CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125554Orig1s041

Trade Name:	OPDIVO
Generic or Proper Name:	nivolumab
Sponsor:	Bristol-Myers Squibb Company
Approval Date:	September 22, 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)
- patients with hepatocellular carcinoma who have been previously treated with sorafenib.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.8)

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125554/S-041

ACCELERATED APPROVAL

Bristol-Myers Squibb Company
Attention: Cynthia Wojtaszek, MSN, RN
Director, Global Regulatory, Safety and Biometrics, U.S. Oncology
Route 206 & Province Line Road, Room D2.248
Princeton NJ 08543

Dear Ms. Wojtaszek:

Please refer to your Supplemental Biologics License Application (sBLA), dated March 24, 2017, received March 24, 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 patients with hepatocellular carcinoma who have been previously treated with sorafenib.

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 September 11, 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

3270-1 Conduct and submit the results, including datasets, of a multicenter, randomized trial or trials to verify and describe the clinical benefit of nivolumab over standard therapy based on an improvement in overall survival in patients with advanced hepatocellular carcinoma.

Trial Completion:	12/19
Final Report Submission:	09/20

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.

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

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3270-2 Submit the final report, including datasets, from patients with hepatocellular carcinoma who have progressed on, or are intolerant to sorafenib and who received nivolumab 3 mg/kg in the dose escalation or dose expansion phase of CHECKMATE-040. In order to further characterize the duration of response in patients who achieve a complete or partial response to nivolumab, duration of response will be assessed by independent central review and responding patients will be followed for at least 12 months from the onset of response.

The timetable you submitted on September 15, 2017, states that you will conduct this trial according to the following schedule:

Trial Completion:	11/18
Final Report Submission:	08/19

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
09/22/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

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

Lactation: Discontinue breastfeeding. (8.2)

Revised: 9/2017

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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.

1.8 Hepatocellular Carcinoma

OPDIVO is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials *[see Clinical Studies (14.8)]*.

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 Recommended Dosage for HCC

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.

2.9 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

Table 1: Recommended Dose Modifications for OPDIVO

Adverse Reaction	Severity*	Dose Modification
Hepatitis/non-HCC[b]	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN	Withhold dose[a]
	AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN	Permanently discontinue
Hepatitis/ HCC[b]	• If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN • If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN • If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Withhold dose[c]
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose[a]
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	 Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).
[a] Resume treatment when adverse reaction improves to Grade 0 or 1.
[b] HCC: hepatocellular carcinoma.
[c] Resume treatment when AST/ALT returns to baseline.

2.10 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 (2.9)]*.

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 (2.9)]*.

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 (2.9)]*.

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.

For patients without hepatocellular carcinoma (HCC): withhold OPDIVO for moderate (Grade 2) immune-mediated hepatitis and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.9)]*.

For patients with HCC, permanently discontinue, withhold, or continue OPDIVO based on severity of immune-mediated hepatitis and baseline AST and ALT levels as described in Table 1 *[see Dosage and Administration (2.9)]*. In addition, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper when OPDIVO is withheld or discontinued due to immune-mediated hepatitis.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

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

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

OPDIVO can cause immune-mediated hypophysitis. Monitor patients for signs and symptoms of hypophysitis. Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or 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 (2.9)]*.

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 (2.9)]*.

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 (2.9)]*.

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 (2.9) 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 (2.9)]*.

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 (2.9)]*.

OPDIVO as a Single Agent

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

OPDIVO with Ipilimumab

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

5.8 Other Immune-Mediated Adverse Reactions

OPDIVO can cause other clinically significant and potentially fatal immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.9)]*.

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

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 (2.9)]*.

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, CHECKMATE-275, which is a single-arm trial in patients with urothelial carcinoma, and CHECKMATE-040, which is an open-label, multiple-cohort trial in patients with HCC.

Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

The safety of OPDIVO as a single agent was evaluated in CHECKMATE-037, a randomized, open-label trial in which 370 patients with unresectable or metastatic melanoma received 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
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)	
Adverse Reaction[a]	**Percentage (%)**	
	All Grades	**Grades 3-4**
General Disorders and Administration Site Conditions		
Fatigue[b]	39	1.9
Pyrexia	29	<1
Gastrointestinal Disorders		
Diarrhea[c]	33	1.5
Nausea	20	0
Vomiting	19	<1
Abdominal pain[d]	16	<1
Constipation	14	0.4
Infections		
Upper respiratory tract infection[e]	44	0.8
Pneumonia/bronchopneumonia[f]	13	3.8
Nasal congestion	11	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough/productive cough	36	0
Dyspnea/exertional dyspnea	15	1.5
Skin and Subcutaneous Tissue Disorders		
Rash[g]	24	1.5
Pruritus	20	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[h]	26	1.1
Arthralgia	16	<1
Endocrine Disorders		
Hypothyroidism/thyroiditis	12	0
Nervous System Disorders		
Headache	17	<1
Neuropathy peripheral[i]	12	<1
Injury, Poisoning and Procedural Complications		
Infusion-related reaction	14	<1

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes asthenia.

[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
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.

Hepatocellular Carcinoma

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

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

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

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

There is no information on overdosage with OPDIVO.

11 DESCRIPTION

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

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, MSI-H CRC, and HCC.

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 HCC (n=152) and in patients with other tumors (n=92) with mild hepatic impairment (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST; n=13). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with severe hepatic impairment (TB greater than 3 times ULN and any AST) *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

CHECKMATE-037 (NCT01721746) was a multicenter, open-label trial that randomized (2:1) patients with unresectable or metastatic melanoma to receive either 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 overall response rate (ORR) as measured by blinded independent central review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and duration of response.

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

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

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

Previously Untreated Metastatic Melanoma

CHECKMATE-066

CHECKMATE-066 (NCT01721772) was a multicenter, double-blind, randomized (1:1) trial conducted in patients with BRAF V600 wild-type unresectable or metastatic melanoma. Patients were randomized to receive either 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 overall response rate (ORR) per RECIST v1.1.

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

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

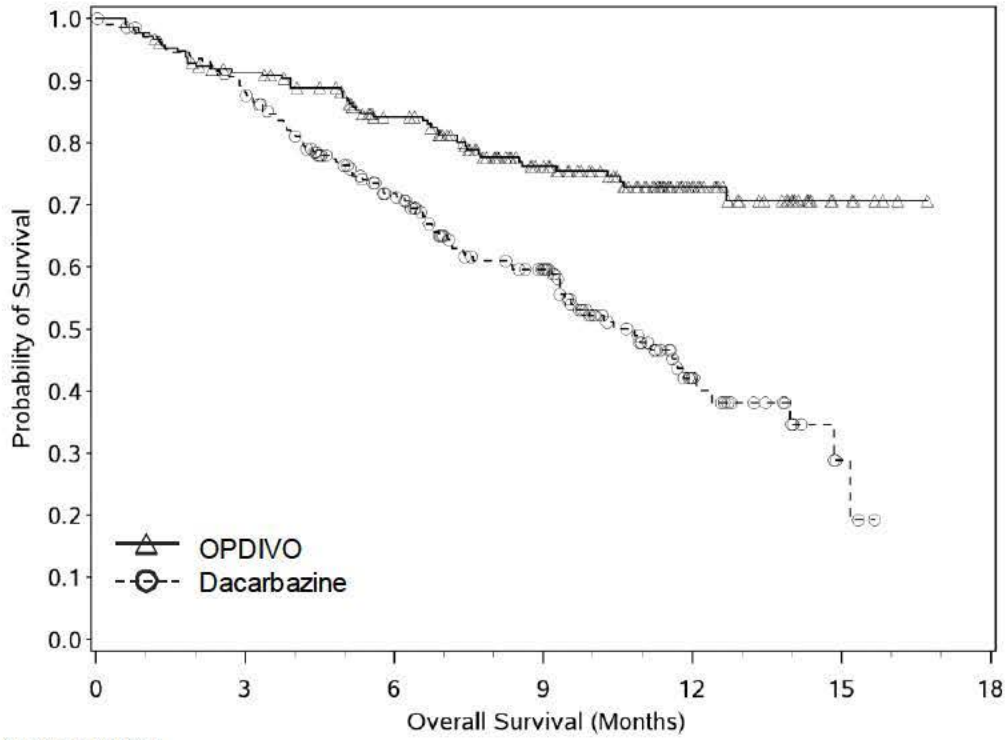
	OPDIVO (n=210)	**Dacarbazine (n=208)**
Overall Survival		
Deaths (%)	50 (24)	96 (46)
Median, months (95% CI)	Not Reached	10.8 (9.3, 12.1)
Hazard ratio (95% CI)[a]	0.42 (0.30, 0.60)	
p-value[b,c]	<0.0001	
Progression-Free Survival		
Disease progression or death (%)	108 (51)	163 (78)
Median, months (95%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

[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

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

Figure 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%).

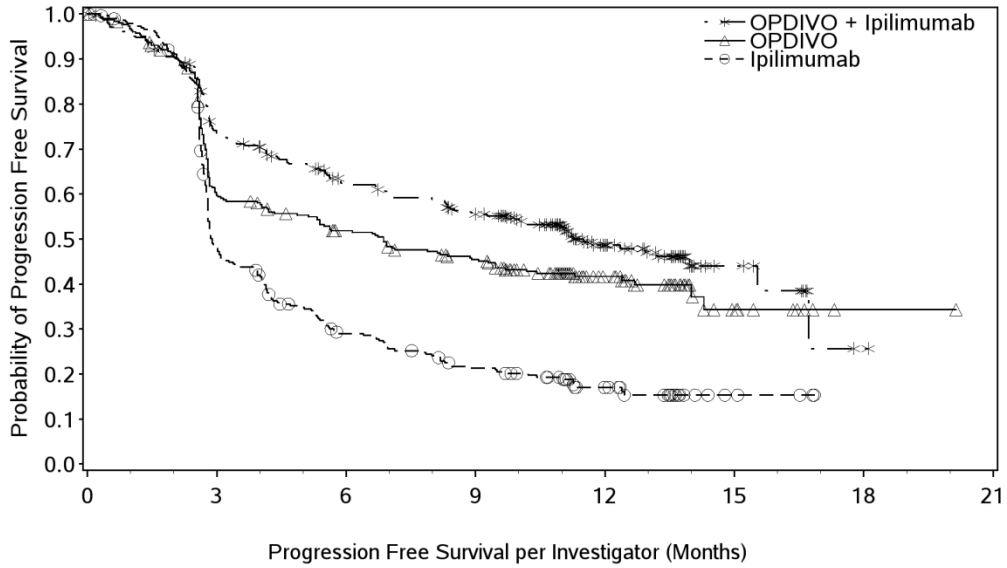
CHECKMATE-067 demonstrated statistically significant improvements in PFS for patients randomized to either OPDIVO-containing arm as compared with the ipilimumab arm. Efficacy results are presented in Table 17 and Figure 2.

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

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

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

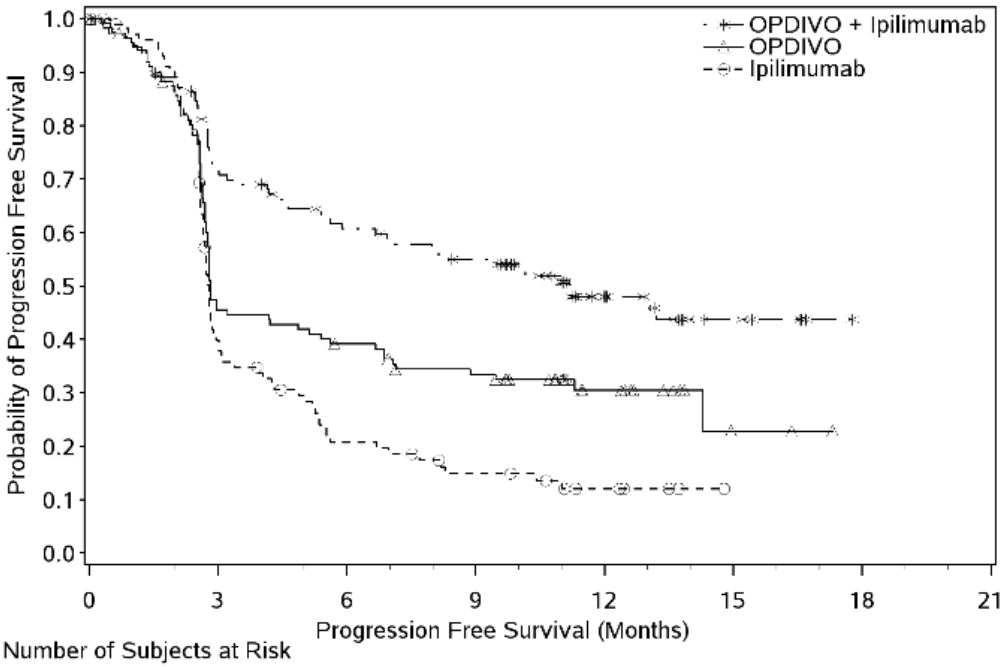


Number of Subjects at Risk

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

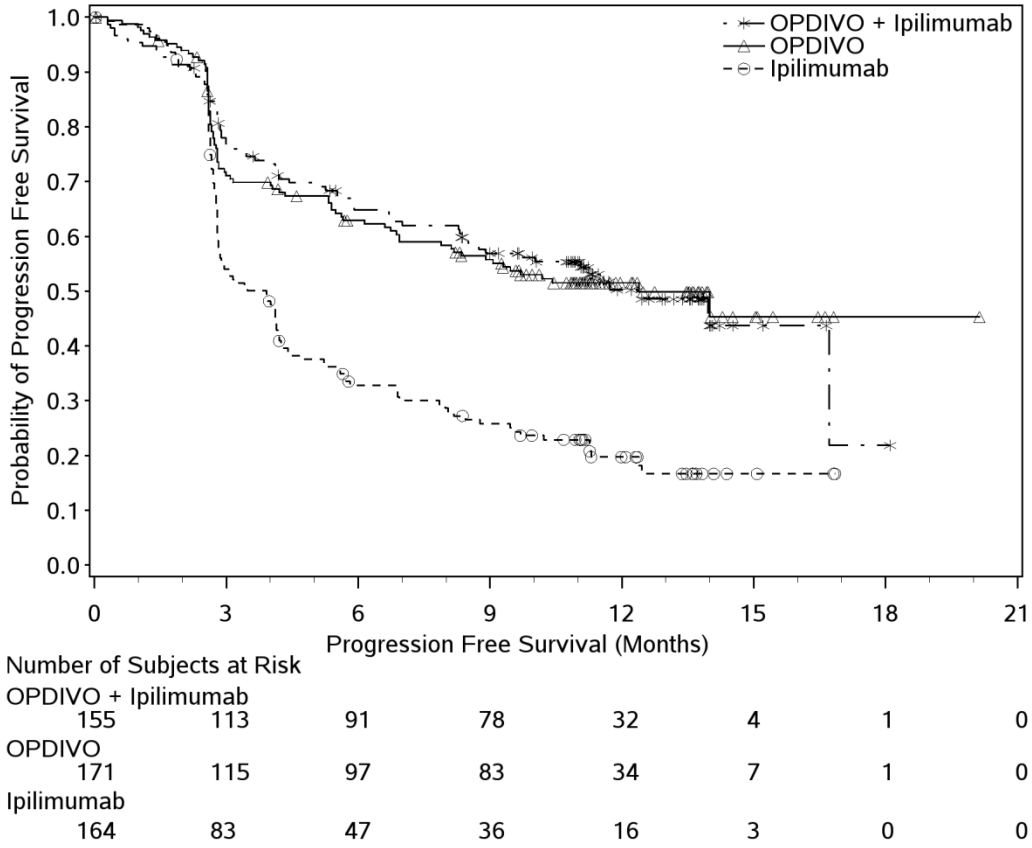
Figures 3 and 4 present exploratory efficacy subgroup analyses of PFS based on defined PD-L1 expression levels determined in archival tumor specimens using the PD-L1 IHC 28-8 pharmDx assay. Tumor samples were available for retrospective assessment for 97% of the study population; PD-L1 expression status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



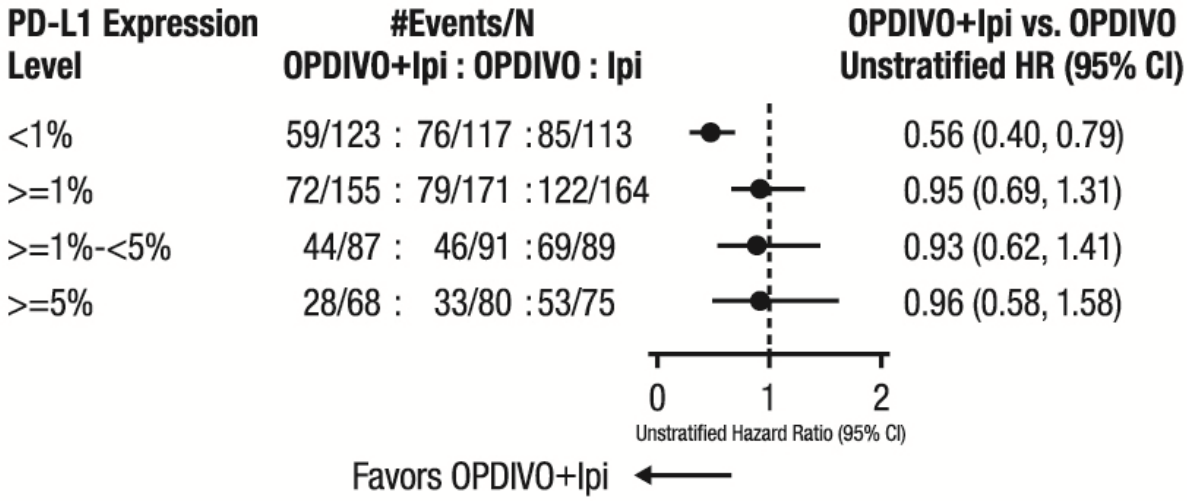
Number of Subjects at Risk							
OPDIVO + Ipilimumab							
123	82	65	57	26	6	0	0
OPDIVO							
117	50	42	34	13	2	0	0
Ipilimumab							
113	39	19	12	5	0	0	0

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

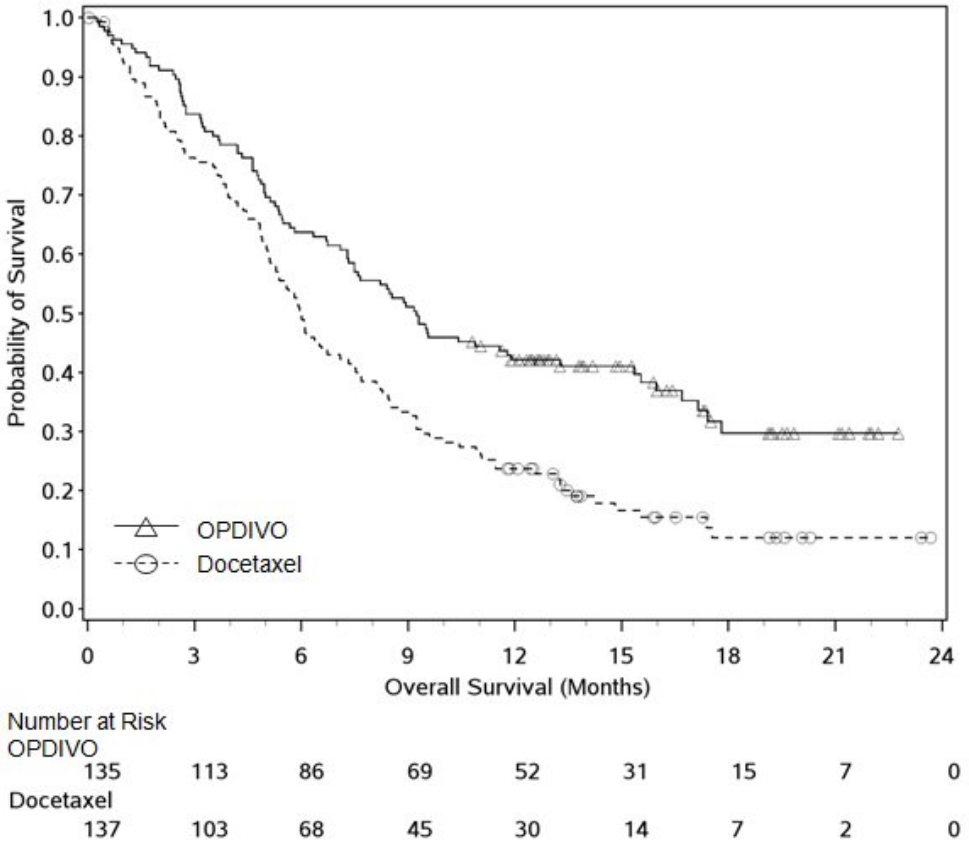
[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

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

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

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

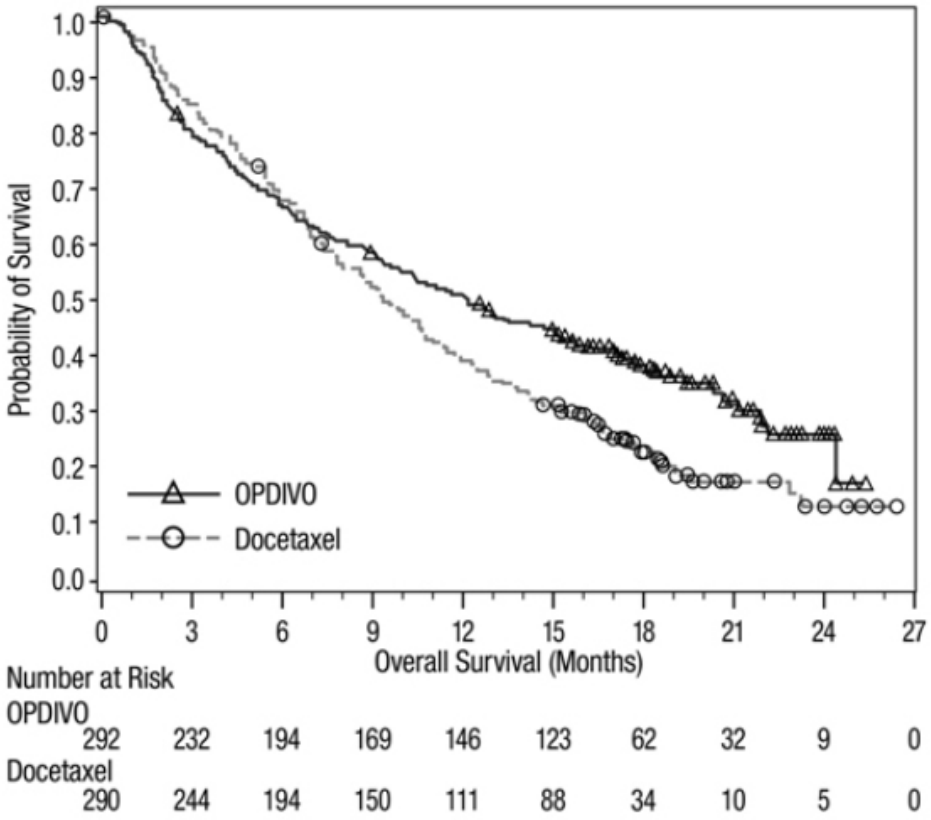
[a] Based on a stratified proportional hazards model.

[b] Based on stratified log-rank test.

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

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

Figure 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

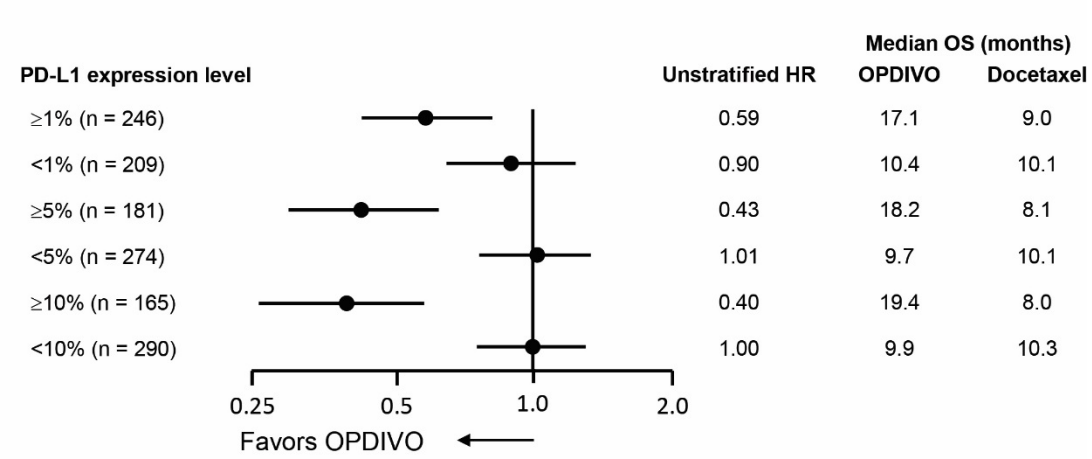
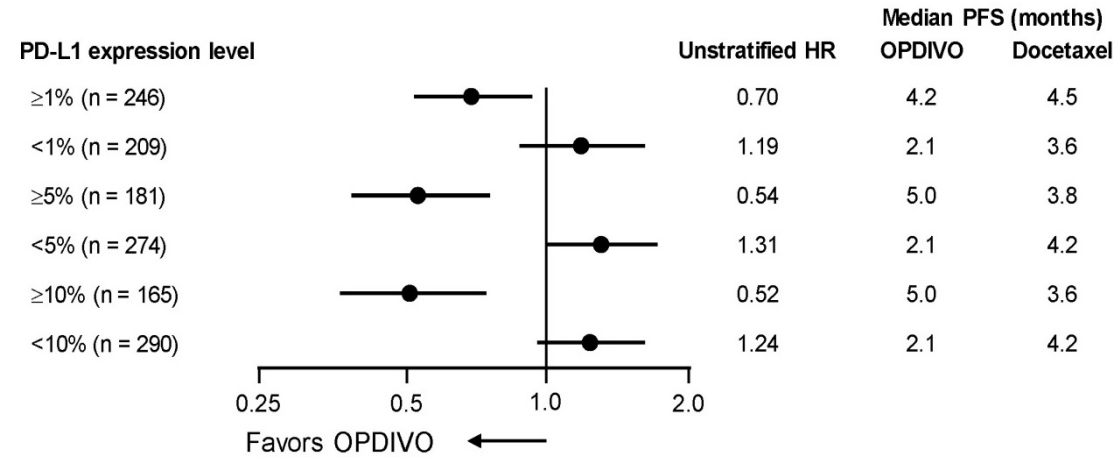


Figure 9: Forest Plot: PFS Based on PD-L1 Expression - CHECKMATE-057



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 overall response rates, which are also presented in Table 20.

Table 20: Efficacy Results - CHECKMATE-025

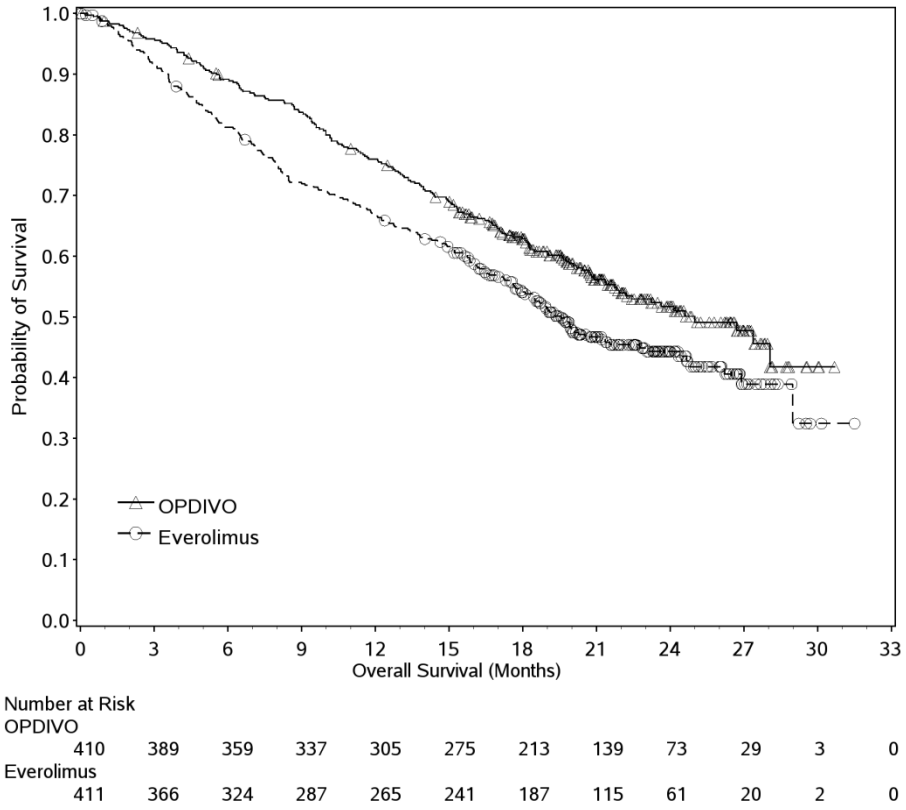
	OPDIVO (n=410)	**Everolimus (n=411)**
Overall Survival		
Deaths (%)	183 (45)	215 (52)
Median survival in months (95% CI)	25.0 (21.7, NE)	19.6 (17.6, 23.1)
Hazard ratio (95% CI)[a]	0.73 (0.60, 0.89)	
p-value[b,c]	0.0018	
Confirmed Overall Response Rate (95% CI)	21.5% (17.6, 25.8)	3.9% (2.2, 6.2)
Median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

[a] Based on a stratified proportional hazards model.

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

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

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

[a] Per 2007 revised International Working Group criteria.

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

[c] A + sign indicates a censored value.

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

Table 22: Efficacy in cHL after Autologous HSCT

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

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

14.5 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

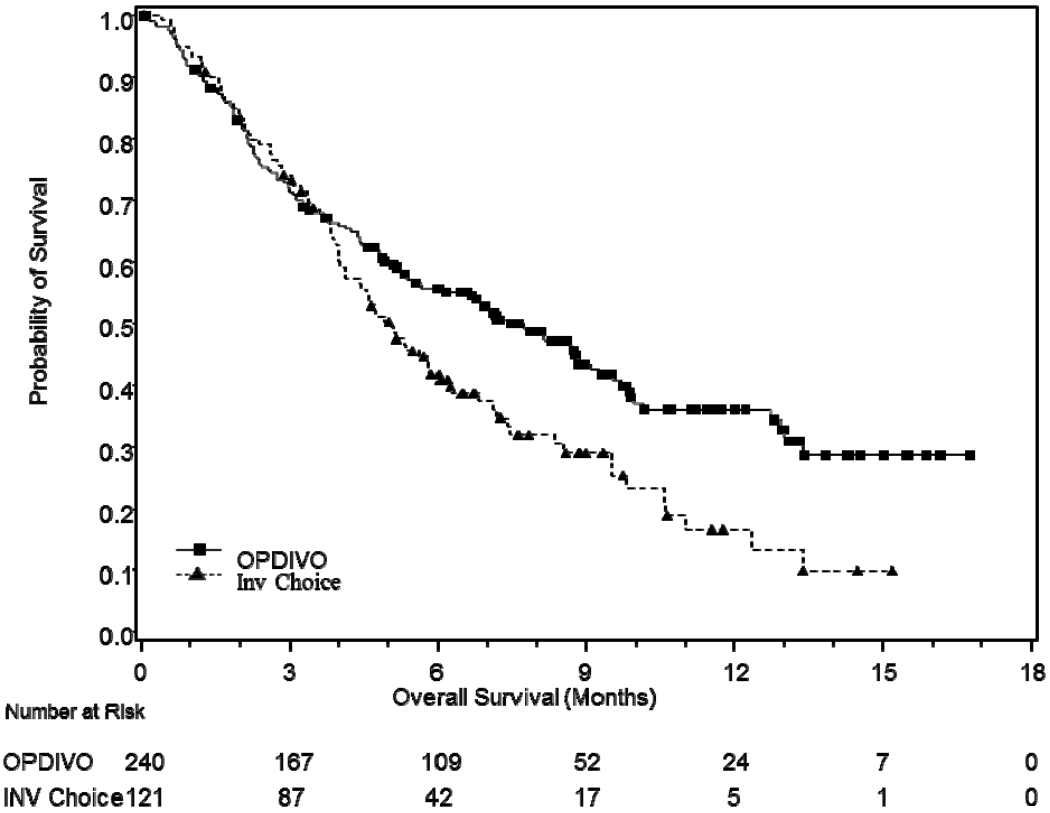
	OPDIVO (n=240)	**Investigator's Choice (n=121)**
Overall Survival		
Deaths (%)	133 (55%)	85 (70%)
Median (months) (95% CI)	7.5 (5.5, 9.1)	5.1 (4.0, 6.0)
Hazard ratio (95% CI)[a]	0.70 (0.53, 0.92)	
p-value[b,c]	0.0101	

[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 overall response rate (ORR) as assessed by independent radiographic review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR).

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

Tumor specimens were evaluated prospectively using the PD-L1 IHC 28-8 pharmDx assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 270 patients, 46% were defined as having PD-L1 expression of ≥1% (defined as ≥1% of tumor cells expressing PD-L1). The remaining 54% of patients, were classified as having PD-L1 expression of <1% (defined as <1% of tumor cells expressing PD-L1). Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 24. Median time to response was 1.9 months (range: 1.6-7.2). In 77 patients who received prior systemic therapy only in the neoadjuvant or adjuvant setting, the ORR was 23.4% (95% CI: 14.5%, 34.4%).

Table 24: Efficacy Results in CHECKMATE-275

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

[a] Estimated from the Kaplan-Meier Curve

14.7 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 overall response rate (ORR) as assessed by independent radiographic review committee (IRRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and duration of response (DOR).

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

Efficacy results are shown in Table 25.

Table 25: Efficacy Results – CHECKMATE-142

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

NR=Not Reached

14.8 Hepatocellular Carcinoma

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

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

A total of 154 patients received OPDIVO 3 mg/kg by intravenous infusion every 2 weeks. The median age was 63 years (range: 19 to 81), 77% were men, and 46% were White. Across the

population, 31% had active HBV infection, 21% had active HCV infection, and 49% had no evidence of active HBV or HCV. The etiology for HCC was alcoholic liver disease in 18% and non- alcoholic liver disease in 6.5% of patients. Baseline ECOG performance status was 0 (65%) or 1 (35%). Child-Pugh class and score was A5 for 68%, A6 for 31%, and B7 for 1% of patients. Seventy one percent (71%) of patients had extrahepatic spread, 29% had macrovascular invasion, and 37% had alfa-fetoprotein (AFP) levels ≥400 μg/L. Prior treatment history included surgical resection (66%), radiotherapy (24%), or locoregional treatment (58%). All patients had received prior sorafenib, of whom 36 (23%) were unable to tolerate sorafenib; 19% of patients had received 2 or more prior systemic therapies.

Efficacy results are summarized in Table 26.

Table 26: Efficacy Results in Trial CHECKMATE-040

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

[a] Overall response rate confirmed by BICR.

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

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)
- **people with liver cancer (hepatocellular carcinoma)**
  - OPDIVO may be used after you have received treatment with sorafenib (Nexavar®).

It is not known if OPDIVO is safe and effective in children less than 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
- weakness
- shortness of breath
- decreased appetite
- upper respiratory tract infection
- rash
- itchy skin
- nausea
- cough
- constipation
- back pain
- fever

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: September 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s041

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 22, 2017
From	Martha Donoghue, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	Supplement 41, BLA 125554
Applicant	Bristol-Myers Squibb Company (BMS)
Date of Submission	March 24, 2017
PDUFA Goal Date	September 24, 2017
Proprietary Name / Non-Proprietary Name	OPDIVO/nivolumab
Dosage Forms/Strength	Injection for intravenous use; 40 mg/4mL and 100 mg/10mL (10 mg/mL) in single-dose vials
Proposed Dosing Regimen	240 mg intravenously every two weeks
Applicant Proposed Indication(s)/Population(s)	OPDIVO is indicated for the treatment of patients with hepatocellular carcinoma (HCC) (b) (4). This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
Recommended Regulatory Action	*Accelerated approval*
Recommended Indication(s)/Population(s)	OPDIVO is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1. Introduction

On March 24, 2017 Bristol-Myers Squibb Company (BMS) submitted Supplement 41 to Biologics License Application (BLA) 125554, seeking approval under the provisions for 21 CFR 601.41 (accelerated approval) of nivolumab (Opdivo) for the treatment of patients with hepatocellular carcinoma (HCC) (b) (4).

Nivolumab, a human monoclonal antibody that blocks the interaction between programmed death receptor-1 (PD-1) and its ligands, PD-L1 and PD-L2, was first approved on December 22, 2014, and is currently approved nivolumab for the following indications:

- for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent
- for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent
- for the treatment of patients with unresectable or metastatic melanoma, in combination with ipilimumab
- for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy
- for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy
- for the treatment of 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.

- 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
- 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.
- 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.

FDA review of the efficacy and safety of nivolumab for the proposed indication focused on data derived from a subset of 154 patients with HCC who received nivolumab 3 mg/kg every two weeks as a single agent in the dose-escalation and dose-expansion cohorts of Study CA209040 (CHECKMATE-040). CHECKMATE-040 is a multicenter, open-label, non-comparative, multiple cohort safety and activity-estimating trial conducted in patients with HCC who progressed on or were intolerant to sorafenib. Additional key eligibility criteria included histologic confirmation of advanced HCC, prior treatment with sorafenib and Child-Pugh Class A. The trial excluded patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection

with hepatitis B virus (HBV) and hepatitis C virus (HCV) or HBV and hepatitis D virus (HDV); however, patients with only active HBV or HCV were eligible.

Tumor assessments were conducted every 6 weeks for 48 weeks and every 12 weeks thereafter. The primary endpoint for the purposes of FDA's review of this supplement was the overall response rate (ORR) as assessed by an independent review committee (IRC). Duration of response was also assessed.

2. Background

Indicated Population and Available Therapy

Hepatocellular carcinoma (HCC) is the 10th most common cancer, with an estimated 40,710 new cases (including intrahepatic bile duct cancers) in 2017. HCC accounts for approximately 28,920 deaths yearly in the United States and is the 5th most common cause of cancer death among men and the 8th among women[1]. The 5-year relative survival is 31% for early stage disease, but only 11% for unresectable localized disease and 3% for metastatic disease[1]. The majority of patients with HCC (70-90%) have chronic liver disease. The most common risk factors for development of HCC are hepatitis B infection (HBV), hepatitis C infection (HCV), alcoholic use and non-alcoholic steatohepatitis[2].

Treatment of HCC is dictated by the cancer stage and by underlying liver function, which is commonly assessed using the Child-Pugh scoring system. For patients presenting with early-stage HCC, surgery and liver transplantation have the potential for cure. Patients with intermediate stage HCC (e.g., localized but unresectable disease) and good liver function are often treated with locoregional therapy (radiofrequency ablation, embolization with beads, intra-arterial chemotherapy, etc.). There are no curative treatments for patients with advanced disease. Patients with advanced HCC may receive locoregional or systemic therapy[2], depending on underlying liver function and prognostic factors, such as ECOG performance status, number of nodules, and presence of portal invasion or extrahepatic spread. Staging systems for HCC include the Barcelona Clinic Liver Cancer staging system and Okuda staging system.

Sorafenib was approved in 2005 for the first-line treatment of advanced or metastatic HCC based on the results of a randomized study (SHARP) that showed an improvement in overall survival in patients randomized to sorafenib compared to placebo (median 10.7 months in the sorafenib group vs. 7.9 months in the placebo group, HR 0.69, $p<0.001$)[3].

In April 2017, the FDA approved regorafenib for the treatment of patients with HCC who have been previously treated with sorafenib[4]. The efficacy of regorafenib for the treatment of patients with advanced HCC was demonstrated in Study 15982 (RESORCE), a multicenter, randomized, placebo-controlled trial comparing once daily regorafenib to placebo in patients with HCC that had progressed on sorafenib. A total of 573 patients were randomized, 379 to the regorafenib arm and 194 to the placebo arm. Median overall survival was 10.6 months in the regorafenib arm and 7.8 months in the placebo arm with a hazard ratio of 0.63 (95% CI: 0.50, 0.79) and an

unstratified log-rank p-value of 0.0002. The median progression free survival (PFS) was 3.1 months (95% CI: 2.8, 4.2) in the regorafenib arm and 1.5 months (95% CI: 1.4, 1.6) in the placebo arm with a hazard ratio of 0.46 (95% CI: 0.37, 0.56) and a p-value of <0.0001. Treatment with regorafenib resulted in an overall response rate (ORR) of 7% (95% CI: 4%, 10%) using RECIST 1.1 and a median duration of response of 3.5 months (95% CI: 1.9, 4.5). Using modified RECIST for HCC (mRECIST), treatment with regorafenib resulted in an ORR of 10.6% (95% CI: 7.6%, 14.1%) and a median duration of response of 2.7 months (95% CI: 1.9, NE); however, ORR was considered an exploratory endpoint as it was not included in the pre-specified hierarchical test order for secondary endpoints. The median duration of regorafenib therapy was 3.5 months (range: 1 day to 29.4 months). Dose interruptions for adverse events were required in 58% of patients and dose reductions for adverse events were required in 48% of patients. The most common adverse reactions requiring dose modification (interruption or dose reduction) were hand-foot skin reaction (HFSR)/ palmar-plantar dysesthesia (PPES) (20.6%), blood bilirubin increase (5.9%), fatigue (5.1%) and diarrhea (5.3%). Adverse reactions resulted in treatment discontinuation in 10.4% of patients. The most common adverse reactions leading to discontinuation were HFSR/PPES (1.9%) and AST increased (1.6%).

Pre-Submission Regulatory History

- On 16 July 2012, the Applicant submitted Protocol CA209040 (CHECKMATE-040) entitled, "A Phase I Dose Escalation Study to Investigate the Safety, Immunoregulatory Activity, Pharmacokinetics, and Preliminary Antitumor Activity of Anti-Programmed-Death-1 (PD-1) Antibody (BMS-936558) in Advanced Hepatocellular Carcinoma in Subjects with or without Chronic Viral Hepatitis." to IND 100052.
- On 5 May 2015, the Applicant administratively transferred Protocol CA209040 to the new IND 126406.
- On 7 May 2015, IND 126406 was granted a 30-day waiver.
- On 2 September 2015, nivolumab was granted orphan designation for the treatment of HCC (#15-4899).
- On 30 September 2015, the Applicant submitted amendment 8 for Protocol CA209040 (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

- (b) (4)
- (b) (4)
- (b) (4)
- On 3 March 2017, a type B pre-BLA meeting was held between FDA and the Applicant to discuss efficacy and safety results from Study CA209040, intended to support this supplemental application. FDA requested, and the Applicant agreed to provide, a pooled analysis of overall response rate and duration of response for patients in the dose escalation and expansion cohorts previously treated with sorafenib. FDA concluded that the results allowed for review of the data in a sBLA.

Submission Regulatory History

- On 23 May 2017, FDA filed sBLA 125554/S-41.
- On 20 July 2017, as requested by FDA, BMS submitted an amendment to include updated efficacy data reflecting a data cut-off date of March 17, 2017. These data reflected a minimum follow-up duration of approximately 15 months for all patients, along with updated BIRC-assessed duration of response for the original 28 responders in the dose escalation ("2L ESC") and dose expansion (2L EXP) cohorts of CHECKMATE-040.
- On 15 September 2017, BMS submitted agreed upon language and milestone dates for the postmarketing requirement to verify and confirm the clinical benefit of nivolumab in patients with advanced HCC and a postmarketing commitment to further characterize the duration of response in patients with advanced HCC who progressed on or were intolerant to sorafenib and who received nivolumab 3 mg/kg in the dose escalation or dose expanses phase of CHECKMATE-040.

3. Product Quality

There are no outstanding product quality issues that preclude approval.

BMS' request for categorical exclusion from the environmental assessment, pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, as provided in 21 CFR 25.31(c) for an action on a BLA supplement, was approved by the Office of Biotechnology Products.

No other CMC information was included in this supplement.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval. This supplement contained the following clinical pharmacology information:

- Population pharmacokinetic (PopPK) data in patients with HCC who received nivolumab 3 mg/kg every two weeks (Q2W) as a single agent and results of an updated PopPK analysis to support the 240 mg Q2W dosing regimen for patients with HCC proposed for the Opdivo package insert.

- PopPK analyses examining the effect of mild and moderate hepatic impairment on the clearance of nivolumab in HCC patients and other tumors

Nivolumab concentration-time data were previously characterized by a linear, two-compartment, zero-order input intravenous (IV) infusion model with time-varying clearance. Tumor type was incorporated into the PopPK model, which showed that tumor type was not a significant covariate for clearance. The clinical pharmacology reviewers determined that first cycle clearance in patients with HCC is comparable with first cycle clearance in patients with NSCLC, melanoma, and renal cell carcinoma. Additionally, no clinically meaningful differences in nivolumab clearance in uninfected patients and patients with HCC related to hepatitis C or hepatitis B virus were found.

The clinical pharmacology reviewers determined that the proposed flat dose of 240 mg Q2W was adequately supported by bridging PopPK modeling and simulation. Based on simulations using the PPK model, overall exposure at the 240 mg Q2W flat dose is approximately 13% to 14% higher compared to the 3 mg/kg Q2W dose; however, the clinical pharmacology reviewers concluded that these differences in exposure between the two dosing regimens are not clinically meaningful, particularly in light of the flat exposure response relationship for safety and efficacy.

The clinical pharmacology reviewers also concluded that nivolumab clearance is similar in patients with normal, mild (defined as total bilirubin [TB] ≤ the upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or TB < 1 to 1.5 times ULN and any AST) , or moderate (TB > 1.5 to 3 times ULN and any AST) hepatic impairment. Specifically, nivolumab clearance in 244 individuals with mild hepatic impairment (including 152 patients with HCC) and 13 patients with HCC and moderate hepatic impairment was comparable to nivolumab clearance observed in 88 individuals with normal hepatic function. The $C_{avg,ss}$ was also comparable among the different liver function groups. For patients with HCC in CHECKMATE-040, the geometric mean exposures of nivolumab in patients with mild (N=152) and moderate (N=13) hepatic dysfunction were approximately 14% and 19% lower, respectively, compared to patients with normal hepatic function (N=88); these differences were not considered to be

clinically meaningful. Based on these results, the clinical pharmacology reviewers determined that no dose adjustment is needed in patients with mild or moderate hepatic impairment.

The clinical pharmacology review team did not recommend a postmarketing requirement (PMR) or postmarketing commitment (PMC) clinical pharmacology study to support approval of this sBLA.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Damiette Smit, the clinical reviewer, and Dr. Sirisha Mushti , the statistical reviewer, recommend accelerated approval of the sBLA, as amended, based on the safety and efficacy data submitted. The joint clinical and statistical review, completed on August 31, 2017, recommends accelerated approval of nivolumab as a single agent (200 mg Q2W) for the treatment of patients with advanced HCC who had progressed on or were intolerant to sorafenib.

Data from a single clinical trial 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.

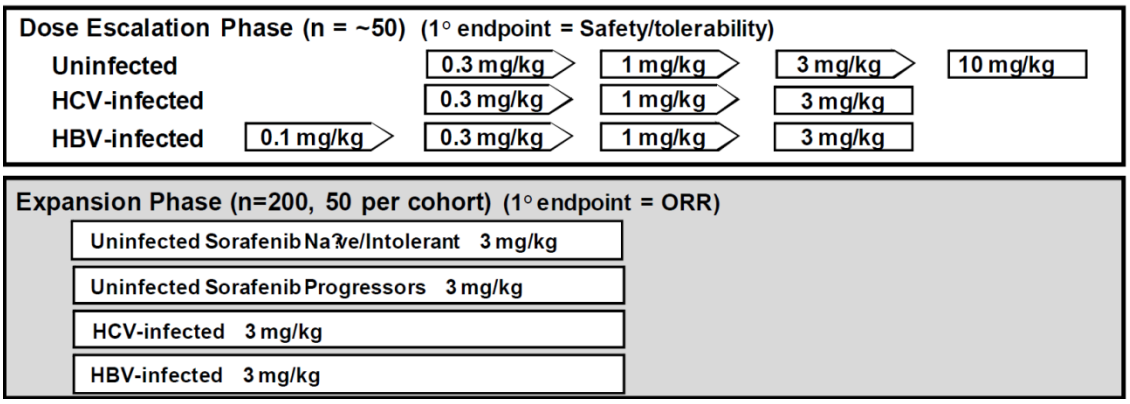
Study Design
Study CA209040 (CHECKMATE-040), entitled "A Phase 1/2, Dose-escalation, Open-label, Non-comparative Study of Nivolumab or Nivolumab in Combination with Ipilimumab in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis; and a Randomized, Open-label Study of Nivolumab vs Sorafenib in Advanced Hepatocellular Carcinoma Subjects who are Naive to Systemic Therapy", was initiated on October 30, 3012, and the data cut-off date used for the sBLA submission was November 29, 2016.

CHECKMATE-040 is an ongoing open-label multi-center study of nivolumab alone or in combination with ipilimumab in adults with hepatocellular carcinoma. The study consists of the following cohorts: a dose escalation phase cohort (nivolumab monotherapy, 3+3 design), a dose expansion phase cohort (nivolumab monotherapy), a first-line randomized cohort (nivolumab vs. sorafenib), and a nivolumab plus ipilimumab combination cohort.

For this efficacy supplement, FDA review focused on analyses of data from patients with HCC who progressed on, or were intolerant to sorafenib, and who were treated with nivolumab monotherapy (3 mg/kg) in the dose escalation and dose expansion phase of the trial.

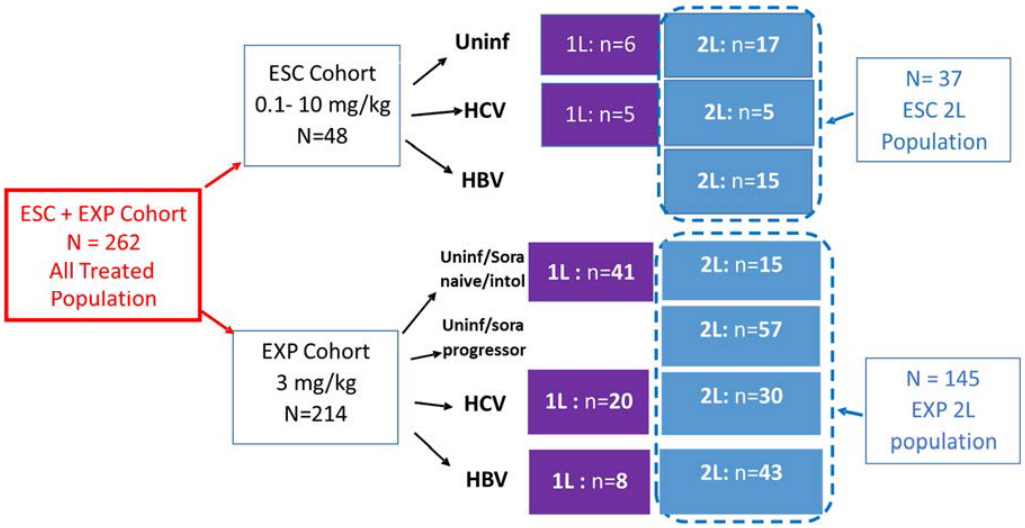
Figures 1 and 2 summarize the design and patient populations enrolled in the parts of the study supporting this sBLA.

Figure 1: Design of the dose escalation and dose expansion phase in Study CA209040



Source: Interim Clinical Study Report, appendix 1.1, study protocol.

Figure 2: Patients enrolled in the dose expansion and dose escalation phase in Study CA209040



Source: Interim Clinical Study Report figure 3.1-1.

The major efficacy outcome measures considered by FDA were confirmed overall response rate (ORR) and duration of response (DOR), as assessed by blinded independent central review using RECIST v1.1. ORR and DOR by BIRC using modified RECIST for HCC was also evaluated.

Protocol-specified secondary objectives included estimation of time to progression (TTP) and progression free survival (PFS) by BICR and investigators using RECIST 1.1, evaluation of overall survival (OS), and investigation of the association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures, including overall survival. Additional secondary objectives for the dose escalation phase were to characterize the pharmacokinetics of nivolumab and to assess the immunogenicity of nivolumab. Exploratory objectives for the dose expansion portion of the trial included assessment of the pharmacokinetics of nivolumab, to assess the immunogenicity of nivolumab, and to assess quality of life measures using the EQ-5D-3L questionnaire.

Key inclusion criteria were: (1) histologically confirmed hepatocellular carcinoma, (2) disease not amenable for management with curative intent by surgery or local therapeutic measures, (3) ECOG performance status 0-1, (4) measurable disease per RECIST 1.1., (5) 18 years of age or older, and (6) adequate organ function (WBC ≥ 2000/ μL, neutrophils ≥1000/ μL, hemoglobin ≥9 g/dL, platelets ≥ 60 x 10^3 /μL, creatinine clearance >40 mL/min, AST and ALT ≤5 x ULN, bilirubin ≤3 mg/dL, INR ≤2.3 or PT ≤6 seconds above control, and albumin ≥2.8 g/dL).

Inclusion criteria specific to the dose escalation phase were: (1) documented radiographic or symptomatic progression during, after, or intolerant to at least one line of systemic treatment (patients who refused sorafenib were allowed to enroll providing their refusal was thoroughly documented and they were informed by the investigator about their treatment options) and (2) Child-Pugh A or B7.

Inclusion criteria specific to the dose expansion phase were: (1) documented radiographic or symptomatic progression during or after sorafenib (for the "uninfected sorafenib progressor cohort"), (2) treatment naïve or intolerance to sorafenib ("uninfected sorafenib naïve or intolerant cohort"), (3) documented radiographic or symptomatic progression or intolerance to sorafenib (HBV and HCV cohorts), and (4) Child-Pugh A.

Inclusion criteria specific to HBV cohorts were: (1) evidence of ongoing viral replication (detectable HBsAg, HBeAg, or HBV DNA; both HBeAg positive and negative patients can be enrolled), (2) HBV DNA viral load <100 IU/mL at screening, (3) already on antiviral therapy or initiating antiviral therapy at time of consent (must continue antiviral therapy through follow-up visit 2).

Inclusion criteria specific to HCV cohorts were: (1) evidence of HCV RNA, and (2) no active HBV (may have prior infection, as determined by detectable HBsAb and HBcAb and undetectable HBsAg and HBV DNA).

Sorafenib intolerance was defined as:

- ≥CTCAE Grade 2 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards AND 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily)
- ≥CTCAE Grade 3 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards OR 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily).

Key exclusion criteria were: (1) suspected or evidence of brain metastases, (2) history of hepatic encephalopathy, (3) active coinfection with both HBV and HCV, (4) hepatitis D infection in a patient with HBV, (5) 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 immunosuppressive medications within 14 days of study drug administration.

Patients in the dose escalation phase received nivolumab 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg intravenously every two weeks until toxicity or disease progression. Of note, prior to Amendment 8 (31 July 2015), patients in the dose escalation phase were treated until either confirmed complete response (CR), completion of 2 years of therapy, unacceptable toxicity, or disease progression. Patients who discontinued nivolumab for confirmed CR were offered re-initiation of study therapy if disease progression occurred within 1 year of treatment discontinuation.

Patients in the dose expansion phase received nivolumab 3 mg/kg IV every two weeks until progression of disease or treatment discontinuation until toxicity or disease progression.

Treatment beyond investigator-assessed RECIST 1.1-defined progression was permitted if the patient experienced investigator-assessed clinical benefit, the patient was tolerating the study treatment, treatment beyond progression would not delay an imminent intervention to prevent serious complications of disease progression, and the patient provided a written informed consent. Patients treated beyond 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.

HBV virologic breakthrough due to antiviral resistance (defined as >1 log IU/mL increase in HBV DNA) was managed by standardized regional guidelines and by withholding nivolumab. Patients were allowed to restart nivolumab once virologic control was re-established and the patient did not have a dose-limiting toxicity or hepatic decompensation, and provided the Principal Investigator and medical monitor determined it to be in the best interest of the patient. For patients who continued to be HCV RNA positive after receiving nivolumab, initiation of direct acting antivirals was allowed at the discretion of the Investigator after discussion with the Medical monitor.

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. Palliative local therapy was allowed if criteria were met and the patient met criteria to continue treatment beyond progression.

Tumor assessments were conducted every 6 weeks for 48 weeks and every 12 weeks thereafter.

The sample size for the CHECKMATE-040 trial was based on the following considerations:

- For the dose escalation phase the sample size was based on a 3 +3 design with 3 cohorts.
- For the dose expansion phase: a total of 50 patients per arm (4 arms) are planned. If 50 patients are treated at 3 mg/kg dose level in any of the four additional expansion arms and 10 of 50 subjects (20%) are responders (best overall response of PR or CR), the lower bound of 95% confidence interval of the response rate calculated using the Clopper-Pearson Method will exclude 10%.

Efficacy Results

Efficacy is based on data from a 154-patient subgroup of patients enrolled in CHECKMATE-040, a single-arm clinical trial conducted in adults with advanced HCC who progressed on, or were intolerant to sorafenib. The key efficacy endpoints supporting this supplemental application are confirmed overall response rate (ORR) and duration of response (DOR) by RECIST 1.1 as assessed by blinded independent central review (BICR).

BMS pre-specified the efficacy population in the protocol as those patients who were treated with nivolumab 3 mg/kg IV every 2 weeks in the dose expansion phase (n= 145); however, an additional nine patients were treated with nivolumab 3 mg/kg in the dose escalation phase of the study. Because these patients are similar to the patients enrolled in the dose expansion phase, FDA also included these patients in the efficacy population; therefore the primary efficacy and safety population comprises 154 patients.

The database lock for clinical data submitted to the sBLA occurred on November 29, 2016 and the database lock for BIRC data was December 12, 2016. In addition, BMS submitted data on updated BIRC-assessed duration of response for *all* responders (including patients treated in the dose escalation phase with doses of nivolumab other than 3 mg/kg), as requested by FDA on July 6, 2017. The data cutoff for this update is March 17, 2017

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

No additional responders were identified between the data cutoff of 29 November 2016 and the data cutoff of 17 March 2017. The efficacy results, which reflect the updated data provided for the duration of response, are summarized in Table l below, extracted from the package insert.

Table 1: Efficacy Results in Trial CHECKMATE-040

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

[a] Overall response rate confirmed by BICR.

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

Of the 22 original responders in the efficacy population, 12 patients (55%) had an ongoing response at the time of the data cutoff. Twenty patients (91%) had a duration of response of at least 6 months and 12 patients (55%) had a duration of response of at least 12 months.

Exploratory analyses did not reveal a correlation between response and PD-L1 expression or presence of active hepatitis; however, the utility of these analyses are limited by the small sample size.

BMS submitted summary analyses of quality of life data collected from patients enrolled in the expansion phase of KEYNOTE-040 through the use of the EQ-5D-3L questionnaire. The majority of patients had no problems with mobility, self-care, usual activities or anxiety/depression; however, patients in the uninfected sorafenib naïve/intolerant cohort and in the uninfected sorafenib progressor cohort reported some problems with pain/discomfort on treatment. The on-treatment visual analogue score (VAS) increased from 74.2 at Week 7 to 75 at the Week 25 assessment. The utility of these analyses are limited due to the open label study design and lack of information regarding questionnaire completion rates.

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 CHECKMATE-040. 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 125 patients who discontinued nivolumab, the majority (84%) discontinued due to progressive disease. A minority (10%) discontinued nivolumab due to adverse events or withdrew consent to continue treatment. Adverse events considered related to nivolumab and leading to discontinuation occurred in 5 patients. Adverse event related to nivolumab that led to discontinuation were Grade 3 pneumonitis, Grade 3 hepatitis, Grade 3 polyarthritis, Grade 2 oral mucositis and type 1 diabetes mellitus.

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

I concur with the clinical review team that risk mitigation and evaluation strategies (REMS) are not required to ensure safe and effective use of nivolumab in the proposed indicated population, given the extensive post-marketing experience with nivolumab.

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

9. Advisory Committee Meeting

This efficacy supplement was not referred to the Oncologic Drugs Advisory Committee because there were no controversial issues that would benefit from advisory committee discussion. There is substantial clinical experience with nivolumab and evaluation of the safety data did not raise safety concerns for the intended population. Additionally, the clinical trial design was acceptable to support accelerated approval for the treatment of patients with advanced HCC in the second-line setting; durable overall response rate has been used as a primary endpoint to support accelerated approval of multiple drugs and biologics for the treatment of refractory cancers.

10. Pediatrics

This application is exempt from the requirements under the Pediatric Research Equity Act because nivolumab received orphan designation for the treatment of patients with hepatocellular

carcinoma on September 2, 2015. On September 11, 2014, FDA issued, a Written Request for the conduct of pediatric studies of nivolumab [redacted (b) (4)]

11. Other Relevant Regulatory Issues

The clinical study report for the study included in this application (CHECKMATE-040) 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).

In accordance with 21 CFR 54, the Applicant submitted a list of investigators for Study CA209040 (module 1.3.4, Table 1 and 2) and independent radiological reviewers ([redacted (b) (4)]; module 1.3.4, Table 3). BMS also provided financial disclosures (FDA form 3454) for Study CA209040 and for the independent radiological reviewers. Eight investigators received significant payments but a review of these financial interests revealed that they were unlikely to impact the study results.

The clinical review team, in conjunction with the Office of Scientific Investigations, determined that site inspections were not necessary because the Applicant and the independent radiology review contractor ([redacted (b) (4)]) have undergone recent site inspections that did not uncover significant findings and subgroup analyses of study results by clinical site did not identify any data trends that would warrant inspection of any particular site.

12. Labeling

This section of the review will focus on high-level issues regarding the labeling submitted by BMS.

Indications and Usage: DOP2 recommended minor editorial revisions to the proposed indication statement. The agreed upon statement is listed below:

> OPDIVO is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials [see Clinical Studies (14.8)].

Dosage and Administration: DOP2 concurred with proposed recommended dosage of 240 mg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

DOP2 recommended revisions to the formatting and presentation of the dose modification table to break out the instructions for dose modifications for immune-mediated hepatitis for patients with Non-HCC cancers from that of immune-mediated hepatitis for patients with HCC because the guidelines for dose modification differ in the two populations.

Warnings and Precautions: There were no new safety signals identified in CHECKMATE-040. Given the large safety database already evaluated for serious adverse reactions of nivolumab, these general risks have been adequately characterized and this section was not updated to include the results from CHECKMATE-040 which would not have altered the current description of serious adverse events in a meaningful way. In the Immune-Mediated Hepatitis subsection, DOP2 recommended revisions to more clearly articulate the dose modification instructions for patients with HCC who develop immune-mediated hepatitis.

Adverse Reactions: This section was updated to include the safety results of CHECKMATE-040. Because the safety profile of nivolumab was generally similar to the safety profile observed for other nivolumab indications, abbreviated information was incorporated into product labeling. Information regarding nivolumab exposure in patients with HCC was added. Additionally, a statement indicating that the toxicity profile was generally similar in HCC with the exception of a higher incidence of elevations in transaminases and bilirubin levels was added, along with the per-patient incidence of these abnormalities and the number of patients with immune-mediated hepatitis requiring systemic corticosteroids.

Use in Specific Populations: The Hepatic Impairment subsection was modified to indicate that no dosage adjustment is necessary in patients with moderate hepatic impairment and that OPDIVO has not been studied in patients with severe hepatic impairment.

Clinical Pharmacology: The Pharmacokinetics subsection was updated to provide information about PK analyses in patients with HCC, including patients with HCC and hepatic impairment.

Clinical Studies Section: Throughout, the term "objective response rate" was modified to "overall response rate" for consistency with terminology used in RECIST 1.1.

In the Hepatocellular Carcinoma subsection, extensive revisions were made to BMS' proposed labeling to more clearly articulate that the data supporting the safety and efficacy of nivolumab was derived from a subset of patients in the CHECKMATE-040 study and the relevant baseline and demographic characteristics of these patients. Efficacy results presented (b) (4) BICR-assessed overall response rate according to RECIST v. 1.1 (including the breakdown of complete and partial responses); BICR-assessed duration of response (DOR) by RECIST v. 1.1 based upon the updated data cutoff date (b) (4) percentage of responding patients with DOR ≥ 6 months and ≥ 12 months were included); and BICR-assessed overall response rate according to mRECIST.

Medication Guide: This section was revised in conjunction with the Patient Labeling Team to provide information about the hepatocellular carcinoma indication. Minor additional editorial/formatting revisions were also incorporated.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
I concur with the clinical review team that a (REMS) is not required based on the favorable risk:benefit assessment for use of nivolumab in patients with advanced HCC who have progressed on or were intolerant to sorafenib and because there is extensive postmarketing experience with nivolumab indicating that a REMS is not required for its safe and effective use.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
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.

3270-1 Conduct and submit the results, including datasets, of a multicenter, randomized trial or trials to verify and describe the clinical benefit of nivolumab over standard therapy based on an improvement in overall survival in patients with advanced hepatocellular carcinoma.

BMS has also agreed to conduct the following PMC under 506B to provide a more precise estimation of the duration of response in this patient population.

3270-2 Submit the final report, including datasets, from patients with hepatocellular carcinoma who have progressed on, or are intolerant to sorafenib and who received nivolumab 3 mg/kg in the dose escalation or dose expansion phase of CHECKMATE-040. In order to further characterize the duration of response in patients who achieve a complete or partial response to nivolumab, duration of response will be assessed by independent central review and responding patients will be followed for at least 12 months from the onset of response.

14. Decision/Action/Risk Benefit Assessment

Recommended Regulatory Action
I recommend accelerated approval of nivolumab for the treatment of patients with hepatocellular carcinoma who have been previously treated with nivolumab

Risk:Benefit Assessment
Hepatocellular carcinoma (HCC) is a serious and life threatening-disease, with a low reported 5-year survival rate of approximately 10%[5]. There is an unmet medical need for patients with this disease. Regorafenib is the only approved treatment for patients with hepatocellular carcinoma who have been previously treated with sorafenib. Although regorafenib is available therapy for patients with HCC who have previously been treated with sorafenib, this approval was based on a modest improvement in median overall survival (2.8 months) in the regorafenib arm (median OS 10.6 months; 95% CI: 9.1, 12.1) compared to the placebo arm (median OS 7.8 months; 95% CI: 6.3, 8.8) . Additionally, the overall response rate (ORR) for regorafenib in the trial supporting approval was relatively low; the ORR was 7% (95% CI: 4%, 10%) in the regorafenib arm compared to 3% (95% CI:1%, 6%) in the placebo arm.

In this supplemental BLA, the efficacy of nivolumab is based on data from a 154-patient subgroup of patients enrolled in CHECKMATE-040, a single-arm clinical trial conducted in adults with advanced HCC who progressed on, or were intolerant to sorafenib. The BICR-assessed overall response rate was 14.3% (95% CI: 9.2, 20.8), including 3 patients (2%) with a complete response and 19 (12.3%) with a partial response to nivolumab.

The review team determined that the efficacy data provided in the sBLA satisfied the criteria for accelerated approval of nivolumab in patients with HCC who had received treatment with sorafenib. This determination was primarily based on the observed response rate and, in particular, the magnitude of the duration of response, indicating that nivolumab provides a meaningful advantage over available therapy (i.e., regorafenib). Although the observed ORR in CHECKMATE-040 is relatively modest, for patients who achieved responses, the duration of responses is striking; with 91% of responders having a duration of response of ≥6 months and 55% of responders having a response of ≥12 months. For patients with HCC who have previously received sorafenib, this duration of response is clinically meaningful, particularly given that a substantial proportion of responding patients had a duration of response of 12 months or longer, which exceeds the median OS observed in patients randomized to regorafenib in the trial supporting its approval. Additionally, clinically meaningful overall response rates that are durable have correlated with an overall survival benefit for nivolumab in patients with lung cancer (squamous and non-squamous), renal cell carcinoma and squamous cell carcinoma of the head and neck.

The toxicity of nivolumab is due to its mechanism of action, which can result in development of autoimmune disease. As with prior approvals in other tumor types, the risks of immune-mediated adverse reactions are acceptable for patients with a life-threatening disease such as HCC given the ability to manage those risks, in most cases, with discontinuation of nivolumab and medical intervention (e.g., administration of corticosteroids). The toxicity profile observed in patients with advanced HCC was generally similar to that observed in patients with other cancers, with the exception of a higher incidence of elevations in transaminases and bilirubin levels. Treatment with nivolumab resulted in treatment-emergent Grade 3 or 4 AST in 27 (18%) patients, Grade 3 or 4 ALT in 16 (11%) patients, and Grade 3 or 4 bilirubin in 11 (7%) patients. Immune-mediated hepatitis requiring systemic corticosteroids occurred in 8 (5%) patients. However, the adverse reaction profile appears generally manageable, with adverse events resulting in discontinuation of nivolumab occurring in only 5% of patients in CHECKMATE-040.

Based on these considerations and taking into account the totality of the data and outcomes with currently available therapy, I agree with the clinical and statistical review teams' conclusion that the benefit-risk profile for nivolumab in patients with HCC who have received prior treatment with sorafenib is favorable.

15. References

1. Cancer Facts and figures 2017.
2. NCCN guidelines for hepatobiliary cancers, version 2.2017, dated 25 May 2017.
3. Sorafenib USPI and clinical review, Drugs@FDA.
4. Regorafenib USPI and clinical review, Drugs@FDA.
5 WT London, KA McGlynn: D Schottenfeld JF Fraumeni Jr Liver cancer, Cancer Epidemiology and Prevention 763– 786,2006 ed 3 New York, NY Oxford University Press

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/s/

MARTHA B DONOGHUE
09/22/2017

PATRICIA KEEGAN
09/22/2017
I concur with this review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s041

MEDICAL REVIEW(S)

CLINICAL AND STATISTICAL REVIEW

Application Type	BLA 351 (a)
Application Number(s)	125554 S-041
Priority or Standard	Priority
Submit Date(s)	24 March 2017
Received Date(s)	24 March 2017
PDUFA Goal Date	24 September 2017
Division / Office	DOP2/OHOP/OND/CDER
Reviewer Name(s)	Damiette Smit, Clinical Sirisha Mushti, Statistical
Review Completion Date	30 August 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)	Hepatocellular carcinoma (HCC) (b) (4) [redacted]
Intended Population(s)	Hepatocellular carcinoma who have been previously treated with sorafenib

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1. Recommendations/Risk Benefit Assessment

1.1. Recommendation on Regulatory Action

The clinical and statistical reviewers recommend that the FDA grant accelerated approval to nivolumab (Opdivo) as a single agent for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib. 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.

This supplemental Biologics License Application (sBLA) was supported by clinical data from single arm Study CA209040, in which treatment of 154 patients with hepatocellular carcinoma who had progressed on, or were intolerant to sorafenib resulted in an overall response rate of 14% (95% CI: 9.2, 20.8). The observed responses appeared durable, with 20 patients (91%) having a duration of response of at least 6 months and 12 patients (55%) having a duration of response of at least 12 months.

1.2. Risk Benefit Assessment

Background:

Hepatocellular carcinoma (HCC) accounts for approximately 28,920 deaths yearly in the United States[1] and is the 5th most common cause of cancer death among men and the 8th among women. The 5- year relative survival is 31% for early stage disease, but only 11% for unresectable localized disease and 3% for metastatic disease. For patients with HCC who are not candidates for curative therapy, treatment options include locoregional or systemic therapy. Sorafenib was approved in 2005 for the first-line treatment of advanced or metastatic HCC based on the SHARP study, which showed an improvement in overall survival (OS) for patients treated with sorafenib compared to placebo (median OS 10.7 months in the sorafenib arm vs. 7.9 months in the placebo arm, HR 0.69, $p<0.001$)[2]. Regorafenib was approved in 2017 for the treatment of patients with HCC who were previously treated with sorafenib. This approval was based on the RESORCE study, which showed an improvement in OS for patients treated with regorafenib compared to placebo (median OS 10.6 months in the regorafenib arm vs. 7.8 months in the placebo arm, HR 0.63, $p<0.0001$), as well as an improvement in progression free survival (PFS) (median PFS 3.4 months in the regorafenib arm vs. 1.5 months in the placebo arm, HR 0.43, $p <0.0001$). The overall response rate in the regorafenib arm was 7%

using RECIST 1.1 and 10.6% using modified RECIST for HCC[3]. Notably, adverse reactions resulted in treatment discontinuation in 10.4% of patients.

Efficacy:

The efficacy of nivolumab for the treatment of patients with HCC who have been previously treated with sorafenib was demonstrated in single arm Study CA209040. Patients with HCC who had progressed on, or were intolerant to sorafenib were treated with nivolumab 3 mg/kg intravenously every 2 weeks until disease progression or toxicity. Patients with and without active hepatitis B or C were included. The primary endpoint for this review was confirmed overall response rate (ORR) by blinded independent central review (BICR) using RECIST 1.1. The population supporting the indication consisted of 154 patients who were treated with nivolumab 3 mg/kg in the dose escalation and dose expansion phases of Study CA209040. Among these 154 patients, 19 (12%) had a partial response and 3 (1.9%) had a complete response, resulting in an ORR of 14% (95% CI: 9.2, 20.8). As the duration of response (DOR) data were immature at the time of BLA submission (data cutoff 29 November 2016), an updated duration of response assessment was submitted by the Applicant with a data cutoff of 17 March 2017. Based on this updated data cutoff, the estimated median DOR was 16.6 months (range: 3.2, 38.2+) for the 22 patients who had achieved a partial or complete response. Twelve patients (55%) had an ongoing response. Twenty patients (91%) had a duration of response of at least 6 months and 12 patients (55%) had a duration of response of at least 12 months. Response assessment by BICR using modified RECIST (mRECIST) for HCC was an exploratory endpoint. The ORR using mRECIST was 18% (95% CI: 12.4, 25.2), with 23 patients (15%) achieving a partial response and 5 patients (3.2%) achieving a complete response.

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 have been observed following nivolumab treatment in other settings with similar response rates. In addition, responses observed following treatment with nivolumab in patients with HCC appear durable. Further characterization of durability, is important, however, given that these data are immature.

Safety:

Although the single arm nature of the data submitted to the sBLA limits assessment of causality of safety events, the overall safety profile was generally similar to the known safety profile of nivolumab, with the exception of a higher incidence of hepatotoxicity. The most common adverse reactions (reported in at least 20% of patients) were fatigue, abdominal pain, musculoskeletal pain, pruritus, diarrhea, rash, cough, and decreased appetite. Eight patients

(5.2%) had immune-mediated hepatitis requiring systemic corticosteroids. Treatment with nivolumab resulted in treatment-emergent Grade 3 or 4 AST in 27 (18%) patients and in Grade 3 or 4 ALT in 16 (11%) patients. Although these events may be attributable to nivolumab, these events may also be attributable to the underlying cancer or to underlying liver disease (e.g., cirrhosis).

Overall Benefit-Risk Assessment for the Recommended Indication:

Although regorafenib has been approved by the FDA for the same indication as the proposed indication for this supplemental BLA and is therefore considered "available therapy" for the purposes of accelerated approval, this approval was based on a relatively modest improvement in overall survival (2.8 months) in the regorafenib arm compared to the placebo arm. Although a relatively low ORR was observed in patients treated with nivolumab in Study CA209040, the responses were durable, with 91% of responders having a duration of response of more than 6 months and 55% of responders having a response of more than 12 months. Clinically meaningful overall response rates that are durable have correlated with an overall survival benefit for nivolumab in patients with lung cancer (squamous and non-squamous), renal cell carcinoma and squamous cell carcinoma of the head and neck. The risk profile of nivolumab further supports accelerated approval; adverse events resulted in discontinuation of regorafenib in 10% of patients, whereas adverse events resulted in discontinuation of nivolumab in 5 % of patients. In addition, the adverse event profile of nivolumab is different from the adverse event profile of regorafenib, providing patients with an alternative option for treatment. Based on these considerations, the review team concluded that the benefit-risk profile for the approved indication is favorable taking into account the totality of the data and currently available therapy.

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

The clinical and statistical reviewers recommend that the accelerated approval of this supplemental application be subject to a postmarketing requirement (PMR) to verify and further describe the clinical benefit conferred by sorafenib in patients with HCC.

The reviewers recommend that the PMR consist of submission of final results and datasets from

(b) (4)

[redacted]

To better characterize the durability of responses to nivolumab, the reviewers recommend a PMC consisting of submission of additional follow-up data from Study CA209040, reflecting a minimum of 12 months of follow up from the onset of response.

2. Introduction and Regulatory Background

2.1. Product Information

This is a supplemental BLA for nivolumab for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

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 40 mg/ml and 100 mg/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:

- Hepatocellular carcinoma (HCC) [redacted].

2.2. Currently Available Treatments for the Proposed Indication

2.2.1. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the 10th most common cancer, with an estimated 40,710 new cases (including intrahepatic bile duct cancers) in 2017. HCC accounts for approximately 28,920 deaths yearly in the United States and is the 5th most common cause of cancer death among men and the 8th among women[1]. The 5- year relative survival is 31% for early stage disease, but only 11% for unresectable localized disease and 3% for metastatic disease[1]. The majority of patients with HCC (70-90%) have chronic liver disease. The most common risk factors for development of HCC are hepatitis B infection (HBV), hepatitis C infection (HCV), alcoholic use and non-alcoholic steatohepatitis[4].

Treatment of HCC is driven by the cancer stage and by underlying liver function, which is commonly assessed using the Child-Pugh scoring system (refer to section 9.1). For patients presenting with early-stage HCC, surgery and liver transplantation have the potential for cure. Patients with intermediate stage HCC (e.g., localized but unresectable disease) and good liver function are often treated with locoregional therapy (radiofrequency ablation, embolization with beads, intra-arterial chemotherapy, etc.). There are no curative treatments for patients with advanced disease. Patients with advanced HCC may receive locoregional or systemic therapy[4], depending on underlying liver function and prognostic factors, such as ECOG performance status, number of nodules, and presence of portal invasion or extrahepatic spread. Staging systems for HCC include the Barcelona Clinic Liver Cancer staging system and Okuda staging system (refer to section 9.2).

Sorafenib was approved in 2005 for the first-line treatment of advanced or metastatic HCC based on the results of a randomized study (SHARP) that showed an improvement in overall survival in patients randomized to sorafenib compared to placebo (median 10.7 months in the sorafenib group vs. 7.9 months in the placebo group, HR 0.69, $p<0.001$)[2].

2.2.2. Currently Available Treatments for the Proposed Indication

In April 2017, the FDA approved regorafenib for the treatment of patients with HCC who have been previously treated with sorafenib[3]. The efficacy of regorafenib for the treatment of patients with advanced HCC was demonstrated in Study 15982 (RESORCE), a multicenter, randomized, placebo-controlled trial comparing once daily regorafenib to placebo in patients with HCC that had progressed on sorafenib. A total of 573 patients were randomized, 379 to the regorafenib arm and 194 to the placebo arm. Median overall survival was 10.6 months in

the regorafenib arm and 7.8 months in the placebo arm with a hazard ratio of 0.63 (95% CI: 0.50, 0.79) and an unstratified log-rank p-value of 0.0002. The median progression free survival (PFS) was 3.1 months (95% CI: 2.8, 4.2) in the regorafenib arm and 1.5 months (95% CI: 1.4, 1.6) in the placebo arm with a hazard ratio of 0.46 (95% CI: 0.37, 0.56) and a p-value of <0.0001. Treatment with regorafenib resulted in an overall response rate (ORR) of 7% (95% CI: 4%, 10%) using RECIST 1.1 and a duration of response of 3.5 months (95% CI: 1.9, 4.5). Using modified RECIST for HCC (mRECIST), treatment with regorafenib resulted in an ORR of 10.6% (95% CI: 7.6%, 14.1%) and a median duration of response of 2.7 months (95% CI: 1.9, NE); however, ORR was considered an exploratory endpoint as it was not included in the pre-specified hierarchical test order for secondary endpoints. The median duration of regorafenib therapy was 3.5 months (range: 1 day to 29.4 months). Dose interruptions for adverse events were required in 58% of patients and dose reductions for adverse events were required in 48% of patients. The most common adverse reactions requiring dose modification (interruption or dose reduction) were hand-foot skin reaction (HFSR)/ palmar-plantar dysesthesia (PPES) (20.6%), blood bilirubin increase (5.9%), fatigue (5.1%) and diarrhea (5.3%). Adverse reactions resulted in treatment discontinuation in 10.4% of patients. The most common adverse reactions leading to discontinuation were HFSR/PPES (1.9%) and AST increased (1.6%).

2.3. Availability of Proposed Active Ingredient in the United States

Nivolumab is approved by the FDA for the treatment of:

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

- 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.
- Patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
- Patients with locally advanced or metastatic urothelial carcinoma who 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.
- Adult and pediatric (12 years and older) 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.

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 16 July 2012, the Applicant submitted Protocol CA209040 to IND 100052 entitled, "A Phase I Dose Escalation Study to Investigate the Safety, Immunoregulatory Activity, Pharmacokinetics, and Preliminary Antitumor Activity of Anti-Programmed-Death-1 (PD-1) Antibody (BMS-936558) in Advanced Hepatocellular Carcinoma in Subjects with or without Chronic Viral Hepatitis."
- On 5 May 2015, the Applicant administratively transferred Protocol CA209040 to the new IND 126406.
- On 7 May 2015, IND 126406 was granted a 30-day waiver.

- On 2 September 2015, nivolumab was granted orphan designation for the treatment of HCC (#15-4899).
- On 30 September 2015, the Applicant submitted amendment 8 of Protocol CA209040 (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- On 3 March 2017, a type B pre-BLA meeting was held between FDA and the Applicant to discuss efficacy and safety results from Study CA209040 intended to support this supplemental application. FDA requested, and the Applicant agreed to provide, a pooled analysis of overall response rate and duration of response for patients in the dose escalation and expansion cohorts previously treated with sorafenib. FDA concluded that the results allowed for review of the data in a sBLA.

2.6. Other Relevant Background Information

None.

3. Ethics and Good Clinical Practices

3.1. Submission Quality and Integrity

The submission was of adequate quality for the clinical and statistical 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.

3.2. Compliance with Good Clinical Practices

The clinical study report for the study included in this application (Study CA209040) 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).

3.3. Financial Disclosures

In accordance with 21 CFR 54, the Applicant submitted a list of investigators for Study CA209040 (module 1.3.4, Table 1 and 2) and independent radiological reviewers ((b) (4); module 1.3.4, Table 3). The Applicant also provided financial disclosures (FDA form 3454) for Study CA209040 and for the independent radiological reviewers. Eight investigators received significant payments. Refer to section 9.8 for a detailed overview and discussion of financial disclosures.

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 for full details.

4.4. Clinical Pharmacology

The Applicant proposes to use a flat dose of 240 mg every two weeks instead of the 3mg/kg every two weeks dosage regimen used in Study CA209040. See the FDA Clinical Pharmacology Review for this supplemental BLA for additional details. The reviewers concurs with the clinical pharmacology review team's conclusion that data support the use of a fixed dose of 240 mg for the proposed indication.

4.4.1. Mechanism of Action

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. 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.

The rationale for using nivolumab in patients with HCC includes evidence that tumor biopsies of patients with HCC express PD-L1 and that tumor-associated antigens are recognized by cytotoxic T-lymphocytes (CTLs) in 50-70% of patients with HCC[5,6]. In addition, low expression of PD-L1 in the tumor environment[7] and presence of a low level of intratumoral regulatory T-lymphocytes with a high level of intratumoral activated CTLs has been associated with improved disease-free survival and overall survival in patients with resectable HCC[8].

4.4.2. Pharmacodynamics

Not applicable for this sBLA.

4.4.3. Pharmacokinetics

See the FDA Pharmacology Review from the original BLA submission and for this supplemental application for full details.

4.5. Center for Devices and Radiological Health

Not applicable for this sBLA.

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 CA209040 (CheckMate 040):

- Trial Design: multi-center, open-label trial with multiple cohorts. The Applicant submitted single arm data from patients treated in the dose-escalation and dose-expansion phases of this trial to support this sBLA.
- Regimen, schedule, and route:
    - Dose escalation phase: nivolumab 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg intravenously (IV) every two weeks.
    - Dose expansion phase: nivolumab 3 mg/kg IV every two weeks.
- Primary endpoint:
    - Dose escalation phase: safety, tolerability, dose limiting toxicities (DLT) and maximum tolerated dose (MTD).
    - Dose expansion phase: overall response rate (ORR) and duration of response (DOR) by blinded independent central review (BICR) using RECIST 1.1.
- Number of patients treated:
    - Patients who have progressed on, or were intolerant to sorafenib: 182 total (37 in the dose escalation phase and 145 in the dose expansion phase).
    - All (including treatment-naïve) patients: 262 total (84 in the dose escalation phase and 214 in the dose expansion phase).

- Study Population: patients with hepatocellular carcinoma who progressed on, were intolerant to, or refused sorafenib.
- Number of centers and countries: 38 centers in 11 countries.
- Status: ongoing

5.2. Review Strategy

The clinical and statistical review of this sBLA included the following:

1. Review of the current literature on hepatocellular carcinoma epidemiology and treatment.
2. Review of Study CA209040 including the clinical study report (CSR), protocols, protocol amendments, and selected datasets.
3. Review and assessment of the Applicant's analysis of nivolumab efficacy and safety.
4. Review of datasets and SAS programming algorithms submitted by the Applicant.
5. Analysis of the datasets to evaluate baseline patient characteristics, efficacy and safety profile of nivolumab.
6. Review of patient narratives of serious adverse events, deaths, and immune-mediated adverse reactions.
7. Review of meeting minutes conducted during drug development.
8. Assessment of the Module 2 summaries including the Summary of Clinical Safety.
9. Requests for additional information from the Applicant and review of Applicant responses.
10. Formulation of the benefit-risk analysis and recommendations.
11. Review and evaluation of proposed labeling.

5.3. Discussion of Individual Studies/Clinical Trials

The primary evidence to support to this supplement application is derived from data from Study CA209040.

5.3.1. Study Design

Study CA209040: "A Phase 1/2, Dose-escalation, Open-label, Non-comparative Study of Nivolumab or Nivolumab in Combination with Ipilimumab in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis; and a Randomized, Open-label Study of Nivolumab vs Sorafenib in Advanced Hepatocellular Carcinoma Subjects who are Naive to Systemic Therapy".

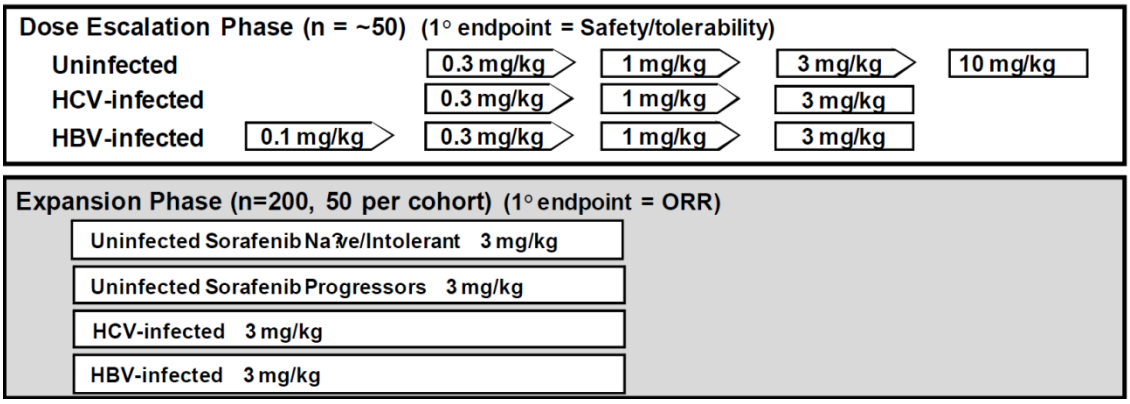
Date of original protocol: 25 May 2012.
Study initiation date: 30 October 2012.
Data submitted: all patients enrolled in the dose escalation and dose expansion phase.
Status: ongoing.
Data cutoff used for sBLA submission: 29 November 2016.

Design

CA209040 is an open-label multi-center study of nivolumab alone or in combination with ipilimumab in adults with hepatocellular carcinoma. The study consists of the following cohorts: dose escalation phase cohort (nivolumab monotherapy, 3+3 design), dose expansion phase cohort (nivolumab monotherapy), first-line randomized cohort (nivolumab vs. sorafenib), and a nivolumab plus ipilimumab combination cohort. The study is ongoing.

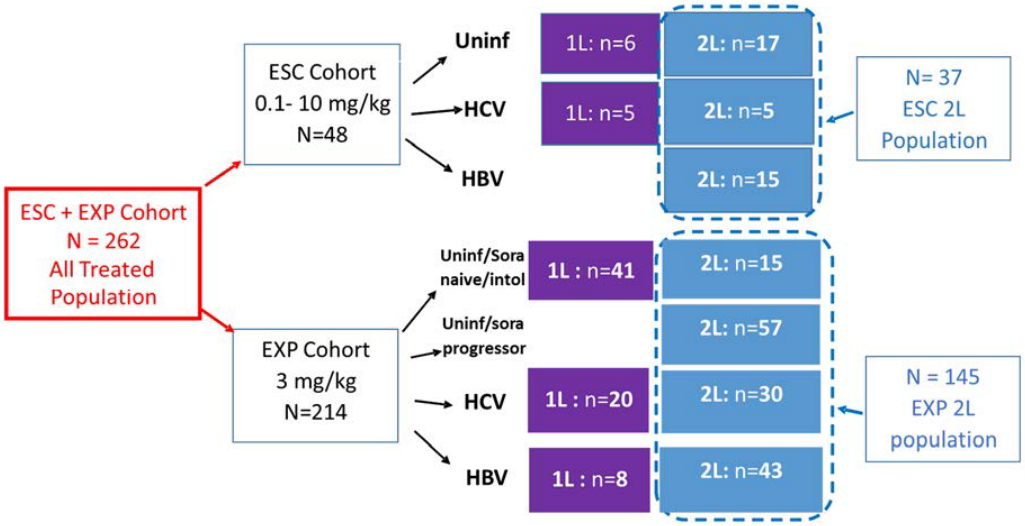
Only data from patients with HCC who progressed on, or were intolerant to sorafenib, and who were treated with nivolumab monotherapy in the dose escalation and dose expansion phase will be included in this review. Figure 1 and 2 summarize the design and patient populations enrolled in the part of the study supporting this sBLA.

Figure 1: Design of the dose escalation and dose expansion phase in Study CA209040



Source: Interim Clinical Study Report, appendix 1.1, study protocol.

Figure 2: Patients enrolled in the dose expansion and dose escalation phase in Study CA209040



Source: Interim Clinical Study Report figure 3.1-1.

Objectives

The primary objective of the dose escalation phase is to assess safety, tolerability, dose limiting toxicities and maximum tolerated dose. The primary objective of the dose expansion phase is to estimate ORR and DOR by BICR using RECIST 1.1.

Secondary objectives are to estimate time to progression (TTP) and progression free survival (PFS) by BICR and investigators using RECIST 1.1, to evaluate OS, to investigate the association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures, including overall survival. Additional secondary objectives for the dose escalation phase are to characterize the pharmacokinetics of nivolumab and to assess the immunogenicity of nivolumab.

Exploratory objectives for the dose escalation phase are to assess antitumor activity using mRECIST for HCC, to investigate the pharmacodynamic activity of nivolumab on antiviral immunologic biomarkers and on antitumor immunologic markers, to describe the effects of nivolumab in patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV), to explore the association of oncologic and antiviral clinical activity and safety measures with SNPs and to assess the relationship between nivolumab exposure and measures of hepatic dysfunction.

Exploratory objectives for the dose expansion phase are to assess the pharmacokinetics of nivolumab, to assess the immunogenicity of nivolumab, and to assess quality of life measures using the EQ-5D-3L questionnaire.

Eligibility

Key inclusion criteria were: (1) histologically confirmed hepatocellular carcinoma, (2) not amenable for management with curative intent by surgery or local therapeutic measures, (3) ECOG performance status 0-1, (4) measurable disease per RECIST 1.1., (5) 18 years or older, and (6) adequate organ function (WBC ≥ 2000/ µL, neutrophils ≥1000/ µL, hemoglobin ≥9 g/dL, platelets ≥ 60 x 10^3 /µL, creatinine clearance >40 mL/min, AST and ALT ≤5 x ULN, bilirubin ≤3 mg/dL, INR ≤2.3 or PT ≤6 seconds above control, and albumin ≥2.8 g/dL).

Inclusion criteria specific to the dose escalation phase were: (1) documented radiographic or symptomatic progression during, after, or intolerant to at least one line of systemic treatment (patients who refused sorafenib were allowed to enroll providing their refusal was thoroughly documented and they were informed by the investigator about their treatment options) and (2) Child-Pugh A or B7.

Inclusion criteria specific to the dose expansion phase were: (1) documented radiographic or symptomatic progression during or after sorafenib (uninfected sorafenib progressor cohort), (2) treatment naïve or intolerance to sorafenib (uninfected sorafenib naïve or intolerant cohort), (3) documented radiographic or symptomatic progression or intolerance to sorafenib (HBV and HCV cohorts), and (4) Child-Pugh A.

Inclusion criteria specific to HBV arms were: (1) evidence of ongoing viral replication (detectable HBsAg, HBeAg, or HBV DNA; both HBeAg positive and negative patients can be enrolled), (2) HBV DNA viral load <100 IU/mL at screening, (3) already on antiviral therapy or initiating antiviral therapy at time of consent (must continue antiviral therapy through follow-up visit 2).

Inclusion criteria specific to HCV arms were: (1) evidence of HCV RNA, and (2) no active HBV (may have prior infection, as determined by detectable HBsAb and HBcAb and undetectable HBsAg and HBV DNA).

Sorafenib intolerance was defined as:

- ≥CTCAE Grade 2 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards AND 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily)
- ≥CTCAE Grade 3 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards OR 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily).

Key exclusion criteria were: (1) suspected or evidence of brain metastases, (2) history of hepatic encephalopathy, (3) active coinfection with both HBV and HCV, (4) hepatitis D infection in a patient with HBV, (5) 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.

Treatment plan

Patients in the dose escalation phase received nivolumab 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, or 10 mg/kg intravenously every two weeks until toxicity or disease progression. Of note, prior to amendment 8 (31 July 2015), patients in the dose escalation phase were treated until either confirmed complete response (CR), completion of 2 years of therapy, toxicity, or disease progression. Patients who discontinued nivolumab for confirmed CR were offered re-initiation of study therapy if disease progression occurred within 1 year of treatment discontinuation.

Patients in the dose expansion phase received nivolumab 3 mg/kg IV every two weeks until progression of disease or treatment discontinuation until toxicity or disease progression.

Treatment beyond investigator-assessed RECIST 1.1-defined progression was permitted if the patient experienced investigator-assessed clinical benefit, the patient was tolerating the study treatment, treatment beyond progression would not delay an imminent intervention to prevent serious complications of disease progression, and the patient provided a written informed consent. Patients treated beyond 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.

HBV virologic breakthrough due to antiviral resistance (defined as >1 log IU/mL increase in HBV DNA) was managed by standardized regional guidelines and by withholding nivolumab. Patients were allowed to restart nivolumab once virologic control was re-established and the patient did not have a dose-limiting toxicity or hepatic decompensation, and provided the PI and medical monitor determined it to be in the best interest of the patient. For patients who continued to be HCV RNA positive after receiving nivolumab, initiation of direct acting antivirals was allowed at the discretion of the investigator after discussion with the medical monitor.

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. Palliative local therapy was allowed if criteria were met and the patient met criteria to continue treatment beyond progression.

Assessments

- Efficacy assessments (CT or MRI chest, abdomen, pelvis with IV contrast including tri-phasic evaluation of the liver) occurred at baseline, then every 6 weeks for the first year, then every 12 weeks. Confirmation of partial response (PR) and/or CR was required after at least 4 weeks from the initial scan reporting response. Confirmation of tumor 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, prior medications and Child-Pugh score.
- A baseline ECG was performed.
- Tumor tissue (archival or fresh) was collected at baseline for biomarker testing.
- The following laboratory tests were collected at baseline: CBC with differential and platelets, Complete Metabolic Panel (Na, K, Cl, HCO3, BUN, creatinine, eGFR, AST, ALT, alkaline phosphatase, albumin, total bilirubin, total protein, calcium, glucose), direct bilirubin, lipase, amylase, magnesium, phosphorous, LDH, urinalysis (dip), TSH, Free T4 and Free T3, PT/INR, aPTT, fibrinogen, pregnancy test, Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B Core antibody, Hepatitis B e antigen and e antibody, HBV DNA, HDV testing for subjects with HBV, Hepatitis C viral load (PCR) and Hepatitis C Antibody, HIV 1/2.
- The following laboratory tests were collected during the study: CBC with differential, Complete Metabolic Panel (Na, K, Cl, HCO3, BUN, Cr, eGFR, AST, ALT, alkaline phosphatase, albumin, total bilirubin, total protein, calcium, glucose), direct bilirubin, amylase, lipase, LDH, magnesium, phosphorus, TSH, Free T4, Free T3, PT/INR, aPTT, fibrinogen, pregnancy test, HBV testing for HBV infected patients (HBV DNA, quant HBsAg, quant HBeAg, HBsAb, HBeAb), HCV testing for HCV infected patients (HCV RNA).
- ECGs were done as follows: a single 12-lead prior to dosing on Cycle 1 Day 1, on Cycle 1 Day 42, Cycle 2 Day 42, and every even numbered Cycle Day 42 thereafter.
- The following was collected at follow-up visit 1 and 2: CBC with differential, Complete Metabolic Panel (Na, K, Cl, HCO3 (if locally available), BUN, Cr, eGFR, AST, ALT, alkaline phosphatase, albumin, total bilirubin, total protein, calcium, glucose), direct bilirubin,

amylase, lipase, LDH, magnesium, phosphorus, pregnancy test (serum or urine) for WOCBP, AFP, TSH with reflexive Free T4 and Free T3, pregnancy test

5.3.2. Protocol Amendments

The original protocol was dated 25 May 2012. The Applicant submitted 8 protocol amendments prior to the data cutoff of 29 November 2016. The following are considered major amendments:

- Amendment 3 (6 September 2013): laboratory and Child-Pugh ranges for inclusion/exclusion criteria were expanded, new safety information concerning virally infected subjects treated with checkpoint inhibitors was added, and a 10 mg/kg dose group was added.
- Amendment 4 (29 October 2014): dose expansion phase was added, re-initiation of treatment after discontinuation and treatment beyond disease progression was introduced, tumor evaluation criteria were switched from mRECIST to RECIST 1.1., and quality of life assessment was added.
- Amendment 8 (31 July 2015): the first-line randomized nivolumab vs. sorafenib cohort and the nivolumab plus ipilimumab combination cohort were added. In addition, prior to this amendment, patients in the dose escalation phase were treated until either confirmed CR, completion of 2 years of therapy, toxicity, or disease progression. With amendment 8, this changed to treatment until toxicity or disease progression.

5.3.3. Statistical Analysis Plan

Sample size calculations:

- Dose escalation phase: the sample size is based on a 3 +3 design with 3 arms.
- Dose expansion phase: 50 patients per arm (4 arms). If 50 patients are treated at 3 mg/kg dose level in any of the four additional expansion arms and 10 of 50 subjects (20%) are responders (best overall response of PR or CR), the lower bound of 95% confidence interval of the response rate calculated using the Clopper-Pearson Method will exclude 10%.

5.3.4. Radiology Charter

The Applicant contracted with (b) (4) for an independent radiology review assessment of radiologic efficacy endpoints to support this sBLA. During the independent radiology review,

radiographic exams were evaluated using RECIST 1.1 criteria for the primary endpoint and mRECIST for an exploratory endpoint. The Applicant was provided with an assessment of tumor response and progression. (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 CA209040 dose escalation and dose expansion phase.

(b) (4) conducted independent review as follows:

- Primary review: two independent radiologists assessed study imaging for a patient on a timepoint by timepoint basis to determine overall tumor assessment at each timepoint according to RECIST 1.1 and mRECIST.
- Global radiology review: the same independent radiologists then globally assessed all timepoints for the patient and updated any of their previous timepoint overall tumor assessments according to RECIST 1.1 and mRECIST.
- Adjudication review: adjudication was required if the independent radiologists' results for the global radiology review were in disagreement. During adjudication radiology review, an independent radiologist who did not participate in the primary or global radiology review for the patient chose the independent radiologist whose global radiology review assessments he/she agreed with most as the final assessment and provide justifying comments. This was done separately for RECIST 1.1 and mRECIST global radiology reviews.
- Secondary review: during secondary radiology review, the primary and global radiology reviews for a subset of patients were repeated. Secondary radiology review was used for determination of intra-observer variability for that subset of patients and did not alter the original read.

Radiology readers were blinded to the following: patient name, date of birth, initials, dose level, investigator site identifiers, clinical information, site lesion selection for tumor assessments, site determination of tumor response, and reason for exam. Furthermore, the independent radiologist was blinded to exam date during the timepoint by timepoint review.

6. Review of Efficacy

Efficacy Summary: refer to section 1.2.

6.1. Indication

Proposed indication: Treatment of patients with hepatocellular carcinoma (HCC) (b) (4)

Recommended indication: Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib.

6.2. Methods

Efficacy is based on data from a 154-patient subgroup of patients enrolled in Study CA209040, a single-arm clinical trial conducted in adults with advanced HCC who progressed on, or were intolerant to sorafenib. The key efficacy endpoints supporting this supplemental application are confirmed overall response rate (ORR) and duration of response (DOR) by RECIST 1.1 as assessed by blinded independent central review (BICR). The secondary endpoints are time to progression (TTP), progression free survival (PFS) and overall survival (OS). Additional efficacy endpoints are antitumor activity as measured by modified RECIST for HCC (mRECIST), ORR and DOR as assessed by investigator, association of hepatitis status with ORR, and association of PD-L1 staining with ORR.

Definition of efficacy population

The Applicant pre-specified the efficacy population in the protocol as those patients who were treated with nivolumab 3 mg/kg IV every 2 weeks in the dose expansion phase (n= 145). However, an additional nine patients were treated with nivolumab 3 mg/kg in the dose escalation phase of the study. Because these patients are similar to the patients enrolled in the dose expansion phase, these patients will be included in the efficacy population.

Efficacy population: 154 patients treated with nivolumab 3 mg/kg every 2 weeks.
Clinical data cutoff: 29 November 2016.
BICR data cutoff: 12 December 2016.

All analyses in this section are based on the efficacy population, unless otherwise stated.

6.3. Demographics and baseline characteristics

Demographics of patients are described in Table 1. The median age of patients was 63 and the majority of patients were male (76%). Most patients were either Asian (52%) or white (46%) and were treated in Asia (49%) or in Europe (39%). The majority of the patients (65%) had an ECOG performance status of 0.

Table 1: Demographics of the efficacy population

		Nivolumab (N=154) n (%)
Age	Median (range)	63 (19, 81)
	≥ 65 years	68 (44)
Sex	M	118 (76)
	F	36 (23)
Race	Asian[a]	80 (52)
	White	71 (46)
	Other	3 (1.9)
Geographical region[b]	Asia	76 (49)
	Europe	60 (39)
	United States/Canada	18 (12)
ECOG performance status	0	100 (65)
	1	54 (35)

Source: FDA analysis. [a] Asian patients were: Chinese (39), Japanese (25), Korean (13), Asian other (2), Asian Indian (1); [b] Patients were enrolled across the following countries: Japan (26), United Kingdom (25), Germany (18), United States (18), Taiwan (17), Hong Kong (16), Spain (13), Korea (13), Italy (4), Singapore (4).

Baseline characteristics are described in Table 2. Most patients had a Child-Pugh score of A5 or A6. Two patients had a Child-Pugh score of B7 at baseline, but on the first visit of cycle 1, these patients had a score of A6. In addition, 90% of patients had Barcelona Clinic Liver Cancer stage C and 77% of patients had Okuda stage I (for staging criteria, refer to section 9.2). Patients had a variety of risk factors for development of HCC including: hepatitis B (34%), hepatitis C (29%), alcoholic liver disease (18%), non-alcoholic fatty liver (6.5%) and hemochromatosis (2.6%). No patients had a known history of aflatoxin exposure. Of note, a patient may have had hepatitis as risk factor for developing HCC, but may not have been enrolled to the hepatitis B or C cohort as evidence of active/ongoing viral replication was required for enrollment to these cohorts (refer to section 5.3.1 for eligibility criteria for each cohort). The majority of patients (71%) had extrahepatic disease at baseline, 29% of patients had vascular invasion, and 45% of patients had >3 liver nodules. Few patients had ascites (9.1%) at baseline.

Table 3 summarizes prior therapy of patients in the efficacy population. All patients had received prior sorafenib. Thirty-six patients (23%) discontinued sorafenib due to toxicity (refer to section 5.3.1 for definition of sorafenib intolerance). However, the majority of patients (74%) discontinued sorafenib due to disease progression. The majority of patients (81%) had only received sorafenib as systemic therapy, but 19% of patients had received 2 or more lines of systemic therapy. In addition to prior systemic therapy, 66% of patients had had a surgical intervention, 24% of patients had received radiotherapy and 58% of patients had received local therapy for their HCC.

Forty-seven patients were enrolled in the hepatitis B cohort (for inclusion criteria, refer to section 5.3.1). Treatment for hepatitis B included: tenofovir (n=13), entacavir (n-32), adefovir (n=1) and herbs (n=1). Thirty-two patients were enrolled in the hepatitis C cohort (for inclusion criteria, refer to section 5.3.1). Treatment for hepatitis C included: ledipasvir-sofosbuvir (n=1) and sofosbuvir/ribavirin/daclatasvir (n=1). All patients had hepatitis C RNA evaluated at screening and during treatment (using various methods). Most patients (n=31) had HCV RNA done at the screening visit. Mean HCV RNA was 5309690, the median was 1990189 (range 25-40220010).

Table 2: Baseline disease characteristics of the efficacy population

		Nivolumab (N=154) n (%)
Child-Pugh score at baseline[a]	A5	105 (68)
	A6	47 (31)
	B7	2 (1.3)
Barcelona Clinic Liver Cancer Stage[b]	A (early)	2 (1.3)
	B (intermediate)	14 (9.1)
	C (advanced)	138 (90)
Okuda stage[b]	I (no factors present)	118 (77)
	II (1-2 factors present)	36 (23)
HCC risk factor	Hepatitis B	53 (34)
	Hepatitis C	45 (29)
	Alcoholic liver disease	28 (18)
	Non-alcoholic fatty liver	10 (6.5)
	Hemochromatosis	4 (2.6)
Pathologic parameters	Presence of vascular invasion	44 (29)
	Presence of extrahepatic disease	110 (71)
	Presence of ascites	14 (9.1)
Radiographic parameters	0 liver nodules	34 (22)
	1-3 liver nodules	50 (32)
	>3 liver nodules	69 (45)
	Tumor invasion in liver above 50%	21 (14)
Alpha-fetoprotein µg/L	Mean	10799.7
	Median	84.6
Alpha-fetoprotein group	≥400 µg/L	57 (37)
	<400 µg/L	92 (60)
	Missing	5 (3.2)
PD-L1	Quantifiable	135 (88)
	Positive using 1% cutoff	26 (19)
	Positive using 5% cutoff	9 (6.7)
	Positive using 10% cutoff	6 (4.4)

Source: FDA analysis. [a] For scoring and staging definitions, refer to section 9.1; [b] For scoring and staging definitions, refer to section 9.2.

Table 3: Prior anti-cancer therapy of efficacy population

		Nivolumab (N=154) n (%)
Type of prior therapy	Surgery	102 (66)
	Radiotherapy	37 (24)
	Local therapy [a]	90 (58)
	Systemic	154 (100)
Setting of prior systemic therapy	(Neo)- adjuvant therapy	3 (1.9)
	Therapy for locally advanced disease	19 (12)
	Therapy for metastatic disease	96 (62)
Reason for discontinuation prior sorafenib	Disease progression	114 (74)
	Maximum clinical benefit	1 (0.6)
	Toxicity	36 (23)
	Other[b]	4 (2.6)
Number of prior systemic treatments[c]	1	124 (81)
	2	15 (9.7)
	≥3	15 (9.7)

Source: FDA analysis. [a] Prior local therapy includes: radiofrequency ablation (RFA), trans-arterial embolization (TAE), trans-arterial chemo-embolization (TACE), percutaneous ethanol injection (PEI), cryoablation, Yttrium-90 microspheres, and hepatic arterial infusion (HAI); [b] Includes: "patient's opinion", "chemotherapy was followed with radiotherapy post vat wedge for lung met", "self-discontinuation", and "only 1 treatment, discontinued due to mild intolerance"; [c] Most common therapy other than sorafenib: investigational agent (30), fluorouracil (16), oxaliplatin (11), capecitabine (6), cisplatin (8), doxorubicin (6), and lenvatinib (4).

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 advanced HCC. Liver function in these patients was relatively intact (Child-Pugh class A) and most patients had Barcelona Clinic Liver Cancer stage C. The majority of patients had received only 1 prior line of systemic treatment, which is expected as only sorafenib was approved as first-line treatment for HCC during the conduct of Study CA209040. In addition, surgery and local therapy are commonly used as palliative management of patients with advanced HCC.

6.4. Patient Treatment and Disposition

The enrollment period for the dose escalation phase lasted from October 2012 to July 2015. The enrollment period for the dose expansion phase lasted January 2015 to November 2015.

Table 4 summarizes enrollment by cohort for patients treated with nivolumab 3 mg/kg in Study CA209040 (efficacy population). Nine patients were enrolled to three cohorts in the dose-escalation phase of the study and 145 patients were enrolled to four cohorts in the dose-expansion phase of the study. In addition to the patients treated with nivolumab 3 mg/kg, an

additional 28 patients were treated with other doses of nivolumab (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg and 10 mg/kg) in the dose-escalation phase of the protocol. However, these patients are not included in the efficacy population (refer to section 6.2).

Table 4: Cohort Enrollment

	Nivolumab n (%)
Cohorts	
Dose escalation - uninfected	3 (1.9)
Dose escalation – hepatitis B	4 (2.6)
Dose escalation – Hepatitis C	2 (1.3)
Dose expansion - uninfected sorafenib naïve/intolerant	15 (9.7)
Dose expansion – uninfected sorafenib progressor	57 (37)
Dose expansion – Hepatitis B	43 (28)
Dose expansion – Hepatitis C	30 (19)
Total by hepatitis status	
Uninfected	75 (49)
Hepatitis B	47 (31)
Hepatitis C	32 (21)

Source: FDA analysis.

Table 5 summarizes the disposition of patients in the efficacy population. The median number of doses received was 11 (range 1, 41). The majority of patients (81%) had discontinued treatment in the main treatment period at the time of data cutoff. Most patients discontinued nivolumab due to disease progression. Five patients discontinued nivolumab due to an adverse event related to 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 6.12.1.

Table 5: Patient Disposition

	Nivolumab n (%)
Patients treated	154 (100)
Patients continuing in the treatment period[a]	29 (19)
Reason for not continuing in the treatment period	
Disease progression	109 (71)
Adverse event related to study drug	5 (3.2)
Adverse event unrelated to study drug	3 (1.9)
Patient request to discontinue study treatment[b]	4 (2.6)
Patient withdrew consent[c]	1 (0.6)
Maximum clinical benefit	1 (0.6)
Other[d]	2 (1.3)
Number of doses and duration of treatment	
Number of doses received - median (range)	11 (1, 41)
Follow-up (months) - median (range)	5.06 (0.03, 19.98)
Re-treatment and treatment beyond progression	
Re-treatment[e]	1 (0.6)
Treatment beyond progression	80 (52)

Source: FDA analysis. [a] This excludes patients who were treated beyond progression; [b] Reasons: patient request, patient felt the study visits and the distance to travel too much, physical inconvenience + recent hospitalization, and patient would like to return home for treatment; [c] Reason: right oculomotor nerve paralysis; [d] Includes: patient no longer meets study criteria, increased ALT; [e] Re-treatment was allowed prior to amendment 8 those patients in the dose escalation cohort who discontinued nivolumab after achieving a complete response (refer to section 5.3.1).

Reviewer comment:

The number of patients discontinuing treatment for adverse events does not exceed the number expected based on other studies with nivolumab.

6.5. Protocol deviations

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

- Eligibility/At Entrance:
    - Patients with a baseline ECOG performance status > 1.
    - Patients with evaluable disease at baseline.
    - Patients with serum albumin <2.8 g/dL.

- Patients with total bilirubin >3 mg/dL.
- Patients with AST > 5 x ULN.
- Patients with ALT > 5 x ULN.
- Patients with Child-Pugh score of B8 or higher (dose escalation cohort).
- Patients with Child-Pugh score of B or higher (dose expansion cohort)

- On-study:
  - Patients receiving concurrent anti-cancer therapy (defined as chemotherapy, radiation therapy, non-systemic therapy, surgery for HCC).

Relevant protocol deviations were reported in 10 (6.5%) of patients. One patient had a relevant protocol deviation at study entry (eligibility) and nine patients had a relevant protocol deviation while receiving nivolumab (Table 6).

Table 6: Protocol Deviations

Category	Study ID	Protocol Deviation	Cohort
Eligibility	CA209040-(b) (6)	Patient did not have evaluable disease as baseline	Expansion
On-treatment	CA209040-(b) (6) [a]	Concurrent anti-cancer therapy (radiotherapy)	Expansion
	CA209040-(b) (6) [a]	Concurrent anti-cancer therapy (radiotherapy)	Expansion
	CA209040-(b) (6) [a]	Concurrent anti-cancer therapy (radiotherapy)	Expansion
	CA209040-(b) (6) [a]	Concurrent anti-cancer therapy (radiotherapy)	Expansion
	CA209040-(b) (6) [a]	Concurrent anti-cancer therapy (radiotherapy)	Expansion
	CA209040-(b) (6) [a]	Concurrent anti-cancer therapy (excision of spinal metastasis)	Expansion
	CA209040-(b) (6) [a]	Concurrent anti-cancer therapy (radiotherapy)	Expansion
	CA209040-(b) (6) [a]	Concurrent anti-cancer therapy (radiotherapy)	Expansion
	CA209040-(b) (6) [a]	Concurrent anti-cancer therapy (excision of lesion, laminectomy, spinal fusion)	Expansion

Source: Interim Clinical Study Report addendum 01, section 3.1 and table s.2.4. [a] Patients received palliative anti-cancer therapy after radiographic or clinical progression, but before discontinuation of nivolumab.

The Applicant stated that the nine patients who received concurrent anti-cancer therapy received this as palliative therapy after radiographical progression (i.e., the patients were treated beyond progression). This was allowed per protocol.

Reviewer comment:

As the patients who had concurrent anti-cancer therapy had this therapy after disease progression, these deviations will not affect the primary endpoint. The one patient who had an eligibility-related protocol deviation is unlikely to substantially affect the efficacy outcomes.

6.6. Analysis of Primary Endpoint

The primary endpoint for the clinical and statistical review of this application is confirmed ORR and DOR by RECIST 1.1 as assessed by blinded independent central review (BICR) in 154 patients with HCC who progressed on or were intolerant to sorafenib enrolled in Study CA209040 and who received 3 mg/kg nivolumab in the dose escalation (n=9) or dose expansion (n=145) phase.

As shown in Table 7, treatment with nivolumab resulted in a BICR-assessed ORR of 14%. Three patients (1.9%) had a complete response and 19 patients (12%) had a partial response. The disease control rate (responders plus patients with stable disease) was 56%. The median time to response was 2.8 months. As 17 responders (77%) were still receiving nivolumab at the time of the data cutoff, the median duration of response was not estimable. However, 91% of patients had a response duration of ≥6 months and 41% of patients had a response duration of ≥12 months. Due to the large number of censored events, FDA requested updated duration of response data (refer to section 6.6.1).

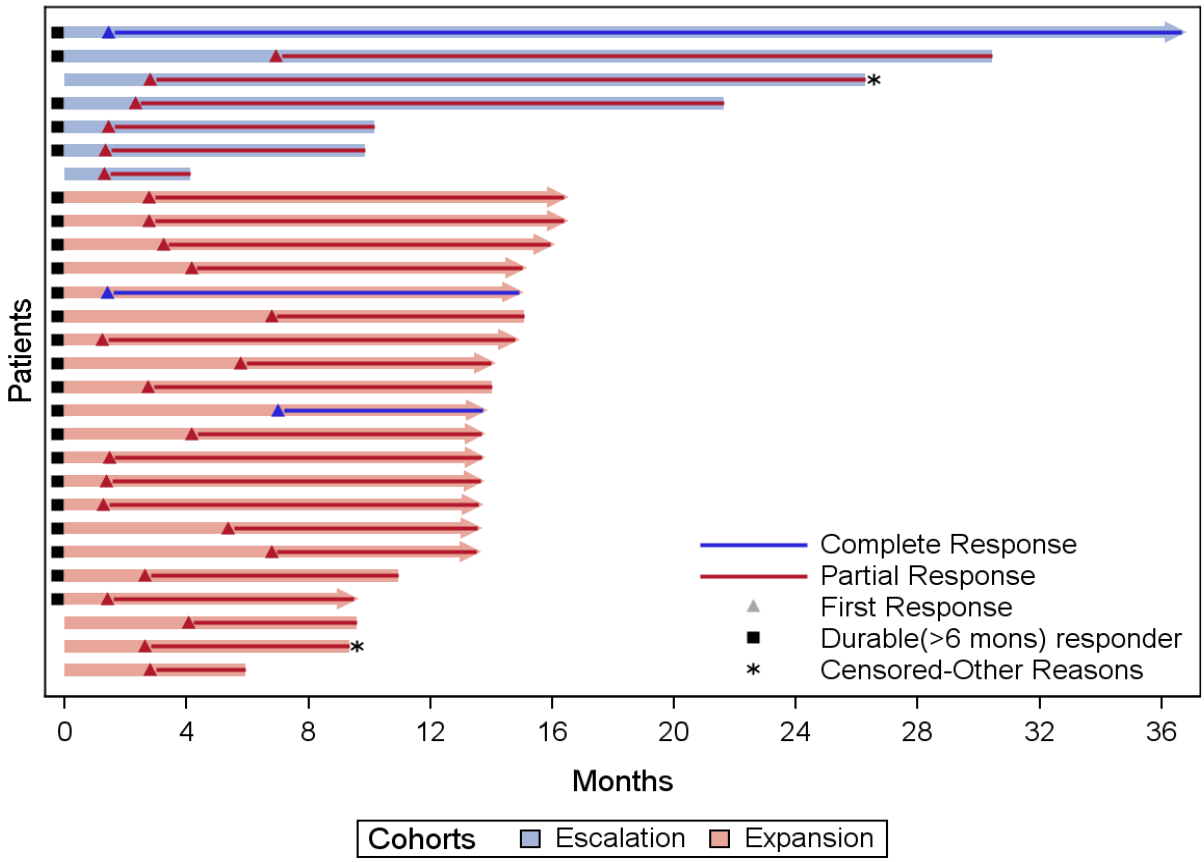
Table 7: Response Assessment per BICR

		Nivolumab (N=154)
Overall response rate	n (%) 95% CI	22 (14) (9.2, 20.8)
Complete response	n (%)	3 (1.9)
Partial response	n (%)	19 (12)
Stable disease	n (%)	65 (42)
Progressive disease	n (%)	59 (38)
Not evaluable	n (%)	4 (2.6)
Missing[a]	n (%)	4 (2.6)
Time to response (months)	Median Range	2.8 (1.2, 7)
Responders still on nivolumab	n (%)	17 (77)
Duration of response	Median Range	Not evaluable 3.2, 35.5+
Patients with duration of response of at least n (%)	≥3 months ≥6 months ≥9 months ≥12 months ≥18 months ≥24 months ≥30 months	22 (100) 20 (91) 12 (55) 9 (41) 1 (4.5) 1 (4.5) 1 (4.5)
Responders with ongoing response	On treatment In follow-up	14 (64) 2 (9.1)

Source: FDA analysis. [a] No follow-up radiological imaging available for assessment.

In addition to the responses in the efficacy population described in Table 7, an additional 6 patients treated in the dose escalation phase had a partial response; one patient treated with nivolumab 0.1 mg/kg, one patient treated with nivolumab 0.3 mg/kg and four patients treated with nivolumab 1 mg/kg. Figure 3 shows the duration of follow-up and duration of response for all responders on Study CA209040.

Figure 3: Duration of Follow-up and Duration of Response for Responders



Horizontal bar represents the sum of time to first response and the time to subsequent progression for each subject. Right arrow cap indicates continued response and * represents the patients who were censored for reasons other than ongoing response.

Source: FDA analysis of duration of response data based on the cutoff date of 29-Nov-2016.

Reviewer comment:

The response rate in patients with HCC who progressed on or were intolerant to sorafenib is 14%. 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, 20% in patients with urothelial carcinoma, and 13.3% in squamous cell carcinoma of the head and neck (source: nivolumab USPI). Although the response rate appears lower than the response rate for nivolumab in some indications, it is similar to the response rate in squamous cell carcinoma of the head and neck. In addition, the confidence intervals of the response rates for some indications overlap with those of HCC. Although the duration of response date are immature (with most patients censored at the time of data cutoff), there are durable responses. Furthermore, response rates in the range of 13-27% have correlated with an overall survival benefit for nivolumab in patients with lung cancer (squamous and non-squamous), renal cell

carcinoma and squamous cell carcinoma of the head and neck (the indication for urothelial carcinoma was under accelerated approval and does not have associated survival data). For comparison, treatment with regorafenib (which was recently approved by the FDA for second-line treatment of patients with HCC) resulted in a response rate of 6.6% and treatment with sorafenib (approved for first-line treatment of patients with HCC) resulted in a response rate of 2.1%.

6.6.1. Updated duration of response

The Applicant submitted an updated duration of response for *all* responders (including patients treated in the dose escalation phase with doses of nivolumab other than 3 mg/kg), as requested by FDA on 6 July 2017. The data cutoff for this update is 17 March 2017.

No additional responders were identified between the data cutoff of 29 November 2016 and the data cutoff of 17 March 2017. Table 8 summarizes duration of response for responders in the efficacy population and for all responders. Of the 22 original responders in the efficacy population, 12 patients (55%) had an ongoing response at the time of the data cutoff. Twenty patients (91%) had a duration of response of at least 6 months and 12 patients (55%) had a duration of response of at least 12 months.

Table 8: Updated Duration of Response

		Responders in efficacy population (N=22)	**All responders (N=28)**
Duration of response	Median	16.6	19.4
	Range	3.2, 38.2+	2.8, 38.2+
Patients with duration of response of at least n (%)	≥3 months	22 (100)	27 (96)
	≥6 months	20 (91)	25 (91)
	≥9 months	17 (77)	20 (71)
	≥12 months	12 (55)	15 (54)
	≥18 months	1 (4.5)	4 (14)
	≥24 months	1 (4.5)	1 (3.6)
	≥30 months	1 (4.5)	1 (3.6)
Responders with ongoing response	On treatment	10 (45)	10 (37)
	In follow-up	2 (9.1)	2 (7.1)

Source: FDA analysis.

Reviewer comment:

The updated duration of response data show that responses can be durable in patients with HCC who progressed on, or were intolerant to sorafenib.

6.7. Analysis of Secondary Endpoints

The secondary endpoints for the clinical and statistical review of this application are time to progression, progression free survival and overall survival.

Data for time to event endpoints not mature. The estimated median TTP per BICR using RECIST was 2.83 months (95% CI: 2.69, 4.11), the estimated median PFS per BICR using RECIST was 2.83 months (95% CI: 2.66, 4.04), and the estimated median OS was14.95 months (95% CI: 13.24, Not Reached).

Reviewer comment:

Because these data are from uncontrolled clinical trials and are not mature, the results for these time-to-event endpoints should be interpreted with caution.

6.8. Exploratory Endpoints

6.8.1. Response assessment by BICR using modified RECIST criteria for HCC

Response assessment using modified RECIST (mRECIST) criteria for HCC was an exploratory endpoint in Study CA209040. Although RECIST 1.1 criteria evaluate response using only tumor measurements, mRECIST takes viable vs. nonviable tissue (necrosis) into account by evaluating the uptake of contrast agent in the arterial phase of dynamic imaging studies[9] (refer to section 9.3 for a comparison of RECIST vs. mRECIST criteria).

Overall response rate by mRECIST was 18% compared to 14% using RECIST 1.1 (Table 9). There were more patients with a complete or partial response and fewer patients with stable disease when assessing response using mRECIST vs. RECIST 1.1. Disease control rate is similar between groups (56%).

Table 9: Response assessments by BICR using mRECIST

		RECIST (N=154)	mRECIST (N=154)
Overall response rate	n (%) 95% CI	22 (14) (9.2, 20.8)	28 (18) (12.4, 25.2)
Complete response	n (%)	3 (1.9)	5 (3.2)
Partial response	n (%)	19 (12)	23 (15)
Stable disease	n (%)	65 (42)	58 (38)
Progressive disease	n (%)	59 (38)	61 (40)
Not evaluable	n (%)	4 (2.6)	3 (1.9)
Missing[a]	n (%)	4 (2.6)	4 (2.6)
Patients with duration of response of at least n (%)	≥3 months ≥6 months ≥9 months ≥12 months ≥18 months ≥24 months ≥30 months	22 (100) 20 (91) 12 (55) 9 (41) 1 (4.5) 1 (4.5) 1 (4.5)	25 (89) 21 (75) 14 (50) 9 (32) 1 (3.6) 1 (3.6) 1 (3.6)
Responders with ongoing response		16 (73)	16 (57)

Source: FDA analysis. [a] No follow-up radiological imaging available for assessment.

Time to event data using mRECIST are not mature and therefore need to be interpreted with caution. The estimated median TTP per BICR using mRECIST was 2.83 (95% CI: 2.69, 4.11) and the estimated median PFS per BICR using mRECIST was 2.83 (95% CI: 2.63, 4.04).

Reviewer comment:

There was discordance between response assessments using RECIST 1.1 vs. mRECIST (i.e., the increase in partial and complete responses using mRECIST) is expected, as these patients would otherwise be evaluated as stable disease due to tumor necrosis. For comparison, treatment with regorafenib resulted in an ORR of 6.6% using RECIST 1.1 vs. 10.6% using mRECIST (source: regorafenib USPI). As the duration of response data are immature, any differences between duration of response should be interpreted with caution. The results for time-to-event endpoints were similar when using RECIST 1.1 vs. mRECIST. However, the results should be interpreted with caution, because these data are from uncontrolled clinical trials.

6.8.2. Response assessment by investigator

As shown in Table 10, the investigator-assessed ORR was 19% compared to 14% by BICR. Investigator-assessment resulted in more complete responses, more partial responses and more stable disease compared to the BICR-assessment.

Table 10: Response assessment per BICR vs. investigator

		BICR	Investigator
Overall response rate	n (%) 95% CI	22 (14) (9.2, 20.8)	29 (19) (13, 25.9)
Complete response	n (%)	3 (1.9)	4 (2.6)
Partial response	n (%)	19 (12)	25 (16)
Stable disease	n (%)	65 (42)	68 (44)
Progressive disease	n (%)	59 (38)	51 (33)
Not evaluable	n (%)	4 (2.6)	6 (3.9)
Missing	n (%)	4 (2.6)	0

Source: FDA analysis.

Reviewer comment:

There was discordance between investigator vs. BICR assessment. This discordance had an effect on ORR, as well as on disease control rate.

6.8.3. Association between biomarkers and efficacy

Table 11 summarizes response assessments by PD-L1 staining results. The ORR increased as PD-L1 staining increased: 13% for patients with <1% PD-L1 expression, 27% for patients with ≥1% PD-L1 expression and 44% for patients with ≥5% PD-L1 expression.

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

		PDL1<1% (N=109)[a]	PDL1 ≥ 1% (N=26)	PDL1≥5% (N=9)
Overall response rate	n (%)	14 (13)	7 (27)	4 (44)
Complete response	n (%)	3 (2.8)	0	0
Partial response	n (%)	11 (10)	7 (27)	4 (44)
Stable disease	n (%)	49 (45)	7 (27)	0
Progressive disease	n (%)	42 (39)	10 (38)	5 (56)
Not evaluable	n (%)	0	2 (7.7)	0
Missing	n (%)	4 (3.7)	0	0

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

Reviewer comment:

Treatment with nivolumab resulted in responses in patients with HCC regardless of PD-L1 staining results. However, it appears that the ORR increased with a higher percentage of cells staining for PD-L1. Due the small sample size, these results should be interpreted with caution.

6.8.4. Association between hepatitis status and efficacy

An exploratory analysis was done evaluating response rates by hepatitis status (Table 12). The ORR for patients without hepatitis was 13%. The ORR for patients with active hepatitis B was also 13%, whereas the ORR for patients with active hepatitis C was 19%. Disease control rate was higher in the patients without hepatitis (65%) compared to patients with either active hepatitis B (47%) or with active hepatitis C (50%).

Table 12: Response assessment by hepatitis status

		Uninfected N=75	Hepatitis B N=47	Hepatitis C N=32
Overall response rate	n (%)	10 (13)	6 (13)	6 (19)
Complete response	n (%)	1 (1.3)	1 (2.1)	1 (3.1)
Partial response	n (%)	9 (12)	5 (11)	5 (16)
Stable disease	n (%)	39 (52)	16 (34)	10 (31)
Progressive disease	n (%)	23 (31)	24 (51)	12 (38)
Not evaluable	n (%)	1 (1.3)	1 (2.1)	2 (6.3)
Missing [a]	n (%)	2 (2.7)	0	2(6.3)

Source: FDA analysis. [a] No follow-up radiological imaging available for assessment.

Reviewer comment:

Treatment with nivolumab resulted in responses in patients regardless of hepatitis status. As the number of patients is small and these subgroup analyses were not pre-specified, the results for this exploratory subgroup analysis should be interpreted with caution.

6.8.5. Quality of life

The Applicant collected quality of life data for patients enrolled in the expansion phase of Study CA209040 through the use of the EQ-5D-3L questionnaire. The EQ-5D-3L measures items described in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at baseline, Week-7, Week-13, Week-19 and Week-25. Each dimension is evaluated using the following levels: no problems, some problems or severe problems. The questionnaire includes a visual analogue scale (VAS), allowing the patient to rate his/her health on a scale from 0-100 (worst-best).

The Applicant submitted a summary of the EQ-5D-3L findings, but did not calculate the completion rate. The majority of patients had no problems with mobility, self-care, usual activities or anxiety/depression. However, patients in the uninfected sorafenib naïve/intolerant cohort and in the uninfected sorafenib progressor cohort reported some problems with pain/discomfort on treatment (source: interim clinical study report, section 11.1 and table s.10.4 and s 10.5).

The on-treatment VAS score increased from week 7 to week 25 from 74.2 to 75 for patients in the 2L EXP cohort. However, when evaluating the VAS scores by cohort, the improvement in VAS score was only present in patients with hepatitis B, hepatitis C or who progressed on sorafenib; The VAS score decreased to 62 by week 19 for the uninfected sorafenib naïve/intolerant cohort (source: interim clinical study report, section 11.1 and table s.10.1.4).

An independent exploratory analysis of the EQ-5D-3L and VAS assessments was performed by FDA (refer to section 9.4).

Reviewer comment:

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

6.9. Subpopulations

6.9.1. Response assessments by demographic and baseline disease characteristics

A sensitivity analysis was performed to identify the influence of demographics, baseline disease characteristics and nivolumab dose on ORR and DOR (Table 13). ORR was similar for sex and ECOG performance status. However, ORR was lower (12%) for patients treated in Europe compared to Asia and US/Canada (16% and 17% resp.). The ORR was 67% in patients treated with nivolumab 1 mg/kg, which is higher than the ORR for patients treated with either lower or higher doses of nivolumab. However, the number of patients in this group was small (n=6). Similarly, ORR was higher in patients with BCLC stage A compared to patients with BCLC stage B or C, but the number of patients was small (n=2). There were small differences in ORR (with overlapping confidence intervals) when comparing alpha-fetoprotein (AFP) at baseline and presence or absence of extrahepatic disease or microvascular invasion.

Table 13: Response assessments for subpopulations

		N	ORR	95% CI of ORR	DOR range
Sex	M	118	17 (14.41%)	(8.62, 22.06)	(3.15 ,13.83+)
	F	36	5 (13.89%)	(4.67, 29.5)	(6.7+ ,35.45+)
ECOG	0	100	15 (15%)	(8.65, 23.53)	(3.15 ,35.45+)
	1	54	7 (12.96%)	(5.37, 24.9)	(5.55 ,13.83+)
Geographical region	Asia	75	12 (16%)	(8.55, 26.28)	(3.15 ,13.73+)
	Europe	60	7 (11.67%)	(4.82, 22.57)	(8.31+ ,35.45+)
	US/Canada	18	3 (16.67%)	(3.58, 41.42)	(11.07+ ,13.83+)
Cohort	ESC	9	1 (11.11%)	(0.28, 48.25)	(11.07+ ,13.83+)
	EXP	145	21 (14.48%)	(9.19, 21.28)	(3.15 ,13.83+)
Nivolumab dose[a]	0.1 mg/kg	5	1 (20%)	(0.51, 71.64)	(8.54 ,8.54)
	0.3 mg/kg	7	1 (14.29%)	(0.36, 57.87)	(23.52 ,23.52)
	1 mg/kg	6	4 (66.67%)	(22.28, 95.67)	(2.83 ,23.49+)
	3 mg/kg	154	22 (14.29%)	(9.17, 20.83)	(3.15 ,35.45+)
	10 mg/kg	10	0	-	-
BCLC stage	A	2	1 (50%)	(1.26, 98.74)	(8.31+ ,8.31+)
	B	14	0	(76.84, 100)	(8.31+ ,8.31+)
	C	138	21 (15.22%)	(9.67, 22.32)	(3.15 ,35.45+)
AFP	≥400 ng/ml	57	10 (17.54%)	(8.75, 29.91)	(3.15 ,13.83+)
	<400 ng/ml	92	11 (11.96%)	(6.12, 20.39)	(6.7+ ,35.45+)
Extrahepatic disease	Yes	110	17 (15.45%)	(9.27, 23.59)	(3.15 ,35.45+)
	No	44	5 (11.36%)	(3.79, 24.56)	(6.93+ ,13.83+)
Macrovascular invasion	Yes	44	7 (15.91%)	(6.64, 30.07)	(6.93+ ,13.73+)
	No	110	15 (13.64%)	(7.84, 21.49)	(3.15 ,35.45+)

Source: FDA analysis. [a] Analysis of response by nivolumab dose was conducted on all patients who progressed on, or were intolerant to sorafenib and who were treated in the dose escalation and dose expansion phase of Study CA209040 (N=182).

Reviewer comment:

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.

6.9.2. Response assessments for patients who were intolerant to sorafenib

Sorafenib intolerance was defined as:

- ≥CTCAE Grade 2 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards AND 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily)
- ≥CTCAE Grade 3 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards OR 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily).

In the efficacy population, there were eleven patients (7.1%) who were sorafenib intolerant. The median duration of sorafenib treatment for these patients was 2.4 months (range 0.8, 7.5). None of the patients had a response to sorafenib treatment. Reasons for discontinuation of sorafenib were: diarrhea (n=6), hand foot skin reaction / palmar plantar erythema syndrome (n=5), weight loss (n=3), acute pancreatitis (n=1), dermatologic adverse event (n=1), hepatotoxicity (n=1), chest pain (n=1), and decreased platelet count (n=1). Treatment with nivolumab resulted in an ORR of 25% (95% CI: 5.5, 27.2) in sorafenib intolerant patients. Median duration of response has not been reached (source: response to FDA information request dated 6 July 2017).

Reviewer comment:

As the number of patients is small and the subgroup analysis was not pre-specified, the results should be interpreted with caution. However, these results do indicate that responses can be achieved in patients with advanced HCC, independent of whether or not patients tolerated sorafenib treatment prior to receiving nivolumab.

6.10. Analysis of Clinical Information Relevant to Dosing Recommendations

All patients in the efficacy population received the 3 mg/kg approved dose of nivolumab. Responses were also seen when patients were treated with lower doses of nivolumab in Study CA209040 (refer to section 6.6). See clinical pharmacology review for dosing considerations.

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

As discussed in section 6.6.1, the treatment effect in responding patients can be durable. 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.

6.12. Additional Efficacy Issues/Analyses

6.12.1. Treatment beyond progression

Out of all patients treated in the dose escalation or dose expansion phase (n=182), 96 patients (53%) were treated with nivolumab beyond radiographic progression per investigator assessment. The median number of doses received beyond initial radiographic progression was 3 (range 1, 42+) and median duration of treatment beyond initial radiographic progression was 1.35 months for patients treated in the dose escalation phase and 1.61 months for patients treated in the dose expansion phase (Table 14).

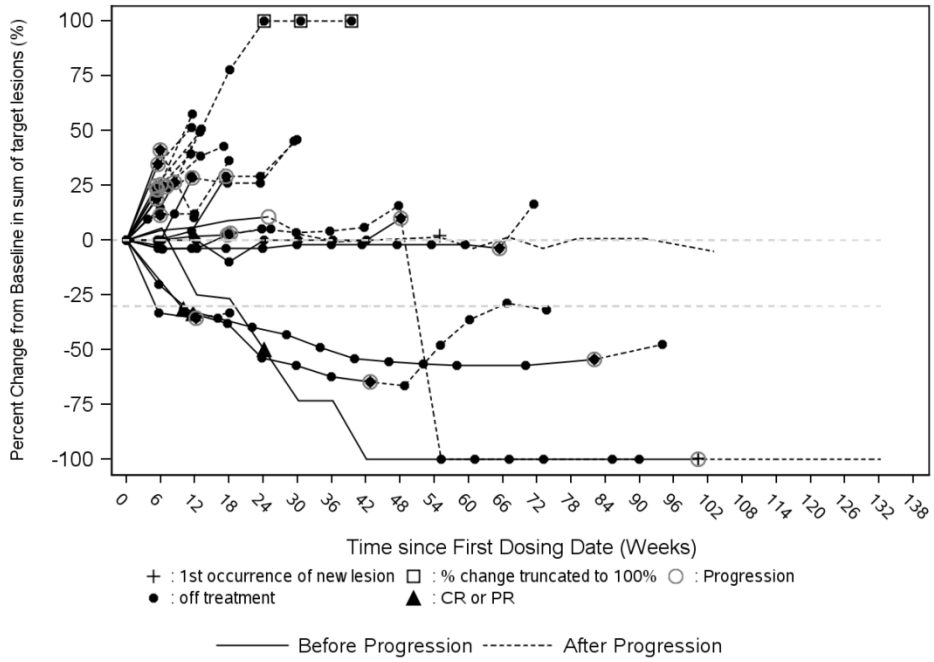
Table 14: Treatment beyond radiographic progression

		Escalation Phase (N=37)	Expansion Phase (N=145)
Treated beyond progression	n (%)	21 (57)	75 (52)
Number of doses received	Median	3	3
	Min, max	1, 42+	1+, 35
Duration of treatment (months)	Median	1.35	1.61
	Min, max	0.5, 18.9+	0, 17.1

Source: Response to FDA information request dated 6 July 2017.

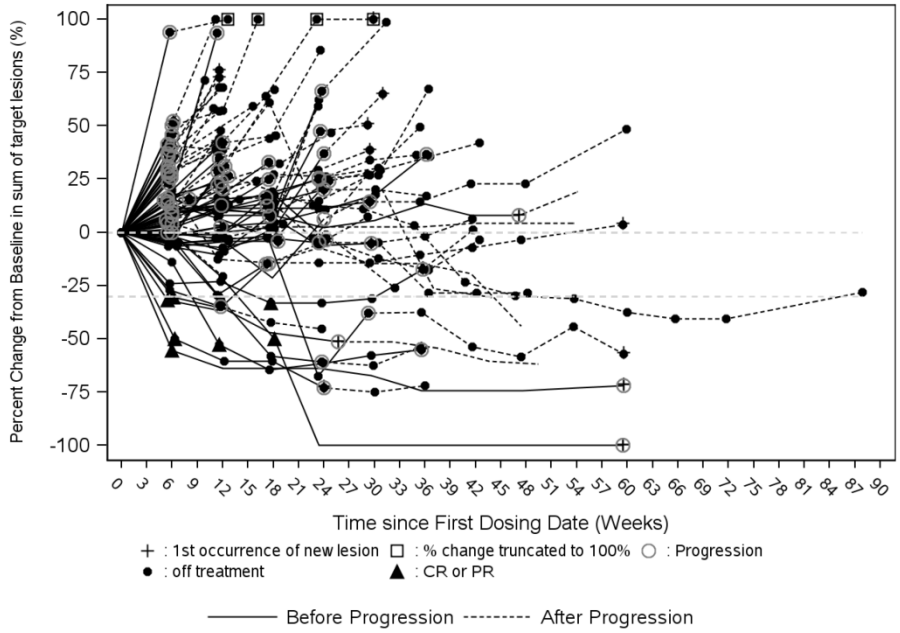
Twenty-eight patients (29%) had a reduction in size of their target lesion of ≥0% and 7 patients (7.3%) had a reduction of ≥30% after progression. Figure 4 and Figure 5 show the tumor burden change over time for both cohorts. Figure 6 and Figure 7 show the best reduction in target lesion for both cohorts.

Figure 4: Tumor burden change over time for patients treated beyond progression in the dose escalation cohort



Assessments are per Investigator using RECIST 1.1 criteria, confirmation of response required.
Source: Response to FDA information request dated 6 July 2017.

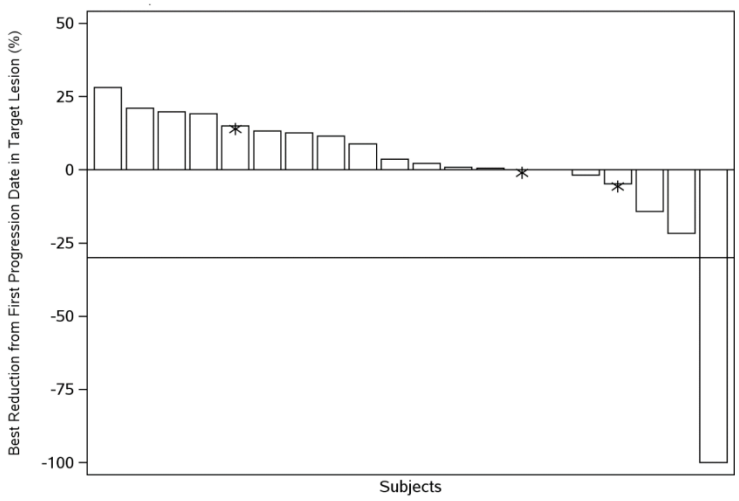
Figure 5: Tumor burden change over time for patients treated beyond progression in the dose expansion cohort



Assessments are per Investigator using RECIST 1.1 criteria, confirmation of response required.

Source: Response to FDA information request dated 6 July 2017.

Figure 6: Best reduction in the sum of diameters of the target lesion (dose escalation cohort)

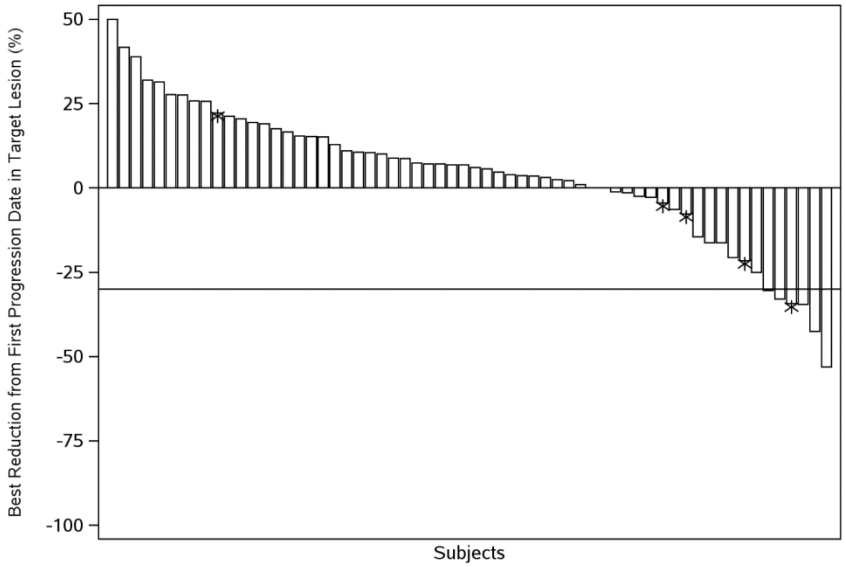


1 subject did not have tumor assessment after progression.

Negative/positive value means maximum tumor reduction /minimum tumor increase.
Best reduction is based on evaluable target lesion measurements up to start of subsequent therapy.
Horizontal reference line indicates the 30% reduction consistent with a response per RECIST 1.1 criteria.
Asterisk symbol represents responders; Square symbol represents % change truncated to 100%.

Source: Response to FDA information request dated 6 July 2017.

Figure 7: Best reduction in the sum of diameters of the target lesion (dose expansion cohort)



13 subjects did not have tumor assessment after progression

Negative/positive value means maximum tumor reduction /minimum tumor increase.
Best reduction is based on evaluable target lesion measurements up to start of subsequent therapy.
Horizontal reference line indicates the 30% reduction consistent with a response per RECIST 1.1 criteria.
Asterisk symbol represents responders; Square symbol represents % change truncated to 100%.

Source: Response to FDA information request dated 6 July 2017.

Reviewer comment:

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

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 safety data in this efficacy supplement came from the 182-patient safety database consisting of adult patients with advanced HCC who were intolerant to, or who progressed on sorafenib and who were treated in the dose escalation and dose expansion phase of Study CA209040.

Definition of safety population

The Applicant pre-specified the safety population in the protocol as those patients who had progressed or were intolerant to sorafenib and who were treated with nivolumab 3 mg/kg IV every 2 weeks in the expansion phase (n=145). However, an additional nine patients were treated with nivolumab 3 mg/kg in the dose escalation phase. Because these patients are similar to the patients enrolled in the dose expansion phase, these patients were included in the safety population.

- Safety population: 154 patients treated with nivolumab 3 mg/kg every 2 weeks.
- Clinical data cutoff: 29 November 2016.

Reviewer comment:

Patients with HCC often have an underlying risk factor that is associated with at least some degree of liver dysfunction. Although only patients with a Child-Pugh score of A or B7 were treated on Study CA209040, the Child-Pugh score (and other staging methods) do not fully describe the degree of patient liver dysfunction, whether or not the liver dysfunction affects how drugs are metabolized, and whether or not the liver dysfunction is primarily driven by the cancer or the underlying risk factor (e.g., hepatitis, alcoholic liver disease, non-alcoholic fatty liver,

etc.). Therefore, patients with HCC are potentially at risk for increased hepatotoxicity compared to patients with other cancers. In addition, patients with active hepatitis who are treated with a checkpoint inhibitor are potentially at risk for hepatotoxicity through induction of a viral-specific immune response.

This review takes these risks into consideration. However, results of safety analyses should be interpreted with caution, because these data are from an uncontrolled clinical trial. In addition, the number of patients treated with active hepatitis B and C is small (47 and 32 respectively).

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 19.1 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.

Events with dictionary-derived terms of malignant neoplasm progression or metastases to spine or central nervous system were 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

As the efficacy and safety population are the same, refer to section 6.3 for exposure and demographics information.

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 during the study: CBC with differential, Complete Metabolic Panel (Na, K, Cl, HCO3, BUN, Cr, eGFR, AST, ALT, alkaline phosphatase, albumin, total bilirubin, total protein, calcium, glucose), direct bilirubin, amylase, lipase, LDH, magnesium, phosphorus, TSH, Free T4, Free T3, PT/INR, aPTT, fibrinogen, pregnancy test, HBV testing for HBV infected patients (HBV DNA, quantitative HBsAg, quantitative HBeAg, HBsAb, HBeAb), and HCV testing for HCV infected patients (HCV RNA).

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 (AEOSI), which included immune-mediated AEs (irAEs) and infusion reactions. These are discussed in Section 7.3.4.

7.3. Major Safety Results

The safety analyses were performed for all patients enrolled in the dose escalation and dose expansion phases in Study CA209040 who received at least one dose of 3 mg/kg nivolumab (n=154; Table 15).

Table 15: Summary of Major Safety Results

	n (%)
Patients who experienced an AE	152 (99)
Patients who experienced a Grade 1-2 AE	151 (98)
Patients who experienced a Grade 3-4 AE	78 (51)
Patients who experienced a nonfatal SAE	60 (39)
Deaths reported as an AE	1[a] (0.6)

Source: FDA analysis. [a] One death was reported as an AE >100 days after discontinuation of nivolumab (refer to section 7.3.1).

7.3.1. Deaths

A total of 42 patients (27%) in the safety population died. Eight patients died within 30 days of receiving the last dose of nivolumab and 24 patients died between 31 and 100 days of receiving the last dose of nivolumab (Table 16).

Table 16: Deaths

	Nivolumab (N=154) n (%)
Total deaths	42 (27)
Deaths within 30 days of last nivolumab dose	8 (5.2)
Disease progression	6 (3.9)
Other [a]	2 (1.3)
Deaths between 31-100 days of last nivolumab dose	24 (16)
Disease progression	24 (16)
Deaths more than 100 days of last nivolumab dose	10 (6.5)
Disease progression	6 (3.9)
Study drug toxicity [b]	1 (0.6)
Other [c]	3 (1.9)

Source: FDA analysis. [a] Suicide and intracranial hemorrhage (patient narrative summarized below); [b] Pneumonitis (patient narrative summarized below); [c] Gastrointestinal bleeding (n=1) and intracranial hemorrhage (n=2).

To following patients died of reasons other than disease progression within 30 days of the last nivolumab dose or due to study drug toxicity (source: interim clinical study report addendum, table s.6):

- Patient (b) (6) died of suicide within 30 days of the last dose of nivolumab. This patient was hospitalized on Day 9 for Grade 3 pneumonitis (attributed as related to nivolumab). The patient was subsequently treated with albuterol/ipratropium, albuterol, sodium, levofloxacin and corticosteroids (80 mg methylprednisolone IV, followed by 24 mg oral

dexamethasone). The patient was discharged from the hospital on Day 12 and subsequently committed suicide on Day 13 (attributed as not related to nivolumab).

- Patient (b) (6) died of non-traumatic intracranial hemorrhage within 30 days of the last dose of nivolumab. This patient discontinued nivolumab on Day 252 due to disease progression. On Day 266 (28 days after the last dose of nivolumab), the patient was hospitalized for Grade 4 intracranial hemorrhage (attributed as not related to nivolumab). On Day 268, the patient died.
- Patient (b) (6) died of pneumonitis (attributed to nivolumab) more than 100 days after the last nivolumab dose. On Day 281 (35 days after discontinuing nivolumab), the patient was hospitalized with Grade 3 pneumonitis. Infectious workup was negative and the patient was treated with high-dose corticosteroids and antibiotics. The patient's pneumonitis worsened 155 days after discontinuing nivolumab. The patient was treated with high-dose corticosteroids, but did not respond to treatment. The patient died on Day 405 (159 days after the last dose of nivolumab).

Reviewer comment:

The incidence of death due to AEs not attributed to disease progression within 30 days or due to study drug toxicity was low (1.9%). Immune-mediated pneumonitis is a suspected adverse event and described in the USPI. Review of the details of the deaths does not raise any new safety concerns.

7.3.2. Nonfatal Serious Adverse Events

In Study CA209040, there were a total of 97 nonfatal SAEs in 60 patients (39%) and 58 nonfatal Grade 3-4 SAEs in 41 patients (27%). The most common (>2% of patients) SAEs were: pyrexia, abdominal pain, ascites and musculoskeletal pain (Table 17).

Table 17: Most common (>2%) nonfatal SAEs

	All grade n (%)	Grade 3-4 n (%)
Pyrexia	5 (3.2)	1 (0.6)
Abdominal pain[a]	4 (2.6)	2 (1.3)
Ascites	4 (2.6)	3 (1.9)
Musculoskeletal pain[b]	4 (2.6)	3 (1.9)

Source: FDA analysis. [a] Includes abdominal discomfort, abdominal tenderness, lower abdominal, and upper abdominal pain; [b] Includes back pain, pain in extremity, myalgia, neck pain and bone pain.

The most common (>1% of patients) Grade 3-4 SAEs were: ascites (1.9%), musculoskeletal pain (1.9%), general physical health deterioration (1.9%), abdominal pain (1.3%), anemia (1.3%), diarrhea (1.3%), gastrointestinal hemorrhage (1.3%), hyperglycemia (1.3%), hypoglycemia (1.3%), hyponatremia (1.3%), and esophageal varices hemorrhage (1.3%).

Reviewer comment:

The incidence of SAE's in this sBLA is similar to those described for nivolumab in other indications or expected in a patient population with HCC (e.g., abdominal pain and ascites).

7.3.3. Dropouts and/or Discontinuations

Adverse events leading to discontinuation of study treatment were reported in 8 patients (5.2%). Five (3.2%) of these adverse events were attributed to nivolumab: Grade 3 pneumonitis, Grade 3 hepatitis, Grade 3 polyarthritis, Grade 2 oral mucositis and type 1 diabetes mellitus. The three adverse events that were attributed as unrelated to nivolumab were: biliary duct obstruction with worsening abdominal pain, biliary sepsis, and brain hemorrhage.

For one patient, reason for discontinuation was "other" (Patient (b) (6)). Upon review of the patient narrative, this patient had a course complicated by hepatitis (attributed to nivolumab) requiring systemic corticosteroids, as well as cytomegalovirus infection (attributed as unrelated to nivolumab). The patient's last (4th) dose of nivolumab was on Day 71 and nivolumab was subsequently held due to continued ALT increase. Nivolumab was eventually discontinued on day 286. Although the increase in ALT may have been due to the underlying HCC or to the cytomegalovirus or concomitant medication, it may also have been due to nivolumab associated hepatotoxicity (immune-related or not).

To determine whether any patients requested to discontinue nivolumab or withdrew their consent due to an adverse event, narratives were reviewed (if available) for those patients (n=5). One patient (patient (b) (6)) withdrew consent due to an oculomotor nerve paralysis. Although this event was originally attributed to nivolumab, the patient was found to have a

small tumor compressing the oculomotor nerve, concerning for metastasis. For the remaining four patients, narratives were not available or uninformative.

Reviewer comment:

The percentage of patients discontinuing nivolumab due to nivolumab-related 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 18 describes immune-mediated adverse events occurring within 100 days of the last dose of nivolumab in Study CA209040. This 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 18: Immune-Mediated Adverse Events requiring systemic corticosteroids

		Systemic steroids n (%)	High-dose systemic steroids n (%)	Expected incidence (USPI) %
Non-endocrine events	Hepatitis	8 (5.2)	6 (3.9)	1.8
	Colitis[a]	7 (4.5)	3 (1.9)	2.9
	Rash	1 (0.6)	1 (0.6)	9.0
	Hypersensitivity / infusion reactions	2 (1.3)	1 (0.6)	6.4
	Pneumonitis	3 (1.9)	2 (1.3)	3.1
	Nephritis / renal dysfunction	0	0	1.2
Endocrine events	Hypothyroidism/ thyroiditis	7 (4.5)	0	9.0
	Hyperthyroidism	2 (1.3)	0	2.7
	Diabetes Mellitus	2 (1.3)	0	0.9
	Adrenal insufficiency	1 (0.6)	0	1
	Hypophysitis	0	0	0.6

Source: FDA analysis. [a] For one patient, the route, dose and name of the steroid is unknown. As colitis is generally treated with systemic steroids, this patient is included in the table. However, it is unknown if the patient received low- or high-dose steroids.

A total of 21 patients (14%) had at least one non-endocrine IMAE requiring systemic corticosteroids. Twenty patients had one non-endocrine IMAE and one patient had two non-endocrine IMAEs (diarrhea/colitis and hepatitis). Of the 22 non-endocrine IMAEs, there were 10 Grade 3 events and 1 Grade 4 event. Thirteen events required high-dose corticosteroids. Nine events had completely resolved (i.e., resolution of the event with completion of immune-modulating or select concomitant medications) at the time of data cutoff (source: interim CSR addendum appendix 6.202).

In addition to the patients with a rash requiring systemic steroids, another 16 patients (1 with Grade 3 event) required either topical or transdermal corticosteroids.

Eleven patients (7.1%) had at least one endocrine IMAE. Ten patients had one endocrine IMAE and one patient had 2 IMAEs (hyperthyroidism and hypothyroidism/thyroiditis). Of the 12 endocrine events, there was 1 Grade 4 event (diabetes mellitus). None of the events had completely resolved (i.e., resolution of the event with completion of immune-modulating or select concomitant medications) at the time of data cutoff (source: interim CSR addendum appendix 6.202).

The events described in Table 18 include IMAEs up to 100 days after the last dose of nivolumab. Three patients had an IMAE more than 100 days after the last dose of nivolumab; one patient

had a rash requiring oral steroids (low-dose), one patient had hypothyroidism and one patient had diabetes mellitus.

The events described in Table 18 only include events that occurred in patients treated with nivolumab 3 mg/kg (safety population). An additional 4 non-endocrine IMAEs and 3 endocrine IMAEs occurred in the 28 patients who were treated with other doses of nivolumab (0.1-10 mg/kg) in the dose escalation phase. The non-endocrine IMAEs were: hypersensitivity (n=1; high-dose corticosteroids), hepatitis (n=1; high-dose corticosteroids), and rash (n=2; low-dose corticosteroids). The endocrine IMAEs were: hypothyroidism/thyroiditis (n=1), diabetes mellitus (n=1), and adrenal insufficiency (n=1; high-dose corticosteroids).

The number of patients with non-endocrine IMAEs is likely higher than shown in Table 18 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 adverse events were reported in 43 patients (28%).
- Hepatic adverse events were reported in 35 patients (23%).
- Renal adverse events were reported in 5 patients (3.2%).
- Pulmonary adverse events were reported in 3 patients (1.9%).
- Hypersensitivity/infusion reactions were reported in 6 patients (3.9%).
- Skin adverse events were reported in 66 patients (43%).
- Endocrine adverse events were reported in 18 patients (12%).

Other events that were potentially immune-mediated, but did not fulfill all criteria for IMAEs, were 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.

In addition to IMAEs, there were adverse events that were not designated as immune-related, but that required systemic steroids. The following events (13 events in 10 patients) were considered drug-related by the investigator: pruritus (n=2), decreased appetite (n=2), lower abdominal pain (n=2), type IV hypersensitivity reaction, skin disorder, polyarthritis, pneumonia, fatigue and dyspnea (each n=1). Two of these events were Grade 3. The remaining events were Grade 1 or 2.

Reviewer comment:

As 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., hepatitis) and without biopsy data on each immune-related adverse event, exact determination of the cause is not possible.

7.3.5. 120-day safety update

The applicant provided a 120-day safety update for hepatic events at the request of FDA. This update included any new cases of, or updated information on previously submitted cases of, viral hepatitis infection or reactivation; auto-immune hepatitis; hepatic decompensation; and sequelae of cirrhosis (e.g., ascites or encephalopathy). The data cutoff for the 120-day safety update was 17 March 2017. Although the Applicant submitted new safety information for all patients treated on Study CA209040, only information regarding the safety population is included here.

- There were no patients with chronic HBV or HCV infection who had significant increases in HBV DNA (>1000 IU/mL) or HCV RNA (>1 $\log_{10}$). No patients had acute viral hepatitis or viral reactivation.
- There were no new cases of immune-mediate hepatitis and no new drug-related hepatotoxicity events. In addition, there were no new hepatotoxicity events meeting DILI criteria.
- There were no patients who developed hepatic failure or encephalopathy. One patient developed ascites (not attributed to nivolumab).
- There were no new deaths attributed to nivolumab.

7.3.6. Submission Specific Primary Safety Concerns

For immune-related adverse events, refer to section 7.3.4. For liver-dysfunction related analyses, refer to sections 7.4.1, 7.4.2, and 7.5.4.

7.4. Supportive Safety Results

7.4.1. Common Adverse Events

Table 19 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, musculoskeletal pain, abdominal pain, diarrhea, pruritus, rash, decreased appetite and cough.

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Table 19: Most common (≥10%) Treatment-Emergent Adverse Events

	All grades n %	Grades 3-4 n %
General Disorders and Administration Site Conditions		
Fatigue[a]	57 (37)	5 (3.2)
Pyrexia	26 (17)	1 (0.6)
Edema[b]	19 (12)	0
Gastrointestinal Disorders		
Abdominal pain[c]	51 (33)	6 (3.9)
Diarrhea[d]	42 (27)	2 (1.3)
Nausea	25 (16)	0
Constipation	24 (16)	0
Vomiting	22 (14)	0
Abdominal distension	17 (11)	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[e]	52 (34)	3 (1.9)
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	33 (21)	0
Dyspnea	16 (10)	2 (1.3)
Skin and Subcutaneous Tissue Disorders		
Rash[f]	42 (27)	1 (0.6)
Pruritus	42 (27)	1 (0.6)
Infections and Infestations		
Upper respiratory tract infection[g]	16 (10)	0
Nervous System Disorders		
Headache	17 (11)	1 (0.6)
Metabolism and Nutrition Disorders		
Decreased appetite	34 (22)	2 (1.3)
Psychiatric disorders		
Insomnia	16 (10)	0

Source: FDA analysis. [a] Includes asthenia; [b] Includes peripheral edema, peripheral swelling, scrotal edema, and testicular edema; [c] Includes upper abdominal pain, lower abdominal pain, abdominal tenderness and abdominal discomfort; [d] Includes colitis, enteritis and gastroenteritis; [e] Includes back pain, pain in extremity, myalgia, neck pain, bone pain, musculoskeletal chest pain and musculoskeletal discomfort; [f] Includes dermatitis, dermatitis acneiform, allergic dermatitis, contact dermatitis, psoriasiform *dermatitis and rash described as maculo-papular, papular, pruritis, pustular, exfoliative, erythematous, and generalized; [g] Includes nasopharyngitis, rhinitis, pharyngitis and sinusitis.*

A total of 18 patients (12%) had adverse events reported that may be sequelae of liver disease (including ascites, gastrointestinal hemorrhage, esophageal varices (with or without hemorrhage) and encephalopathy.

Reviewer comment:

As these data are from an uncontrolled clinical trial, the results of this analysis should be interpreted with caution. 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 abdominal distension may also be related to the underlying HCC and/ or underlying liver dysfunction.

7.4.2. Laboratory Findings

Table 20 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, and electrolyte abnormalities. For TSH abnormalities, Refer to section 7.3.4.

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Table 20: Treatment-Emergent Laboratory Findings in ≥10% of patients

	All grades n (%)	Grades 3-4 n (%)
Hematology		
Anemia	72 (48)	7 (4.6)
Lymphopenia	87 (58)	22 (15)
Leukopenia	40 (26)	5 (3.3)
Neutropenia	29 (19)	2 (1.3)
Thrombocytopenia	53 (35)	11 (7.3)
Chemistry (liver function)		
Increased AST	89 (59)	27 (18)
Increased ALT	73 (48)	16 (11)
Increased alkaline phosphatase	65 (43)	9 (5.9)
Increased bilirubin	56 (37)	11 (7.2)
Increased lipase	55 (37)	20 (13)
Increased amylase	43 (31)	8 (5.7)
Chemistry (other)		
Hyponatremia	61 (40)	16 (11)
Hypocalcemia	41 (27)	0
Hyperkalemia	30 (20)	4 (2.6)
Increased creatinine	26 (17)	2 (1.3)
Hypomagnesemia	20 (13)	0
Hypokalemia	18 (12)	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 140-152).

Table 21 summarizes the incidence of select hepatic-function associated laboratory findings compared to the nivolumab USPI. The incidence of these events is increased compared to the incidence described in other indications in the nivolumab USPI.

Table 21: Select Treatment-Emergent Laboratory Findings Compared to Nivolumab USPI

	All grades CA209040 (%)	All grades USPI (%)	Grades 3-4 CA209040 (%)	Grades 3-4 USPI (%)
Thrombocytopenia	35	<15	7.3	<10
Increased AST	59	24-33	18	<3.6
Increased ALT	48	16-32	11	<3.2
Increased alkaline phosphatase	43	21-37	5.9	<5.5
Increased bilirubin	37	<14	7.2	<10

Source: FDA analysis and nivolumab USPI (drugs@FDA). Represents maximum grade post-baseline, occurring during or within 30 days of the last dose of nivolumab, if new or worsening from baseline.

In addition to the laboratory abnormalities described in Table 21, 24 patients (16%) had concurrent ALT or AST elevation >3 x ULN with total bilirubin >2 x ULN within 30 days of the last dose of nivolumab. Narratives for these patients were reviewed. For the majority of patients (n=17), the timing of these laboratory abnormalities coincides with disease progression. Five patients were treated with systemic corticosteroids for suspected IMAEs of hepatitis. One patient had a course complicated by Grade 3 biliary dilatation, Grade 3 ascites and Grade 3 biliary sepsis and had these laboratory abnormalities on several days throughout study therapy. For one patient, timing of meeting these laboratory abnormalities coincided with an admission for abdominal distension and coffee ground vomiting, which is likely due to underlying HCC/liver dysfunction.

Reviewer comment:

The majority of treatment-emergent laboratory events were consistent with the known adverse event profile of nivolumab. Several laboratory events appeared to have a higher incidence than expected (e.g. liver function associated laboratory events and thrombocytopenia). However, these events may be related to (progression of) the underlying cancer and/or to underlying liver disease (e.g., cirrhosis). As these data are from an uncontrolled clinical trial, the results of this analysis should be interpreted with caution.

7.4.3. Vital Signs

Vital signs were not reviewed. Changes in vital signs due to the administration of nivolumab were considered in the assessment of infusion reactions during the clinical trial.

7.4.4. Electrocardiograms (ECGs)

A QT substudy was conducted and was reviewed as part of the original nivolumab BLA submission. Nivolumab at doses 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 38 out of 146 patients (26%) who had baseline and post-baseline ADA measurements. One patient had neutralizing ADA and two patients had persistently positive ADAs. One patient with ADA had a hypersensitivity reaction requiring corticosteroids (source: FDA analysis).

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 safety.

7.5. Other Safety Explorations

7.5.1. Dose Dependency for Adverse Events

All patients in the safety population analyzed were given the same nivolumab dosage regimen (3 mg/kg IV every 2 weeks). Another 28 patients received different doses of nivolumab (0.1 mg/kg- 10mg/kg). However, the small sample size does not permit adequate analyses of dose dependency for adverse events.

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

Exploratory analyses were done to evaluate safety in patients without hepatitis vs. patients with hepatitis B and patients with hepatitis C. Table 22 summarizes major safety results for these subgroups and compares them to the overall safety population. The incidence of grade 3-4 adverse events was higher in the hepatitis C cohort compared to patients without hepatitis (45%) or patients with hepatitis B (49%). The incidence of grade 1-2 events and the incidence of nonfatal SAEs was similar between all groups.

Table 22: Select safety results by hepatitis status

	All patients N=154 n (%)	Uninfected N=75 n (%)	Hepatitis B N= 47 n (%)	Hepatitis C N= 32 n (%)
Patients who experienced an AE	152 (99)	74 (99)	46 (98)	32 (100)
Patients who experienced a Grade 1-2 AE	151 (98)	73 (97)	46 (98)	32 (100)
Patients who experienced a Grade 3-4 AE	78 (51)	34 (45)	23 (49)	21 (66)
Patients who experienced a nonfatal SAE	60 (39)	31 (41)	16 (34)	13 (41)

Source: FDA analysis.

To further explore toxicity in these subgroups, Table 23 summarizes select common TEAEs by hepatitis status. There are small differences in adverse events between the cohorts. Patients with either hepatitis B or C had a higher incidence of abdominal pain and a lower incidence of fatigue compared to patients without hepatitis. Patients with hepatitis B had a higher incidence of musculoskeletal pain compared to patients with hepatitis C and patients without hepatitis.

Table 23: Select Treatment-Emergent Adverse Events (Grade 1-4) by hepatitis status

	All patients N=154 n (%)	Uninfected N=75 n (%)	Hepatitis B N= 47 n (%)	Hepatitis C N= 32 n (%)
Fatigue[a]	57 (37)	34 (45)	12 (26)	11 (34)
Musculoskeletal pain[b]	52 (34)	22 (29)	21 (45)	9 (28)
Abdominal pain[c]	51 (33)	17 (23)	20 (43)	14 (44)
Diarrhea[d]	42 (27)	19 (25)	13 (28)	10 (31)
Decreased appetite	34 (22)	17 (23)	12 (26)	5 (16)
Nausea	25 (16)	13 (17)	5 (11)	7 (22)
Constipation	24 (16)	11 (15)	8 (17)	5 (16)
Vomiting	22 (14)	10 (13)	6 (13)	6 (19)
Abdominal distention	17 (11)	7 (9.3)	6 (13)	4 (13)
Ascites	13 (8.4)	8 (9.3)	4 (8.5)	2 (6.3)

Source: FDA analysis. [a] Includes asthenia; [b] Includes back pain, pain in extremity, myalgia, neck pain, bone pain, musculoskeletal chest pain and musculoskeletal discomfort; [c] Includes upper abdominal pain, lower abdominal pain, abdominal tenderness and abdominal discomfort; [d] Includes colitis, enteritis and gastroenteritis.

Table 24 summarizes select treatment-emergent laboratory findings. Patients with hepatitis C had a higher incidence of all grade thrombocytopenia and increased AST and ALT compared to patients with hepatitis B or patients without hepatitis. The incidence of Grade 3-4 thrombocytopenia was similar to the other cohorts, but the incidence of Grade 3-4 increase AST and ALT remained higher in patients with hepatitis C compared to other cohorts.

Table 24: Select Treatment-Emergent Laboratory Findings by hepatitis status

	All patients		Uninfected		Hepatitis B		Hepatitis C	
	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)	All grades n (%)	Grade 3-4 n (%)
Thrombocytopenia	53 (35)	11 (7.3)	25 (34)	5 (6.7)	15 (32)	4 (8.5)	13 (43)	2 (6.7)
Increased AST	89 (59)	27 (18)	42 (57)	13 (18)	26 (55)	6 (13)	21 (70)	8 (27)
Increased ALT	73 (48)	16 (11)	35 (47)	7 (9.4)	19 (40)	2 (4.3)	19 (63)	7 (23)
Increased alkaline phosphatase	65 (43)	9 (5.9)	28 (37)	3 (4.1)	23 (49)	3 (6.4)	14 (47)	3 (10)
Increased bilirubin	56 (37)	11 (7.2)	28 (37)	4 (5.3)	19 (40)	6 (13)	9 (30)	1 (0.3)

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 (all patients: 151- 152; uninfected: 74-75; hepatitis B: 47; hepatitis C: 30).

Table 25 summarizes the patients with immune-mediated hepatitis. Patients with hepatitis B or C did not have an increased incidence of immune-mediated hepatitis compared to patients without hepatitis.

Table 25: Immune-Mediated Hepatitis by hepatitis status

	All patients N=154 n (%)	Uninfected N=75 n (%)	Hepatitis B N= 47 n (%)	Hepatitis C N= 32 n (%)
Requiring systemic steroids	8 (5.2)	6 (8.0)	1 (2.1)	1 (3.1)
Requiring high-dose systemic steroids	6 (3.9)	5 (6.7)	0	1 (3.1)

Source: FDA analysis.

Reviewer comment:

As these data are from an uncontrolled clinical trial and from unplanned subgroup analyses with small numbers of patients, the results should be interpreted with caution.

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 assigned Pregnancy Category D. See pharmacology-toxicology review of original BLA submission.

7.6.3. Pediatrics and Assessment of Effects on Growth

Hepatocellular carcinoma, comprising about 0.5%-1% of all pediatric tumors, occurs only rarely in pediatric patients[10,11,12]. Although there are several ongoing pediatric clinical trials of nivolumab, no pediatric data were submitted to this sBLA and nivolumab is currently indicated only in adult patients. The indication sought by the Applicant is restricted to adult patients with advanced HCC who have received prior sorafenib treatment.

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, squamous cell carcinoma of the head and neck and metastatic colorectal cancer with microsatellite instability or mismatch repair deficiency.

The most recent Periodic Adverse Drug Experience Report (PADER) was submitted 10 July 2017 and covered the period 22 March to 21 June 2017. The Applicant recommended no changes to the package insert based on these reports.

9. Appendices

9.1. Child-Pugh Score

Score	Points
Child-Pugh A	5 - 6
Child-Pugh B	7 - 9
Child-Pugh C	> 9

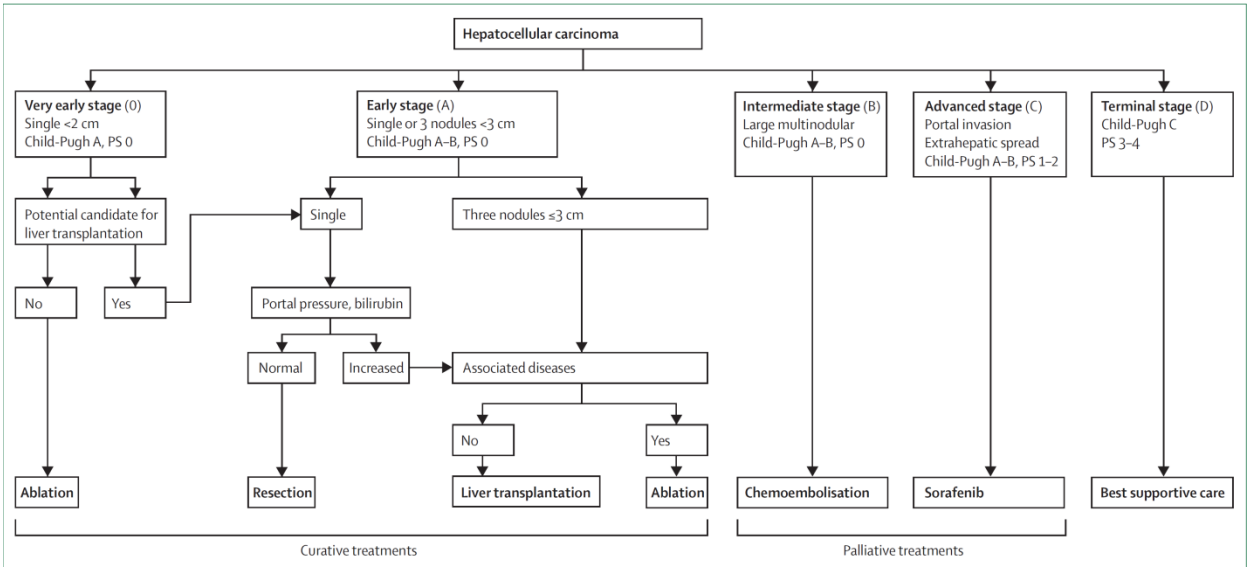
	Score		
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dl)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
PT prolongation or INR	< 4 sec < 1.7	4 - 6 sec 1.7 - 2.3	> 6 sec > 2.3
Encephalopathy grade	None	1 - 2	3 - 4

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unrousable coma, no personality/behavior, decerebrate

Source: interim clinical study report addendum; protocol appendix 3.

9.2. HCC Staging Systems

9.2.1. Barcelona Clinic Liver Cancer staging



Source: Forner et al., Lancet 2012 [13].

9.2.2. Okuda staging

Stage	Tumor size >50% (+)	Tumor size <50% (−)	Ascites (+)	Ascites (−)	Albumin <3g/dl (+)	Albumin >3g/dl (−)	Bilirubin >3mg/dl (+)	Bilirubin <3mg/dl (−)
I	(−)		(−)		(−)		(−)	
II				1 or 2 (+)				
III				3 or 4 (+)				

+: sign of advanced disease.

Source: Okuda et al. Cancer 1985 [14].

9.3. Modified RECIST vs. RECIST 1.1 criteria

Target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Non-target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all non-target lesions	Disappearance of any intratumoral arterial enhancement in all non-target lesions
IR/SD	Persistence of one or more non-target lesions	Persistence of intratumoral arterial enhancement in one or more non-target lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
mRECIST recommendations		
Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.	
Porta hepatis lymph node	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2 cm.	
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group.	
New lesion	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth.	

RECIST, Response Evaluation Criteria In Solid Tumors; mRECIST, modified Response Evaluation Criteria In Solid Tumors; CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.

Source: EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma[15].

9.4. FDA analysis of patient-reported outcomes

9.4.1. EQ-5D-3L QoL results

The FDA review team has performed exploratory analyses of quality of life assessments to evaluate the impact on health status (as measured by the 5 items of EQ-5D-3L) when treated with nivolumab. The descriptive results for each of the five items were compared longitudinally using the graphical visualization.

Table 26 presents the completion rates at each visit for each of the 5 items on EQ-5D-3L assessment questionnaire in patients who were treated. The completion rate was defined as the number of patients who reported the outcome assessments over the number of patients who were treated with nivolumab in the expansion cohort that have an assessment at baseline (prior to administration of drug) and at least 1 subsequent assessment through Week 24 (n=120). The overall completion rates (who responded at least one item) were 100% at Baseline, 95.8% at Week-7, 73.3% at Week-13, 59.2% at Week-19 and 51.7% at Week-25.

Table 26: EQ-5D Item level completion rates at each visit

n(%*)	Baseline	Cycle-2 (Week-7)	Cycle-3 (Week-13)	Cycle-4 (Week-19)	Cycle-5 (Week-25)
Activity	120 (100%)	115 (95.8%)	88 (73.3%)	71 (59.2%)	62 (51.7%)
Anxiety	120 (100%)	115 (95.8%)	88 (73.3%)	71 (59.2%)	62 (51.7%)
Mobility	120 (100%)	115 (95.8%)	88 (73.3%)	71 (59.2%)	62 (51.7%)
Pain	120 (100%)	115 (95.8%)	88 (73.3%)	71 (59.2%)	62 (51.7%)
Self-care	119 (99.2%)	114 (95%)	88 (73.3%)	71 (59.2%)	62 (51.7%)

* The completion rate was defined as the number of patients who reported the outcome assessments over the number of patients who were treated with nivolumab in the expansion cohort at each week that have an assessment at baseline (prior to administration of drug) and at least 1 subsequent assessment through Week 25 (n=120).

Figure 8 to Figure 12 presents the percentage of patients who reported the severity of the problem on a 3-level scale (1-no problems, 2-some problems or 3-severe problems) over time. For the baseline time point, each bar represents the percentage of patients who reported the severity of the problem as none, some and severe at baseline. Similarly, at each post-baseline visit, each bar represents the baseline response scores and the shaded categories within each bar represent the severity levels as reported at each corresponding cycle. The increased levels of severity over time for each item can be assessed visually through these graphs. The majority of patients had no problems with mobility, self-care, usual activities or anxiety/depression. Comparatively, patients reported higher levels of pains throughout the assessment duration.

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

Figure 8: EQ-5D-3L - Activity assessment longitudinal responses categorized by baseline responses

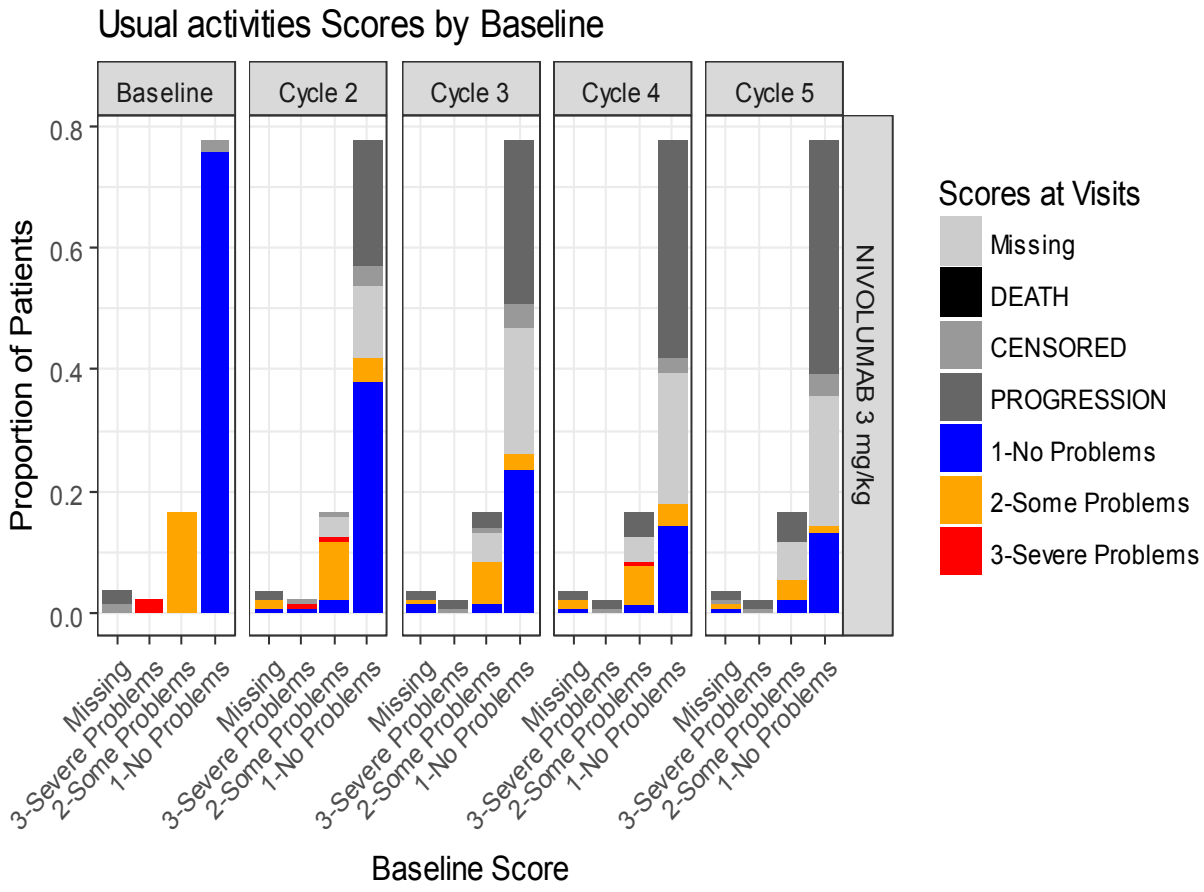


Figure 9: EQ-5D-3L - Anxiety assessment longitudinal responses categorized by baseline responses

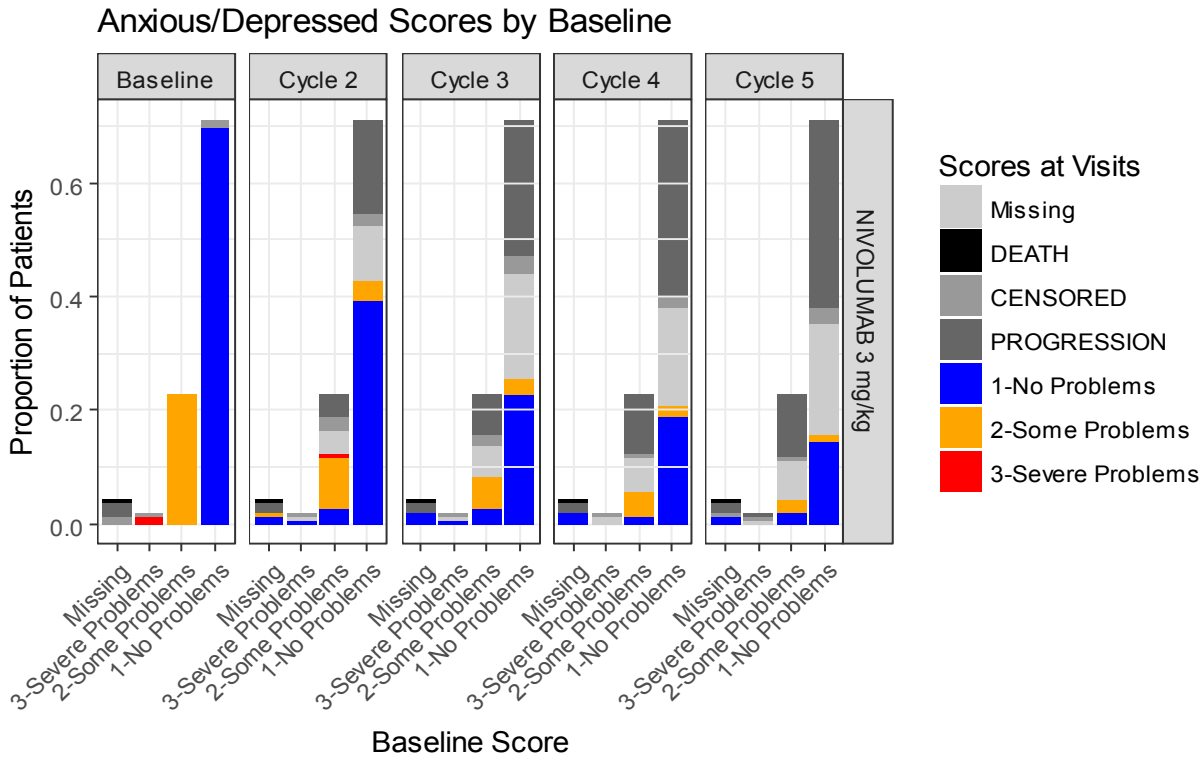


Figure 10: EQ-5D-3L - Mobility assessment longitudinal responses categorized by baseline responses

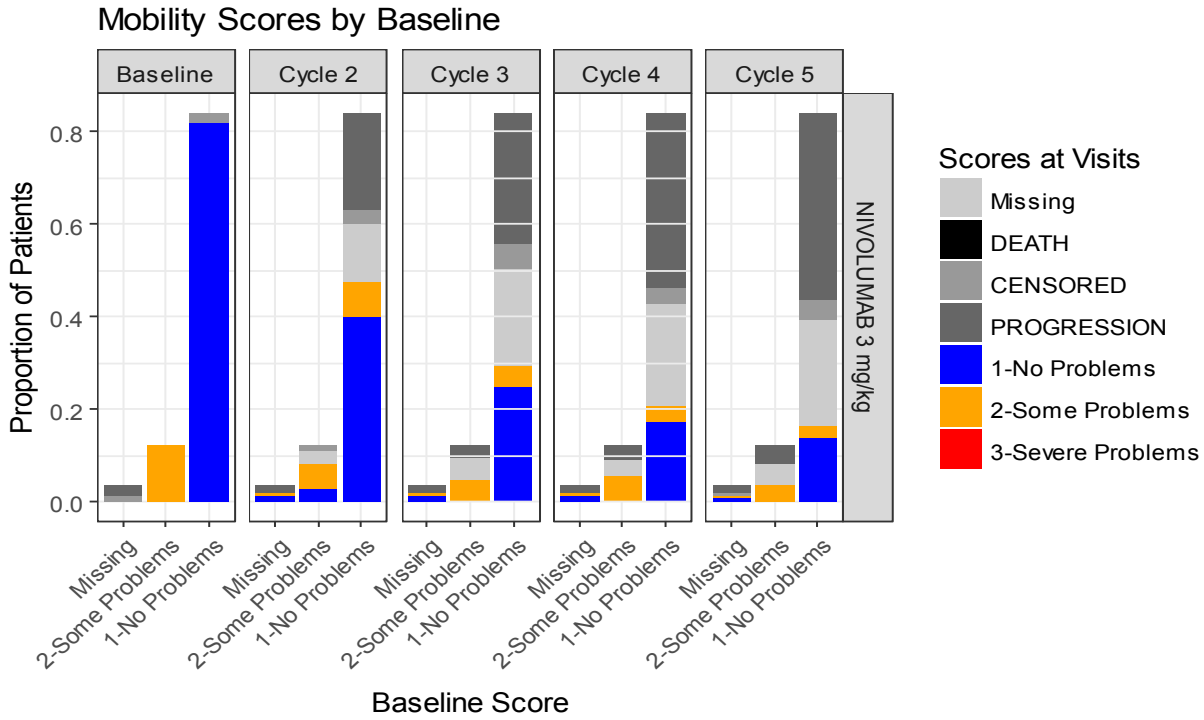


Figure 11: EQ-5D-3L - Pain assessment longitudinal responses categorized by baseline responses

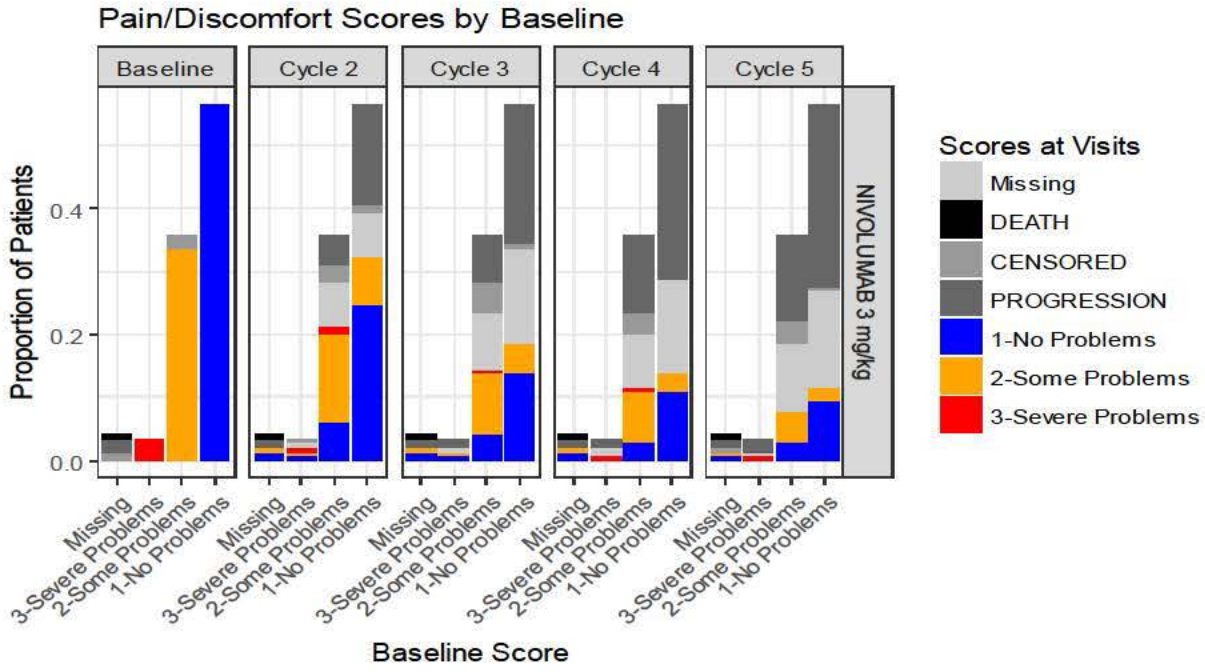
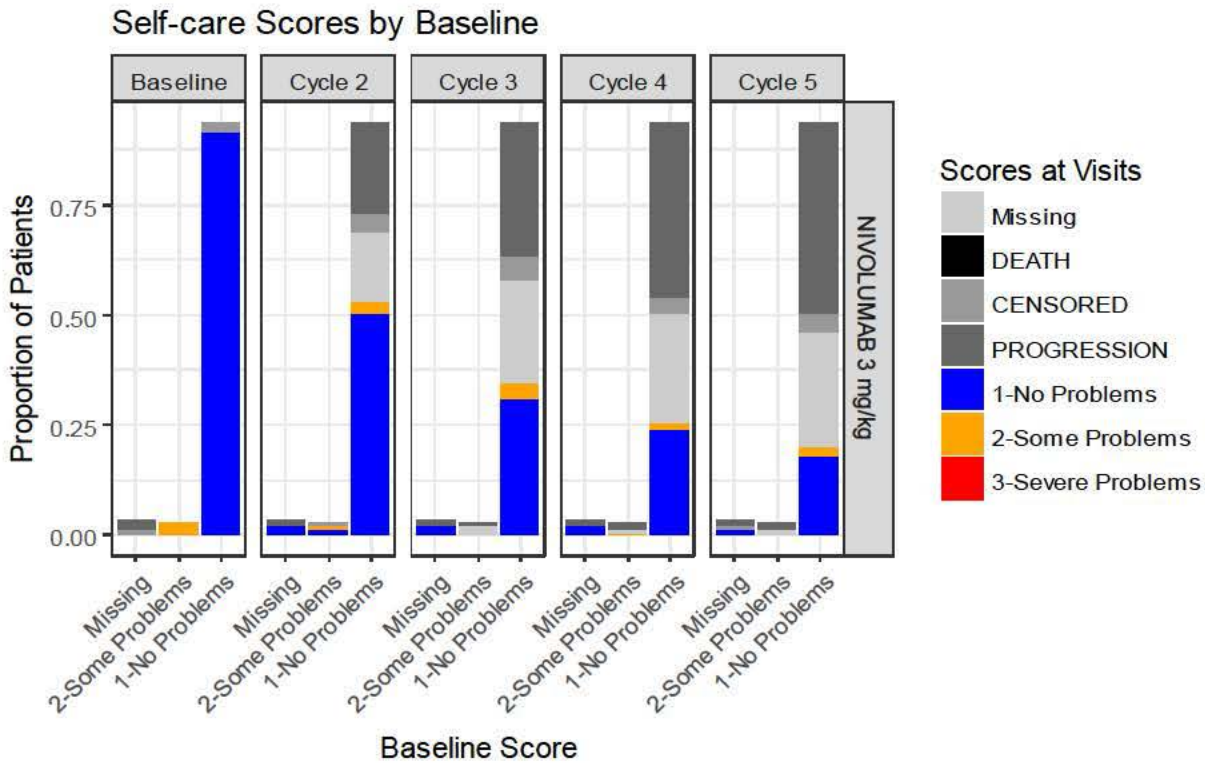


Figure 12: EQ-5D-3L – Self-care assessment longitudinal responses categorized by baseline responses



9.4.2. EQ-5D-VAS score results

The EQ-5D questionnaire also includes a visual analogue scale (VAS), allowing the patient to rate his/her overall health on a scale from 0-100 (worst-best). Table 27 summarizes the EQ-5D-VAS scores collected on Study CA209040.

Table 27: Summary of EQ-5D-VAS scores

	Baseline	Cycle-2 (Week-7)	Cycle-3 (Week-13)	Cycle-4 (Week-19)	Cycle-5 (Week-25)
# patients who reported the VAS score (Completion rate*)	119 (99.2%)	115 (95.8%)	87 (72.5%)	71 (59.2%)	62 (51.7%)
Average VAS score	71.4173	74.1525	73.3611	74.3243	75.0385

* The completion rate was defined as the number of patients who reported the outcome assessments over the number of patients who were treated with nivolumab in the expansion cohort at each week that have an assessment at baseline (prior to administration of drug) and at least 1 subsequent assessment through Week 25 (n=120).

The on-treatment VAS score increased from week 7 to week 25 from 74.2 to 75 for patients in the 2L EXP cohort. and Figure 14 display the average change in the observed and baseline adjusted VAS scores.

Figure 13: Average VAS scores

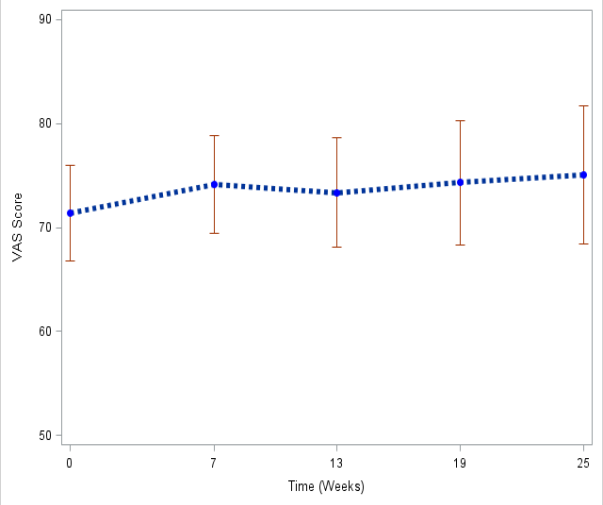
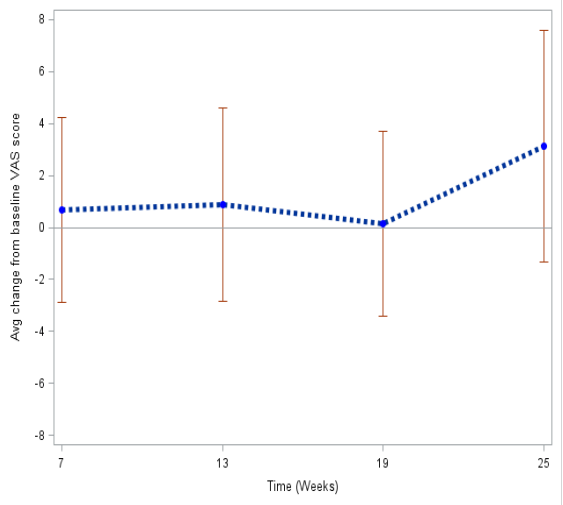


Figure 14: Mean Change from Baseline in VAS Scores



9.5. Literature References

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9.6. Labeling Recommendations

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

- Accelerated approval of nivolumab for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib.
- For the new indication, include demographics, ORR and DOR using RECIST 1.1 and ORR using mRECIST for the efficacy population.
- As the safety profile of nivolumab has been established and safety is better described in controlled trials rather than in single-arm trials, include only pertinent information, such as auto-immune hepatitis and Grade 3 or 4 increases in AST and ALT, in the safety section.
- Include discontinuation criteria specifically for patients with HCC who have Grade 1 or 2 AST or ALT increases at baseline.

9.7. 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 hepatocellular carcinoma who have previously been treated with sorafenib, 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.

9.8. Financial disclosure

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 410		
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): 8		
If there are investigators with disclosable financial interests/arrangements, identify the		

number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 8 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

In accordance with 21 CFR 54, BMS submitted a list of trial investigators for Study CA209040 (module 1.3.4, Table 1) and independent radiological reviewers ([(b) (4)]; module 1.3.4, Table 2). BMS also provided financial disclosures (FDA form 3454) for Study CA209040 and for the independent radiological reviewers. A total of 8 investigator or radiological reviewers held financial interests or arrangements requiring disclosure per the criteria described on Form 3454. The Applicant attempted to minimize bias via the use of blinded independent radiological review (BICR). In addition, 100% source data verification was conducted for the dose escalation and dose expansion cohort.

Disclosable interest was provided for 8 investigators as outlined in the table below. The disclosable financial interest for the [(b) (6)] site, while significant, is unlikely to impact the study results due to the primary endpoint of ORR being evaluated by BICR and not by the investigational site. In addition, this financial interest was restricted to a single site (one out of many) involved in the conduct of the study and treated a small percentage of patients.

Table 28: Financial Interests or Arrangements

Site	Principal (P) or Sub (S)	Investigator Name (Last, First)	Financial Interest or Arrangements	Site Name	Patients treated[a]
		(b) (6)	Financial Disclosure dated 10/4/2016 states that the institution participates in the BMS funded II-ON program (funding received: $3,544,500 beginning (b) (6)).		(b) (6)
			Financial Disclosure dated 10/4/2016 states that the institution participates in the BMS funded II-ON program (funding received: $3,544,500 beginning (b) (6)).		
			Financial Disclosure dated 10/4/2016 states that the institution participates in the BMS funded II-ON program (funding received: $3,544,500 beginning (b) (6)).		
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Site	Principal (P) or Sub (S)	Investigator Name (Last, First)	Financial Interest or Arrangements	Site Name	Patients treated[a]
[redacted]	[redacted]	[redacted]	Financial Disclosure dated 10/4/2016 states that [redacted] received consultant fees for [redacted] (funding received: $59.000 from [redacted] to [redacted]).	[redacted]	[redacted]
			Financial Disclosure dated 8-June-2016 states that [redacted] participates in the BMS funded II-ON network and his institution has received funding from an II-ON research grant of $10.000 (beginning [redacted]) and $100.000 (beginning [redacted]).		

[a] Limited to patients who were treated in the dose escalation and dose expansion cohort of Study CA209040 and who had received prior sorafenib (i.e., those patients included in this sBLA submission to support the proposed indication).

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/s/

MARIE-ANNE D SMIT
08/31/2017

SIRISHA L MUSHTI
08/31/2017

MARTHA B DONOGHUE
08/31/2017
I concur with the analyses and conclusions contained in this review.

LISA R RODRIGUEZ
08/31/2017

KUN HE
08/31/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s041

CHEMISTRY REVIEW(S)

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

MEMORANDUM

DATE:	April 5, 2017
BLA:	**125554**
SUPPLEMENT:	**041**
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:	Hepatocellular Carcinoma (HCC)
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

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BACKGROUND:

On Mar. 24, 2017, the sponsor submitted s-041 supplement to request accelerated approval of Opdivo for the treatment of patients with hepatocellular carcinoma (HCC) (b) (4) This review supports the environmental assessment the sponsor submitted in the supplement 041 on 03/24/2017 (sequence #0325).

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:

125554Orig1s041

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BLA Clinical Pharmacology Review	
NDA/SDN/eCTD Sequence No.	BLA125554/Supplement-41/325
Type/Category	Efficacy
Brand Name	OPDIVO®
Generic Name	Nivolumab
Receipt Date	Mar. 24th 2017
PDUFA Date	Sep. 24th 2017
Proposed Indication	Hepatocellular carcinoma (HCC)
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., Edwin Chiu Yuen Chow, Ph.D.
Secondary Reviewers	Jeanne Fourie Zirkelbach, Ph.D., Jiang Liu, Ph.D.

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1 EXECUTIVE SUMMARY

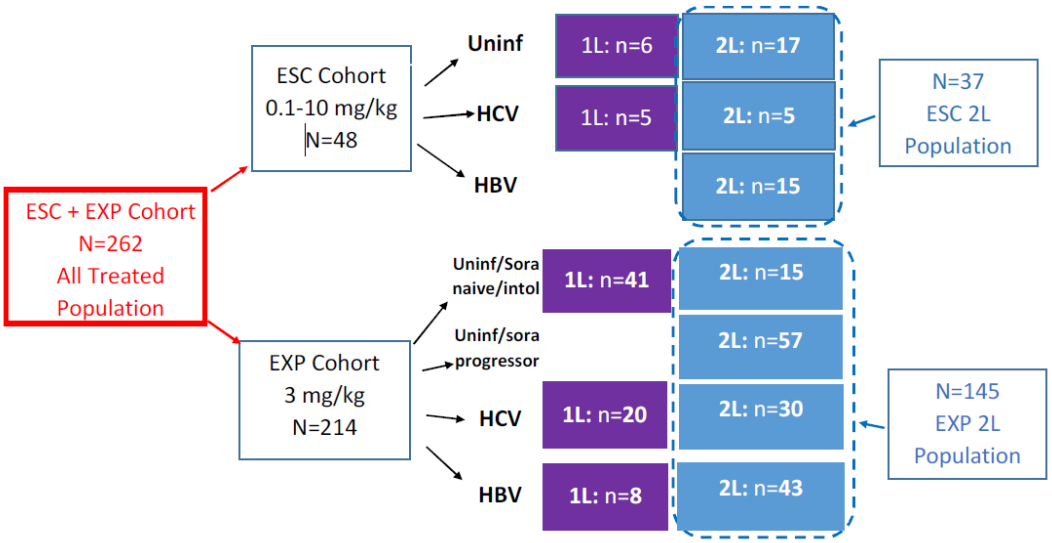
The applicant submitted an efficacy supplement to support the accelerated approval of nivolumab for the treatment of hepatocellular carcinoma (HCC) [redacted] (b) (4). The proposed dosing regimen of nivolumab is 240 mg every 2 weeks, which is also the regimen used for the other approved indications, namely unresectable or metastatic melanoma, metastatic non-small cell lung cancer, advanced renal cell carcinoma, locally advanced or metastatic urothelial carcinoma, and microsatellite instability-high (HIS-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer.

The primary evidence to support the proposed indication is based on clinical data in the Phase 1/2 trial (CA209040), a dose-escalation, open-label, non-comparative study of nivolumab monotherapy in subjects with HCC with or without chronic viral hepatitis.

The study design of CA209040 is described below and in Figure 1:

- **2L Dose Escalation (ESC) Cohort:** N = 37 prior sorafenib-treated subjects administered 0.1 to 10 mg/kg nivolumab monotherapy Q2W in the dose escalation phase
- **2L Expansion (EXP) Cohort:** N = 145 prior sorafenib-treated subjects administered 3 mg/kg nivolumab monotherapy Q2W in the expansion phase
- **ESC + EXP Cohort:** N = 262 total treated subjects, composed of both sorafenib-naive and sorafenib prior treated (48 subjects administered 0.1 to 10 mg/kg nivolumab monotherapy Q2W in the **ESC** and 214 subjects administered 3 mg/kg nivolumab monotherapy Q2W in **ESC** cohorts)
- **2L ESC + 2L EXP (efficacy):** N = 182 prior sorafenib-treated subjects, used to further characterize ORR and DOR

Figure 1: Analysis Population by Sorafenib-Naive (1L) and Sorafenib-treated (2L) subjects in the ESC and EXP Cohorts



Note: Dose levels included in Escalation Phase were 0.1, 0.3, 1, 3, and 10 mg/kg.

Abbreviations: 1L = first line; 2L = second line; Esc = escalation; Exp = expansion; HBV = hepatitis B virus; HCV = hepatitis C virus; intol = intolerant; sora = sorafenib; Uninf = uninfected.

Source: Figure 3.1-1 of sponsor's clinical efficacy summary_HCC 2L-CA209040

Efficacy in prior sorafenib-treated subjects was demonstrated with an ORR response in the 2L EXP population of 14.5% (95% CI: 9.2%, 21.3%) which was also supported by the ORR of 18.9% (95% CI: 8.0%, 35.2%) in the 2L ESC population.

Overall, Study CA209040 demonstrates that nivolumab pharmacokinetics is comparable between patients with HCC and NSCLC. Additionally, HCC etiology and hepatic impairment do not display a clinically meaningful effect on nivolumab clearance, and thus no dose adjustment is needed. A population pharmacokinetics (PPK) modeling and simulation bridge was provided to support the 240mg Q2W dosing regimen proposed by the applicant in the package insert and the 3mg/kg Q2W dosing regimen used in trial CA209040. The model predicted exposure of the 240mg flat dose is approximately 15% higher than that of the 3mg/kg body weight based dose. This difference is not considered clinically meaningful based on the relatively flat exposure/dose-efficacy and exposure-safety relationships. Thus, the applicant proposed dosing regimen of 240mg Q2W for the HCC indication is acceptable.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the pertinent information contained in this supplement for BLA 125554. The information submitted supports the nivolumab 240 mg Q2W regimen for the treatment of HCC (b) (4).

The labeling proposed by the applicant is acceptable from a clinical pharmacology perspective.

Signatures:

Yuan Yu, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Jiang Liu, Ph.D. Pharmacometrics Team Leader Division of Pharmacometrics
Edwin Chiu Yuen Chow, Ph.D. Reviewer Division of Clinical Pharmacology V	Jeanne Fourie Zirkelbach, Ph.D. Team Leader Division of Clinical Pharmacology V

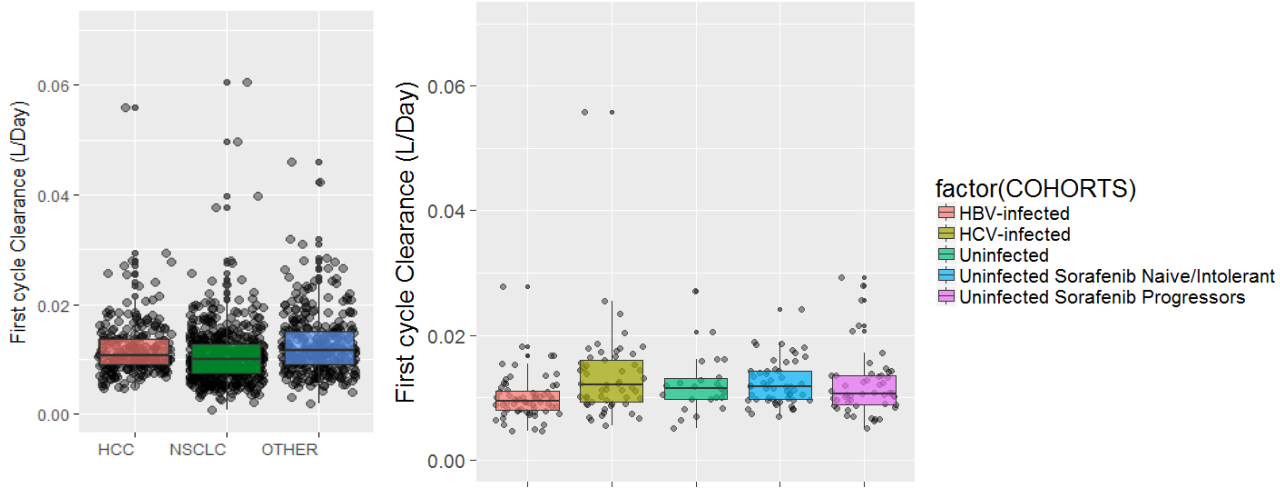
Cc: DOP2: RPM – M Libeg; MTL –S Lemery; MO – D Smit;
DCPV: DDD - B Booth; DD - A Rahman

2 QUESTION BASED REVIEW

2.1 Is the Nivolumab Pharmacokinetics in Patients with HCC Comparable to Patient 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 the PPK model and was showed not to be a significant covariate for clearance. In patients with HCC, the first cycle clearance is comparable with that in patients with NSCLC and patients with other indications such as melanoma or renal cell carcinoma (Figure 2; left). There are no clinically meaningful differences in nivolumab clearance between uninfected patients and patients with HCC etiology (either hepatitis C (HCV) or hepatitis B (HBV)). Thus, there is no dose adjustment needed for patients with HCC that have different HCC etiologies (Figure 2; Right).

Figure 2: Comparison of First Cycle Clearance between HCC Patients with Other Indications and Etiologies



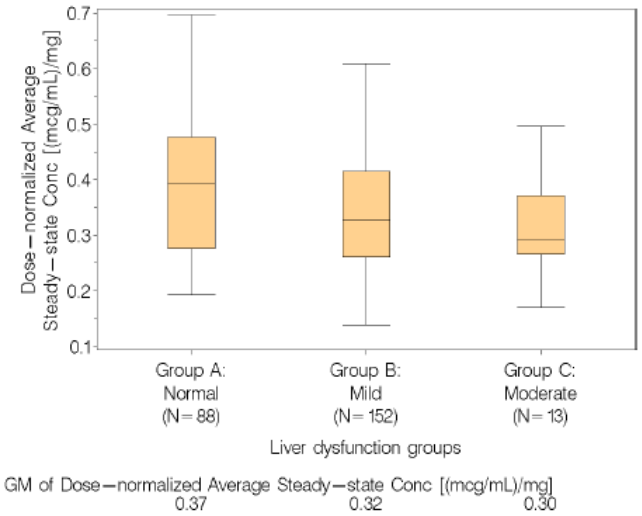
FDA reviewer analysis: Comparison of first cycle clearance within different indications and etiologies.

HBV-infected N=64; HCV-infected N=53; uninfected: N=23; uninfected sorafenib Naïve/Intolerant N=52, uninfected sorafenib progressors N=50.

2.2 Is Dose Adjustment Needed in Hepatic Impairment Patients?

No, nivolumab clearance is similar for patients with normal, mild, or moderate liver dysfunction, as assessed by NCI criteria (Figure 3). Nivolumab clearance in 152 individuals with mild hepatic dysfunction and 13 individuals with moderate hepatic dysfunction is comparable to that in 88 individuals with normal hepatic function. The $C_{avg,ss}$ was also comparable among the different liver function groups. For patients who had HCC in trial CA209040, the geometric mean exposures of nivolumab in patients with mild (N=152) and moderate (N=13) hepatic dysfunction were approximately 14% and 19% lower, respectively, compared to patients with normal hepatic function (N=88), and these differences were not considered to be clinically meaningful. Thus, there is no dose adjustment needed in patients with mild and moderate hepatic impairment.

Figure 3: Nivolumab Dose-Normalized Cavgss versus NCI Criteria for Hepatic Dysfunction

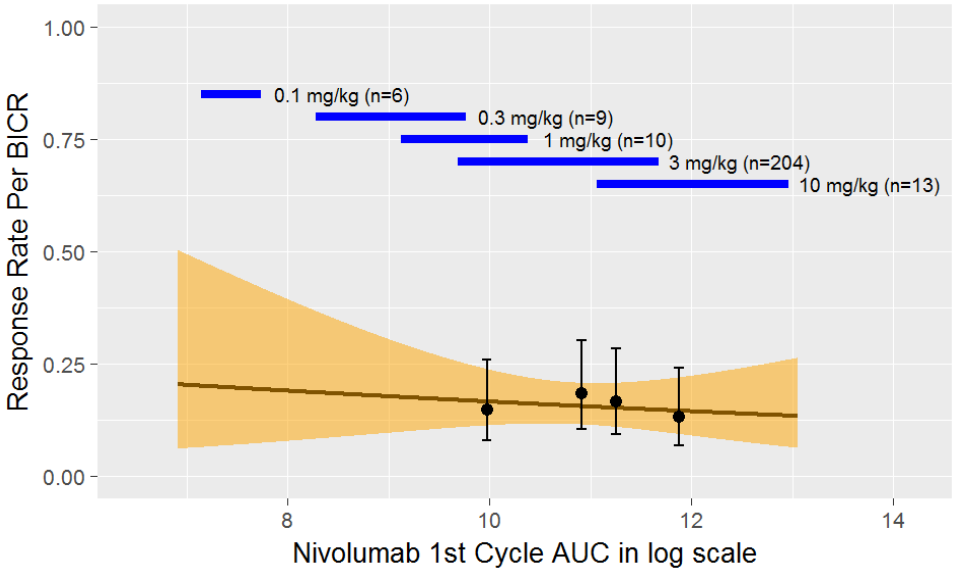


Source: Figure 3.1.2.3-2 of summary of Clinical Pharmacology

2.3 What Are the Exposure/Dose-Response Relationships for Efficacy in Patients with HCC?

In study CA209040, the exposure-response relationship for efficacy in patients with HCC who were previously treated with sorafenib (N=168), is relatively flat. The relationship between nivolumab AUC after the first cycle and response rate per BICR was analyzed by logistic regression (Figure 4). Simulations from the PPK model suggest that nivolumab AUC is not a significant covariate for response rate when ECOG performance status was included as a covariate.

Figure 4: Exposure response relationship in HCC patients



FDA reviewer's analysis: Solid line is the logistic regression of the predicted probability of response rate BICR. 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.

A dose-response analysis using data from the second line HCC patients enrolled in the dose escalation portion of the study, (37 patients in 5 dosing groups) showed that the ORR is similar across dose levels ranging from 0.1 mg/kg up to 10 mg/kg (Table 1).

Table 1: Response Rate per BICR in Second Line HCC Patient in Escalation Cohort

Nivolumab	Responder per BICR	Total number	ORR (%)
0.1 mg/kg	1	5	0.20
0.3 mg/kg	1	7	0.14
1 mg/kg	4	6	0.67
3 mg/kg	1	9	0.11
10 mg/kg	0	10	0.00
Total	7	37	18.9

Source: FDA reviewer's analysis

2.4 What Are The Exposure-Response Relationships For Safety In Patients With HCC?

The exposure-response (E-R) relationship for safety was evaluated using nivolumab exposure time averaged concentration over the first dosing interval (C_{avg1}) and Grade 3+ DR-AEs in 254 patients with HCC who had nivolumab exposure estimates available. Time to first Grade 3+ DR-AEs was used as the safety endpoint. The E-R relationship was characterized by a semi-parametric cox proportional hazards CPH model, and included assessments of the modulatory effect of covariates (etiology, extrahepatic spread / vascular invasion, and Alpha-fetoprotein) on the E-R relationship. There was no evidence that the risk of Grade 3 or greater drug related DR-AEs increased with increasing nivolumab exposure (Figure 9).

2.5 Is the Proposed 240 mg Q2W Flat Dose in the Package Insert instead of the 3 mg/kg Q2W Dose used in the Efficacy Trial Supported by Clinical Pharmacology Findings?

Yes, the dosing regimen change has been bridged by PPK modeling and simulation. A flat dose of 240 mg Q2W is proposed in the package insert for nivolumab. Based on simulations using the PPK model, the overall exposure at the 240 mg Q2W flat dose is approximately 13% to 14% higher compared to the 3 mg/kg Q2W dose (Table 2). However, these differences between the two dosing regimens are not considered to be clinically meaningful. In addition, the difference identified may be due to the lower median body weight (70.8 kg) compared to the overall body weight used for the nivolumab dose conversion (80kg). With the flat exposure response relationship for safety and efficacy, this difference will not be considered clinically meaningful. Thus, the nivolumab dosing regimen of 240mg Q2W for the HCC indication is acceptable.

Table 2: Exposure Comparison between Nivolumab 240mg Q2W versus 3 mg/kg Q2W

Summary Exposure	Wt-Based Dosing - 3 mg/kg GM [µg/mL] (%CV)	Flat Dose - 240 mg GM [µg/mL] (%CV)	% Difference in GMs[a]	Wt Based Dosing - 3 mg/kg Median [µg/mL] (5th, 95th Percentile)	Flat Dose - 240 mg Median [µg/mL] (5th, 95th Percentile)
Cavgss	79.7 (63.4)	90.7 (68.7)	13.8	79.8 (31.9, 189)	90.2 (34.9, 234)
Cminss	60.6 (75.3)	69 (80.7)	13.9	63.1 (18.1, 168)	70.6 (20, 212)
Cmaxss	122 (48.7)	139 (54.8)	13.9	120 (62.8, 246)	137 (65.4, 298)
Cavg1	24.6 (25)	28 (26.3)	13.8	24.4 (16.6, 36.9)	27.9 (18.5, 43.3)
Cmin1	15.6 (29.9)	17.8 (32)	14.1	15.6 (9.54, 25.3)	17.9 (10.4, 29.8)
Cmax1	55.3 (33)	62.9 (38.1)	13.7	54.8 (32.8, 93.9)	62.2 (35.2, 115)

Source: Source: Table 3.4.1-1 of summary of Clinical Pharmacology

3 DETAILED LABELING RECOMMENDATIONS

8.7 Hepatic Impairment

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in HCC patients (n=152) and other tumor patients (n=92) 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~~) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST; n=13). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with moderate ~~(TB greater than 1.5 to 3 times ULN and any AST)~~severe hepatic impairment (TB greater than 3 times ULN and any AST) *[see Use in Specific Populations (8.7)]*.

FDA Comments: The labeling proposed by sponsor is acceptable from clinical pharmacology aspect.

4 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 has 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.

5 RESULTS OF APPLICANT'S ANALYSIS

OBJECTIVES

- Characterize the PK of nivolumab in subjects with advanced HCC, and to determine the effect of key covariates on nivolumab PK and exposure
- Compare nivolumab exposures produced by nivolumab 240 mg Q2W to exposures produced by 3 mg/kg Q2W in HCC subjects
- Characterize the relationship between nivolumab exposure and efficacy (as measured by BICR-assessed OR) in subjects with advanced HCC who have been previously treated with sorafenib and were subsequently treated with nivolumab
- Assess the potential impact of nivolumab 240 mg Q2W vs 3 mg/kg Q2W on efficacy
- Characterize the relationship between nivolumab exposure and safety (as measured by Grade 3+ DR-AEs) in all subjects with advanced HCC who were treated with nivolumab
- Assess the potential impact of nivolumab 240 Q2W vs 3 mg/kg Q2W on the hazard of safety

DATA

Population Pharmacokinetic (PPK) Analysis: The PPK analysis dataset included all subjects who received nivolumab, and for whom nivolumab measurable serum concentration data were available following nivolumab monotherapy in the following studies: 2 Phase 1 studies (MDX-1106-01 and MDX-1106-03), 1 Phase 2 study (CA209063), and 2 Phase 3 studies (CA209017 and CA209057). CA209040, a Phase 1/2 study, allowed assessment of nivolumab PK in subjects with advanced HCC. The analysis dataset included data for nivolumab treatment doses ranging from 0.1 to 10 mg/kg.

Exposure-Response (ER) of OR (Efficacy): The E-R of BICR-assessed OR included data from subjects with advanced HCC who had been previously treated with sorafenib in CA209040. This was the only study which included data from HCC subjects.

E-R of Grade 3+ DR-AEs (Safety): The E-R of Grade 3+ DR-AEs included the available data from subjects with advanced HCC in CA209040. This was the only study which included data from HCC subjects.

METHODS

Population Pharmacometrics Model

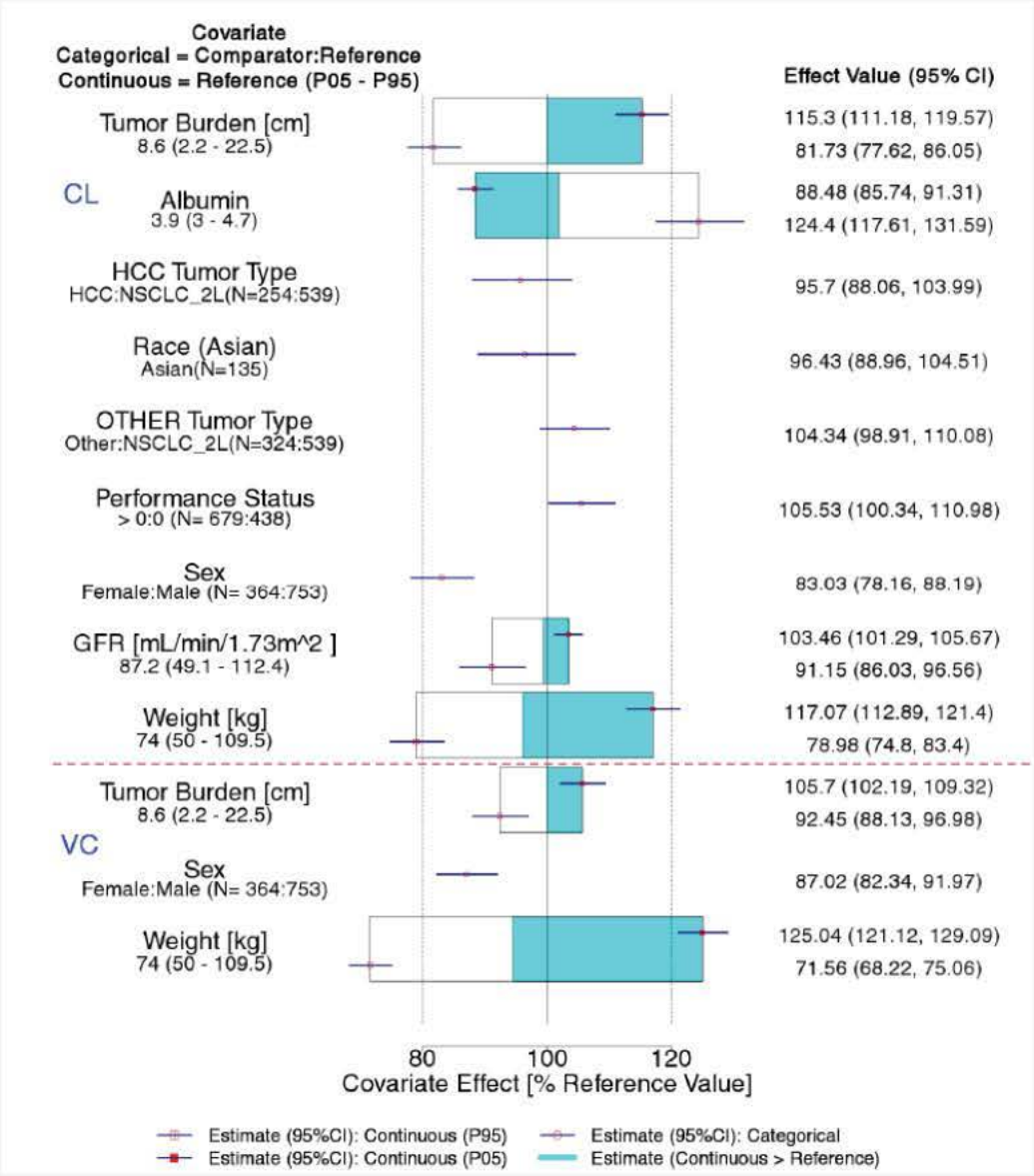
First, base model development consisted of re-estimation of the final model from a previous analysis developed with data that included CA209001, CA209003, CA209017, CA209057, and CA209063 as well as 14 other studies, but not CA209040, for which PK data had not been analyzed previously. This approach leveraged the previously determined structural, interindividual variability, residual error, and covariate effect components of the prior nivolumab PPK model.

Second, a full model was developed to obtain unbiased estimates of the magnitude of covariate effects on model parameters. This was achieved by simultaneously incorporating all pre-specified covariate parameter relationships of interest into the model. The pre-specified covariate-parameter effects of interest assessed in the full model were sex, baseline body weight, tumor type, baseline estimated glomerular filtration rate (eGFR), baseline performance status (PS), race, and baseline albumin on CL, sex and baseline weight on the volume of the central compartment (VC), tumor type on the maximum

effect (Emax), and tumor type on time to achieve 50% of the maximum response (T50). Tumor type was assessed using non-small cell lung cancer - second line (NSCLC 2L+) as the reference versus HCC versus Other tumor types.

In the third stage, the final model was developed from the full model (NSCLC 2L+ [reference] vs HCC vs OTHER) using stepwise backward elimination of covariates, based on Bayesian information criterion (BIC). The final model was determined to be the model with the lowest value of BIC determined by stepwise backward elimination from the full model. The inferences on the magnitude of covariate effects were based on the full model (Figure5). The parameter estimates of full model is listed in Table 3.

Figure5: Covariate Effects on PPK Model Parameters for Tumor Burden Sensitivity Analysis



Source: Figure 2 of sponsor's Pop-PK ER report

Table 3: PPK Model Parameter Estimates (Full Model)

Parameter	Final Parameter Estimate		Interindividual Variability[a] / Residual Variability	
	Estimate	%RSE	Estimate	%RSE
CL: Clearance (mL/h)[b]	11.6	4.36	0.103	8.95
CL: Power of BBWT on CL[c]	0.529	11.4		
CL: Power of GFR on CL[c]	0.158	29.9		
CL: Sex Effect on CL[d]	-0.208	14.8		
CL: PS Effect on CL[d]	0.0747	33.3		
CL: Tumor Type (OTHER) Effect on CL[d]	0.0642	49.0		
CL: Race (Asian) Effect on CL[d]	-0.0630	60.2		
CL: Tumor Type (HCC) Effect on CL[d]	-0.0211	203		
CL: Baseline Albumin Effect on CL[c]	-0.800	11.9		
VC: Central Volume (L)[b]	4.27	1.36	0.0938	18.1
VC: Power of BBWT on VC[c]	0.734	6.63		
VC: Sex Effect on VC[d]	-0.142	19.1		
Q: Intercompartmental CL (mL/h)	33.1	8.96	NE	NA
VP: Peripheral Volume (L)	3.06	4.10	0.193	14.9
EMAX: Time-varying CL	-0.302	21.1	0.165	26.6
T50: Time-varying CL (h)	1530	17.9	NE	NA
T50: Tumor Type (HCC) Effect on T50[d]	1.38	22.2		
HILL: Coefficient for Time-varying CL	1.63	17.8	NE	NA
cov(IIV in VC, IIV in CL)[e]	0.0476	15.0	NA	NA
RV: Residual Error (Proportional)	NE	NA	0.0529	4.07
Minimum value of the objective function = 43638.77				

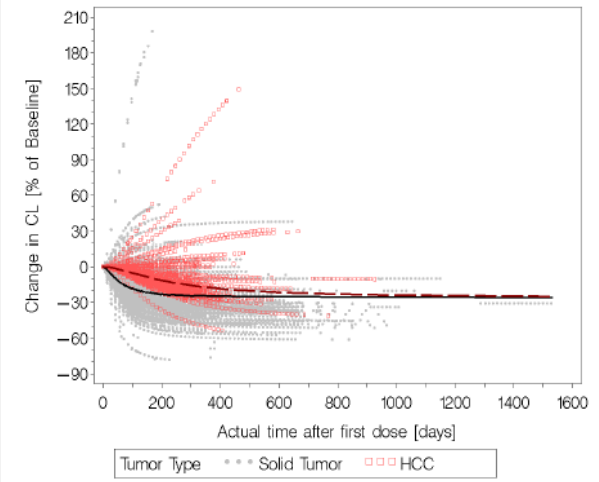
[a] Eta shrinkage: ETA_CL: 16.7%, ETA_VC: 19.8%, ETA_VP: 43.6%; ETA_EMAX; 47.1%; Epsilon shrinkage: 12.9%

[b] CLREF and VCREF are typical values of CL and VC at the reference covariate values. Covariate effects were estimated relative to a reference subject who is a male, weighing 80 kg, estimated GFR of 90 mL/min/1.73 m^2, serum albumin of 4 g/dL, PS of 0, tumor type of NSCLC 2L+, and race = white or other, defined as not African American and not Asian. The reference values for continuous valued covariates were selected to be approximately the median of the covariate values in the analysis dataset.

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

The model estimated (typical value) of Emax (-0.302) indicated that nivolumab CL decreased with time, and that the maximal decrease was approximately 26% [calculated as: 1 −exp(Emax)], as shown in Figure 6. The change in CL was estimated to occur relatively slowly compared to other solid tumors (T50 = approximately 8 months in patients with HCC versus 2 months for other solid tumor types). Although the time to steady state CL was slower in HCC, steady state CL was expected to be similar in both groups since there was no effect of tumor type on EMAX, the maximum reduction in CL. The results showed that the HCC tumor type was associated with an increase in T50 in the time-varying CL of nivolumab, but estimated Emax in HCC was similar to the NSCLC 2L+ reference group.

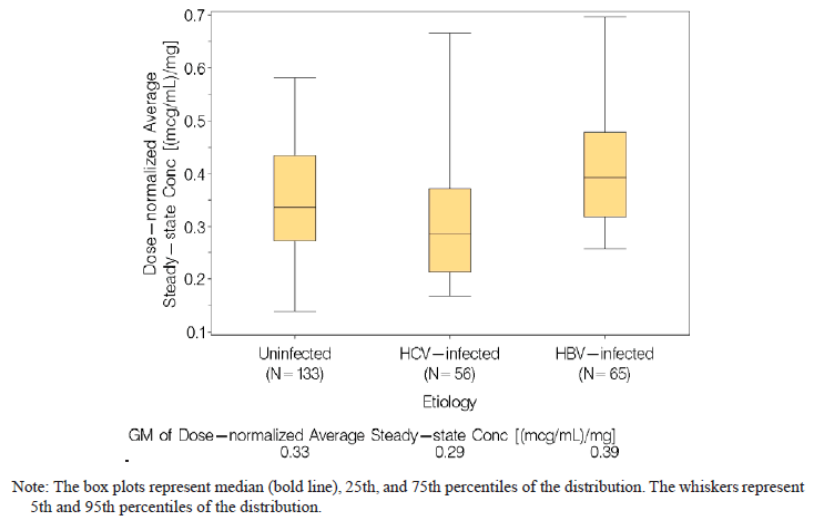
Figure 6: Model Estimated Change in Clearance versus Time from the Final Model



Source: Figure 3.1.2.1-2 of summary of Clinical Pharmacology

HCC etiology does not have a clinically relevant effect on nivolumab exposure as shown in Figure 7 with dose-normalized average steady-state concentration values being generally similar between uninfected subjects and those with HCV or HBV. The CL (expressed as a % typical value) was also similar for uninfected subjects and those with HBV, but slightly higher (~10%) for those with HCV. Overall, this slight difference was not considered to be clinically meaningful.

Figure 7: Nivolumab Dose-Normalized Cavgss versus Etiology



Source: Figure 3 of sponsor's nivolumab-hcc-ppk-er-report

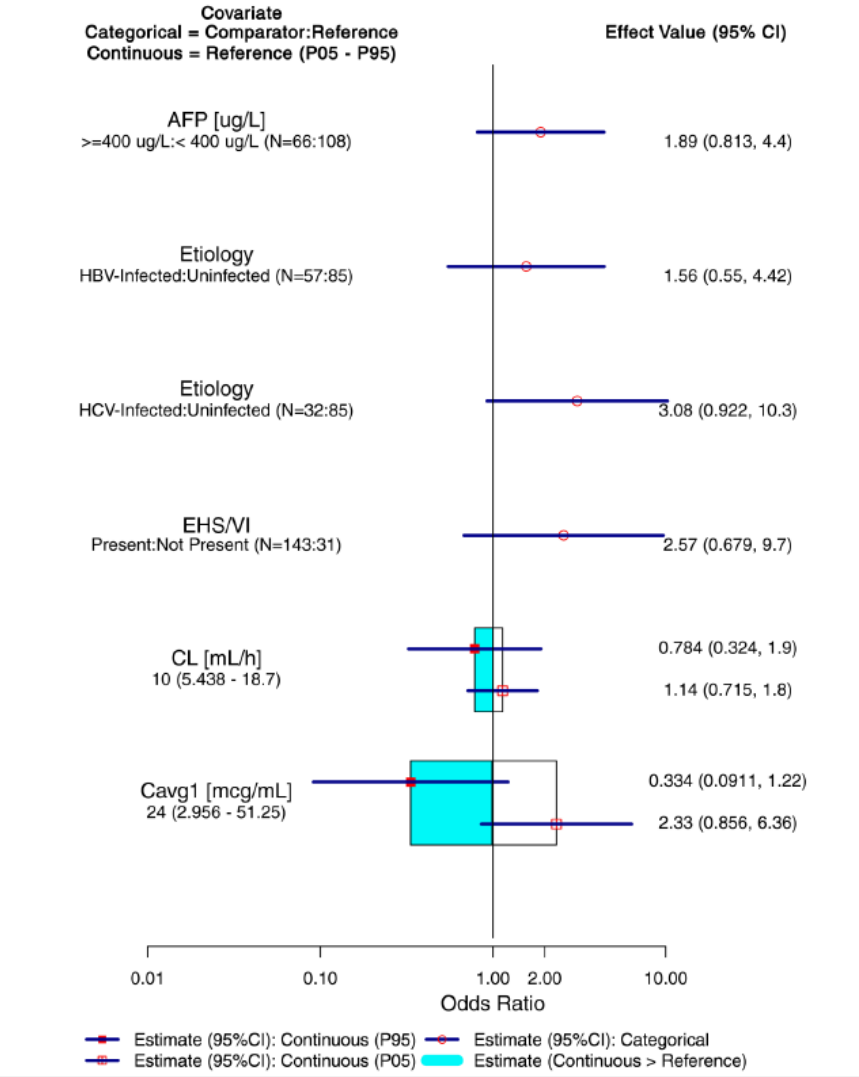
E-R of OR (Efficacy)

The exposure-response relationship was characterized for nivolumab exposure (Cavg1) and BICR-assessed OR using 174 HCC subjects from study CA209040 who had been previously treated with sorafenib and who had nivolumab exposure data available. The relationship between the nivolumab exposure and OR was characterized using a logistic regression model that incorporated the effects of covariates that may modulate the E-R relationship. The covariate variables investigated in the E-R

analysis of OR included etiology, EHS/VI, AFP, baseline CL, and nivolumab Cavg1. PPK model predicted Cavg1 was used as the measure of nivolumab exposure for the characterization of the E-R of efficacy, as Cavg1 was not confounded by CL. Furthermore, other measures of exposure (such as Cminss, Cmaxss, Cavgss and Cmin1) were highly correlated with Cavg1.

Cavg1 was not found to be a significant predictor of Pr(OR) in the full model (95% CI included 1), similar to the finding of the base model. The 95% CI of all other predictor variables evaluated (EHS/VI, etiology, baseline AFP, baseline clearance) also included unity, indicating a lack of evidence for the effect of these variables on Pr(OR). The estimated covariate effects are shown in Figure 8.

Figure 8: Estimated Covariate Effects on the Odds of OR (Full Model)



Source: Table 3.2-1 of summary of Clinical Pharmacology

E-R of OR (Safety)

The E-R relationship for safety was characterized for nivolumab exposure (Cavg1) and Grade 3+ DR-AEs in 254 HCC subjects who had nivolumab exposure estimates available in CA209040. Time to first Grade 3+ DR-AEs was used as the safety endpoint. The E-R relationship was characterized by a semi-parametric CPH model, and included assessments of the modulatory effect of covariates (etiology, EHS/VI, and AFP) on the E-R relationship.

Figure 9 presents the estimated effects of all of the predictor variables on the hazard of Grade 3+ DR-AEs in the Full Model. There was no evidence that the risk of Grade 3 or greater drug related DR-AEs increased with increasing nivolumab exposure (Cavg1). In fact, the estimated effect of Cavg1 in the final CPH model suggested a trend towards a decrease in the risk of Grade 3+ DR-AEs with increasing nivolumab exposure. This inverse relationship between exposure and risk of Grade 3+ DR-AEs may be due to several reasons. One potential confounding effect is that there were no Grade 3+ DR AEs in the highest dose group (10 mg/kg), while the incidence of Grade 3+ DR AEs was higher in the lower dose groups. While the highest and lowest dose groups (0.1, 0.3 and 1 mg/kg) had smaller sample sizes relative to the nivolumab 3 mg/kg group (n = 13 and n = 25 for the highest and lowest groups relative to n = 216 for the 3 mg/kg group), the differing Grade 3+ AE rates in these groups could have influenced the E-R analyses at the extreme dose ranges. Another potentially confounding effect may be due to an association between CL and safety. In particular, the exposure of mAb drugs in cachexic subjects may be lower due to higher CL of these drugs as a result of the elevated whole body protein turnover in these subjects. This may manifest as an apparent inverse exposure response for Grade 3+ AEs. EHS/VI and AFP were not significant predictors of the risk of Grade 3+ DR-AEs in patients with HCC. The effect of etiology of HBV-infected subjects was not a significant predictor of experiencing a Grade 3+ DR-AE. The effect of etiology in HCV-infected subjects was a significant predictor of experiencing a Grade 3+ DR-AE, relative to uninfected subjects. This difference could be due to asymptomatic increases in AST/ALT (more common in HCV). Overall, these results were consistent with the observed data.

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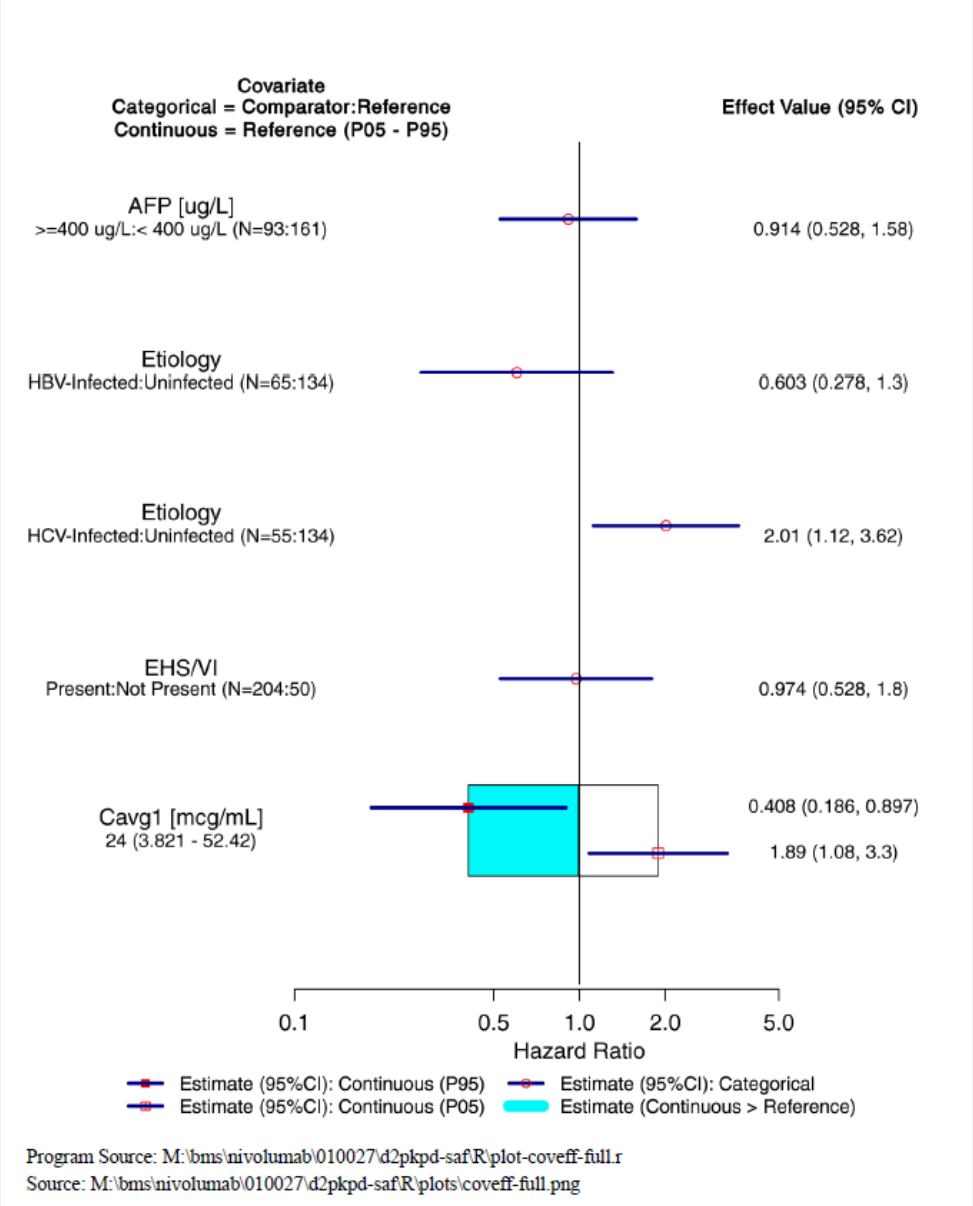
Figure 9: Estimated Covariate Effects of E-R Grade 3+ DR-AEs (Full Model)



Source: Table 3.3-1 of summary of Clinical Pharmacology

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

As a model application, the exposures of nivolumab 240 mg Q2W dosing regimen were compared to nivolumab 3 mg/kg Q2W dosing regimen using the abovementioned PPK model. The results demonstrated that nivolumab 240 mg Q2W dosing regimen would produce comparable exposures to that following nivolumab 3 mg/kg Q2W dosing regimen. A comparison of the simulated exposures between 240 mg Q2W and 3 mg/kg Q2W for the HCC subjects in Table 2. Across all exposure metrics, the maximal difference between the geometric means for the 2 regimens is < 15%.

Conclusions:

Population Pharmacokinetics

- Nivolumab PK was described by a linear 2-compartment model with time-varying CL, such that CL decreased with time (~ 26%)
- Nivolumab CL in HCC subjects was similar relative to the NSCLC 2L+ tumor type (2% difference, 95% CI included 1)
- Nivolumab exposures (Cavgss) were similar (< 20% different) in HCC subjects regardless of etiology (uninfected, HCV, or HBV) or hepatic impairment status (mild or moderate)
- Tumor burden of HCC subjects with prior sorafenib treatment did not appear to be a clinically relevant covariate on nivolumab CL, as the magnitude of this effect was within ± 20% boundary
- The change in CL over time was slower in HCC patients relative to patients with NSCLC and other solid tumors (T50 was 8 months for HCC vs 2 months for other solid tumors) but the steady state CL in HCC was similar to that in other solid tumors
- Effects of other covariates on nivolumab CL and VC:
- CL and VC were higher with higher baseline body weight (approximately 18% for CL and 26% for VC, between the median and 95th percentile values for body weight)
- CL was higher in subjects with lower baseline ALB (approximately 26% increase between the median and 5th percentile values of baseline ALB)
- Baseline GFR, PS, sex, race, and tumor-types Other were not clinically relevant predictors of nivolumab CL (< 20% effect)
- A flat dose regimen of 240 mg Q2W is predicted to provide comparable exposures to those following
- administration of nivolumab 3 mg/kg Q2W for subjects with HCC (< 15% difference in geometric means of simulated Cmin1, Cmax1, Cavg1, Cminss, Cmaxss, and Cavgss).

E-R Efficacy Analysis: OR

- Nivolumab Cavg1 was not a significant predictor of BICR-assessed OR in subjects with HCC who had been previously treated with sorafenib
- Baseline clearance, etiology, EHS/VI, and AFP were not significant predictors of Pr(OR) in subjects with HCC
- The average Pr(OR)s are predicted to be similar for nivolumab 3 mg/kg Q2W and nivolumab 240 mg Q2W dose regimens (0.15 and 0.13, respectively) in the simulated population

E-R Safety Analysis: Grade 3+ DR-AEs

- Risk of Grade 3+ DR-AEs was lower in subjects who had higher nivolumab exposure (Cavg1)
- Etiology (HCV-infected subjects) was a significant predictor of the risk of Grade 3+ DR-AEs in subjects with HCC; HCV-infected subjects experienced an increased risk of Grade 3+ DR-AEs as compared to uninfected subjects
- EHS/VI and AFP were not significant predictors of the risk of Grade 3+ DR-AEs in subjects with HCC
- The hazard of Grade 3+ DR-AEs are predicted to be generally similar for nivolumab 3 mg/kg Q2W and nivolumab 240 mg Q2W dose regimens in the simulated population (difference of HR between regimens predicted to be less than 20%)

FDA Reviewer's Comments: *Please refer to section 2 .*

6 RESULTS OF REVIEWER'S ANALYSIS

6.1 OBJECTIVES

- To determine if there is exposure-response relationship for efficacy in the indication of HCC.
- To determine if there is a need to adjust dose in the proposed indication of HCC

6.2 METHODS

Dataset PKHCC2L5FD.csv was extracted with sponsor's PPK dataset PKHCC2L5.csv to access the 1st dose clearance.

6.2.1 Data and Code

File	Description	Link to EDR
007 mod	Pop-PK 1st cycle model control panel	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Nivolumab_BLA125554S41_YX\Pop-PK\nivo_S41
PKHCC2L5FD.csv	Pop-PK 1ST cycle model dataset	
007sdtab_pirana.csv	Pop-PK 1ST cycle model output	
007.lst	Pop-PK 1ST cycle model list file	
Nivo_S41_ER_2.R	ER-efficacy code	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Nivolumab_BLA125554S41_YX\ER\Nivo_S41_ER
ADEFRESP.csv	ER-efficacy dataset	
adsl.csv	ER-efficacy demographic dataset	

6.2.2 Software

R3.2.2 and NONMEN7.3

6.3 RESULTS

Please refer to *section 2*.

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/s/

YUAN XU
08/23/2017

EDWIN C CHOW
08/24/2017

JEANNE FOURIE ZIRKELBACH
08/24/2017

JIANG LIU
08/24/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s041

OTHER REVIEW(S)

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:	September 11, 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)** Sharon R. Mills, BSN, RN, CCRP Acting Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Lidoshore, PharmD 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 use
Application Type/Number:	BLA 125554
Supplement Number:	S-041
Applicant:	Bristol-Myers Squibb Company

1 INTRODUCTION

On March 24, 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-041 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 patients with hepatocellular carcinoma (HCC) previously treated with sorafenib.

Based on discussion with DOP2 on September 6, 2017, it is our understanding that the proposed labeling changes for S-041 have not been wrapped into the labeling for the approved supplements 034 and 040; however, this is will be addressed once the Applicant submits updated labeling (expected on September 11, 2017). Therefore, this review focuses on making necessary changes to the proposed Medication Guide (MG) to be consistent with the proposed revisions to the Prescribing Information (PI) for supplement S-041, and does not reflect the labeling changes from approved supplements 034 and 040.

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 April 20, 2017, for DMPP and OPDP to review the Applicant's proposed MG for OPDIVO (nivolumab) injection.

2 MATERIAL REVIEWED

- Draft OPDIVO (nivolumab) injection MG received on March 24, 2017, and amended on May 8, 2017, and received by DMPP and OPDP on September 1, 2017.
- Draft OPDIVO (nivolumab) injection Prescribing Information (PI) received on March 22, 2017, and amended on May 8, 2017, and revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 1, 2017.
- Approved OPDIVO (nivolumab) injection labeling dated April 25, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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/s/

RUTH I LIDOSHORE
09/11/2017

NICHOLAS J SENIOR
09/11/2017

SHARON R MILLS
09/11/2017