CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125554Orig1s034

Trade Name:	OPDIVO
Generic or Proper Name:	nivolumab
Sponsor:	Bristol-Myers Squibb Company
Approval Date:	July 31, 2017
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. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials (1.1) • patients with unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)

- 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. (1.2)
- patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.3)
- 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.

  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.4)
- patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy (1.5)
- 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. (1.6)

- 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.
  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. (1.7)

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554/S-034

ACCELERATED APPROVAL

Bristol-Myers Squibb Company
Attention: Linda Gambone, Ph.D.
Director, Global Regulatory, Safety & Biometrics
Route 206 & Province Line Road
Princeton, NJ 08543

Dear Dr. Gambone:

Please refer to your Supplemental Biologics License Application (sBLA), dated February 2, 2017, received February 2, 2017, and your amendments, submitted under section 351 of the Public Health Service Act for OPDIVO (nivolumab) injection, 40 mg/4 mL and 100 mg/10 mL.

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

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the prescribing information and Medication Guide)

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

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated July 26, 2017. This requirement, along with required completion dates, is listed below.

This postmarketing clinical trial is subject to the reporting requirements of 21 CFR 601.70

3243-1 Submit the final report, including datasets, from trials conducted to verify and describe the clinical benefit of nivolumab 240 mg intravenously every two weeks in patients with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer who have progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan, including at least 150 patients enrolled in BMS-initiated trials. In order to characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

Final Report Submission: 09/21

Submit clinical protocols to your IND 126406 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

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

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

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3243-2 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry based in vitro diagnostic device that is essential to the safe and effective use of nivolumab for patients with tumors that are mismatch repair deficient.

The timetable you submitted on July 26, 2017, states that you will support the submission of a Premarket Approval (PMA) Application to FDA/CDRH according to the following schedule:

Final Report Submission: 09/21

3243-3 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of nivolumab for patients with tumors that are microsatellite instability high.

The timetable you submitted on July 26, 2017, states that you will support the submission of a Premarket Approval (PMA) Application to FDA/CDRH according to the following schedule:

Final Report Submission: 09/21

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

"**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved prescribing information (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

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

Alternatively, you may submit promotional materials for accelerated approval products 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).

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
07/31/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

Indications and Usage (1)	7/2017
Dosage and Administration (2)	7/2017
Warnings and Precautions (5)	10/2016

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

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

- patients with BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent. (1.1)
- patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- patients with unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.1)
- 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. (1.2)
- patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. (1.3)
- 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.

  This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.4)
- patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy. (1.5)
- 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. (1.6)
- 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.

  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. (1.7)

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

Administer as an intravenous infusion over 60 minutes.

- Unresectable or metastatic melanoma
  - OPDIVO 240 mg every 2 weeks. (2.1)
  - OPDIVO with ipilimumab: OPDIVO 1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then OPDIVO 240 mg every 2 weeks. (2.1)
- Metastatic non-small cell lung cancer
  - OPDIVO 240 mg every 2 weeks. (2.2)
- Advanced renal cell carcinoma
  - OPDIVO 240 mg every 2 weeks. (2.3)
- Classical Hodgkin lymphoma
  - OPDIVO 3 mg/kg every 2 weeks. (2.4)
- Recurrent or metastatic squamous cell carcinoma of the head and neck
  - OPDIVO 3 mg/kg every 2 weeks. (2.5)
- Locally advanced or metastatic urothelial carcinoma
  - OPDIVO 240 mg every 2 weeks (2.6)
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
  - OPDIVO 240 mg every 2 weeks. (2.7)

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

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

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

None. (4)

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

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis: Withhold OPDIVO when given as a single agent for moderate or severe and permanently discontinue for life-threatening colitis. Withhold OPDIVO when given with ipilimumab for moderate and permanently discontinue for severe or life-threatening colitis. (5.2)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.3)
- Immune-mediated endocrinopathies: Withhold for moderate or severe and permanently discontinue for life-threatening hypophysitis. Withhold for moderate and permanently discontinue for severe or life-threatening adrenal insufficiency. Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. Monitor for hyperglycemia. Withhold for severe and permanently discontinue for life-threatening hyperglycemia. (5.4)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate or severe and permanently discontinue for life-threatening serum creatinine elevation. (5.5)
- Immune-mediated skin adverse reactions: Withhold for severe and permanently discontinue for life-threatening rash. (5.6)
- Immune-mediated encephalitis: Monitor for changes in neurologic function. Withhold for new-onset moderate to severe neurological signs or symptoms and permanently discontinue for immune-mediated encephalitis. (5.7)
- Infusion reactions: Discontinue OPDIVO for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. (5.9)
- Complications of allogeneic HSCT after OPDIVO: Monitor for hyperacute graft-versus-host-disease (GVHD), grade 3-4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions. Transplant-related mortality has occurred. (5.10)
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.11, 8.1, 8.3)

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

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

- OPDIVO as a single agent: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia. (6.1)
- OPDIVO with ipilimumab: fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea. (6.1)

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

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

Lactation: Discontinue breastfeeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Unresectable or Metastatic Melanoma

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

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

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

1.2 Metastatic Non-Small Cell Lung Cancer

OPDIVO is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO *[see Clinical Studies (14.2)]*.

1.3 Renal Cell Carcinoma

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

1.4 Classical Hodgkin Lymphoma

OPDIVO is indicated for the treatment of 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 (14.4)]*.

1.5 Squamous Cell Carcinoma of the Head and Neck

OPDIVO is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy *[see Clinical Studies (14.5)]*.

1.6 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 (14.6)]*.

1.7 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 (14.7)]*.

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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Melanoma

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

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

2.2 Recommended Dosage for NSCLC

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

2.3 Recommended Dosage for RCC

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

2.4 Recommended Dosage for cHL

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

2.5 Recommended Dosage for SCCHN

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

2.6 Recommended Dosage for Urothelial Carcinoma

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

2.7 Recommended Dosage for CRC

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

2.8 Dose Modifications

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

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

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

Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose[a]
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue

Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose[a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

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

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

2.9 Preparation and Administration

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

Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.

Storage of Infusion

The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

- at room temperature for no more than 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.

Administration

Administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

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

Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.8)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

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

5.2 Immune-Mediated Colitis

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

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

Withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon re-initiation of OPDIVO *[see Dosage and Administration (2.8)]*.

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 (2.8)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases. The median time to onset of immune-mediated colitis was 1.6 months (range: 3 days to 15.2 months). Immune-mediated colitis led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 16% and 7% of patients, respectively. Approximately 96% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 1.1 month (range: 1 day to 12 months). Approximately 23% of patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 75% of patients. Approximately 28% of patients had recurrence of colitis after re-initiation of OPDIVO with ipilimumab.

5.3 Immune-Mediated Hepatitis

OPDIVO can cause immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.8)]*.

OPDIVO as a Single Agent

In patients receiving OPDIVO as a single agent, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients; the median time to onset was 3.3 months (range: 6 days to 9 months). Immune-mediated hepatitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 1% of patients. All patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 23 days (range: 1 day to 2 months). Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 29% of patients had recurrence of hepatitis after re-initiation of OPDIVO.

OPDIVO with Ipilimumab

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

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

OPDIVO can cause immune-mediated hypophysitis. Monitor patients for signs and symptoms of hypophysitis. Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3). Permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.8)]*.

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 (2.8)]*.

In patients receiving OPDIVO as a single agent, adrenal insufficiency occurred in 1% (20/1994) of patients and the median time to onset was 4.3 months (range: 15 days to 21 months). Adrenal insufficiency led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.5% of patients. Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy and 25% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 11 days (range: 1 day to 1 month).

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

Hypothyroidism and Hyperthyroidism

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

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

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

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

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

Type 1 Diabetes Mellitus

OPDIVO can cause Type 1 diabetes mellitus. Monitor for hyperglycemia. Withhold OPDIVO in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia *[see Dosage and Administration (2.8)]*.

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

In patients receiving OPDIVO with ipilimumab, diabetes occurred in 1.5% (6/407) of patients; the median time to onset was 2.5 months (range: 1.3 to 4.4 months). OPDIVO with ipilimumab was withheld in a patient and permanently discontinued in a second patient who developed diabetes.

5.5 Immune-Mediated Nephritis and Renal Dysfunction

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

Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3) increased serum creatinine. Permanently discontinue OPDIVO for life-threatening (Grade 4) increased serum creatinine *[see Dosage and Administration (2.8) and Adverse Reactions (6.1)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

In patients receiving OPDIVO with ipilimumab, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients; the median time to onset was 2.7 months (range: 9 days to 7.9 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation or withholding of OPDIVO with ipilimumab in 0.7% and 0.5% of patients, respectively. Approximately 67% of patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 13.5 days (range: 1 day to 1.1 months). Complete resolution occurred in all patients. Two patients resumed OPDIVO with ipilimumab without recurrence of nephritis or renal dysfunction.

5.6 Immune-Mediated Skin Adverse Reactions

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue OPDIVO *[see Dosage and Administration (2.8)]*.

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

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

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

5.7 Immune-Mediated Encephalitis

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

Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis *[see Dosage and Administration (2.8)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

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

5.8 Other Immune-Mediated Adverse Reactions

OPDIVO can cause other clinically significant immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.8)]*.

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

5.9 Infusion Reactions

OPDIVO can cause severe infusion reactions, which have been reported in less than 1.0% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions *[see Dosage and Administration (2.8)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

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

5.10 Complications of Allogeneic HSCT after OPDIVO

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from 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, without an identified infectious cause, was reported in six patients (35%) within the first 6 weeks post-transplantation, with five patients responding to steroids. Two cases of encephalitis were reported: one case of Grade 3 lymphocytic encephalitis without an identified infectious cause, which occurred and resolved on steroids, and one case of Grade 3 suspected viral encephalitis which was resolved with antiviral treatment. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure.

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

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

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

5.11 Embryo-Fetal Toxicity

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Colitis *[see Warnings and Precautions (5.2)]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions (5.3)]*
- Immune-Mediated Endocrinopathies *[see Warnings and Precautions (5.4)]*
- Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions (5.5)]*
- Immune-Mediated Skin Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Immune-Mediated Encephalitis *[see Warnings and Precautions (5.7)]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.8)]*
- Infusion Reactions *[see Warnings and Precautions (5.9)]*
- Complications of Allogeneic HSCT after OPDIVO *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

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

The data in the Warnings and Precautions section reflect exposure to OPDIVO, as a single agent, for clinically significant adverse reactions in 1994 patients enrolled in 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 (5.1, 5.8)]*. 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 (5.1, 5.8)]*.

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-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, and CHECKMATE-275, which is a single-arm trial in patients with urothelial carcinoma.

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 OPDIVO 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m^2 every 3 weeks *[see Clinical Studies (14.1)]*. The median duration of exposure was 5.3 months (range: 1 day to 13.8+ months) in OPDIVO-treated patients and was 2 months (range: 1 day to 9.6+ months) in chemotherapy-treated patients. In this ongoing trial, 24% of patients received OPDIVO for greater than 6 months and 3% of patients received OPDIVO for greater than 1 year.

In 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 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.

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 OPDIVO 3 mg/kg every 2 weeks (n=206) or dacarbazine 1000 mg/m^2 every 3 weeks (n=205) *[see Clinical Studies (14.1)]*. The median duration of exposure was 6.5 months (range: 1 day to 16.6 months) in OPDIVO-treated patients. In this trial, 47% of patients received OPDIVO for greater than 6 months and 12% of patients received OPDIVO for greater than 1 year.

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

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

Adverse reactions led to permanent discontinuation of OPDIVO in 7% of patients and dose interruption in 26% of patients; no single type of adverse reaction accounted for the majority of OPDIVO discontinuations. Serious adverse reactions occurred in 36% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 41% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in at least 2% of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%).

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

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

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 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.

[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).

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 (14.2)]*. Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks or docetaxel administered intravenously at 75 mg/m^2 every 3 weeks. The median duration of therapy in OPDIVO-treated patients in 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%).

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

Table 8: Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (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%).

Table 9: Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of OPDIVO-Treated Patients for all NCI CTCAE Grades and at a Higher Incidence than Docetaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (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 OPDIVO 3 mg/kg every 2 weeks (n=406) or everolimus 10 mg daily (n=397) *[see Clinical Studies (14.3)]*. The median duration of treatment was 5.5 months (range: 1 day to 29.6+ months) in OPDIVO-treated patients and 3.7 months (range: 6 days to 25.7+ months) in everolimus-treated patients.

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

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

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

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

	OPDIVO (n=406)		Everolimus (n=397)	
	Percentage (%) of Patients			
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
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

Investigations: weight decreased

Skin Disorders: Palmar-plantar erythrodysesthesia

The most common laboratory abnormalities which have worsened compared to baseline in ≥30% of patients include increased creatinine, lymphopenia, anemia, increased AST, increased alkaline phosphatase, hyponatremia, elevated triglycerides, and hyperkalemia. Table 11 summarizes the laboratory abnormalities that occurred in greater than 15% of OPDIVO-treated patients.

Table 11: Grade 1-4 Laboratory Values Worsening from Baseline Occurring in >15% of Patients on OPDIVO (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 OPDIVO 3 mg/kg 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 (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 12 summarizes the adverse reactions, excluding laboratory terms that occurred in at least 10% of patients in the safety population.

Table 12: Non-Laboratory Adverse Reactions Occurring in ≥10% of Patients with cHL (CHECKMATE-205 and CHECKMATE-039)

	OPDIVO cHL Safety Population (n=266)	
	Percentage (%)	
Adverse Reaction[a]	**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

	OPDIVO cHL Safety Population (n=266)	
	Percentage (%)	
Adverse Reaction[a]	**All Grades**	**Grades 3-4**
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.

[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 13 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.

Table 13: 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 (14.5)]*. Patients received 3 mg/kg of OPDIVO (n=236) administered intravenously (IV) over 60 minutes every 2 weeks or investigator's choice of either:

- cetuximab (n=13), 400 mg/m^2 loading dose IV followed by 250 mg/m^2 weekly
- or methotrexate (n=46) 40 to 60 mg/m^2 IV weekly, or
- docetaxel (n=52) 30 to 40 mg/m^2 IV weekly.

The median duration of exposure to nivolumab was 1.9 months (range: 1 day to 16.1+ months) in OPDIVO-treated patients. In this trial, 18% of patients received OPDIVO for greater than 6 months and 2.5% of patients received OPDIVO for greater than 1 year.

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.

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

Table 14: 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

	OPDIVO Urothelial Carcinoma	
	Percentage (%) of Patients	
	All Grades	Grades 3-4
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
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 15: 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.

6.2 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.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *[see Data]*. Human IgG4 is known to cross the placental barrier and nivolumab is an immunoglobulin G4 (IgG4); therefore, nivolumab has the potential to be transmitted from the mother to the developing fetus. The effects of OPDIVO are likely to be greater during the second and third trimesters of pregnancy. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

The safety and effectiveness of OPDIVO have 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 *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3), and Clinical Studies (14)]*. 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 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.

CHECKMATE-037, CHECKMATE-205, CHECKMATE-039, CHECKMATE-141, and CHECKMATE-142 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 hepatic impairment. OPDIVO has not been studied in patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no information on overdosage with OPDIVO.

11 DESCRIPTION

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

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous infusion is supplied in single-dose vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

OPDIVO as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life ($t_{1/2}$) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

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

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

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

The ORR was 32% (95% confidence interval [CI]: 23, 41), consisting of 4 complete responses and 34 partial responses in OPDIVO-treated patients. Of 38 patients with responses, 33 patients (87%) had ongoing responses with durations ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of 6 months or longer.

There were objective responses in patients with and without BRAF V600 mutation-positive melanoma.

Previously Untreated Metastatic Melanoma

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 OPDIVO 3 mg/kg by intravenous infusion every 2 weeks or dacarbazine 1000 mg/m^2 by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by PD-L1 status (greater than or equal to 5% of tumor cell membrane staining by immunohistochemistry vs. less than 5% or indeterminate result) and M stage (M0/M1a/M1b versus M1c). Key eligibility criteria included histologically confirmed, unresectable or metastatic, cutaneous, mucosal, or acral melanoma; no prior therapy for metastatic disease; completion of prior adjuvant or neoadjuvant therapy at least 6 weeks prior to randomization; ECOG performance status 0 or 1; absence of autoimmune disease; and absence of active brain or leptomeningeal metastases. The trial excluded patients with ocular melanoma. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year and then every 12 weeks thereafter.

The major efficacy outcome measure was overall survival (OS). Additional outcome measures included investigator-assessed progression-free survival (PFS) and objective response rate (ORR) per RECIST v1.1.

A total of 418 patients were randomized to OPDIVO (n=210) or dacarbazine (n=208). The median age was 65 years (range: 18 to 87), 59% were men, and 99.5% were white. Disease characteristics were M1c stage disease (61%), cutaneous melanoma (74%), mucosal melanoma (11%), elevated LDH level (37%), PD-L1 greater than or equal to 5% tumor cell membrane expression (35%), and history of brain metastasis (4%). More patients in the OPDIVO arm had an ECOG performance status of 0 (71% vs. 58%).

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 16 and Figure 1 summarize the efficacy results.

Table 16: Efficacy Results - CHECKMATE-066

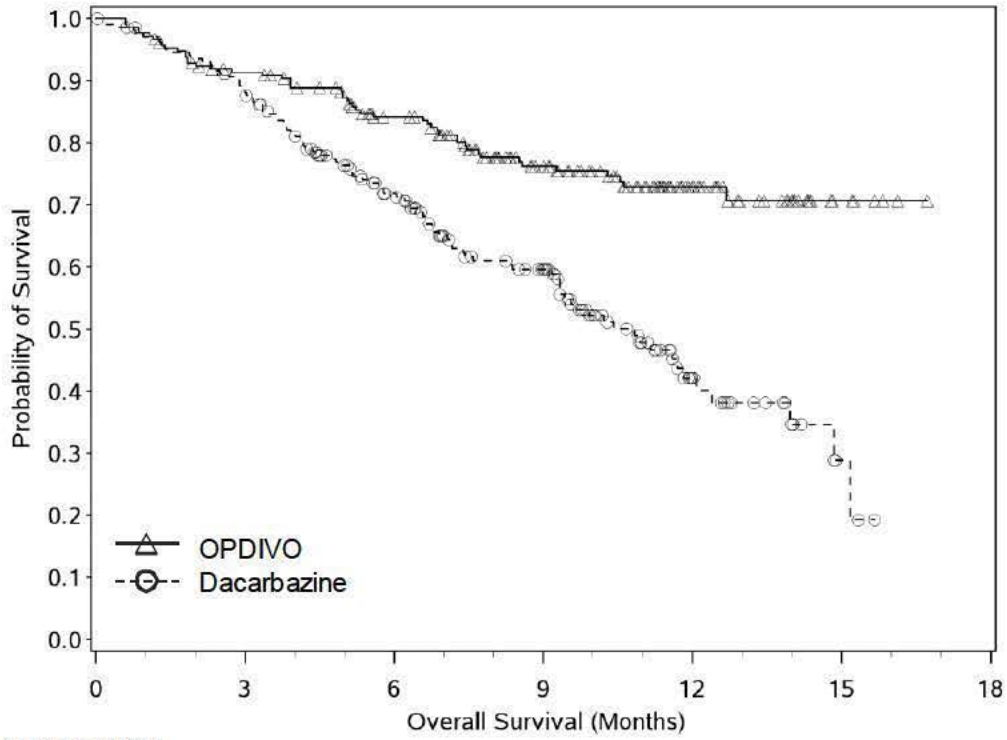
	OPDIVO (n=210)	**Dacarbazine (n=208)**
Overall Survival		
Deaths (%)	50 (24)	96 (46)
Median, months (95% CI)	Not Reached	10.8 (9.3, 12.1)
Hazard ratio (95% CI)[a]	0.42 (0.30, 0.60)	
p-value[b,c]	<0.0001	
Progression-Free Survival		
Disease progression or death (%)	108 (51)	163 (78)
Median, months (95%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

[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

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

Figure 1: **Kaplan-Meier Curves of Overall Survival - 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).

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%).

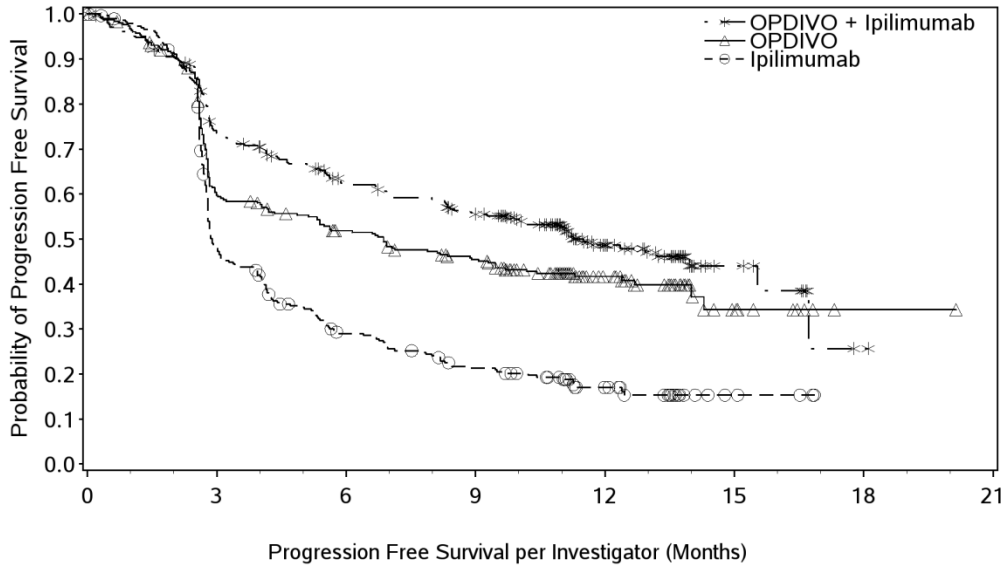
CHECKMATE-067 demonstrated statistically significant improvements in PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. Efficacy results are presented in Table 17 and Figure 2.

Table 17: 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 Objective Response Rate	50%	40%	14%
(95% CI)	(44, 55)	(34, 46)	(10, 18)
p-value[d]	<0.0001	<0.0001	
Complete response	8.9%	8.5%	1.9%
Partial response	41%	31%	12%
Duration of Response			
Proportion ≥6 months in duration	76%	74%	63%
Range (months)	1.2+ to 15.8+	1.3+ to 14.6+	1.0+ to 13.8+

[a] Based on a stratified proportional hazards model.
[b] Based on stratified log-rank test.
[c] p-value is compared with .005 of the allocated alpha for final PFS treatment comparisons.
[d] Based on the stratified Cochran-Mantel-Haenszel test.

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

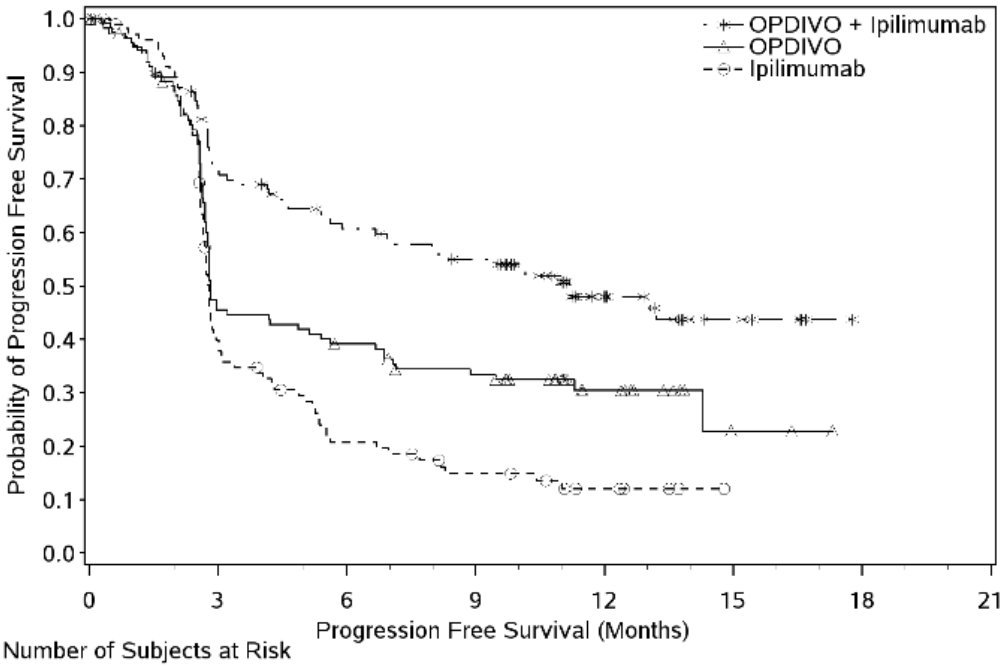


Number of Subjects at Risk

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

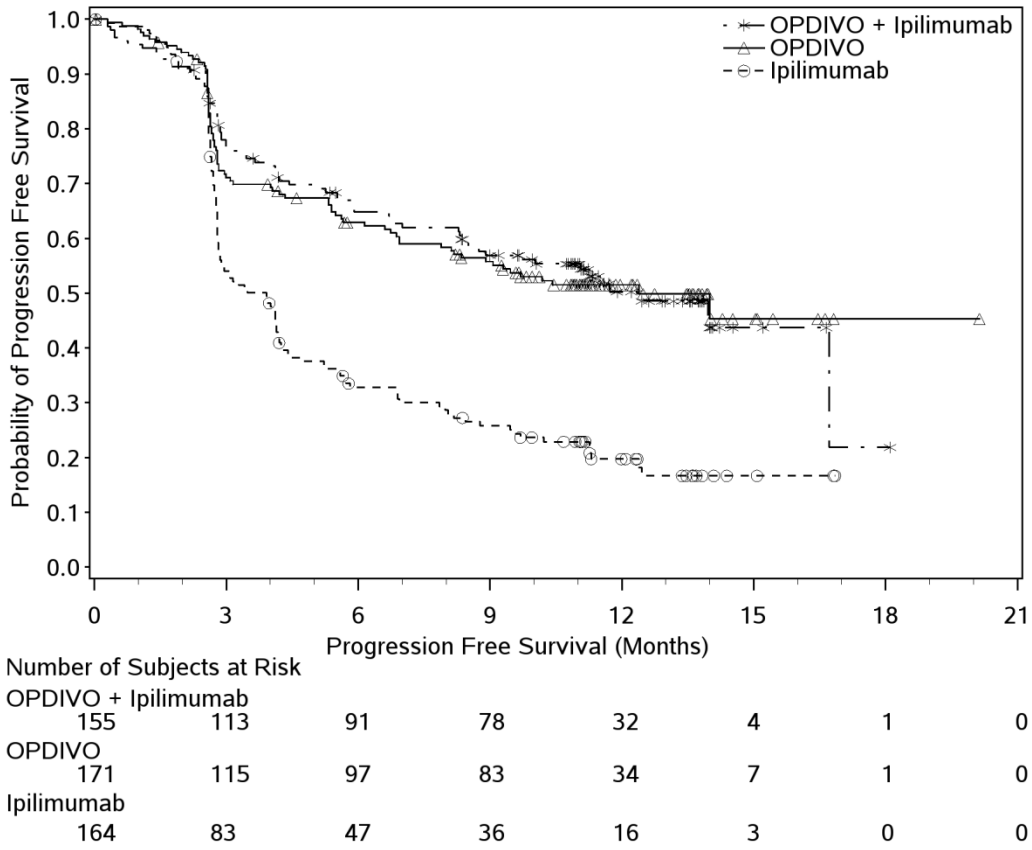
Figures 3 and 4 present exploratory efficacy subgroup analyses of PFS based on defined PD-L1 expression levels determined in archival tumor specimens using the PD-L1 IHC 28-8 pharmDx assay. Tumor samples were available for retrospective assessment for 97% of the study population; PD-L1 expression status 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.

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



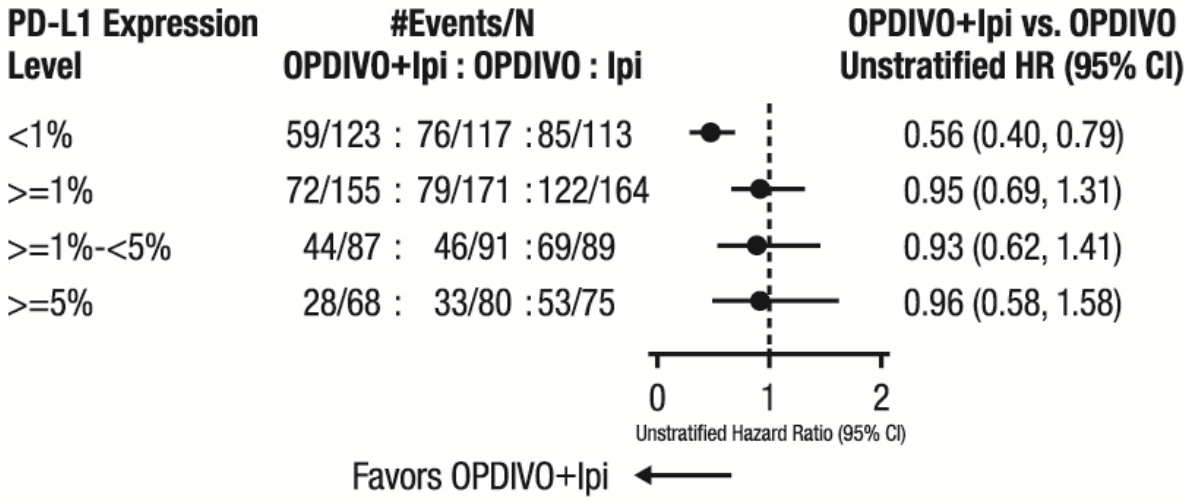
Number of Subjects at Risk							
OPDIVO + Ipilimumab							
123	82	65	57	26	6	0	0
OPDIVO							
117	50	42	34	13	2	0	0
Ipilimumab							
113	39	19	12	5	0	0	0

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



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

Figure 5: Forest Plot: PFS Based on PD-L1 Expression Comparing OPDIVO-Containing Arms - CHECKMATE-067



14.2 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 OPDIVO (n=135) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=137) administered intravenously at 75 mg/m^2 every 3 weeks. Randomization was stratified by prior paclitaxel vs. other prior treatment and region (US/Canada vs. Europe vs. Rest of World). This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrollment, and either off corticosteroids, or on a stable or decreasing dose of <10 mg daily prednisone equivalents. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS.

In 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 18 and Figure 6).

Table 18: 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	
Objective Response Rate	27 (20%)	12 (9%)
(95% CI)	(14 , 28)	(5, 15)
p-value[d]	0.0083	
Complete response	1 (0.7%)	0
Median duration of response, months (95% CI)	NR (9.8, NR)	8.4 (3.6, 10.8)
Progression-free Survival		
Disease progression or death (%)	105 (78%)	122 (89%)
Median (months)	3.5	2.8
Hazard ratio (95% CI)[a]	0.62 (0.47, 0.81)	
p-value[b]	0.0004	

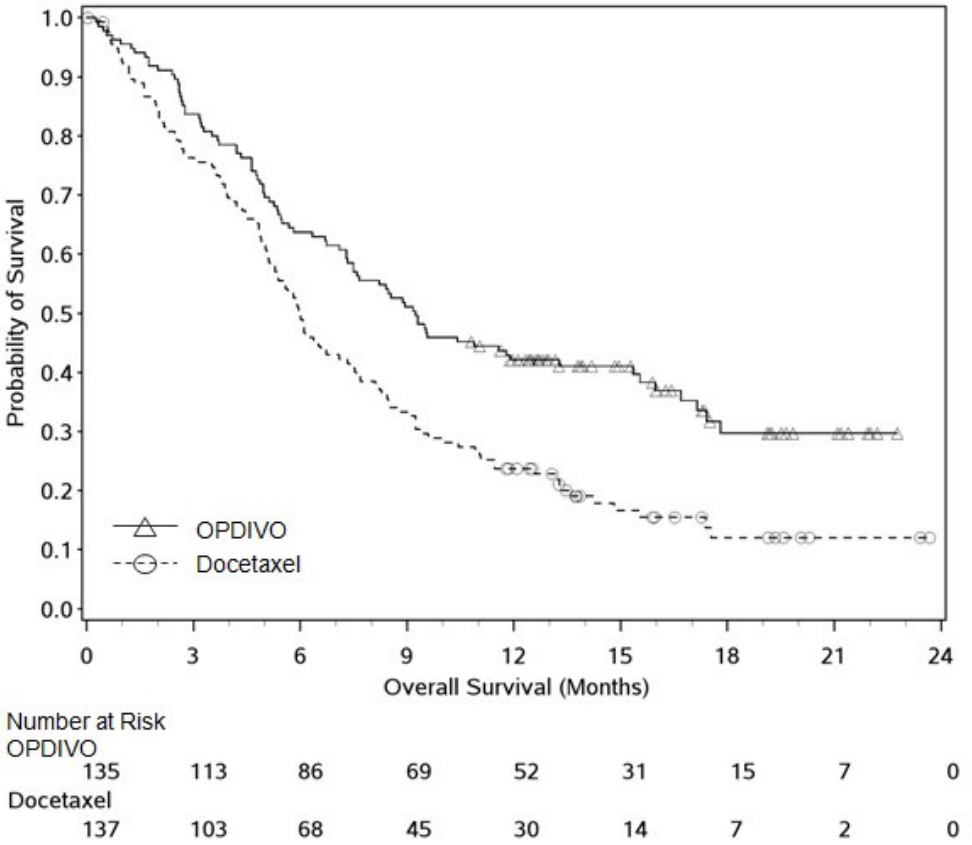
[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

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

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

Figure 6: Overall Survival - 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 OPDIVO (n=292) administered intravenously at 3 mg/kg every 2 weeks or docetaxel (n=290) administered intravenously at 75 mg/m^2 every 3 weeks. Randomization was stratified by prior maintenance therapy (yes vs. no) and number of prior therapies (1 vs. 2). The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, symptomatic interstitial lung disease, or untreated brain metastasis. Patients with treated brain metastases were eligible if neurologically stable. The first tumor assessments were conducted

9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. Additional efficacy outcome measures were investigator-assessed ORR and PFS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression.

In 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 19 and Figure 7).

Table 19: 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	
Objective Response Rate	56 (19%)	36 (12%)
(95% CI)	(15, 24)	(9, 17)
p-value[d]	0.02	
Complete response	4 (1.4%)	1 (0.3%)
Median duration of response (months) (95% CI)	17 (8.4, NR)	6 (4.4, 7.0)
Progression-free Survival		
Disease progression or death (%)	234 (80%)	245 (84%)
Median (months)	2.3	4.2
Hazard ratio (95% CI)[a]	0.92 (0.77, 1.11)	
p-value[b]	0.39	

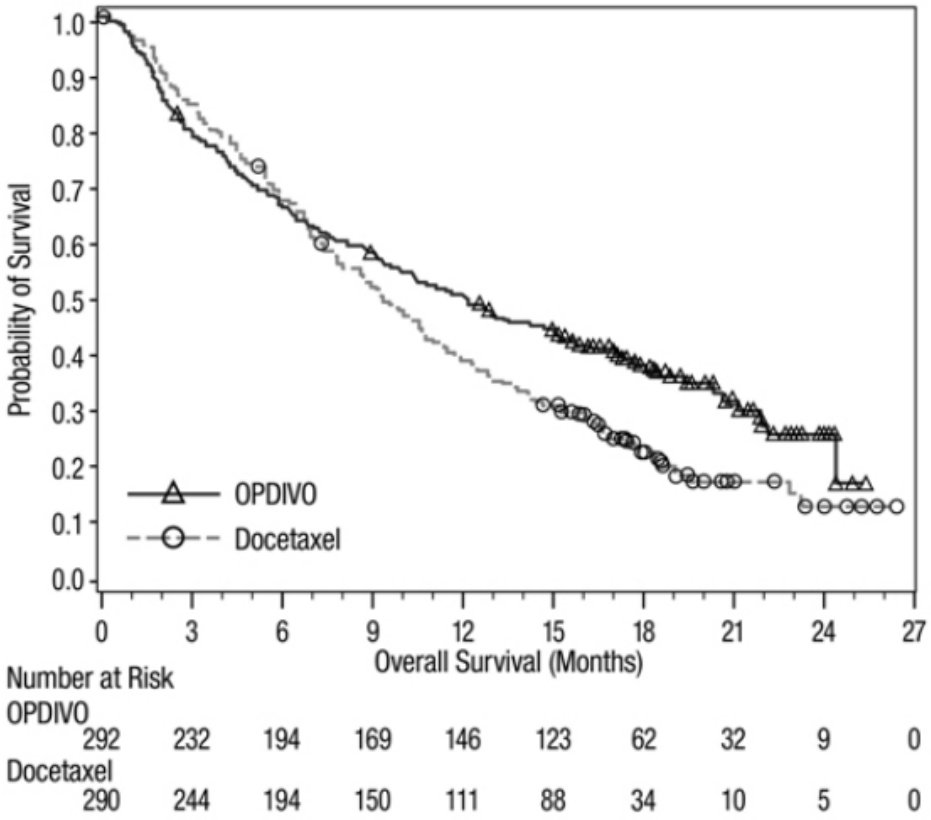
[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

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

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

Figure 7: Overall Survival - 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 8 summarizes the results of prespecified analyses of survival in subgroups determined by percentage of tumor cells expressing PD-L1. Figure 9 summarizes the results of prespecified analyses of progression-free survival in subgroups determined by percentage of tumor cells expressing PD-L1.

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

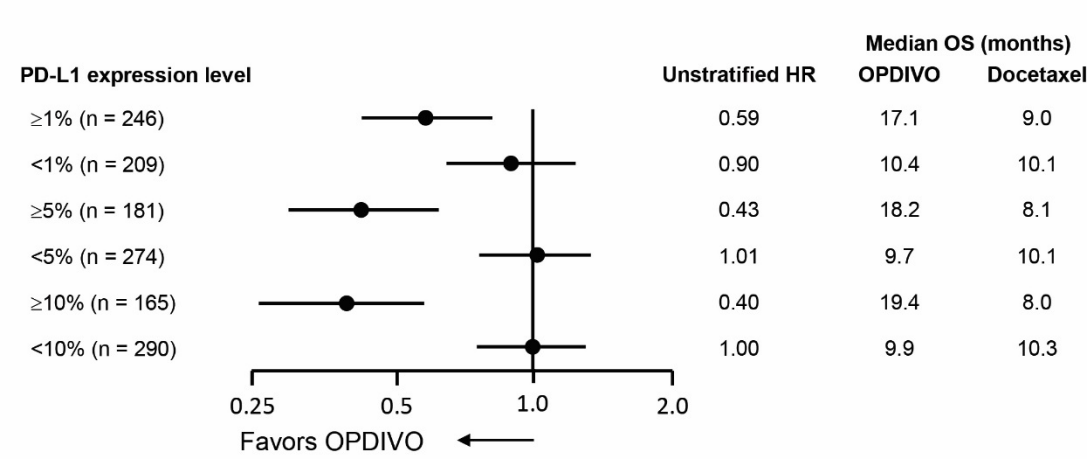
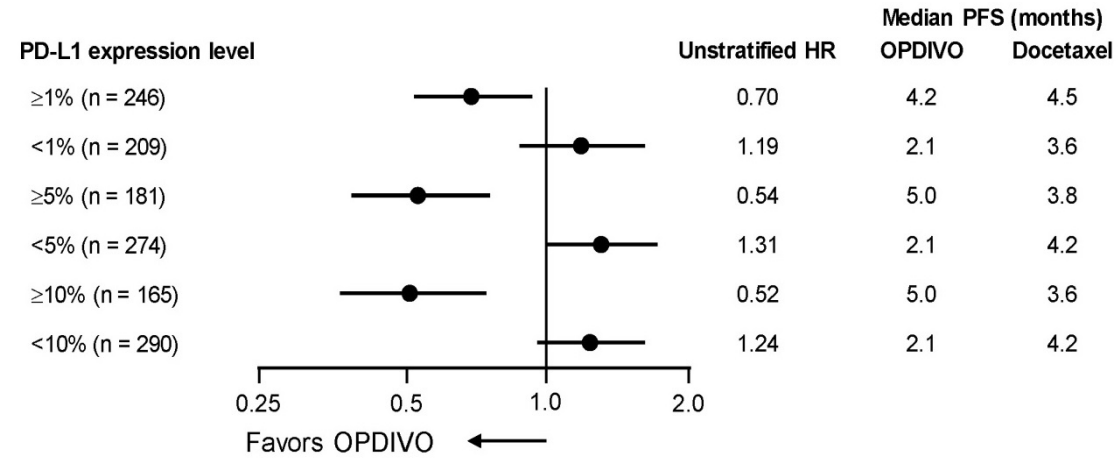


Figure 9: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



14.3 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.

Patients were randomized to OPDIVO (n=410) administered intravenously at 3 mg/kg every 2 weeks or everolimus (n=411) administered orally 10 mg daily. The median age was 62 years (range: 18 to 88) with 40% ≥65 years of age and 9% ≥75 years of age. The majority of patients were male (75%) and white (88%) and 34% and 66% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. The majority of patients (77%) were treated with one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 34% favorable, 47% intermediate, and 19% poor.

The first tumor assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later.

The major efficacy outcome measure was overall survival (OS). The trial demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO as compared with everolimus at the prespecified interim analysis when 398 events were observed (70% of the planned number of events for final analysis) (Table 20 and Figure 10). OS benefit was observed regardless of PD-L1 expression level.

Other endpoints include confirmed objective response rates, which are also presented in Table 20.

Table 20: Efficacy Results - CHECKMATE-025

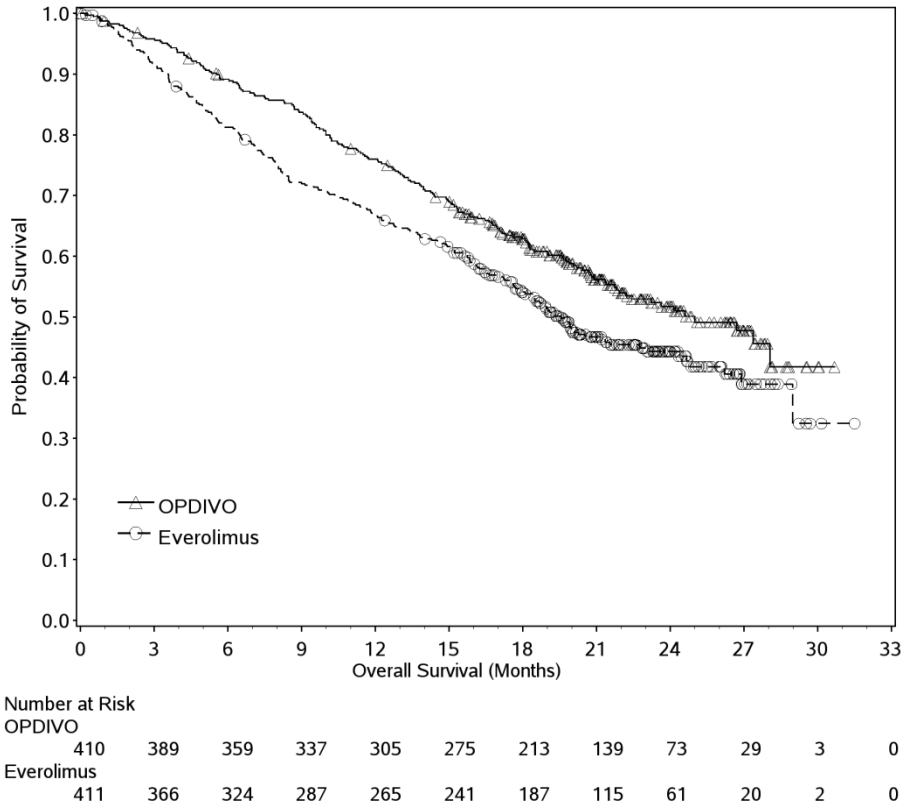
	OPDIVO (n=410)	**Everolimus (n=411)**
Overall Survival		
Deaths (%)	183 (45)	215 (52)
Median survival in months (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0018	
Confirmed Objective Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median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

[a] Based on a stratified proportional hazards model.

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

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

Figure 10: Overall Survival - CHECKMATE-025



14.4 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 administered intravenously over 60 minutes every 2 weeks until disease progression, maximal clinical benefit, or unacceptable toxicity. A cycle consisted of one dose. Dose reduction was not permitted.

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

Efficacy was evaluated in 95 patients in CHECKMATE-205 and CHECKMATE-039 combined who had failure of autologous HSCT and post-transplantation brentuximab vedotin. The median age was 37 years (range: 18 to 72). The majority were male (64%) and white (87%). Patients had received a median of 5 prior systemic regimens (range: 2 to 15). They received a median of 27 doses of OPDIVO (range: 3 to 48), with a median duration of therapy of 14 months (range: 1 to 23 months). Results are shown in Table 21.

Table 21: Efficacy in cHL after Autologous HSCT and Post-transplantation Brentuximab Vedotin

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

[a] Per 2007 revised International Working Group criteria.

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

[c] A + sign indicates a censored value.

Efficacy was also evaluated in 258 patients in CHECKMATE-205 and CHECKMATE-039 combined who had relapsed or progressive cHL after autologous HSCT. The analysis included the group described above. The median age was 34 years (range: 18 to 72). The majority were male (59%) and white (86%). Patients had a median of 4 prior systemic regimens (range: 2 to 15), with 85% having 3 or more prior systemic regimens and 76% having prior brentuximab vedotin. Of the 195 patients having prior brentuximab vedotin, 17% received it only before autologous HSCT, 78% received it only after HSCT, and 5% received it both before and after HSCT. Patients received a median of 21 doses of OPDIVO (range: 1 to 48), with a median duration of therapy of 10 months (range: 0 to 23 months). Results are shown in Table 22.

Table 22: Efficacy in cHL after Autologous HSCT

	CHECKMATE-205 and CHECKMATE-039 (n=258)
Objective 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.

14.5 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 OPDIVO administered intravenously (IV) at 3 mg/kg every 2 weeks or investigator's choice of:

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

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

In 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 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 23 and Figure 11. There were no statistically significant differences between the two arms for PFS (HR=0.89; 95% CI: 0.70, 1.13) or ORR (13.3% [95% CI: 9.3, 18.3] vs. 5.8% [95% CI: 2.4, 11.6] for nivolumab and investigator's choice, respectively).

Table 23: Overall Survival in CHECKMATE-141

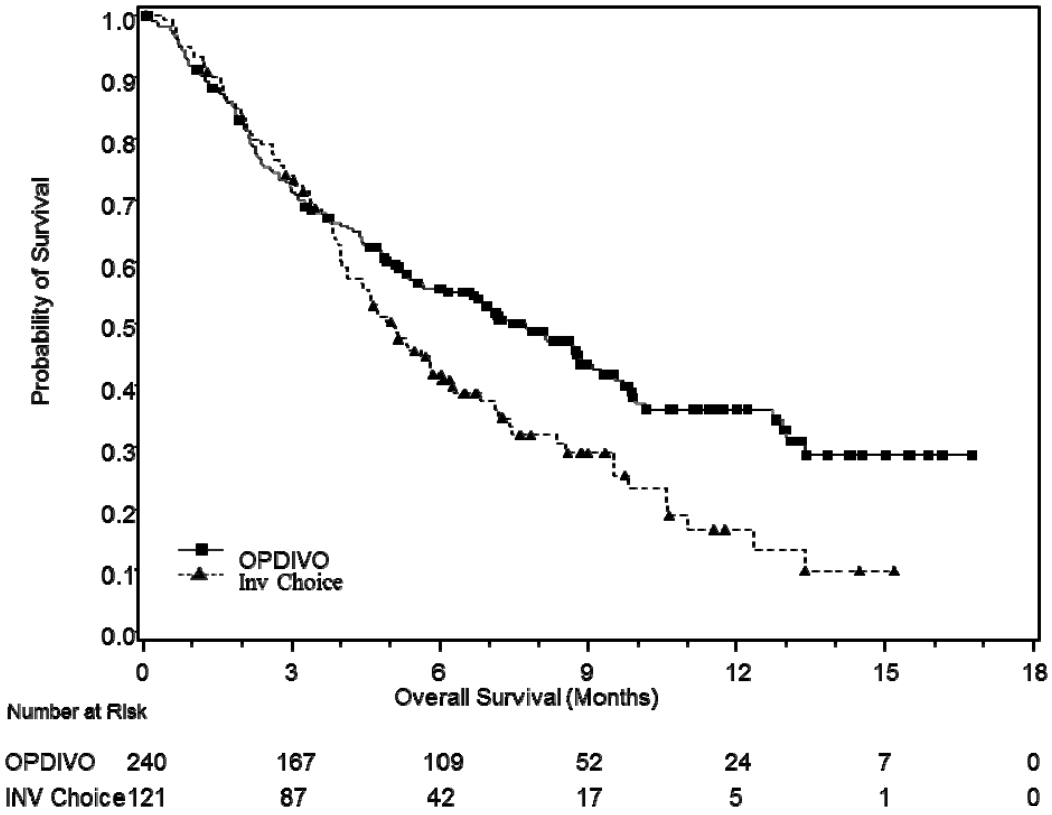
	OPDIVO (n=240)	**Investigator's Choice (n=121)**
Overall Survival		
Deaths (%)	133 (55%)	85 (70%)
Median (months) (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
Hazard ratio (95% CI)[a]	0.70 (0.53, 0.92)	
p-value[b,c]	0.0101	

[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.

Figure 11: 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.

14.6 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 an intravenous infusion of 3 mg/kg of OPDIVO every 2 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 8 weeks for the first 48 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed objective 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 24. Median time to response was 1.9 months (range: 1.6 to 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 24: Efficacy Results in CHECKMATE-275

	All Patients N=270	**PD-L1 <1% N=146**	**PD-L1 ≥1% N=124**
Confirmed Objective 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

14.7 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 OPDIVO 3 mg/kg by intravenous infusion every 2 weeks until unacceptable toxicity or radiographic progression. Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Efficacy outcome measures included objective 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 25.

Table 25: Efficacy Results – CHECKMATE-142

	All Patients (n=74)	**Prior Treatment with Fluoropyrimidine, Oxaliplatin, and Irinotecan (n=53)**
IRC-Confirmed Objective 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

16 HOW SUPPLIED/STORAGE AND HANDLING

OPDIVO® (nivolumab) is available as follows:

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

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

17 PATIENT COUNSELING INFORMATION

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

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

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.4)]*.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.5)]*.
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions (5.6)]*.
- Encephalitis: Advise patients to contact their healthcare provider immediately for neurological signs or symptoms of encephalitis *[see Warnings and Precautions (5.7)]*.
- Infusion Reactions: Advise patients of the potential risk of infusion reaction *[see Warnings and Precautions (5.9)]*.
- Complications of allogeneic HSCT after OPDIVO: Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.10)]*.

- Females of Reproductive Potential: Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months following the last dose of OPDIVO *[see Use in Specific Populations (8.3)]*.
- Lactation: Advise women not to breastfeed while taking OPDIVO *[see Use in Specific Populations (8.2)]*.

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

U.S. License No. 1713

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

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

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

OPDIVO is a medicine that may treat 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.
- **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),
  - has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, **and**
  - is mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H)

It is not known if OPDIVO is safe and effective in children less than 18 years of age for treatment of any cancer other than metastatic, MSI-H or dMMR, colorectal cancer.

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

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. OPDIVO can harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during and for at least 5 months after the last dose of OPDIVO. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant during treatment with OPDIVO.
- are breastfeeding or plan to breastfeed. It is not known if OPDIVO passes into your breast milk. Do not breastfeed during treatment with OPDIVO.

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

How will I receive OPDIVO?

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

What are the possible side effects of OPDIVO?
OPDIVO can cause serious side effects, including:

- **See "What is the most important information I should know about OPDIVO?"**
- **Severe infusion reactions.** Tell your doctor or nurse right away if you get these symptoms during an infusion of OPDIVO:
  - chills or shaking
  - itching or rash
  - flushing
  - difficulty breathing
  - dizziness
  - fever
  - feeling like passing out
- **Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO.** These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

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

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

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

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

These are not all the possible side effects of OPDIVO. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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

What are the ingredients in OPDIVO?
Active ingredient: nivolumab
Inactive ingredients: mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and Water for Injection. May contain hydrochloric acid and/or sodium hydroxide.

Manufactured by: Bristol-Myers Squibb Company Princeton, NJ 08543 USA U.S. License No. 1713
For more information, call 1-855-673-4861 or go to www.OPDIVO.com.
This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: July 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

SUMMARY REVIEW

Division Director Summary Review

Date	July 31, 2017
From	Patricia Keegan
Subject	Division Director Summary Review
BLA Supplement #	BL 125554/S-034
Applicant Name	Bristol-Myers Squibb Company
Date of Submission	February 2, 2017
PDUFA Goal Date	August 2, 2017
Proprietary Name / Established (USAN) Name	Opdivo/ nivolumab
Dosage Forms / Strength	Injection for intravenous use; 40 mg/4 mL and 100 mg/10 mL (10 mg/mL) in single-dose vials
Proposed Indication(s)	OPDIVO is indicated for the treatment of (b) (4) This indication is approved under accelerated approval based on overall response rate and (b) (4) Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Approved Indication	OPDIVO is indicated for the treatment of adult and pediatric 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 (14.7)]*. 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.
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Meredith Libeg
Medical Officer Review	Damiette Smit
Statistical Review	Uma Siangphoe
Pharmacology Toxicology Review	Yuan Xu & Saeho Chong
OBP Review	N. Sarah Arden
DMPP/OPDP	Sharon R. Mills
OPDP	Nicholas J. Senior
OSI	Lauren Iacono-Connors

OND=Office of New Drugs; OBP=Office of Biotechnology Products; OPDP=Office of Prescription Drug Promotion; DMPP-Division of Medical Policy Programs; OSI=Office of Scientific Investigations

Division Director Summary Review

1. Introduction

This efficacy supplement supports a new indication for nivolumab for the "treatment of [redacted (b) (4)] " based on the results of a single trial, Study CA209142, also known as CheckMate142. Nivolumab was approved on December 22, 2014 and is currently approved for the following indications:

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

This supplement relies on the findings of safety and efficacy observed in Study CA209142, an open-label, non-comparative, multiple cohort, and activity-estimating trial. The key eligibility criteria were metastatic colorectal cancer (mCRC) with dMMR/MSI-H as detected by an accredited laboratory per local regulations, ECOG PS 0-1, disease progression during or after, or intolerance to, at least one line treatment for metastatic disease, which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan; and measurable disease per RECIST v1.1. Patients with any of the following were excluded: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

The analysis of supporting this supplement were limited to the nivolumab monotherapy arm, in which nivolumab administered at 3 mg/kg intravenously (IV) every 2 weeks until disease progression or unacceptable toxicity. Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The primary endpoint for purposes of FDA's

review of this supplement was the overall response rate (ORR) as assessed by an independent review committee (IRC) according to RECIST v1.1 in patients with local test determined MSI-H or dMMR, metastatic colorectal cancer with disease progression following prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The trial was designed as a Simon 2-stage trial to estimate the overall response rate of nivolumab alone or with ipilimumab in MSI-H mCRC. The trial was designed to test the null hypothesis that the true ORR is ≤ 30% (not considered clinically compelling) with either nivolumab monotherapy or the combination of nivolumab/ipilimumab. The final analysis was to occur at least 6 months after the last enrolled subject's first dose of study drug.

A total of 74 patients with locally confirmed MSI-H/dMMR, metastatic colorectal cancer with disease progression after 1 or more prior lines of chemotherapy for metastatic disease were enrolled; of these, 53 patients had received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Across all 74 patients, the median age was 53 years (range: 26-79) 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%); 36% were reported to have Lynch Syndrome. Across the 74 patients, 42% of patients had received an anti-EGFR antibody.

Among the 53 patients with locally confirmed MSI-H or dMMR mCRC with disease progression following prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, the BIRC-assessed ORR was 28% (95% CI: 17, 42) with 67% (38, 88) of response durable for 6 months or longer. This was supported by the results in all 74 patients, with a BIRC-assessed ORR of 32% (95% CI: 22, 44), with 63% (41, 81) of response durable for 6 months or longer. Similar results were observed in the subset of patients with centrally confirmed MSI-H or dMMR colorectal cancer. Responses were also observed in patients whose tumor expressed or did not express PD-L1 and there was no apparent association between the intensity of PD-L1 expression and observed response rate. The results observed in Study CA209142 are similar to those observed in the cohort of patients with previously treated, MSI-H/dMMR mCRC treated with pembrolizumab, another PD-L1 inhibiting antibody, where the ORR was 36% (95% CI:26, 46); 78% of responding patients had response durations of ≥ 6 months. Pembrolizumab was approved under the provisions of 21 CFR 601 Subpart E (accelerated approval) on May 23, 2017 for the treatment of adult and pediatric patients with metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

The toxicity profile of nivolumab is well-characterized in studies supporting previous approvals under BLA 125554. The results of CA209142 did not demonstrate new safety signals; however it is notable that 21% of patients discontinued treatment due to the following adverse reactions: gastritis, diarrhea, increased ALT, acute renal failure, oral mucositis, and a duodenal ulcer. An additional patient discontinued treatment for the adverse event of myocardial infarction that was identified as unrelated to nivolumab.

The results of Study CA209142 demonstrated an ORR that was superior to that achieved with available therapy (1% ORR with regorafenib and 1.5% ORR with tipiracil/trifluridine (TAS-

102) in similar heavily pre-treated patients, with clinically important durability of response. In addition, while nivolumab carries the risks of immune-mediated adverse reactions in any organ or tissue in the body, given the expected median survival of less than 1 year for this population, the risks are outweighed by the potential benefits of durable responses in approximately one-third of patients.

The major issues considered during this application were the imprecision of the estimated treatment effect and inadequate characterization of durability of response due to the short-follow-up. (b) (4)

as a post-marketing requirement.

The other issue with this application is the discordance between central and local testing results. The basis for this discrepancy is unclear; however given that this indication is applicable to only 20% of the patients with mCRC with MSI-H or dMMR tumors, further investigation and identification of an analytically and clinically validated assay was requested. While approval of a drug and its companion diagnostic test is generally concurrent, approval was not withheld until the companion diagnostic test was identified in this instance, given the importance of nivolumab as a treatment option for this population in which nivolumab represents an improvement over available therapy.

2. Background

Indicated Population and Available Therapy
Colorectal cancer is the third most common cancer diagnosed in the United States, with an estimated 95,520 new cases of colon cancer and 39,910 new cases of rectal cancer expected in the U.S. in 2017.[1] It is estimated that 50,260 deaths due to colorectal cancer will occur in the US in 2017. The 5-year survival rate for patients with metastatic colorectal cancer is 11%.[2]

Median survival in patients with metastatic colorectal cancer that has been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy can be estimated from two recently conducted, randomized, placebo-controlled trials, in which median survival was less than 1 year for patients receiving either regorafenib or TAS-102. Among patients randomized to regorafenib median survival was 6.4 months (compared with 5.0 months for placebo) in the CORRECT trial and among patients randomized to TAS-102, the median survival was 7.1 months (compared with 5.3 months for placebo) in the major efficacy trial.

[1] https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics html accessed March 28, 2017
[2] https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html accessed March 28, 2017

Available therapy for the treatment of patients with metastatic colorectal cancer who have been previously treated with, or are not candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy include the following FDA-approved drugs:

Regorafenib was approved September 27, 2012, for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. This approval was based on demonstration of improved overall survival [HR 0.77 (0.64, 0.94); p=0.01], with a median survival of 6.4 months in the regorafenib arm and 5 months in the placebo arm, in an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial enrolling 760 patients with previously treated metastatic colorectal cancer. All patients had received treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab. All but one patient with KRAS mutation-negative tumors received panitumumab or cetuximab. Supportive evidence of efficacy was based on a statistically robust but clinically modest improvement in progression-free survival [HR 0.49 (0.42, 0.58)], with a median PFS of 2.0 months in the regorafenib arm and 1.7 months in the placebo arm. The overall response rate observed in the major efficacy (CORRECT) trial was 1% (95% CI: 0.3, 2.3).

Tipiracil hydrochloride/trifluridine (TAS-102) was approved on September 22, 2015 for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. This approval was based on demonstration of improved overall survival [HR 0.68 (95% CI: 0.58, 0.81); p<0.001], with a median survival of 7.1 months for the TAS-102 arm and 5.3 months in the placebo arm. The trial also demonstrated a significant improvement in progression-free survival [HR 0.47 (95% CI: 0.40, 0.55); p<0.001]. The trial supporting approval was an international, randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic colorectal cancer (CRC). A total of 800 patients were randomized 2:1 to receive LONSURF (N=534) plus best supportive care (BSC) or matching placebo (N=266) plus BSC. Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months), and region (Japan vs. US, Europe, and Australia). Patients were required to have received at least 2 standard lines of chemotherapy for treatment of metastatic CRC. The trial demonstrated an improvement in progression-free survival [HR 0.47 (0.40, 0.55); p<0.001] with median PFS of 3.2 months in the TAS-102 arm and 1.9 months in the placebo arm (NB: the medians overestimate the treatment effect) and an overall response rate of 1.5% (95% CI: 0.6, 2.9).

Pre-submission Regulatory History

On January 10, 2014, IND 119381 was submitted for the investigation of nivolumab in MSI-H colorectal cancer; the initial protocol submitted in this IND was Study CA209142. The IND was allowed to proceed on February 4, 2014.

On February 19, 2014, a revised protocol was submitted which clarified that the primary endpoint of the trial was to evaluate the investigator–assessed overall response rate (ORR) and that evaluation of IRRC-assessed ORR in patients with metastatic MSI-H CRC was the (sole) secondary endpoint.

On July 22, 2014, the Statistical Analysis Plan for Study CA209142 was submitted to the IND.

On August 4, 2015, a revised version of Protocol CA209142 was submitted which contained the following changes: 1) addition of a biomarker collection schedule for subjects dosed with the combination of nivolumab plus ipilimumab and 2) inclusion of an appendix regarding MSI testing panel descriptions (PCR and IHC), classification of MSI status, and sample prioritization.

On May 10, 2016, a Type C meeting was held with BMS seeking preliminary information on the development program and the needs for the future marketing application, (b) (4) BMS proposed to submit the results of Study CA209142 (b) (4) During the meeting, the following issues and key agreements were reached:

- FDA will consider the response rate as determined by independent review as the primary endpoint for regulatory purposes. The data should indicate that nivolumab provides for a meaningful advantage over available therapies in the proposed supplement. FDA recommended that BMS (b) (4) in the sBLA.
- FDA expressed concern regarding the unexpectedly high discrepant results between local and central testing in Study CA209142 (e.g., across both arms, approximately 20% of patients who were MSI-H by the local test were not MSI-H when assessed using the central test). In the sBLA, provide the local laboratory result confirming that each patient's tumor was determined to be MSI-H. Additionally, indicate whether any of the patients who responded had MSI-H-positive tumors by local testing but non-MSI-H by central testing. Also provide information regarding whether the discrepant results were limited to patients whose tumors were tested by IHC locally or whether patients whose tumors were evaluated by PCR locally were also discrepant.
- Although FDA may take action on an application in the absence of a PMA for a test for MSI-H status, based on these results, FDA may need to re-evaluate whether development of a test may be necessary (e.g., in the post-marketing setting).
- BMS stated that they would provide a summary of their findings regarding the discrepancies for the MSI-H test results prior to the filing of the supplemental BLA.

On August 3, 2016, BMS generated a revised statistical analysis plan (SAP) for Study CA209142 to support generation of an interim Clinical Study Report (CSR) for inclusion in the sBLA describing the results of the nivolumab monotherapy cohort.

On December 16, 2016, a Type B meeting was held with BMS to discuss the discuss the results from Study CA209142, intended to support a planned supplemental BLA (sBLA) seeking a new claim for nivolumab, as a single agent, for the proposed indication of the treatment of (b) (4) The following advice and key agreements were reached:

- BMS agreed to provide the results of ORR as determined by an IRC in all patients enrolled with centrally confirmed MSI-H mCRC who have been followed for at least six months from the onset of response; ORR by IRC in the first 19 and first 48 patients enrolled with centrally confirmed MSI-H mCRC, and all patients with MSI-H mCRC by local testing.
- BMS agreed to provide updated results for duration of response by Day 45 following submission of the sBLA.
- BMS agreed to provide information on the type of local test used to screen patients for eligibility, including the type of panel used for the PCR test, if known; the central test used for confirmation; and information on discordance between central and local testing.
- FDA will request a Postmarketing Commitment (PMC) to identify optimal testing strategies to identify patients with tumors having deficient mismatch repair or microsatellite instability. Data supporting such testing strategies will require submission of both the analytical assessment and bridging studies to clinical performance.
- FDA agreed (b) (4) (b) (4) therefore, FDA agreed t

3. CMC/Biopharmaceutics/Device

The OBP reviewer concurred with BMS's request for categorical exclusion from the preparation of an environmental assessment (EA) for nivolumab according to section 505(b) of the Federal Food, Drug, and Cosmetic Act.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Pharmacogenomics

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval. The application provided pharmacokinetic data and exposure-responses analyses based on data obtained in Study CA209142, in which nivolumab was administered at a dose of 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. In addition, the application contained the results of a population PK analysis, which served to bridge exposures between the 3 mg/kg every 2 week dosage regimen and the proposed 240 mg every 2 week dosage regimen for inclusion in product labeling.

The reviewers concluded that the pharmacokinetics in patients with MSI-H/dMMR, metastatic colorectal cancer is comparable to that observed in patients with other cancers. The exposure-response relationship (for response rate by IRC) was flat over the exposures observed in cycle 1 of Study CA209042; however the number of patients included in the analysis was limited (60 patients) and all patients received the same dose (3 mg/kg). While the dosage regimen administered in Study CA209142 was 3 mg/kg every 2 weeks, BMS requested approval for a recommended dose of 240 mg every 2 weeks. The clinical pharmacology reviewers concluded that the proposed dosage regimen was adequately supported by the results of population pharmacokinetic modeling and simulation. These analyses showed less than 7% difference in exposure between the 3 mg/kg and 240 mg dosage regimens; this difference would not result in clinically meaningful differences in exposure.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

A single study was submitted in support of the proposed indication, however there are multiple indications for which nivolumab is approved, which serve as supportive evidence that nivolumab is effective for the treatment of patients with advanced cancers.

Bioresearch monitoring was limited to the contract research organization, (b) (4) , which conducted the analysis of the primary efficacy endpoint. The inspection of (b) (4) did not identify any major deficiencies and FDA's compliance staff concluded that the data from Study CA209142 submitted to the Agency in support of sBLA 125554 S-034, appear reliable based on available information.

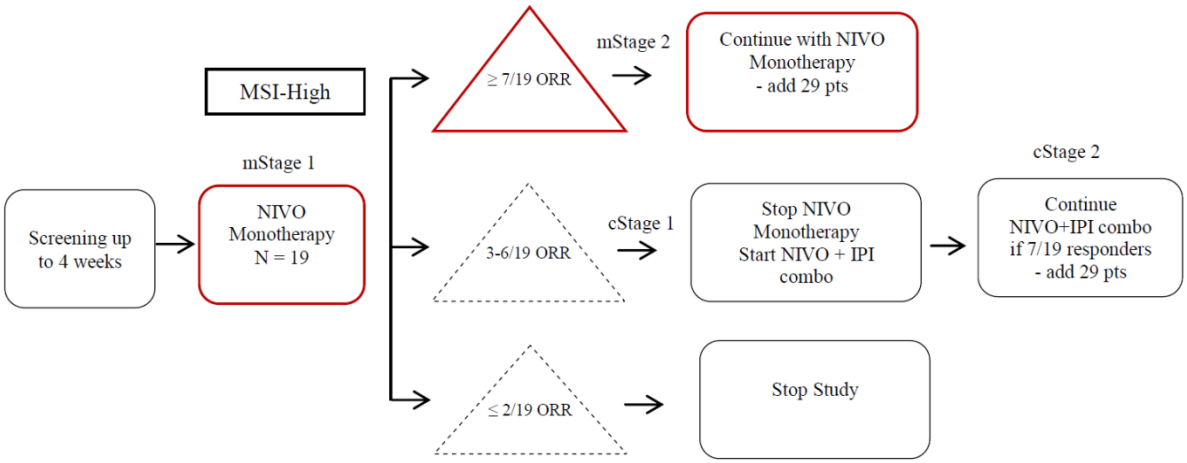
Study Design
Study 209142, titled "A Phase 2 Clinical Trial of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Microsatellite Instability High Colon Cancer"

Key eligibility criteria were dMMR/MSI-H metastatic colorectal cancer (mCRC), ECOG PS 0-1, progression during, after, or intolerant to at least one line treatment for metastatic disease, which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan; microsatellite instability expression detected by an accredited laboratory per local regulations; and measurable disease per RECIST v1.1. Patients with any of the following were excluded: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression.

The treatment plan for patients enrolled in the nivolumab monotherapy cohort nivolumab was administered at 3 mg/kg intravenously (IV) every 2 weeks until disease progression or unacceptable toxicity.

Tumor assessments were conducted every 6 weeks for the first 24 weeks and every 12 weeks thereafter.

The study schema, abstracted from the protocol, is provided below.



The primary endpoint was overall response rate (ORR) per investigator assessment according to RECIST v1.1 and secondary endpoints were ORR as assessed by an independent review committee (IRC) according to RECIST v1.1 and duration of response. [Refer to summary of the May 10, 2016, meeting in which BMS was informed that for regulatory purposes, FDA considered IRC-assessed ORR would be the endpoint of interest.

The trial was designed as a Simon 2-stage trial to estimate the overall response rate of nivolumab alone or with ipilimumab in MSI-H mCRC. An additional cohort evaluated the safety of nivolumab plus ipilimumab in non-MSI-H mCRC. As stated in the protocol, the planned sample size was 96 patients across two cohorts: a non-MSI-H cohort enrolling up to 29 patients and an MSI-H cohort enrolling up to 48 MSI-H patients. For the non-MSI-H safety cohort, sample size was not based on power considerations and was dependent on the observed toxicity. For the MSI-H cohort, the trial was designed to test the null hypothesis that the true ORR is $\leq 30\%$ (not considered clinically compelling) with either nivolumab monotherapy or the combination of nivolumab/ipilimumab. The final analysis of the primary endpoint was to

occur at least 6 months after the last enrolled subject's first dose of study drug. The MSI-H cohort was defined as subjects who are defined as MSI-H based on standard diagnostic testing documented in the subject's medical history and prospectively confirmed in the current study by repeat testing using a PCR test.

Results
A total of 74 patients were enrolled in the nivolumab monotherapy cohort from March 2014 to March 2016. The database lock occurred on September 19, 2016.

All 74 patients had MSI-H mCRC, as identified by local laboratory testing, conducted using either MMR IHC or PCR-based MSI screening and disease progression during or after ≥ 1 line of treatment that included at least a fluoropyrimidine and oxaliplatin or irinotecan; 53 patients (72%) received a fluoropyrimidine, oxaliplatin, and irinotecan. The median age was 53 years (range: 26-79) 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, 42% of patients had received an anti-EGFR antibody. Of these 74 patients, 72% had centrally confirmed MSI-H or dMMR test results.

The efficacy results in patients with MSI-H or dMMR mCRC that was determined by local laboratory tests as assessed by the BIRC per RECIST v1.1 are summarized in the table below, (b) (4)

Efficacy Results – CA209142

	All Patients (n=74)	**Prior Treatment with Fluoropyrimidine, Oxaliplatin and Irinotecan (n=53)**
IRC-Confirmed Objective 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[a] (months)	**(n=24)**	**(n=15)**
% with duration ≥ 6 months (95%CI)	63% (41, 81)	67% (38, 88)
Range	1.4+, 26.5+	2.8+, 22.1+

[a] Based on Kaplan-Meier estimation, median DOR has not been reached.

In the subset of the 74 patients enrolled who had centrally confirmed MSI-H or dMMR colorectal cancer, the BIRC-assessed ORR was 36% (95% CI: 23, 50). Concern was raised by the review team for the discrepancies between local and central MSI-H and dMMR testing, as displayed in the table abstracted from the medical officer review, below.

Table 5: Local vs. central MSI/MMR testing

		Local test (N=74)	Central test MSIH (N=53)	Central test MSS (N=14)	Central not reported (N=7)
PCR	n (%)	22 (30)	17 (32)	2 (14)	3 (43)
IHC	n (%)	40 (54)	27 (51)	10 (71)	3 (43)
PCR/IHC	n (%)	12 (16)	9 (17)	2 (14)	1 (14)

Source: FDA analysis.

In PCR testing for germline mutations in the mismatch repair genes, among the 19 patients with central test results, MSI-H status could not be confirmed in 2 patients, for a potential false positive rate of 11% (95% CI: 1.3, 33).

In immunohistochemistry testing for loss of staining for mismatch repair proteins (e.g., MLH1, MSH2, MSH6, and PMS2 proteins), among the 37 patients with central test results, dMMR status could not be confirmed in 10 patients, for a potential false positive rate of 27% (95% CI: 14, 44).

Finally, for patients whose tumors were centrally tested by both IHC and PCR, there were two negative results among the 11 patients evaluated, for a potential false positive rate of 18% (95% CI 2.3, 52).

Based on these data, it remains unclear whether the local tests have an unacceptably high false positive rate or whether central testing results are unreliable based on the quality of the tumor specimens provided. However it remains clear that this is an issue that should be addressed to ensure that patients likely to benefit from nivolumab, which is limited to approximately 20% of all patients with colorectal cancer in the U.S., can be reliably identified. Thus, FDA requested and BMS agreed to conduct studies with analytically validated IHC and PCR tests to clinically validate the utility of these tests for use in clinical practice and as possible companion diagnostic tests.

8. Safety

Based on previously submitted safety data supporting prior approvals for nivolumab and extensive post-marketing experience, there is sufficient data characterizing the safety of nivolumab at the dose (3 mg/kg every 2 weeks) administered in the clinical study. The safety of the proposed dosage regimen (240 mg/kg every 2 weeks) is supported by clinical studies and by pharmacokinetic bridging data between the two dosage regimens.

No new safety signals were identified in the review of this application. Of the 38 patients who discontinued nivolumab, the majority (71%) discontinued treatment for progressive disease but a significant minority (21%) discontinued nivolumab for adverse events or withdrew consent to continue. Adverse events related to the study drug that led to discontinuation were gastritis, diarrhea, increased ALT, acute renal failure, oral mucositis, and a duodenal ulcer. An

additional patient discontinued treatment for the adverse event of myocardial infarction that was identified as unrelated to nivolumab.

I concur with the clinical review team that risk mitigation and evaluation strategies (REMS) were not required to ensure safe and effective use of nivolumab in the proposed indicated population, given the extensive post-marketing experience with nivolumab and 11% 5-year survival rate for patients with metastatic colorectal cancer.

There were no post-marketing commitments requested under the provisions of 505(o) to evaluate safety risks of nivolumab.

9. Advisory Committee Meeting

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

10. Pediatrics

BMS submitted a copy of their Agreed iPSP, as attached to FDA's July 28, 2016 Agreed-iPSP letter, describing their plan to seek a full waiver from the requirements of the Pediatric Research Equity Act for "(b) (4) BMS also submitted a request for a full waiver from the requirements of PREA for "(b) (4)" in the sBLA, due to the low incidence of colorectal cancer in pediatric patients making clinical studies impossible to conduct. The Pediatric Review Committee (PeRC) reviewed the waiver request on July 19, 2017, and both the Division and PeRC agreed that the waiver should be granted.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Physician labeling
  - Indications and Usage: proposed indication modified to (b) (4)
  - Dosage and Administration: Dosage regimen of 240 mg IV over 60 minutes every 2 weeks is supported by population PK analyses indicating overlap in exposure between patients receiving nivolumab 3 mg/kg and 240 mg every 2 weeks. .
  - Replacement of study number (Study 1, 2, 3, etc.) with protocol title (e.g., CHECKMATE-017) throughout product labeling: NCT numbers provided for all studies described in Section 14.
  - Adverse Reactions: Safety results of Study CA209142 were not included in labeling as these results add no new information over that currently described in the labeling and were obtained in an uncontrolled study.
  - Use in Specific Populations, Pediatric Use subsection (8.4) revised to provide the basis for extending the new indication to adolescents based on extrapolation of efficacy from adults and adequate data in population PK studies to determine a dosage regimen providing comparable exposure as in adults.
  - Clinical Pharmacology, Pharmacodynamics subsection (12.2) modified to reference the new indication.
  - Clinical Studies modified to include the results of the overall population and the subset who with disease progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Deleted references to (b) (4) information on (b) (4) Deleted replaced with the proportion of responding patients with durable response of 12 months or longer, as this information was deemed more informative to prescribers.
- (b) (4)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  Metastatic colorectal cancer is a serious and life-threatening disease with an 11% 5-year survival rate and median survival of less than one year based on recent clinical trials in patients with disease progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. MSI-H mCRC comprise approximately 20% of all colorectal cancers. Based on published literature,[3] patients with MSI-H or MMR-deficient colorectal cancers

[3] *Journal of Clinical Oncology* 23, no. 3 (January 2005) 609-618.

appear to have a more favorable prognosis than MSS (microsatellite stable) colorectal cancers; the extent to which this holds true in patients receiving third-line therapy for metastatic disease is unclear. Available therapy for patients with mCRC with progressive disease following a fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy is regorafenib and tipiracil/trifluridine (TAS-102), which provide modest improvements in survival and response rates of less than 2%.

Study CA209142 demonstrated an IRC-assessed confirmed overall response rate of 28% (95% CI: 17, 42) with 67% of responses durable for 6 months or longer among the 53 patients with locally confirmed MSI-H or dMMR mCRC with disease progression following prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. This was supported by the ORR of 32% (95% CI: 22, 44), with 63% (41, 81) of response durable for 6 months or longer observed in 74 patients locally confirmed MSI-H or dMMR mCRC who received one or more lines of therapy for metastatic disease containing a fluoropyrimidine and either irinotecan or oxaliplatin. Similar results were observed in the subset of patients with centrally confirmed MSI-H or dMMR colorectal cancer. Responses were also observed in patients whose tumor expressed or did not express PD-L1 and there was no apparent association between the intensity of PD-L1 expression and observed response rate.

Additional supportive evidence is based on the similarity of the results observed in Study CA209142 to those observed in the cohort of patients with previously treated, MSI-H/dMMR mCRC treated with pembrolizumab, another PD-L1 inhibiting antibody, where the ORR was 36% (95% CI:26, 46); 78% of responding patients had response durations of ≥ 6 months. Pembrolizumab was approved under the provisions of 21 CFR 601 Subpart E (accelerated approval) on May 23, 2017 for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or with metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

The toxicity profile of nivolumab is well-characterized in studies supporting previous approvals under BLA 125554. The results of CA209142 did not demonstrate new safety signals; however it is notable that 21% of patients discontinued treatment due to the following adverse reactions: gastritis, diarrhea, increased ALT, acute renal failure, oral mucositis, and a duodenal ulcer. An additional patient discontinued treatment for the adverse event of myocardial infarction that was identified as unrelated to nivolumab.

The results of Study CA209142 demonstrated an ORR that was superior to that achieved with available therapy (1% ORR with regorafenib and 1.5% ORR with tipiracil/trifluridine (TAS-102) in heavily pre-treated patients, with a clinically important durability of response. In addition, while nivolumab carries the risks of immune-mediated adverse reactions in any organ or tissue in the body, given the expected median survival of less than 1 year for this population, the risks are outweighed by the potential benefits of durable responses in approximately one-third of patients.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the conclusion of the clinical review team that based on the favorable risk: benefit assessment in the proposed indication and extensive post-marketing experience with nivolumab, REMS is not required for the safe and effective use of nivolumab in the indicated population.

- Recommendation for other Postmarketing Requirements (PMR) and Commitments (PMC)
  BMS is required to conduct the following PMR to further describe the clinical benefit of nivolumab for this indication. This PMR is required under 21 CFR 601 Subpart E and will provide a more precise estimation of the overall response rate and duration of response in this patient population.

  3243-1 Submit the final report, including datasets, from trials conducted to verify and describe the clinical benefit of nivolumab 240 mg intravenously every two weeks in patients with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer who have progressed following treatment with fluoropyrimidine, oxaliplatin and irinotecan, including at least 150 patients enrolled in BMS-initiated trials. In order to characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

  BMS has also agreed to conduct the following PMCs under 506B to support the approval in a PMA or PMA supplement with appropriate labeling for companion in vitro diagnostic tests for selection of patients with dMMR or MSI-H, colorectal cancers, respectively, for whom nivolumab is indicated. The need for companion diagnostic tests to select these patients was considered essential given the discrepancies between local and central testing for detection of MSI-H and dMMR colorectal cancers.

  3243-2 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry based in vitro diagnostic device that is essential to the

safe and effective use of nivolumab for patients with tumors that are mismatch repair deficient.

3243-3 Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of nivolumab for patients with tumors that are microsatellite instability high.

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/s/

PATRICIA KEEGAN
07/31/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

OFFICER/EMPLOYEE LIST

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

Memorandum

Date: July 24, 2017

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

Subject: ***BLA 125554/S-034 – OPDIVO (nivolumab injection for intravenous injection)***
Officer / Employee List

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

Officer / Employee
Fuller, Barbara
Griffiths, LaShawn
He, Kun
Hughes, Monica L
Keegan, Patricia
Lemery, Steven
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Rodriguez, Lisa
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Senior, Nicholas
Smit, Damiette
Summers, Jeff
Thompson, Susan
Xu, Yuan

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA 351 (a)
Application Number(s)	125554 S-034
Priority or Standard	Priority
Submit Date(s)	2 February 2017
Received Date(s)	2 February 2017
PDUFA Goal Date	2 August 2017
Division / Office	DOP2/OHOP/OND/CDER
Reviewer Name(s)	Damiette Smit
Review Completion Date	6 July 2017
Established Name	Nivolumab
(Proposed) Trade Name	OPDIVO
Therapeutic Class	Programmed death receptor (PD-1) blocking antibody

Applicant	Bristol Myers Squibb
Formulation(s)	Solution
Dosing Regimen	240 mg iv every 2 weeks
Indication(s)	(b) (4)
Intended Population(s)	(b) (4)

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1. Recommendations/Risk Benefit Assessment

1.1. Recommendation on Regulatory Action

This reviewer recommends accelerated approval of nivolumab (Opdivo) as a single agent for the treatment of [redacted] (b) (4) [redacted]. The recommended dosing schedule is 240 mg administered intravenously every 2 weeks until disease progression or unacceptable toxicity. This approval recommendation is contingent upon reaching final agreement on labeling and post marketing commitments and requirements.

The indication after progression following treatment with a fluoropyrimidine, oxaliplatin and irinotecan is based on a subgroup analysis of adults with mismatch repair deficient or microsatellite instability high metastatic colorectal cancer in the single-arm trial CA209142. In 53 patients who had progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan, nivolumab monotherapy resulted in a 28% objective response rate (ORR). The median duration of response was not estimable (range: 2.8+, 22.1+). However, responses observed to date appear durable, with 6 patients (40%) having a duration of response of at least 12 months and 5 patients (33%) having a duration of response of at least 18 months.

The safety profile of nivolumab was acceptable, based on the analysis of all 74 patients with mismatch repair deficient or microsatellite instability high metastatic colorectal cancer treated with nivolumab monotherapy on trial CA209142.

1.2. Risk Benefit Assessment

Background:

Colorectal cancer (CRC) accounts for approximately 50,260 deaths yearly in the United States and is the second highest cause of death due to cancer[1]. Although the 5-year relative survival for localized colorectal cancer is 89.9%, the 5-year relative survival for metastatic colorectal cancer (mCRC) is 13.9%[1]. For patients with mCRC, first- and second-line treatment usually consists of administration of fluorouracil in combination with oxaliplatin or irinotecan and may include monoclonal antibodies, depending on patient and physician preference, location of the tumor (left vs. right colon), and the biomarker profile of the patient's cancer (e.g., an anti-VEFG

pathway drug or if RAS wild-type, an anti-EGFR antibody)[2]. For patients who have progressed on fluorouracil, oxaliplatin and irinotecan, limited treatment options are available. Treatment options for patients with RAS wild-type mCRC include panitumumab and cetuximab. However, for patients with RAS mutations or unknown mutational status, only regorafenib and TAS-102 have been approved by FDA. Response rates to these drugs are low (1% for regorafenib and 1.5% for TAS-102) and, although both have shown a survival benefit, the benefit is modest (median 1.4 months for regorafenib compared to placebo and 1.8 months for TAS-102 compared to best supportive care). Although pembrolizumab was recently approved under the accelerated approval program for treatment of patients with microsatellite instability-high (MSIH) or mismatch repair deficient (dMMR) mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, the FDA has not granted regular approval for any drugs for this indication.

Efficacy:

The efficacy of nivolumab for the treatment of (b) (4) was demonstrated in single-arm study CA209142. Patients with MSIH/dMMR mCRC who had progressed during, after, or were intolerant to at least one line of treatment for metastatic disease (including a fluoropyrimidine, oxaliplatin or irinotecan) were treated with nivolumab 3 mg/kg intravenously every 2 weeks until disease progression or treatment discontinuation. All patients had MSIH/dMMR mCRC as determined by immunohistochemistry (IHC) or polymerase chain reaction (PCR) at a local laboratory.

The primary endpoint for the clinical review of this application was confirmed overall response rate (ORR) as assessed by an independent radiology review committee (IRRC).

The population supporting the indication consisted of 53 adult patients with MSIH-dMMR mCRC as determined by local testing who progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan. Nivolumab produced an ORR of 28% (95% CI: 17, 42) in these patients. Fourteen patients had a partial response and one patient had a complete response. The median DOR was not estimable (range: 2.8+, 22.1+). Fourteen patients (93%) had an ongoing response at the time of submission. Ten patients (67%) had a duration of response of at least 6 months, six patients (40%) had a duration of response of at least 12 months and five patients (33%) had a duration of response of at least 18 months.

In contrast to time-to-event endpoints, which are difficult to interpret in uncontrolled single arm trials, response rate can be measured in single arm trials because, in general, tumors do not decrease in size in the absence of therapy. Although response rate does not directly

measure whether a patient feels better or live longer, improvements in OS and PFS have been observed following nivolumab treatment in other settings with similar response rates. In addition, responses observed following treatment with nivolumab in patients with MSIH/dMMR mCRC appear more durable than responses observed following traditional cytotoxic treatment. Confirmation of durability will be important, however, given that these data are immature.

Safety:

The safety population consisted of all 74 adult patients with MSIH/dMMR mCRC as determined by local testing who progressed following treatment with a fluoropyrimidine, oxaliplatin or irinotecan. The overall safety profile was largely consistent with the safety profile in the USPI or expected in a patient population with mCRC.

Overall Benefit-Risk Assessment for the Recommended Indication:

Patients with refractory MSIH/dMMR mCRC have unmet medical needs. Nivolumab demonstrated meaningful clinical activity, based on ORR and DOR, in patients who progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan. The benefit-risk profile for the approved indication is favorable.

1.3. Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no safety issues identified at this time requiring Risk Evaluation and Mitigations Strategies (REMS).

1.4. Recommendations for Postmarket Requirements and Commitments

1.4.1. Confirmatory trial

This reviewer recommends that BMS conduct a post-marketing requirement in order to verify and describe the effect on ORR and DOR in additional patients with mCRC. The data on DOR submitted in the sBLA were immature and additional data and follow-up are needed in order to determine the durability of the responses to nivolumab. At this time, the specific size of the trial and the duration of follow-up are being negotiated with BMS. This reviewer's recommendation for approval of this BLA is contingent upon reaching agreement on this accelerated approval PMR.

(b) (6)

[redacted] (b) (6)

1.4.2. MSI/MMR testing

The Applicant has agreed to support the development of in vitro companion diagnostic tests for MSIH and dMMR as PMCs. Availability of reproducible IVDs will facilitate the effective use of nivolumab in patients with MSIH or dMMR mCRC.

2. Introduction and Regulatory Background

2.1. Product Information

This is a supplemental BLA for nivolumab for the treatment of [redacted] (b) (4) .

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Nivolumab is supplied as 40mg/ml and 100mg/10ml solution in a single-dose vial.

The Applicant proposed the following supplemental indication for the nivolumab label:

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

- [redacted] (b) (4) This indication is approved under accelerated approval based on overall response rate and [redacted] (b) (4). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2.2. Currently Available Treatments for the Proposed Indication

2.2.1. Colorectal cancer

Colorectal cancer (CRC) accounts for approximately 50,260 deaths yearly in the United States and is the second highest cause of death due to cancer[1]. CRC accounts for 8% of all new cancer cases, with an estimated 135,430 new cases in 2017. Although the 5-year relative survival for localized colorectal cancer is 89.9%, the 5-year relative survival for metastatic colorectal cancer is 13.9%[1].

For patients diagnosed with metastatic colorectal cancer (mCRC), first- and second-line treatment usually consists of administration of fluorouracil in combination with oxaliplatin or irinotecan[2]. Monoclonal antibodies may be added to these regimens, depending on patient and physician preference, location of the tumor (left vs. right colon), and the biomarker profile of the patient's cancer (e.g., an anti-VEFG pathway drug or if RAS wild-type, an anti-EGFR antibody). With the exception of metastatic disease confined to the liver and completely resected, mCRC is generally considered incurable and the aim of therapy is to prolong survival and improve quality of life. The standard of care is to administer chemotherapy in first-line until the disease progresses, recurs, or the toxicity of therapy is deemed intolerable or detrimental to the patient's quality of life. Treatment of metastatic disease is a continuum of care, and if disease progresses during first-line treatment, treatment continues with a different chemotherapy regimen that has not been used before in that particular patient (for example, if a patient received an oxaliplatin-based regimen for first line, an irinotecan-based regimen may be used for the second-line treatment). The following FDA-approved drugs are indicated for the treatment of patients with mCRC who progress after a fluoropyrimidine, oxaliplatin and irinotecan: panitumumab, cetuximab, regorafenib, and TAS-102. In addition, patients who progress after a fluoropyrimidine, oxaliplatin and irinotecan may be treated on a clinical trial or with best supportive care. Table 1 describes the efficacy endpoints evaluated in the clinical trials that supported registration for panitumumab, cetuximab, regorafenib, and TAS-102. Response rates for panitumumab and cetuximab, indicated in patients with (K)RAS wild-type mCRC only, were 9-14%. Response rates for regorafenib and TAS-102 were 1-1.5%.

Table 1: Activity of FDA approved therapy for patients with mCRC after progression on fluoropyrimidine, oxaliplatin and irinotecan

	Panitumumab	Cetuximab	Regorafenib	TAS-102[a]
Indication	RAS WT mCRC after fluoropyrimidine, oxaliplatin and irinotecan	KRAS WT, EGFR expressing mCRC after fluoropyrimidine, oxaliplatin and irinotecan	mCRC after fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF therapy, and anti-EGFR therapy if KRAS WT	mCRC after fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF therapy, and anti-EGFR therapy if KRAS WT
Study	Randomized: panitumumab + BSC vs. BSC	Randomized: cetuximab + BSC vs. BSC	Randomized: regorafenib vs. placebo	Randomized: TAS-102 + BSC vs. placebo + BSC
Overall response rate	31%	9-14%	1%	1.5%
Duration of response (median)	NA	4.2 months	NA	7.4 months
Progression free survival (median)	5.2 months (vs. 1.7 months in the control arm)	NA	2 months (vs. 1.7 months in the control arm)	2 months (vs. 1.7 months in the control arm)
Overall survival (median)	10 months (vs. 6.9 months in the control arm)	8.6 months (vs. 5 months in the control arm)	6.4 months (vs. 5 months in the control arm)	7.1 months (vs. 5.3 months in the control arm)

Source: drugs@FDA (data are based on the registration trial supporting the indication).
NA: not available. BSC: best supportive care.
[a] TAS-102 = tifluridine + tipiracil.

In addition to the studies described in table 1, overall survival for cetuximab vs. panitumumab was assessed in a randomized non-inferiority trial in patients with KRAS exon 2 wild-type mCRC who progressed on a fluoropyrimidine, oxaliplatin and irinotecan[3]. Median overall survival was 10.4 months for patients treated with panitumumab vs. 10 months in patients treated with cetuximab. Response rates across both arms were similar (22% for panitumumab vs. 19.8% for cetuximab). However, per the published report, duration of response in both arms was less than 6 months (3.8 months for panitumumab versus 5.4 months for cetuximab).

2.2.2. MSIH/dMMR colorectal cancer

An estimated 15% of patients with CRC have microsatellite instability (MSIH) or a deficiency in mismatch repair (dMMR)[4]. However, the prevalence appears to be lower (approx. 5%) in patients with metastatic disease[5]. Patients may have germ-line mutations in mismatch repair (MMR) genes (e.g., Lynch syndrome[6]) or sporadic dMMR, either through epigenetic changes[7,8] or through biallellic somatically acquired MMR gene mutations[9]. Loss of function of MRR proteins leads to an accumulation of mistakes in DNA replication, particularly in short sequences of nucleotide bases that are repeated dozens to hundreds of times within the genome (microsatellites), resulting in genetic instability and a high mutational load[10]. The immune microenvironment of MSIH/dMMR CRC contains both activated $CD8^+$ cytotoxic T lymphocytes (CTLs) and activated T-helper 1 (TH1) cells. However, these tumors also selectively upregulate expression of immune checkpoints, including PD-1, PDL-1, CTLA-4, LAG-3 and IDO [11], which may explain why MSIH/dMMR tumors are not naturally eliminated. In patients with stage II/III CRC, presence of MSI/dMMR was associated with reduced 5-year recurrence rates, delayed time to recurrence and fewer distant recurrences compared to microsatellite stable (MSS)/ proficient mismatch repair (pMMR) CRC [12]. However, the prognosis of patients with metastatic MSIH/dMMR CRC appears to be similar or worse to the prognosis of patients with MSS/pMMR mCRC [13]. The NCCN guidelines recommend MMR/MSI testing for patients with a personal history of colon or rectal cancer. For a discussion on MSI/MMR testing, refer to section 2.6.

On 23 May 2017, the FDA approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSIH) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or metastatic, microsatellite instability-high (MSIH) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This approval falls under the FDA's accelerated approval program and was supported by data from single-arm studies (n=90), in which treatment with pembrolizumab resulted in an ORR of 33% (95% CI 23.7%-44.1%). The median duration of response was not reached.

The FDA has not approved any drugs specifically for the treatment of patients with MSIH/dMMR mCRC under the regular approval program. The NCC guidelines recommend nivolumab or pembrolizumab as first-line treatment in patients with MSIH/dMMR mCRC who are not appropriate candidates for intensive therapy, and for second- or third-line treatment in patients with MSIH/dMMR mCRC[2] . These recommendations are based on available literature

and not on the abovementioned approval of pembrolizumab, as this approval occurred after the most recent NCCN guideline revision (13 March 2017).

Reviewer comment:

As the Applicant is requesting accelerated approval in this sBLA, the efficacy of nivolumab will be compared to available therapy. The only therapy specifically approved for patients with MSIH/dMMR mCRC (pembrolizumab) was approved under the accelerated approval program and will therefore not be considered available therapy. Both panitumumab and cetuximab are approved as monotherapy after a fluoropyrimidine, oxaliplatin and irinotecan, but are also approved in combination with chemotherapy for first-line treatment. In addition, these agents are approved in patients with RAS wild-type (panitumumab) and KRAS wild-type, EGFR-expressing (cetuximab) mCRC only. Since patients with MSIH/dMMR mCRC do not necessarily have (K)RAS wild-type cancer, and if they do, are likely to have received panitumumab or cetuximab in an earlier line setting, these agents will not be considered available therapy for the indicated population. Since both regorafenib and TAS-102 are approved for the treatment of patients with mCRC after a fluoropyrimidine, oxaliplatin and irinotecan, and since their use it not restricted to a patient population identified by a (non-MSIH/dMMR) biomarker, these agents will be considered available therapy for the indication population.

2.3. Availability of Proposed Active Ingredient in the United States

Nivolumab is FDA approved for the treatment of patients with:

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.
- BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival.
- Unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival.
- Metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy.

- Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and 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.
- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
- Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who 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.

2.4. Important Safety Issues With Consideration to Related Drugs

The safety profile of nivolumab is well characterized. Similar to other drugs targeting the PD-1 pathway, such as pembrolizumab, or drugs targeting cytotoxic T-lymphocyte antigen (CTLA-4), such as ipilimumab, severe or serious immune-mediated adverse reactions have been observed in patients treated with nivolumab.

2.5. Summary of Presubmission Regulatory Activity Related to Submission

- On 10 January 2014, a new IND was submitted which contained clinical protocol CA209142.
- On 4 February 2014, IND 119381 was allowed to proceed.
- On 11 May 2016, a type C meeting was held between FDA and the Applicant to discuss and obtain FDA feedback on the use of data from Study CA209142, (b) (4) to support a new indication for nivolumab.
- On 28 July 2016, FDA issued an Agreed iPSP for nivolumab, alone or in combination with ipilimumab, for the treatment of (b) (4)

- On 16 December 2016, a pre-sBLA meeting was held between FDA and BMS to discuss the results from study CA209142 intended to support this supplement.

For protocol amendments, including dates of submission to FDA, refer to section 5.3.3.

2.6. Other Relevant Background Information: MSI/MMR testing

Both immunohistochemistry (IHC) and polymerase chain reaction (PCR) testing is available in the United States. There is currently no FDA-approved in vitro diagnostic test available and different laboratory developed tests (LDTs) have been used to date. Patients with MSIH/dMMR mCRC enrolled on study CA209142 (used to support the sBLA) were locally tested with either IHC or PCR. If positive, patients were enrolled on the study. MSIH status was then confirmed with central PCR testing.

IHC testing for mismatch repair assesses four MMR proteins: MLH1, MSH2, MSH6, and PMS2. If at least 1 marker shows loss of the protein, the tumor is designated as dMMR. Different PCR tests for MSI exist and generally involve testing for three to seven tumor microsatellite loci. The Bethesda panel interrogates five microsatellite loci and was recommended by the 1997 National Cancer Institute-sponsored MSI workshop[4]. This panel evaluates three dinucleotide (D5S346, D2S123, D17S250) and two mononucleotide repeats (BAT25 and BAT26). If 2 or more markers show instability, the tumor is designated as MSIH. However, not all centers use the Bethesda panel, with some centers evaluating only mononucleotide repeats and some centers evaluating additional loci.

Although variations between IHC and PCR may exist, in general, literature reports describe high concordance (e.g., > 95%) when the same laboratory or group assesses both IHC and PCR[14]. However, concordance across laboratories may be lower. Reasons for false positive local PCR or IHC testing include: laboratory error, misinterpretation of results, and assay failure due to tissue samples lacking normal stromal or immune cells that serve as internal positive controls. In addition, IHC testing may be falsely positive due to markers decreasing in stain intensity after chemoradiation[15], as well as the presence of redundant pathways. For example, some patients with MSH6 germline mutations are microsatellite stable when assessed via PCR due to a functional redundancy in the MMR system[16]. Reasons for false negative central PCR testing include: inadequate tissue, laboratory error, or misinterpretation of results. In addition to the abovementioned reasons for discordance, different samples may have different MSI/MMR testing results due to intra-tumor heterogeneity or due to different sites of biopsy (e.g., primary tumor vs. metastasis).

3. Ethics and Good Clinical Practices

3.1. Submission Quality and Integrity

The submission was of adequate quality for the clinical review. Data in the datasets were determined to be acceptable for review through an audit of the case report forms (CRFs) versus the datasets in approximately 10% of patients.

During this audit, inconsistencies were identified between adverse event narratives in SAE reports and terms that were listed in the CRFs (i.e., on adverse event pages) that ultimately were included in the datasets. As such, multiple serious adverse events, including at least one potential serious immune-related adverse event, were not accurately captured in the dataset.

For example, the following information was described in SAE CRF pages and not in the dataset:

- Patient (b) (6) SAE1: the event description states that the patient had fever due to *Klebsiella* pneumonia. However, *Klebsiella* pneumonia was not listed as an SAE in the dataset (the SAE term was "fever").
- Patient (b) (6) SAE2: the event description states that the patient presented with diarrhea, abdominal pain and vomiting, and then had a colonoscopy that found colitis. However, colitis was not listed as a SAE (the SAE terms were "diarrhea," "vomiting," and "worsening abdominal pain").

Given that the safety profile of nivolumab has been well characterized, it is not expected that these inaccuracies in the safety database would affect the overall safety profile.

3.2. Compliance with Good Clinical Practices

The interim clinical study report for the study included in this application (CA209142) contained a statement that the study was conducted in accordance with Good Clinical Practice, as defined by the International Council on Harmonization and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (section 4.1 of interim clinical study report).

An Office of Scientific Investigations (OSI) consult was requested for clinical inspection of (b) (4), which conducted the independent review of radiographs.

3.3. Financial Disclosures

In accordance with 21 CFR 54, the Applicant submitted a list of trial investigators for study CA209142 (module 1.3.4, Table 1) and independent radiological reviewers ((b) (4) ; module 1.3.4, Table 2). The Applicant also provided financial disclosures (FDA form 3454) for study CA209142 and for the independent radiological reviewers. No investigator or radiological reviewer held financial interests or arrangements requiring disclosure per the criteria described on Form 3454 (also refer to section 9.4).

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1. Chemistry Manufacturing and Controls

See the FDA Chemistry Review from the original BLA submission. There were no significant safety or efficacy issues identified related to Chemistry, Manufacturing, and Controls (CMC).

4.2. Clinical Microbiology

See the FDA Microbiology Review from the original BLA submission. There were no significant safety or efficacy issues identified related to product quality from a microbiology standpoint.

4.3. Preclinical Pharmacology/Toxicology

See the FDA Pharmacology/Toxicology Review from the original BLA submission. There were no significant safety or efficacy issues identified related to preclinical pharmacology or toxicity studies.

4.4. Clinical Pharmacology

The Applicant proposes to use a flat dose of 240mg instead of the 3mg/kg dose used in study CA209142. See the FDA Clinical Pharmacology Review from this sBLA for full details.

4.4.1. Mechanism of Action

Nivolumab is a humanized monoclonal antibody of the IgG4/kappa isotype that binds to PD-1 and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Activation of the PD-1 pathway may inhibit the immune response and this may be one of the mechanisms that tumors use to avoid immune rejection.

MSIH/dMMR tumors are characterized by a high mutational burden[10] and the immune microenvironment of these tumors is characterized by the presence of activated CD8+ CTLs and TH1 cells, as well as the upregulation of immune checkpoints, including PD-1[11] (refer to section 2.2.2). Therefore, interruption of the PD-1 pathway has the potential to facilitate immune rejection of the tumor.

4.4.2. Pharmacodynamics

Not applicable for this sBLA.

4.4.3. Pharmacokinetics

See the FDA Pharmacology Review from the original BLA submission for full details.

4.5. Center for Devices and Radiological Health

See FDA CDRH Review for a discussion of MSIH/dMMR testing used during the conduct of study CA209142. In addition, refer to sections 2.6, 6.5, and 6.9.3.

5. Sources of Clinical Data

5.1. Tables of Studies/Clinical Trials

The primary evidence to support to this supplement application is derived from data from study CA209142:

- Trial Design: single arm, efficacy study.
- Regimen, schedule, and route: nivolumab 3 mg/kg intravenously every two weeks.
- Study endpoints:

  - Primary: overall response rate (ORR) by investigator.
  - Secondary: ORR by independent radiology review committee (IRRC).

- Number of patients treated: 74.
- Study population: patients with recurrent or metastatic colorectal cancer with microsatellite instability- high tumors who have progressed on, or have been intolerant to ≥1 line of treatment, which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan.
- Number of centers and countries: 25 centers in 8 countries.

5.2. Review Strategy

The clinical review included the following:

- Review of the current literature on the epidemiology and treatment of metastatic colorectal cancer.
- Review of the current literature on microsatellite instability and mismatch repair testing for colorectal cancer.
- Review of Applicant study CA209142 including interim clinical study report, protocols, protocol amendments and selected datasets.
- Review and assessment of Applicant analysis of nivolumab efficacy and safety, for evaluation of Applicant's claims.
- Review of datasets and SAS programming algorithms submitted by the Applicant.
- Use of the datasets to determine the baseline patient characteristics, response rate, and adverse event profile.
- Review of patient narratives of serious adverse events, deaths, and immune-mediated AEs.
- Review of meeting minutes conducted during drug development.
- Assessment of the Module 2 summaries including the Summary of Clinical Safety.
- Evaluation of reviews conducted by other FDA disciplines including Biostatistics.
- Review of consultation reports from the Office of Scientific Investigations.

- Requests for additional information from the Applicant and review of Applicant responses.
- Formulation of the benefit-risk analysis and recommendations.
- Review and evaluation of proposed labeling.

5.3. Discussion of Individual Studies/Clinical Trials

The primary evidence to support to this application is derived from data from study CA209142.

5.3.1. Study Design

CA209142 is an open-label, multi-center study of nivolumab alone or in combination with ipilimumab in adults with recurrent or metastatic colorectal cancer. The study consists of the following four cohorts: nivolumab monotherapy in patients with MSIH/dMMR mCRC, nivolumab plus ipilimumab in patients with non-MSIH mCRC, nivolumab plus ipilimumab in patients with MSIH mCRC, and nivolumab in combination with ipilimumab and cobimetinib in patients with non-MSIH mCRC. The study is ongoing. Only data from patients with MSIH/dMMR mCRC treated with nivolumab in the monotherapy cohort will be included in this review. This cohort includes patients who have MSIH/dMMR mCRC based on standard (local) diagnostic testing using either an immunohistochemistry (IHC) or polymerase chain reaction (PCR) test. All patients had their MSIH status prospectively confirmed by a central laboratory using a PCR test (for MSI testing procedures, see section 5.3.2).

Proposed sample size: 48 treated patients.

Final sample size: 53 patients with centrally confirmed MSIH mCRC (74 with locally tested MSIH/dMMR mCRC).

Study initiation date: 12 March 2014.

Data cutoff used for original sBLA submission: 19 September 2016.

Data cutoff used for Ad Hoc Efficacy Report (requested by FDA during pre-sBLA meeting): 6 February 2017.

The primary objective of the study is ORR as assessed by the investigator. The secondary objective is ORR as assessed by an independent radiology review committee (IRRC). Exploratory objectives were: safety and tolerability, to estimate PFS and OS, to characterize the pharmacokinetics, pharmacodynamics and immunogenicity of nivolumab monotherapy, to

investigate the associated between biomarkers in the peripheral blood and tumor tissue with safety and efficacy, to characterize the discordance rate between local and central MSI testing, and to evaluate health related quality of life (EORTC QLQ-C30 questionnaire) and patient-reported general health status (EQ-5D questionnaire).

Key inclusion criteria were (1) histologically confirmed recurrent or metastatic colorectal cancer, (2) progression during, after, or intolerant to at least one line of treatment for metastatic disease which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan (patients who refused chemotherapy were allowed to enroll providing their refusal was thoroughly documented and they were informed by the investigator about their treatment options), (3) microsatellite instability expression detected by an accredited laboratory per local regulations (by IHC or PCR) (4) measurable disease per RECIST v1.1., (5) ECOG PS 0-1, and (6) 18 years or older.

Key exclusion criteria were (1) brain and leptomeningeal metastases (patients with treated brain metastases were eligible if there was no evidence of progression for at least 8 weeks and patient required less than 10mg/day of prednisone equivalents for at least 2 weeks prior to study drug administration) (2) prior treatment with agents targeting T-cell co-stimulation or immune checkpoint pathways, (3) autoimmune disease, and (4) conditions requiring systemic treatment with corticosteroids or other immunesuppressive medications within 14 days of study drug administration.

Study treatment:

- Nivolumab was administered at 3 mg/kg intravenously (IV) over 60 minutes every 2 weeks until progression of disease or treatment discontinuation.
- Treatment beyond investigator-assessed RECIST 1.1-defined progression was permitted if the patient experienced investigator-assessed clinical benefit, the patient did not have rapid disease progression and had a stable performance status, the patient was tolerating the study treatment and the patient provided a written informed consent. Patients treated through progression discontinued study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression.
- Dose reductions were not permitted, but dose delay was permitted for toxicity for up to 6 weeks from the last dose.

- Except to treat a drug-related adverse event, prohibited concurrent medications included immunosuppressive agents, systemic corticosteroids equivalent to > 10 mg prednisone daily, and any concurrent antineoplastic therapy.

Assessments:

- Efficacy assessments occurred at baseline, then every 6 weeks for the first 24 weeks, then every 12 weeks. Confirmation of PR and/or CR was required after at least 4 weeks from the initial scan reporting response. Confirmation of progression was not required. Patients who discontinued treatment for reasons other than tumor progression continued to have tumor imaging assessments at the schedule described above until disease progression or the initiation of systemic cancer treatment outside of the study.
- The following information was collected on all study patients at screening/baseline:
    - Medical history and prior medications.
    - MSIH/dMMR testing results (as assessed by local laboratory; refer to section 5.3.2).
    - KRAS and BRAF mutation status.
    - Recorded history of Lynch syndrome.
- A baseline ECG was performed.
- Tumor tissue was collected at baseline for central MSI testing and for exploratory biomarker testing.
- The following laboratory tests were collected at baseline: CBC with differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4 and Free T3, pregnancy test, hepatitis B surface antigen, hepatitis C antibody or RNA.
- The following laboratory tests were collected during the study: CBC with differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4 and Free T3 were collected on Day 1 of Cycle 1, every cycle until week 23 and then every other cycle. A pregnancy test was done every 4 weeks.
- Quality of life assessments (with EORTC QLQ-C30 and EQ-5D questionnaires) occurred before the first dose and every 6 weeks thereafter.

- The following was collected at follow-up visit 1 and 2: ECG, laboratory testing (CBC with differential and platelet count, LFTs, BUN, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4 and Free T3, and pregnancy test). Patients were followed for a minimum of 100 days after the last dose. After completion of the first two follow-up visits, patients were/will be followed every 3 months for survival for up to 3 years.

5.3.2. MMR/MSI testing procedures

The protocol specified that all local testing for MMR/MSI should have been performed with one of the following methods:

Microsatellite instability testing (PCR method):

- Reference (Bethesda) panel: BAT25, BAT26, D5S346, D2S123, D17S250
- Alternative loci: BAT40, BAT34C4, TGF-β-RII, ACTC (635/636)
- If 5 loci tested (reference panel):
    - MSIH: ≥ 2 markers with instability
    - MSI-L: 1 marker with instability
    - MSS or MSI-L: 0 markers with instability
- If > 5 loci tested (reference panel plus alternative loci):
    - MSIH: ≥ 30-40% markers with instability
    - MSI-L: < 30-40% markers with instability
    - MSS or MSI-L: 0 markers with instability
- In the case of 1 PCR amplification failure:
    - If ≥3 markers of 4: MSIH
    - If 1 marker of 4: re-amplify

Mismatch repair deficiency testing (IHC method):

- Panel: hMSIH2, hMLH1, hMSH6, hPMS2
- MSIH: ≥1 markers with instability
- MSS: 0 markers with instability

- MSI-L: not evaluable with this technique

5.3.3. Protocol Amendments

The original protocol was dated 18 November 2013. The Applicant submitted 6 protocol amendments prior to the data cutoff of 19 September 2016. The following are considered major amendments:

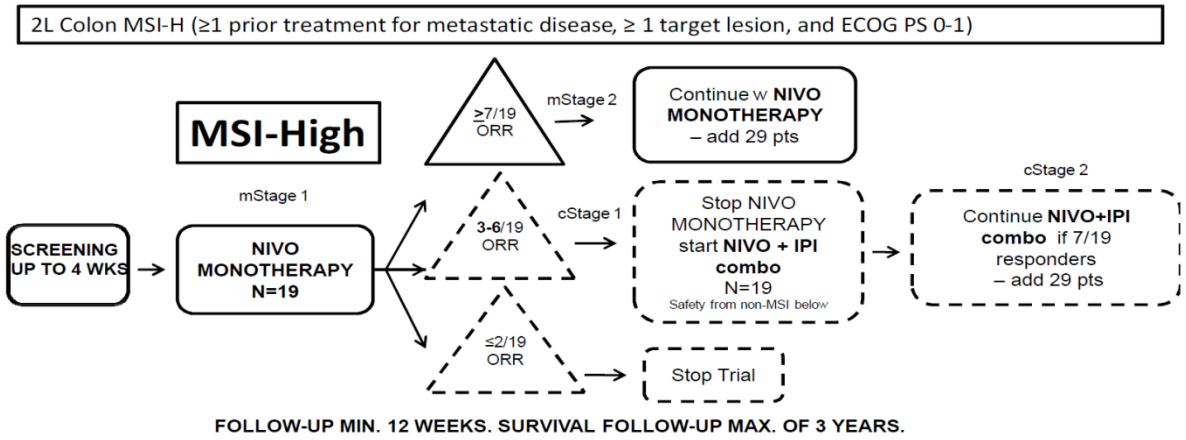
- Amendment 1 (6 February 2014, in response to comments by health authorities): the eligibility criteria regarding prior treatment for the MSIH cohort were clarified. Exclusion criteria regarding prior treatment, hepatitis infection, and prior toxicities were clarified.
- Amendment 3 (23 April 2014): nivolumab adverse event algorithms were updated for consistency across the nivolumab development program. In addition, BRAF status documentation at screening was implemented.
- Amendment 4 (10 June 2015): MSI-testing panel descriptions, classification of MSI status and sample prioritization were appended to the protocol.
- Amendment 5 (10 August 2016): MSI testing requirements were clarified, adverse event algorithms were revised.

5.3.4. Statistical Analysis Plan

A Simon optimal two-stage design was used to test the null hypothesis that the true ORR is ≤30%.

In the first stage (mStage 1), 19 patients were to be treated with nivolumab monotherapy. If there were 2 or fewer responses in these first 19 treated patients, the protocol was to be closed to further enrollment. If there were more than 2 but fewer than 7 responses in the first 19 treated patients, accrual to the monotherapy arm was to be stopped and the combination arm was to be opened for accrual. Otherwise, if there were 7 or more responses in the first 19 treated patients, approximately 29 additional patients would be accrued to the monotherapy arm (mStage 2) to target a total of 48 treated patients (see figure 1). Patients whose repeat (central) testing did not confirm MSIH status were to be replaced in order to obtain the required number of patients in each stage of the Simon design.

Figure 1: Study design (MSIH cohort)



Source: CA209142 study protocol

The null hypothesis was to be rejected if 20 or more responses are observed in 48 treated patients. This design yields a one-sided type I error rate of 5% and power of 90% when the true response rate is 52%.

5.3.5. Radiology Charter

The Applicant contracted with [redacted] (b) (4), for an independent radiology review charter. During the independent radiology review, radiographic exams were evaluated using RECIST v. 1.1 criteria and the Applicant was provided with an assessment of tumor response and progression. [redacted] (b) (4) also provided the Time Point Response (TPR), the confirmed Best Response, the Date of Progression, and the Date of First Response for all patients enrolled in the CA209142 MSIH monotherapy cohort.

[redacted] (b) (4) utilized a [redacted] (b) (4) digital read application which allowed for multiple sessions during the radiology review, as summarized below:

- Session 1: Screening scans were provided to independent reviewers for identification of disease to be followed throughout the study.
- Session 2: On study time points were presented to independent reviewers sequentially. All lesions identified at screening were evaluated during Session 2.
- Session 3: All time points were presented to independent reviewers, who were provided the opportunity to correct or adjust any previous assessments.

- Session 4: Following completion of Session 3, adjudication may be performed, as required.

Radiology readers were blinded to the following: patient demographics per GCP and HIPAA requirements, treatment arm, site assessment of response, site choice of target and non-target lesions and the identification of new lesions, clinical history, and read number 1 (or read number 2) results. Readers were also restricted from communicating directly with study sites.

The adjudication variables for this study were: Best Response and the Date of Progression. Adjudication was performed by a physician who was not involved in the primary radiology review and who was blinded to the identity of the two (2) primary readers. The adjudicating physician reviewed the images, annotation files, and the results of read number 1 and read number 2. The adjudicator could use their own measurements to verify those made by the primary readers, and could choose the read that he or she believes most accurately represents Best Response and the Date of Progression. In the event the adjudicator does not agree with either of the primary reads, the case was sent for a formal review.

6. Review of Efficacy

Efficacy Summary: refer to section 1.2.

6.1. Indication

Proposed indication: (b) (4)

Recommended indication: (b) (4)

6.2. Methods

Efficacy is based on single-arm clinical trial data in adults with MSIH/dMMR mCRC who progressed after treatment with fluoropyrimidine, oxaliplatin *or* irinotecan. The primary endpoint for review of this application is confirmed ORR by RECIST 1.1 as assessed by

independent radiology review committee (IRRC). The secondary endpoint is confirmed ORR by RECIST 1.1 as assessed by the investigator.

The Applicant originally submitted efficacy data based on a data cutoff of 19 September 2016. However, as agreed upon during the pre-sBLA meeting (refer to section 2.5), the Applicant submitted an ad hoc efficacy report (supported by revised datasets) with a data cutoff of 6 February 2017 in order to provide additional duration of response data. All efficacy data below are based on the data cutoff of 6 February 2017, unless otherwise stated. In addition, all response assessments are based on confirmed responses as per IRC assessment using RECIST 1.1, unless otherwise stated.

Definition of efficacy population

The Applicant pre-specified the efficacy population in the protocol as those patients with MSIH mCRC based on standard diagnostic testing as documented in the patient's medical history and *prospectively confirmed* in the current study by repeat testing using a PCR test. A total of 74 patients were determined to have MSIH/dMMR mCRC, but only 53 patients had their MSIH status confirmed by central laboratory. As local MSI/MMR testing for CRC is the current standard of care in the United States and due to this reviewer's concerns regarding possible false negative central testing results in several patients (refer to section 6.5), the primary efficacy population for this review will consist of all 74 patients who underwent local MSI/MMR testing.

Efficacy population to support the proposed indication

As the Applicant has requested that this sBLA is reviewed under FDA's Accelerated Approval Program and thereby has to show that nivolumab has a meaningful advantage over available therapy, the Applicant proposes to use nivolumab in patients who have progressed after treatment with a fluoropyrimidine, oxaliplatin *and* irinotecan.

6.3. Demographics

Demographics and disease characteristics of patients are described in table 2. The majority of patients were white. The median age of patients with MSIH/dMMR mCRC (53) was lower than the median age of patients with CRC in an unselected patient population with colorectal cancer in the United States (67) [1]. As 27 patients (36%) had a history of lynch syndrome, this *may*, in part, be related to the younger age in which patients with Lynch syndrome are diagnosed with mCRC. The majority of patients were white (88%) and were treated in the United States, Canada and Europe (95%). Slightly more patients with an ECOG performance status of 1 were

enrolled (53%) than with an ECOG performance status of 0 (43%). One patient with an ECOG performance status of 3 was enrolled (protocol deviation; refer to section 6.6).

In addition to demographic data, table 2 provides information on the percentage of patients with a known history of Lynch syndrome, and with KRAS and BRAF mutations (NRAS data were not collected). It also includes results of PD-L1 staining on a baseline tumor sample. The Applicant provided data regarding various cutoff levels for staining (≥1%, ≥5% and ≥10%). Of note, nivolumab has not been approved for any indication with a restriction based on PD-L1 staining.

Table 2: Demographics and baseline characteristics in patients with MSIH/dMMR mCRC by local testing

		Nivolumab (N=74) n (%)
Age	Median (range)	53 (26,79)
	≥ 65 years	17 (23)
Sex	Male	44 (59)
	Female	30 (41)
Race	White	65 (88)
	Black	7 (9.5)
	Other	2 (2.7)
Geographical region[b]	Europe	39 (53)
	United States/Canada	31 (42)
	Rest of world	4 (5.4)
ECOG performance status	0	32 (43)
	1	41 (55)
	3	1 (1.4)[a]
KRAS	Mutant	26 (35)
	Wild Type	44 (59)
BRAF	Mutant	12 (16)
	Wild type	50 (68)
Lynch syndrome	Yes	27 (36)
PD-L1	Quantifiable	66 (89)
	Positive using 1% cutoff	21 (32)
	Positive using 5% cutoff	11 (17)
	Positive using 10% cutoff	6 (9.1)
Central MSI testing result	MSIH	53 (72)
	Non-MSIH	14 (19)
	Not reported	7 (9.5)

Source: FDA analysis.
[a] Enrollment of a patient with ECOG 3 was a protocol violation. Refer to section 6.6.
[b] Patients were enrolled across the following countries: U.S. 30, Canada 1, Australia 4, Spain 2, Belgium 6, France 13, Ireland 5, and Italy 13.

As determined by IRRC, seventy-three patients (99%) had at least one lesion at baseline. The most common sites of lesions were: liver (52.7%), lung (28.4%) and peritoneum (27%). Seventy-one patients (95.9%) had at least one target lesion. The median sum of reference diameters of target lesions was 85 mm (source: interim clinical study report, table s.3.7a).

Prior therapy of patients in the efficacy population is summarized in table 3. Twelve patients (16%) had received 0-1 lines of therapy (one patient had refused first-line therapy and 11 had received one line of therapy). Thirty-four patients (46%) had received 0-2 lines of therapy and 40 patients (54%) had received 3 or more lines of therapy. Sixty-nine patients (93%) received prior therapy for metastatic disease and 37 patients (50%) received therapy for localized and metastatic disease. Four patients (5.4%) received treatment for localized disease only. Almost all patients had received a fluoropyrimidine (99%) with the majority having received oxaliplatin (96%), irinotecan (74%) and a VEGF inhibitor (77%). Fewer patients received EGFR inhibitors (42%). However, these agents are indicated in (K)RAS wild-type mCRC only. Twelve patients (15%) had received regorafenib and 11 patients had received other treatments, which included hyperthermic intraperitoneal chemotherapy (HIPEC), nab-paclitaxel or various investigational agents (dabrafenib, trametinib, vemurafenib, LGX818, WNT974 and BBI608). All patients had prior surgery related to their cancer and 27 patients (37%) had prior radiotherapy.

Fifty-three patients (72%) had received a fluoropyrimidine, oxaliplatin, and irinotecan as prior therapy. This is the patient population that the Applicant proposes for the indication of this sBLA.

Table 3. Prior anti-cancer therapy of patients with MSIH/dMMR mCRC by local testing

	Nivolumab (N=74) n (%)
Lines of prior therapy [a]	
≤1	12 (16)
2	22 (30)
≥3	40 (54)
Setting of prior therapy [a]	
(Neo) adjuvant only	4 (5.4)
Metastatic	69 (93)
Both	37 (50)
Type of prior therapy	
Fluorouracil and/or capecitabine	73 (99)
Oxaliplatin	71 (96)
Irinotecan	55 (74)
VEGF inhibitors[b]	57 (77)
EGFR inhibitors[c]	31 (42)
Regorafenib	12 (16)
Other	11 (15)
Prior fluoropyrimidine, irinotecan and oxaliplatin	53 (72)

Source: FDA analysis.
[a] One patient did not receive prior therapy.
[b] Bevacizumab and/or aflibercept, c) cetuximab and/or panitumumab.

Reviewer comment:

The demographic, baseline disease characteristic data and prior therapy data were reviewed and are consistent with the patient population expected in a patient population with MSIH/dMMR mCRC. This was a heavily pretreated population, with the majority of patients (84%) having received at least 2 lines of prior therapy. In addition, 72% of patients had received prior fluoropyrimidine, oxaliplatin and irinotecan, which supports the use of this population for the proposed indication.

6.4. Patient Treatment and Disposition

The enrollment period lasted approximately 24 months (March 2014 to March 2016). A total of 74 patients with MSIH/dMMR mCRC as determined by local testing were treated with nivolumab. The median number of cycles of nivolumab was 22.5 and median follow-up was 12 months. At the data cutoff, 36 patients (49%) remained on treatment. The most common reason for discontinuation was disease progression (table 4). Adverse events led to discontinuation in 7 patients. Adverse events related to the study drug that led to discontinuation were gastritis, diarrhea, ALT increase, acute renal failure and oral mucositis. One patient discontinued nivolumab due to a duodenal ulcer and one patient discontinued nivolumab due to an adverse event unrelated to the study drug (myocardial infarction).

Table 4. Patient disposition

	Nivolumab n (%)
Patients treated	74 (100)
Patients continuing in the treatment period [a]	36 (49)
Reason for not continuing in the treatment period:	
Disease progression	27 (36) [b]
Study drug toxicity	6 (8.1)
Adverse event unrelated to study drug	1 (1.4)
Patient request to discontinue study treatment	1 (1.4)
Patient withdrew consent	1 (1.4)
Maximum clinical benefit	1 (1.4)
Other[c]	1 (1.4)
Treatment	
Number of cycles median (range)	22.5 (1,66)
Follow-up (months) median (range)	12 (0.3,31.7)

Source: FDA analysis.
[a] This excludes 19 patients who were treated beyond progression.
[b] One patient who was described having discontinued due to disease progression in the ADSL dataset was described in the ADAE dataset as discontinuation due to abdominal pain/vomiting (with colitis found on biopsy).
[c] Reason for discontinuation: travel distance.

Reviewer comment:

The number of patients discontinuing treatment for adverse events does not exceed the number expected based on other studies with nivolumab. For a detailed discussion of adverse events resulting in discontinuation, refer to section 7.3.3. For a detailed discussion of patients treated beyond progression, refer to section 6.13.1.

6.5. MSI/MMR testing

Table 5 summarizes local and central testing results of the efficacy population. All patients with MSIH/dMMR mCRC as determined by local testing using either PCR or IHC were eligible for the study. For each patient, a tumor sample was collected at study entry and sent to a central laboratory for confirmatory testing using PCR. For panel descriptions, refer to section 5.3.2. Forty patients (54%) had local testing by IHC, 22 patients (30%) by PCR, and 12 (16%) by both IHC and PCR. Fifty-three patients (72%) had their MSIH status confirmed by central testing. For seven patients (9.5%), central testing was not possible due to inadequate tumor sample being available for testing or nonviable tissue. Fourteen patients (19%) were determined to be MSS by central testing.

Table 5: Local vs. central MSI/MMR testing

		Local test (N=74)	Central test MSIH (N=53)	Central test MSS (N=14)	Central not reported (N=7)
PCR	n (%)	22 (30)	17 (32)	2 (14)	3 (43)
IHC	n (%)	40 (54)	27 (51)	10 (71)	3 (43)
PCR/IHC	n (%)	12 (16)	9 (17)	2 (14)	1 (14)

Source: FDA analysis.

6.5.1. Discussion of patients who had discordance in local vs. central testing

The Applicant provided additional information regarding the discordance between local and central testing, both at the time of sBLA submission (supplemental efficacy report, dated 19 January 2017) and after an information request was sent by FDA (response to FDA information request 25 May 2017). In this section, the fourteen patients who were determined to be MSS using central PCR testing will be discussed in more detail. For a general discussion on local vs. central MSIH testing methods and reasons for false positive and false negative results, refer to section 2.6.

Local testing for the fourteen patients with discrepant testing results was performed at multiple investigational sites in multiple countries and with various vendors providing testing material.

This makes it unlikely that there was a single cause resulting in false positive local MSIH/dMMR determination. Local testing results were obtained through medical records with the majority of patients having a local testing date >300 days before the treatment date on study CA209142.

Two patients who had MSS mCRC by central testing had two local testing methods (IHC and PCR). The first patient had 2 different samples evaluated by the local vs. central laboratories: one sample was MSIH by local testing; the other (from a lymph node metastasis) was MSS by central testing. The second patient had discordant results by local testing (MSS by IHC and MSIH by PCR), with central testing showing MSS. It is not known whether or not this patient had different samples sent to local vs. central laboratory or to the local laboratory performing IHC and the local laboratory performing PCR.

The Applicant provided tumor DNA concentrations for all 14 patient samples tested at the central laboratory. Tumor DNA concentrations varied greatly, from 0.5799 ng/µl to 160.7 ng/µl. However, the three patients with the lowest DNA concentrations had a partial response or stable disease, making it unlikely that the central test was false negative due to insufficient DNA.

The following information supports the possibility that central testing was false negative (at least in several cases):

- Five out of the fourteen patients (36%) with MSS mCRC by central testing had a history of Lynch syndrome. Although it is unknown how these patients were diagnosed with Lynch syndrome (family history and/or testing for germline MMR mutations), the strong correlation of Lynch syndrome with mismatch repair deficiency makes it unlikely that these patients had MSS mCRC.
- Three patients (21%) with MSS mCRC by central testing (but MSIH or dMMR by local testing) had a partial response and another 3 patients with MSS mCRC by central testing (21%) had stable disease. Although it is possible that patients with MSS mCRC could respond to nivolumab through mechanisms other than high antigen load due to mismatch repair deficiency, it is unlikely that such a high number would respond or have disease stabilization.

Reviewer comment:

The data regarding discordant cases submitted by the Applicant was reviewed. Although no direct explanations were identified for either false positive local testing or false negative central testing, the fact that several patients with MSS mCRC by central testing had a history of Lynch

syndrome and that six (42%) patients with MSS mCRC by central testing had a partial response or stable disease, makes it likely that false negative central testing occurred in at least several cases. Given that local MSI/MMR testing is the current standard of care in the United States for patients with CRC, this finding supports including all patients with MSIH/dMMR mCRC by local testing in the efficacy population instead of only those patients who had MSIH mCRC by central testing (refer to section 6.2 and 6.9.3).

6.6. Protocol deviations

Protocol deviations described for study CA209142 are based on the data cutoff of 19 September 2016.

Relevant protocol deviations were defined as significant protocol deviations that could potentially affect the interpretability of trial results. These were pre-specified in the statistical analysis plan as follows:

- Eligibility/at Entrance:
    - Patients without recurrent or metastatic MSIH colon cancer.
    - Patients with measurable disease per RECIST 1.1 criteria at baseline.
    - Patients with a baseline ECOG performance status > 1.
    - Prohibited anti-cancer therapy.
- On-study:
    - Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, surgical resection of lesions, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer).

Relevant protocol deviations were reported in 3 (4%) patients. Two patients had a relevant protocol deviation at study entry (eligibility) and one patient had a relevant protocol deviation while on treatment (table 6).

Table 6: Protocol deviations

Category of relevant protocol deviation	Study ID	Specific Protocol Deviation	Response
Eligibility	CA209142-(b) (6)	Baseline ECOG performance status > 1 (ECOG PS 3)	Progressive disease
	CA209142-(b) (6)	Patient did not have measurable disease at baseline	Stable disease
On-treatment	CA209142-(b) (6)	Patient Receiving Concurrent Anti-Cancer Therapy (intra-ocular bevacizumab for a non-cancer indication)	Partial response

Source: Interim Clinical Study Report section 4.3.

Reviewer comment:

Because of the small percentage of patients involved, the reported protocol deviations are unlikely to substantially affect the efficacy outcomes.

6.7. Analysis of the Primary Endpoint

The primary endpoint for the clinical review of this application is confirmed ORR by RECIST 1.1 as assessed by independent radiology review committee (IRRC) in patients with MSIH/dMMR mCRC by local testing (n=74).

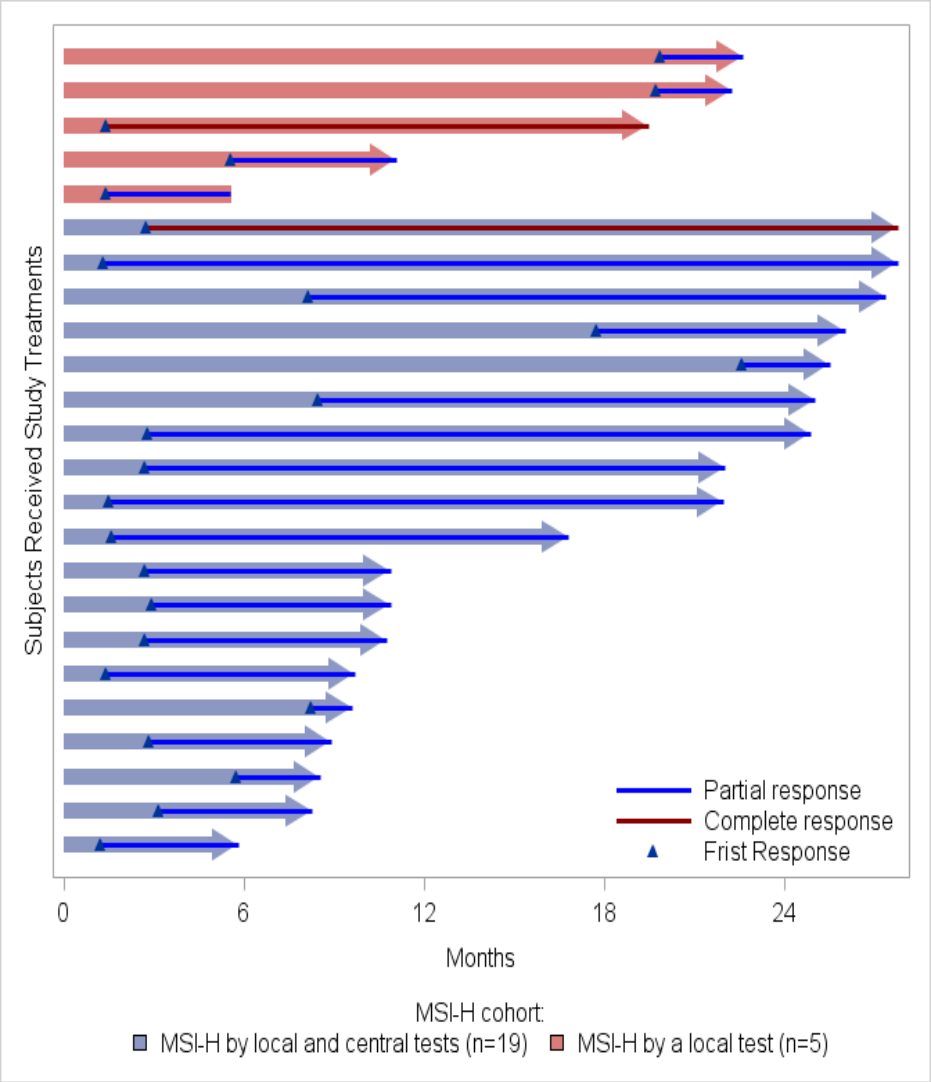
As shown in the table 7, the IRRC-assessed ORR was 32% in study CA209142. Two patients (2.7%) had a complete response and 22 patients (30%) had a partial response. The median time to response was 2.8 months and the longest time to response was 22.6 months. As 19 responders (79%) were still receiving nivolumab at the time of the data cutoff, the median duration of response was not estimable. However, 63% of patients had a response duration of ≥ 6 months, 38% had a response duration of ≥ 12 months, 29% had a response duration of ≥ 18 months, and 8.3% had a response duration of ≥24 months. Figure 2 shows the duration of follow-up and duration of response for all responders.

Table 7: Response assessment per IRRC for all patients and those patients who progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan

		MSIH/dMMR mCRC by local testing	
		All patients (N=74)	**Prior fluoropyrimidine, oxaliplatin and irinotecan (N=53)**
Objective response rate	n (%) 95% CI	24 (32) (22, 44)	15 (28) (17,42)
Complete response	n (%) 95% CI	2 (2.7) (0.3, 9.4)	1 (1.9) (0.05, 10)
Partial response	n (%) 95% CI	22 (30) (20, 42)	14 (26) (15,40)
Stable disease	n (%)	25 (34)	16 (30)
Progressive disease	n (%)	21 (28)	18 (34)
Not evaluable	n (%)	4 (5.4)	4 (7.5)
Time to response (months)	Median Range	2.8 (1.2, 22.6)	2.9 (1.2, 22.6)
Patients with ongoing response	n (%)	20 (83)	14 (93)
Responders still on nivolumab	n (%)	19 (79)	13 (87)
Duration of response (months)	Median Range	Not estimable (1.4+, 26.5+)	Not estimable (2.8+, 22.1+)
Patients with duration of response of at least: n (%)	≥3 months ≥6 months ≥9 months ≥12 months ≥18 months ≥24 months	19 (79) 15 (63) 9 (38) 9 (38) 7 (29) 2 (8.3)	12 (80) 10 (67) 6 (40) 6 (40) 5 (33) 0

Source: FDA analysis.

Figure 2: Duration of follow-up and duration of response for responders

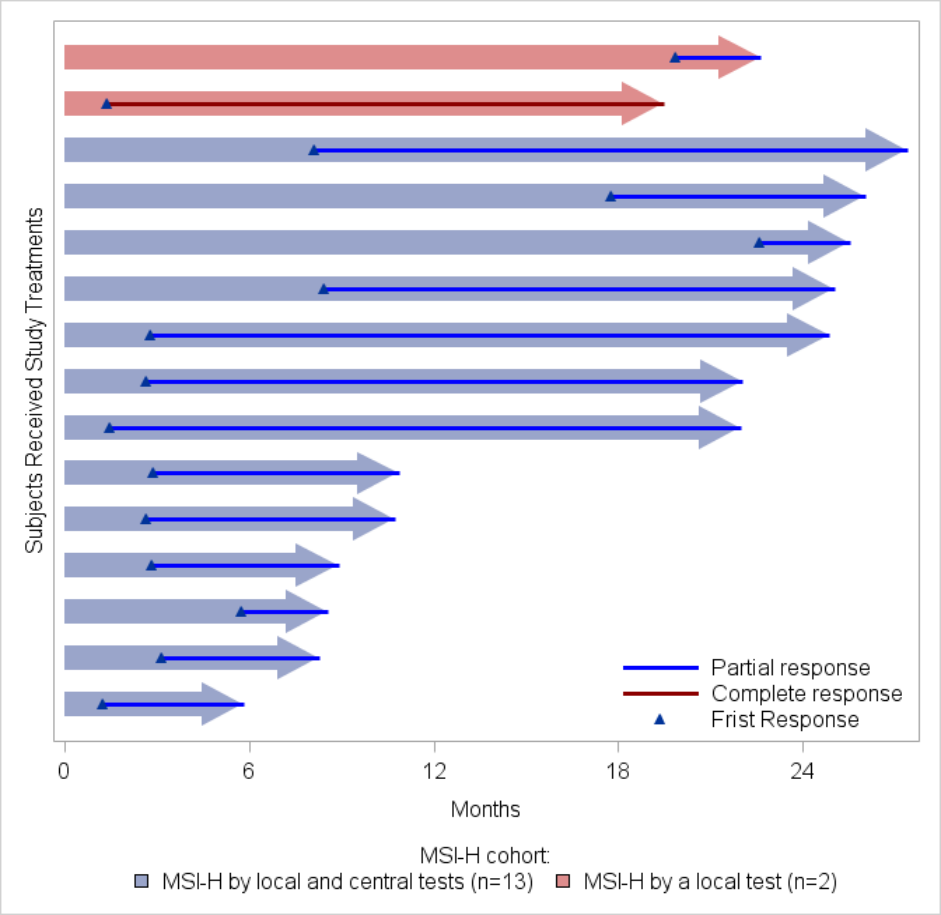


Source: FDA analysis (courtesy of statistical reviewer).

As the population to support the Applicant's proposed indication consists of those patients who progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan (N=53), efficacy results of this population were included in table 7. The ORR was 28%, with the 95% confidence interval overlapping that of the efficacy population. One patient (1.9%) had a complete response and 14 patients (26%) had a partial response. Median time to response was 2.9 months and the longest time to response was 22.6 months. As 13 responders (87%) were still receiving nivolumab at the time of the data cutoff, the median was not estimable. However, 67% of patients had a response duration of ≥ 6 months, 40% had a response duration of ≥ 12

months, and 33% had a response duration of ≥ 18 months. Figure 3 shows the duration of follow-up and duration of response for all responders.

Figure 3: Duration of follow-up and duration of response for responding patients who progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan



Source: FDA analysis (courtesy of statistical reviewer).

Reviewer comment:

The response rate in patients with MSIH/dMMR mCRC was 32%. For comparison, response rates were 32-40% in patients with melanoma, 19-27% in patients with non-small cell lung cancer, 22% in patients with renal cell carcinoma, 66-69% in patients with classical Hodgkin's lymphoma and 20% in patients with urothelial carcinoma (source: nivolumab USPI). Pembrolizumab, which has recently been approved for MSIH cancers under the accelerated approval program, resulted in an overall response rate of 36% in patients with mCRC. Although the duration of response data are immature, responses appear durable.

6.8. Analysis of Secondary Endpoints

The secondary endpoint for the clinical review of this application is confirmed ORR by RECIST 1.1 as assessed by the investigator in patients with MSIH-dMMR mCRC by local testing (n=74).

As shown in table 8, the investigator-assessed ORR was 31% (compared to 32% by IRRC). There were fewer patients with complete response (0 vs. 2 by IRRC) and more patients with partial response (23 vs. 22 by IRRC). In addition, the investigator assessment resulted in more patients with stable disease and less with progressive disease compared to IRRC assessment.

Table 8: Response assessment per IRRC vs. investigator

		MSIH/dMMR mCRC by local testing (N=74)	
		IRRC	**Investigator**
Objective response rate	n (%) 95% CI	24 (32) (22, 44)	23 (31) (21,43)
Complete response	n (%) 95% CI	2 (2.7) (0.3, 9.4)	0 0
Partial response	n (%) 95% CI	22 (30) (20, 42)	23 (31) (21,43)
Stable disease	n (%)	25 (34)	28 (38)
Progressive disease	n (%)	21 (28)	19 (26)
Not evaluable	n (%)	4 (5.4)	4 (5.4)

Source: FDA analysis

Table 9 shows response rates by IRRC vs. investigator assessment for the population supporting the proposed indication (i.e., patients who have progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan). The investigator assessed ORR was 26% compared to 28% when assessed by IRRC. Similar to the results in the efficacy population, assessment by the investigator resulted in fewer patients with a complete response, more patients with stable disease, and fewer patients with progressive disease compared to IRRC assessed responses.

Table 9: Response assessment per IRRC vs. investigator for patients who progressed after treatment with a fluoropyrimidine, oxaliplatin and irinotecan

		Prior fluoropyrimidine, oxaliplatin and irinotecan (N=53)	
		IRRC	**Investigator**
Objective response rate	n (%) 95% CI	15 (28) (17,42)	14 (26) (15,40)
Complete response	n (%) 95% CI	1 (1.9) (0.05, 10)	0 0
Partial response	n (%) 95% CI	14 (26) (15,40)	14 (26) (15,40)
Stable disease	n (%)	16 (30)	19 (36)
Progressive disease	n (%)	18 (34)	16 (30)
Not evaluable	n (%)	4 (7.5)	4 (7.5)

Source: FDA analysis

Reviewer comment:

There was discordance between investigator vs. IRRC assessment. The discordance had a small effect on ORR (difference of 1 patient), but a larger effect on disease control rate (which includes patients with stable disease).

6.9. Exploratory Endpoints

6.9.1. Progression free survival and overall survival

Survival data are not mature. With a median follow-up for PFS of 5.44 months (range: 0.03 to 27.76), the estimated median PFS per IRRC was 8.31 months (95% CI: 2.96, NE). With a median follow-up for OS of 12.02 months (range: 0.03 to 31.74), the estimated median OS per IRRC was not reached (95% CI: 18, NE) (source: FDA statistician).

Reviewer comment:

The results for time-to-event endpoints such as survival should be interpreted with caution, because these data are from uncontrolled clinical trials.

6.9.2. Association between biomarkers and efficacy

Exploratory analyses were done to evaluate differences in response rates for patients with and without history of lynch syndrome and for patients with or without KRAS and/or BRAF mutations (table 10). The ORR for patients without a history of lynch syndrome was slightly higher than the ORR of patients with a history of lynch syndrome (36 vs. 30%). The response rates of patients with BRAF or KRAS mutation and for patients with BRAF and KRAS wild-type mCRC were similar (31-33%).

Table 10: Response assessment per IRRC by history of lynch syndrome and KRAS/BRAF status

		All patients (N=74)	Lynch negative[a] (N=28)	Lynch positive (N=27)	KRAS/ BRAF wild-type[b] (N=29)	KRAS mutated (N=26)	BRAF mutated (N=12)
Objective response rate	n (%)	24 (32)	10 (36)	8 (30)	9 (31)	8 (31)	4 (33)
Complete response	n (%)	2 (2.7)	0	1 (3.7)	1 (3.4)	1 (3.8)	0
Partial response	n (%)	22 (30)	10 (36)	7 (26)	8 (28)	7 (27)	4 (33)
Stable disease	n (%)	25 (34)	12 (43)	9 (33)	14 (48)	5 (19)	6 (50)
Progressive disease	n (%)	21 (28)	5 (18)	9 (33)	6 (21)	11 (42)	0
Not evaluable	n (%)	4 (5.4)	1 (3.6)	1 (3.7)	0	2 (7.7)	2 (17)

Source: FDA analysis.
[a] Patients with unknown lynch status were excluded.
[b] Patients with unknown KRAS or BRAF status were excluded.

An additional exploratory analysis was done evaluating response rates by PD-L1 staining results (table 11). The ORR for patients with <1% PD-L1 expression vs. ≥1% PD-L1 expression at baseline was 29% compared to 33%. The ORR increased as PD-L1 staining increased: patients with ≥5% PD-L1 expression had an ORR of 36% and patients with ≥10% PD-L1 expression had an ORR of 50%.

Table 11: Response assessment per IRRC by PD-L1 status

		All patients (N=74)	PDL1<1% (N=45)[a]	PDL1 ≥ 1% (N=21)	PDL1≥5% (N=11)	PDL1≥10% (N=6)
Objective response rate	n (%)	24 (32)	13 (29)	7 (33)	4 (36)	3 (50)
Complete response	n (%)	2 (2.7)	0	0	0	0
Partial response	n (%)	22 (30)	13 (29)	7 (33)	4 (36)	3 (50)
Stable disease	n (%)	25 (34)	17 (38)	5 (24)	2 (18)	0
Progressive disease	n (%)	21 (28)	12 (27)	8 (38)	4 (36)	2 (33)
Not evaluable	n (%)	4 (5.4)	3 (6.7)	1 (4.8)	1 (9)	1 (17)

Source: FDA analysis.
[a] Patients with unknown PD-L1 status were not included.

Reviewer comment:

Treatment with nivolumab resulted in responses in patients regardless of PD-L1 staining results. There were no clear differences in response rate between patients who had a history of lynch syndrome and those who did not. In addition, there was no difference in response between patients who had a KRAS or BRAF mutation or who were KRAS or BRAF wild-type.

As the number of patients is small and these subgroup analyses were not pre-specified, the results for these exploratory subgroup analyses should be interpreted with caution.

6.9.3. Association between efficacy and local vs. central MSI/MMR testing

Table 12 summarizes response rates for patients with MSIH/dMMR mCRC as determined by local testing vs. central testing. The ORR for patients with MSIH mCRC by central testing vs. local testing was 36% vs. 32%. Refer to section 6.5 for a discussion about the local vs. central testing results.

Table 12: Response assessment per IRRC by MSI/MMR testing (local vs. central).

		Local testing (N=74)	Central testing (N=53)
Objective response rate	n (%) 95% CI	24 (32) (22, 44)	19 (36) (23,50)
Complete response	n (%) 95% CI	2 (2.7) (0.3, 9.4)	1 (1.9) (0.05, 10)
Partial response	n (%) 95% CI	22 (30) (20, 42)	18 (34) (22,49)
Stable disease	n (%)	25 (34)	19 (36)
Progressive disease	n (%)	21 (28)	12 (22)
Not evaluable	n (%)	4 (5.4)	3 (5.7)

Source: FDA analysis.

Reviewer comment:

Although the ORR was slightly higher in the patients with MSIH mCRC by central testing compared to those with MSIH/dMMR mCRC by local testing, the confidence intervals overlap and therefore no conclusion can be drawn as to whether or not there is a true difference between ORR rates by local vs. central testing. As discussed in section 6.5, this reviewer has concerns that central testing results were false negative in several patients.

6.9.4. Quality of life

The Applicant collected quality of life data through the use of 2 questionnaires: the EORTC-QLQ-C30 and the EQ-5D-3L questionnaires. The EORTC-QLQ-C30 measures 30 items divided into 5 functional scales (physical, role, cognitive, emotional and social), 9 symptoms and global health/quality of life. The EQ-5D measures items described in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). It includes a visual analogue scale (VAS), as well as a descriptive system.

The EORTC-QLQ-C30 questionnaire completion rate was 94.6% at baseline and remained about 70% through Week 79. The applicant reported that patients had improvements in emotional, role and social functioning and in several symptom scores (fatigue, pain, insomnia, appetite loss, constipation and diarrhea). An improvement in overall health status was observed by the Applicant by week 13 and, with the exception of one time point, maintained through week 37. Patients had no improvements in physical functioning, nausea/vomiting and dyspnea. In

addition, worsening in cognitive function was observed at a single time point (source: interim clinical study report, section 11.1 and tables s.10.1.1, s.10.1.2, and s.10.1.3).

The EQ-5D-3L questionnaire was not calculated, but baseline completion of the VAS component was 87.8% and baseline completion of the descriptive components ranged from 87.8% to 89.2%. Reductions were noted for all dimensions and (according to the interim clinical study report) the mean VAS score had improved by more than 10 points by week 7 (source: interim clinical study report, section 11.1 and table s.10.1.4 and s.10.1.5).

Reviewer comment:

As these data are from an uncontrolled clinical trial and are incomplete, the results should be interpreted with caution.

6.10. Subpopulations

Due to the sample size limitations and lack of pre-specified subgroup analysis, formal subgroup analysis (other than those described in section 6.6), were not performed.

6.11. Analysis of Clinical Information Relevant to Dosing Recommendations

All patients enrolled into study CA209142 received the approved dose of nivolumab. See clinical pharmacology review for additional dosing considerations.

6.12. Discussion of Persistence of Efficacy and/or Tolerance Effects

A discussion of tolerance effects is not applicable to this review. Data to inform the adequacy of a shorter course of therapy, or transition to a reduced dose-schedule upon achievement of maximal response, are not available.

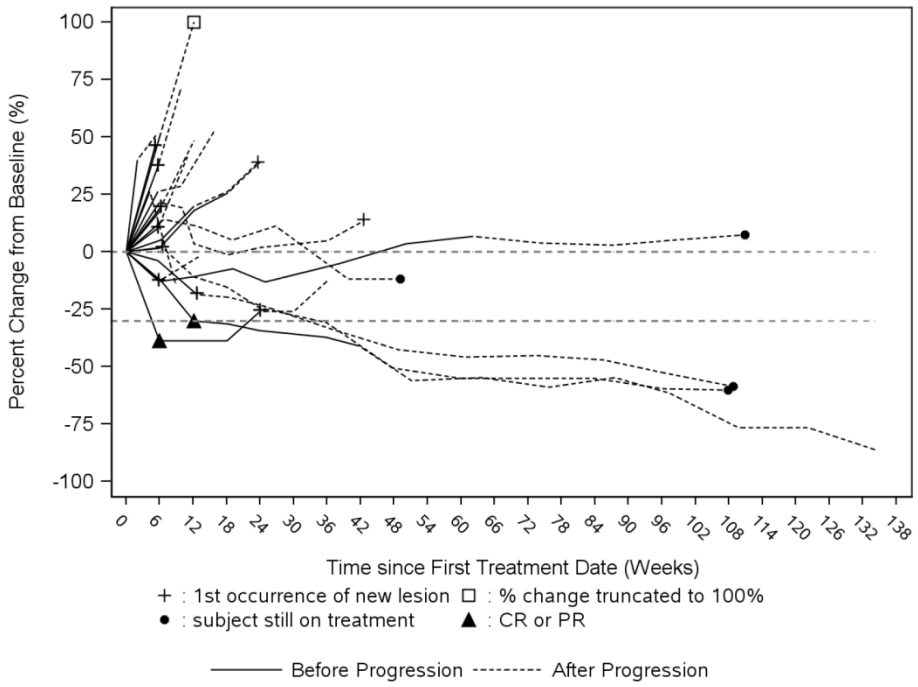
6.13. Additional Efficacy Issues/Analyses

6.13.1. Treatment Beyond Progression

Nineteen patients (26%) were treated beyond investigator-assessed progression on study CA209142. Fifteen patients had discontinued nivolumab at the time of the data cutoff and 4

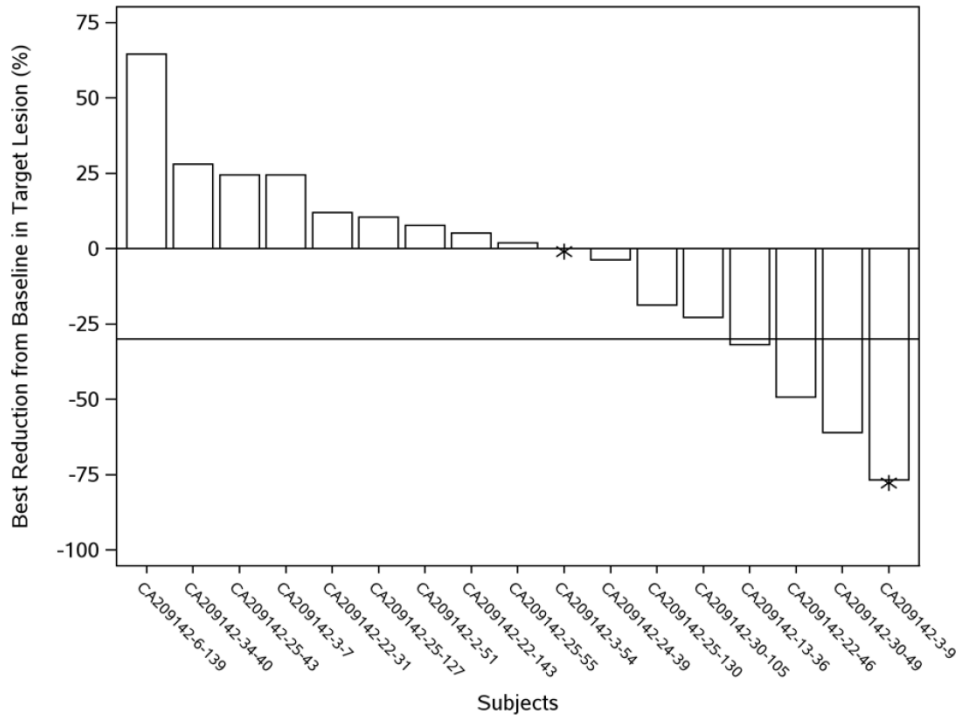
patients were still receiving treatment. Nivolumab was discontinued due to continued disease progression in 13 patients, due to maximum clinical benefit in one patient, and due to travel distance in one patient. The median number of doses received beyond progression was 3 (range 1, 53+). The median duration of treatment beyond progression was 1.25 months (range 0.0, 24.5+). Figure 4 shows the tumor burden change over time for these patients. Seven patients had a reduction in size of their target lesion(s) after progression. Four patients had a reduction of ≥30% in their target lesion(s). Figure 5 shows the best reduction in the sum of diameters of the target lesion(s) per investigator.

Figure 4: Tumor burden change over time as assessed by investigator



Source: Response to FDA information request 20 June 2017.

Figure 5: Best reduction in the sum of diameters of the target lesion(s) as assessed by investigator



Best reduction is maximum reduction in sum of diameters of target lesions (negative value means true reduction, positive value means increase only observed over time)
Horizontal reference line indicates the 30% reduction consistent with a RECIST 1.1 response.
Two patients were excluded.
Asterisk symbol represents responders

Source: Response to FDA information request 20 June 2017.

Reviewer comment:

Although there were patients who continued to progress immediately despite treatment beyond progression, there appears to be a subset of patients who benefited from treatment beyond progression.

6.13.2. Differences in response assessment between September and February data cutoff

There were some differences in response data between the original data cutoff of 19 September 2016 and the data cutoff of 6 February 2017 (source: ad hoc efficacy report, dated 8 March 2017), partly due to changes in the adjudicator reading the scans.

- One patient originally had a partial response based on the initial adjudicator, but was re-assessed as having stable disease after a change in adjudicator.
- Two patients had an updated date of first response, which shortened the duration of response in both patients.
- One patient had a best response as not reported, which was updated to progressive disease.
- One patient had an incorrect surgery date in the original dataset leading to best response of not evaluable. After correction, this patient had stable disease.
- There were 5 new responders.
    - Two patients had an unconfirmed partial response at the time of the 19 September 2016 data cutoff and were then confirmed to have a partial response after this data cutoff.
    - Three patients had unconfirmed stable disease at the time of the September 2016 data cutoff. One patient had an unconfirmed and confirmed response between the September and February data cutoffs. However, the other 2 patients had responses that occurred prior to the September data cutoff. All three patients required an adjudicator to determine the response as there was disagreement (PR vs. SD) between radiologist 1 and 2.
    - Time to response for these patients ranged between 2 and 22 months.

Reviewer comment:

The changes in responses based on the change in adjudicator between the 19 September 2016 and 6 February 2017 do not substantially affect the response rate.

7. Review of Safety

Safety Summary: refer to section 1.2.

7.1. Methods

7.1.1. Studies/Clinical Trials Used to Evaluate Safety

The primary source of the safety data in this efficacy supplement is the 74 patients who received at least one dose of nivolumab on study CA209142. Three of the 74 patients (4%) had no adverse events and 71 of the 74 patients (96%) had at least one reported adverse event.

Reviewer comment:

Adverse events were analyzed based on the Applicant's data cutoff of 19 September 2016. Based on the safety experience of nivolumab in other uses, it is not expected that the safety dataset from study CA209142 with a limited number of patients would contribute substantive new information.

7.1.2. Categorization of Adverse Events

The severity of adverse events was documented using Common Terminology Criteria for Adverse Event, NCI-CTCAE version 4.0. The MedDRA 19.0 dictionary was used to code adverse event data.

Adverse events were assessed during the treatment period and for 30 days after the last dose of nivolumab. Given the half-life of monoclonal antibodies and the potential for late consequences of immune activation beyond the 30 day period, adverse events were also followed between 31 and 100 days after the last dose of nivolumab.

Disease progression was excluded from adverse event analysis.

7.1.3. Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable, as only one study was submitted.

7.2. Adequacy of Safety Assessments

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

The safety population consists of all 74 patients who received at least one dose of nivolumab. As the efficacy and safety population are the same, refer to section 6.3 for demographics information.

The median duration of therapy was 6.01 months and the mean number of doses administered was 17.1 (range 1-54; median 13). The majority of patients (51%) were exposed for ≥6 months at the time of the data cutoff of 19 September 2016.

7.2.2. Explorations for Dose Response

See the FDA Clinical Pharmacology Review from the original BLA submission.

7.2.3. Special Animal and/or In Vitro Testing

See the FDA Pharmacology/Toxicology Review from the original BLA submission.

7.2.4. Routine Clinical Testing

The following laboratory tests were collected at baseline, on Day 1 of Cycle 1, every cycle until week 23 and then every other cycle: CBC with differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, and lipase. TSH with reflexive Free T4 and Free T3 were assessed every 2 weeks. A pregnancy test was performed every 4 weeks.

7.2.5. Metabolic, Clearance, and Interaction Workup

See the FDA Clinical Pharmacology review for details.

7.2.6. Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Similar to other drugs targeting the PD-1 pathway, such as pembrolizumab, immune-mediated adverse reactions have been observed in patients treated with nivolumab. The safety information submitted by the Applicant included an evaluation of adverse events of special interest (AESIs) and immune-mediated AEs (IMAEs). These are discussed in Section 7.3.4.

7.3. Major Safety Results

The safety analyses were performed for all patients enrolled in the MSIH cohort in study CA209142 who received at least one dose of nivolumab (n=74) with a data cutoff date of 19 September 2016 (table 13).

Table 13: CA209142 Summary of Major Safety Results[a]

	n (%)
Patients who experienced an AE	71 (96)
Patients who experienced a Grade 1-2 AE	69 (93)
Patients who experienced a Grade 3-4 AE	40 (54)
Patients who experienced an SAE	29 (39)
Deaths reported as an AE	1 (1.4)

Source: FDA analysis.
[a] Numbers differ from those submitted by the Applicant as FDA analyses excludes patients with disease progression.

7.3.1. Deaths

A total of 19 patients enrolled on study CA209142 died. Four patients died within 30 days of receiving the last dose of nivolumab and 7 patients died between 31 and 100 days of receiving the last dose of nivolumab (table 14).

Table 14: CA209142 Deaths

	n (%)
Total deaths	19 (26)
Deaths within 30 days of last nivolumab dose	4 (5.4)
Disease progression	3 (4.1)
Sudden death	1 (1.4)
Deaths between 31-100 days of last nivolumab dose	7 (9.5)
Disease progression	7 (9.5)
Deaths more than 100 days of last nivolumab dose	8 (11)
Disease progression	7 (9.5)
Unknown	1 (1.4)

Source: FDA analysis.

Of the 13 deaths reported in the safety data set, 12 patients died due to complications of disease progression and one patient died due to an adverse event not attributed to disease progression (patient (b) (6)). The Applicant provided a narrative for this patient. The patient presented to the ER 4 days with fever and abdominal pain after the first nivolumab infusion. She was found to have Grade 3 nivolumab-related colitis and treated with broad-spectrum antibiotics, analgesics, oxygen and fluid support. Two days later, IV methylprednisolone was started and she was given RBC transfusion for anemia. Her symptoms improved, but abdominal pain continued, for which she was given additional opioid analgesics. On day 10 of study treatment, the patient was found unresponsive and pulseless. CPR was performed, but unsuccessful. The autopsy results were reported as "unknown cause."

Reviewer comment:

The incidence of death due to AEs not attributed to disease progression was low (1%). Review of the details of the deaths does not raise any new safety concerns relative to the safety profile of nivolumab reflected in the current USPI.

7.3.2. Nonfatal Serious Adverse Events

For study CA209142, there were 52 nonfatal SAEs in 29 (39%) patients and 38 nonfatal Grade 3-4 SAEs in 25 patients (34%). The most common (>2% of patients) SAEs were: intestinal obstruction, diarrhea, vomiting, pyrexia, abdominal pain and abdominal abscess (table 15).

Table 15: Most common (>2%) nonfatal SAEs

	All grade n (%)	Grade 3-4 n (%)
Diarrhea[a]	4 (5.4)	4 (5.4)
Intestinal obstruction[b]	4 (5.4)	4 (5.4)
Vomiting	3 (4.1)	1 (1.4)
Abdominal pain[c]	3 (4.1)	0 (0)
Pyrexia	2 (2.7)	0 (0)
Abdominal abscess[d]	2 (2.7)	2 (2.7)

Source: FDA analysis.
[a] Includes colitis and gastroenteritis
[b] Includes small intestinal obstruction
[c] Includes abdominal discomfort, lower abdominal and upper abdominal pain
[d] Includes abdominal wall abscess

Reviewer comment:

The incidence of SAE's in this sBLA is similar to those described for nivolumab in other indications. The frequent incidence of intestinal obstruction, abdominal pain and abdominal abscess would be expected in a patient population with metastatic colorectal cancer.

7.3.3. Dropouts and/or Discontinuations

Adverse events leading to discontinuation of study treatment were reported in 5 (6.8%) patients in Study CA209142. Four (5.4%) of these adverse events were attributed to nivolumab: Grade 3 colitis, Grade 3 ALT increase, Grade 3 acute kidney injury (in the setting of Grade 3 diarrhea), and Grade 3 stomatitis. One patient experienced two adverse events leading to discontinuation (abdominal pain and vomiting). Both were attributed as not related to the study drug. However, the description in the CRF of the event stated that the patient had a colonoscopy where colitis was found. Given this finding, and the fact that the patient was treated with steroids, this event may have been an immune-mediated colitis associated with nivolumab.

Reviewer comment:

The percentage of patients discontinuing nivolumab due to adverse events is similar to or lower than those described in other indications.

7.3.4. Significant Adverse Events

The significant adverse events associated with nivolumab are thought to arise from the ability of nivolumab to block programmed death receptor 1 (PD-1). Normally, binding to PD-1 inhibits T cell proliferation and cytokine production. Blocking this pathway releases the T cell from this inhibition. This has been associated with an increase in autoimmune disease.

Immune–mediated adverse event (IMAE) definitions and analyses were limited to patients who received systemic immunosuppressive treatment, with the exception of endocrine events (hypothyroidism/ thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency) which are often managed without immunosuppression. Specific evaluations for autoimmune endocrinopathies were not required or collected systematically. Therefore, specific laboratory criteria were not required to meet the case definition of endocrine IMAEs. Table 16 describes immune-mediated adverse events occurring within 100 days of the last dose of nivolumab in study CA209142. The table also includes the number of patients receiving high-dose steroids, defined as the equivalent of 40 mg of prednisone orally for at least 1 day. The expected incidence of these events is derived from the nivolumab label.

Table 16: Immune-Mediated Adverse Events requiring systemic corticosteroids

	Patients n (%)	Requiring high-dose steroids n (%)	Expected incidence (USPI) %
Non-endocrine events			
Nephritis / renal dysfunction	3 (4.1)	2 (2.7)	1.2
Colitis[a]	2 (2.7)	2 (2.7)	2.9
Hepatitis	2 (2.7)	2 (2.7)	1.8
Hypersensitivity / infusion reactions	1 (1.4)	0	6.4
Rash[b]	1 (1.4)	1 (1.4)	9.0
Pneumonitis	0	0	3.1
Endocrine events			
Hypothyroidism/ thyroiditis	4 (5.4)	0	9.0
Hyperthyroidism	3 (4.1)	0	2.7
Adrenal insufficiency	1 (1.4)	0	1
Diabetes Mellitus	0	0	0.9
Hypophysitis	0	0	0.6

Source: FDA analysis.
[a] Although the Applicant reported 1 patient with colitis in the adverse event datasets, one patient was described in the narratives as having colitis and requiring steroids
[b] An additional 4 patients with a rash required topical corticosteroids

The number of patients with some of these events is higher than shown in table 16 because most patients did not receive steroids. Although these events were not treated with corticosteroids, they may be immune-related. The incidences of these events are bulleted below.

- Gastrointestinal events: diarrhea, colitis, frequent bowel movements and enteritis were reported in 35 (47%) patients.
- Hepatic events: increases in AST, ALT, bilirubin, GGT, and alkaline phosphatase were reported in 17 (23 %) patients.
- Nephritis: acute kidney injury or increased creatinine were reported in 9 (12%) patients.
- Pneumonitis was reported in 2 (2.7%) patients.
- Hypersensitivity/infusion reactions were reported in 3 (4.1%) patients.

- Skin events: rash, pruritus, dermatitis, eczema, erythema, palmar-plantar erythrodysesthesia syndrome or skin exfoliation was reported in 24 (32%) patients.

In addition to the immune-related adverse events described in table 16, the following adverse events, not designated as immune-related by the Applicant, required systemic steroids: Grade 2 lower respiratory tract infection (one patient), Grade 3 cauda equine syndrome (one patient), Grade 3 gastritis (one patient), Grade 2 ascites (one patient), Grade 1 pyrexia (one patient), and Grade 3 stomatitis (one patient).

Other events that were potentially immune-mediated, but did not fulfill all criteria for IMAEs, were also considered adverse events of special interest (AESIs). In contrast to IMAE analyses, analyses of AESIs were limited to events considered drug-related by the investigator, regardless of whether corticosteroids were given. One patient had pancreatitis. There were no reports of uveitis, encephalitis, myasthenic syndrome, demyelination, Guillain-Barre syndrome, myocarditis, myositis, or rhabdomyolysis.

Reviewer comment:

As the number of patients is small and these data are from an uncontrolled clinical trial, the results of this analysis should be interpreted with caution. However, in general, the incidence of immune-mediated adverse events is consistent with the package insert. Certain events may be related to the underlying cancer (e.g. diarrhea/colitis and hepatitis) and without biopsy data on each immune-related adverse event, exact determination of the cause is not possible.

7.3.5. Submission Specific Primary Safety Concerns

Refer to section 7.3.4.

7.4. Supportive Safety Results

7.4.1. Common Adverse Events

Table 17 summarizes commonly reported treatment-emergent adverse events (for laboratory abnormalities, refer to section 7.4.2). The most common (≥20%) treatment-emergent adverse events occurring in the safety population within 30 days of the last dose of nivolumab, regardless of grade or causality, included fatigue, pyrexia, gastrointestinal events, musculoskeletal pain, rash, and upper respiratory tract infection.

Table 17: Most common (≥10%) Treatment-Emergent Adverse Events

	All grades n %	Grades 3-4 n %
General Disorders and Administration Site Conditions		
Fatigue[a]	40 (54)	4 (5.4)
Pyrexia	18 (24)	0
Edema[b]	11 (15)	0
Gastrointestinal Disorders		
Diarrhea[c]	33 (45)	4 (5.4)
Abdominal pain[d]	25 (34)	2 (2.7)
Nausea	25 (34)	1 (1.4)
Vomiting	21 (28)	3 (4.1)
Constipation	15 (20)	0
Dyspepsia	8 (11)	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[e]	22 (30)	1 (1.4)
Arthralgia	14 (19)	0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	19 (26)	0
Skin and Subcutaneous Tissue Disorders		
Rash[f]	17 (23)	1 (1.4)
Pruritus	14 (19)	0
Infections and Infestations		
Upper respiratory tract infection[g]	17 (23)	0
Endocrine Disorders		
Hyperglycemia	14 (19)	2 (2.7)
Nervous System Disorders		
Headache	12 (16)	0
Dizziness[h]	10 (14)	0
Metabolism and Nutrition Disorders		
Decreased appetite	10 (14)	1 (1.4)

Source: FDA analysis. [a] Includes asthenia; [b] Includes face edema, generalized edema, localized edema, peripheral edema, peripheral swelling, and lymphedema; [c] Includes colitis and gastroenteritis; [d] Includes upper abdominal , pain, lower abdominal pain and abdominal discomfort; [e] Includes back pain, pain in extremity, myalgia, neck pain, bone pain, right neck/shoulder pain and non-cardiac chest pain; [f] Includes dermatitis, dermatitis acneiform, and rash described as maculo-papular, erythematous, and generalized; [g] Includes nasopharyngitis, rhinitis, pharyngitis and sinusitis; [h] includes vertigo.

Reviewer comment:

Treatment-emergent adverse event data were reviewed and are consistent with the known adverse event profile of nivolumab. Some events, such as abdominal pain and diarrhea may also be related to the underlying cancer.

7.4.2. Laboratory Findings

Table 18 summarizes commonly reported treatment-emergent laboratory abnormalities. The most common (≥20%) treatment-emergent laboratory events occurring in the safety population within 30 days after the last dose of nivolumab, regardless of grade or causality, included cytopenias, liver function abnormalities, elevated lipase and electrolyte abnormalities. For TSH abnormalities, refer to section 7.3.4.

Table 18: Treatment-Emergent Laboratory Findings in ≥10% of patients

	All grades n (%)	Grades 3-4 n (%)
Hematology		
Anemia	35 (50)	5 (6.9)
Lymphopenia	25 (36)	5 (7.2)
Leukopenia	14 (20)	3 (4.2)
Neutropenia	14 (20)	3 (4.2)
Thrombocytopenia	11 (16)	1 (1.4)
Chemistry		
Increased alkaline phosphatase	26 (37)	2 (2.8)
Increased lipase	23 (33)	13 (19)
Increased ALT	23 (32)	2 (2.8)
Increased AST	22 (31)	1 (1.4)
Hyponatremia	19 (27)	3 (4.2)
Hypocalcemia	15 (22)	0
Hypomagnesemia	12 (17)	0
Increased amylase	10 (16)	3 (4.8)
Increased bilirubin	10 (14)	3 (4.2)
Hypokalemia	10 (14)	0
Increased creatinine	8 (12)	0
Hyperkalemia	8 (11)	0

Source: FDA analysis. Represents maximum grade post-baseline, occurring during or within 30 days of the last dose of nivolumab, if new or worsening from baseline. The denominator for each percentage is the amount of patients with both baseline and post-baseline measurements available (range 62-72).

In addition to the laboratory abnormalities described in table 18, 3 (4.2%) patients had concurrent ALT or AST elevation >3 x ULN with total bilirubin >2 x ULN within 30 days of the last dose of nivolumab and 4 (5.6%) patients had concurrent ALT or AST elevation >3 x ULN with total bilirubin >2 x ULN within 100 days of the last dose of nivolumab. Two of these patients had bile duct obstruction that was attributed to the underlying cancer. One patient showed progression of liver metastasis, but also had a liver biopsy showing "chemotherapy associated liver injury with mild portal lymphocytic infiltrate and lymphocytic cholangitis with prominent cytologic evidence of cholangiocyte injury". This patient was treated with steroids. The 4th patient (who had concurrent ALT/AST elevation 31-100 days after the last dose) presented to the emergency room with "frank asthenia, total almost anorexia, some vomiting episodes, palpitations and dry mouth sensation", after which the patient was diagnosed with hyponatremia, acute renal failure, hyperkalemia and cholestatic jaundice. The patient died several days later and his death was attributed to disease progression.

Reviewer comment:

Treatment-emergent laboratory findings were reviewed and are consistent with the known adverse event profile of nivolumab (or progression of the patients' underlying malignancy).

7.4.3. Vital Signs

Vital signs were not reviewed. Changes in vital signs due to the administration of nivolumab are considered under Infusion Reactions above.

7.4.4. Electrocardiograms (ECGs)

A QT substudy was conducted and was reviewed as part of the original nivolumab BLA submission. Nivolumab up to 10 mg/kg did not substantially affect the QTc interval.

7.4.5. Special Safety Studies/Clinical Trials

There were no special safety studies/clinical trials conducted for this sBLA.

7.4.6. Immunogenicity

Anti-drug antibodies (ADAs) were identified in 8 out of 52 (15%) patients who had baseline and post-baseline ADA measurements. One patient had neutralizing ADA and one patient had persistently positive ADAs. One patient with ADA had a hypersensitivity reaction requiring corticosteroids. The patient with neutralizing ADA had PD as best response. Of the remaining 7 patients, 5 had a PR, one SD, and one PD.

Reviewer comment:

Given the small number of patients with ADA, it is not possible to draw conclusions regarding the relationship of the presence of ADA to efficacy or safety.

7.5. Other Safety Explorations

7.5.1. Dose Dependency for Adverse Events

Not applicable as all patients were given the same dose (3 mg/kg IV every 2 weeks).

7.5.2. Time Dependency for Adverse Events

Patient numbers do not permit adequate analyses of time dependency for adverse events.

7.5.3. Drug-Demographic Interactions

Patient numbers do not permit adequate analyses of safety according to demographic parameters such as age and race.

7.5.4. Drug-Disease Interactions

Not applicable.

7.5.5. Drug-Drug Interactions

No analyses of drug-drug interactions were conducted for this supplement.

7.6. Additional Safety Evaluations

7.6.1. Human Carcinogenicity

Carcinogenicity studies were not conducted for this anti-cancer drug.

7.6.2. Human Reproduction and Pregnancy Data

Reproductive toxicology studies were conducted and nivolumab was given Pregnancy Category D. See pharmacology-toxicology review of original BLA submission.

7.6.3. Pediatrics and Assessment of Effects on Growth

Nivolumab has not been studied in pediatric populations.

7.6.4. Overdose, Drug Abuse Potential, Withdrawal and Rebound

No experience with overdose with nivolumab is available. On the basis of its pharmacological properties, there are no concerns regarding the potential for abuse, withdrawal, or rebound with nivolumab.

7.7. Additional Submissions / Safety Issues

None.

8. Postmarketing Experience

Nivolumab was approved in December 2014 for the treatment of melanoma. Nivolumab has subsequently been approved for the treatment of non-squamous non-small cell lung cancer, for use in combination with ipilimumab to treat melanoma, for renal cell carcinoma, urothelial carcinoma, classical Hodgkin lymphoma, and squamous cell carcinoma of the head and neck.

The most recent PADER was submitted 3 April 2017 and covered the period 22 December 2016 to 21 March 2017. During that period there were 151 initial and 9 follow-up domestic serious expected adverse drug experience reports included in this submission. There were 1920 initial

and 1873 follow-up worldwide 15-Day Alert reports submitted during this period. The Applicant has recommended no changes to the package insert based on these reports.

Reviewer comment:

The Applicant has not identified any new safety concerns based on postmarketing experience. In general, these reports appeared consistent with expected adverse events related to immunotherapy or due to underlying cancers.

9. Appendices

9.1. Literature Review/References

1) National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER), seer.cancer.gov, accessed 1 June 2017
2) NCCN guidelines, version 2.2017, dated 13 March 2017.
3) Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol 2014;15:569-79.
4) Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998 Nov 15;58(22):5248-57.
5) Venderbosch S, Nagtegaal ID, Maughan TS, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clinical cancer research: an official journal of the American Association for Cancer Research 2014;20:5322-30.
6) Lynch HT, Snyder CL, Shaw TG, et al. Milestones of Lynch syndrome: 1895–2015. Nat Rev Cancer. 2015;15:181–194
7) Veigl ML, Kasturi L, Olechnowicz J, Ma AH, et al. Biallelic inactivation of hMLH1 by epigenetic gene silencing, a novel mechanism causing human MSI cancers. Proc Natl Acad Sci U S A. 1998;95(15):8698.
8) Cui H, Horon IL, Ohlsson R, Hamilton SR, Feinberg AP. Loss of imprinting in normal tissue of colorectal cancer patients with microsatellite instability. Nat Med. 1998;4(11):1276.
9) Sourrouille I, Coulet F, Lefevre JH, et al. Somatic mosaicism and double somatic hits can lead to MSI colorectal tumors. Fam Cancer. 2013 Mar;12(1):27-33.

10) Giannakis M, Mu XJ, Shukla SA, et al. Genomic Correlates of Immune-Cell Infiltrates in Colorectal Carcinoma. Cell Rep 2016;17:1206.
11) Llosa NJ, Cruise M2, Tam A, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov. 2015 Jan;5(1):43-51.
12) Sinicrope FA, Foster NR, Thibodeau SN, et al. DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy. J Natl Cancer Inst. 2011 Jun 8;103(11):863-75.
13) Copija A, Waniczek D, Witkoś A, et al. Clinical Significance and Prognostic Relevance of Microsatellite Instability in Sporadic Colorectal Cancer Patients. Int J Mol Sci. 2017 Jan; 18(1): 107.
14) Bartley AN, Luthra R, Saraiya DS, et al. Identification of cancer patients with Lynch syndrome: clinically significant discordances and problems in tissue-based mismatch repair testing. Cancer Prev Res (Phila) 2012;5:320-7.
15) Bao F, Panarelli NC, Rennert H, et al. Neoadjuvant therapy induces loss of MSH6 expression in colorectal carcinoma. Am J Surg Pathol 2010;34:1798-804.
16) Klarskov L, Holck S, Bernstein I, et al. Challenges in the identification of MSH6-associated colorectal cancer: rectal location, less typical histology, and a subset with retained mismatch repair function. Am J Surg Pathol 2011;35:1391-9.

9.2. Labeling Recommendations

The following are recommendations for Opdivo labeling based on this review:

- Accelerated approval of nivolumab for the treatment of (b) (4) .
- For the new indication, include demographics, ORR and DOR for both the efficacy population (i.e., patients who received fluorouracil, oxaliplatin or irinotecan) and for the population used to support the indication (i.e., patients who received fluorouracil, oxaliplatin and irinotecan).
- As the safety profile of nivolumab has been established, this supplement does not provide additional safety information, and safety is better described in controlled trials rather than in single-arm trials, defer updates to the safety section.

9.3. Advisory Committee Meeting

There was no advisory committee meeting for this application because the safety profile of nivolumab is acceptable for the treatment of patients with metastatic MSIH/dMMR mCRC, the application did not raise significant public health questions regarding the role of nivolumab for this indication, and outside expertise was not necessary as there were no controversial issues that could benefit from an Advisory Committee discussion.

9.4. Financial disclosure

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 368		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

In accordance with 21 CFR 54, BMS submitted a list of trial investigators for study CA 209142 (module 1.3.4, Table 1) and independent radiological reviewers ([redacted]; module 1.3.4, Table 2). BMS also provided financial disclosures (FDA form 3454) for study CA 209142 and for the independent radiological reviewers. No investigator or radiological reviewer held financial interests or arrangements requiring disclosure per the criteria described on Form 3454. The investigator attempted to minimize bias via the use of an independent radiological review.

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

/s/

MARIE-ANNE D SMIT
07/06/2017

STEVEN J LEMERY
07/07/2017
I agree with the recommendation made in this review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

CHEMISTRY REVIEW(S)

MEMORANDUM

DATE:	April 5, 2017
BLA:	**125554**
SUPPLEMENT:	**034**
FROM:	N. Sarah Arden, Ph.D., Product Quality Reviewer CDER/OPQ/OBP/DBRR II
THROUGH:	Patrick Lynch, Ph.D., Product Quality Reviewer CDER/OPQ/OBP/DBRR II
PRODUCT:	OPDIVO (Nivolumab/BMS-936558/MDX-1106) fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) target to the programmed death-1 (PD-1) receptor
ROUTE OF ADMIN:	Intravenous infusion
INDICATION:	Metastatic Colorectal Cancer
DOSE REGIMEN:	Flat dose of 240 mg every two weeks
STRENGTHS:	40mg/4ml (10mg/ml) vial, 100mg/10ml (10mg/ml) vial
SPONSOR:	Bristol-Myers Squibb
CLINICAL DIVISION:	CDER/OHOP/DOP 2
REVIEW TEAM:	Clinical: Maitreyee Hazarika Nonclinical: Shawna Weis OBP Product Quality: N. Sarah Arden RPM: Meredith Libeg Clin Pharm: Jun Yang

BACKGROUND:

On Feb. 2, 2017, the sponsor submitted s-034 supplement to request accelerated approval of Opdivo for the treatment of [redacted] (b) (4).

This review supports the environmental assessment the sponsor submitted in the supplement 034 on 02/02/2017 (sequence #0296).

ADMINISTRATIVE INFORMATION

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

Bristol-Myers Squibb Company is requesting a categorical exclusion from the preparation of an environmental assessment (EA) for nivolumab according to section 505(b) of the Federal Food, Drug, and Cosmetic Act. The subject of the proposed action (sBLA for nivolumab) will not significantly affect the quality of the environment and meets the requirements for a categorical exclusion from submitting an environmental assessment under 21 CFR 25.31(c). In addition, to

Bristol-Myers Squibb Company's knowledge, no extraordinary circumstances exist, as referenced in 21 CFR 25.15(d). This drug is a protein which is expected to rapidly degrade to amino acids and mineralize to carbon dioxide. It is not derived from any wild-sourced plant and/or animal material 21 CFR 25.21(b).

This is considered appropriate.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 125-554
Supplement #:	S-34
Drug Name:	OPDIVO ® (Nivolumab)
Indication(s):	Treatment of (b) (4)
Applicant:	Bristol-Myers Squibb Company
Date(s):	Received date: February 2, 2017
	PDUFA date: August 2, 2017
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Uma Siangphoe, PhD
Concurring Reviewers:	Lisa Rodriguez, PhD
	Kun He, PhD
Medical Division:	Division of Oncology Products 2
Clinical Team:	Marie-Anne Smit, MD, MS
	Steven Lemery, MD, MHS
	Patricia Keegan, MD
Project Manager:	Meredith Libeg, PMP, RAC, CCRP

Keywords: Objective Response Rate, Duration of Response, mCRC, Microsatellite Instability-High (MSI-H) Cancer

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1 EXECUTIVE SUMMARY

Nivolumab, a monoclonal antibody directed against the programmed death-1 (PD-1) receptor, was approved for the treatment of patients with: unresectable or metastatic melanoma, metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy, advanced renal cell carcinoma with prior antiangiogenic therapy, classical Hodgkin lymphoma that has relapsed or progressed after stem cell transplantation and post-transplantation brentuximab vedotin, and recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy.

In this supplemental biologics license application (sBLA), the applicant submitted data based on the CA209142 study to seek an accelerated approval of nivolumab monotherapy for treatment of (b) (4) . The CA209142 study was a phase II, open-label, and multicenter study of nivolumab alone or in combination with ipilimumab in patients with MSI-H mCRC and of nivolumab in combination with ipilimumab in patients with non-MSI-H mCRC. Patients with MSI-H were identified using a local-laboratory test either immunohistochemistry (IHC) or polymerase chain reaction (PCR) methods. The patients were subsequently evaluated per a central PCR with Bethesda panel method.

The primary efficacy endpoint was independent radiology review committee (IRRC)-assessed ORR defined as the number of patients with a best overall response (BOR) of confirmed complete (CR) or partial (PR), according to RECIST 1.1. The secondary endpoint included investigator-assessed ORR.

Seventy-four patients with local laboratory MSI-H test were enrolled in the study. The IRRC-assessed ORR was 32% (95% CI: 22%, 44%). The duration of response (DOR) via IRRC ranged from 1.4 to 26.5 months, while the median was not estimable. Among 24 responders, there were 9 patients whose the DOR was greater than 12 months. The Kaplan-Meier method estimated 95% of the responders with the DOR greater than 12 months (95% CI: 68%, 99%).

There were 53 patients who had prior 5FU-Oxa-Iri. Of these, the IRRC-assessed ORR was 28% (95% CI: 17%, 42%) and the DOR ranged from 2.8 to 22.1 months. Among 15 responders, there were 6 patients whose the DOR was greater than 12 months. The Kaplan-Meier method estimated 100% of the responders with the DOR greater than 12 months.

From a statistical point of view, the results support the approval of the proposed indication.

2 INTRODUCTION

The applicant submitted a supplemental Biologics License Application (sBLA) for nivolumab monotherapy in [redacted] (b) (4)

2.1 Overview

2.1.1 Product and Proposed Indication

Nivolumab, a monoclonal antibody directed against the programmed death-1 (PD-1) receptor, was approved for the treatment of patients with: unresectable or metastatic melanoma, metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy, advanced renal cell carcinoma with prior antiangiogenic therapy, classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin, and recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy. The proposed indication for this sBLA was the treatment of [redacted] (b) (4)

2.1.2 Disease Overview

Colorectal cancer is the third most common cancer in men and the second most common cancer in women with approximately 10% and 9.4% of the total cancers yearly worldwide, respectively.[1] Approximately 15% of CRCs display MSI-H/dMMR either to epigenetic silencing of MLH1 or a germline mutation in one of the mismatch repair genes MLH1, MSH2, MSH6 or PMS2.[2]

Treatment options of patients with mCRC are 5-fluorouracil and leucovorin containing regimens in combination with either oxaliplatin or irinotecan (FOLFOX or FOLFIRI) with a biologic agent, such as bevacizumab. Cetuximab is also an option if KRAS status is non-mutated. Bevacizumab and ziv-afilbercept have indications for second-line treatments in combination with chemotherapy. Regorafenib has also indications for patients who have been previously treated with 5FU-Oxa-Iri, an anti-VEGF therapy, and anti-EGFR therapy if KRAS wild type.

[1] Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc fr, accessed on 12 Sept 2013.

[2] Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998; 338:1481–87.

2.1.3 Clinical Studies

The data of the nivolumab monotherapy arm in the CA209142 study, entitled "A Phase II Clinical Trial of Nivolumab and Nivolumab plus Ipilimumab in Recurrent and Metastatic Microsatellite Instability High Colon Cancer", were submitted to support the proposed indication. The CA209142 study was a phase II, open-label, and multi-center study of nivolumab alone or in combination with ipilimumab in patients with MSI-H mCRC and of nivolumab in combination with ipilimumab in patients with non-MSI-H mCRC. The study consists of three cohorts: MSI-H, non-MSI-H, and MSI-H with no prior therapy. The data of nivolumab monotherapy in the MSI-H were used in this review.

2.2 Data Sources

Materials reviewed for this application include the study protocol, statistical analysis plans, study reports, submitted raw datasets, analytic datasets, and SAS programs of the CA209142 study.

The applicant submitted data on February 2, 2017 with legacy data formats: raw data in the study data tabulation model (SDTM) datasets and analytic data in analysis data model (ADaM) datasets, including SAS programs for key analyses. Datasets are located at: \\cdsesub1\evsprod\BLA125554\0296\m5\datasets\ca209142\analysis\adam\datasets.

At filing meeting, the review team requested that the applicant submits the analysis of durability of response with a minimum follow-up of six months from onset of response in all responding patients prior to day 45 after submission of the application. The applicant submitted the updated clinical study report on March 14, 2017 at \\cdsesub1\evsprod\bla125554\0320\m5\53-clin-stud-rep\535-rep-effic-safety-stud\colorectal-cancer\5351-stud-rep-contr\ca209142\ca209142-ad-hoc-efficacy-crc-mono-2017.pdf

During this sBLA review, the review team requested that the applicant submits the updated datasets supporting the updated clinical study report submitted to FDA on March 14. The applicant submitted the updated data on April 3, 2017 at \\cdsesub1\evsprod\BLA125554\0330\m5\datasets\ca209142\analysis\adam\datasets

3 STATISTICAL EVALUATION

The statistical evaluation consists of data analysis quality, evaluation of efficacy, and statistical methodology.

3.1 Data and Analysis Quality

The data cut-off dated February 6, 2017 were provided electronically with legacy (applicant company standard) formats. Data quality appeared to be appropriate. The derivation of the analysis-ready variables was appropriate. The submitted data allowed this reviewer to replicate the applicant's primary analysis and other submitted efficacy results. The updated version of the study protocol dated August 10, 2016 was submitted with this sBLA. The statistical analysis plan version 2.0 dated August 2, 2016 was submitted before submitting this sBLA.

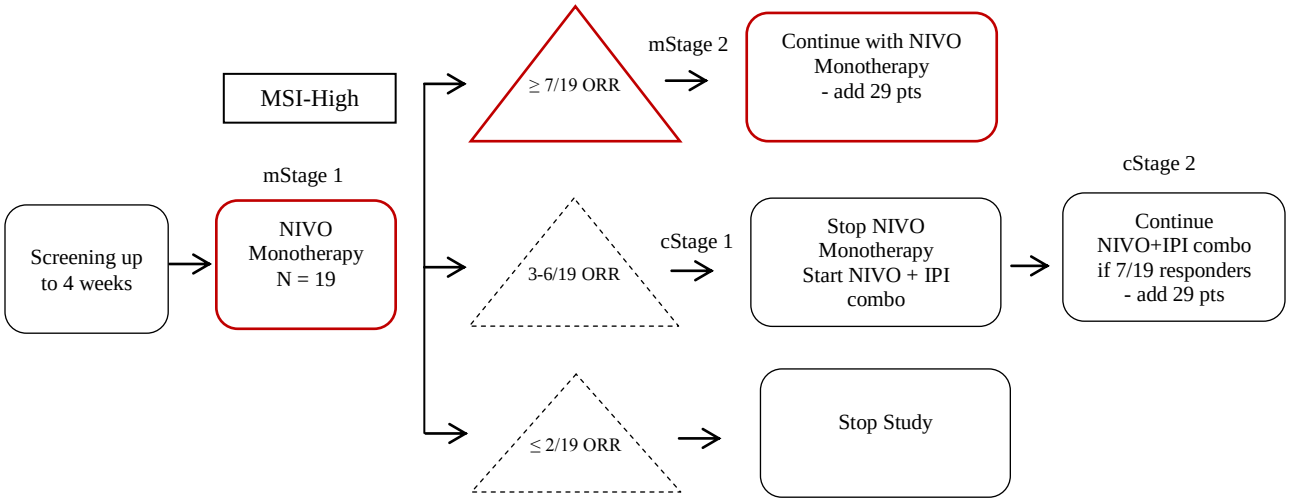
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The data of nivolumab monotherapy cohort in the CA209142 ongoing study was submitted to support the proposed indication. The CA209142 study was a phase II, open-label, multi-center, of nivolumab alone or in combination with ipilimumab in patients with MSI-H mCRC and of nivolumab in combination with ipilimumab in patients with non-MSI-H mCRC. The study was designed as a 2-stage Simon study to estimate the ORR (Figure 1). The proposed dose was 240 mg IV every 2 weeks until disease progression or unacceptable toxicity. The MSI-H was tested by a local-laboratory test either immunohistochemistry (IHC) or polymerase chain reaction (PCR) methods and was subsequently confirmed by a central PCR with Bethesda panel method.

Figure 1. CA209142 Study Design Schematic

2L Colon MSI-H (≥ 1 prior treatment for metastatic disease, ≥ 1 target lesion, and ECOG PS 0-1)



Follow-up minimum 12 weeks. Survival follow-up maximum of 3 years

Source: CA209142 Protocol Study, Figure 1. 2L: second line, mStage: monotherapy stage, cStage: combination stage, Arm N: nivolumab monotherapy, Arm N+I: nivolumab in combination with ipilimumab, and nMSI-H N+I: non-MSI-H nivolumab in combination with ipilimumab. The nivolumab monotherapy cohort was remarked with red borders.

Based on the pre-sBLA meetings between the Agency and the applicant dated May 10, 2016 and December 16, 2016 for the use of data in the nivolumab monotherapy cohort in the CA209142 study to support the proposed indication, the primary efficacy population was patients with local MSI-H after 5FU-Oxa-Iri. The primary endpoint was an independent radiology review committee (IRRC)-assessed ORR defined as the number of patients with a best overall response (BOR) of confirmed complete (CR) or partial (PR), according to RECIST 1.1 criteria. The secondary endpoint included an investigator-assessed ORR.

3.2.2 Sample Size Determination

The planned sample size for the nivolumab monotherapy arm in the CA209142 study was 48 patients. The first stage was planned to treat 19 patients. If there were 7 or more responses, approximately 29 additional patients was planned to be accrued to treat a target of 48 treated patients. If 6 or less responses observed, the accrual to the monotherapy arm was planned to be stopped and the first stage of the combination therapy was planned to be opened for accrual. The null hypothesis will be rejected if 20 or more responses are observed in 48 treated patients in the remaining open arm. Within a given treatment arm, this design yields a one-sided type I error of 5% and power of 90% when the true response rate is 52%. The actual sample size was 74 patients with local MSI-H mCRC and 53 patients with central confirmed MSI-H mCRC.

3.2.3 Statistical Methodologies

The Clopper-Pearson method was used to estimate 95% confidence interval (CI) for ORR. The DOR was summarized using the Kaplan-Meier (KM) method.

3.2.4 Patient Disposition, Demographic, and Baseline Characteristics

Table 1 presents patient disposition.

Table 1. Patient Disposition

Disposition	Local MSI-H N=74	Local MSI-H and After Prior 5FU-Oxa-Iri N=53
Patients treated, n (%)	74 (100)	53 (100)
Discontinued in the treatment period, n (%)	38 (51)	26 (49)
Reason for discontinuation, n (%)		
Disease progression	27 (36)	20 (38)
Study drug toxicity	6 (8.1)	4 (7.5)
Patient requested to discontinue study treatment	1 (1.4)	0
Patient withdraw consent	1 (1.4)	1 (1.9)
Maximum clinical benefit	1 (1.4)	0
Toxicity unrelated to study drug	1 (1.4)	0
Travel inconvenience	1 (1.4)	1 (1.9)
Patients continuing in the study, n (%)	67 (91)	47 (89)
Discontinued in the study, n (%)	7 (9.5)	6 (11)

Table 2 presents patient baseline characteristics.

Table 2. Baseline Characteristics

Characteristic	Local MSI-H N=74	Local MSI-H and After Prior 5FU-Oxa-Iri N=53
Gender, n (%)		
Male	44 (59)	30 (57)
Female	30 (41)	23 (43)
Median age, year (range)	52.5 (26, 79)	52 (26, 79)
Age group, n (%)		
< 65 years	57 (77)	42 (79)
≥ 65 years	17 (23)	11 (21)
Race, n (%)		
White	65 (88)	45 (85)
African American	7 (9.5)	6 (11)
Others	2 (2.7)	2 (4)
Stage, n (%)		
I	2 (2.7)	2 (3.8)
II	13 (18)	10 (19)
III	26 (35)	19 (36)
IV	33 (45)	22 (42)
ECOG, n (%)		
0	32 (43)	21 (40)
1	41 (55)	31 (59)
3	1 (1.4)	1 (1.9)
Regions, n (%)		
Europe	39 (53)	26 (49)
US/Canada	31 (42)	24 (45)
Others	4 (5.4)	3 (5.7)
Smoking status, n (%)		
Current/former	33 (45)	23 (43)
Never smoker	41 (55)	30 (57)
BRAF/KRAS mutation status, n (%)		
KRAS/BRAF wild type	29 (39)	20 (38)
BRAF mutation	12 (16)	6 (11)
KRAS mutation	26 (35)	22 (42)
Unknown	7 (9)	5 (9.4)
Lynch syndrome, n (%)		
Yes	27 (36)	20 (38)
No	28 (38)	15 (28)
Unknown	19 (26)	18 (34)
Central MSI-H, n (%)		
MSI-H	53 (72)	40 (76)
Non MSI-H	14 (19)	8 (15)
Not reported	7 (9.5)	5 (9.4)

3.2.5 Efficacy Results

3.2.5.1 Primary Endpoint: IRRC-Assessed Objective Response Rate

Table 3 presents IRRC-assessed ORR. Among the 74 patients, the ORR was 32% (95% CI: 22%, 44%). The IRRC-assessed DOR ranged from 1.4 to 26.5 months, while the median was not estimable. Among 24 responders, there were 9 patients whose the DOR was greater than 12 months. The Kaplan-Meier method estimated 95% of the responders with the DOR greater than 12 months (95% CI: 68%, 99%). There were 53 patients who had prior 5FU-Oxa-Iri. Of these, the IRRC-assessed ORR was 28% (95% CI: 17%, 42%) and the DOR ranged from 2.8 to 22.1 months. Among 15 responders, there were 6 patients whose the DOR was greater than 12 months. The Kaplan-Meier method estimated 100% of the responders with the DOR greater than 12 months.

Table 3. IRRC-Assessed Overall Response Rate

Response	Local MSI-H N=74	Local MSI-H and After Prior 5FU-Oxa-Iri N=53
Objective Response Rate (CR+PR), n (%)	24 (32)	15 (28)
(95% CI)	(22, 44)	(17, 42)
Complete response (CR), n (%)	2 (2.7)	1 (1.9)
Partial response (PR), n (%)	22 (30)	14 (26)
Duration of Response	(n=24)	(n=15)
Median in month (range)	NE (1.4+, 26.5+)	NE (2.8+, 22.1+)
% with duration ≥ 12 months[†]	95%	100%
(95%CI)	(68, 99)	(100, 100)

5FU-Oxa-Iri, fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, IRRC: independent radiology review committee, NE: not estimable, CI: confidence interval. [†] Based on Kaplan-Meier estimation.

3.2.5.2 Secondary Endpoint: Investigator-Assessed Objective Response Rate

Table 4 presents investigator-assessed ORR. Among the 74 patients, the ORR was 31% (95% CI: 21%, 43%). The investigator-assessed DOR ranged from 3.9 to 26.5 months, while the median was not estimable. Among 23 responders, there were 8 patients whose the DOR was greater than 12 months. The Kaplan-Meier method estimated 86% of the responders with the DOR greater than 12 months (95% CI: 62%, 95%). Of the 53 patients with prior 5FU-Oxa-Iri, the investigator-assessed ORR was 26% (95% CI: 15%, 40%). The investigator-assessed DOR ranged from 3.9 to 23.5 months and the median was not estimable. Among 14 responders, there were 5 patients whose the DOR was greater than 12 months. The Kaplan-Meier method estimated 100% of the responders with the DOR greater than 12 months.

Table 4. Investigator-Assessed Overall Response Rate

Responses	Local MSI-H N=74	Local MSI-H and After Prior 5FU-Oxa-Iri N=53
Objective Response Rate (CR+PR), n (%)	23 (31)	14 (26)
(95% CI)	(21, 43)	(15, 40)
Complete response (CR), n (%)	0	0
Partial response (PR), n (%)	23 (31)	14 (26)
Duration of Response	(n=23)	(n=14)
Median in month (range)	NE: (3.9+, 26.5+)	NE (3.9+, 23.5+)
% with duration ≥ 12 months[†]	86%	100%
(95%CI)	(62, 95)	(100, 100)

5FU-Oxa-Iri, fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, IRRC: independent radiology review committee, NE: not estimable, CI: confidence interval. [†] Based on Kaplan-Meier estimation.

Reviewer's Comments:

- *The ORR and DOR results based on IRRC and investigator assessments were similar.*

3.3 Evaluation of Safety

Please refer to the clinical review of this supplemental application for details of the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The reviewer performed the analysis of the ORR across subgroups defined by gender, race, age, and geographic region, smoking status, BRAF/KRAS mutation status, and lynch syndrome.

4.1 Gender, Race, Age, and Geographic Region

Table 6 presents IRRC-assessed ORRs in the subgroups.

Table 6. IRRC-Assessed Objective Response Rate in Subgroups

Subgroups	Local MSI-H N=74	Local MSI-H and After Prior 5FU-Oxa-Iri N=53
	n/N (%)	n/N (%)
Gender		
Male	14/44 (32)	9/30 (30)
Female	10/30 (33)	6/23 (26)
Age group		
< 65 years	19/57 (33)	13/42 (31)
≥ 65 years	5/17 (29)	2/11 (18)
Race		
White	20/65 (31)	12/45 (27)
African American	3/7 (43)	2/6 (33)
Others	1/2 (50)	1/2 (50)
Regions		
Europe	11/39 (28)	7/36 (27)
US/Canada	13/31 (42)	8/24 (33)
Others	0/4 (0)	0/3 (0)
Smoking status		
Current/former	8/33 (24)	3/23 (13)
Never smoker	16/41 (39)	12/30 (40)
BRAF/KRAS mutation status		
KRAS/BRAF wild type	4/12 (33)	1/6 (17)
BRAF mutation	8/26 (31)	7/22 (32)
KRAS mutation	9/29 (31)	6/20 (30)
Unknown	3/7 (43)	1/5 (20)
Lynch syndrome		
Yes	8/27 (30)	6/20 (30)
No	10/28 (36)	3/15 (20)
Unknown	6/19 (32)	3/18 (33)

IRRC: independent radiology review committee, n: number of response, N: number of total subgroup patients.

Reviewer's Comments:

The IRRC-assessed ORRs in majority subgroups were consistent with the results of all patients.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues identified during the review.

5.2 Collective Evidence

The proposed indication in this sBLA submission was the treatment of (b) (4) The IRRC-assessed ORR in the 74 enrolled patients was 32% (95%CI: 22%, 44%). The IRRC-assessed DOR ranged from 1.4 to 26.5 months. The median DOR was not estimable. Among 24 responders, there were 9 patients whose the DOR was greater than 12 months. The Kaplan-Meier method estimated 95% of the responders with the DOR greater than 12 months (95% CI: 68%, 99%).

There were 53 patients who had prior 5FU-Oxa-Iri. The IRRC-assessed ORR was 28% (95%CI: 17%, 42%). The DOR ranged from 2.8 to 22.1 months. Among 15 responders, there were 6 patients whose the DOR was greater than 12 months. The Kaplan-Meier method estimated 100% of the responders with the DOR greater than 12 months.

5.3 Conclusions and Recommendations

From a statistical point of view, the results support the approval of the proposed indication.

5.4 Labeling Recommendations

The IRRC-assessed ORRs and DORs in patients with local MSI-H and the local MSI-H with prior 5FU-Oxa-Iri can be included in the product label.

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/s/

UMAPORN SIANGPHOE
07/05/2017

LISA R RODRIGUEZ
07/06/2017

KUN HE
07/06/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BLA Clinical Pharmacology Review	
NDA/SDN/eCTD Sequence No.	BLA125554/296, Supplement-34
Type/Category	Efficacy
Brand Name	OPDIVO®
Generic Name	Nivolumab
Receipt Date	02/02/2017
PDUFA Date	08/02/2017
Proposed Indication	(b) (4)
Dosing Regimen	240mg IV infusion over 60 minutes every 2 weeks (Q2W)
Dosage Form and Strengths	40 mg/4 mL and 100 mg/10 mL solution in a single-dose vial
Route of Administration	Intravenous
Applicant	Bristol-Myers Squibb Company
OCP Division	Division of Clinical Pharmacology V (DCPV)
OND Division	Division of Oncology Products 2 (DOP2)
Reviewers	Yuan Xu, Ph.D., Saeho Chong, Ph.D.
Secondary Reviewers	Hong Zhao, Ph.D., Jiang Liu, Ph.D.

Table of Contents

1 EXECUTIVE SUMMARY

In this efficacy supplement, BMS is proposing to use nivolumab for the treatment of (b) (4) under accelerated approval. The proposed dose of nivolumab is 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks (Q2W) until disease progression or unacceptable toxicity.

The primary evidence to support the proposed indication is based on the trial CA209142, an open-label, multi-center, 2-stage Simon design study of nivolumab monotherapy to estimate the response rate in MSI-H CRC and mismatch repair deficient (dMMR)/non-MSI-H CRC. The primary objective is to evaluate the investigator-assessed objective response rate (ORR) of nivolumab 3 mg/kg Q2W monotherapy in patients with dMMR/MSI-H CRC. The investigator-assessed ORR using RECIST 1.1 was 31.1% (23/74) in all nivolumab monotherapy treated patients and 26.4% (14/53) in patients with prior 5FU-Oxa-Iri; with all responders achieving a PR. The investigator-assessed disease control rate (DCR) was 68.9% in all nivolumab monotherapy treated patients and 62.3% in patients with prior 5FU-Oxa-Iri.

Nivolumab pharmacokinetics in patients with MSI-H/dMMR colorectal cancer is comparable with previous NSCLC patients. A flat exposure response relationship was observed between nivolumab AUC in the first cycle and the response rate. The overall difference in the nivolumab exposure between the proposed 240mg Q2W dosing regimen in label and the 3mg/kg Q2W dosing regimen in trial CA209142 was bridged by population PK (PPK) modeling and simulation and it is below 7%. With the flat exposure response relationship, this small difference is unlikely to cause clinically meaningful difference. Thus the 240mg Q2W proposed in the label for MSI-H/dMMR CRC indication is acceptable.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology, Divisions of Clinical Pharmacology V and Pharmacometrics have reviewed the pertinent information contained in this supplement for BLA 125554. The information supports the approval of the nivolumab 240 mg Q2W dosing regimen for the proposed indication, for the treatment of (b) (4) .

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

Signatures:

Yuan Xu, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Jiang Liu, Ph.D. Pharmacometrics Team Leader Division of Pharmacometrics
Saeho Chong, Ph.D. Reviewer Division of Clinical Pharmacology V	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V

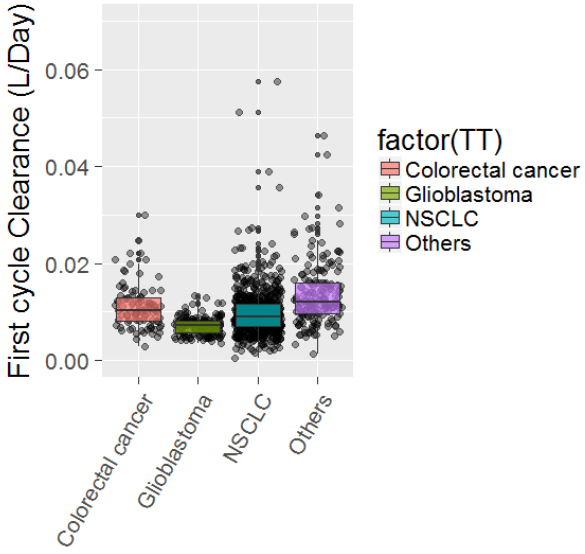
Cc: DOP2: RPM – M Libeg; MTL –S Lemery; MO – D Smit;
DCPV: DDD - B Booth; DD - A Rahman

2 QUESTION BASED REVIEW

2.1 Is nivolumab pharmacokinetics in MSI-H/dMMR CRC patients comparable to that in patients with other indications?

Yes. Nivolumab concentration-time data were well described by a previously-developed linear, two-compartment, zero-order input intravenous (IV) infusion model with time-varying clearance. Tumor type was incorporated into PPK model and was proved not a significant covariate. The first cycle clearance was generated by PPK model and compared within different indications demonstrating no difference cross tumor types (Figure 1). Thus the same dose of 240 mg Q2W for other approved indications can be used for MSI-H/dMMR CRC patients.

Figure 1: Comparison of First Cycle Clearance between CRC Patients with Other Indications

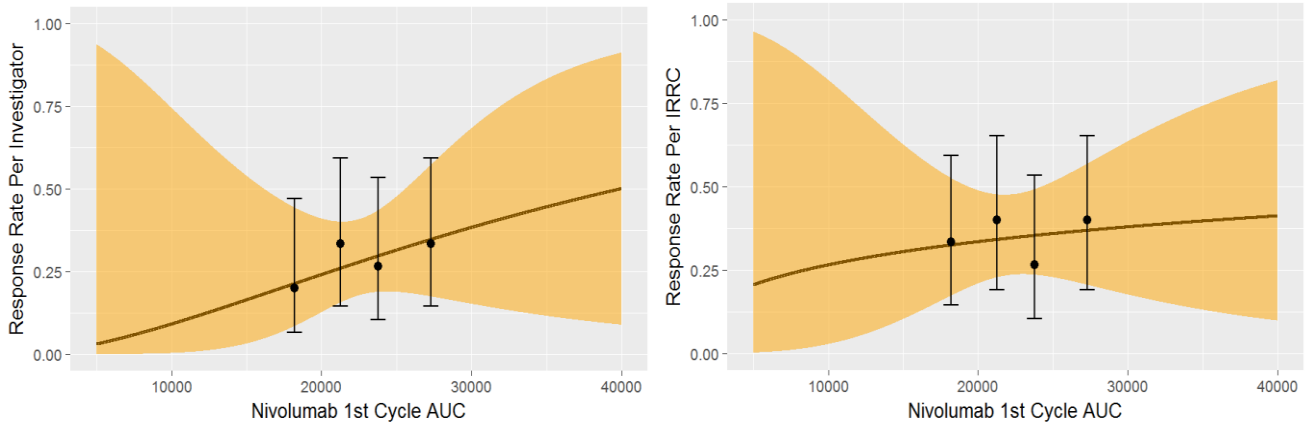


FDA reviewer analysis: Comparison of first cycle clearance within different indications

2.2 What are the exposure-response relationships for efficacy in MSI-H/dMMR CRC patients?

The exposure-response relationship for efficacy in MSI-H/dMMR CRC patients is relatively flat (Figure 2). ER-efficacy relationship was conducted with 60 MSI-H/dMMR CRC patients in study CA209142. The relationship between nivolumab first cycle AUC and response rate per investigator and IRRC was analyzed by logistic regression and nivolumab AUC is not a significant covariate for response rate when included ECOG as covariate.

Figure 2: Exposure response relationship in MSI-H/dMMR CRC patients



FDA reviewer's analysis: Solid line is the logistic regression of the predicted probability of response rate (Left: per investigator; Right: per IRRC) and the yellow area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as circle and error bar vs the mean concentration.

2.3 Is the proposed 240 mg q2w flat dosing in label to replace the 3 mg/kg q2w dose in trial supported by clinical pharmacology findings?

Yes, the two different dosing regimens, 3 mg/kg Q2W and 240 mg Q2W have been bridged by PPK modeling and simulation. The 240 mg Q2W flat dosing is currently approved in the label for metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, and urothelial carcinoma. Based on simulations, the overall exposure at 240 mg Q2W flat dose is similar (<7% difference) to that at 3 mg/kg Q2W (Table 1). Such small difference in exposure is unlikely to have any clinically meaningful impact on efficacy and safety.

Table 1: Exposure Comparison between 240 mg Q2W versus 3 mg/kg Q2W

Tumor Type	Exposure Parameter (μg/mL)	Geometric Mean [CV%]		GM Diff[a] Percent (%)	Median (P05, P95)[b]	
		240 mg Q2W	3 mg/kg Q2W		240 mg Q2W	3 mg/kg Q2W
CRC	CMIN1	17.8[32.3]	16.8[30.6]	5.95	17.9[11.4-28.9]	17.3[10.1-26.7]
	CMAX1	61.1[29.6]	57.7[19.2]	5.89	61.9[37.2-97.1]	59.5[41.4-76.7]
	CAVG1	28.1[26]	26.5[24.5]	6.04	28.4[18.7-41.5]	26.5[17-38.1]
	CMINSS	72.8[56.1]	68.7[48.8]	5.97	74.1[35-179]	71.3[32.8-156]
	CMAXSS	136[41.6]	128[33.5]	6.25	136[75.9-270]	131[76-228]
	CAVGSS	93.2[48.5]	87.9[41.8]	6.03	94.2[50.2-205]	90.8[49.3-178]

[a] GM Diff Percent = [(Geometric mean of 240 mg Q2W - Geometric mean of 3 mg/kg Q2W) / Geometric mean of 3 mg/kg Q2W] * 100

[b] P05: the 5th percentile; P95 the 95th percentile

Source: Table 5.1.3.4-1 of sponsor's Pop-PK report

3 DETAILED LABELING RECOMMENDATIONS

None

4 APPENDIX: PHARMACOMETRICS REVIEW

The primary information to support this efficacy supplement is based on the Phase 2 trial CA209142, an open-label, multi-center, 2-stage Simon design study of nivolumab monotherapy to estimate the response rate in MSI-H CRC and mismatch repair deficient (dMMR)/non-MSI-H CRC. The primary objective is to evaluate the investigator-assessed ORR of nivolumab 3 mg/kg Q2W monotherapy in dMMR/MSI-H CRC.

To facilitate straightforward comparisons to currently available 3L therapies for unselected mCRC, and to demonstrate the consistency of efficacy and safety of nivolumab monotherapy in a heavily-pretreated MSI-H/dMMR mCRC population, a subset analysis was also performed on those patients previously treated at any time with fluoropyrimidine + oxaliplatin and irinotecan-based chemotherapy (heretofore called subjects with prior 5FU-Oxa-Iri).

- **MSI-H/dMMR per local lab- all subjects (all nivolumab monotherapy treated subjects):** n = 74, of which 73 had 1 prior therapies (median of 3 prior lines of therapy); treated with nivolumab 3 mg/kg administered as a 60-minute IV infusion Q2W

- **MSI-H/dMMR per local lab- subjects with prior 5FU-Oxa-Iri:** n = 53, treated with nivolumab 3 mg/kg administered as a 60-minute IV infusion Q2W

4.1 Regulatory History

Nivolumab is a humanized monoclonal antibody currently approved for the treatment of patients with:

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.

- BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

- Unresectable or metastatic melanoma, in combination with ipilimumab. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy.

- Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.

- Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who 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.

4.2 RESULTS OF APPLICANT'S ANALYSIS

OBJECTIVES

- Characterize nivolumab pharmacokinetics (PK) in subjects with mCRC and GBM, and assess the effect of tumor type on nivolumab clearance and central volume of distribution in comparison to NSCLC.

- Compare the nivolumab exposures in mCRC and GBM subjects produced by nivolumab 3 mg/kg Q2W with thecorresponding exposures in NSCLC subjects (3 mg/kg Q2W).

- Compare the nivolumab exposures in mCRC and GBM subjects produced by nivolumab 3 mg/kg Q2W, with the corresponding exposures produced by 240 mg/kg Q2W in these subjects

DATA

PPK Analysis: Nivolumab monotherapy data were obtained from seven clinical studies (MDX-1106-01 [Phase 1], MDX-1106-03 [Phase 1], CA209017 [Phase 3], CA209057 [Phase 3], CA209063 [Phase 2], CA209142 [Phase 2], and CA209143 [Phase 3]). The selected studies include all studies in which nivolumab PK in mCRC and GBM subjects was available, as well as two Phase 1 studies in which nivolumab PK was sampled intensively. These studies were selected to enable a robust characterization of nivolumab PK in mCRC and GBM, relative to that of NSCLC.

METHODS

Population Pharmacometrics Model

The PPK analysis serves to further characterize nivolumab PK in subjects with solid tumors, based on the previously established nivolumab PPK model, with a focus on nivolumab PK in subjects with mCRC or GBM. The PPK analysis includes assessment of the effect of tumor type.

The PPK model development consisted of two steps applied to the data in the seven studies considered here: First, a base model was developed by re-estimating the parameters of a previously-developed model. Second, a full model was developed to assess the effect of tumor type on nivolumab PK. Baseline covariates examined in the full model included body weight, race, sex, baseline estimated glomerular filtration rate (eGFR), and tumor type.

Prediction-corrected visual predictive check (pcVPC) was used to evaluate the prediction performance of the developed full PPK model, given the data. The following six summary measures of individual nivolumab exposure were obtained and summarized from the full model for each subject for whom maximum a posteriori (MAP) Bayesian estimates of the PK parameters were available: Cmin1, Cminss, Cmax1, Cmaxss, Cavg1, and Cavgss.

The relationship between these measures of exposure and tumor type (NSCLC 2L+ versus CRC versus GBM) were also presented.

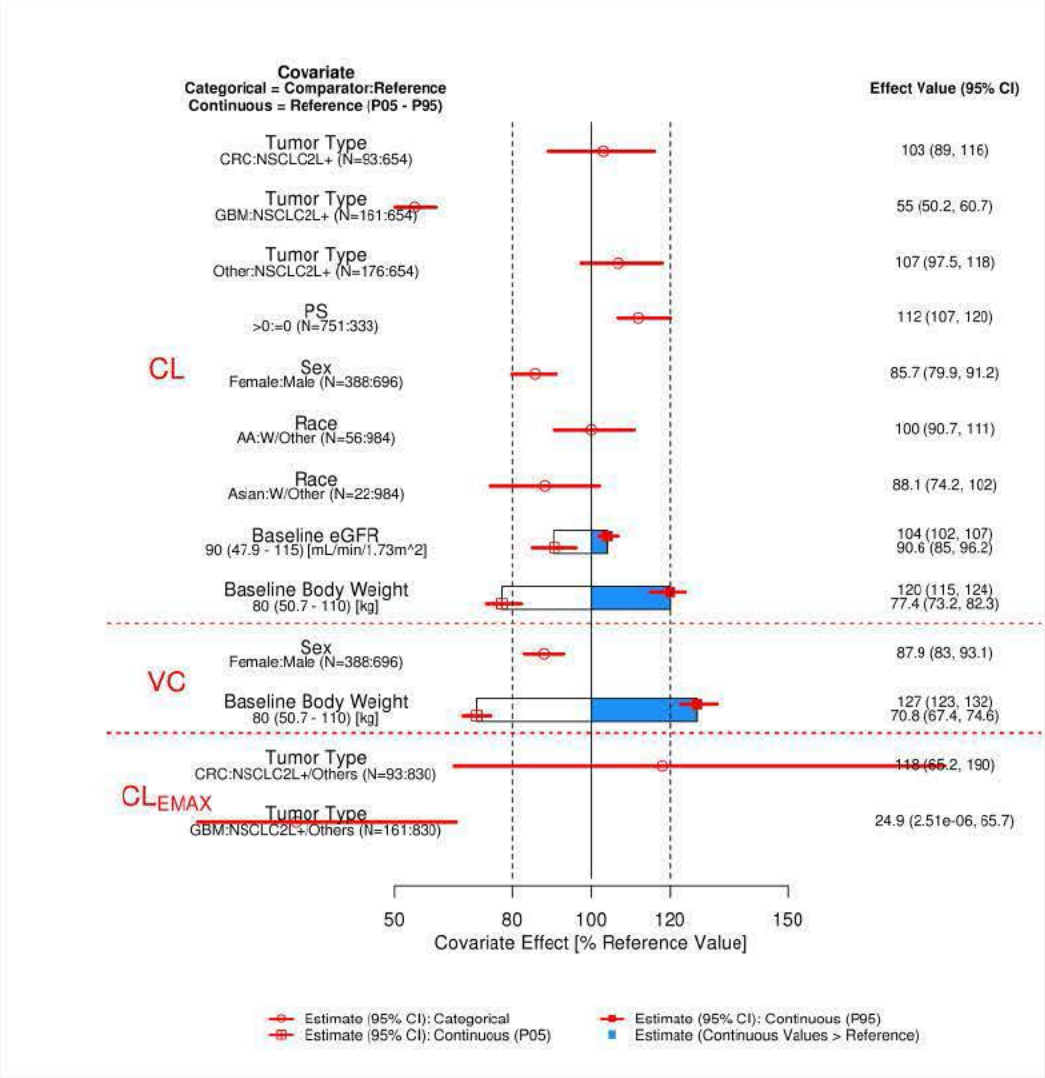
Comparison of Exposures of 240mg Q2W Dose Regimen and 3mg/kg Dose Regimen

Two-treatment regimens: a weight-based 3 mg/kg Q2W dose and the flat 240 mg Q2W dose regimen. The full population PK model and the MAP Bayesian parameter estimates, including measures of interindividual variability, was used as a basis for these simulations. Six measures of individual exposure (Cmin1, Cminss, Cmax1, Cmaxss, Cavg1, and Cavgss), were simulated for each subject for the 3 mg/kg Q2W and 240 mg Q2W treatment regimens using the full population PK model. Graphical displays of nivolumab exposure measures were compared between the two-dose regimens (3 mg/kg Q2W and 240 mg Q2W).

RESULTS

Nivolumab concentration-time data were well described by a previously-developed linear, two-compartment, zero-order input intravenous (IV) infusion model with time-varying clearance. The covariate effects estimated in the full model are shown in Figure 3. Parameter estimates from the full PPK model are provided in Table 2.

Figure 3: Covariate Effects on PPK Model Parameters (Full PPK Model)



Source: Figure 1 of sponsor's Pop-PK report

Table 2: PPK Model Parameter Estimates (Full Model)

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
CL [L/h]	θ_1	0.0113	5.32E-04 (4.71)	0.0102 - 0.0126
VC [L]	θ_2	4.19	0.0649 (1.55)	4.06 - 4.30
Q [L/h]	θ_3	0.0311	0.00380 (12.2)	0.0256 - 0.0441
VP [L]	θ_4	2.90	0.160 (5.52)	2.56 - 3.27
PERR [-]	θ_6	0.233	0.0107 (4.59)	0.214 - 0.255
CL_{BBWT}	θ_7	0.561	0.0653 (11.6)	0.428 - 0.682
CL_{BGFR}	θ_9	0.157	0.0508 (32.4)	0.0609 - 0.257
CL_{SEX}	θ_{12}	-0.154	0.0326 (21.2)	-0.224 - -0.0921
CL_{PS}	θ_{13}	0.117	0.0290 (24.8)	0.0640 - 0.179
VC_{BBWT}	θ_{14}	0.758	0.0544 (7.18)	0.641 - 0.864
VC_{SEX}	θ_{15}	-0.129	0.0297 (23.0)	-0.186 - -0.0714
CL_{EMAX}	θ_{16}	-0.354	0.0692 (19.5)	-0.502 - -0.190
CL_{T50}	θ_{17}	1.50E+03	246 (16.4)	954 - 2130
CL_{HILL}	θ_{18}	1.96	0.614 (31.3)	1.23 - 12.3
CL_{RAAA}	θ_{19}	0.00409	0.0486 (1.19E+03)	-0.0972 - 0.107
CL_{RAAS}	θ_{20}	-0.127	0.0787 (62.0)	-0.299 - 0.0176
CL_{CRC}	θ_{22}	0.0342	0.0615 (180)	-0.116 - 0.151
CL_{GBM}	θ_{23}	-0.598	0.0501 (8.38)	-0.689 - -0.500
CL_{OTH}	θ_{24}	0.0669	0.0455 (68.0)	-0.0251 - 0.165
$EMAX_{CRC}$	θ_{27}	0.164	0.248 (151)	-0.427 - 0.641
$EMAX_{GBM}$	θ_{28}	-1.39	0.864 (62.2)	-17.5 - 0.420
Random Effects[f,g]				
$\omega^2 CL$ [-]	$\omega_{1,1}$	0.113 (0.336)	0.0108 (9.56)	0.0911 - 0.140
$\omega^2 VC$ [-]	$\omega_{2,2}$	0.103 (0.321)	0.0182 (17.7)	0.0691 - 0.138
$\omega^2 VP$ [-]	$\omega_{3,3}$	0.261 (0.511)	0.0390 (14.9)	0.191 - 0.349
$\omega^2 CL_{EMAX}$	$\omega_{4,4}$	0.0988 (0.314)	0.0344 (34.8)	0.0472 - 0.172
$\omega^2 CL$: $\omega^2 VC$	$\omega_{1,2}$	0.0543 (0.503)	0.00886 (16.3)	0.0360 - 0.0712

[a] Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

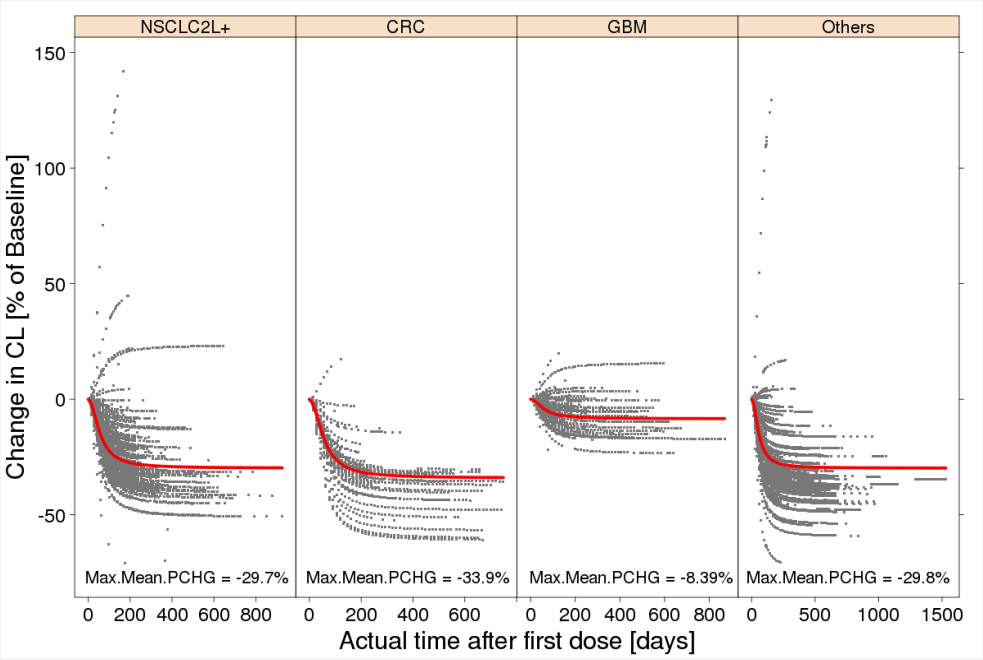
[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

Source: Table 1 of Sponsor's Pop-PK report

Nivolumab CL decreases with time, and that the maximal decrease is approximately 30% from baseline [calculated as: 1-exp(CLEMAX)]. When the tumor type effects are taken into consideration, the magnitude of CL change over time of GBM subjects appeared to be different relative to NSCLC 2L+ while that of mCRC subjects appeared to be comparable to the reference NSCLC 2L+ population, as shown in Figure 4

The change in CL is estimated to occur soon after initiation of treatment, with the half-maximal change estimated to occur at approximately 2 months (CLT50 = 1500 h). The geometric mean CL for mCRC subjects of 11.7 mL/hr (after the first dose) reaches a steady-state value of 7.71 mL/hr while the GBM subjects have a geometric mean CL of 6.21 mL/hr reaching a steady-state value of 5.69 mL/hr.

Figure 4: Model-Estimated Change in Clearance versus Time (Full Model) by Tumor Type



Source: Figure 5.1.3.1-1 sponsor's Pop-PK report

Conclusions:

- Nivolumab PK was well described by a linear two-compartment model with time-varying CL, with typical CL decreasing over time (~30%). The primary PK parameters and the estimated covariate effects on CL (baseline body weight, baseline eGFR, Sex, and PS) and VC (baseline body weight and Sex) are comparable to what was reported previously.
- Baseline CL in mCRC was slightly higher (~3%) relative to NSCLC 2L+ subjects, and the magnitude of CL decrease over time was also slightly higher relative to NSCLC 2L+ (~34% vs 30%).
- Subjects with mCRC have comparable exposures to those of subjects with NSCLC 2L+, (geometric mean differences in Cmax1, Cmin1, Cavg1, Cminss, Cmaxss, and Cavgss are less than 10%).
- A flat dose regimen 240 mg Q2W is predicted to provide comparable exposures to those following administration of nivolumab 3 mg/kg Q2W for both mCRC and GBM subjects (less than 7% differences in Cmin1, Cmax1, Cavg1, Cminss, Cmaxss, and Cavgss).

FDA Reviewer's Comments: *Exposure response for efficacy was not conducted by sponsor since just 3mg/kg dosing regimen is tested in clinical trial CA209402. FDA pharmacometrics reviewer analysis exposure response for efficacy with exposure versus response rate per investigator and IRRC (Section 4.3.3). The sponsor's Pop-PK model and conclusion that MSI-H/dMMR CRC patients pop-PK is comparable to NSCLC patients is acceptable. The proposed 240mg Q2W flat dose regimen in label is acceptable according to previous review (Yuan Xu DARRTS Aug. 3rd 2016).*

4.3 Results of reviewer's analysis

4.3.1 Objectives

- To determine if there is exposure-response relationship for efficacy in the indication of MSI-H/dMMR CRC.
- To determine if there is a need to adjust dose in the proposed indication of MSI-H/dMMR CRC

4.3.2 Methods

Dataset ppkmega2FD.csv was extracted with sponsor's PPK dataset PPKMEGA2.csv to access the 1st dose clearance.

4.3.2.1 Data and Code

File	Description	Link to EDR
full-v5-3-ctm-first-dose_retry8 mod	Pop-PK 1st cycle model control panel	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Nivolumab_BLA125554s34_YX\POP-PK\final model for 1 cycle clearance
ppkmega2FD.csv	Pop-PK 1ST cycle model dataset	
full-v5-3-ctm-first-dose_retry8.patab002_pirana.csv	Pop-PK 1ST cycle model output	
full-v5-3-ctm-first-dose_retry8.lst	Pop-PK 1ST cycle model list file	
Nivo_S34_ER.R	ER-efficacy code	\\cdsnas\pharmacometrics \Reviews\Ongoing PM Reviews\Nivolumab_BLA125554s34_YX\ER
ADEFRESP 2.csv ADEFTTES.csv adsl.csv PPKMEGA2.csv	ER-efficacy dataset	\\cdsnas\pharmacometrics \Reviews\Ongoing PM Reviews\Nivolumab_BLA125554s34_YX\ER

4.3.2.2 Software

R3.2.2 and NONMEN7.3

4.3.3 Results

Please refer to sections above.

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/s/

YUAN XU
07/06/2017

HONG ZHAO
07/06/2017
I concur.

JIANG LIU
07/06/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

OTHER REVIEW(S)

MEMORANDUM

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

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

Date: July 19, 2017

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

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

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

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OPDP has reviewed the proposed product labeling (PI) for OPDIVO (nivolumab) injection, for intravenous use (Opdivo) as requested in the consult dated February 7, 2017. The following comment, using the proposed substantially complete, marked-up version of the PI emailed to OPDP by Meredith Libeg on June 27, 2017, is provided below.

We have no comments at this time.

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

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/s/

NICHOLAS J SENIOR
07/19/2017

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

PATIENT LABELING REVIEW

Date:	July 12, 2017
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nicholas Senior, PharmD, JD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	OPDIVO (nivolumab)
Dosage Form and Route:	injection, for intravenous infusion
Application Type/Number:	BLA 125554
Supplement Number:	S-034
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On February 2, 2017, Bristol-Myers Squibb Company submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved Biologics License Application (BLA) 125554/S-034 for OPDIVO (nivolumab) injection. With this supplement, the Applicant proposes to include a new indication under accelerated approval for OPDIVO (nivolumab) injection for the treatment of (b) (4) OPDIVO (nivolumab) injection was originally approved under Accelerated Approval on December 22, 2014.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on February 7, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for OPDIVO (nivolumab) injection, for intravenous injection.

2 MATERIAL REVIEWED

- Draft OPDIVO (nivolumab) injection MG received on February 2, 2017 and further revised on May 5, 2017, and received from the Review Division by DMPP and OPDP on June 27, 2017.
- Draft OPDIVO (nivolumab) injection Prescribing Information (PI) received on February 2, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on June 27, 2017.
- Approved OPDIVO (nivolumab) injection labeling dated April 25, 2017.

3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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/s/

SHARON R MILLS
07/12/2017

NICHOLAS J SENIOR
07/12/2017

BARBARA A FULLER
07/12/2017

LASHAWN M GRIFFITHS
07/12/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s034

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119381

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Linda Gambone, Ph.D.
Director, Global Regulatory, Safety & Biometrics
Route 206 & Province Line Road
Princeton, NJ 08543

Dear Dr. Gambone:

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

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2016. The purpose of the meeting was to discuss the discuss the results from study CA209142, titled "A Phase 2 Clinical Trial of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Microsatellite Instability High [MSI-H] Colon Cancer), intended to support a planned supplemental BLA (sBLA) seeking a new claim for nivolumab, as a single agent, for the proposed indication of the treatment of (b) (4) [redacted]".

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	Friday, December 16, 2016; 3:00 to 4:00 PM (ET)
Meeting Location:	White Oak Building 22, Conference Room: 1311
Application Number:	IND 119381
Product Name:	Nivolumab
Indication:	Treatment of (b) (4)
Sponsor/Applicant Name:	Bristol-Myers Squibb (BMS)
Meeting Chair:	Steven Lemery
Meeting Recorder:	Gina Davis

FDA ATTENDEES

Patricia Keegan, M.D.	Division Director, DOP2
Steven Lemery, M.D., M.H.S.	Clinical Team Leader, DOP2
Damiette Smit, M.D.	Medical Officer, DOP2
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, DCP5, OCP
Brian Furmanski, Ph.D.	Clinical Pharmacology Reviewer, DCP5, OCP
Lisa Rodriguez, Ph.D.	Statistical Team Leader, DBV
Saeho Chong, Ph.D.	Clinical Pharmacology Reviewer, DCP5, OCP
Gina Davis	Senior Regulatory Health Project Manager, DOP2
Janaki Veeraraghaven, Ph.D.	Reviewer, CDRH

SPONSOR ATTENDEES

Rebecca Moss, M.D.	Director Oncology, Global Clinical Research
Ian Waxman, M.D.	Development Lead, Opdivo/Yervoy, G.I.
Jingli Song, Ph.D.	Director Global Biometric Sciences Research
Linda Gambone, Ph.D.	Director, U.S. Regulatory Sciences
Alexandra Park, Ph.D.	Director Global Regulatory Sciences

Eric Richards	Executive Director Global Regulatory Sciences
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences, Oncology
George Green, Ph.D.	Group Director, Pharmacodiagnostics
Louis Kayitalire, M.D.	Clinical Team Leader, Opdivo/Yervoy
Alexander Cao, Ph.D.	Director, Biomarkers-Oncology
Theresa Sanchez, M.D.	Program Lead, Opdivo/Yervoy, GI

BACKGROUND

Nivolumab, a monoclonal antibody directed against the programmed death-1 (PD-1) receptor, is approved for the treatment of patients with: unresectable or metastatic melanoma, metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy; advanced renal cell carcinoma in patients who have received prior antiangiogenic therapy; classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin; and recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

BMS plans to submit a supplemental Biologics License Application (sBLA) for nivolumab, as a single agent, for the treatment of (b) (4) in Q42016. The sBLA will be supported primarily by efficacy and safety data from a single clinical trial, Study CA209142, entitled "A Phase 2 Clinical Trial of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Microsatellite Instability High Colon Cancer."

The goal of the meeting is to obtain FDA feedback, and to reach an agreement on the adequacy of the sBLA submission for review to support a potential registration for the proposed indication.

Regulatory History

- On January 10, 2014, a new IND was submitted which contained the clinical protocol, Protocol CA209142 entitled, "A Phase II clinical trial of nivolumab in recurrent and metastatic microsatellite instability high (MSI-H) colon cancer." This trial is also referred to as Checkmate (Checkpoint Pathway and Nivolumab Clinical Trial Evaluation) 142.
- On February 4, 2014, IND 119381 was allowed to proceed.
- On February 19, 2014, a revised protocol was submitted which clarified that the primary endpoint of the trial was to evaluate the investigator–assessed overall response rate (ORR) and that evaluation of IRRC-assessed ORR in patients with metastatic MSI-H CRC was the (sole) secondary endpoint.
- On May 10, 2016, a Type C teleconference was held between FDA and BMS to discuss and obtain FDA feedback on the use of data from Study CA209142, (b) (4). BMS proposed to submit data from approximately

62 patients with dMMR/MSI-H CRC enrolled in CA209142 who had a minimum of 6 months of follow up data. BMS provided the following results obtained as of November 2015:

	Nivolumab 3 mg/kg		Nivolumab 3 mg/kg + ipilimumab 1	
	MSI-H (local lab) N=33	MSI-H (central lab) N=20*	MSI-H (local lab) N=26	MSI-H (central lab) N=17**
ORR, n (%)	9/33 (27.3)	6/20 (30)	4/26 (15.4)	3/17 (17.6)
Best overall response				
CR	0	0	0	0
PR	9 (27.3)	6	4 (15.4)	3
SD	8 (24.2)	5	17 (65.4)	10 (58.8)
PD	11 (33.3)	5	3 (11.5)	3
Not	4 (12.1)	4	0	0
Not reported	1 (3)		2	1
Additional responders (one subject with unconfirmed PR as of database lock but subsequently				
ORR, n (%)	10/33 (30.3)	7/20 (35)	4/26 (15.4)	3/17 (17.6)
* Of the 33 subjects, 20 have been confirmed by central lab to be MSI-H; 5 non-MSI-H, and 8 with not enough tissue for central lab testing ** Of the 26 subjects, 17 have been confirmed by central lab to be MSI-H; 5 non-MSI-H,				

During the meeting, BMS confirmed that ORR as assessed by the IRRC will be used as the primary endpoint. BMS noted that the lower limit of the 95% confidence interval (CI) for the projected response rates of 25% to 35% ranged from 14.7% to 23.1%, which exceeded the response rates observed with Lonsurf and regorafenib, which are approved for use in patients who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. Thus the data could provide evidence that nivolumab provided a significant improvement over available therapy in patients who been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy.

In addition, FDA expressed concern regarding the unexpectedly high rate of discrepancy between local and central MSI-H results in Study CA209142. FDA stated that the sBLA should contain information on local and central testing for MSI-H for all patients. BMS planned to assess the possible reasons for these discrepancies based on a case-by-case review and agreed to provide a summary of their findings prior to the filing of the sBLA.

- On July 28, 2016, FDA issued an Agreed iPSP for nivolumab, (b) (4) [redacted]

- On August 4, 2015, a revised version of Protocol CA209142 was submitted which contained the following changes: 1) addition of a biomarker collection schedule for subjects dosed with the combination of nivolumab plus ipilimumab and 2) inclusion of an appendix regarding MSI testing panel descriptions (PCR and IHC), classification of MSI status, and sample prioritization.

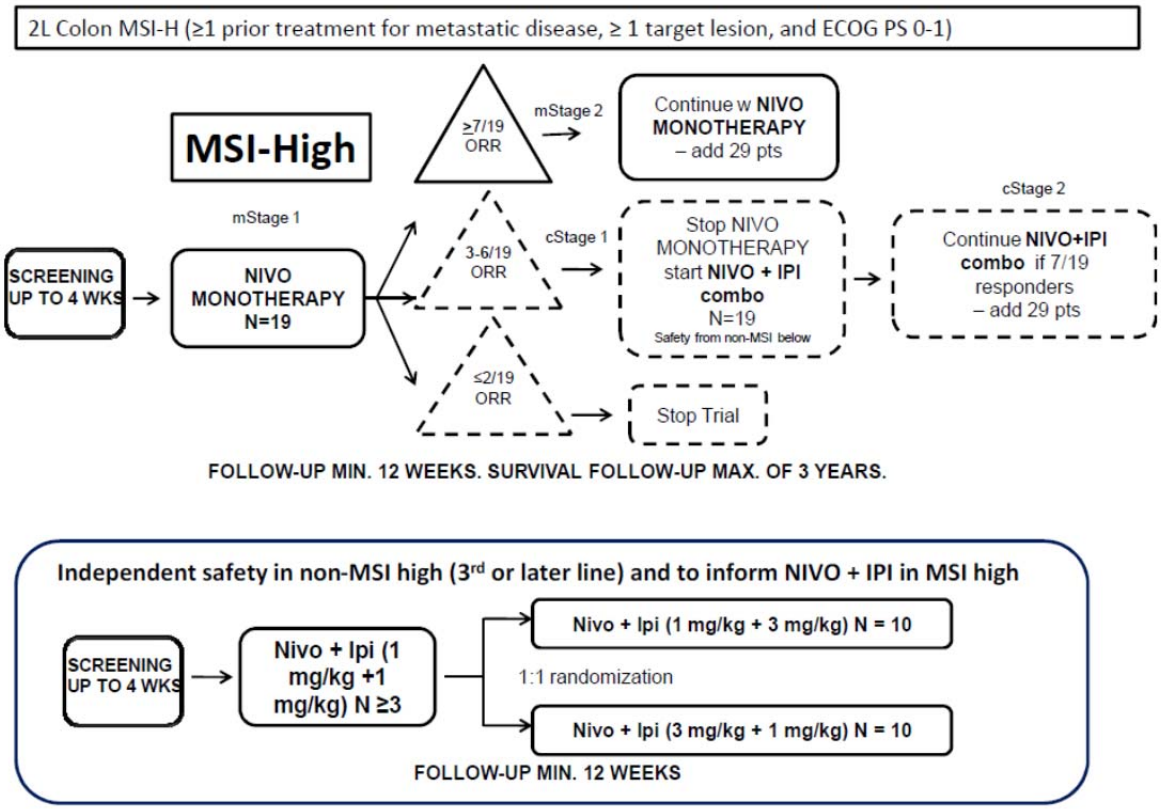
- On August 3, 2016, BMS generated a revised statistical analysis plan (SAP) for Study CA209142 to support generation of an interim Clinical Study Report (CSR) for inclusion in the sBLA describing the results of the nivolumab monotherapy cohort.

Study CA209142:

Design:

CA209142 is an ongoing open-label, multi-center, multi-arm, parallel group study of nivolumab alone or in combination with ipilimumab in adults with MSI-H mCRC and of nivolumab in combination with ipilimumab in patients with non-MSI-high mCRC. For patients with MSI-H colon cancer, key eligibility criteria were progression during, after, or intolerant to at least one line treatment for metastatic disease, which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan; microsatellite instability expression detected by an accredited laboratory per local regulations; and measurable disease per RECIST v1.1. The treatment plan for patients enrolled in the nivolumab monotherapy cohort nivolumab was administered at 3 mg/kg intravenously (IV) every 2 weeks until progression. The schema for the original protocol is provided in the figure below.

Figure 1: Study Design Schematic



The efficacy criteria for enrollment in the nivolumab alone and nivolumab plus ipilimumab cohorts were specified in the following table, below.

Table 1: Efficacy Criteria to proceed from Stage 1 to Stage 2

mStage 1 Efficacy Criteria	**Next Step**
≥ 7/19 subjects have confirmed CR or PR	Go into mStage 2
3-6/19 subjects have confirmed CR or PR	Close mStage 1 & open cStage 1
≤ 2/19 subjects have confirmed CR or PR	Close Trial
cStage 1 Efficacy Criteria	
≥ 7/19 subjects have confirmed CR or PR	Go into cStage 2
< 7/19 subjects have confirmed CR or PR	Close Trial

The primary endpoint of the study was investigator-assessed ORR with Independent Review Committee (IRC)-assessed ORR as the secondary endpoint.

The trial was designed as a Simon 2-stage trial to estimate the overall response rate of nivolumab alone or with ipilimumab in MSI-H mCRC. An additional cohort evaluated the safety of nivolumab plus ipilimumab in non-MSI-H mCRC. As stated in the protocol, the planned sample size was 96 patients across two cohorts: a non-MSI-H cohort enrolling up to 29 patients and an MSI-H cohort enrolling up to 67 MSI-H patients. For the non-MSI-H safety cohort, sample size was not based on power considerations and was dependent on the observed toxicity. For the MSI-H cohort, a Simon optimal two-stage design was to be used to test the null hypothesis that the true ORR is ≤ 30% (not considered clinically compelling) with either nivolumab monotherapy or the combination of nivolumab/ipilimumab.

In the first stage (mStage 1), 19 subjects were to be treated with nivolumab monotherapy. If there were 2 or fewer responses in these first 19 treated subjects, the protocol was to be closed to further enrollment. If there were more than 2 but less than 7 responses in the first 19 treated subjects, accrual to the monotherapy arm was to be stopped and the combination arm will be opened for accrual. Otherwise, if there were 7 or more responses in the first 19 treated subjects, approximately 29 additional subjects would be accrued to the monotherapy arm (mStage 2) to target a total of 48 treated subjects.

The primary objective was determination of the investigator-assessed ORR in the MSI-H cohort, defined as the number of confirmed MSI-H subjects with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR), according to RECIST 1.1 criteria, divided by the number of treated confirmed MSI-H subjects. The final analysis of the primary endpoint was to occur at least 6 months after the last enrolled subject's first dose of study therapy. The MSI-H cohort was defined as subjects who are defined as MSI-H based on standard diagnostic testing documented in the subject's medical history and prospectively confirmed in the current study by repeat testing using a PCR test. The non-MSI-H cohort was defined as all subjects testing non-MSI-H by the repeat PCR test, including those who were MSI-H by medical history but not confirmed by repeat testing.

Efficacy Results:

A total of 74 patients were enrolled in the monotherapy cohort from March 2014 to March 2016. All 74 patients had MSI-H mCRC, as identified by local laboratory testing, conducted using either MMR IHC or PCR-based MSI screening and disease progression during or after ≥ 1 line of treatment that included at least a fluoropyrimidine and oxaliplatin or irinotecan (53 or 72% received all three drugs). At the time of the database lock of September 19, 2016, 40 (54%) patients remain on nivolumab, including 30 (56.6%) patients who received prior flurouracil, oxaliplatin, and irinotecan (5FU-Oxa-Iri subgroup).

BMS provided the following results in patients with recurrent or metastatic MSI-H CRC:

- The confirmed ORR (RECIST) by IRC in the local MSI-H test positive mCRC population was 27% (95% CI: 16.9, 37.1) observed in 20 of 74 patients.
- The confirmed ORR by IRC in the subgroup of patients with local MSI-H test positive mCRC who received prior oxaliplatin, irinotecan, and 5FU (5FU-Oxa-Iri subgroup) was 22.6% (95% CI: 11.3, 33.9) observed in 12 of the 53 patients in this subgroup.
- The median duration of response per IRRC was not reached in the overall population or in the 5FU-Oxa-Iri subgroup.
- Objectives responses were observed in patients with PD-L1 expressing mCRC and in patients with PD-L1 negative mCRC.

Safety Results:

The most common reason (36.5%) for termination of nivolumab was disease progression in all patients (38% of patients in the 5FU-Oxa-Iri subgroup). Adverse reactions led to discontinuation of treatment for 4 (5.4%) patients for the following adverse reactions: colitis, stomatitis, increased ALT, and acute kidney injury (1 patient each).

No new safety concerns with nivolumab monotherapy were identified. The most common adverse events (AEs) were diarrhea (43%), fatigue (42%), anemia (36%), nausea (34%), vomiting (29%), abdominal pain and cough (26% each), and fever (24%). The most common Grade 3-4 AEs were anemia (8%), followed by fatigue (4%), vomiting (4%), diarrhea (3%), and abdominal pain (3%).

Proposed content of the planned sBLA:

BMS stated that the proposed sBLA will include efficacy and safety data from the 74 treated patients in the nivolumab monotherapy cohort who have MSI-H/dMMR.

Efficacy: BMS will submit a summary of clinical efficacy from study CA209142, but not an integrated efficacy analysis. BMS will also submit a detailed summary of the local and central MSI-H/dMMR testing results and will address the discordance between local and central testing outcomes.

Safety: BMS will submit a summary of clinical safety from study CA209142, as well as an integrated summary of clinical safety. BMS will also provide analyses of immune-mediated adverse events (IMAEs) (to include those reported within 100 days of the last dose). Safety narratives will be submitted for the following: deaths within 100 days of last dose due to reasons other than progressive disease, serious adverse events (SAEs) regardless of causality, all AEs leading to drug discontinuation, pregnancy, overdose (as defined by preferred terms for AE of overdose), any grade IMAEs within 100 days of last dose, excluding rash treated only with topical steroids (endocrine events are considered immune-mediated events even if they do not require treatment with immunosuppressive medications), and any causality concurrent (within 1 day) ALT or AST > 3x ULN and T.Bili > 2x ULN within 100 days of last dose.

DISCUSSION

Clinical:

1. *Background: See Pages 6 to 18 and Appendix 1 to 3 of the Briefing Document.*

Does FDA agree that the results of study CA209142 are adequate to support the review of an application to support the potential indication: (b) (4) ?

FDA Response: FDA agrees that the results of study CA209142 are adequate to support the review of an application submitted under provisions of 21 CFR 601.41 provided that the following information is provided:

- overall response rate as determined by an IRC in all patients enrolled with centrally confirmed MSI-H mCRC who have been followed for at least six months from the onset of response
- overall response rate as determined by an IRC in the first 19 patients enrolled with centrally confirmed MSI-H mCRC who have been followed for at least six months from the onset of response
- overall response rate as determined by an IRC in the first 48 patients enrolled with centrally confirmed MSI-H mCRC who have been followed for at least six months from the onset of response
- overall response rate as determined by an IRC in all patients enrolled with MSI-H mCRC as per local test who have been followed for at least six months from the onset of response
- justification that the data provided in the application demonstrate a significant improvement over available therapy for the indicated population
- discussion of how any sources of bias were controlled during the course of the study because of the multiple unplanned looks at the data. This should include a

summary of how decisions were made to modify the conduct of the study as described in the protocol.

FDA does not agree with the proposed indication [redacted] (b) (4) .

BMS' email responses of 12/14/16: BMS acknowledges the FDA comment and is providing a table summarizing the ORR/DOR and Duration of follow up, for discussion and feedback. BMS notes that 85-88% of the responses per IRRC are on-going across these populations; with only 2 disease progression for all responders (20 responders), indicating lasting durability of response. We also note that the median DOR has not yet been reached, even for the first 19 subjects with central confirmed MSI-H where the minimum follow-up is 18 months. The overall duration of follow up ranged from 5 to 27 months for all subjects; and 3-22 months for the responders (i.e. from onset of response).

Population	**Number of Responders n**	**ORR (95% CI)**	**DOR > 3 months n/N (%)**	**DOR > 6 months n/N (%)**	**DOR > 12 months n/N (%)**	**Duration of follow-up*** Range (months)	
	IRRC	**IRRC**	**IRRC**	**IRRC**	**IRRC**	**All patients**	**All responders IRRC**
Overall Treated Population (N=74)	20	27.0% (17.4, 38.6)	15/20 (75%)	8/20 (40%)	7/20 (35%)	5-27	3-22
All 53 patients (central confirmed MSI-H)	17	32.1% (19.9, 46.3)	12/17 (70.6%)	7/17 (41.2%)	6/17 (35.3%)	5-27	3-22
First 48 patients (central confirmed MSI-H)	15	31.3% (18.7, 46.3)	12/15 (80%)	7/15 (46.7%)	6/15 (40%)	6-27	3-22
First 19 patients (central confirmed MSI-H)	8	42.1% (20.3, 66.5)	7/8 (87.5%)	6/8 (75%)	5/8 (62.5%)	18-27	4.5-22**

*Duration of follow-up is defined from first patient first dose date to clinical data cutoff date for all subjects.
*Duration of follow-up is defined from first response date to clinical data cutoff date for all responders
**Represents one subject, who responded at 17 months after First Dose Date

Discussion during meeting of 12/16/16: FDA acknowledged BMS's presentation (above) of the data by the requested subgroups. FDA requested, and BMS agreed to provide, an updated analysis of durability of response with a minimum follow-up of six months from onset of response in all 20 responding patients to be submitted prior to day 45 after submission of the application.

FDA also requested that the application contain information on the type of local test used to screen patients for eligibility; the information should include the type of panel used for the PCR test, if known. FDA also stated that with regard to the central test used for confirmation, the panel should be identified. FDA also requested information on discordance between central and local testing. BMS agreed to provide the requested data in the supplement.

2. *Background: See Pages 18 to 20 and Appendix 1 to 3 of the Briefing Document.*

Does FDA agree with the proposed plans for the efficacy and safety presentations?

FDA Response: No, as described in the guidance "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document," an integrated summary of effectiveness should be submitted. However, it is acceptable to submit the narrative portion in module 2 and appendices, tables, and figures to module 5.

Discussion during meeting of 12/16/16: None.

3. *Background: See Pages 20 to 21 of the Briefing Document.*

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

FDA Response: Yes, FDA agrees.

Discussion during meeting of 12/16/16: None.

4. *Background: Based on the April 2016 pre-submission meeting for nivolumab monotherapy to treat squamous cell cancer of the head and neck (SCCHN), the FDA Division of Oncology Products-2 advised that the submission of a Safety Update Report is not necessary for the planned sBLA for SCCHN, given the large safety database across advanced malignancies and lack of any new safety signals.*

Therefore, BMS proposes that a 120-day Safety Update Report for the proposed sBLA for MSI-H/dMMR mCRC not be provided, given the extensive safety database for nivolumab monotherapy, in addition to the recent (Oct-2016) update and consolidation of the Warnings & Precautions section of the Opdivo USPI.

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

FDA Response: Yes, FDA agrees that a 120-day safety update is not required for this supplemental application.

Discussion during meeting of 12/16/16: None.

5. *Background: See Pages 21 to 23 of the Briefing Document.*

Does FDA agree with the proposed content of the sBLA?

FDA Response: Yes, FDA agrees with the proposed content of the sBLA. In addition to the proposed content in Module 5.3.5.1, please confirm that the proposed sBLA will include a define file (.pdf and .xml formats) to show the variables included in the datasets used to perform the efficacy and safety analyses. Please include in your submission:

- SAS programs by which the derived variables were produced from the raw variables, and
- SAS programs that produced all efficacy results.

Discussion during meeting of 12/16/16: None.

Additional Comments:

6. In the sBLA, provide plans for submission of a companion in vitro diagnostic test for selection of patients with MSI-H metastatic colorectal cancer from whom treatment with nivolumab would be indicated.

BMS' email responses of 12/14/16: BMS agrees that appropriate testing for DNA mismatch repair deficiency is important to inform selection of this subgroup of CRC patients. Practitioners are currently using well-established local MSI/MMR test methods as SOC for patient management, as specified in NCCN guidelines. These tests are provided as LDT's under CLIA regulations. Does FDA anticipate that the indication for use in labeling (in the refractory population studied) will specify use of an FDA approved test?

Discussion during meeting of 12/16/16: FDA stated their concerns that local testing is less able to select patients likely to benefit from nivolumab. Therefore, FDA will request a Postmarketing Commitment (PMC) to identify optimal testing strategies to identify patients with tumors having deficient mismatch repair or microsatellite instability. Data supporting such testing strategies will require submission of both the analytical assessment and bridging studies to clinical performance.

FDA recommended that a proposal for the approach to fulfill such a PMC be submitted to the supplement for discussion during review of the application. FDA also stated that a pre-supplemental meeting could be held with BMS prior to identification of a companion diagnostic partner(s).

7. In the sBLA, provide your plans to conduct confirmatory trials to verify clinical benefit.

BMS' email responses of 12/14/16: BMS comment: Given the potential availability of approved PD-L1 agents, in addition to the current inclusion of PD-L1 agents in the NCCN guidelines for MSI-H CRC in the >=2L setting, conducting a randomized phase 3 trial in the same patient population will present a challenge. Therefore, in order to satisfy our SubPart E commitment to further verify the clinical benefit of nivolumab in dMMR/MSI-H tumors in this refractory CRC population, BMS proposes to submit updated report(s) on the patients in study CA209-142 at a schedule to be agreed upon (e.g. 12, 24 and or 36 months) to describe the long term efficacy and safety. This approach appears to be in line with other agents recently approved by FDA on basis of long term data from single arm responses seen in rare biomarker selected populations (e.g. crizotinib for ROS-1 positive mNSCLC). (b) (4) BMS would like to discuss at our meeting with you whether such an approach could be acceptable to the agency.

Discussion during meeting of 12/16/16: FDA agreed (b) (4) therefore, FDA agreed (b) (4) . In addition, follow-up should be provided in the patients enrolled in Study CA209142. FDA also suggested that patients enrolled in a Postmarketing Requirement study could be included in bridging studies for the companion diagnostic assay.

PREA REQUIREMENTS

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

FDA acknowledges receipt of BMS' Agreed Initial Pediatric Study Plan submitted on June 29, 2016, and also refers to the July 28, 2016, letter confirming FDA's agreement to the Agreed iPSP for the proposed indication of "(b) (4)" This fulfills BMS' requirements at this stage of development to reach an Agreed Initial Pediatric Study Plan with the Agency.

PRESCRIBING INFORMATION

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

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

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

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is

the actual physical site(s) where documents are maintained and would be available for inspection

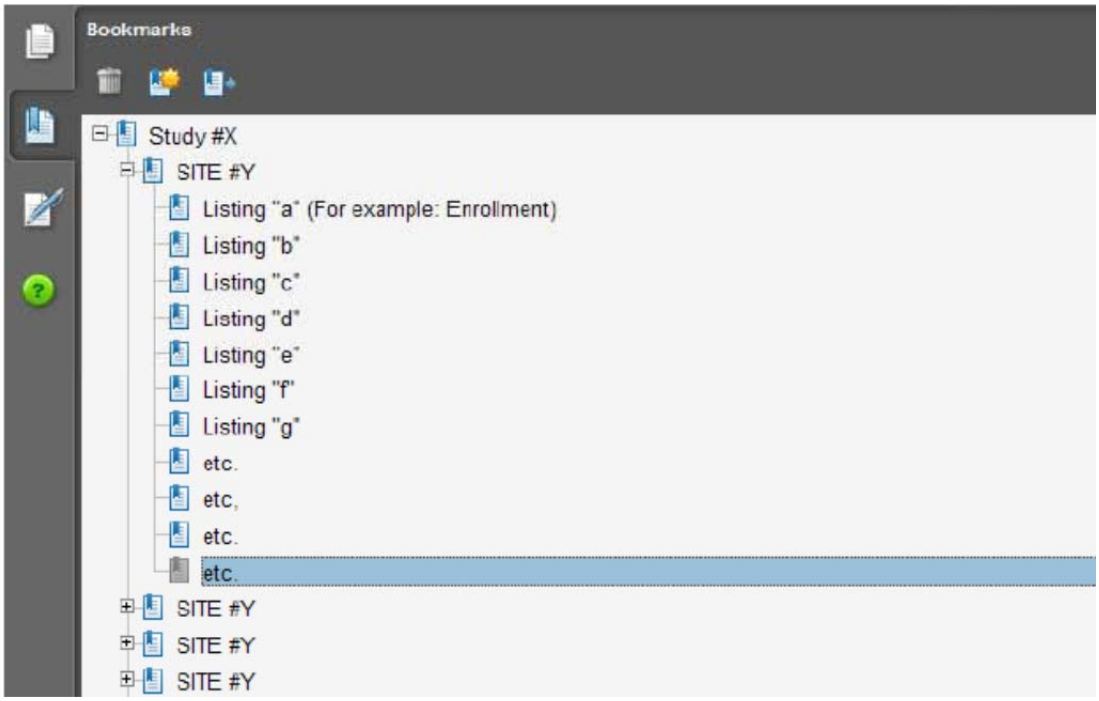
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Patient Level Data Listings by Site

1. For each pivotal trial: Site-specific individual patient data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each patient consented/enrolled; for patients who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Patient listing for treatment assignment (randomization)
   c. Listing of patients that discontinued from study treatment and patients that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol patients/ non-per protocol patients and reason not per protocol
   e. By patient listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By patient listing, of AEs, SAEs, deaths and dates
   g. By patient listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By patient listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By patient listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By patient listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

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

Attachment 1

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

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

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

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

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

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

References:

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

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

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

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

/s/

MEREDITH LIBEG
01/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119381

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Linda Gambone, Ph.D.
Director, Global Regulatory, Safety & Biometrics
Route 206 & Province Line Road
Princeton, NJ 08543

Dear Dr. Gambone:

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

We also refer to the teleconference between representatives of your firm and the FDA on May 10, 2016. The purpose of the meeting was to discuss and obtain FDA feedback on the use of data from Study CA209142, (b) (4) to support potential registration of an efficacy supplement for nivolumab seeking the proposed indication for the treatment of (b) (4)

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	General Guidance
Meeting Date and Time:	Tuesday, May 10, 2016; 11:00 to 12:00 PM (ET)
Meeting Location:	White Oak Building 22, Conference Room: 4266
Application Number:	IND 119381
Product Name:	Nivolumab
Indication:	(b) (4) [redacted]
Sponsor/Applicant Name:	Bristol-Myers Squibb (BMS)
Meeting Chair:	Sandra Casak
Meeting Recorder:	Meredith Libeg

FDA ATTENDEES

Steven Lemery, M.D., M.H.S.	Associate Director (Acting), DOP2
Sandra Casak, M.D.	Medical Officer, DOP2
Kun He, Ph.D.	Statistical Team Leader, DBV
Sirisha Mushti, Ph.D.	Statistical Reviewer, DBV
Meredith Libeg	Senior Regulatory Health Project Manager, DOP2

SPONSOR ATTENDEES

Rebecca Moss, M.D.	Director Oncology, Global Clinical Research
Arvin Yang, M.D.	Group Director, I-O Medical lead for Opdivo/Yervoy
Jingli Song, Ph.D.	Director Global Biometric Sciences Research
Linda Gambone, Ph.D.	Director, US Regulatory Sciences
Linda Gustavson, Ph.D.	Group Director, Global Regulatory Sciences
George Green, Ph.D.	Group Director, Pharmacodiagnostics
Monica Goldberg	Senior Research Investigator: Biomarkers-IO
Mark Moyer, M.S.	Vice President, Global Regulatory Sciences, Oncology
Eric Richards	Executive Director Global Regulatory Sciences, Oncology
Louis Kayitalire, M.D.	Vice President Immuno-Oncology Solid Tumors
David Feltquate, M.D., Ph.D.	Team Leader Opdivo/Yervoy

BACKGROUND

Nivolumab is a monoclonal antibody directed against the programmed death-1 (PD-1) receptor. Nivolumab is approved for the treatment of patients with unresectable or metastatic melanoma, the treatment of patients with metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy and for the treatment of advanced renal cell carcinoma in patients who have received prior antiangiogenic therapy.

BMS plans to submit a supplemental Biologics License Application (sBLA) for nivolumab for the treatment of (b) (4) [redacted]. The sBLA will be supported primarily by efficacy and safety data from clinical trial, Study CA209142, entitled "A Phase 2 Clinical Trial of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Microsatellite Instability High Colon Cancer," (b) (4) [redacted] The goal of the meeting is to obtain preliminary information on the development program and the needs for the future marketing application, (b) (4) [redacted]

Tumors with alterations in the mismatch repair pathway are thought to be present in 15% of patients with CRC (b) (4) [redacted]

CA209142 is an ongoing open label study investigating the efficacy and safety of nivolumab alone and in combination with ipilimumab in patients with recurrent or metastatic dMMR/MSI-H CRC. The study began enrollment in April 2014 and enrolled patients with dMMR/MSI-H (per local laboratory testing via PCR or IHC, respectively) mCRC with ECOG PS 0-1 and with disease progression following at least 1 prior treatment for metastatic disease. The study's primary endpoint is overall response rate (ORR) per investigator assessment. BMS states that as of November 2015, 33 patients have received nivolumab 3 mg/kg monotherapy and 26 patients have received nivolumab 3 mg/kg with ipilimumab 1 mg/kg. The majority of these 59 patients had received 2 or more prior systemic regimens in both the nivolumab (27/33, 81.8%) and the nivolumab plus ipilimumab (24/26, 92.3%) treatment arms.

The following table (modified from the briefing package) summarizes the preliminary efficacy results from Study CA209142. Median duration of response is not estimable.

	Nivolumab 3 mg/kg		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	
	MSI-H (local lab) N=33	**MSI-H (central lab) N=20***	**MSI-H (local lab) N=26**	**MSI-H (central lab) N=17****
ORR, n (%)	9/33 (27.3)	6/20 (30)	4/26 (15.4)	3/17 (17.6)
Best overall response				
CR	0	0	0	0
PR	9 (27.3)	6 (30)	4 (15.4)	3 (17.6)
SD	8 (24.2)	5 (25)	17 (65.4)	10 (58.8)
PD	11 (33.3)	5 (25)	3 (11.5)	3 (17.6)
Not determined	4 (12.1)	4 (20)	0	0
Not reported	1 (3)		2 (7.7)	1 (5.9)
Additional responders (one subject with unconfirmed PR as of database lock but subsequently confirmed)				
ORR, n (%)	10/33 (30.3)	7/20 (35)	4/26 (15.4)	3/17 (17.6)
* Of the 33 subjects, 20 have been confirmed by central lab to be MSI-H; 5 non-MSI-H, and 8 with not enough tissue for central lab testing ** Of the 26 subjects, 17 have been confirmed by central lab to be MSI-H; 5 non-MSI-H, and 4 with unknown central MSI status.				

The summary of safety is consistent with the known toxicity of nivolumab and of nivolumab administered with ipilimumab.

In order to support approval for the proposed indication (nivolumab is indicated for the treatment of (b) (4) BMS proposes to provide data from CA209142 based on approximately 62 patients with dMMR/MSI-H CRC who have a minimum of 6 months of follow up data. The primary endpoint will be Investigator-assessed ORR per RECIST 1.1. In addition, an independent radiology review committee (IRRC) will perform central review of imaging per RECIST 1.1 criteria and these data will be included in the application. The determination of dMMR/MSI-H status in the proposed analysis population will be based on local laboratory testing.

(b) (4)

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- (b) (4)

(b) (4)

(b) (4)

DISCUSSION

Clinical:

1. *Background: See Pages 9 to 13 and Appendix 1 to 4 of the Briefing Document.*

   Does FDA agree that efficacy and safety data from CA209142 may be adequate to support approval for the indication of nivolumab monotherapy for the treatment of
   (b) (4)

FDA Response: Insufficient information was provided for FDA to answer this question. BMS indicated that data from approximately 62 patients with a minimum of six months of follow-up would be submitted in the sBLA; however, BMS did not indicate how many of these patients received nivolumab as a single agent. The data provided by BMS in the briefing package were from a database lock of 17 Nov 2015. Presumably, updated data are now available which might include additional patients and additional follow-up data. FDA expects that up-to-date information be submitted in the sBLA in regards to ORR and duration of response. Additionally, FDA will consider the response rate as determined by independent review as the primary endpoint for regulatory purposes.

Confirm that BMS will provide data indicating that nivolumab provides for a meaningful advantage over available therapies in the proposed supplement. FDA recommends that BMS (b) (4)

BMS' Emailed Response of 5/9/16: (b) (4) BMS confirms that IRRC will be used as the primary endpoint. Table 1 shows the exact 95% CIs when observed ORRs are 25% to 35% respectively.

Table 1: ORR and 95% CIs for a Sample Size of 60 Subjects - CA209142

Event (No. responders)	ORR	95% Lower Limit	95% Upper Limit
15	25.0	14.7	37.9
16	26.7	16.1	40.0
17	28.3	17.5	41.4
18	30.0	18.9	43.2
19	31.7	20.3	45.0
20	33.3	21.7	46.7
21	35.0	23.1	48.4

The existing Standards of Care (FDA approved therapies) for metastatic 3L CRC are Lonsurf and Regorafenib. Regorafenib demonstrated a RR of 1% (0.3, 2.3) vs 0.4% (Placebo); with a median duration of stable disease of 2.0 months (*reference 1*); and Lonsurf with objective response rates of 1.6% and 0.4% vs placebo (P=0.29, *reference 2*); with DOR reported in 1 patient (225 days, *reference 3*).

1. Mayer RJ, Van Cutsem E, Falcone A, et al: Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. New England Journal of Medicine 372:1909-1919, 2015

2: Grothey A, Cutsem EV, Sobrero A, et al: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. The Lancet 381:303-312

3: Yoshino T, Mizunuma N, Yamazaki K, et al: TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. The Lancet Oncology 13:993-1001, 2012.

BMS Question: Does the agency agree that, at this time, these therapies would be the appropriate standards of care that we would use as references?

Discussion During Meeting of 5/10/16: FDA agrees that TAS-102 or regorafenib are appropriate standards of care in the third-line setting. FDA also stated that the Agency could consider certain patients in the second-line setting if they have previously received a fluoropyrimidine, oxaliplatin, and irinotecan (citing FOLFOXIRI as an example).

2. *Background: See Pages13 to 15 and Appendix 1 to 4 of the Briefing Document.*

Does FDA agree with the proposed (b) (4) **?**

FDA Response: No. FDA recommends that (b) (4) .

See FDA's response to question #4 (b) (4)

BMS' Emailed Response of 5/9/16: BMS acknowledged FDA's response. There was no discussion during the meeting.

3. *Background: See Pages 16 to 19 and Appendix 1 to 4 of the Briefing Document*

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

FDA Response: No. See FDA's response to question #2.

(b) (4)

BMS' Emailed Response of 5/9/16: BMS acknowledged FDA's response. There was no discussion during the meeting.

4. *Background: See Pages13 to 15 and Appendix 1 to 4 of the Briefing Document.*

Does FDA agree [redacted] (b) (4)

FDA Response: [redacted] (b) (4)

BMS' Emailed Response of 5/9/16: BMS acknowledged FDA's response. There was no discussion during the meeting.

5. *Background: See Pages13 to 15 and Appendix 1 to 4 of the Briefing Document*

Does FDA agree [redacted] (b) (4)

FDA Response: No. FDA strongly recommends [redacted] (b) (4) .

BMS' Emailed Response of 5/9/16: BMS acknowledged FDA's response. There was no discussion during the meeting.

6. *Background: See Pages 16 to 19 of the Briefing Document.*

a) **Does FDA agree that both MSI-H and dMMR are appropriate measures of dysregulation of DNA repair pathways to support the proposed indications?**

FDA Response: FDA will determine the indication based on the population of patients studied in the clinical trial(s).

BMS' Emailed Response of 5/9/16: BMS acknowledged FDA's response. There was no discussion during the meeting.

b) **Does FDA agree that MSI-H and dMMR testing by local laboratory is adequate for the proposed indication for accelerated approval for CRC subjects based on CA209142?**

FDA Response: Yes; however, FDA is concerned regarding the unexpectedly high discrepant results between local and central testing in Study CA209142 (e.g., across both arms, approximately 20% of patients who were MSI-H by the local test were not MSI-H when assessed using the central test). In the sBLA, provide the local laboratory result confirming that each patient's tumor was determined to be MSI-H. Additionally, indicate whether any of the patients who responded had MSI-H-positive tumors by local testing but non-MSI-H by central testing. Also provide information regarding whether the discrepant results were limited to patients whose tumors were tested by IHC locally or whether patients whose tumors were evaluated by PCR locally were also discrepant.

Although FDA may take action on an application in the absence of a PMA for a test for MSI-H status, based on these results, FDA may need to re-evaluate whether development of a test may be necessary (e.g., in the post-marketing setting). (b) (4)

Discussion During Meeting of 5/10/16: FDA inquired whether BMS could provide any additional insight regarding the discrepancies for the MSI-H test results. BMS stated that they are looking into this further on a case-by-case basis and will provide a summary of their findings prior to the filing of the supplemental BLA.

c) **Does FDA agree** (b) (4)

FDA Response: See FDA's response to question #6b.

Discussion During Meeting of 5/10/16: See discussion during meeting under question #6b.

d) **BMS does not anticipate any regulatory filings for clearance or approval for MSI or MMR assays; does FDA agree?**

FDA Response: See FDA's response to question #6b.

Discussion During Meeting of 5/10/16: See discussion during meeting under question #6b.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) for nivolumab for the proposed indication of the treatment of (b) (6) within 60 days of an End of Phase (EOP2) meeting.

We acknowledge your February 19, 2016, iPSP submission and we remind you that, as stated in our April 29, 2016, letter you must submit a letter within 90 days of receipt of the April 29, 2016, communication, stating your agreement or disagreement with the iPSP. If you agree, the cover letter should be titled "Agreed Initial Pediatric Study Plan" and should document your agreement with the iPSP as re-stated by the FDA and the submission should include a MS Word copy of the agreed upon iPSP.

Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

BMS' Emailed Response of 5/9/16: BMS acknowledged FDA's advice. There was no discussion during the meeting.

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/s/

MEREDITH LIBEG
05/11/2016