hepatocellular carcinoma following progression on sorafenib (S-066).

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are 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 prescribing information) 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.

Because the biological product for the following indications, have been granted orphan designation, you are exempt from this requirement for the new dosing regimen for these indications: for the treatment of patients with (b) (4) melanoma; for the treatment of patients with Hodgkin Lymphoma; and hepatocellular carcinoma.

In addition, we are waiving the pediatric study requirement for the new dosing regimen to the following indications because necessary studies are impossible or highly impracticable since the disease/condition does not exist in children: for the treatment of patients with non-small cell lung cancer, advanced renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, and metastatic colorectal cancer.

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 prescribing information 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 prescribing information, 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
03/05/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Origs052

<u>LABELING</u>

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)	12/2017
Dosage and Administration (2)	3/2018
Warnings and Precautions, Immune-Mediated Hepatitis (5.3)	9/2017
Warnings and Precautions, Other Immune-Mediated Adverse Reactions (5.8)	2/2018
Warnings and Precautions, Infusion Reactions (5.9)	1/2018

----------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)
- patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent.[a] (1.1)
- patients with unresectable or metastatic melanoma, in combination with ipilimumab.[a] (1.1)
- patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting. (1.2)
- patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO. (1.3)
- patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.4)
- adult patients with classical Hodgkin lymphoma that has relapsed or progressed after[b]: (1.5)
  - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy that includes autologous HSCT.
- patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy. (1.6)
- patients with locally advanced or metastatic urothelial carcinoma who[b]:
  - have disease progression during or following platinum-containing chemotherapy
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.7)
- adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[b] (1.8)
- patients with hepatocellular carcinoma who have been previously treated with sorafenib.[b] (1.9)

[a] 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.

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

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

Administer as an intravenous infusion over 30 minutes.

- Unresectable or metastatic melanoma
  - OPDIVO 240 mg every 2 weeks or 480 mg every 4 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 or 480 mg every 4 weeks. (2.1)
- Adjuvant treatment of melanoma
  - OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks. (2.2)
- Metastatic non-small cell lung cancer
  - OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks. (2.3)
- Advanced renal cell carcinoma
  - OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks. (2.4)
- Classical Hodgkin lymphoma
  - OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks. (2.5)
- Recurrent or metastatic squamous cell carcinoma of the head and neck
  - OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks. (2.6)
- Locally advanced or metastatic urothelial carcinoma
  - OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks. (2.7)
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
  - OPDIVO 240 mg every 2 weeks. (2.8)
- Hepatocellular carcinoma
  - OPDIVO 240 mg every 2 weeks or 480 mg every 4 weeks. (2.9)

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

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

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

None. (4)

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

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis: Withhold OPDIVO when given as a single agent for moderate or severe and permanently discontinue for life-threatening colitis. Withhold OPDIVO when given with ipilimumab for moderate and permanently discontinue for severe or life-threatening colitis. (5.2)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.3)
- Immune-mediated endocrinopathies: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis. Withhold for moderate and permanently discontinue for severe or life-threatening adrenal insufficiency. Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. Monitor for hyperglycemia. Withhold for severe and permanently discontinue for life-threatening hyperglycemia. (5.4)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation. (5.5)
- Immune-mediated skin adverse reactions: Withhold for severe and permanently discontinue for life-threatening rash. (5.6)
- Immune-mediated encephalitis: Monitor for changes in neurologic function. Withhold for new-onset moderate to severe neurological signs or symptoms and permanently discontinue for immune-mediated encephalitis. (5.7)
- Infusion 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, headache, and abdominal pain. (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:3/2018

Reference ID: 4229975

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- 1.5 Classical Hodgkin Lymphoma
- 1.6 Squamous Cell Carcinoma of the Head and Neck
- 1.7 Urothelial Carcinoma
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*Sections or subsections omitted from the full prescr bing information are not listed.

Reference ID: 4229975

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 Adjuvant Treatment of Melanoma

OPDIVO is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection *[see Clinical Studies (14.2)]*.

1.3 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 (14.3)]*.

1.4 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 (14.4)]*.

1.5 Classical Hodgkin Lymphoma

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

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

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials *[see Clinical Studies (14.5)]*.

Reference ID: 4229975

1.6 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 (14.6)]*.

1.7 Urothelial Carcinoma

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

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

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials *[see Clinical Studies (14.7)]*.

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

OPDIVO is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan *[see Clinical Studies (14.8)]*.

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

1.9 Hepatocellular Carcinoma

OPDIVO is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on 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 *[see Clinical Studies (14.9)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Unresectable or Metastatic Melanoma

<u>Single Agent</u>

The recommended dose of OPDIVO as a single agent is either:

- 240 mg every 2 weeks or
- 480 mg every 4 weeks

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

Reference ID: 4229975

With Ipilimumab

The recommended dose of OPDIVO is 1 mg/kg administered as an intravenous infusion over 30 minutes, followed by ipilimumab on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer OPDIVO as a single agent, either:

- 240 mg every 2 weeks or
- 480 mg every 4 weeks

as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity. Review the Full Prescribing Information for ipilimumab for additional information prior to initiation.

2.2 Recommended Dosage for Adjuvant Treatment of Melanoma

The recommended dose of OPDIVO is either:

- 240 mg every 2 weeks or
- 480 mg every 4 weeks

administered as an intravenous infusion over 30 minutes until disease recurrence or unacceptable toxicity for up to 1 year.

2.3 Recommended Dosage for NSCLC

The recommended dose of OPDIVO is either:

- 240 mg every 2 weeks or
- 480 mg every 4 weeks

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

2.4 Recommended Dosage for RCC

The recommended dose of OPDIVO is either:

- 240 mg every 2 weeks or
- 480 mg every 4 weeks

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

2.5 Recommended Dosage for cHL

The recommended dose of OPDIVO is either:

- 240 mg every 2 weeks or
- 480 mg every 4 weeks

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

Reference ID: 4229975

2.6 Recommended Dosage for SCCHN

The recommended dose of OPDIVO is either:

- 240 mg every 2 weeks or
- 480 mg every 4 weeks

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

2.7 Recommended Dosage for Urothelial Carcinoma

The recommended dose of OPDIVO is either:

- 240 mg every 2 weeks or
- 480 mg every 4 weeks

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

2.8 Recommended Dosage for CRC

The recommended dose of OPDIVO is

- 240 mg every 2 weeks

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

2.9 Recommended Dosage for HCC

The recommended dose of OPDIVO is either:

- 240 mg every 2 weeks or
- 480 mg every 4 weeks

administered as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

2.10 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.

Reference ID: 4229975

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

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Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	 Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

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

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

[b] HCC: hepatocellular carcinoma.

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

2.11 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. The total volume of infusion must not exceed 160 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 8 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.

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Administration

Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

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

Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.10)]*.

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

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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 (2.10)]*.

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 (2.10)]*.

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.

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5.3 Immune-Mediated Hepatitis

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

For patients without hepatocellular carcinoma (HCC): withhold OPDIVO for moderate (Grade 2) immune-mediated hepatitis and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.10)]*.

For patients with HCC, permanently discontinue, withhold, or continue OPDIVO based on severity of immune-mediated hepatitis and baseline AST and ALT levels as described in Table 1 *[see Dosage and Administration (2.10)]*. In addition, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper when OPDIVO is withheld or discontinued due to immune-mediated hepatitis.

OPDIVO as a Single Agent

In patients 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

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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 (2.10)]*.

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 (2.10)]*.

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.

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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 (2.10)]*.

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.

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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 (2.10)]*.

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 (2.10)]*.

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

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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 (2.10)]*.

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 and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.10)]*.

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

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

5.9 Infusion 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 (2.10)]*.

OPDIVO as a Single Agent

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

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

OPDIVO with Ipilimumab

In patients receiving OPDIVO as a 60-minute intravenous infusion prior to the infusion of 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 the CHECKMATE-205 and CHECKMATE-039 trials 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,

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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)]*

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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 the CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 trials or a single-arm trial in NSCLC (n=117) administering OPDIVO as a single agent *[see Warnings and Precautions (5)]*. In addition, clinically significant adverse reactions of OPDIVO administered with ipilimumab were evaluated in 407 patients with melanoma enrolled in CHECKMATE-067 (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)]*.

The data described below reflect exposure to OPDIVO as a single agent in CHECKMATE-037, CHECKMATE-066, and CHECKMATE-067, and to OPDIVO with ipilimumab in CHECKMATE-067, which are randomized, active-controlled trials conducted in patients with unresectable or metastatic melanoma. Also described below are single-agent OPDIVO data from CHECKMATE-238, a randomized trial for the adjuvant treatment of patients with completely resected Stage IIIB/C and IV melanoma, CHECKMATE-017 and CHECKMATE-057, which are randomized trials in patients with metastatic NSCLC, CHECKMATE-025, which is a randomized trial in patients with advanced RCC, CHECKMATE-205 and CHECKMATE-039, which are open-label, multiple-cohort trials in patients with cHL, CHECKMATE-141, a randomized trial in patients with recurrent or metastatic SCCHN, CHECKMATE-275, which is a single-arm trial in patients with urothelial carcinoma, and CHECKMATE-040, which is an open-label, multiple-cohort trial in patients with HCC.

Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-037, a randomized, open-label trial in which 370 patients with unresectable or metastatic melanoma received 3 mg/kg of OPDIVO by intravenous infusion 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 CHECKMATE-037, 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

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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 CHECKMATE-037. 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]) (CHECKMATE-037)

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.

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Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in CHECKMATE-037 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]) (CHECKMATE-037)

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

CHECKMATE-066

The safety of OPDIVO was also evaluated in CHECKMATE-066, a randomized, double-blind, active-controlled trial in which 411 previously untreated patients with BRAF V600 wild-type unresectable or metastatic melanoma received 3 mg/kg of OPDIVO by intravenous infusion 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,

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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]) (CHECKMATE-066)

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.

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Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO in CHECKMATE-066 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]) (CHECKMATE-066)

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).

CHECKMATE-067

The safety of OPDIVO, administered with ipilimumab or as a single agent, was evaluated in CHECKMATE-067 *[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.

CHECKMATE-067 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

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stage disease; 36% with elevated LDH at baseline, 4% with a history of brain metastasis, and 22% had received adjuvant therapy.

In CHECKMATE-067, 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 CHECKMATE-067.

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]) (CHECKMATE-067)

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.

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[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 CHECKMATE-067 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]) (CHECKMATE-067)

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).

Adjuvant Treatment of Melanoma

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-238, a randomized (1:1), double-blind trial in which 905 patients with completely resected Stage IIIB/C or Stage IV melanoma received 3 mg/kg of OPDIVO by intravenous infusion every 2 weeks (n=452) or 10 mg/kg ipilimumab (n=453), by intravenous infusion every 3 weeks for 4 doses then every 12 weeks

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beginning at Week 24 for up to a 1 year *[see Clinical Studies (14.2)]*. The median duration of exposure was 11.5 months in OPDIVO-treated patients and was 2.7 months in ipilimumab-treated patients. In this ongoing trial, 74% of patients received OPDIVO for greater than 6 months.

Study therapy was discontinued for adverse reactions in 9% of OPDIVO-treated patients and 42% of ipilimumab-treated patients. Twenty-eight percent of OPDIVO-treated patients had at least one omitted dose for an adverse reaction. Grade 3 or 4 adverse reactions occurred in 25% of OPDIVO-treated patients. The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of OPDIVO-treated patients were diarrhea and increased lipase and amylase. Serious adverse reactions occurred in 18% of OPDIVO-treated patients.

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

Table 8 summarizes the adverse reactions that occurred in at least 10% of OPDIVO-treated patients in CHECKMATE-238.

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Table 8: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients (CHECKMATE-238)

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

Toxicity was graded per NCI CTCAE v4.

[a] Includes asthenia.

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

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

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

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

[f] Includes postural dizziness and vertigo.

[g] Includes secondary hypothyroidism and autoimmune hypothyroidism.

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Table 9: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients (CHECKMATE-238)

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

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

Metastatic Non-Small Cell Lung Cancer

The safety of OPDIVO in metastatic NSCLC was evaluated in CHECKMATE-017, a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen and in CHECKMATE-057, a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen *[see Clinical Studies (14.3)]*. Patients received 3 mg/kg of OPDIVO over 60 minutes by intravenous infusion 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 CHECKMATE-017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1 year and in CHECKMATE-057, 30% of patients received OPDIVO for greater than 6 months and 20% of patients received OPDIVO for greater than 1 year.

CHECKMATE-017 and CHECKMATE-057 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%).

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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 CHECKMATE-057, in the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. 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 10 summarizes selected adverse reactions occurring more frequently in at least 10% of OPDIVO-treated patients.

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

Adverse Reaction	OPDIVO (n=418)		Docetaxel (n=397)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	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%).

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Table 11: 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]) (CHECKMATE-017 and CHECKMATE-057)

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 CHECKMATE-025, 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 3 mg/kg of OPDIVO by intravenous infusion every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.4)]*. 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 12 summarizes adverse reactions that occurred in greater than 15% of OPDIVO-treated patients.

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Table 12: Grade 1-4 Adverse Reactions in >15% of Patients Receiving OPDIVO (CHECKMATE-025)

	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 CHECKMATE-025 were:

General Disorders and Administration Site Conditions: peripheral edema/edema

Gastrointestinal Disorders: abdominal pain/discomfort

Musculoskeletal and Connective Tissue Disorders: extremity pain, musculoskeletal pain

Nervous System Disorders: headache/migraine, peripheral neuropathy

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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 13 summarizes the laboratory abnormalities that occurred in greater than 15% of OPDIVO-treated patients.

Table 13: Grade 1-4 Laboratory Values Worsening from Baseline Occurring in >15% of Patients on OPDIVO (CHECKMATE-025)

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 3 mg/kg of OPDIVO by intravenous infusion every 2 weeks was evaluated in 266 adult patients with cHL (243 patients in the CHECKMATE-205 and 23 patients in the CHECKMATE-039 trials). 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: 2 to 15). Patients received a median of 23 doses

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(cycles) of OPDIVO (range: 1 to 48), with a median duration of therapy of 11 months (range: 0 to 23 months).

OPDIVO was discontinued due to adverse reactions in 7% of patients. Dose delay for an adverse reaction occurred in 34% of patients. Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in at least 1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last nivolumab dose, 2 from infection 8 to 9 months after completing nivolumab, and 6 from complications of allogeneic HSCT.

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

Table 14 summarizes the adverse reactions, excluding laboratory terms, that occurred in at least 10% of patients in the safety population.

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Table 14: Non-Laboratory Adverse Reactions Occurring in ≥10% of Patients with cHL (CHECKMATE-205 and CHECKMATE-039)

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

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes asthenia.

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[c] Includes colitis.

[d] Includes abdominal discomfort and upper abdominal pain.

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

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

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

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

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

Additional information regarding clinically important adverse reactions:

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

Peripheral neuropathy: In CHECKMATE-205 and CHECKMATE-039, treatment-emergent peripheral neuropathy was reported in 14% (31/266) of all patients receiving OPDIVO. Twenty-eight patients (11%) had new-onset peripheral neuropathy, and 3 of 40 patients had worsening of neuropathy from baseline. These adverse reactions were Grade 1 or 2, except for 1 Grade 3 event (<1%). The median time to onset was 50 (range: 1 to 309) days.

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

Table 15 summarizes laboratory abnormalities that developed or worsened in at least 10% of patients with cHL. The most common (reported in at least 20%) treatment-emergent laboratory events included cytopenias, liver function abnormalities, and elevated lipase. Other common findings (reported in at least 10%) included elevated creatinine, electrolyte abnormalities, and elevated amylase.

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Table 15: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients with cHL (CHECKMATE-205 and CHECKMATE-039)

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

[a] Number of evaluable patients for the safety population ranges from 203 to 266.

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

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

Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

The safety of OPDIVO was evaluated in CHECKMATE-141, a randomized, active-controlled, open-label, multicenter trial in patients with recurrent or metastatic SCCHN with progression during or within 6 months of receiving prior platinum-based therapy *[see Clinical Studies (14.6)]*. Patients received 3 mg/kg of OPDIVO (n=236) over 60 minutes by intravenous infusion 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

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- 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.

CHECKMATE-141 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.

Urothelial Carcinoma

The safety of OPDIVO was evaluated in CHECKMATE-275, a single arm study in which 270 patients with locally advanced or metastatic urothelial carcinoma had disease progression during or following platinum-containing chemotherapy or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy received OPDIVO 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 3.3 months (range: 0 to 13.4+). Forty-six percent (46%) of patients had a drug delay for an adverse reaction.

Fourteen patients (5.2%) died from causes other than disease progression. This includes 4 patients (1.5%) who died from pneumonitis or cardiovascular failure which was attributed to treatment with OPDIVO. OPDIVO was discontinued for adverse reactions in 17% of patients. Serious adverse reactions occurred in 54% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration.

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Twenty-five (9%) patients received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5)]*.

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, nausea, and decreased appetite.

Table 16 summarizes adverse reactions that occurred in greater than 10% of patients.

Table 16: Adverse Reactions Occurring in ≥10% of Patients (CHECKMATE-275)

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

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Endocrine Disorders		
Thyroid disorders[d]	15	0

Toxicity was graded per NCI CTCAE v4.

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

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

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

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

Table 17: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients (CHECKMATE-275)

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

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

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Hepatocellular Carcinoma

The safety of OPDIVO was evaluated in a 154-patient subgroup of patients with HCC and Child-Pugh A cirrhosis who progressed on or were intolerant to sorafenib enrolled in CHECKMATE-040, a multicenter, open-label trial. Patients were required to have an AST and ALT of no more than five times the upper limit of normal and total bilirubin of less than 3 mg/dL. The median duration of exposure to OPDIVO was 6 months.

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

6.2 Postmarketing Experience

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

Eye disorders: Vogt-Koyanagi-Harada (VKH) syndrome

6.3 Immunogenicity

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

Of 2085 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, 233 patients (11.2%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 15 patients (0.7%) 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.

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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.

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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 been established in pediatric patients age 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of OPDIVO for this indication is supported by evidence from adequate and well-controlled studies of OPDIVO in adults with MSI-H or dMMR mCRC with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of nivolumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MSI-H or dMMR mCRC is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater for this indication is the same as that in adults for this indication *[see Dosage and Administration (2.8), Clinical Pharmacology (12.3), and Clinical Studies (14.8)]*. The safety and effectiveness of OPDIVO have not been established (1) in pediatric patients less than 12 years old with MSI-H or dMMR mCRC or (2) in pediatric patients less than 18 years old for the other approved indications.

8.5 Geriatric Use

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

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

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

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

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

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 or moderate hepatic impairment. OPDIVO has not been studied in patients with 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. It is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line.

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

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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.

12.3 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 as a 60-minute intravenous infusion every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. Nivolumab clearance does not decrease over time in patients with completely resected melanoma, as the geometric mean population clearance is 24% lower in this patient population compared with patients with metastatic melanoma at steady-state. The geometric mean 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 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion.

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

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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 HCC (n=152) and in patients with other tumors (n=92) with mild hepatic impairment (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST; n=13). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with 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

CHECKMATE-037 (NCT01721746) was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either 3 mg/kg of OPDIVO by intravenous infusion 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.

Reference ID: 4229975

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

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

The ORR was 32% (95% confidence interval [CI]: 23, 41), consisting of 4 complete responses and 34 partial responses in OPDIVO-treated patients. Of 38 patients with responses, 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 responses in patients with and without BRAF V600 mutation-positive melanoma.

Previously Untreated Metastatic Melanoma

CHECKMATE-066

CHECKMATE-066 (NCT01721772) 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 3 mg/kg of OPDIVO 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 overall 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%).

Reference ID: 4229975

CHECKMATE-066 demonstrated a statistically significant improvement in OS for the OPDIVO arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS. Table 18 and Figure 1 summarize the efficacy results.

Table 18: Efficacy Results - CHECKMATE-066

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

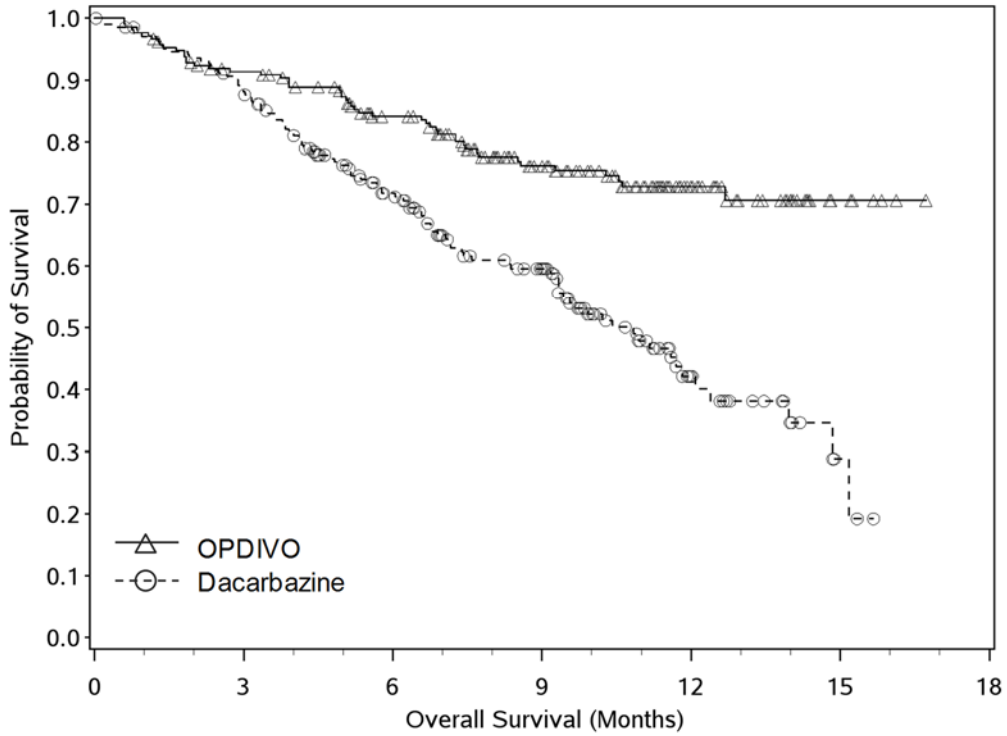
[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

[c] p-value is compared with the allocated alpha of 0.0021 for this interim analysis.

Reference ID: 4229975

Figure 1: Kaplan-Meier Curves of Overall Survival - CHECKMATE-066



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.

CHECKMATE-067

CHECKMATE-067 (NCT01844505) 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).

Reference ID: 4229975

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%).

CHECKMATE-067 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 19 and Figure 2.

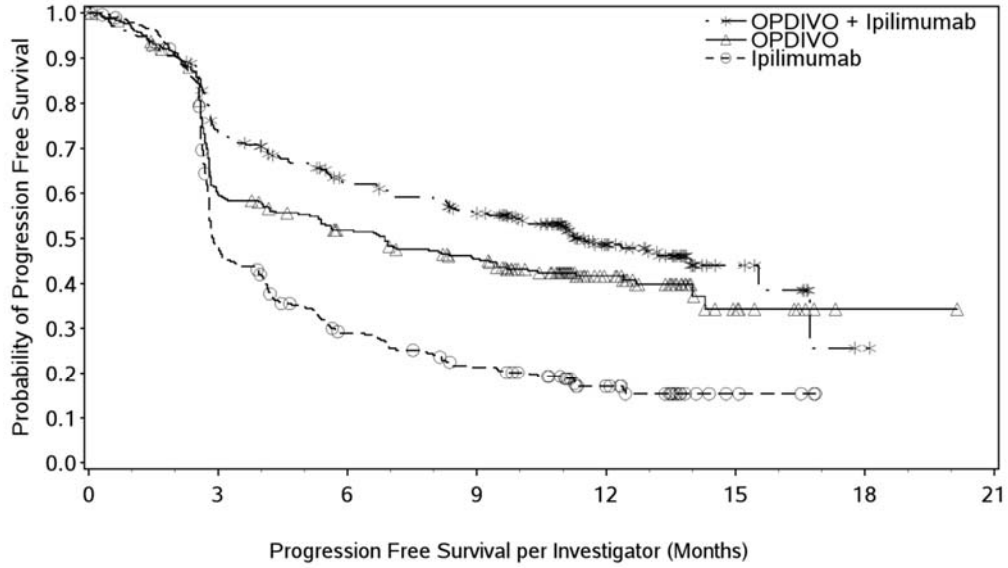
Table 19: Efficacy Results in CHECKMATE-067

	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 Overall 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.

Reference ID: 4229975

Figure 2: Progression-free Survival: Unresectable or Metastatic Melanoma - CHECKMATE-067

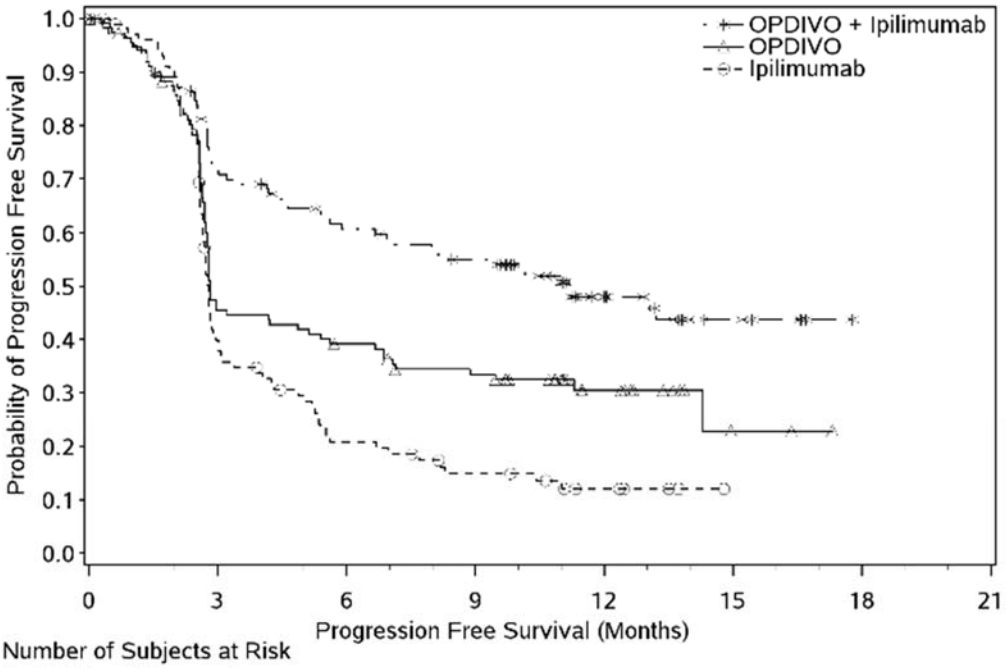


Number of Subjects at Risk							
OPDIVO + Ipilimumab							
314	219	173	151	65	11	1	0
OPDIVO							
316	177	147	124	50	9	1	0
Ipilimumab							
315	137	77	54	24	4	0	0

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.

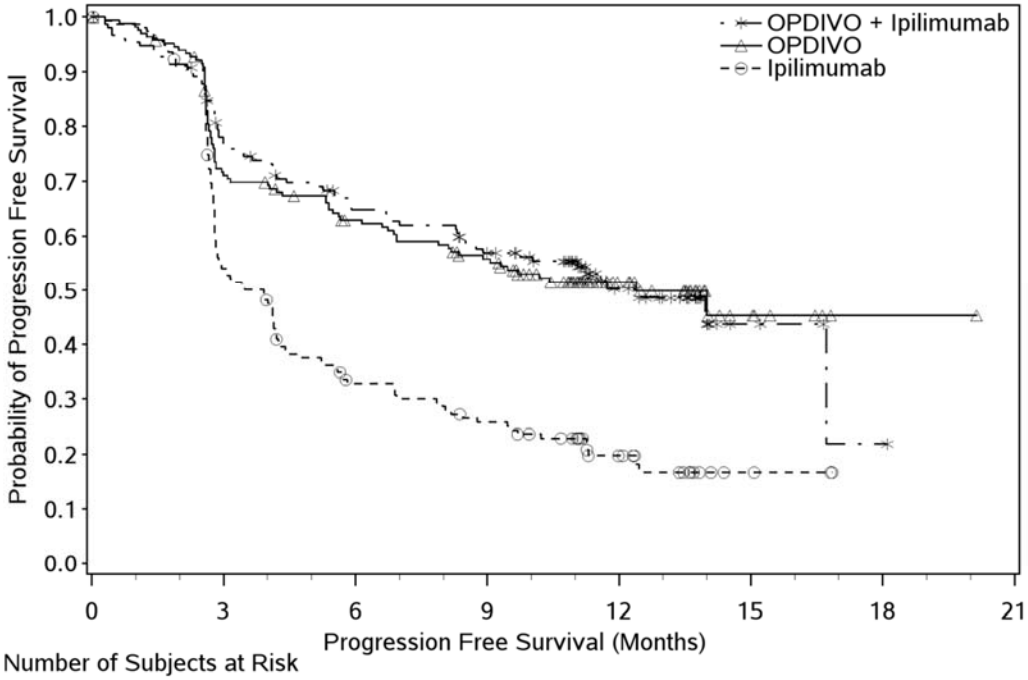
Reference ID: 4229975

Figure 3: **Progression-free Survival by PD-L1 Expression (<1%) - CHECKMATE-067**



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

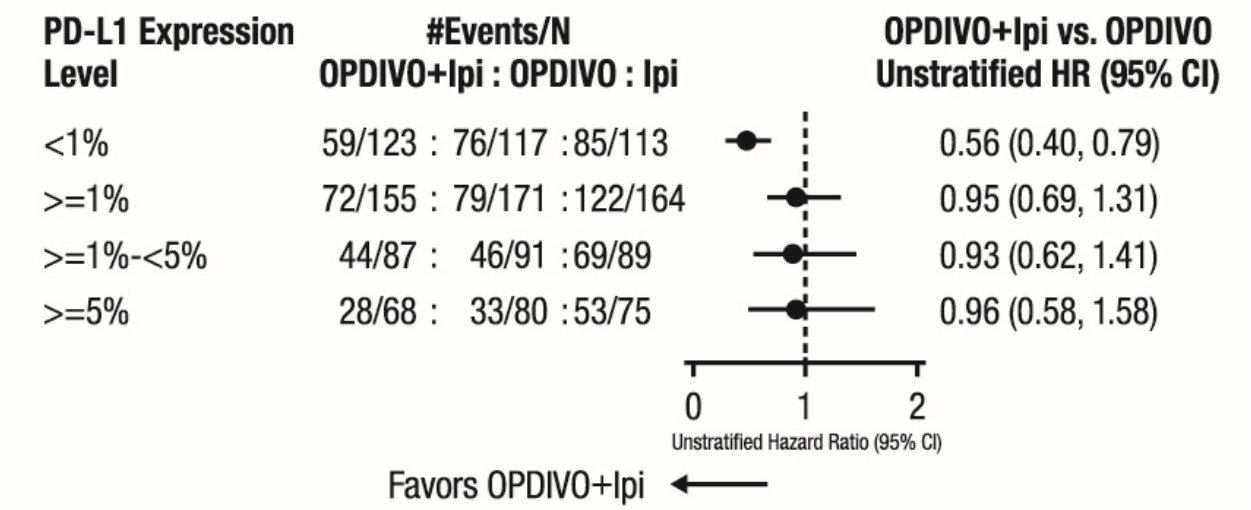
Figure 4: **Progression-free Survival by PD-L1 Expression (≥1%) - CHECKMATE-067**



Number of Subjects at Risk							
OPDIVO + Ipilimumab	155	113	91	78	32	4	1	0
OPDIVO	171	115	97	83	34	7	1	0
Ipilimumab	164	83	47	36	16	3	0	0

The data presented in Figure 5 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 - CHECKMATE-067**



14.2 Adjuvant Treatment of Melanoma

CHECKMATE-238 (NCT02388906) was a randomized, double-blind trial that enrolled patients with completely resected Stage IIIB/C or Stage IV melanoma. Patients were randomized (1:1) to receive 3 mg/kg of OPDIVO over 60 minutes by intravenous infusion every 2 weeks or ipilimumab administered as an intravenous infusion at 10 mg/kg every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. Enrollment required complete resection of melanoma with margins negative for disease within 12 weeks prior to randomization. The trial excluded patients with a history of ocular/uveal melanoma, autoimmune disease, and any condition requiring systemic treatment with either corticosteroids (≥10 mg daily prednisone or equivalent) or other immunosuppressive medications, as well as patients with prior therapy for melanoma except surgery, adjuvant radiotherapy after neurosurgical resection for lesions of the central nervous system, and prior adjuvant interferon completed ≥6 months prior to randomization. Randomization was stratified by PD-L1 status (positive [based on 5% level] vs negative/indeterminate) and American Joint Committee on Cancer (AJCC) stage (Stage IIIB/C vs Stage IV M1a-M1b vs Stage IV M1c).The major efficacy outcome measure was recurrence-free survival (RFS) defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death, from any cause, whichever occurs first and as assessed by the investigator. Patients underwent imaging for tumor recurrence every 12 weeks for the first 2 years then every 6 months thereafter.

In CHECKMATE-238, a total of 906 patients were randomized: 453 to OPDIVO and 453 to ipilimumab. Median age was 55 years (range: 18 to 86), 58% were male, 95% were White, and 90% had an ECOG performance status of 0. Disease characteristics were AJCC Stage IIIB (34%), Stage IIIC (47%), Stage IV (19%), M1a-b (14%), BRAF V600 mutation positive (42%), BRAF wild-type (45%), elevated LDH (8%), PD-L1 ≥ 5% tumor cell membrane expression determined by clinical trial assay (34%), macroscopic lymph nodes (48%), and tumor ulceration (32%).

CHECKMATE-238 demonstrated a statistically significant improvement in RFS for patients randomized to the OPDIVO arm compared with the ipilimumab 10 mg/kg arm.

Efficacy results are presented in Table 20 and Figure 6.

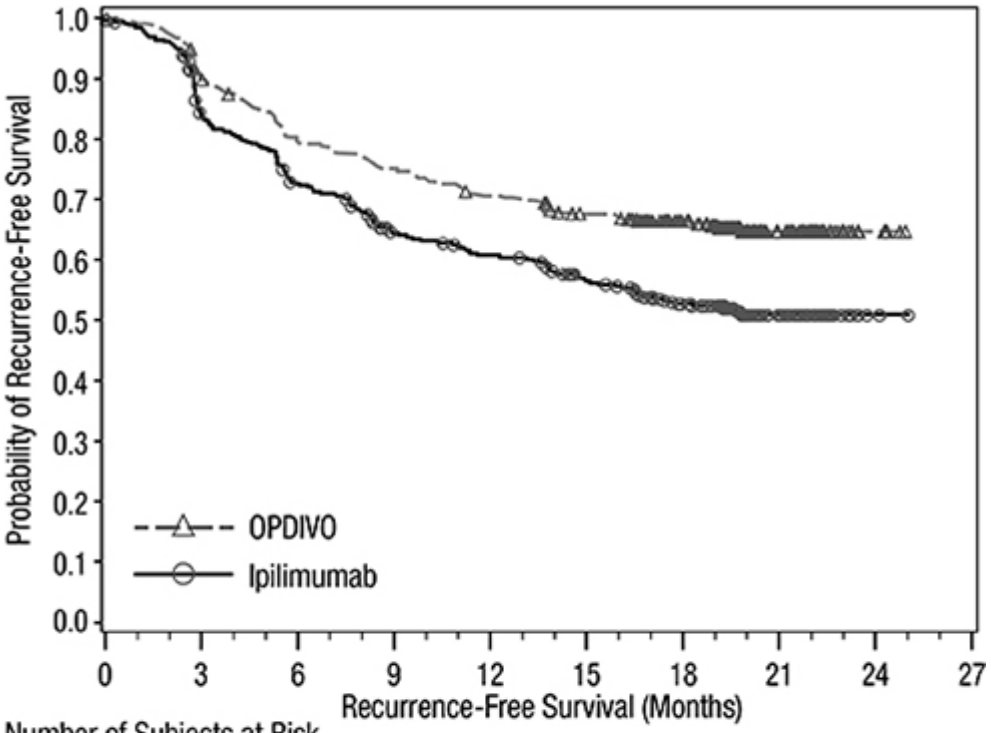
Reference ID: 4229975

Table 20: Efficacy Results in CHECKMATE-238

Recurrence-free Survival	OPDIVO N=453	Ipilimumab 10 mg/kg N=453
Number of Events, n (%)	154 (34.0%)	206 (45.5%)
Median (months) (95% CI)	NR[a]	NR[a] (16.56, NR[a])
Hazard Ratio[b] (95% CI) p-value[c,d]	0.65 (0.53, 0.80) p<0.0001	

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

Figure 6: Recurrence-free Survival -CHECKMATE-238



Number of Subjects at Risk

OPDIVO	453	399	353	332	311	291	249	71	5	0
Ipilimumab 10 mg/kg	453	364	314	269	252	225	184	56	2	0

Reference ID: 4229975

14.3 Metastatic Non-Small Cell Lung Cancer (NSCLC)

Second-line Treatment of Metastatic Squamous NSCLC

CHECKMATE-017 (NCT01642004) 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 3 mg/kg of OPDIVO (n=135) by intravenous infusion 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 CHECKMATE-017, 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 21 and Figure 7).

Reference ID: 4229975

Table 21: Efficacy Results in CHECKMATE-017

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

[a] Based on a stratified proportional hazards model.

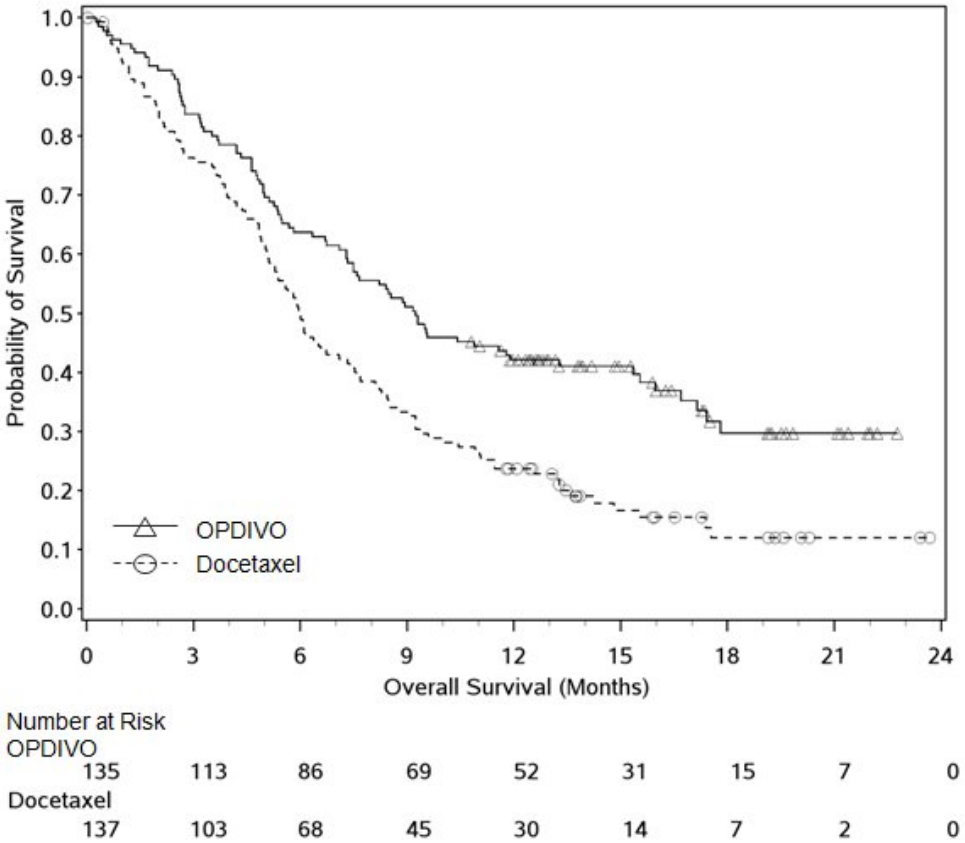
[b] Based on stratified log-rank test.

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

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

Reference ID: 4229975

Figure 7: Overall Survival - CHECKMATE-017



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

CHECKMATE-057 (NCT01673867) 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 3 mg/kg of OPDIVO (n=292) by intravenous infusion 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

Reference ID: 4229975

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 CHECKMATE-057, 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%).

CHECKMATE-057 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with docetaxel at the prespecified interim analysis when 413 events were observed (93% of the planned number of events for final analysis) (Table 22 and Figure 8).

Table 22: Efficacy Results in CHECKMATE-057

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

[a] Based on a stratified proportional hazards model.

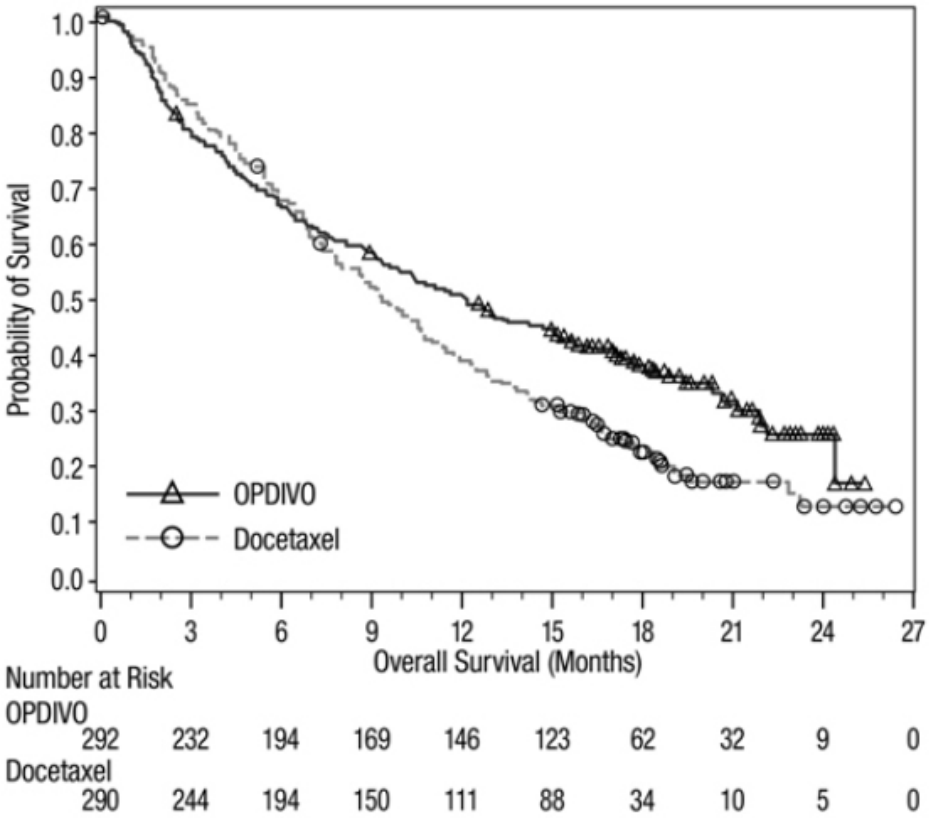
[b] Based on stratified log-rank test.

[c] p-value is compared with .0408 of the allocated alpha for this interim analysis.

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

Reference ID: 4229975

Figure 8: Overall Survival - CHECKMATE-057



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 9 summarizes the results of prespecified analyses of survival in subgroups determined by percentage of tumor cells expressing PD-L1. Figure 10 summarizes the results of prespecified analyses of progression-free survival in subgroups determined by percentage of tumor cells expressing PD-L1.

Reference ID: 4229975

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

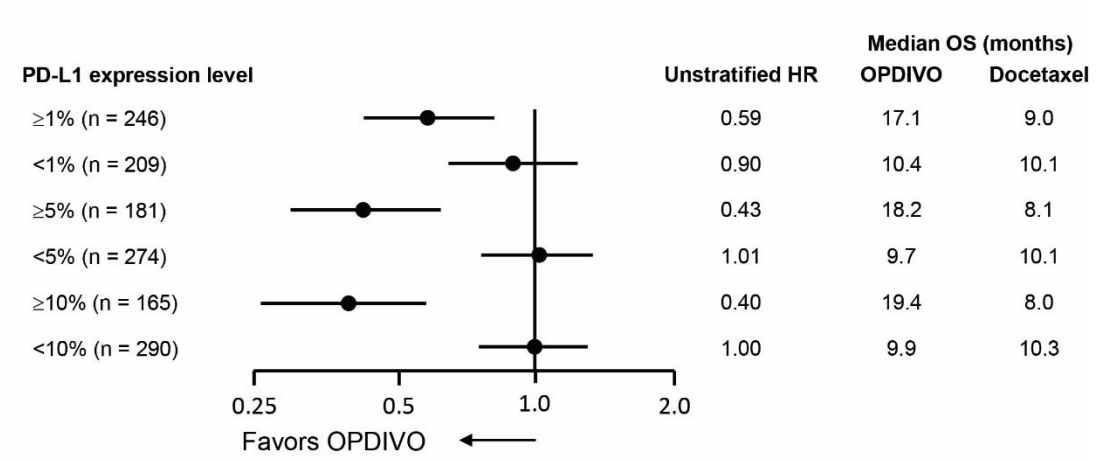
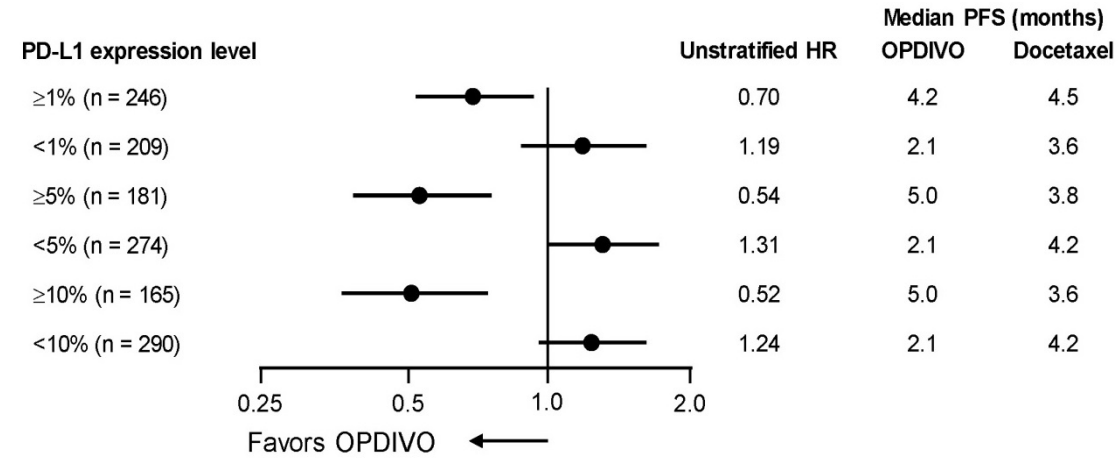


Figure 10: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



14.4 Renal Cell Carcinoma

CHECKMATE-025 (NCT01668784) 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. CHECKMATE-025 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.

Reference ID: 4229975

Patients were randomized 3 mg/kg of OPDIVO (n=410) by intravenous infusion 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 23 and Figure 11). OS benefit was observed regardless of PD-L1 expression level.

Other endpoints include confirmed overall response rates, which are also presented in Table 23.

Table 23: Efficacy Results - CHECKMATE-025

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

[a] Based on a stratified proportional hazards model.

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

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

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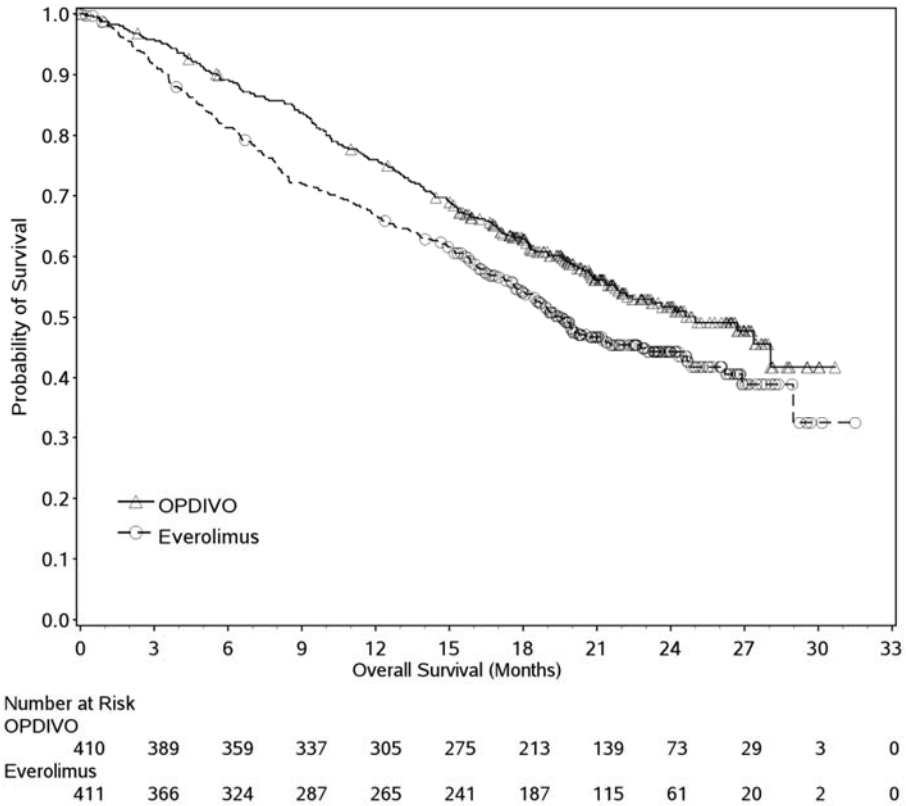
Figure 11: Overall Survival - CHECKMATE-025



14.5 Classical Hodgkin Lymphoma

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

CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort study in cHL. CHECKMATE-039 (NCT01592370) 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 over 60 minutes by intravenous infusion every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity. A cycle consisted of one dose. Dose reduction was not permitted.

Efficacy was evaluated by overall response rate (ORR) as determined by an independent radiographic review committee (IRRC). Additional outcome measures included duration of response (DOR).

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Efficacy was evaluated in 95 patients in CHECKMATE-205 and CHECKMATE-039 combined who had failure of autologous HSCT and post-transplantation brentuximab vedotin. The median age was 37 years (range: 18 to 72). The majority were male (64%) and white (87%). Patients had received a median of 5 prior systemic regimens (range: 2 to 15). They received a median of 27 doses of OPDIVO (range: 3 to 48), with a median duration of therapy of 14 months (range: 1 to 23 months). Results are shown in Table 24.

Table 24: Efficacy in cHL after Autologous HSCT and Post-transplantation Brentuximab Vedotin

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

[a] Per 2007 revised International Working Group criteria.

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

[c] A + sign indicates a censored value.

Efficacy was also evaluated in 258 patients in CHECKMATE-205 and CHECKMATE-039 combined who had relapsed or progressive cHL after autologous HSCT. The analysis included the group described above. The median age was 34 years (range: 18 to 72). The majority were male (59%) and white (86%). Patients had a median of 4 prior systemic regimens (range: 2 to 15), with 85% having 3 or more prior systemic regimens and 76% having prior brentuximab vedotin. Of the 195 patients having prior brentuximab vedotin, 17% received it only before autologous HSCT, 78% received it only after HSCT, and 5% received it both before and after HSCT. Patients received a median of 21 doses of OPDIVO (range: 1 to 48), with a median duration of therapy of 10 months (range: 0 to 23 months). Results are shown in Table 25.

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Table 25: Efficacy in cHL after Autologous HSCT

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

[a] Kaplan-Meier estimate. Among responders, the median follow-up for DOR, measured from the date of first response, was 6.7 months.
[b] The estimated median duration of PR was 13.1 months (95% CI, 9.5, NE). The median duration of CR was not reached.

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

CHECKMATE-141 (NCT02105636) 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 3 mg/kg of OPDIVO by intravenous infusion 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 CHECKMATE-141, 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

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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 26 and Figure 12. 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 26: Overall Survival in CHECKMATE-141

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

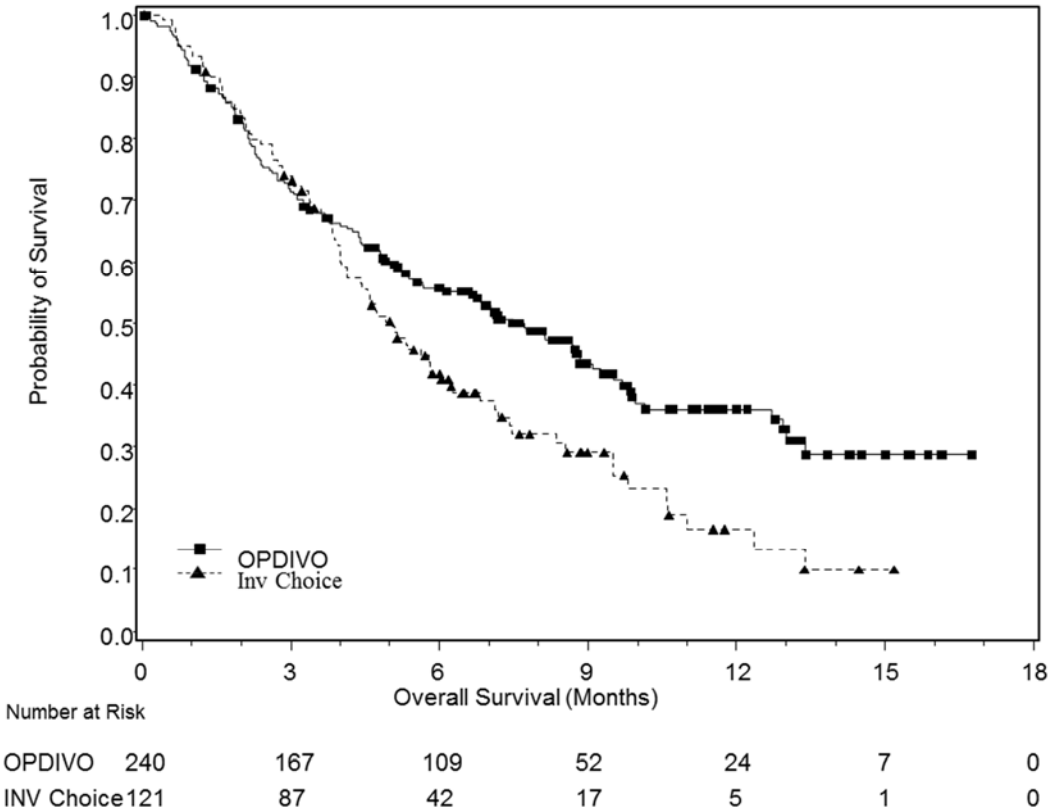
[a] Based on stratified proportional hazards model.

[b] Based on stratified log-rank test.

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

Reference ID: 4229975

Figure 12: Overall Survival - CHECKMATE-141



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

14.7 Urothelial Carcinoma

In CHECKMATE-275 (NCT02387996), 270 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen were treated with OPDIVO. Patients were excluded for active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, and ECOG performance status >1. Patients received 3 mg/kg of OPDIVO by intravenous infusion every 2 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every

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8 weeks for the first 48 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed overall response rate (ORR) as assessed by independent radiographic review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR).

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

Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients, were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 27. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%).

Table 27: Efficacy Results in CHECKMATE-275

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

[a] Estimated from the Kaplan-Meier Curve

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

CHECKMATE-142 (NCT02060188) was a multicenter, open-label, single arm study conducted in patients with locally determined dMMR or MSI-H metastatic CRC who had disease progression during, after, or were intolerant to, prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Key eligibility criteria were at least one prior line of treatment for metastatic disease, ECOG 0 or 1, and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. All patients received 3 mg/kg of OPDIVO by intravenous infusion every 2 weeks until unacceptable toxicity

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or radiographic progression. Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included overall response rate (ORR) as assessed by independent radiographic review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR).

A total of 74 patients were enrolled. The median age was 53 years (range: 26 to 79) with 23% ≥65 years of age and 5% ≥75 years of age, 59% were male and 88% were white. Baseline ECOG performance status was 0 (43%), 1 (55%), or 3 (1.4%) and 36% were reported to have Lynch Syndrome. Across the 74 patients, 72% received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; 15%, 30%, 30%, and 24% received 1, 2, 3, or ≥4 prior lines of therapy, respectively, and 42% of patients had received an anti-EGFR antibody.

Efficacy results are shown in Table 28.

Table 28: Efficacy Results – CHECKMATE-142

	All Patients (n=74)	**Prior Treatment with Fluoropyrimidine, Oxaliplatin, and Irinotecan (n=53)**
IRC-Confirmed Overall Response Rate, n (%)	24 (32%)	15 (28%)
(95% CI)	(22, 44)	(17, 42)
Complete response (%)	2 (2.7%)	1 (1.9%)
Partial response (%)	22 (30%)	14 (26%)
Duration of Response		
Median in months (range)	NR (1.4+, 26.5+)	NR (2.8+, 22.1+)

NR=Not Reached

14.9 Hepatocellular Carcinoma

The efficacy of OPDIVO was evaluated in a 154-patient subgroup of CHECKMATE-040, (NCT 01658878), a multicenter, open-label trial conducted in patients with hepatocellular carcinoma (HCC) who progressed on or were intolerant to sorafenib. Additional eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible. Patients received 3 mg/kg of OPDIVO by intravenous infusion every 2 weeks. Tumor assessments were conducted every 6 weeks for 48 weeks and every 12 weeks thereafter.

The major efficacy outcome measure was confirmed overall response rate, as assessed by blinded independent central review using RECIST v1.1 and modified RECIST (mRECIST) for HCC. Duration of response was also assessed.

A total of 154 patients received 3 mg/kg of OPDIVO by intravenous infusion every 2 weeks. The median age was 63 years (range: 19 to 81), 77% were men, and 46% were White. Across the population, 31% had active HBV infection, 21% had active HCV infection, and 49% had no

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evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 18% and non- alcoholic liver disease in 6.5% of patients. Baseline ECOG performance status was 0 (65%) or 1 (35%). Child-Pugh class and score was A5 for 68%, A6 for 31%, and B7 for 1% of patients. Seventy one percent (71%) of patients had extrahepatic spread, 29% had macrovascular invasion, and 37% had alfa-fetoprotein (AFP) levels ≥400 µg/L. Prior treatment history included surgical resection (66%), radiotherapy (24%), or locoregional treatment (58%). All patients had received prior sorafenib, of whom 36 (23%) were unable to tolerate sorafenib; 19% of patients had received 2 or more prior systemic therapies.

Efficacy results are summarized in Table 29.

Table 29: Efficacy Results in Trial CHECKMATE-040

	OPDIVO (n = 154)
BICR-Assessed Overall Response Rate[a], n (%), RECIST v1.1	22 (14.3%)
(95% CI)[b]	(9.2, 20.8)
Complete response	3 (1.9%)
Partial response	19 (12.3%)
BICR-Assessed Duration of Response, RECIST v1.1	(n=22)
Range (months)	(3.2, 38.2+)
% with duration ≥ 6 months	91%
% with duration ≥ 12 months	55%
BICR-Assessed Overall Response Rate[a], n (%), mRECIST	28 (18.2%)
(95% CI)[b]	(12.4, 25.2)
Complete response	5 (3.2%)
Partial response	23 (14.9%)

[a] Overall response rate confirmed by BICR.

[b] Confidence interval is based on the Clopper and Pearson method.

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16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) Injection is available as follows:

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

Store 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)]*.

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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

Reference ID: 4229975

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

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

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

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

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

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

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

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

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

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

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

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:

- **people with 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, **or**
  - to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.
- **people with a type of advanced stage lung cancer (called non-small cell lung cancer).**
- **OPDIVO may be used when your lung cancer:**
  - has spread or grown, **and**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

  If your tumor has an abnormal EGFR or ALK gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, **and** it did not work or is no longer working.
- **people with kidney cancer (renal cell carcinoma).**
  - OPDIVO may be used when your cancer has spread or grown after treatment with other cancer medications.
- **adults with a type of blood cancer called classical Hodgkin lymphoma.**
- **OPDIVO may be used if:**
  - your cancer has come back or spread after a type of stem cell transplant that uses your own stem cells (autologous), **and**
  - you used the drug brentuximab vedotin (Adcetris®) before or after your stem cell transplant, **or**
  - you received at least 3 kinds of treatment including a stem cell transplant that uses your own stem cells (autologous).
- **people with head and neck cancer (squamous cell carcinoma)**
- **OPDIVO may be used when your head and neck cancer:**
  - has come back or spread, **and**
  - you have tried chemotherapy that contains platinum and it did not work or is no longer working.
- **people with bladder cancer (urothelial carcinoma).**
- **OPDIVO may be used when your bladder cancer:**
  - has spread or grown, **and**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- **adults and children 12 years of age and older with a type of colon or rectal cancer (colorectal cancer).**
- **OPDIVO may be used when your colon or rectal cancer**:
  - has spread to other parts of the body (metastatic),
  - is mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H), **and**
  - you have tried chemotherapy with a fluoropyrimidine, oxaliplatin, and irinotecan, and it did not work or is no longer working.
- **people with liver cancer (hepatocellular carcinoma)**
  - OPDIVO may be used after you have received treatment with sorafenib (Nexavar®).

It is not known if OPDIVO is safe and effective:

- in children less than 12 years of age with MSI-H or dMMR metastatic colorectal cancer, **or**
- in children less than 18 years of age for the treatment of any other cancers.

What should I tell my healthcare provider before receiving OPDIVO?
Before you receive OPDIVO, tell your healthcare provider if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical conditions

- are pregnant or plan to become pregnant. OPDIVO can harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during and for at least 5 months after the last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant during treatment with OPDIVO.
- are breastfeeding or plan to breastfeed. It is not known if OPDIVO passes into your breast milk. Do not breastfeed during treatment with OPDIVO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them to show your healthcare providers and pharmacist when you get a new medicine.

How will I receive OPDIVO?

- Your healthcare provider will give you OPDIVO into your vein through an intravenous (IV) line over 30 minutes.
- OPDIVO is usually given every 2 weeks or 4 weeks depending on the dose you are receiving.
- 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 or 4 weeks depending on the dose you are receiving.
- 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
- weakness
- shortness of breath
- decreased appetite
- upper respiratory tract infection
- headache
- rash
- itchy skin
- nausea
- cough
- constipation
- back pain
- fever
- stomach pain

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.

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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: March 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Origs052

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo	
Date	02/28/2018
From	Jiang Liu, Ph.D.
NDA/SDN/eCTD Sequence No.	BLA125554/ SDN 1482-1486,2029,2033/S48-52/0344-0348, S61-62/0468-0469
Type/Category	Efficacy supplement
Brand Name	OPDIVO®
Generic Name	Nivolumab
Receipt Date	S48-52: 05/05/2017, S61-62: 01/05/2018
PDUFA Date	03/05/2018
Dosage Form and Strengths	40 mg/4 mL and 100 mg/10 mL solution in a single-dose vial
Route of Administration	Intravenous
Proposed Indication and Dosing Regimen	To include 480 mg every four-week dosage regimen in addition to the currently approved 240 mg every two-week dosage regimen for the following approved indications: • Metastatic Melanoma • Non-Small Cell Lung Cancer • Advanced Renal Cell Carcinoma • Classical Hodgkin's Lymphoma • Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) • Locally Advanced or Metastatic Urothelial Carcinoma • Adjuvant Treatment of Melanoma • Hepatocellular Carcinoma
Recommendation on Regulatory Action	Approval

Reference ID: 4229982

In the seven BLA supplements, Bristol-Myers Squibb (BMS) proposes to add a new nivolumab dosage regimen of 480 mg every 4 weeks (Q4W) for the approved indications listed below:

- Unresectable or metastatic melanoma
- Adjuvant treatment of melanoma
- Metastatic non-small cell lung cancer (NSCLC)
- Advanced renal cell carcinoma (RCC)
- Classical Hodgkin's lymphoma (CHL)
- Recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN)
- Locally advanced or metastatic urothelial carcinoma (UC)
- Hepatocellular carcinoma (HCC)

The proposed new dosage regimen is supported by the pharmacokinetics modeling and simulation, flat dose/exposure response relationships for efficacy and safety in the indicated patient populations, and available clinical safety data with the 480 mg Q4W dosage regimen. No clinical efficacy data of the every 4-week dosage regimen was submitted in these seven supplements. Overall, the steady state Cavg and Cmin with 480 mg Q4W were predicted to be comparable to 3 mg/kg Q2W across all approved indications (majority within 20%). Dose-efficacy profiles for melanoma and NSCLC with Q2W regimens and for RCC with Q3W regimens and exposure-efficacy profiles based on Cavg and Cmin for all approved indications suggest that efficacy profile with 480 mg Q4W will not be compromised compared to approved dose 3 mg/kg Q2W. Clinical experience with other anti-PD-1 mAb and other anti-cancer mAb also suggest that a dosage regimen with the same total monthly dose and comparable Cmin but decreased dose frequency is unlikely to compromise the efficacy. No safety liability is expected with 480 mg Q4W as the predicted Cmax were well below the median of Cmax achieved with 10 mg/kg Q2W, which was tested to be tolerable in patients with solid tumors.

The review team concluded that adding a new nivolumab dosage regimen of 480 mg every 4 weeks to the currently approved dosage regimen of 240 mg every 2 weeks for the above approved indications is acceptable (see Clinical Pharmacology Review by Dr. Youwei Bi dated March 1st, 2018, and Clinical Review by Dr. Christy Osgood dated March 5th, 2018). I concur with this assessment. (b) (4)

The major labeling changes were made in Section 2. There are no Postmarketing Requirement (PMR) or Postmarketing Commitment (PMC) studies.

Nivolumab was granted Orphan Drug Designation for treatment of classical Hodgkin lymphoma on 07-Aug-2014 (Designation Request #14-4426), treatment of melanoma on 23-Jan-2013 (Designation Request # 12-3876), and treatment of hepatocellular carcinoma on 02-Sept-2015 (Designation Request #15-4899) and therefore is exempt from the PREA requirement. In addition, the pediatric study requirements for the treatment of patients with, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and

neck, and urothelial carcinoma were granted a full waiver because necessary studies are impossible or highly impracticable since the disease/condition does not exist in children. Financial disclosures for relevant clinical studies can be found in previous clinical reviews of the original BLA and subsequent supplements (Dated on: Dec 7th, 2014; July 23rd, 2015, Sep 30th, 2015, Nov 18th, 2015, Jan 22nd, 2016, May 12th, 2016, Oct 24th, 2016, Jan 30th, 2017, Sep 19th, 2017, and Nov 29th, 2017).

There are no other unresolved regulatory issues. I recommend approval for all the seven efficacy supplements (S48, S49, S50, S51, S52, S61, and S62).

Reference ID: 4229982

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

/s/

JIANG LIU
03/05/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Origs052

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy supplements
Application Number(s)	125554-S48-52, S61-62, S64-66
Priority or Standard	Standard
Received Date(s)	05/05/2017 (S48-52), 01/05/2018 (S61-62); 02/13/2018 (S64-66)
PDUFA Goal Date	03/05/2018
Division / Office	DOP2/OHOP
Reviewer Name(s)	Christy L Osgood, MD Ashley Ward, MD, Acting Team leader
Established Name	Nivolumab/ BMS-936558
Trade Name	Opdivo
Therapeutic Class	Monoclonal antibody (PD-1 inhibitor)
Applicant	Bristol-Myers Squibb Company
Formulation(s)	Solution
Dosing Regimen	Nivolumab as a single-agent 480 mg intravenous (IV) over 30 minutes every 4 weeks Nivolumab as a single-agent 240mg intravenous (IV) over 30 minutes every 2 weeks
Indication(s)	For Nivolumab as a single-agent 480 mg intravenous (IV) over 30 minutes every 4 weeks: melanoma, non-small cell lung cancer, renal cell carcinoma, classic Hodgkin lymphoma, hepatocellular carcinoma, squamous cell carcinoma of the head and neck, and urothelial carcinoma For Nivolumab as a single-agent 240mg intravenous (IV) over 30 minutes every 2 weeks: treatment of adjuvant melanoma, hepatocellular carcinoma, and colorectal cancer
Intended Population(s)	≥18 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The reviewer recommends regular approval of nivolumab, 480 mg, administered every 4 weeks as an as a single agent for the treatment of patients with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), classical Hodgkin's lymphoma (cHL) and hepatocellular carcinoma (HCC).

The reviewer recommends regular approval of nivolumab administered as an intravenous infusion over 30 minutes for the treatment of patients with colorectal carcinoma (CRC), HCC, and for patients with melanoma in the adjuvant setting.

1.2 Risk Benefit Assessment

The Applicant proposes to add a dosage regimen of 480 mg IV Q4W to the currently approved 240 mg IV Q2W dosage regimen. The evidence to support the proposed additional dosage regimen of 480 mg IV Q4W as a single-agent in in melanoma, NSCLC, RCC, SCCHN, UC, cHL, and HCC is based upon the following:

- Comparison of nivolumab exposures achieved by 240 mg Q2W, 480 mg Q4W and 3 mg/kg Q2W in subjects with melanoma, NSCLC, RCC, SCCHN, cHL, HCC and UC
- Efficacy bridging evaluation
  - Comparison of the efficacy of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in melanoma, NSCLC, and RCC with respect to the following endpoints: overall survival(OS), objective response (OR)
  - Comparison of predicted receptor occupancy (RO) with nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W, including sensitivity of RO to parameters that may vary across solid tumor types
- Safety bridging evaluation
  - Assessment of safety margins, by comparison of predicted exposures with 240 mg Q2W and 480 mg Q4W relative to the well-tolerated 10 mg/kg Q2W regimen
  - Comparison of the safety of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in subjects with melanoma, SQ and NSQ NSCLC, RCC, HCC, SCCHN, cHL, and UC with respect to the following 3 endpoints: Adverse events leading to discontinuation or death (AEDC/D), Grade 3+ adverse events (AE-Grade 3+), and Grade 2+ immune-mediated adverse events (AE-IM Grade 2+)

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- Clinical safety data from subjects treated with nivolumab 480 mg Q4W administered over a 30-minute infusion from Trial CA209511

The proposed 480 mg Q4W flat dose is supported by the population PK simulations, flat dose/exposure response relationships for efficacy and safety in the patient populations with approved indications, and available clinical safety data with the 480 mg Q4W dosage regimen. Overall, the average serum concentration at steady state and the trough serum concentration at steady state with 480 mg Q4W were predicted to be comparable to 3 mg/kg Q2W across all approved indications (within 20%).

Dose-efficacy profiles for melanoma and NSCLC with Q2W regimens and for RCC with Q3W regimens and exposure-efficacy profiles based on the time-averaged concentration over the first 28 days of treatment and the trough concentration at Day 28 for all approved indications suggest efficacy profile with 480 mg Q4W will not be compromised compared to approved dose 3 mg/kg Q2W.

The dose response analyses for safety events were characterized based on event rates of AE-DC/D, AE-Grade 3+ and AE-IM Grade 2+ in 2560 patients with melanoma, SQ NSCLC, NSQ NSCLC, RCC, SCCHN, UC and CHL. No statistically significant differences in the event rate of AE-DC/D, AE-Grade 3+ and AE-IM Grade 2+ were identified in patients who received 1 mg/kg, 2 mg/kg and 10 mg/kg when compared to patients who received the reference dose of 3 mg/kg based on logistic regression analysis. Additionally, no safety liability is expected with 480 mg Q4W as the predicted peak concentration of the 480 mg Q4W dose is well below the median of peak concentrations achieved with 10 mg/kg Q2W, which was found to be tolerable in patients with solid tumors on clinical trials.

To support the clinical pharmacology review of the population PK simulation, the dose-response analysis and the dose exposure safety analysis, the clinical safety data from 142 patients with unresectable or metastatic melanoma treated with nivolumab 480 mg Q4W on Trial CA209511 was evaluated and compared to adverse event profiles of prior clinical trials of nivolumab where nivolumab was given at 3 mg/kg or 240 mg Q2W. This analysis focus on Grade 3-4 adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation and immune mediate adverse events. The safety evaluation of patients treated with nivolumab 480 mg IV Q4W showed that the safety profile is is consistent with the established safety profile of nivolumab (240 mg Q2W or 3 mg/kg Q2W administered IV over 60 minutes) and no new safety concerns were identified.

The most common AEs (≥ 5%) in patients treated with nivolumab 480 mg Q4W were asthenia and nausea (7.7%), headache (6.3%) and cough (5.6%). Five patients (3.5%) of patients had AEs that led to discontinuation; the adverse event that lead to dose discontinuation were pneumonitis (2 patients), pancreatitis, general physical condition deterioration, and malignant neoplasm progression (1 patient each). Non-fatal SAEs occurred in 15.5% of patients. The SAEs that occurred in ≥ 1% of patients were pneumonitis, and anemia (1.7% each).

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Assessment of the population PK simulations, the exposure response relationship for efficacy and safety in the patient populations with approved indications demonstrate that the benefit-risk profile with nivolumab 480 mg Q4W is predicted to be similar to the 3 mg/kg Q2W dosing regimen studied in the registration trials across multiple tumor types. The safety of this dosing regimen is supported by the safety obtained from patients with metastatic melanoma treated with nivolumab 480 mg Q4W in Trial CA209511 demonstrating a similar safety profile observed in prior clinical trials of nivolumab and did not identify any new safety signals. This alternative dosing regimen will provide another treatment schedule option for patients and prescribers. The risk benefit assessment is favorable for dosing regimen of nivolumab 480 mg Q4W.

No new clinical pharmacology or clinical trials or data were submitted by the sponsor to support the 30-minute infusion for the treatment of patients with colorectal carcinoma (CRC), HCC, and for patients with melanoma in the adjuvant setting. The applicant refers to the data submitted for the approval of the 30-minutes infusion for the indications of melanoma, NSCLC, RCC, SCCHN, cHL, and UC submitted on March 9, 2017 as SDN 1374-1378. At the time of approval, the risk benefit assessment was based on extrapolation of the assessment following administration of the 30-minute infusion from a study in NSCLC to the additional proposed indications of melanoma, NSCLC, RCC, SCCHN, cHL, and UC based on demonstrated similarities of nivolumab exposure and safety findings across these tumor types. The risk benefit assessment is favorable for the use of nivolumab as a 30-minute infusion. This extrapolation can be extended to the indications of CRC, HCC and for patients with melanoma in the adjuvant setting. Please see the clinical review dated January 9, 2018 for details.

2 Introduction and Regulatory Background

2.1 Product Information (from FDA-approved USPI)

Nivolumab is a humanized monoclonal antibody of the IgG4/kappa isotype that binds to PD-1 and blocks the interaction between PD-1 and PD-L1 and PD-L2.

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2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Table of FDA-approved Therapies Indicated for the Treatment of Patients with Metastatic Melanoma

Drug (population)	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
Dacarbazine	1975	Single-Arm	ORR	ORR 5-20%
Aldesleukin	1998	Multicenter Single Arm	ORR	cORR 16% mDOR (range) CR: ≥59 m (3 to ≥122 m) CR or PR: ≥59 m (1 to ≥122 m)
Ipilimumab (unresectable or metastatic melanoma)	2011	Multicenter, blinded, RCT	OS ORR	Ipilimumab vs. gp100 mOS 10 m vs. 6 m HR: 0.66 (95% CI: 0.51, 0.87) p=0.0026 cORR 10.9% vs. 1.5% mDOR: not reached in either arm
Pembrolizumab[a] (ipilimumab-refractory, unresectable or metastatic melanoma)	2014	Multicenter, Single-arm trial	ORR	cORR 24% (95% CI: 15, 34) DOR range: 1.4+m to 8.5+m • 18 of 21 (86%) patients with responses were ongoing • 13 (44%) of the patients with ongoing responses had response duration of ≥6 m
Pembrolizumab (ipilimumab-naïve, unresectable or metastatic melanoma)	2015	Multicenter, open-label, RCT	OS PFS ORR	Pembrolizumab vs. ipilimumab OS HR 0.69 (95% CI: 0.52, 0.90); p=0.004 mPFS 4.1 m vs. 2.8 m HR 0.58 (95% CI: 0.47, 0.72); p<0.001 cORR 33% vs. 12% DOR range: 1.4+ m to 8.1+ m
Pembrolizumab (ipilimumab-refractory, unresectable or metastatic melanoma)	2015	Multicenter, RCT	PFS ORR	Pembrolizumab vs. chemotherapy mPFS 2.9 m vs. 2.7 m HR 0.57 (95% CI: 0.45, 0.73); p <0.001 cORR 21% (95% CI: 15, 28) vs. 4% (95% CI: 2, 9) DOR range: 1.3+m to 11.5+m
Nivolumab[a] (ipilimumab-refractory, unresectable or metastatic melanoma)	2014	Single-arm, analysis or ORR within a multicenter, open-label, RCT.	ORR	cORR 32% (95% CI: 23, 41) DOR range: 2.6+m to 10+m • 33 of 38 (87%) patients with responses were ongoing • 13 (40%) of the patients with ongoing responses had response duration of ≥6 m
Nivolumab (previously untreated, BRAF V600 WT unresectable or metastatic melanoma)	2015	Multicenter, blinded, RCT	OS PFS ORR	Nivolumab vs. dacarbazine mOS NR vs. 10.8 m HR 0.42 (95% CI: 0.30, 0.60); p<0.0001 mPFS 5.1 m vs. 2.2 m HR 0.43 (95% CI: 0.34, 0.56); p<0.0001 cORR 34% (95% CI: 28, 41) vs.

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Drug (population)	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
				9% (95% CI: 5, 13) • 63 of 72 (88%) patients with responses were ongoing • 43 (68%) of the patients with ongoing responses had response durations of ≥6 m
Nivolumab[a,b] (previously untreated, unresectable or metastatic melanoma)	2016	Multicenter, double-blind, RCT	PFS ORR	Nivolumab vs. ipilimumab mPFS 6.9 m vs. 2.9 m HR 0.57 (95% CI: 0.47, 0.69); p<0.0001 cORR 8.5% (95% CI: 34%, 46%) vs. 14% (95% CI: 10%, 18%); p<0.0001 • 74% of nivolumab patients had responses of ≥6 m and 63% of ipilimumab patients of ≥ 6 m

Source: Reviewer generated table-summarized from the USPI for Interluekin-2; ipilimumab; dacarbazine; pembrolizumab; and nivolumab
Abbreviations in table: cORR=confirmed overall response; CR=complete response; HR=hazard ratio; m=months; mDOR=median duration of response; mOS=median overall survival; mPFS=median progression-free survival; PR=partial response; ORR=overall response rate; OS=overall survival; PFS=progression free survival; RCT = randomized controlled trial; +=response is ongoing

a. Accelerated approval as per 21 CFR 601.41, subpart E
b. Received accelerated approval under 21 CFR 601.41 Subpart E for the treatment of patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma and, in combination with ipilimumab, for treatment of patients with unresectable or metastatic melanoma. Labeling includes information from the trial supporting this accelerated approval concerning PFS results in subgroups defined by PD-L1 expression and a "complementary" in vitro diagnostic device to test for PD-L1 expression in melanoma was approved concurrently

2.3 Availability of Proposed Active Ingredient in the United States

Nivolumab as a 60-minute IV infusion was first approved in the United States (U.S.) on December 22, 2014, as a single-agent for patients with unresectable or metastatic melanoma. Subsequently, nivolumab has received approval for use in combination with ipilimumab in unresectable or metastatic melanoma, metastatic NSCLC with progression on or after platinum-based chemotherapy, advanced RCC who have received prior anti-angiogenic therapy, cHL that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin, recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy, and locally advanced or metastatic UC with disease progression during or following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy. The initial approved dose of nivolumab was 3 mg/kg IV over 60 minutes every 2 weeks. On September 9, 2017 and February 15, 2018, FDA approved the flat dose of 240 mg IV Q2W for all approved indications. Additionally, on January 9 2018, FDA approved a 30-min infusion time for patients with unresectable or metastatic melanoma, NSCLC, RCC, cHL, SCCHN, and UC (all indications that had been approved at the time the supplement was submitted).

2.4 Important Safety Issues with Consideration to Related Drugs

The important safety issues with anti-CTLA-4 antibodies, such as ipilimumab and other anti-PD1/PD-L1 antibodies, such as pembrolizumab, atezolizumab, avelumab, and durvalumab, are immune-mediated adverse reactions which include pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, skin adverse reactions, infusion-related reactions, pancreatitis, myasthenia syndrome, ocular toxicity, infections, and other immune mediated adverse events.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following summarizes the presubmission regulatory activity for nivolumab relevant to Protocol CA209511:

- June 6, 2006: Initial submission of IND 100052 for the study of nivolumab as a single agent
- July 27, 2010: Initial submission of IND104225 for the study if nivolumab plus ipilimumab
- December 22, 2014: FDA granted accelerated approval for nivolumab under BLA 125554 for the treatment of unresectable or metastatic melanoma with disease progression following ipilimumab, and if BRAF mutation-positive, a BRAF inhibitor. Approval was based on demonstration of durable objective responses.
- March 5, 2015: FDA approved 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 nivolumab under BLA 125554 in combination with ipilimumab, for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma. The recommended dosage regimen is nivolumab 3 mg/kg administered as an as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
- October 9, 2015: FDA approved 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. The recommended dosage regimen is nivolumab 3 mg/kg administered as an as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
- November 23, 2015: FDA approved 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 under BLA 125554 for the following indications:

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  - use, in combination with ipilimumab, for the treatment of patients with unresectable or metastatic melanoma. The recommended dose of nivolumab 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; then nivolumab, as a single agent, as 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
  - For the treatment of patients with BRAF V600 mutation positive, unresectable or metastatic melanoma. The recommended dosage regimen is nivolumab 3 mg/kg administered as an as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
- January 23, 2016: FDA approved nivolumab under BLA 125554 for the treatment in advanced renal cell carcinoma patients who have received prior antiangiogenic therapy. The recommended dosage regimen is nivolumab 3 mg/kg administered as an as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
- May 17, 2016. FDA granted accelerated approval for nivolumab under BLA 125554 for the treatment of patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and posttransplantation brentuximab vedotin. The recommended dosage regimen is nivolumab 3 mg/kg administered as an as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
- June 01, 2016: BMS submitted a type C meeting request to discuss the data to support a proposed new dosage regimen for nivolumab of 480 mg every 4 weeks (Q4) for the approved indications in which the recommended dosage regimen of nivolumab is 3 mg/kg and/or 240 mg every 2 weeks.
- July 28, 2016: Written responses were sent to BMS for a Type C meeting regarding advice on the proposed data package and content for a planned BLA supplement for the new dosage regimen of nivolumab 480 mg Q4 based on pharmacokinetic and exposure-response modeling methodology as well as clinical trial safety data from a subgroup of patients from trial CA209511.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and

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integrity of the application appears acceptable.

3.2 Compliance with Good Clinical Practices

The Applicant stated the following in the sNDA clinical study report for Trial 309: "This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2008)
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- For studies in US: Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312…."

3.3 Financial Disclosures

The Applicant submitted a list of investigators (sNDA Section 1.3.4, Attachment 1) and FDA form 3454 certifying that all the investigators listed in Attachment 1 had no financial arrangements as defined in 21 CFR 54.2 (a, b, and f) that could affect the outcome of the trial.

Financial disclosure information was collected and reported for 375 Principal Investigators and subinvestigators. The applicant states that all Investigators except for one have signed Financial Disclosure Forms. Disclosable interest information was provided for four Principal Investigators and subinvestigators, all due to receipt of significant payments of other sorts.
The following Investigators had disclosable financial information:

- (b) (6) reported disclosable financial information in the category of significant payments of other sorts from BMS totaling $110,000 for his participation in the BMS funded II-ON (International Immuno Oncology Network). (b) (6) patients were treated at this site
- (b) (6) reported disclosable financial information in the category of significant payments of other sorts totaling $300,000 for his participation in the BMS funded II-ON (International Immuno Oncology Network). (b) (6) patients were treated at this site.
- (b) (6) reported disclosable financial information in the category of significant payments of other sorts totaling $200,000 for his participation in the BMS funded II-ON (International Immuno Oncology Network). (b) (6) patients were treated at this site.
- (b) (6) reported disclosable financial information in the category of significant payments of other sorts totaling $280,000 for his

Reference ID: 4229532

participation in the BMS funded II-ON (International Immuno Oncology Network). (b) (6) patients were treated at this site.

Reviewer's Comment:
The impact of the potential bias on the outcome in CA209511 is minimized by the small number of patients treated by investigators with potential conflicts of interest compared to the total number treated in the study.

4 Sources of Clinical Data

4.1 Review Strategy

The FDA clinical review was tailored to specific safety review performed to support the review by clinical pharmacology. The clinical pharmacology review of the 480 mg every 4-week dose was primarily based on a previously developed composite population PK model which included data from 3458 patients in 19 clinical studies with various types of solid and hematological tumors, including melanoma, NSCLC, RCC, SCCHN, UC and CHL. This model was applied to predict the nivolumab exposure produced by a nivolumab 480 mg Q4W dosage regimen in subjects across different approved indications. Additionally, the clinical pharmacology review evaluated the following:

- Efficacy bridging evaluation
  - Comparison of the efficacy of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in melanoma, NSCLC, and RCC with respect to the following endpoints: overall survival(OS), objective response (OR)
  - Comparison of predicted receptor occupancy (RO) with nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W, including sensitivity of RO to parameters that may vary across solid tumor types
- Safety bridging evaluation
  - Assessment of safety margins, by comparison of predicted exposures with 240 mg Q2W and 480 mg Q4W relative to the well-tolerated 10 mg/kg Q2W regimen
  - Comparison of the safety of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in subjects with melanoma, SQ and NSQ NSCLC, RCC, HCC, SCCHN, cHL, and UC with respect to the following 3 endpoints: Adverse events leading to discontinuation or death (AEDC/D), Grade 3+ adverse events (AE-Grade 3+), and Grade 2+ immune-mediated adverse events (AE-IM Grade 2+)

Additionally, the BLA submission contained safety data from Trial CA209511, a randomized, double blinded, study of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in patients with previously untreated, unresectable or metastatic melanoma followed by treatment with nivolumab 480 mg every 4 weeks.

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The clinical review included the following:

- Review of trial CA209511 including the clinical study report, protocol, and protocol amendments submitted by the Applicant
- Review and assessment of the Applicant's analysis of the safety of nivolumab 480 mg administered every 4-weeks, for evaluation of Applicant's claims
- Review of datasets submitted as SAS transport files
- Assessment of the Module 2 summaries
- Review of reviews conducted by Clinical Pharmacology
- Requests for additional information from the Applicant and review of Applicant response
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

4.2 Discussion of Individual Studies/Clinical Trials

Clinical Trial Title

Phase IIIb/IV, Randomized, Double Blinded, Study of Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg vs Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma

Objectives

Primary Objective

- The primary objective is to compare the incidence of drug-related Grade 3 - 5 AEs of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg to nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg in treatment-naive subjects with unresectable or metastatic melanoma.

Key Secondary Objectives

- To evaluate the objective response rate (ORR), as determined by investigators, of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg and nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg in treatment-naïve subjects with unresectable or metastatic melanoma.
- To evaluate progression free survival (PFS) of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg and nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg in treatment-naive subjects with unresectable or metastatic melanoma.
- To assess overall survival (OS)
- To assess Health Related Quality of Life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30). Exploratory Objectives

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- To evaluate duration of and time to objective response of nivolumab combined with ipilimumab in both N3I1 and N1I3 arms
- To assess the overall safety and tolerability of nivolumab combined with ipilimumab in both N3I1 and N1I3 arms
- To characterize the immunogenicity of nivolumab and ipilimumab when combined in both N3I1 and N1I3 arms
- To characterize the overall safety, tolerability, PK, immunogenicity of nivolumab combined with ipilimumab administered sequentially in both N3I1 and N1I3 arms.
- To analyze biomarkers, such as serum inflammatory factors and circulating T cell subsets, that are modulated by nivolumab+ipilimumab combination treatment and may be associated with clinical efficacy or incidence of adverse events in N3I1 and N1I3 arms
- To explore potential biomarkers associated with clinical efficacy (ORR, PFS and OS) by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, PBMCs) in comparison to clinical outcomes in both N3I1 and N1I3 arms
- To assess the effects of natural genetic variation (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA-4 on clinical endpoints and/or on the incidence of adverse events in both N3I1 and N1I3 arms.
- To assess changes in health status using the EuroQoL EQ-5D.

Trial Design

Trial CA209511 was a randomized, double blinded study of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg ipilimumab in combination with 3 mg/kg in adult subjects with previously untreated, unresectable or metastatic melanoma. Patients were randomized 1:1 and stratified by programmed cell death receptor-ligand 1 (PD-L1) expression (≥5% tumor cell surface expression vs < 5% tumor cell surface expression/indeterminate), and American Joint Commission on Cancer (AJCC) M stage (M0/M1a/M1b vs M1c). The trial was completed in two parts.

- Part 1: patients treated with nivolumab and ipilimumab every 3 weeks for 4 cycles
- Part 2: patients treated with nivolumab 480 mg every four weeks, beginning 6 weeks after the last combination dose.

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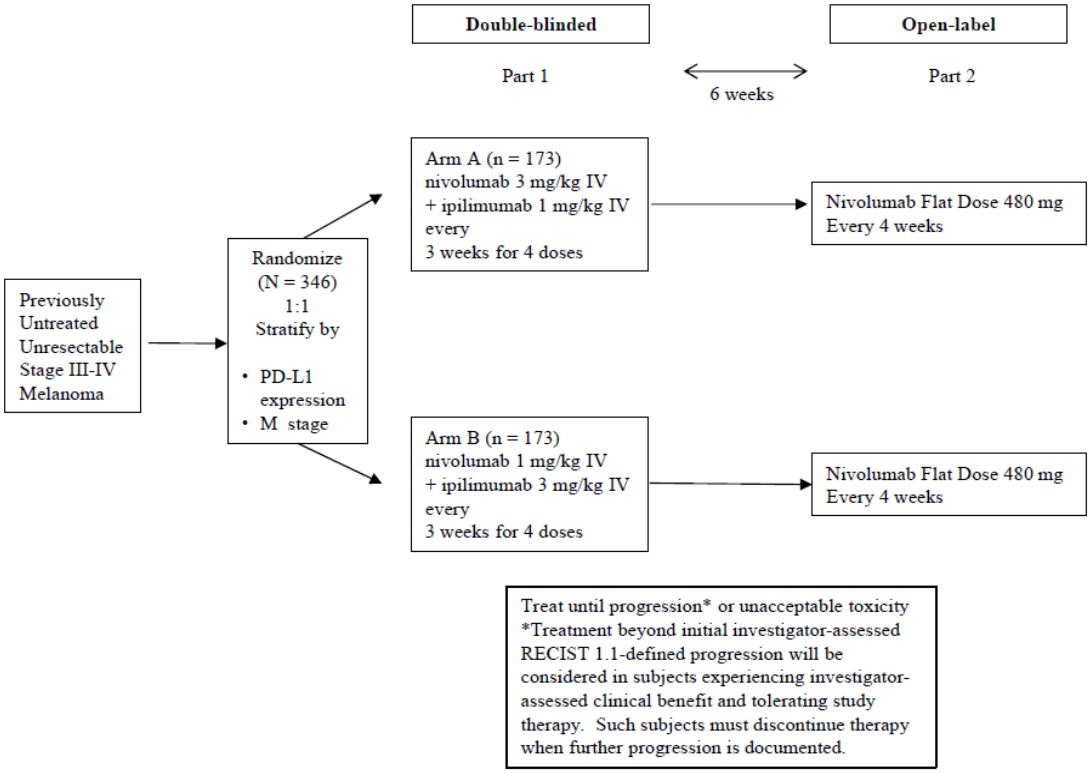
Figure 1: Study Scheme for Trial CA209511



Source: Reproduced from the protocol for Trial CA209511

Trial Population *(key eligibility criteria)*

Inclusion criteria:

1. Adult subjects (≥18 years) with histologically confirmed unresectable Stage III or Stage IV Melanoma as per AJCC staging system.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
3. No prior systemic anticancer therapy for unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to date of first dose, and all related adverse events have either returned to baseline or stabilized.
4. Measurable disease as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) criteria
5. Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses.
6. Known BRAF V600 mutation status as determined by local institutional standard or subject to consent to BRAF V600 mutation testing per local institutional standards during the Screening Period, the results of which must be reported

within 3 months of randomization. All BRAF statuses (BRAF wild-type or BRAF 600 mutation positive) are eligible.
7. Prior radiotherapy must have been completed at least 2 weeks prior to study drug administration.
8. Adequate bone marrow and organ function

Exclusion criteria:
1. Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no evidence of progression via magnetic resonance imaging (MRI, except where contraindicated in which CT scan is acceptable) for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for high doses of systemic corticosteroids that could result in immunosuppression (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
2. Ocular melanoma
3. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
4. Prior active malignancy within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast
5. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
6. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD37, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways. This includes utilization of these agents in the adjuvant, neo-adjuvant, and metastatic melanoma setting.
7. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
8. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
9. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic Infection
10. History of allergy or hypersensitivity to study drug components

Dose Modification and Management Algorithms

Dose Delays:

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Regardless of whether the event is attributed to nivolumab, ipilimumab, or both, all study drugs must be delayed until treatment can resume. Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥2 non-skin, drug-related adverse event, with the following exceptions:
    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
- Grade 2 drug-related creatinine, AST, ALT or Total Bilirubin abnormalities
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
    - Grade 3 lymphopenia does not require dose delay
    - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥2 toxicity
    - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥3 toxicity
    - Any Grade ≥3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Dose Reductions:

Dose reductions were not permitted.

Criteria to Resume Treatment:

Subjects should resume treatment with nivolumab and ipilimumab in both arms A and B given the blinded nature of the study when the drug-related AE(s) resolve(s) to Grade ≤1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 2 AST/ALT or total bilirubin may resume treatment when laboratory values return to baseline and management with corticoids, if needed, is completed.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued

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- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes. If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy.

Criteria for Permanent Discontinuation of Study Treatment:

All discontinuation criteria apply for nivolumab and ipilimumab in both Arms A and B (during Part 1) given the blinded nature of this study.
Treatment should be permanently discontinued for the following:

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, diarrhea, hypersensitivity reactions, infusion reactions and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation
            - Grade ≥3 drug-related AST/ALT or Total Bilirubin abnormality
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
        - In most cases of Grade 3 AST or ALT elevation, study drugs) will be permanently discontinued. If the investigator determines a possible favorable risk/benefit ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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- Any Grade 4 drug-related adverse event or laboratory abnormality (including, but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events which do not require discontinuation:
    - ≥Grade 4 neutropenia >7 days
    - Grade 4 lymphopenia or leucopenia
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
    - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
    - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.
    - Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of Progressive Disease (PD). Subjects will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and
- Subject is tolerating study drug.
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving additional study medication, all other elements of the main informed consent including the

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description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

Monitoring Plan

Table 5.1-2: On-Study Assessments Part 1 (CA209511)		
Procedure	**For Part 1, Study Drug Every 3 Weeks for 4 Cycles (Both Arm A and Arm B)**	**Notes**
	Cycle 1, 2, 3, 4 (Day 1)	
Safety Assessments		
Targeted Physical Examination	X	To be performed only as clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, temperature. (Section 5.3)
Physical Measurements (including performance status)	X	Weight and ECOG Performance status within 72 hours prior to dosing
Adverse Events Assessment	Continuously	
Review of Concomitant Medications	X	
Laboratory Tests	X	Within 72 hrs prior to dosing to include 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), albumin if clinically indicated).
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to administration of first dose and every 3 weeks thereafter in Part 1 of the study.
Pharmacokinetic and Immunogenicity Assessments		
Immunogenicity blood sample	See Section 5.5 for details regarding specific sample timing	
PK Samples	See Section 5.5 for details regarding specific sample timing	

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Table 5.1-2: On-Study Assessments Part 1 (CA209511)		
Procedure	**For Part 1, Study Drug Every 3 Weeks for 4 Cycles (Both Arm A and Arm B)**	**Notes**
	Cycle 1, 2, 3, 4 (Day 1)	
Exploratory Biomarker Testing		
Exploratory Serum Biomarkers	X	To be collected pre-dose; before first 4 combination doses only.
Peripheral Blood Mononuclear Cells (PBMCs)	X	To be collected pre-dose; before first 4 combination doses only. To be collected in USA and Canada only.
Whole Blood Sample (DNA)	X	X = before first combination dose only.
Myeloid-Derived Suppressor Cell (MDSCs)	X	To be collected pre-dose; before the first and the third combination dose only
Efficacy Assessment		
Tumor Assessment	See Notes	FIRST tumor assessment should be performed at 12 weeks (± 1 wk) following randomization. CT Chest, CT (or MRI) abdomen, pelvis 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: On-Study Assessments Part 1 (CA209511)		
Procedure	**For Part 1, Study Drug Every 3 Weeks for 4 Cycles (Both Arm A and Arm B)**	**Notes**
	Cycle 1, 2, 3, 4 (Day 1)	
Outcomes Research Assessments		
EORTC QLQ-C30 and EQ-5D	X	To be completed at the start of the clinic visit every 6 weeks. First questionnaire should be completed after IRT randomization but before dosing. (Cycle 1, 3)
Health Care Utilization	X	Health Care Utilization will be collected at each visit
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	Within 24 hours prior to dosing
Administer Study Treatment	X	First dose to be administered within 3 days following randomization. See Section 4.3.

Table 5.1-3: On-Study Assessments - Part 2 (CA209511)		
Procedure	**For Part 2, Study Drug is Administered Every 4 Weeks (Both Arm A and Arm B)** **Cycle 5 and beyond (Day 1)**	**Notes** **Cycle 5 will begin 6 weeks after Cycle 4**
Safety Assessments		
Targeted Physical Examination	X	To be performed only if clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, temperature (Section 5.3)
Physical Measurements (including performance status)	X	Weight and ECOG Performance status within 72 hours prior to dosing
Adverse Events Assessment	Continuously	
Review of Concomitant Medications	X	
Laboratory Tests	X	Beginning at Cycle 5 and every alternate dose thereafter (Cycle 7, 9, 11, 13, etc), on-study local laboratory assessments should be done within 72 hours prior to the first (Part 2) dose 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. (Albumin if clinically indicated) Beginning at Cycle 6 and every alternate dose thereafter (Cycle 8, 10, 12, 14, etc), on-study local laboratory assessment should be done within 72 hours prior to the second (Part 2) dose and include: LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to first dose and every 4 weeks thereafter in Part 2

Table 5.1-3: On-Study Assessments - Part 2 (CA209511)		
Procedure	**For Part 2, Study Drug is Administered Every 4 Weeks (Both Arm A and Arm B)** **Cycle 5 and beyond (Day 1)**	**Notes** **Cycle 5 will begin 6 weeks after Cycle 4**
Outcomes Research Assessments		
EORTC QLQ-C30 and EQ-5D	X	To be completed at the start of the clinic visit every 4 weeks from Cycles 5 to 11
Health Care Utilization		Health Care Utilization will be collected at each visit
Pharmacokinetic and Immunogenicity Assessments		
Immunogenicity blood sample	See Section 5.5 for details regarding specific sample timing	
PK Samples	See Section 5.5 for details regarding specific sample timing	
Efficacy Assessment		
Tumor Assessment	See Notes	First tumor assessment during Part 2 should occur after 8 weeks (± 1wk) relative to previous tumor assessment performed at week 12. Subsequent tumor assessments should occur every 8 weeks (± 1 wk) for the first 12 months from randomization. From the second year from randomization, tumor assessments should occur every 12 wks (± 2 wk) until disease progression. CT Chest, CT (or MRI) abdomen, pelvis 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: On-Study Assessments - Part 2 (CA209511)		
Procedure	**For Part 2, Study Drug is Administered Every 4 Weeks (Both Arm A and Arm B)**	**Notes**
	Cycle 5 and beyond (Day 1)	**Cycle 5 will begin 6 weeks after Cycle 4**
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	
Administer Study Treatment	X	See Section 4.3. Note: Within 3 days from vial assignment, the subject must receive the dose of study medication.

Adverse Event Collection

Adverse events were graded according to CTCAE v.4. All AEs, regardless of relationship to study treatment or procedure, were collected beginning from the time the subject signs the study consent through the last visit and for 100 days following study treatment discontinuation. All AEs were to be followed until stabilization or resolution. Immune-mediated adverse events (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

Protocol Amendments

The Applicant submitted eight amendments to Protocol CA209511. Key revisions are provided below:

- Amendment 03 (January 2016): increased the interval between the end of the combination regimen and the beginning of the nivolumab flat dose monotherapy from 3 weeks to 6 weeks
- Amendment allowed for continued enrollment beyond 780 patients in two of the study subgroups.
- Amendment 04 (December 2014): allowed all patients to receive nivolumab by IV infusion administered over 30 minutes, including new and existing patients enrolled in the study. Enrollment would continue until a total of 1280 patients were treated.

5 Review of Exposure Profile

The exposure profile of the proposed 480 mg Q4W over 30-minute effusion was based on a previously developed composite population pharmacokinetic model which included data from 3458 patients across 19 studies in patients with melanoma, NSCLC, RCC, SCCHN, UC and cHL. The geometric mean of summary exposure metrics achieved with nivolumab 480 mg Q4W is compared with corresponding exposures achieved with

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3 mg/kg Q2W. In general, the time-average serum concentrations at steady state and peak concentrations were higher with the 480 mg Q3W dose and the trough serum concentration at steady was lower for the 480 mg Q3W regimen. For the overall population, the geometric means of average serum concentration at steady state (Cavgss), peak serum concentration at steady state (Cmaxss) and trough serum concentration at steady state (Cminss) with 480 mg Q4W were 5.7% higher, 43.7% higher, and 16.2% lower compared to same exposure metrics at 3 mg/kg Q2W. The difference in the for each patient population are as follows:

- Melanoma 480 mg Q4W regimen 17.5% decrease in Cminss, 40.6% increase and 3.3% increase in Cavgss compared to 3 mg/kg Q2W regimen
- NSCLC 480 mg Q4W regimen 13% decrease in Cminss, 54.8% increase and 11.1% increase in Cavgss compared to 3 mg/kg Q2W regimen
- RCC 480 mg Q4W regimen 23.6% decrease in Cminss, 31.4% increase and 3.1% decrease in Cavgss compared to 3 mg/kg Q2W regimen
- cHL 480 mg Q4W regimen 8.1% decrease in Cminss, 39.7% increase and 8.2% increase in Cavgss compared to 3 mg/kg Q2W regimen
- SCCHN 480 mg Q4W regimen 5.2% decrease in Cminss, 68.4% increase and 21.3% increase in Cavgss compared to 3 mg/kg Q2W regimen
- UC 480 mg Q4W regimen 16.7% decrease in Cminss, 41.4% increase and 4.1% increase in Cavgss compared to 3 mg/kg Q2W regimen
- Adjuvant melanoma 480 mg Q4W regimen 14.5% decrease in Cminss, 35.2% increase and 1.3% increase in Cavgss compared to 3 mg/kg Q2W regimen

The clinical pharmacology review concluded that the average and trough steady state serum concentrations were comparable across all approved indications (within 20% for melanoma, NSCLC, cHL, UC, HCC and adjuvant melanoma and within 25% for RCC and SCCHN). While the predicted peak concentration at steady state for the 480 mg Q4W were 31.4% to 68.4% higher than the peak concentration of 3 mg/kg Q2W dosage regimen, the median peak serum concentration predicted for patients receiving 480 mg Q4W is lower than the median peak concentration observed in patients treated with nivolumab 10 mg/kg Q2W, which was found to be tolerable in patients with solid tumors.

6 Review of Efficacy

To determine whether the 480 mg Q4W flat dose may result in a clinically meaningful reduction in efficacy in patients with melanoma, NSCLC, RCC, cHL, SCCHN, UC, and HCC, this reviewer evaluated the exposure-response (E-R) analyses conducted for OS and ORR in melanoma, RCC, and NSCLC. For all efficacy endpoints, the E-R analysis used the time-averaged concentration over the first 28 days (Cavgd28) of treatment and the trough concentration at Day 28 (Cimind28). Additionally, the efficacy exposure response analysis employed data from patients treated with nivolumab 1 to 10 mg/kg Q2W and 0.3 to 10 mg/kg Q3W.

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Reviewer Comment: This reviewer concludes that the use of multiple efficacy endpoints for this evaluation is appropriate. The evaluation of OS is a measurement of long term benefit and the evaluation of ORR represents an early measure of treatment effect. Using average serum concentration during the first 28 days is an appropriate measurement of exposure as to capture the relevant drug concentration over the entire duration of the dosing interval for Q2W as well as Q4W regimens. Additionally, since nivolumab Cmind28 was the only measure of exposure that was lower with the 480 mg Q4W regimen relative to that of the 3 mg/kg Q2W regimen used in the pivotal studies, the exposure response at Cmind28 was evaluated to ensure that at the lowest exposure there would not be a decrease in efficacy.

6.1 Overall Survival E-R Analysis

The E-R analyses to characterize the relationship between nivolumab exposure and OS in patients with NSCLC, melanoma, and RCC was conducted using Cox proportional-hazard models. The E-R analyses showed that patients with RCC and NSCLC with a higher Cavgd28 had a lower risk of death than those with a lower Cavgd28. However once these results are corrected for sample size, these differences were not significant. In patients with melanoma, a high Cavgd28 was associated with a higher risk of death; however, this difference was not clinically or statistically significant.

Reviewer Comment: In the NSCLC population, there was a statistically significant benefit in OS comparing the 3 mg/kg dose regimen to the 1 mg/kg dose regimen based on the Cox proportional hazard ration analysis; however, once the analysis was adjusted for sample size and study effects, the comparison was not significant with hazard ratios in the final model of 2.08 (95%CI 0.866, 5) for Squamous cell NSCLC and 1.92 (95%CI: 0.819, 4.52) for non-squamous cell NSCLC.

Based on this exposure response analysis, exposure response models of OS were used to predict the survival of patient treated with nivolumab at 480 mg Q4W and 3 mg/kg Q2W and these predictions were used to calculate the hazard ratios relative to the control arm of studies in which OS was the primary endpoint. Overall, these evaluations showed the Kaplan-Meier curves of OS were overlapping for the 3mg/kg Q2W and the 480 mg Q4W regimens and were superior to the observed survival in the respective comparator arms across all tumor types. Table 2 displays the hazard ratios with nivolumab treatment of 480 mg Q4W were predicted to be similarly to 3 mg/kg Q2W across tumor types. These results were consistent when using both Cavgd28 as well as Cmind28, indicating that 480 mg Q4W is expected to have similar efficacy to the 3 mg/kg Q2W dosing regimen and no impact on survival is anticipated.

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Table 2: Efficacy Bridging Summary Across Tumor Types-Mean Hazard Ration of Overall Survival

Tumor Type	Exposure Measure	Overall Survival		
		3 mg/kg Q2W (HR)[a]	240 mg Q2W (HR)[a]	480 mg Q4W (HR)[a]
Melanoma (N = 178)	Cavgd28	0.363	0.374	0.403
	Cmind28	0.363	0.374	0.335
RCC (N =403)	Cavgd28	0.733	0.733	0.732
	Cmind28	0.734	0.733	0.755
SQ NSCLC (N = 125)	Cavgd28	0.585	0.577	0.558
	Cmind28	0.588	0.577	0.632
NSQ NSCLC (N = 280)	Cavgd28	0.746	0.743	0.738
	Cmind28	0.745	0.742	0.749

Note: Refer to Figure 3.2.1-2 (Cavgd28) and Figure 3.2.1-4 (Cmind28) in Module 2.7.2 SCP for confidence intervals
Analysis Directory: /global/pkms/data/CA/209/dose-optimization/prd/gpa/final/Final-April.2017
Program Source: Analysis Directory/nivo-master/lab-notebook/pivotalstudies /alltumor_hr_comparison_apr2017.Rmd// alltumor_hr_comparison_cmin.Rmd
Source: Analysis Directory/ nivo-master/ lab-notebook /pivotalstudies/alltumor_hr_comparison_apr2017.docx// alltumor_hr_comparison_cmin.docx
[a] Hazard ratio relative to control arm in the following phase 3 study for each tumor type: CA209066 (melanoma; reference arm dacarbazine, N = 208),[18] CA209025 (RCC; reference arm everolimus; N = 411),[19] CA209017 (SQ NSCLC; reference arm docetaxel; N = 137),[20] and CA209057 (NSQ NSCLC; reference arm docetaxel, N = 290).[21]

Soure (Reproduced from Module 2.5: Clincial Overview)

6.2 Objective Response Rate E-R Analysis

To characterize the relationship between exposure and the probability of achieving an objective response as defined by RECIST criteria, the ORRs for melanoma, RCC, NSCLC ands HCC were compared among tested doses ranging from 1 mg/kg to 10 mg/kg Q2W and 0.3 mg/kg to 10 mg/kg Q3W, in a data set compiled from several clinical trials. The ORRs appear to be comparable among tested doses from 1 mg/kg to 3 mg/kg for patients with melanoma, RCC and HCC. However, it appears in patients with NSCLC the ORR is lower in patients that received 1 mg/kg compared to those that received higher doses. The odds ratio of ORR for 1 mg/kg relative to 3 mg/kg in patient with non-squamous cell NSCLC was estimated to be 0.126 (95% CI: 0.006, 0.976). There were no responses out of 11 patients with squamous cell NSCLC who received 1 mg/kg of nivolumab.

Reviewer Comment: This reviewer concludes that the clinical data in NSCLC patients shows a decrease in the ORR of the 1 mg/kg compared to the 3 mg/kg dose. However this finding must be interpreted in the context of small sample size and heterogeneous patient populations and regimens included in the analysis. Given this, and data that shows that in other tumor types (i.e. RCC and melanoma), doses as low as 0.3 mg/kg

yielded no differences in ORR compared to higher doses, this reviewer concludes that the totality of the clinical data across indications is generally consistent with the modeling data (see below), and the apparent dose-response relationship in NSCLC is considered unreliable with respect to predicting dose-response in the broader NSCLC patient population.

As displayed in Table 3, the ORR exposure response analyses based on modeling shows that the probability of achieving a ORR after nivolumab treatment of 480 mg Q4W is predicted be similar to the 3 mg/kg Q2W regimen across tumor types

Table 3: Efficacy Bridging Summary Across Tumor Types -Mean ORR

Tumor Type	Exposure Measure	Objective Response		
		3 mg/kg Q2W (ORR)[a]	240 mg Q2W (ORR)[a]	480 mg Q4W (ORR)[a]
Melanoma (N = 178)	Cavgd28	0.38	0.38	0.38
	Cmind28	0.38	0.38	0.38
RCC (N = 403)	Cavgd28	0.26	0.26	0.26
	Cmind28	0.26	0.26	0.26
SQ NSCLC (N = 125)	Cavgd28	0.19	0.19	0.19
	Cmind28	0.19	0.19	0.19
NSQ NSCLC (N = 280)	Cavgd28	0.2	0.2	0.2
	Cmind28	0.2	0.2	0.2

Note: Refer to Figure 3.2.2-2 (Cavgd28) and Figure 3.2.2-4 (Cmind28) in Module 2.7.2 SCP for confidence intervals
Analysis Directory: /global/pkms/data/CA/209/dose-optimization/prd/gpa/final/Final-April.2017
Program Source: Analysis Directory/nivo-master/lab-notebook/pivotalstudies /alltumor_hr_comparison_apr2017.Rmd// alltumor_hr_comparison_cmin.Rmd
Source: Analysis Directory/ nivo-master/ lab-notebook /pivotalstudies/alltumor_hr_comparison_apr2017.docx// alltumor_hr_comparison_cmin.docx

[a]Objective response rate in the following phase 3 studies for each tumor type: CA209066 (melanoma), CA209025 (RCC), CA209017 (SQ NSCLC), and CA209057 (NSQ NSCLC).

Soure (Reproduced from Module 2.5: Clincial Overview)

Reviewer Comment: Dose-efficacy profiles for melanoma and NSCLC with Q2W regimens and for RCC with Q3W regimens and exposure-efficacy profiles based on average serum concentration and trough serum concentrations for all approved indications suggest efficacy profile with 480 mg Q4W will not be compromised compared to approved dose 3 mg/kg Q2W.

7 Review of Safety

Safety Summary

The safety of the dosing regimen of nivolumab 480 mg IV Q4W in patients with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), classical Hodgkin's lymphoma (cHL) and hepatocellular carcinoma (HCC) was evaluated by the following methods:

- Safety bridging evaluation
  - Assessment of safety margins, by comparison of predicted exposures with 240 mg Q2W and 480 mg Q4W relative to the well-tolerated 10 mg/kg Q2W regimen
  - Comparison of the safety of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in subjects with melanoma, SQ and NSQ NSCLC, RCC, HCC, SCCHN, cHL, and UC with respect to the following 3 endpoints: Adverse events leading to discontinuation or death (AEDC/D), Grade 3+ adverse events (AE-Grade 3+), and Grade 2+ immune-mediated adverse events (AE-IM Grade 2+)
- Clinical safety data from subjects treated with nivolumab 480 mg Q4W administered over a 30-minute infusion from Trial CA209511 focusing on Grade 3-4 adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation and immune mediate adverse events (IMAEs).

The dose response analyses for safety events were characterized based on event rates of AE-DC/D, AE-Grade 3+ and AE-IM Grade 2+ in 2560 patients with melanoma, SQ NSCLC, NSQ NSCLC, RCC, SCCHN, UC and CHL. No statistically significant differences in the event rate of AE-DC/D, AE-Grade 3+ and AE-IM Grade 2+ were identified in patients who received 1 mg/kg, 2 mg/kg and 10 mg/kg when compared to patients who received the reference dose of 3 mg/kg based on logistic regression analysis. Additionally, no safety liability is expected with 480 mg Q4W as the predicted peak concentration of the 480 mg Q4W dose is well below the median of peak concentrations achieved with 10 mg/kg Q2W, which was found to be tolerable in patients with solid tumors on clinical trials.

Table 4: Adverse Event Summary, Trial CA209511

	Nivolumab 480 mg IV Q4W N=142	
	Any Grade n(%)	**Grade 3-4 n(%)**
Serious adverse events	22 (15.5)	16 (11.3)
Discontinued due to adverse event	5 (3.5)	5 (3.5)
Dose interruption due to adverse event	2 (1.4)	1 (0.7)
All grade adverse events	85 (59.9)	20 (4.1)

	Nivolumab 480 mg IV Q4W N=142	
	Any Grade n(%)	Grade 3-4 n(%)
Immune mediated adverse events*	17 (12.0)	5 (3.3)
Treated with immune modulating agents	6 (4.2)	3 (2.1)
Endocrine immune mediated	11 (9.9)	2 (1.4)

(Source: Reviewer Generated Table from ADEX, ADSL)
*Follow up for 100 days from the last day of therapy

Additional safety evaluation results are as follows:

- Non-fatal serious adverse events
  Non-fatal serious adverse events (SAEs) occurred in 15.5% of patients. The SAEs of pneumonitis and anemia occurred most commonly (2 patients each).

- Adverse events leading to study drug discontinuation
  Adverse events leading to discontinuation of therapy occurred in 5.6% of patients. The adverse events leading to discontinuation of nivolumab were pneumonitis (2 patients), pancreatitis, general physical condition abnormal, and malignant neoplasm progression (1 patient each).

- Grade 3-4 treatment-emergent adverse events
  Grade 3 and 4 adverse events occurred in 14.1% of patients treated with nivolumab.

The most common AEs (≥ 5%) in patients treated with nivolumab 480 mg Q4W were asthenia and nausea (7.7%), headache (6.3%) and cough (5.6%).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant submitted one clinical trial to evaluate the safety of nivolumab 480 mg IV Q4W. This trial included data from 142 subjects treated with nivolumab 480 mg IV over 30 minutes Q4W in part 2 of the on-going study CA2095111. In part 1 of CA209511, patients were previously untreated for unresectable or metastatic melanoma and were treated with 4 doses of nivolumab + ipilimumab (either 3 mg/kg pf nivolumab + 1 mg/kg of ipilimumab or 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab. In Part 2 of the study patients treated with nivolumab 480 mg every four weeks, beginning 6 weeks after the last combination dose.

7.1.2 Categorization of Adverse Events

The Applicant used the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 to map verbatim terms from the CRFs to PT terms to code all adverse events in Study CA209511. The Applicant defined adverse events (AEs) as any adverse event

that occurred after the initiation of nivolumab 480 mg IV Q4W up to 30 days after the last dose of study drug fro all safety events, except immune mediated adverse events (IMAEs). IMAEs included events occurring within 100 days of the last dose.

Reviewer Comment: This reviewer analyzed the 285 verbatim terms that were used in Part 2 of Study CA209511 in the adverse event dataset to determine the appropriateness of the coding of the MedDRA preferred terms. The analysis determined that 164 of the verbatim terms were identical to the MedDRA preferred terms. This reviewer conducted a manual analysis of the remaining 121 and determined that the preferred term adequately represented the verbatim term.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In Study CA209511, patients could continue nivolumab therapy until disease progression, patient death, development of unacceptable toxicity, withdrawal of consent, or Sponsor discontinuation of the study. Table 5 displays the exposure and duration of therapy of patients in part 2 of Study CA209511 receiving nivolumab 480mg IV Q4W. Patients received a median duration of therapy of (30.44 days; range 0 days to 143 weeks). Thirty-two (22.5%) patients received nivolumab 480 mg IV Q4W for ≥ 4 cycles. The median cumulative dose was 960 mg (range 480 mg to 2880 mg).

Table 5: Exposure to Nivolumab 480 mg IV Q4W

Exposure	Nivolumab 480 mg IV Q4W N=142 n (%)
Number of doses n (%)	
1	43 (30.3)
2	37 (26.1)
3	30 (21.1)
4	21 (14.8)
>4	11 (7.7)
Duration of treatment (days)	
Median (min, max)	30.4 (0, 143)
Mean (std dev)	43.5 (38.05)
Cumulative dose per patient (mg)	
Median (min, max)	960 (480, 2880)
Mean (std dev)	1179.7 (635.6)
Dose interruptions/reductions	
Dose interruptions	0
Dose reduction	2 (1.4)

(Source: Reviewer Generated Table from ADEX.xpt)

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7.3 Major Safety Results

7.3.1 Deaths

Overview of the Applicant's methods

Deaths listed include deaths during treatment and occurring up to 100 days of last dose of study drug, as of the database lock date (February 21, 2017).

For Study CA209511, the Applicant performed an analysis of the cause of death for all patients who had died as of the data cut-off of February 21, 2017. The Applicant provided detailed narratives of all patient deaths.

Table 6 summarizes the primary causes of death reported for patients treated in Trial CA209511. In part 2 of Trial CA209511, 4 (2.8%) of patients died prior to the data cutoff.

Table 6: Primary Reason for All Deaths

Primary Cause of Death	Nivolumab 480 mg IV Q4W N=142 n (%)
Patients who Died	4 (2.8)
Disease Progression	3 (2.1)
Unknown	1 (0.7)
30 Days of Last Dose	3 (2.1)
Disease Progression	2 (1.4)
Unknown	1 (0.7)
100 Days of Last Dose	4 (2.8)
Disease Progression	3 (2.1)
Unknown	1 (0.7)

(Source: Reviewer generated table from ADSL.xpt, ADAE.xpt)

Reviewer Comment: This reviewer conducted analyses of the narrative summaries provided for any patient that died during part 2 of Study CA209511. This review agreed that 3 of the 4 patients that died due to progressive disease and that the fourth patient had no adverse events while on Part 2 of the study and died 23 days after the first does of nivolumab 480 mg IV Q4W. There was one patient that died to an AE not associated with disease progression and the review of the details of the deaths in Study CA209511 dies not raise any new safety concerns about nivolumab 480 mg IV Q4W.

7.3.2 Nonfatal Serious Adverse Events

In study CA209511, adverse events were designated serious adverse events (SAEs) if they met one of the following criteria:

- Results in death

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- Is life-threatening (i.e. the patient was at immediate risk of death from the adverse event as it occurred)
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the child of a patient who was exposed to the study treatment
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization, but when based on appropriate medical judgment, may jeopardize the patient or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered serious adverse events.

SAEs, regardless of causality assessment, were collected for 30 days following study drug discontinuation and through the termination visit, whichever was longer. SAEs that were judged by the investigator to be related to study drug treatment were reported to the sponsor, regardless of the length of time that passed since study treatment completion.

Reviewer Comment: This definition of SAE is in accordance with 21 CFR 312.32.

A total of 20 (14.1%) patients in Part 2 of Study CA209511 treated with nivolumab 480 mg IV Q4W experienced a total of 29 non-fatal SAEs. Table 7 summarizes the incidence of SAEs by SOC.

Table 7: Nonfatal SAE by System Organ Class

System Organ Class	Nivolumab 480mg IV Q4W N=142 n (%)
Infections and infestations	4 (2.8)
Gastrointestinal disorders	3 (2.1)
Investigations	3 (2.1)
Respiratory, thoracic and mediastinal disorders	3 (2.1)
Blood and lymphatic system disorders	2 (1.4)
Endocrine disorders	2 (1.4)
General disorders and administration site conditions	2 (1.4)
Neoplasms benign, malignant and unspecified	2 (1.4)
Metabolism and nutrition disorders	1 (0.7)
Musculoskeletal and connective tissue disorders	1 (0.7)
Nervous system disorders	1 (0.7)
Renal and urinary disorders	1 (0.7)
Skin and subcutaneous disorders	1 (0.7)
Surgical and medical procedures	1 (0.7)

(Source: Reviewer generated table from ADAE.xpt)

Table 8 summarizes the incidence of SAEs by preferred term. General physical health deterioration, lung infection, anemia and pneumonitis (1.4%, each) were the most common SAEs reported.

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Table 8: Nonfatal SAE by Preferred Term

System Organ Class Preferred Term	Nivolumab 480 mg IV Q4W N=142	
	All Grades n (%)	Grade 3-4 n (%)
All patients with a nonfatal SAE	22 (15.5)	16 (11.3)
General disorders and administration site conditions		
General physical health deterioration[a]	2 (1.4)	1 (0.7)
Inflammation	1 (0.7)	1 (0.7)
Infections and infestations		
Lung infection[b]	2 (1.4)	2 (1.4)
Influenza	1 (0.7)	0
Wound infection	1 (0.7)	0
Blood and lymphatic system disorders		
Anemia	2 (1.4)	2 (1.4)
Respiratory, thoracic, and mediastinal disorders		
Pneumonitis	2 (1.4)	2 (1.4)
Respiratory tract congestion	1 (0.7)	1 (0.7)
Renal and urinary disorders		
Acute kidney injury	1 (0.7)	1 (0.7)
Endocrine disorders		
Adrenocorticotropic hormone deficiency	1 (0.7)	0
Hypophysitis	1 (0.7)	1 (0.7)
Surgical and medical procedures		
Brain tumor operation	1 (0.7)	1 (0.7)
Gastrointestinal disorders		
Diverticular perforation	1 (0.7)	1 (0.7)
Nausea	1 (0.7)	1 (0.7)
Pancreatitis	1 (0.7)	1 (0.7)
Metabolism and nutritional disorders		
Hyponatremia	1 (0.7)	0
Neoplasms benign, malignant, and unspecified		
Malignant neoplasm progression	1 (0.7)	1 (0.7)
Tumor hemorrhage	1 (0.7)	0
Investigations		
Increased lipase	1 (0.7)	1 (0.7)
Increased transaminases	1 (0.7)	1 (0.7)
Musculoskeletal and connective tissue disorders		
Pain in extremity	1 (0.7)	1 (0.7)
Nervous system disorder		
Seizure	1 (0.7)	1 (0.7)
Skin and subcutaneous tissue disorders		
Urticaria	1 (0.7)	1 (0.7)

(Source: Reviewer Generated table ADAE.xpt)
[a.] includes PT terms general physical health deterioration and general physical condition abnormal
[b.] includes PT terms lung abscess, lung infection

Reviewer Comment: In the initial review of nivolumab in patients with metastatic and unresectable melanoma, 50.4% of patients experinced an SAE compared to only 15.5%

of patients in Trial CA209511. Due the low patient numbers in Trial CA209511 and the low incidence of SAEs, this reviewer concludes that there is no new information about SAEs provided by the analysis of the safety data from Trial CA209511.

7.3.3 Dropouts and/or Discontinuations

The majority of patients remained on treatment at the time of data cut off. Seventeen (12.0%) of patients had discontinued part 2 of therapy at the time of data cut off. As shown in Table 9, the most common reason for discontinuing study therapy in Study CA209511 was progressive disease, which occurred in 7.7% of patients. Five (3.5%) of patients discontinued therapy secondary to an adverse event.

Table 9: Study Discontinuations

	Nivolumab 480mg IV Q4W N=142 n (%)
All patients discontinued	17 (12.0)
Progressive disease	11 (7.7)
Adverse event[a]	5 (3.5)
ithdrawn consent	1 (0.7)

(Source: Reviewer Generated Table from ADSL.xpt)
[a.] Includes Adverse event unrelated to study drug, and study drug toxicity

Table 10 outlines the adverse events leading to discontinuation of therapy in Trial CA209511. There was not a large proportion of patients that discontinued therapy secondary to a AE. The most common AE leading to nivolumab discontinuation was pneumonitis (1.4%).

Table 10: Adverse Events Leading to Discontinuation of Therapy

System Organ Class Preferred Term	**Nivolumab 480 mg IV Q4W**	
	Any Grade N=142 n (%)	**Grade 3-4 N=142 n (%)**
All patients with event	5 (3.5)	5 (3.5)
Respiratory, thoracic and mediastinal disorders		
Pneumonitis	2 (1.4)	2 (1.4)
Gastrointestinal disorders		
Pancreatitis	1 (0.7)	1 (0.7)
General disorders and administration site conditions		
General physical condition abnormal	1 (0.7)	1 (0.7)
Neoplasms benign, malignant, and unspecified		
Malignant neoplasm progression	1 (0.7)	1 (0.7)

(Source: Reviewer generated table from ADSL.xpt, ADAE.xpt)

Reviewer Comment: In the original evaluation of of nivolumab in patients with metastatic and unresectable melanoma 9.3% of patients had an AE leading to treatment

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discontinuation with the majoirty of these being due to progresive disease. In Trial CA209511 3.5% of patients had an AE leading to discontinuation and none of AEs occurred in more that 2 patients. Two patients did discontinue due to pneumonitis which is a well described AE associated with nivolumab and is consistent with data obtained in other clinical trials.

Two patients (1.4%) had AEs leading to an interruption in therapy that did no result in study discontinuation. Table 11 shows the AEs that led to dose interruptions. One patient had anemia while the second had adrenal insufficiency

Table 11: Adverse Events Leading to Dose Interruption

System Organ Class Preferred Term	Nivolumab 480mg IV Q4W	
	Any Grade N=142 n (%)	Grade 3-4 N=142 n (%)
All patients with event	2 (1.4)	1 (0.7)
Blood and lymphatic system disorders		
Anemia	1 (0.7)	1 (0.7)
Endocrine disorders		
Adrenal insufficiency	1 (0.7)	0

(Source: Reviewer generated table ADAE.xpt)

Table 12 shows the adverse events that lead to dose delays without leading to study termination. Fifteen patients (10.6%) experienced an AE that lead to dose delay. The most common dose delays experienced by patients in Study CA209511 were abdominal pain, increased lipase, increased amylase, and renal failure (1.4%, each).

Table 12: Adverse Events Leading to Dose Delays

System Organ Class Preferred Term	Nivolumab 480mg IV Q4W	
	Any Grade N=142 n (%)	Grade 3-4 N=142 n (%)
All patients with event	15 (10.6)	8 (5.6)
Gastrointestinal disorders		
Abdominal pain	2 (1.4)	0
Diarrhea	1 (0.7)	0
Nausea	1 (0.7)	0
Investigations		
Increased lipase	2 (1.4)	2 (1.4)
Increased amylase	2 (1.4)	1 (0.7)
Increased creatinine	1 (0.7)	0
Renal and urinary disorders		
Acute kidney injury	2 (1.4)	2 (1.4)
General disorders and administration site conditions		
Chest pain	1 (0.7)	0
Inflammation	1 (0.7)	1 (0.7)
Pyrexia	1 (0.7)	0

System Organ Class Preferred Term	Nivolumab 480mg IV Q4W	
	Any Grade N=142 n (%)	Grade 3-4 N=142 n (%)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (0.7)	0
Exertional dyspnea	1 (0.7)	0
Infections and infestations		
Ear infection	1 (0.7)	0
Lung infection	1 (0.7)	1 (0.7)
Wound infection	1 (0.7)	0
Endocrine disorders		
Hypothyroidism	1 (0.7)	0
Hypophysitis	1 (0.7)	0
Metabolism and nutrition disorders		
Malnutrition	1 (0.7)	1 (0.7)
Musculoskeletal and connective tissue disorders		
Pain in extremity	1 (0.7)	1 (0.7)
Blood and lymphatic system disorders		
Thrombocytopenia	1 (0.7)	0
Eye disorders		
Transient visual acuity decrease	1 (0.7)	0

(Source: Reviewer Generated Table ADAE.xpt)
[a.] Includes PT terms acute kidney injury and renal failure

Dose reductions were not allowed in Trial CA209511

7.3.4 Immune Mediated Adverse Events

According to the protocol for Trial CA209511 immune mediated adverse events (IMAEs) are defined as AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out occurring within 100 days of the last dose of nivolumab. Table displays the IMAEs from Trial CA209511. The majority of IMAEs were Grade 1 or 2. The most common IMAEs were hypothyroidism/thyroiditis (4.2%) and diarrhea/colitis (2.1%). The majority of IMAEs were manager with immune modulating medication or hormonal replacement therapy.

Table 13: Immune Mediated Adverse Events within 100 days of Last Dose, Trial CA209511

System Organ Class Preferred Term	Nivolumab 480mg IV Q4W	
	Any Grade N=142 n (%)	Grade 3-4 N=142 n (%)
All patients with event	18 (12.7)	6 (4.2)
Treated with Immune Modulating Agents		

System Organ Class Preferred Term	Nivolumab 480mg IV Q4W	
	Any Grade N=142 n (%)	Grade 3-4 N=142 n (%)
Diarrhea/Colitis	3 (2.1)	1 (0.7)
Pneumonitis	2 (1.4)	2 (1.4)
Hepatitis	1 (0.7)	1 (0.7)
Rash	1 (0.7)	0
Endocrine Immune Mediated Adverse Events		
Hypothyrodism/Thyroiditis	6 (4.2)	0
Adrenal insufficiency	2 (1.4)	1 (0.7)
Hypophysitis	2 (1.4)	1 (0.7)
Hyperthyroidism	1 (0.7)	0

(Source: Reviewer Generated Table from ADAE.xpt, ADCM.xpt)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

This review analyzed common AEs in Trial CA209511 based upon the system organ class, the preferred term, the high-level term, and high level group term of the MedDRA hierarchy. Table 14 shows all adverse events by System Organ Class.

Table 14: Adverse events occurring in Part 2 by MedDRA System Organ Class

System Organ Class	Nivolumab 480 mg Q3W N=142 n (%)		
	All Grades n (%)	Grade 3-4 n (%)	Grade 5 n (%)
General disorders and administration site conditions	22 (15.5)	2 (1.4)	1 (0.7)
Gastrointestinal disorders	17 (12.0)	1 (0.7)	0
Skin and subcutaneous tissue disorders	17 (12.0)	2 (1.4)	0
Musculoskeletal and connective tissue disorders	16 (11.3)	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders	15 (10.6)	4 (2.8)	0
Nervous system disorders	14 (9.9)	1 (0.7)	0
Investigations	11 (7.7)	2 (1.4)	0
Endocrine disorders	6 (4.2)	0	0
Infections and infestations	6 (4.2)	0	0
Eye Disorders	5 (3.5)	3 (2.1)	0
Psychiatric Disorders	5 (3.5)	2 (1.4)	0
Blood and lymphatic system disorders	4 (2.8)	0	0
Metabolism and nutrition disorders	4 (2.8)	2 (1.4)	0
Injury, poisoning and procedural complications	3 (2.1)	1 (0.7)	0
Renal and urinary disorders	3 (2.1)	1 (0.7)	0
Neoplasms benign, malignant and unsuspected	1 (0.7)	0	0
Vascular Disorders	1 (0.7)	1 (0.7)	0

(Source: ADAE.xpt)

Reference ID: 4229532

Table 15 lists the most common adverse events (≥2 patients) that occurred in Part 2 of the study by MedDRA preferred terms and grouped by MedDRA system organ class. The most common AEs by preferred term (≥5% of patients) were asthenia and nausea (7.7% each), headache (6.3%), cough (5.6%), and hypothyroidism (5.0%).

Table 15: Most Common Adverse Events (≥2 patients) occurring in Part by MedDRA Preferred Term

System Organ Class Preferred Term	Nivolumab 480 mg Q4W N=142		
	All Grades n (%)	Grade 3-4 n (%)	Grade 5 n (%)
All patients with adverse event	85 (59.9)	20 (14.1)	2 (1.4)
General Disorders and Administration Site Conditions			
Asthenia	11 (7.7)	1 (0.7)	0
Peripheral Edema	4 (2.8)	0	0
Pain	2 (1.4)	0	0
Gastrointestinal Disorders			
Nausea	11 (7.7)	1 (0.7)	0
Diarrhea	5 (3.5)	0	0
Abdominal pain[a]	4 (2.8)	0	0
Vomiting	4 (2.8)	0	0
Constipation	3 (2.1)	0	0
Nervous System Disorders			
Headache	9 (6.3)	0	0
Dizziness	3 (2.1)	0	0
Amnesia[b]	2 (1.4)	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	8 (5.6)	0	0
Dyspnea[c]	4 (2.8)	0	0
Pneumonitis	2 (1.4)	2 (1.4)	0
Rhinorrhea	2 (1.4)	0	0
Investigations			
Decreased weight	5 (3.5)	1 (0.7)	0
Increased AST	3 (2.1)	0	0
Increased creatinine	3 (2.1)	0	0
Increased lipase	3 (2.1)	2 (1.4)	0
Increased ALT	2 (1.4)	0	0
Increased amylase	2 (1.4)	1 (0.7)	0
Endocrine disorders			
Hypothyrodism	7 (4.9)	0	0
Hypophysitis	4 (2.8)	1 (0.7)	0
Adrenal insufficiency	2 (1.4)	0	0
Hypopituitarism	2 (1.4)	0	0
Skin and Subcutaneous disorders			
Rash[d]	8 (5.6)	1 (0.7)	0
Pruritus	6 (4.2)	0	0
Vitiligo	3 (2.1)	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia/myalgia	6 (4.2)	0	0

System Organ Class Preferred Term	Nivolumab 480 mg Q4W N=142		
	All Grades n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Back pain	4 (2.8)	0	0
Musculoskeletal pain	2 (1.4)	0	0
Muscular weakness	2 (1.4)	0	0
Pain in extremity	2 (1.4)	1 (0.7)	0
Infections and infestations			
Upper respiratory tract infection[e]	5 (3.2)	0	0
Psychiatric disorders			
Insomnia	3 (2.1)	0	0
Anxiety	2 (1.4)	0	0
Blood and lymphatic system disorders			
Anemia	4 (2.8)	3 (2.1)	0
Metabolism and nutrition disorders			
Decreased appetite	4 (2.8)	1 (0.7)	0
Malnutrition	2 (1.4)	2 (1.4)	0
Vascular disorders			
Hypertension	2 (1.4)	1 (0.7)	0

(Source: ADAE.xpt)
[a.] includes PT terms abdominal pain upper, abdominal pain
[b.] includes PT terms amnesia, memory impairment
[c.] includes PT terms dyspnea, exertional dyspnea
[d.] inlcudes PT terms maculopapular rash, pruitic rash, follicular rash, rash, macular rash, papular rash
[e.] includes PT terms nasopharyngitis, rhinitis, upper respiratory tract infection

This review of safety evaluated additional potential toxicities of study drug therapy through analyses of the incidence of AEs based on hierarchical composites of MedDRA preferred terms (i.e., high level terms) and a hierarchical composite of MedDRA high-level terms (i.e., high-level group terms) in each treatment group. Table 16 summarizes the incidence of AEs by high level group terms occurring in ≥ 2 patients. The most common AEs by high level group term (occurring in ≥5% of patients) are general system disorders NEC (17.6%), epidermal and dermal conditions (12.7%), gastrointestinal signs and symptoms (11.3%), respiratory disorders NEC (9.9%), infections-pathogen unspecified (7.7%), headaches (6.3%), gastrointestinal and motility and defecation conditions, musculoskeletal and connective tissue disorders NEC, and thyroid gland disorders (5.6% each).

Table 16: Adverse Events (≥ 2 patients) in Part 2 by MedDRA High Level Term

High Level Group Term	Nivolumab 480 mg Q4W N=142		
	All Grades n (%)	Grade 3-4 n (%)	Grade 5 n (%)
General System Disorders NEC	25 (17.6)	2 (1.4)	1 (0.7)
Epidermal and dermal conditions	18 (12.7)	1 (0.7)	0
Gastrointestinal signs and symptoms	16 (11.3)	1 (0.7)	0
Respiratory disorders NEC	14 (9.9)	0	0
Infections – pathogen unspecified	11 (7.7)	2 (1.4)	0
Headaches	9 (6.3)	0	0
Gastrointestinal motility and defecation conditions	8 (5.6)	0	0

Musculoskeletal and connective tissue disorders NEC	8 (5.6)	1 (0.7)	0
Thyroid gland disorders	8 (5.6)	0	0
Hypothalamus and pituitary gland disorders	7 (4.9)	1 (0.7)	0
Neurological disorders NEC	7 (4.9)	0	0
Hepatobiliary investigations	6 (4.2)	1 (0.7)	0
Muscle disorders	6 (4.2)	0	0
Appetite and general nutritional disorders	5 (3.5)	2 (1.4)	0
Physical examination and organ system status topics	5 (3.5)	1 (0.7)	0
Anemias - nonhemolytic and marrow depression	4 (2.8)	3 (2.1)	0
Joint disorders	4 (2.8)	0	0
Vision disorders	4 (2.8)	0	0
Gastrointestinal investigations	3 (2.1)	2 (1.4)	0
Oral soft tissue conditions	3 (2.1)	0	0
Pigmentation disorders	3 (2.1)	0	0
Renal and urinary tract investigations and urinalysis	3 (2.1)	0	0
Sleep disorders and disturbances	3 (2.1)	0	0
Adrenal gland disorders	2 (1.4)	0	0
Anxiety disorders and symptoms	2 (1.4)	0	0
Electrolyte and fluid balance conditions	2 (1.4)	0	0
Fungal infectious disorders	2 (1.4)	0	0
Injuries NEC	2 (1.4)	0	0
Lower respiratory tract disorders (excl obstruction and infection)	2 (1.4)	2 (1.4)	0
Mental impairment disorders	2 (1.4)	0	0
Renal disorders (excl nephropathies)	2 (1.4)	2 (1.4)	0
Urinary tract signs and symptoms	2 (1.4)	0	0
Vascular hypertensive disorders	2 (1.4)	1 (0.7)	0

(Source: ADAE.xpt)

Table 17 summarizes the incidence of AEs by high level term occurring in ≥2 patients treated with nivolumab 480 mg IV Q4W. The common AEs by high level term occurring in ≥5 % of patients are nausea and vomiting symptoms (9.9%), asthenic conditions (9.2%), headaches NEC (6.3%), and coughing and associated symptoms, musculoskeletal and connective tissue pain and discomfort, and pruritus NEC (5.6% each).

Table 17: Treatment Emergent Adverse Events (≥ 10%) by High Level Group Term, Study 309

High Level Group Term	Nivolumab 480 mg Q4W N=142		
	All Grades n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Nausea and vomiting symptoms	14 (9.9)	1 (0.7)	0
Asthenic conditions	13 (9.2)	1 (0.7)	0
Headaches NEC	9 (6.3)	0	0
Coughing and associated symptoms	8 (5.6)	0	0
Musculoskeletal and connective tissue pain and discomfort	8 (5.6)	1 (0.7)	0
Pruritus NEC	8 (5.6)	0	0
Thyroid hypofunction disorders	7 (4.9)	0	0
Liver function analyses	6 (4.2)	1 (0.7)	0
Diarrhea (excl infective)	5 (3.5)	0	0

High Level Group Term	Nivolumab 480 mg Q4W N=142		
	All Grades n (%)	Grade 3-4 n (%)	Grade 5 n (%)
General signs and symptoms NEC	5 (3.5)	0	1 (0.7)
Pain and discomfort NEC	5 (3.5)	0	0
Physical examination procedures and organ system status	5 (3.5)	1 (0.7)	0
Rashes, eruptions and exanthemas NEC	5 (3.5)	1 (0.7)	0
Upper respiratory tract infections	5 (3.5)	0	0
Anemias NEC	4 (2.8)	3 (2.1)	0
Appetite disorders	4 (2.8)	1 (0.7)	0
Breathing abnormalities	4 (2.8)	0	0
Gastrointestinal and abdominal pains (excl oral and throat)	4 (2.8)	0	0
Hypothalamic and pituitary disorders NEC	4 (2.8)	1 (0.7)	0
Edema NEC	4 (2.8)	0	0
Anterior Pituitary hypofunction	3 (2.1)	0	0
Digestive enzymes	3 (2.1)	2 (1.4)	0
Disturbances in initiating and maintaining sleep	3 (2.1)	0	0
Gastrointestinal atonic and hypomotility disorders NEC	3 (2.1)	0	0
Hypopigmentation disorders	3 (2.1)	0	0
Joint related signs and symptoms	3 (2.1)	0	0
Muscle pains	3 (2.1)	0	0
Neurological signs and symptoms NEC	3 (2.1)	0	0
Paresthesia and dysesthesias	3 (2.1)	0	0
Renal function analyses	3 (2.1)	0	0
Upper respiratory tact signs and symptoms	3 (2.1)	0	0
Adrenal cortical hypofunction	2 (1.4)	0	0
Anxiety symptoms	2 (1.4)	0	0
Ear infections	2 (1.4)	0	0
General nutritional disorders NEC	2 (1.4)	2 (1.4)	0
Infections NEC	2 (1.4)	0	0
Lower respiratory tract and lung infections	2 (1.4)	2 (1.4)	0
Lower respiratory tract and inflammatory conditions	2 (1.4)	2 (1.4)	0
Memory loos (excl dementia)	2 (1.4)	0	0
Muscle weakness conditions	2 (1.4)	0	0
Renal failure and impairment	2 (1.4)	2 (1.4)	0
Stomatitis and ulceration	2 (1.4)	0	0
Tinea infections	2 (1.4)	0	0
Vascular and hypertensive disorders NEC	2 (1.4)	1 (0.7)	0
Visual disorders NEC	2 (1.4)	0	0

(Source: ADAE.xpt)

7.5 Other Safety Exploration

None

7.6 Additional Safety Evaluations

None

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7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Analysis of postmarketing data suggests that the overall safety profile of nivolumab is consistent with the current labeling information.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Sections 2.1-2.9 were updated to include new 480 mg Q4W dosage regimen. Section 2.2, 2.8 and 2.9 updated to reduce infusion time to 30 minutes. Labeling negotiations are ongoing at the time of completion of this review. Refer to the package insert of Opdivo®.

9.3 Advisory Committee Meeting or Outside Consultants

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this supplemental application.

9.4 Clinical Investigator Financial Disclosure

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
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): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Reference ID: 4229532

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/s/

CHRISTY L OSGOOD
03/05/2018

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03/05/2018