CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s009

Trade Name:	KEYTRUDA
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp & Dohme Corp.
Approval Date:	August 5, 2016
Indication:	KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of: • patients with unresectable or metastatic melanoma. • patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberattions prior to receiving KEYTRUDA. This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. • patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on the 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

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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 125514/S-9

ACCELERATED APPROVAL

Merck Sharp and Dohme Corp.
Attention: Margaret McCann, D.V.M., Ph.D.
Director, Worldwide Regulatory Affairs
126 East Lincoln Ave.
P.O. Box 2000
RY34-B293
Rahway, NJ 07065

Dear Dr. McCann:

Please refer to your Supplemental Biologics License Application (sBLA), dated February 9, 2016, received February 9, 2016, and your amendments, submitted under section 351 of the Public Health Service Act for Keytruda (pembrolizumab).

This Prior Approval supplemental biologics application adds a new indication for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert and Medication Guide and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry

titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

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

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 June 24, 2016. 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:

3100-1 Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of pembrolizumab over available therapy as determined by an improvement in overall survival in patients with metastatic squamous cell carcinoma of the head and neck.

Final Protocol Submission:	March 2016 (completed)
Trial Completion:	October 2017
Final Report Submission:	April 2018

Submit clinical protocols to your IND 122325 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable because squamous cell carcinoma of the head and neck does not occur in children.

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 package insert (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, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

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:
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
08/05/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KEYTRUDA safely and effectively. See full prescribing information for KEYTRUDA.

KEYTRUDA® (pembrolizumab) for injection, for intravenous use
KEYTRUDA® (pembrolizumab) injection, for intravenous use
Initial U.S. Approval: 2014

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

Indications and Usage (1.1)	12/2015
Indications and Usage (1.2)	10/2015
Indications and Usage (1.3)	08/2016
Dosage and Administration (2.1, 2.3)	10/2015
Dosage and Administration (2.2)	08/2016
Warnings and Precautions (5.1, 5.2, 5.3, 5.5, 5.6, 5.7)	12/2015
Warnings and Precautions (5.4)	08/2016

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

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

- patients with unresectable or metastatic melanoma. (1.1)
- patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.2)
- patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
  This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.3)

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

- Melanoma and NSCLC: 2 mg/kg every 3 weeks. (2.2)
- HNSCC: 200 mg every 3 weeks. (2.2)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

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

- For injection: 50 mg lyophilized powder in single-use vial for reconstitution (3)
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial (3)

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

None. (4)

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

- Immune-mediated Pneumonitis: Withhold for moderate, and permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated Colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated Hepatitis: Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue. (5.3)
- Immune-mediated Endocrinopathies (5.4):
  - Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  - Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or life-threatening hyperthyroidism.
  - Type 1 diabetes mellitus: Monitor for hyperglycemia. Withhold KEYTRUDA in cases of severe hyperglycemia.
- Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis. (5.5)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.7)
- Embryofetal toxicity: KEYTRUDA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.8)

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

Most common adverse reactions (reported in ≥20% of patients) were fatigue, decreased appetite, and dyspnea (6.1).
Other common adverse reactions in patients with:

- melanoma included pruritus, rash, constipation, diarrhea, and nausea. (6.1)
- NSCLC included cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Lactation: Discontinue nursing or discontinue KEYTRUDA. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma *[see Clinical Studies (14.1)]*.

1.2 Non-Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA *[see Clinical Studies (14.2)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.3 Head and Neck Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy *[see Clinical Studies (14.3)]*.

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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for second line or greater treatment of metastatic NSCLC with KEYTRUDA based on the presence of positive PD-L1 expression *[see Clinical Studies (14.2)]*. Information on FDA-approved tests for the detection of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosing

Melanoma and Non-Small Cell Lung Cancer

The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

Head and Neck Cancer

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.3)]*.

2.3 Dose Modifications

Withhold KEYTRUDA for any of the following:

- Grade 2 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 2 or 3 colitis *[see Warnings and Precautions (5.2)]*
- Grade 3 or 4 endocrinopathies *[see Warnings and Precautions (5.4)]*
- Grade 2 nephritis *[see Warnings and Precautions (5.5)]*
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN

- Any other severe or Grade 3 treatment-related adverse reaction *[see Warnings and Precautions (5.6)]*

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA for any of the following:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity *[see Warnings and Precautions (5.1)]*
- Grade 3 or 4 nephritis *[see Warnings and Precautions (5.5)]*
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions *[see Warnings and Precautions (5.7)]*
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- Any severe or Grade 3 treatment-related adverse reaction that recurs *[see Warnings and Precautions (5.6)]*

2.4 Preparation and Administration

Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Reconstituted and Diluted Solutions

The product does not contain a preservative.

Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

Administration

- Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg lyophilized powder in a single-use vial for reconstitution
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, including fatal cases, occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Pneumonitis occurred in 32 (2.0%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3, including Grade 1 (0.8%), Grade 2 (0.8%), and Grade 3 (0.4%) pneumonitis. The median time to development of pneumonitis was 4.3 months (range: 2 days to 19.3 months). The median duration was 2.6 months (range: 2 days to 15.1 months). Twelve (38%) of the 32 patients received corticosteroids, with 9 of the 12 receiving high-dose systemic corticosteroids for a median duration of 8 days (range: 1 day to 1.1 months) followed by a corticosteroid taper. Pneumonitis led to discontinuation of KEYTRUDA in 9 (0.6%) patients. Pneumonitis completely resolved in 21 (66%) of the 32 patients.

NSCLC

Pneumonitis occurred in 19 (3.5%) of 550 patients with NSCLC, including Grade 2 (1.1%), Grade 3 (1.3%), Grade 4 (0.4%), or Grade 5 (0.2%) pneumonitis in patients receiving KEYTRUDA in Trial 3. The median time to development of pneumonitis was 1.7 months (range: 4 days to 12.9 months). In patients receiving KEYTRUDA 10 mg/kg every 14 days, the median time to development of pneumonitis was shorter (1.5 months) compared with patients receiving 10 mg/kg every 21 days (3.5 months). Sixteen of the 19 patients (84%) received corticosteroids, with 14 of the 19 (74%) requiring high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day). The median starting dose of high-dose corticosteroid treatment for these fourteen patients was 60 mg/day with a median duration of treatment of 8 days (range: 1 day to 4.2 months). The median duration of pneumonitis was 1.2 months (range: 5 days to 12.4 months). Pneumonitis occurred more frequently in patients with a history of asthma/chronic obstructive pulmonary disease (5.4%) than in patients without a history of these diseases (3.1%). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.0%) than in patients who did not receive prior thoracic radiation (2.6%). Pneumonitis led to discontinuation of KEYTRUDA in 12 (2.2%) patients. Pneumonitis completely resolved in 9 patients.

Pneumonitis was reported as ongoing in 9 patients and one patient with ongoing pneumonitis died within 30 days of the last dose of KEYTRUDA.

5.2 Immune-Mediated Colitis

Immune-mediated colitis occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Colitis occurred in 31 (2.0%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3, including Grade 2 (0.5%), Grade 3 (1.1%), and Grade 4 (0.1%) colitis. The median time to onset of colitis was 3.4 months (range: 10 days to 9.7 months). The median duration of colitis was 1.4 months (range: 1 day to 7.2 months). Twenty-one (68%) of the 31 patients received corticosteroids, all of whom required high-dose systemic corticosteroids for a median duration of 6 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of KEYTRUDA in 14 (0.9%) patients. Colitis resolved in 27 (87%) of the 31 patients.

NSCLC

Colitis occurred in 4 (0.7%) of 550 patients, including Grade 2 (0.2%) or Grade 3 (0.4%) colitis in patients receiving KEYTRUDA in Trial 3. The median time to onset of colitis was 1.6 months (range: 28 days to 2.2 months) and the median duration was 16 days (range: 7 days to 1.3 months). Two patients were started on high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) and two patients were started on low dose corticosteroids. One patient (0.2%) discontinued KEYTRUDA due to colitis. Three patients with colitis experienced complete resolution of the event.

5.3 Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in patients receiving KEYTRUDA. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Hepatitis occurred in 16 (1.0%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3, including Grade 2 (0.1%), Grade 3 (0.7%), and Grade 4 (0.1%) hepatitis. The time to onset was 26 days (range: 8 days to 21.4 months). The median duration was 1.2 months (range: 8 days to 4.7 months). Eleven (69%) of the 16 patients received corticosteroids, with 10 of the 11 receiving high-dose systemic corticosteroids for a median duration of 5 days (range: 1 to 14 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of KEYTRUDA in 6 (0.4%) patients. Hepatitis resolved in 14 (88%) of the 16 patients.

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

Hypophysitis occurred in patients receiving KEYTRUDA. Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis and withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Hypophysitis occurred in 13 (0.8%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3 including Grade 2 (0.3%), Grade 3 (0.3%), and Grade 4 (0.1%) hypophysitis. The time to onset was 3.3 months

(range: 1 day to 7.2 months). The median duration was 2.7 months (range: 12 days to 12.7 months). Twelve (92%) of the 13 patients received corticosteroids, with 4 of the 12 patients receiving high-dose systemic corticosteroids. Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.3%) patients. Hypophysitis resolved in 7 (54%) of the 13 patients.

NSCLC
In Trial 3, hypophysitis occurred in 1 (0.2%) of 550 patients, which was Grade 3 in severity. The time to onset was 3.7 months. The patient was treated with systemic corticosteroids and physiologic hormone replacement therapy. The patient did not discontinue KEYTRUDA due to hypophysitis.

Thyroid Disorders
Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma
Hyperthyroidism occurred in 51 (3.3%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, or 3, including Grade 2 (0.6%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months). The median duration was 1.7 months (range: 1 day to 12.8 months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (0.1%) patients. Hyperthyroidism resolved in 36 (71%) of the 51 patients.

Hypothyroidism occurred in 127 (8.1%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3 including Grade 3 (0.1%) hypothyroidism. The median time to onset of hypothyroidism was 3.3 months (range: 5 days to 18.9 months). The median duration was 5.4 months (range: 6 days to 24.3 months). No patients discontinued KEYTRUDA due to hypothyroidism. Hypothyroidism resolved in 24 (19%) of the 127 patients.

NSCLC
Hyperthyroidism occurred in 10 (1.8%) of 550 patients receiving KEYTRUDA in Trial 3, including Grade 2 (0.7%) or Grade 3 (0.3%) hyperthyroidism. The median time to onset was 1.8 months (range: 2 days to 3.4 months), and the median duration was 4.5 months (range: 4 weeks to 7.5 months). No patients discontinued KEYTRUDA due to hyperthyroidism.

Hypothyroidism occurred in 38 (6.9%) of 550 patients receiving KEYTRUDA in Trial 3, including Grade 2 (5.5%) or Grade 3 (0.2%) hypothyroidism. The median time to onset was 4.2 months (range: 20 days to 11.2 months), and the median duration was 5.8 months (range: 11 days to 22.8 months). No patients discontinued KEYTRUDA due to hypothyroidism.

HNSCC
New or worsening hypothyroidism occurred in 28 (14.6%) of 192 patients receiving KEYTRUDA in Trial 4, including Grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of hypothyroidism.

Type 1 Diabetes mellitus
Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 3 (0.1%) of 2117 patients with melanoma or NSCLC receiving KEYTRUDA in Trials 1, 2, and 3. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.5 Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis occurred in patients receiving KEYTRUDA. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

Nephritis occurred in 7 (0.4%) of 1567 patients receiving KEYTRUDA in Trials 1, 2, and 3, including Grade 2 (0.2%), Grade 3 (0.2%), and Grade 4 (0.1%) nephritis. The median time to onset of nephritis was 5.1 months (range: 12 days to 12.8 months). The median duration was 1.1 months (range: 3 days to 3.3 months). Six (86%) of the 7 patients received corticosteroids, with 5 of the 6 receiving high-dose systemic corticosteroids for a median duration of 15 days (range: 3 days to 1.6 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 2 (0.1%) patients. Nephritis resolved in 4 (57%) of the 7 patients.

5.6 Other Immune-Mediated Adverse Reactions

Other clinically important immune-mediated adverse reactions can occur.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].*

Melanoma

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 1567 patients with melanoma treated with KEYTRUDA in Trials 1, 2, and 3: arthritis (1.6%), exfoliative dermatitis, bullous pemphigoid, uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma.

NSCLC

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of 550 patients with NSCLC treated with KEYTRUDA in Trial 3: rash, vasculitis, hemolytic anemia, serum sickness, and myasthenia gravis.

5.7 Infusion-Related Reactions

Severe and life-threatening infusion-related reactions have been reported in 3 (0.1%) of 2117 patients receiving KEYTRUDA in Trials 1, 2, and 3. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.3)]*.

5.8 Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA *[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)]*.
- Other immune-mediated adverse reactions *[see Warnings and Precautions (5.6)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.7)].*

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 described in the WARNINGS AND PRECAUTIONS section reflect exposure to KEYTRUDA in 2117 patients in two randomized, open-label, active-controlled clinical trials, which enrolled 912 patients with unresectable or metastatic melanoma and one single-arm trial which enrolled 655 patients with metastatic melanoma and 550 patients with NSCLC. In addition, these data reflect exposure to KEYTRUDA in a non-randomized, open-label, multi-cohort trial which enrolled 192 patients with HNSCC. Across all studies, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among these 2117, 43% of the patients were exposed for 6 months or more and 10% of the patients were exposed for 12 months or more.

The data described below were obtained in two randomized, open-label, active-controlled clinical trials which enrolled 912 patients with unresectable or metastatic melanoma and two non-randomized, open-label, multi-cohort trials which enrolled 550 patients with NSCLC and 192 patients with HNSCC. In these trials, KEYTRUDA was administered at 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks.

Melanoma

Ipilimumab-Naive Melanoma (Trial 1)

The safety of KEYTRUDA for the treatment of patients with unresectable or metastatic melanoma who had not received prior ipilimumab and who had received no more than one prior systemic therapy was investigated in Trial 1. Trial 1 was a multicenter, open-label, active-controlled trial where patients were randomized (1:1:1) and received KEYTRUDA 10 mg/kg every 2 weeks (n=278) or KEYTRUDA 10 mg/kg every 3 weeks (n=277) until disease progression or unacceptable toxicity or ipilimumab 3 mg/kg every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity (n=256) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA 10 mg/kg every 2 or 3 weeks, respectively, for ≥6 months. No patients in either arm received treatment for more than one year.

The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 32% had an elevated lactate dehydrogenase (LDH) value at baseline, 65% had M1c stage

disease, 9% with history of brain metastasis, and approximately 36% had been previously treated with one or more lines of systemic therapy which included a BRAF inhibitor (15%), chemotherapy (13%), and immunotherapy (6%).

In Trial 1, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both KEYTRUDA arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions (reported in at least 20% of patients) were fatigue and diarrhea. Table 1 and Table 2 summarize the incidence of selected adverse reactions and laboratory abnormalities, respectively, that occurred in at least 10% of patients receiving KEYTRUDA.

Table 1: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA (Trial 1)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
Adverse Reaction	**All Grades† (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	28	0.9	28	3.1
Skin and Subcutaneous Tissue Disorders				
Rash‡	24	0.2	23	1.2
Vitiligo§	13	0	2	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	0.4	10	1.2
Back pain	12	0.9	7	0.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	7	0.4
Dyspnea	11	0.9	7	0.8
Metabolism and Nutrition Disorders				
Decreased appetite	16	0.5	14	0.8
Nervous System Disorders				
Headache	14	0.2	14	0.8

* Adverse reactions occurring at same or higher incidence than in the ipilimumab arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and exfoliative rash.
§ Includes skin hypopigmentation

Other clinically important adverse reactions occurring in ≥10% of patients receiving KEYTRUDA were diarrhea (26%), nausea (21%), and pruritus (17%).

Table 2: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA (Trial 1)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks		Ipilimumab	
Laboratory Test†	**All Grades‡ %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	45	4.2	45	3.8
Hypertriglyceridemia	43	2.6	31	1.1
Hyponatremia	28	4.6	26	7
Increased AST	27	2.6	25	2.5
Hypercholesterolemia	20	1.2	13	0
Hematology				
Anemia	35	3.8	33	4.0
Lymphopenia	33	7	25	6

* Laboratory abnormalities occurring at same or higher incidence than in ipilimumab arm

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: KEYTRUDA n=429 and ipilimumab n=183; hypercholesterolemia: KEYTRUDA n=484 and ipilimumab n=205).

‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were increased hypoalbuminemia (27% all Grades; 2.4% Grades 3-4), increased ALT (23% all Grades; 3.1% Grades 3-4), and increased alkaline phosphatase (21% all Grades, 2.0% Grades 3-4).

Ipilimumab-Refractory Melanoma (Trial 2)

The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was evaluated in Trial 2. Trial 2 was a multicenter, partially blinded (KEYTRUDA dose), randomized (1:1:1), active-controlled trial in which 528 patients received KEYTRUDA 2 mg/kg (n=178) or 10 mg/kg (n=179) every 3 weeks or investigator's choice of chemotherapy (n=171), consisting of dacarbazine (26%), temozolomide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%) *[see Clinical Studies (14.1)]*. The trial excluded patients with autoimmune disease, severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 16.6 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 16.8 months). The data described below reflect exposure to KEYTRUDA 2 mg/kg in 36% of patients exposed to KEYTRUDA for ≥6 months and in 4% of patients exposed for ≥12 months. In the KEYTRUDA 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA for ≥6 months and 6% of patients were exposed to KEYTRUDA for ≥12 months.

The study population characteristics were: median age of 62 years (range: 15 to 89 years), 61% male, 98% White, 41% with an elevated LDH value at baseline, 83% with M1c stage disease, 73% received two or more prior therapies for advanced or metastatic disease (100% received ipilimumab and 25% a BRAF inhibitor), and 15% with history of brain metastasis.

In Trial 2, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving KEYTRUDA; the

most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). The most common adverse reactions (reported in at least 20% of patients) of KEYTRUDA were fatigue, pruritus, rash, constipation, nausea, diarrhea, and decreased appetite.

Table 3 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 3: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA (Trial 2)

	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks n=357		Chemotherapy† n=171	
Adverse Reaction	**All Grades‡ (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Pyrexia	14	0.3	9	0.6
Asthenia	10	2.0	9	1.8
Skin and Subcutaneous Tissue Disorders				
Pruritus	28	0	8	0
Rash§	24	0.6	8	0
Gastrointestinal Disorders				
Constipation	22	0.3	20	2.3
Diarrhea	20	0.8	20	2.3
Abdominal pain	13	1.7	8	1.2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	18	0	16	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	14	0.6	10	1.2

* Adverse reactions occurring at same or higher incidence than in chemotherapy arm
† Chemotherapy : dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin
‡ Graded per NCI CTCAE v4.0
§ Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (43%), nausea (22%), decreased appetite (20%), vomiting (13%), and peripheral neuropathy (1.7%).

Table 4: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA (Trial 2)

	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks		Chemotherapy	
Laboratory Test†	**All Grades‡ %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	49	6	44	6
Hypoalbuminemia	37	1.9	33	0.6
Hyponatremia	37	7	24	3.8
Hypertriglyceridemia	33	0	32	0.9
Increased Alkaline Phosphatase	26	3.1	18	1.9
Increased AST	24	2.2	16	0.6
Bicarbonate Decreased	22	0.4	13	0
Hypocalcemia	21	0.3	18	1.9
Increased ALT	21	1.8	16	0.6

* Laboratory abnormalities occurring at same or higher incidence than in chemotherapy arm.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 320 to 325 patients) and chemotherapy (range: 154 to 161 patients); hypertriglyceridemia: KEYTRUDA n=247 and chemotherapy n=116; bicarbonate decreased: KEYTRUDA n=263 and chemotherapy n=123).
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were anemia (44% all Grades; 10% Grades 3-4) and lymphopenia (40% all Grades; 9% Grades 3-4).

NSCLC
Among the 550 patients with metastatic NSCLC enrolled in Trial 3, the median duration of exposure to KEYTRUDA was 2.8 months (range: 1 day to 25.6 months). Patients with NSCLC and autoimmune disease, a medical condition that required immunosuppression, or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible for Trial 3. The median age of patients was 64 years (range: 28 to 93), 47% were age 65 years or older, 53% were male, 83% were White, and 67% received two or more prior systemic treatments. Disease characteristics were Stage III (4%), Stage IV (96%), and brain metastases (11%). Baseline ECOG performance status (PS) was 0 (35%) or 1 (65%).

KEYTRUDA was discontinued due to adverse reactions in 14% of patients. Serious adverse reactions occurred in 38% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pleural effusion, pneumonia, dyspnea, pulmonary embolism, and pneumonitis. The incidence of adverse reactions, including serious adverse reactions, was similar between the two 10 mg/kg dosing schedules; therefore, these data were pooled. The majority of patients treated with KEYTRUDA 2 mg/kg every three weeks had shorter follow-up compared with patients treated with the 10 mg/kg schedules; therefore, comparisons of adverse reactions between doses were not appropriate.

Table 5 summarizes adverse reactions that occurred in at least 10% of patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, decreased appetite, dyspnea, and cough.

Table 5: Adverse Reactions in ≥10% of Patients with NSCLC (Trial 3)

	KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=550	
Adverse Reaction	All Grades (%)	Grade 3* (%)
General Disorders and Administration Site Conditions		
Fatigue†	44	4
Pyrexia	12	1
Peripheral Edema	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	25	1
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	23	4
Cough‡	29	<1
Gastrointestinal Disorders		
Nausea	18	1
Diarrhea	15	1
Constipation	15	<1
Vomiting	12	1
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	15	1
Back pain	10	2
Blood and Lymphatic System Disorders		
Anemia	12	2
Skin and Subcutaneous Tissue Disorders		
Pruritus	12	0
Rash§	18	<1

* Of the ≥10% adverse reactions, none was reported as Grade 4 or 5.
† Includes the terms fatigue and asthenia
‡ Includes the terms cough, productive cough and hemoptysis
§ Includes the terms dermatitis, dermatitis acneiform, erythema multiforme, drug eruption, rash, rash generalized, rash pruritic, rash macular/maculo-papular, papular

Table 6: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with NSCLC (Trial 3)

	KEYTRUDA n=550	
Laboratory Test	**All Grades %**	**Grades 3-4 %**
Chemistry		
Hyperglycemia	48	3*
Hyponatremia	38	6
Hypoalbuminemia	32	1
Increased alkaline phosphatase	26	1
Hypertriglyceridemia	23	0
Increased aspartate aminotransferase	20	1
Hypercholesterolemia	20	1*
Hematology		
Anemia	36	2*

* Grade 4 abnormalities in this table limited to hyperglycemia (n=4), hypercholesterolemia (n=3), and anemia (n=1).

HNSCC
Among the 192 patients with HNSCC enrolled in Trial 4, the median duration of exposure to KEYTRUDA was 3.3 months (range: 1 day to 27.9 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for Trial 4. The median age of patients was 60 years (range: 20 to 84), 35% were age 65 years or older, 83% were male, 77% were White, 15% were Asian, and 5% were Black. Sixty-one percent of patients had two or more lines of therapy in the recurrent or metastatic setting, and 95% had prior radiation therapy. Baseline ECOG PS was 0 (30%) or 1 (70%) and 86% had M1 disease.

KEYTRUDA was discontinued due to adverse reactions in 17% of patients. Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); these data were pooled. The most common adverse reactions (occurring in ≥20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism *[see Warnings and Precautions (5.4)]*.

6.2 Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every two or three weeks, 20 (1.7%) of 1149 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies. Among the 20 patients who tested positive for treatment emergent anti-pembrolizumab antibodies, only 4 patients were tested for neutralizing antibodies and one was positive. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding 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 KEYTRUDA with the incidences of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue *[see Data]*. Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. There are no available human data informing the risk of embryo-fetal toxicity. Apprise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development, but an assessment of the effects on reproduction was provided. 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 result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

8.2 Lactation

Risk Summary

It is not known whether KEYTRUDA is excreted in human milk. No studies have been conducted to assess the impact of KEYTRUDA on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for at least 4 months following the final dose.

8.4 Pediatric Use

Safety and effectiveness of KEYTRUDA have not been established in pediatric patients.

8.5 Geriatric Use

Of 2309 patients treated with KEYTRUDA in clinical studies, 43% were 65 years and over. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

10 OVERDOSAGE

There is no information on overdosage with KEYTRUDA.

11 DESCRIPTION

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

KEYTRUDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

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. Pembrolizumab is a 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.

12.3 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 2195 patients with various cancers who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on population pharmacokinetic analyses in patients with solid tumors, the geometric mean [% coefficient of variation (CV%)] for clearance (CL), steady-state volume of distribution, and terminal half-life were 202 mL/day (38%), 7.38 L (19%) and 27 days (38%), respectively.

Steady-state concentrations of pembrolizumab were reached by 19 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Specific Populations: The following factors had no clinically important effect on the CL of pembrolizumab: age (range: 15 to 94 years), sex, race (94% White), renal impairment (eGFR greater than or equal to 15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or tumor burden. There is insufficient information to determine whether there are clinically important differences in the CL of pembrolizumab in patients with moderate or severe hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-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 resulted in an increased 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 (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

14 CLINICAL STUDIES

14.1 Melanoma

Ipilimumab-Naive Melanoma (Trial 1)

The safety and efficacy of KEYTRUDA were evaluated in Trial 1, a randomized (1:1:1), open-label, multicenter, active-controlled trial. Patients were randomized to receive KEYTRUDA at a dose of 10 mg/kg every 2 weeks or 10mg/kg every 3 weeks as an intravenous infusion until disease progression

or unacceptable toxicity or to ipilimumab 3 mg/kg every 3 weeks as an intravenous infusion for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma with progression of disease; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors [RECIST v1.1]). Additional efficacy outcome measures were overall response rate (ORR) and response duration.

A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease , 69% ECOG PS of 0, 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor.

The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab (Table 7 and Figure 1).

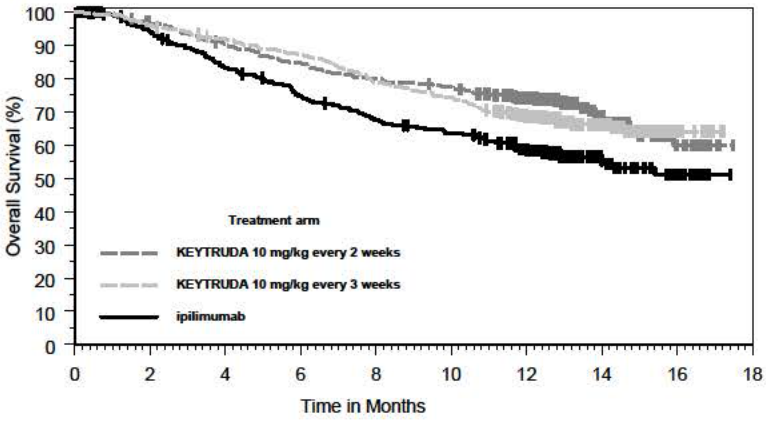
Table 7: Efficacy Results in Trial 1

	KEYTRUDA 10 mg/kg every 3 weeks n=277	**KEYTRUDA 10 mg/kg every 2 weeks n=279**	**Ipilimumab 3 mg/kg every 3 weeks n=278**
OS			
Deaths (%)	92 (33%)	85 (30%)	112 (40%)
Hazard ratio* (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value (stratified log-rank)	0.004	<0.001	---
PFS by BICR			
Events (%)	157 (57%)	157 (56%)	188 (68%)
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Hazard ratio* (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Best overall response by BICR			
ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response %	6%	5%	1%
Partial response %	27%	29%	10%

* Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model

Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to KEYTRUDA 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months.

Figure 1: Kaplan-Meier Curve for Overall Survival in Trial 1



Number at Risk										
KEYTRUDA 10 mg/kg every 2 weeks:	279	266	248	233	219	212	177	67	19	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	266	251	238	215	202	158	71	18	0
ipilimumab:	278	242	212	188	169	157	117	51	17	0

Ipilimumab-Refractory Melanoma (Trial 2)

The safety and efficacy of KEYTRUDA were evaluated in Trial 2, a multicenter, randomized (1:1:1), active-controlled trial. Patients were randomized to receive one of two doses of KEYTRUDA in a blinded fashion or investigator's choice chemotherapy. The treatment arms consisted of KEYTRUDA 2 mg/kg or 10 mg/kg intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens: dacarbazine 1000 mg/m^2 intravenously every 3 weeks (26%), temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 plus paclitaxel 175 mg/m^2 every 3 weeks (25%), paclitaxel 175 mg/m^2 intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 intravenously every 3 weeks (8%). Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. Patients received KEYTRUDA until unacceptable toxicity; disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumor status was performed at 12 weeks after randomization, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced progression of disease were offered KEYTRUDA. The major efficacy outcomes were progression-free survival (PFS) as assessed by BICR per RECIST v1.1 and overall survival (OS). Additional efficacy outcome measures were confirmed overall response rate (ORR) as assessed by BICR per RECIST v1.1 and duration of response.

The treatment arms consisted of KEYTRUDA 2 mg/kg (n=180) or 10 mg/kg (n=181) every 3 weeks or investigator's choice chemotherapy (n=179). Among the 540 randomized patients, the median age was 62 years (range: 15 to 89 years), with 43% age 65 or older; 61% male; 98% White; and ECOG performance score was 0 (55%) and 1 (45%). Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease.

The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm (Table 8). There was no statistically significant difference

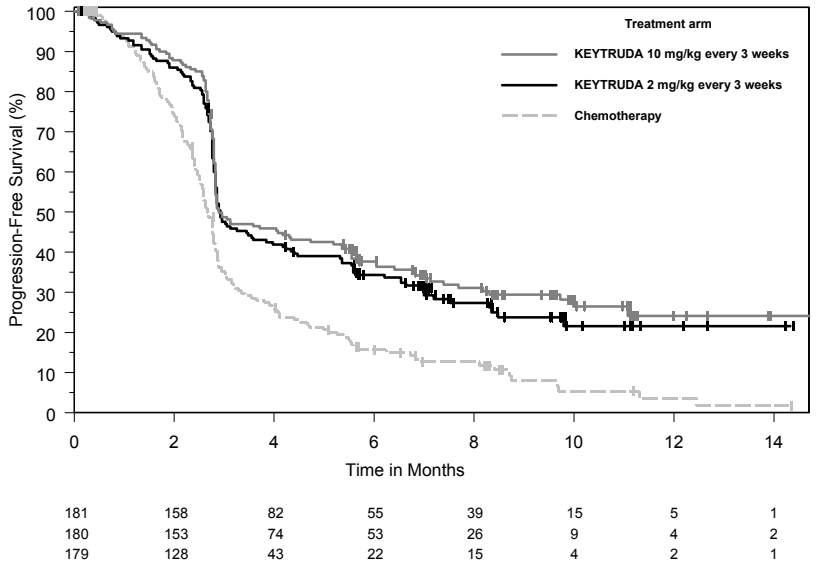
between KEYTRUDA 2 mg/kg and chemotherapy or between KEYTRUDA 10 mg/kg and chemotherapy in the interim OS analysis with 220 deaths (59% of required events for the final analysis).

Table 8: Efficacy Results in Trial 2

	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
Progression-Free Survival			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
P Value (stratified log-rank)	<0.001	<0.001	---
Hazard ratio* (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
Objective Response Rate			
ORR, n% (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response %	2%	3%	0%
Partial response %	19%	23%	4%

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

Figure 2: Kaplan-Meier Curve for Progression-Free Survival in Trial 2



Among the 38 patients randomized to KEYTRUDA 2 mg/kg with an objective response, response durations ranged from 1.3+ to 11.5+ months. Among the 46 patients randomized to KEYTRUDA 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months.

14.2 Non-Small Cell Lung Cancer

The efficacy of KEYTRUDA was investigated in a sub-group of a cohort of 280 patients enrolled in a multicenter, open-label multi-cohort, activity-estimating study (Trial 3). The cohort consisted of patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations and any evidence of PD-L1 expression by a clinical trial immunohistochemistry assay. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

A prospectively defined sub-group was retrospectively analyzed using an analytically validated test for PD-L1 expression tumor proportion score (TPS). This retrospectively identified sub-group of 61 patients accounts for 22% of the 280 patients in the cohort. Patients included in this sub-group had a PD-L1 expression TPS of greater than or equal to 50% tumor cells as determined by the PD-L1 IHC 22C3 pharmDx Kit. Patients received KEYTRUDA 10 mg/kg every 2 (n=27) or 3 (n=34) weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1 as assessed by BICR and duration of response.

Among the 61 patients with a TPS greater than or equal to 50%, the baseline characteristics were: median age 60 years (34% age 65 or older); 61% male; 79% White; and 34% and 64% with an ECOG PS 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (75%); M1 (98%); brain metastases (11%); one (26%), two (30%), or three or more (44%) prior therapies; and the incidence of genomic aberrations was EGFR (10%) or ALK (0%).

Efficacy results are summarized in Table 9. The ORR and duration of response were similar regardless of schedule (every 2 weeks or every 3 weeks) and thus the data below are pooled.

Table 9: Efficacy Results

Endpoint	n=61
Overall Response Rate	
ORR %, (95% CI)	41% (29, 54)
Complete Response	0%
Partial Response	41%

Among the 25 responding patients, 21 (84%) patients had ongoing responses at the final analysis of ORR; 11 (44%) patients had ongoing responses of 6 months or longer.

In a separate subgroup of 25 patients with limited follow-up with PD-L1 expression TPS greater than or equal to 50% receiving KEYTRUDA at a dose of 2 mg/kg every 3 weeks in Trial 3, activity was also observed.

14.3 Head and Neck Cancer

The efficacy of KEYTRUDA was investigated in Trial 4, a multicenter, nonrandomized, open-label, multi-cohort study that enrolled 174 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy. Patients with active autoimmune disease, a medical condition that required immunosuppression, evidence of interstitial lung disease, or ECOG PS ≥ 2 were ineligible.

Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=53) or 200 mg every 3 weeks (n=121) until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 174 patients, the baseline characteristics were median age 60 years (32% age 65 or older); 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumors;

63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; and the median number of prior lines of therapy administered for the treatment of HNSCC was 2.

The ORR was 16% (95% CI: 11, 22) with a complete response rate of 5%. The median follow-up time was 8.9 months. Among the 28 responding patients, the median duration of response had not been reached (range 2.4+ to 27.7+ months), with 23 patients having responses of 6 months or longer. The ORR and duration of response were similar irrespective of dosage regimen (10 mg/kg every 2 weeks or 200 mg every 3 weeks) or HPV status.

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA for injection (lyophilized powder): carton containing one 50 mg single-use vial (NDC 0006-3029-02).

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

KEYTRUDA injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-use vial (NDC 0006-3026-02)

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not 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 interruption or discontinuation of KEYTRUDA, including:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for 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, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
  - Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.
  - Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.4)]*.
  - Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes *[see Warnings and Precautions (5.4)].*
  - Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*.
- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7)]*.
- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.3, 5.4, 5.5)]*.
- Advise women that KEYTRUDA can cause fetal harm. Instruct women of reproductive potential to use highly effective contraception during and for 4 months after the last dose of KEYTRUDA *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.3)]*.
- Advise nursing mothers not to breastfeed while taking KEYTRUDA and for 4 months after the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
U.S. License No. 0002

For KEYTRUDA for injection, at:
Schering-Plough (Brinny) Co.,
County Cork, Ireland

For KEYTRUDA injection, at:
MSD Ireland (Carlow)
County Carlow, Ireland

For patent information: www.merck.com/product/patent/home.html

uspi-mk3475-iv-1608r005

MEDICATION GUIDE

KEYTRUDA® (key-true-duh)
(pembrolizumab)
for injection

KEYTRUDA® (key-true-duh)
(pembrolizumab)
injection

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

KEYTRUDA is a medicine that may treat your melanoma, lung cancer, or head and neck cancer by working with your immune system. KEYTRUDA can cause your immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

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

Lung problems (pneumonitis). Symptoms of pneumonitis may include:
- shortness of breath
- chest pain
- new or worse cough

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:
- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- 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
- nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine
- feeling less hungry than usual
- bleeding or bruising more easily than normal

Hormone gland problems (especially the thyroid, pituitary, adrenal glands, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:
- rapid heart beat
- weight loss or weight gain
- increased sweating
- feeling more hungry or thirsty
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- muscle aches
- dizziness or fainting
- headaches that will not go away or unusual headache

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:
- change in the amount or color of your urine.

Problems in other organs. Signs of these problems may include:
- rash
- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness
- low red blood cells (anemia)

Infusion (IV) reactions, that can sometimes be severe and life-threatening. Signs and symptoms of infusion reactions may include:

- chills or shaking
- shortness of breath or wheezing
- itching or rash
- flushing
- dizziness
- fever
- feeling like passing out

Getting medical treatment right away may help keep these problems from becoming more serious.
Your doctor will check you for these problems during treatment with KEYTRUDA. Your doctor may treat you with corticosteroid or hormone replacement medicines. Your doctor may also need to delay or completely stop treatment with KEYTRUDA, if you have severe side effects.

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat:

- a kind of skin cancer called melanoma. KEYTRUDA may be used when your melanoma has spread or cannot be removed by surgery (advanced melanoma).
- a kind of lung cancer called non-small cell lung cancer (NSCLC). KEYTRUDA may be used when your lung cancer:
  - has spread **and,**
  - tests positive for "PD-L1" **and,**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working **and,**
  - if your tumor has an abnormal "EGFR" or "ALK" gene, and you have also tried an EGFR or ALK inhibitor medicine.
- a kind of cancer called head and neck squamous cell cancer (HNSCC). KEYTRUDA may be used when your HNSCC:
  - has returned or spread **and**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

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

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor 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 problems
- are pregnant or plan to become pregnant
  - KEYTRUDA 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 4 months after the final dose of KEYTRUDA. Talk to your doctor about birth control methods that you can use during this time.
  - Tell your doctor right away if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed.
  - It is not known if KEYTRUDA passes into your breast milk.
  - Do not breastfeed during treatment with KEYTRUDA and for 4 months after your final dose of KEYTRUDA.

Tell your doctor 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 doctor and pharmacist when you get a new medicine.

How will I receive KEYTRUDA?

- Your doctor will give you KEYTRUDA into your vein through an intravenous (IV) line over 30 minutes.
- KEYTRUDA is usually given every 3 weeks.
- Your doctor will decide how many treatments you need.
- Your doctor will do blood tests to check you for side effects.
- If you miss any appointments, call your doctor as soon as possible to reschedule your appointment.

What are the possible side effects of KEYTRUDA?

KEYTRUDA can cause serious side effects. See "What is the most important information I should know about KEYTRUDA?"

Common side effects of KEYTRUDA include:

- in people who receive KEYTRUDA: feeling tired, decreased appetite, and shortness of breath
- in people with melanoma:
  - o itching
  - o rash
  - o constipation
  - o diarrhea
  - o nausea
- in people with NSCLC:
  - o cough

These are not all the possible side effects of KEYTRUDA. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you or that does not go away.

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 KEYTRUDA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about KEYTRUDA, talk with your doctor. You can ask your doctor or nurse for information about KEYTRUDA that is written for healthcare professionals. For more information, go to www.keytruda.com.

What are the ingredients in KEYTRUDA?

Active ingredient: pembrolizumab

Inactive ingredients:

KEYTRUDA for injection: L-histidine, polysorbate 80, and sucrose. May contain hydrochloric acid/sodium hydroxide.

KEYTRUDA injection: L-histidine, polysorbate 80, sucrose, and Water for Injection, USP.

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Whitehouse Station, NJ 08889, USA	For KEYTRUDA for injection, at: Schering-Plough (Brinny) Co., County Cork, Ireland For KEYTRUDA injection, at: MSD Ireland (Carlow), County Carlow, Ireland U.S. License No. 0002 For patent information: www.merck.com/product/patent/home.html usmg-mk3475-iv-1608r005

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: August 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s009

SUMMARY REVIEW

Division Director Summary Review

Date	(electronic stamp)
From	Patricia Keegan
Subject	Division Director Summary Review
BLA Supplement #	STN BL 125514/S-009
Applicant Name	Merck, Sharp, and Dohme, Corp.
Date of Submission	February 9, 2016
PDUFA Goal Date	August 9, 2016
Proprietary Name / Established (USAN) Name	KEYTRUDA/ pembrolizumab
Dosage Forms / Strength	• For injection/50 mg lyophilized powder in single-use vial for reconstitution • Injection/ 100 mg/4 mL (25 mg/mL) solution in a single-use vial
Proposed Indication(s)	KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Sharon Sickafuse
Medical Officer Review	Erin Larkin
Statistical Review	Weishi Yuan
CMC Review/OBP Review	Mark Paciga
Clinical Pharmacology Review	Sriram Subramaniam
OPDP Review	Nicholas Senior
Patient Labeling Team Review	Sharon R. Mills

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion

Division Director Summary Review

1. Introduction

Pembrolizumab is a 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. Pembrolizumab is approved for the treatment of patients with unresectable or metastatic melanoma and, under the provisions of accelerated approval, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.

This efficacy supplement is supported by the demonstration of durable objective tumor responses observed in a defined subpopulation, as agreed upon with FDA, who were enrolled in a single-arm, open-label study, KEYNOTE-012. KEYNOTE-012 is a multicenter, non-randomized, open-label, activity-estimating study, which was amended on multiple occasions to include new disease-specific cohorts or new dosage regimens of pembrolizumab. The subpopulation of that study supporting this efficacy supplement consists of 174 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy. The study excluded patients with active autoimmune disease, a medical condition that required immunosuppression, evidence of interstitial lung disease, or ECOG PS $\geq$ 2.

Patients in this subpopulation received pembrolizumab either at 10 mg/kg every 2 weeks (n=53) or 200 mg every 3 weeks (n=121) as a 30-minute intravenous infusion until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 8 weeks. The major efficacy endpoints, as agreed upon with FDA, to support this efficacy supplement were overall response rate (ORR) according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

In this subpopulation, the baseline characteristics were a median age 60 years (32% age 65 or older); 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumors; 63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; 71% had PD-L1 positive disease as determined by an investigational assay, and the median number of prior lines of therapy administered for the treatment of HNSCC was

2. The ORR was 16% (95% CI: 11, 22) with a complete response rate of 5%. The median follow-up time was 8.9 months. Among the 28 responding patients, duration of response ranged from 2.4+ to 27.7+ months), with 23 patients having responses durable for ≥ 6 months. The ORR and duration of response appeared similar across subgroups defined by age, gender, race (White vs. non-White), dosage regimen (10 mg/kg every 2 weeks or 200 mg every 3 weeks), HPV status, or PD-L1 tumor status. The higher response rate in the subgroup who was cetuximab naïve (as compared to those who had received prior cetixumab) may be spurious, given the substantially overlapping confidence intervals around the observed point estimates.

The efficacy results in the subset of patients enrolled in KEYNOTE-012 were supported by an interim analysis of efficacy in the first 50 patients enrolled in Study KEYNOTE-055, which enrolled a similar patient population and administered pembrolizumab at a dose of 200 mg every three weeks, as in KEYNOTE-012 Cohort B2. In this interim analysis of KEYNOTE-ORR, the confirmed ORR as assessed by independent central radiology review according to RECIST 1.1 was 18% (95% CI: 8.6, 31.4). The median duration of response was 6.9 months; with responses ranging from 3.0 months to 8.3+ months.

The safety database was limited by the small sample size, differences in dosage regimens used, and lack of an internal control providing comparison over background rates of adverse events in this patient population. In this context, the apparent increase in the incidence of facial edema and new or worsening hypothyroidism over that observed in other approved indications is challenging as the background rates of these events may be higher in this indication due to the underlying cancer and the prior treatment modalities (surgical resection with nodal dissection and irradiation to the head and neck).

The major considerations in this supplement were whether the clinical pharmacology data were sufficient to support the proposed dosage regimen of pembrolizumab 200 mg intravenously every three weeks, given the limited clinical experience in KEYNOTE-012, and whether the results presented in the supplement demonstrated a substantial improvement over the available therapies of cetuximab and methotrexate. These issues are further discussed in Sections 4 and 13 of this summary review. For further information refer to the reviews by Drs. Larkin, Yuan, Subramanian, and Paciga.

2. Background

Proposed Indication and Available Therapy
Recurrent, unresectable locally advanced or metastatic head and neck squamous cell carcinoma (HNSCC) is a serious and life-threatening disease.Squamous cell cancers of the head and neck cancers, arising in the oral cavity, larynx, and pharynx, are hetergeneous tumors with variable prognosis depending on the site of origin. Risk factors include tobacco exposure, alcohol use, and infection with certain subtypes of the human papilloma virus (HPV) for oropharyngeal HNSCC or Epstein Barr virus for nasopharyngeal HNSCC. Initial treatment with curative intent consists of surgical resection or definitive radiation, with cisplatin-based chemoradiotherapy as adjuvant or neoadjuvant treatment in patients with higher stage disease.

There will be an estimated 48,330 new cases of HNSCC and a projected 9,570 deaths due to HNSCC in the United States in 2016.[1] Survival rates vary based on extent of disease (stage) and location of the primary tumor, however based on the Surveillance and Epidemiologic End Results (SEER) data, 5-year survival rates have been improving over the period from 1982 to 2010; this trend in improved survival has been largely attributed to the introduction of platinum-based chemotherapy as neoadjuvant therapy. Despite this trend, 5-year survival rates for patients with distant metastatic disease remain at less than 50%.[2]

FDA-approved therapy for the treatment of the indicated population (those with disease progression following a platinum-containing chemotherapy regimen) includes cetuximab, methotrexate, and bleomycin. All of these drugs were approved based on demonstration of a durable overall response rate. . In this setting, the overall response rate for cetuximab is 13% (95% confidence interval 7%–21%), with a median duration of response of 5.8 months (range 1.2–5.8 months)[3]. The reported responses rates for bleomycin and methotrexate are not described in product labeling; however, bleomycin is no longer considered an appropriate treatment option for this population and the reported responses rates in published literature with methotrexate are generally less than 15%. While taxotere, in combination with cisplatin and fluorouracil, is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck, both taxotere and paclitaxel are commonly used off-label in patients who have not received a taxane and have progressed following a platinum-containing regimen. However, based on the population studied, in which approximately 75% received a prior taxane, this would not be considered an available therapy for population studied.

Pre-Submission History

The development program for HNSCC is comprised of three clinical studies in resistant, recurrent, or metastatic disease (KEYNOTE 055, KEYNOTE 040 and KEYNOTE 048) and supported by data obtained in Cohort B and B2 of KEYNOTE 012.

On December 9, 2010, Merck submitted IND 110080 for the development of pembrolizumab for the treatment of cancer. The IND was allowed to proceed on January 7, 2011

On February 21, 2013, KEYNOTE 012, entitled "A Phase 1b Multi-Cohort Study of MK-3475 in Subjects with Advanced Solid Tumors" was submitted to IND 110080. A more detailed description of this clinical protocol and its various revisions are discussed in Section 7 of this review and in Dr. Larkin's and Yuan's reviews.

On September 12, 2013, following receipt of the August 14, 2013 amendment containing a revised protocol and statistical analysis plan (SAP) for KEYNOTE-012, FDA advised this Merck to submit a new protocol, rather than expanding cohorts of interest in protocol PN012, should clinical development be pursued for pembrolizumab for the treatment of

[1] http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf accessed August 5, 2016.

[2] Pulte B and Brenner H. Changes in Survival in Head and Neck Cancers in the Late 20th and Early 21st Century: A Period Analysis. The Oncologist 2010 (Sept) 15(9): 994-1001.

[3] http://www.accessdata fda.gov/drugsatfda_docs/label/2015/125084s262lbl.pdf

patients with triple negative breast cancer, urothelial tract cancer, head and neck cancer, or gastric cancer.

On March 21, 2014, FDA advised that in order to evaluate an additional 100 patients with HNSCC, Merck should either submit a new disease-specific IND or Merck should evaluate the efficacy of pembrolizumab for the treatment of HNSCC under a new protocol submitted to IND 110080.

A preIND meeting for pIND 122325 was held on June 11, 2014, to discuss this program and gain FDA feedback regarding the design of Protocol PN-040, a randomized, multicenter, open-label trial comparing pembrolizumab with physicians' choice of systemic chemotherapy (b) (4)

On June 26, 2014, Merck requested additional advice regarding their planned activity-estimating trial, KEYNOTE- 055 (PN055), which was intended to study the efficacy, safety and tolerability of single agent MK-3475 (pembrolizumab) in approximately 150 patients with recurrent and/or metastatic head and neck squamous cell carcinoma with disease progression on or within 6 months of receipt of platinum and cetuximab-containing regimens. (b) (4)

On July 30, 2014, Merck submitted IND 122325 for the continuation of the development program of pembrolizumab for the treatment of patients with HNSCC. The IND was allowed to proceed on August 25, 2014.

On September 5, 2014, a teleconference was held to discuss and gain FDA feedback regarding the design of KEYNOTE Protocol 048, "MK-3475 in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma," to support an efficacy supplement for a new indication for MK-3475 (pembrolizumab).

On June 30, 2015, a meeting was held between Merck and FDA to discussion the clinical program for pembrolizumab for the treatment of head and neck squamous cell carcinoma (HNSCC) (b) (4)

In response to Merck's question as to whether the results obtained in Cohorts B and B2 of KEYNOTE 012 established the efficacy of pembrolizumab based on evidence of durable response rates that surpass the historical response rate of standard of care (methotrexate), FDA advised that based on the information provided in the pre-meeting briefing document, there is insufficient data to support a conclusion (b) (4)

[redacted] (b) (4) FDA stated that the data necessary to support an expanded labeling claim for this population would be based on the totality of evidence assessed in all patients who have received any part of any dose of pembrolizumab regardless of the determination of presence of measurable disease by central radiology review or the availability of follow-up scans including observed response rate and durability of response sufficient to show a meaningful advantage over available therapy. FDA further advised that, based on the proposed justification, including evidence of a flat exposure-response relationship on evidence of a flat exposure-response relationship in other tumor types, similar response rates in B and B2 using different dosage regimens, and similar PK between the dosage regimens used in Cohort B of KEYNOTE 012 and KEYNOTE 055, it would be acceptable to pool the data from Cohorts B and B2.

On November 23, 2015, a pre-sBLA meeting was held to discuss the content and format of a submission of data from KEYNOTE-012 to support a request for support accelerated approval for the proposed indication of [redacted] (b) (4). In order to provide a more accurate estimation of the treatment effect, Merck should also include response data on all patients enrolled in KN055 with at least 6 months follow-up. Merck agreed to provide data on approximately 50 patients enrolled in KN-055 with at least 6 months of follow-up, where an interim CSR and datasets would be provided in the sBLA. In addition, FDA agreed to review data from the subgroup of all 174 patients in KEYNOTE 012, Cohorts B and B2, with disease progression following platinum-based chemotherapy. FDA advised that whether these data would support an indication that [redacted] (b) (4) would be determined during review of the supplement. FDA further agreed that FDA agreed, in light of the extensive safety experience with this product, with the proposal to submit datasets from 192 patients enrolled in KN012 cohorts B (10 mg/kg Q2W) and B2 (200 mg Q3W) with advanced HNSCC who received at least one dose of pembrolizumab. Given the limited safety data available for pembrolizumab at the proposed dose (200 mg IV every 3 weeks) in patients with HNSCC from KEYNOTE 012 (n=132), Merck should also submit available safety data from ongoing HNSCC clinical trials (KN055, KN040, and KN048) consisting of

narrative summaries for each serious adverse event (SAE) for events not currently listed in the prescribing information for pembrolizumab.

3. CMC/Device

Merck ‘s request for a categorical exclusion from the preparation of an 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 supplemental Biologics License Application was accepted.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Pharmacometrics

I concur with the conclusions reached by the clinical pharmacology/pharmacometrics reviewers that there are no outstanding clinical pharmacology issues that preclude approval. Merck proposed a new dosage regimen for this expanded indication of pembrolizumab 200 mg administered as an intravenous infusion of 30 minutes every 21 days for 24 months or until disease progression or intolerable toxicity. This new dosage regimen was supported by the clinical safety observed in 132 patients enrolled in Cohort B2 of KEYNOTE-012 and 50 patients enrolled in the interim analysis subset of KEYNOTE-055, efficacy results in the subpopulation of X patients in KEYNOTE-012 and 50 patients in KEYNOTE-055, and updated population pharmacokinetic (popPK) analyses using pooled data from KEYNOTE-012, KEYNOTE-055, and Studies PN001, PN002, and PN006, which supported approvals for the treatment of patients with melanoma and non-small cell lung cancer. The popPK analyses indicated that:

- the pharmacokinetics of pembrolizumab in patients with HNSCC is similar to the PK profile in patients with other cancers;
- the observed exposures in patients with HNSCC receiving pembrolizumab 200 mg every three weeks are similar to that observed with pembrolizumab 2 mg/kg every three weeks in previous studies; and ,
- dose-response analyses that pooled data from KEYNOTE-012 and KEYNOTE-055 suggested a flat dose-response relationship for overall response rate over the exposures achieved with pembrolizumab 200 mg every three weeks and pembrolizumab 2 mg/kg every two weeks.

Based on the pharmacokinetic analyses, the safety and activity of the proposed new dosage regimen is adequately supported by the clinical pharmacology data package.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This supplement is supported by a retrospectively identified subgroup of patients enrolled in a disease-specific cohort of a single, multicenter, open-label, multiple disease-specific cohort protocol, KEYNOTE 012. As described below, KEYNOTE 012 was amended on multiple occasions and was not intended to support labeling claims. Thus the analysis of this study is based on agreements with FDA as to the acceptable study population, duration of follow-up, primary and key secondary endpoints, and sample size necessary to support the request for accelerated approval based on demonstration of an improvement in overall response rate and response duration as compared to available therapy. Key interactions in the pre-submission regulatory history are described in Section 2 of this review.

The results of this retrospectively identified subgroup analysis are supported by prior approvals for pembrolizumab, particularly in squamous cell carcinoma of the lung, and by the interim results of KEYNOTE 055.

KEYNOTE 012, entitled "A Phase 1b Multi-Cohort Study of MK-3475 in Subjects with Advanced Solid Tumors" was submitted to IND 110080 on February 21, 2013. The original protocol evaluated the antitumor activity of pembrolizumab at 10 mg/kg IV every 2 weeks (Q2W) in the four cancer types: HNSCC, urothelial tract cancer, triple negative breast cancer, and gastric cancer. The study objectives were to assess safety and tolerability of pembrolizumab 10 mg Q2W and to evaluate the anti-tumor activity of pembrolizumab as determined by response rates and duration of response. Patients were required to have PD-L1 positive tumors, defined as ≥1% PD-L1 membrane staining of tumor cells or stroma by immunohistochemistry (IHC) using a research only assay (Qualtek). In the original protocol for KEYNOTE 012, a total of 60 patients with either human papilloma virus (HPV)-positive or HPV-negative, PD-L1 positive HNSCC were to be enrolled cohort B.

KEYNOTE 012 was amended to include additional cohorts (Cohort B2) studying pembrolizumab at a lower dose and less frequent schedule (fixed dose of 200 mg IV every 3 weeks); based on this amendment, 132 patients with either PD-L1-positive and PD-L1-negative, HNSCC in cohort B2.

Efficacy Results

The efficacy supplement was submitted with a clinical study report based on a data with a cut-off date of September 1, 2015, and was amended to include an updated report based on data with cut-off date February 9, 2016. Review of this supplement is based on the data cut-off date of February 9, 2016, which provided 5.5 months of additional follow-up on responding patients. Additionally, FDA determined that the dataset of 174 patients with disease progression on or following platinum-based chemotherapy, regardless of prior treatment with cetuximab, would form the primary efficacy population for this review.

KEYNOTE-012 was conducted at 16 sites in 6 countries. Among the 174 patients included in FDA's efficacy analysis population, the median age was 60 years (32% age 65 or older); 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumors; 63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; and 71% had PD-L1 positive HNSCC according to an investigational assay. The median number of prior lines of therapy administered for the treatment of HNSCC was 2, with 100% of patients have received platinum-based chemotherapy, 95% of patients having received radiation therapy, 72% having received a prior taxane, and 37% having received prior cetuximab.

Among the 174 patients, there were 28 patients with independent review committee-determined responses per RECIST 1.1, for an ORR of 16.1% (95% CI: 11.0, 22.4). The complete response rate was 6.4% and partial response rate of 11.5%. Among the 28 responders, response duration ranged from 2.4+ months to 27.7+ months. The median duration of response is not yet estimable; 82% of responders had durations of response of ≥ 6 months and 73% had durations of response of ≥12 months. Of note, the ORR as assessed by independent central radiology review in accordance with immune-related RECIST was 16.1% (95% CI 11, 22.4). The ORR was similar in subgroups defined by age, race (White vs. non-White), gender, dosage regimen, PD-L1 status, and HPV status. The point estimate for ORR was lower in those who had progressed following platinum-based chemotherapy and cetuximab [ORR 13.6% (95% CI: 7.8, 21.5)] as compared to those who had progressed following platinum-based chemotherapy but had not received cetuximab [ORR 20.6% (O95% CI: 11.3, 32.2)]; however the confidence intervals around the observed point estimate had considerable overlap.

Supportive efficacy data
Interim results from 50 patients enrolled in KEYNOTE-055 were submitted in support of this supplement. This interim analysis used a data cut-off date November 25, 2015, which provided a minimum of 6 months following from initiation of pembrolizumab on all 50 patients and a median duration of followup of 8.4 months. Demographic, tumor characteristic, and prior treatment data for the patients in KEYNOTE-055 were similar to those in Cohorts B and B2 of KEYNOTE-012 with the exception that more patients (100% vs. 63%) in the KEYNOTE-055 interim analysis had received both prior platinum-based chemotherapy and prior cetuximab, the HPV status was unknown in a higher proportion of patients (≈50%), and a lower proportion of patients (30% vs. 49%) had received neoadjuvant/adjuvant treatment as compared to the KEYNOTE-012 subgroup.

The confirmed ORR as assessed by independent central radiology review according to RECIST 1.1 was 18% (95% CI: 8.6, 31.4); all were partial responses. The median duration of response was 6.9 months; responses ranged from 3.0 months to 8.3+ months.

8. Safety

The risks of pembrolizumab have been characterized more clearly from the results of randomized clinical trials enrolling 2799 patients with metastatic melanoma or non-small cell lung cancer which permitted an assessment of the increase in incidence of background rates. In supplement, Merck provided safety information on all 192 patients enrolled in cohorts B and B2 of KEYNOTE 012, supplemented by safety information in the first 50 patients accrued to KEYNOTE 055. Based on KEYNOTE 012, there were 132 patients who received pembrolizumab at 200 mg intravenously every three weeks, which was the proposed recommended dose for this indication. The exposure to pembrolizumab in these 132 patients was 14.4 weeks, with 42 patients exposed for more than 6 months with this dosage regimen and 26 patients exposed for more than 12 months.

Given the extensive safety experience with pembrolizumab in randomized clinical trials, the clinical review focused primarily assessment for previously unidentified adverse reactions or an increased risk of known adverse reactions. Based on the observed incidence, there appeared to be a higher incidence of facial edema and new or worsening hypothyroidism in this patient population, however in the absence of an internal control, the increased incidence of these adverse events may reflect a higher background rate in this patient population due to both the underlying cancer and treatment (i.e., surgical resection and radiation therapy).

Serious adverse reactions occurred in 45% of patients receiving pembrolizumab in KEYNOTE-012. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); these data were pooled. The most common adverse reactions (occurring in ≥20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism in 14.6%) of 192 patients in KEYNOTE-012, including Grade 3 (0.5%) hypothyroidism. Among these 28 patients, 15 had no prior history of hypothyroidism.

I concur with the clinical reviewer's determination that risk evaluation and mitigation strategies (REMS) are not required to ensure safe use of pembrolizumab at the proposed dosage regimen for the indicated population. I also concur that there are no outstanding safety issues which require a post-marketing requirement for assessment of safety.

9. Advisory Committee Meeting

This efficacy supplement for pembrolizumab, which was approved for two previous cancer indications (metastatic melanoma and non-small cell lung cancer) was not referred to the Oncologic Drugs Advisory Committee for review because this is a marketed biologic (not the

first in its class), the safety profile is acceptable for treatment of metastatic or unresectable squamous cell carcinoma of the head and neck that has progressed following a platininum-containing regimen, the clinical trial design is acceptable, and the application did not raise significant public health questions on the role of the biologic in the treatment of this disease. Therefore, outside expertise was not necessary since there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

Merck's proposal to seek a waiver from the requirements of the Pediatric Research Equity Act (PREA) for all pediatric age groups for the proposed indication, as described in their Agreed Initial Pediatric Study Plan, was reviewed by the Pediatric Review Committee (PeRC) on April 6, 2016. The committee agreed with the Division of Oncology Product 2 that the waiver should be granted since the disease does not exist in children.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Physician labeling
  - The proposed indication statement was adequately supported by the data
  - The proposed new dosage regimen was modified for consistency with KEYNOTE-012 protocol which limited pembrolizumab to 24 months; the resumption of pembrolizumab at the time of disease progression was included with the description of the clinical study (KEYNOTE-012) in Section 14.3 of product labeling but not included in in the Dosage and Administration section, as this would constitute a new claim, which was not supported by substantial evidence of effectiveness (only one patient was treated in this manner).
  - The Warnings and Precautions section (5.4) was modified to clarify that the incidence included both new cases of hypothyroidism and patients with pre-existing hypothyroidism (b) (4) .
  - The Adverse Reactions section was modified to include information on the most serious and most common adverse reactions reported in the 192 patients enrolled in Cohorts B and B2 of KEYNOTE-012. Section 6.2 was updated to include new information regarding the development of neutralizing antibodies in patients with anti-pembrolizumab binding antibodies.
  - Section 7 was removed, consistent with PLR format and FDA Guidances on product labeling, as there are no actionable drug interactions identified for pembrolizumab.

- Sections 8.6 and 8.7 were removed, consistent with PLR format and FDA Guidances on product labeling, as there are no recommended dose modifications for patients with organ impairment.
- Section 12.3 edited for brevity.
- Section 14.3 edited for brevity; data on overall response rate in those who received and those who did not receive cetuximab were pooled given the overlapping confidence intervals around the point estimates in these two subpopulations and the similarity in response rate in KEYNOTE-055 in which all patients had received prior cetuximab.

- The Medication guide was updated to reflect the new indication, new dosage regimen, and common adverse reactions observed in the clinical studies supporting this supplement.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.

- Risk Benefit Assessment
  I concur with the recommendations of the discipline review teams that this supplement be approved. Recurrent, unresectable or metastatic, HNSCC which has progressed following platinum-based chemotherapy is a serious and life-threatening disease with an estimated 5-year survival rate of less than 50%. The available therapy for this patient population is limited to cetuximab and methotrexate; treatment with these agents results in overall responses rates of less than 20% with reported median durations of response of less than 6 months.

  The data presented in this supplement demonstrate similar overall response rates (16% in KEYNOTE-012 and 18% in KEYNOTE-055) however the durability of responses in the KEYNOTE-012 are strikingly in that 82% of responders had durations of response of ≥ 6 months and 73% had durations of response of ≥12 months. Thus the efficacy observed in KEYNOTE-012 represents a substantial improvement over the available therapies of cetuximab and methotrexate. In addition, an ORR of 18% was observed in KEYNOTE-055, in which all patients had received prior cetuximab. The adverse reaction profile includes serious adverse reactions due to drug-induced autoimmunity affecting any organ system in the body; however, the incidence of immune-mediated adverse events other than endocrinopathies is generally less than 5% and can be mitigated with suspension of pembrolizumab and administration of corticosteroid in the majority of cases. Based on clinical studies previously submitted and clinical experience post-marketing, the toxicities of pembrolizumab are acceptable in this patient population with unsatisfactory alternative therapy for an incurable, life-threatening stage of HNSCC.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the clinical reviewer's determination that risk evaluation and mitigation strategies (REMS) are not required to ensure safe use of pembrolizumab at the proposed

dosage regimen for the indicated population. I also concur that there are no outstanding safety issues which require a post-marketing requirement for assessment of safety.

- Recommendation for other Postmarketing Requirements and Commitments
  - A post-marketing commitment will be required under the provisions of 21 CFR 601 Subpart E to verify the clinical benefit of pembrolizumab for the treatment of patients with recurrent, unresectable or metastatic HNSCC.

  - I concur with the clinical reviewer's determination that there are no new or outstanding safety issues which require a post-marketing requirement for assessment of safety. Further assessment of the safety of pembrolizumab in this patient population will be provided by the results of the randomized clinical trial to be performed to verify clinical benefit and fulfill the requirements for a PMR under 21 CFR 601 Subpart E.

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/s/

PATRICIA KEEGAN
08/05/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s009

OFFICER/EMPLOYEE LIST

Officer/Employee List
BLA 125514/S-9

The following officers or employees of FDA participated in the decision to approve this supplement and consented to be identified:

Blumenthal, Gideon
Fuller, Barbara
Griffiths, LaShawn
He, Kun
Hughes, Monica
Keegan, Patricia
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Yuan, Weishi (Vivian)
Zhao, Hong

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s009

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125514/9
Priority or Standard	Priority
Submit Date(s)	February 9, 2016
Received Date(s)	February 9, 2016
PDUFA Goal Date	August 9, 2016
Division / Office	DOP2/OHOP
Reviewer Name(s)	Erin Larkins
Review Completion Date	July 18, 2016
Established Name	Pembrolizumab
Trade Name	Keytruda
Therapeutic Class	Programmed death 1 (PD-1) receptor blocking antibody
Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	50 mg lyophilized powder in single-use vial for reconstitution 100 mg/4 mL (25 mg/mL) solution in a single-use vial
Dosing Regimen	200 mg, 30 min IV every 3 weeks
Indication(s)	Treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy
Intended Population(s)	Previously treated patients with recurrent or metastatic HNSCC

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the review of the clinical data, the reviewer recommends accelerated approval of supplemental biologics application (sBLA) 125514/9 pembrolizumab (KEYTRUDA) for the following indication:

KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy.

In the opinion of the reviewer, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The objective response rate observed in KEYNOTE 012 patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy (the efficacy population) was 16.1%, with a 95% confidence interval (11.0, 22.4) that does not exclude response rates reported with currently available treatments. Among responders, however, median duration of response had not been reached, and the upper limit of the duration of response range was 27.7 months (with response ongoing). After a median follow-up of 8.9 months for the efficacy population, duration of response was ≥6 months for 82% of responders and ≥12 months for 73% of responders. The observed durations of response are clinically meaningful when considering the intended patient population and available information on durations of response reported for currently available treatments. This clinical benefit outweighs the risks associated with pembrolizumab for the patient population specified in the proposed indication.

Approval is contingent upon reaching agreement with the Applicant on product labeling. Continued approval for this indication may be contingent upon verification and description of benefit in confirmatory trials. Such a confirmatory trial is currently ongoing, assessing pembrolizumab versus standard treatment in patients with recurrent or metastatic HNSCC.

1.2 Risk Benefit Assessment

HNSCC is a serious and life-threatening condition, and median survival for patients with recurrent or metastatic HNSCC in most clinical series is 6-10 months. While methotrexate and cetuximab are approved for the treatment of recurrent or metastatic HNSCC, these are associated with response rates of 4-13% in HNSCC patients whose disease has progressed on or after treatment with platinum-containing chemotherapy. In the trial leading to its approval for this indication, the upper limit of duration of response reported for cetuximab was 5.8 months. There is an unmet medical need for

patients with recurrent or metastatic HNSCC whose disease has progressed following platinum-containing chemotherapy.

This pembrolizumab sBLA is primarily supported by the results from a non-randomized, open-label, multi-cohort study, KEYNOTE 012. The primary efficacy population considered for this review consists of 174 patients with recurrent or metastatic HNSCC who had disease progression on or after treatment with platinum-containing chemotherapy. While the objective response rate of 16% is similar to that observed with cetuximab, among the 28 responders in the KEYNOTE 012 HNSCC efficacy analysis population, the median duration of response had not been reached, and the upper limit of the duration of response range was 27.7 months (with response ongoing). In addition, after a median follow-up of 8.9 months for the efficacy population, duration of response was ≥6 months for 82% of responders and ≥12 months for 73% of responders. Prolonged durations of response were observed across all of the various subgroups of patients assessed in this review. These observed durations of response are consistent with a clinically meaningful improvement compared to available therapies.

Supportive efficacy data comes from the first 50 patients with ≥6 months of follow-up treated on KEYNOTE 055, an ongoing, non-randomized, open-label, single arm study in patients with recurrent or metastatic HNSCC with progression of disease following previous treatment with platinum and cetuximab. The ORR of 18% is similar to that reported for KEYNOTE 012. The median duration of response for the 9 responders in KEYNOTE 055 was 6.9 months (upper limit of range 8.3 months [with response ongoing]). The difference in duration of response in KEYNOTE 055 compared to KEYNOTE 012 is most likely attributable to the difference in duration of follow-up between the trials, with a maximum follow-up duration of 8.3 months for KEYNOTE 055 versus 30 months in KEYNOTE 012. Importantly, a significant number of responders in KEYNOTE 055 had response durations of ≥6 months.

Overall, the safety profile of pembrolizumab appears to be acceptable relative to the benefits. The rate of permanent discontinuation of pembrolizumab due to adverse events was 17%. The most common adverse reactions, reported in ≥20% of patients, were fatigue, decreased appetite, and dyspnea. The safety profile of pembrolizumab has been well characterized in patients with other advanced malignancies, specifically melanoma and non-small cell lung cancer (NSCLC). Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, with the exception of a significantly higher incidence of facial edema (10% all grades, 2.1% grades 3-4) observed in HNSCC patients in KEYNOTE 012. Immune-mediated adverse reactions were observed in HNSCC patients treated with pembrolizumab, with no suggestion of an increased incidence for these reactions compared to that observed in the melanoma and NSCLC populations, except in the case of hypothyroidism. Such immune-mediated adverse reactions are adequately addressed by information in the Warnings and Precautions section and the dose

modification recommendations included in pembrolizumab product labeling. There were no significant safety concerns identified during sBLA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS). The safety profile of pembrolizumab appears to compare favorably with other therapies currently used in the treatment of this condition, although this assessment is limited by the lack of controlled safety data in this patient population.

In conclusion, the submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed durations of response are clinically meaningful when considering the intended patient population and currently available therapies. The clinical benefits outweigh the risks associated with pembrolizumab identified during the review of this sBLA.

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

A clinical post-marketing requirement (PMR) is recommended to further assess efficacy and to support traditional approval. This study, KEYNOTE 040, entitled “A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer”, is already underway, and the Applicant has provided milestone dates for this PMR. The primary endpoint is overall survival (OS).

Clinical PMR: Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of pembrolizumab over available therapy as determined by OS in patients with metastatic refractory HNSCC.

Milestone dates:

- Final protocol submission – March 2016
- Study / trial completion – October 2017
- Final report submission – April 2018

2 Introduction and Regulatory Background

2.1 Product Information

Pembrolizumab is a humanized monoclonal antibody of the IgG4/kappa (IgG4κ) isotype that binds to programmed death 1 (PD-1) receptor and directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is supplied as a lyophilized powder in single-use vials for reconstitution and as a 100 mg/4 mL (25 mg/mL) solution in single-use vials.

2.2 Tables of Currently Available Treatments for Proposed Indication

Table 1: Currently Available Therapies for Proposed Indicition (Reviewer Table)

	Study Design	**ORR, % (95% CI)**	**Median DoR (range), months**
Methotrexate	Randomized vs afatinib, 161 patients MTX	6 (not reported)	Not reported[a]
	vs gefitinib, 161 patients MTX	4 (not reported)	Not reported
Cetuximab	Single arm, 103 patients[b]	13 (7, 21)	5.8 (1.2, 5.8)

[a]Median progression-free survival 1.7 months (95% CI 1.5-2.4)
[b]Progressive disease within 30 days of platinum-based regimen
CI, confidence interval; DOR, duration of response; ORR, objective response rate

Methotrexate was initially approved for the treatment of HNSCC in the 1950s. The studies[1,2] in Table 1 represent contemporary data on the treatment effects of methotrexate in a population similar to that in the proposed indication for this sBLA. In 2006, cetuximab received approval simultaneously for use in combination with radiation for the treatment of patients with locally or regionally advanced HNSCC based on an improvement in locoregional control, and as monotherapy for the treatment of patients with recurrent or metastatic HNSCC with disease progression following platinum-based chemotherapy based on the results of the single arm trial[3,4] presented in Table X. Cetuximab later received approval for use as first-line treatment in combination with platinum-based therapy for patients with recurrent or metastatic HNSCC[5].

While the taxanes docetaxel and paclitaxel are not FDA-approved for the proposed indication, these are commonly used for the treatment of patients with recurrent or

metastatic HNSCC who have progression on or after platinum-containing chemotherapy and are considered a standard of care option for the proposed indication in the United States. For reference, a single arm trial of docetaxel in 23 patients with recurrent or metastatic HNSCC who had progressive disease following treatment with platinum-based chemotherapy reported an ORR of 13% (95% CI: 8, 26) and median duration of response (DOR) of 4.4 months (range 1.8 to 5.5 months)[6].

2.3 Availability of Proposed Active Ingredient in the United States

Pembrolizumab is FDA approved for use for the treatment of patients with unresectable or metastatic melanoma. Pembrolizumab has been granted accelerated approval for use for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

2.4 Important Safety Issues With Consideration to Related Drugs

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 110080 for the development of pembrolizumab was filed on December 9, 2010. IND 122325 for the development of pembrolizumab in head and neck cancers was filed on July 30, 2014. A listing of the pertinent regulatory history for pembrolizumab is included in Table 2.

Table 2: Regulatory History for Pembrolizumab (Reviewer Table)

Date	Description
Dec 2010	Initial pembrolizumab IND submitted.
Feb 2013	Initial KEYNOTE 012 protocol submitted to IND 110080, assessing pembrolizumab at a dose of 10 mg/kg IV every 2 weeks. Design included a cohort of up to 34 patients with PD-L1-positive advanced HNSCC.
May 2014	Protocol for KEYNOTE 012 amended to add a new cohort assessing pembrolizumab at a fixed dose of 200 mg IV every 3 weeks in 110 patients with advanced HNSCC regardless of PD-L1 status (Cohort B2).
June 2014	Type B (pre-IND / End of Phase 2) meeting to discuss design of KEYNOTE 040, a randomized, multicenter, open-label trial to compare pembrolizumab with chemotherapy for the treatment of patients with recurrent or metastatic HNSCC. Key points discussed and agreed upon – requirement for prior platinum-containing therapy, choice of standard of care for comparator arm.
July 2014	IND 122325 for development of pembrolizumab in head and neck cancers filed with submission of initial protocol for KEYNOTE 055, a single arm, multicenter, open-label trial of pembrolizumab in patients with (b) (4) .
Sept 2014	KEYTRUDA accelerated approval for unresectable or metastatic melanoma.
Sept 2014	Type C meeting to discuss design of KEYNOTE 048, a randomized, 3-arm, multicenter, open-label trial to compare pembrolizumab monotherapy, pembrolizumab plus platinum/5-FU, and platinum/5-FU/cetuximab for the first-line treatment of recurrent or metastatic HNSCC.
Sept 2014	Initial KEYNOTE 040 protocol submitted
Dec 2014	Initial KEYNOTE 048 protocol submitted
Jul 2015	Type B meeting which included discussion of the clinical program for pembrolizumab in HNSCC.

	Key points discussed related to HNSCC – importance of sufficient maturity of data from KEYNOTE 012 to obtain adequate information on durability of observed responses, acceptability of pooling data from KEYNOTE 012 Cohorts B and B2.
Oct 2015	KEYTRUDA accelerated approval for metastatic PD-L1-positive non-small cell lung cancer.
Nov 2015	Type B pre-sBLA meeting to discuss the results from KEYNOTE 012 and to reach agreement on the content and format of the proposed sBLA. Key points discussed and agreed upon – sBLA should include response data on all patients in KEYNOTE 055 with at least 6 months of follow-up; safety information to be submitted; submission of updated response durations for responding patients at the time of submission of the 90-Day Safety Update Report.
Dec 2015	Regular approval for melanoma indication.
Feb 2016	sBLA 125514/9 submitted for HNSCC indication.

2.6 Other Relevant Background Information

HNSCC may occur at various primary sites, including the lip, oral cavity, oropharynx, hypopharynx, and larynx. Patients with primary nasopharyngeal tumors are generally excluded from clinical trials of HNSCC. The Surveillance, Epidemiology, and End Results (SEER) Program database reports statistics for two broad categories relevant to HNSCC - 1) oral cavity and pharynx and 2) larynx. Of the cancers in these areas, 90-95% are squamous cell carcinoma. It is estimated there will be 48,330 new cases of oral cavity and pharyngeal cancer and 13,430 cases of laryngeal cancer diagnosed in the United States in 2016, with approximately 13,190 deaths due to these cancers[7,8]. This represents approximately 2% of all cancer deaths in the United States. At the time of initial diagnosis, distant metastases are present in approximately 18% of patients with oral cavity/pharyngeal cancer[7] and 19% of patients with laryngeal cancer[8]. In addition, regional lymph node involvement (without distant metastasis) is present in approximately 47% of patients with oral cavity/pharyngeal cancer[7] and 22% of patients with laryngeal cancer[8] at the time of initial diagnosis; for patients with such locally advanced disease, 20-30% will recur locally, while another 10-15% can be expected to develop distant metastases. Median survival for patients with recurrent or metastatic HNSCC in most clinical series is 6-10 months.

Standard of care options for locally advanced HNSCC include platinum-containing chemotherapy given in conjunction with radiation (e.g., as induction therapy, as

concurrent therapy with radiation, or as part of adjuvant therapy with radiation following surgical resection). Standard first-line chemotherapy for metastatic HNSCC consists of a multi-agent platinum-containing chemotherapy regimen, such as cisplatin or carboplatin plus 5-fluorouracil plus cetuximab[9].

Standard therapy for recurrent or metastatic HNSCC which has progressed following treatment with a platinum-containing regimen usually consists of single agent chemotherapy. As discussed in Section 2.2 of this review, agents currently FDA approved for this indication are methotrexate and cetuximab. While docetaxel is only FDA approved for use in combination with cisplatin and fluorouracil as induction therapy for locally advanced SCCHN, it is commonly used as a single agent for the treatment of recurrent or metastatic HNSCC which has progressed following treatment with a platinum-containing regimen, as is paclitaxel.

Preclinical *in vitro* and *in vivo* experiments have shown that PD-1 and/or PD-L1 blockade using monoclonal antibodies enhances tumor-cell specific T-cell activation, cytokine production, anti-tumor effector mechanisms, and clearance of tumor cells by the immune system[10-15]. Clinical data from agents which block the PD-1 / PD-L1 pathway have demonstrated clinical activity in many cancer types, including demonstration of clinical benefit for pembrolizumab in the treatment of patients with melanoma and NSCLC. Anti-PD-1 antibodies have demonstrated anti-tumor responses in models of squamous cell carcinoma[14,16].

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is of adequate quality for clinical review. There are no concerns regarding the integrity of the submission.

3.2 Compliance with Good Clinical Practices

All study reports contained in the sBLA included a statement that the trials were conducted in accordance with Good Clinical Practices.

3.3 Financial Disclosures

In accordance with 21 CFR 54, the Applicant submitted the following financial information:

A list of KEYNOTE 012 and KEYNOTE 055 trial investigators (sBLA section 1.3.4, Table 2) and FDA form 3454 certifying that the 292 investigators from KEYNOTE 012 and the 149 investigators from KEYNOTE 055 listed in Table 2 of sBLA section 1.3.4 had no financial arrangements as defined in 21 CFR 54.2(a, b, and f) that could affect the outcome of the trial.

No investigators were sponsor employees. Submission of FDA form 3455 was not required, as no KEYNOTE 012 or KEYNOTE 055 investigator participated in financial arrangements or held financial interests required to be disclosed.

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. The Applicant conducted 1- and 6-month repeat-dose toxicology studies in cynomolgus monkeys. There were no severe toxicities, but there was a pattern of changes consistent with the immune-based mechanism of action of the drug. There was no evidence of cytokine release when pembrolizumab was evaluated by the Applicant in a cytokine release assay.

4.4 Clinical Pharmacology

For full details, see the FDA Clinical Pharmacology Review of the current sBLA submission.

4.4.1 Mechanism of Action

Pembrolizumab is a humanized monoclonal antibody of the IgG4κ isotype designed to bind to PD-1 and directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues[17]. Although healthy organs express little, if any, PD-L1, a variety of cancers were demonstrated to express abundant levels of PD-L1, which is thought to contribute to inhibition of active T-cell immune surveillance of tumors. By inhibiting the PD-1 receptor from binding to its ligands, pembrolizumab reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity.

4.4.2 Pharmacodynamics

The following is an excerpt from the FDA Clinical Pharmacology Review of the original BLA submission:

"Two types of pharmacokinetics and pharmacodynamics (PK/PD) evaluations provided the foundation for the selection of the lowest dose studied in the clinical program. The first was a clinical biomarker (IL-2 release) based PK/PD approach and the second was a translational PK/PD projection of clinical response based on preclinical activity of an anti-PD-1 antibody. While these two approaches utilized different techniques, data, and assumptions, they converged on 1 to 2 mg/kg Q3W as the lowest doses with a high likelihood of providing substantial clinical benefit and supported the use of 2 mg/kg Q3W in the program."

4.4.3 Pharmacokinetics

See the FDA Clinical Pharmacology Review from the original BLA submission for general PK information.

For the current submission, the Applicant proposes a fixed dosing regimen of 200 mg IV every 3 weeks (Q3W). While pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W) studied in the first-in-human trial of pembrolizumab, no maximum tolerated dose was identified. The Applicant states that in the pembrolizumab clinical program, flat dose-response and exposure-response relationships for efficacy were found in melanoma and NSCLC patients in the range of doses between 2 mg/kg and 10

mg/kg, and the Applicant argues that clinical data suggest 2 mg/kg Q3W is on or near the plateau of the exposure-response curve achieving maximal clinical efficacy.

The dose initially selected for study in KEYNOTE 012 was the highest dose studied, 10 mg/kg Q2W. The Applicant later selected the fixed dose of 200 mg Q3W for study in Cohort B2 of KEYNOTE 012 and in later phase clinical trials in HNSCC based on simulations performed using the population PK model of pembrolizumab. Per the Applicant, according to this model the fixed dose of 200 mg Q3W will: 1) provide exposures that are optimally consistent with those obtained with the 2 mg/kg Q3W dose; 2) maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response; and 3) maintain individual patient's exposure in the exposure range established in melanoma that are well tolerated and safe.

Based on population PK analysis, the exposure with pembrolizumab 200 mg Q3W is approximately 30% higher than with a 2 mg/kg Q3W dosage regimen. The exposure with the 10 mg/kg Q2W dosage regimen is approximately 4-fold higher than the exposure with the 200 mg Q3W fixed dose. For specific details related to the fixed dosing regimen proposed in the current application, see the FDA Clinical Pharmacology Review of the current sBLA submission.

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5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3: Listing of Clinical Trials Relevant to Clinical Review of sBLA (Reviewer Table)

Trial Identity	Trial Design	Regimen/ schedule/ route	Primary Endpoint(s)	No. of patients	No. of Centers and Countries
Pivotal Study to Support Efficacy and Safety					
KEYNOTE 012	Non-randomized, open-label, multi-cohort study including two cohorts with R/M HNSCC (Cohorts B & B2)	Cohort B 10 mg/kg Q2W Cohort B2 200 mg Q3W	ORR by independent central radiology review Safety	192 enrolled in Cohorts B & B2 (174 with PD following platinum)	16 sites in 6 countries
Supportive Study for Efficacy and Safety					
KEYNOTE 055	Non-randomized, open-label, single arm study in patients with R/M HNSCC with PD following platinum and cetuximab	200 mg Q3W	ORR by independent central radiology review Safety	First 50 treated patients with follow-up of ≥6 months	41 sites in 3 countries (32 sites allocated patients to treatment)

ORR, objective response rate; PD, progressive disease; R/M, recurrent or metastatic

Pooled safety data from 2799 clinical trial patients with NSCLC (treated in KEYNOTE 001 and 010) or melanoma (treated in KEYNOTE 001, 002, and 006), referred to as "pooled melanoma and NSCLC population", was also relevant to the clinical review of this sBLA.

5.2 Review Strategy

The clinical review is based on the Clinical Study Reports (CSRs) for the pivotal study, KEYNOTE 012, and the supportive study, KEYNOTE 055, outlined in Section 5.1, as well as the Integrated Summary of Efficacy (ISE), the Integrated Summary of Safety (ISS), the updated Summary of Clinical Efficacy (SCE), and the updated Summary of Clinical Safety (SCS) – Safety Update Report. The data cut-off dates for KEYNOTE 012 and KEYNOTE 055 for the CSRs, ISS, and ISE were September 1, 2015, and

November 25, 2015, respectively. The data cut-off date for the updated safety and efficacy analyses of KEYNOTE 012 included in the updated SCE and SCS was February 9, 2016, and the data cut-off date for the updated efficacy analysis of KEYNOTE 055 was January 29, 2016. Among the items reviewed were primary datasets (for baseline characteristics, efficacy, and toxicity) submitted by the Applicant, selected case report forms (CRFs), selected narratives, and a literature review of agents studied for the treatment of recurrent or metastatic HNSCC. The clinical review was conducted by Dr. Erin Larkins. The statistical review was conducted by Dr. Weishi Yuan.

Using the primary data from the pivotal and the supportive study, the statistician confirmed, and in collaboration with the clinical reviewer, supplemented the Applicant's efficacy analyses. The clinical reviewer confirmed the Applicant's safety analyses of the pivotal and the supportive studies, conducting analyses of primary data using the MedDRA Adverse Event Diagnostics (MAED) program. Methods used to perform analyses for specific issues (i.e., detailed assessment of a particular safety issue), are explained in the pertinent section of the review.

The Review of Efficacy in Section 6 is focused primarily on the efficacy results of KEYNOTE 012. A review of efficacy data from the first 50 patients with ≥6 months of follow-up treated on KEYNOTE 055 is included in Section 6.1.10.

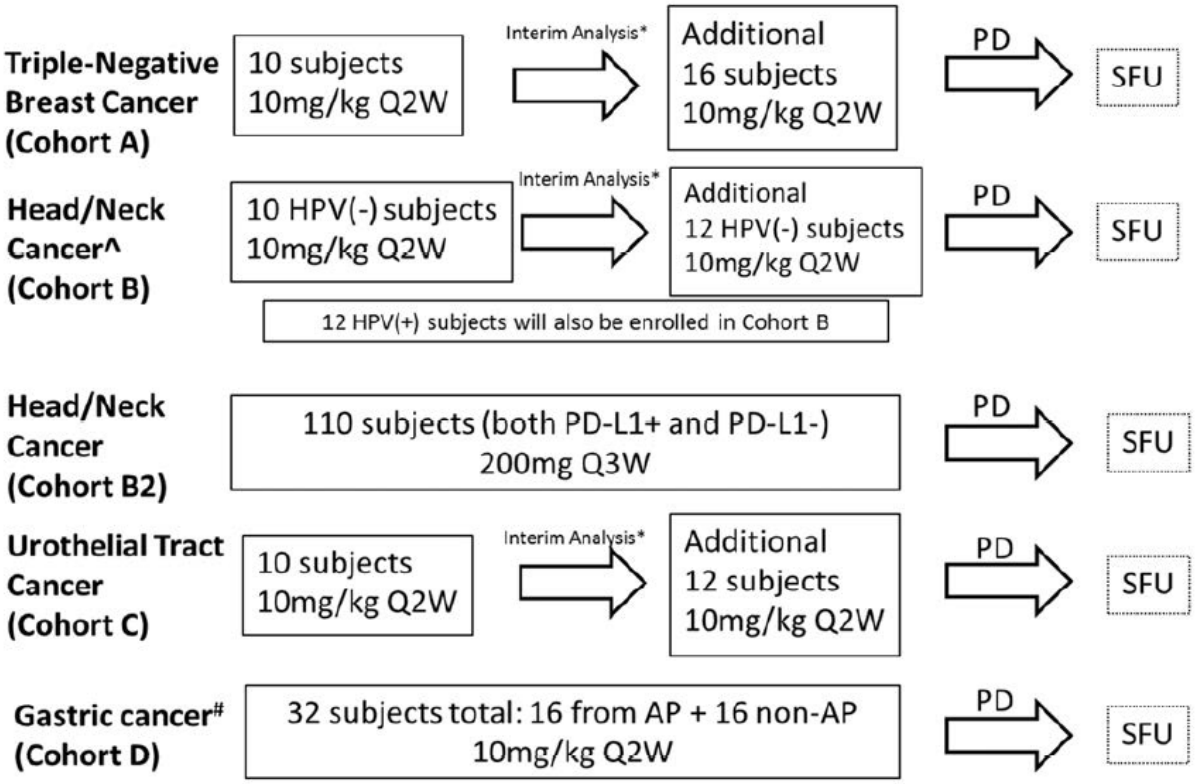
5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 KEYNOTE 012

Trial Design

The protocol design for KEYNOTE 012 was a non-randomized, open-label, multi-cohort study. The study was initially designed to assess the activity and safety of pembrolizumab at a dose of 10 mg/kg Q2W in 3 cohorts of patients with PD-L1-positive tumors, patients with triple-negative breast cancer (Cohort A), HNSCC (Cohort B), and urothelial tract cancer (Cohort C). Amendment 1 added a cohort of patients with PD-L1-positive gastric cancer. Cohort B2, consisting of patients with recurrent or metastatic HNSCC with any PD-L1 status, was added with Amendment 2 (dated April 7, 2014) in order to investigate pembrolizumab at a fixed dose of 200 mg IV Q3W in this patient population. Figure 1, abstracted from the protocol (Amendment 2), summarizes the trial design following the addition of Cohort B2.

Figure 1: KEYNOTE 012 Trial Design (Applicant Figure)



*An interim analysis for each cohort may be performed depending on the rate of enrollment or other factors determined during the course of the trial. This interim analysis would only be performed when ≥ 10 patients in the respective cohort have had at least two post-baseline scans.
^A total of 34 subjects with head/neck cancer will be enrolled in Cohort B of the study
# The gastric cancer cohort will be stratified to enroll 16 patients in Asia Pacific (AP) and 16 patients ex-AP. No interim analysis will be performed in this cohort.
PD = Progressive Disease
SFU = Survival Follow-up

The initial enrollment of patients in cohorts requiring PD-L1-positive tumors was done using a prototype PD-L1 immunohistochemical (IHC) assay, which assessed PD-L1 expression in the stroma or in ≥1% of tumor cells using the same 22C3 antibody as used in the PD-L1 IHC 22C3 pharmDx™ Kit from Dako. PD-L1 expression status was later assessed using the PD-L1 IHC 22C3 pharmDx™ Kit from Dako. For this assay, PD-L1-expression status was defined based on the Tumor Proportion Score (TPS or overall percent positive); the TPS is defined as the percentage of neoplastic cells expressing PD-L1 at any intensity. PD-L1-positive was defined as TPS ≥1%, based on scoring methodology from the NSCLC Companion Diagnostic guidelines.

Key inclusion criteria

- Histologically or cytologically confirmed diagnosis of cancer that is recurrent, metastatic, or persistent. There was no limit to the number of prior treatment regimens. Enrollment to Cohorts B and B2 required a diagnosis of squamous cell carcinoma of the head and neck.
- For Cohorts A, B, C, and D: PD-L1-positive tumor as determined by IHC at a central laboratory from either an archived formalin-fixed paraffin embedded (FFPE) tumor sample or a newly obtained biopsy.
- Measurable disease based on RECIST 1.1.
- Age ≥18 years.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
- Adequate organ function, defined as:
  - Absolute neutrophil count (ANC) ≥1500/μL
  - Platelets ≥100,000/μL
  - Hemoglobin ≥9.0 g/dL
  - Serum creatinine ≤1.5 x ULN
  - Measured or calculated creatinine clearance ≥60 mL/min for patients with creatinine levels >1.5 x ULN
  - Total bilirubin ≤1.5 x the upper limit of normal (ULN) or direct bilirubin ≤ULN for patients with total bilirubin levels >1.5 x ULN
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN or ≤5 x ULN for patients with liver metastases
  - International normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (aPTT) ≤1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Key exclusion criteria

- Diagnosis of immunosuppression or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. This does not include patients with vitiligo, diabetes mellitus type I, or resolved childhood asthma/atopy; patients that require intermittent use of bronchodilators or local steroid injections; or patients with hypothyroidism stable on hormone replacement or Sjogren's syndrome.
- Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

- Evidence of interstitial lung disease.
- Active infection requiring systemic therapy.
- Known history of human immunodeficiency virus or known active hepatitis B or C.
- Received a live vaccine within 30 days of planned start of study therapy.
- Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
- Prior anti-cancer monoclonal antibody within 4 weeks prior to study Day 1.
- Not recovered (i.e., grade ≤1 or at baseline) from adverse events (AEs) due to a previously administered agent. Patients with grade ≤2 neuropathy related to prior chemotherapy are an exception to this criterion and may qualify for the study.

Treatment

The starting dose chosen for the initial study design and used for treatment of patients in Cohort B was 10 mg/kg Q2W, while the dose used in Cohort B2 was a fixed dose of 200 mg Q3W. For details regarding the rationale for dose selection, see Section 4.4.3 of this review. In both Cohort B and B2, pembrolizumab was administered as a 30-minute intravenous (IV) infusion and per protocol was to be administered for up to 24 months.

Dose modification guidelines are summarized in Table 4, abstracted from the KEYNOTE 012 protocol. Supportive care guidelines, including use of corticosteroids, were included in the protocol and also provided to investigators in a separate document, the Events of Clinical Interest Guidance Document. The protocol also included supportive care treatment guidelines for infusion reactions.

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Table 4: Dose Modification Guidelines for Drug-Related Adverse Events (Applicant Table)

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	2[2]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[3]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 5– Infusion Reaction Treatment Guidelines for further management details.

[3] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

If toxicity did not resolve to grade ≤1 within 12 weeks after the last infusion of pembrolizumab, trial treatment was to be discontinued after consultation with the study Sponsor. With investigator and Sponsor agreement, patients with a laboratory AE still

at grade ≥2 after 12 weeks could continue treatment on study only if asymptomatic and controlled.

Use of the following medications was prohibited during the study:

- Other anti-neoplastic systemic therapy.
- Other immunotherapy
- Glucocorticoids for any purpose other than to modulate acute symptoms from an AE. The use of physiologic doses for patients requiring ongoing corticosteroids could be approved after consultation with the Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial.

Radiation therapy to a symptomatic solitary lesion or to the brain could be allowed after consultation with the Sponsor.

Study flow charts, abstracted from the KEYNOTE 012 protocol, outlining the timing of procedures and evaluations are included among the appendices of this review (see Section 9.4).

Treatment with pembrolizumab was to continue until confirmed radiologic progressive disease (PD), unacceptable toxicity, or completion of 24 months of study therapy. Patients who stopped pembrolizumab after 24 months could be eligible for up to 1 year of additional study treatment if they progressed after stopping study treatment. Protocol-specified reasons for early treatment discontinuation included: patient withdrawal of consent, intercurrent illness that prevents further administration of treatment, pregnancy, investigator decision to withdraw the patient, noncompliance with trial treatment or procedure requirements, or patient is lost to follow-up. In addition, discontinuation of treatment could be considered for patients who attained a confirmed complete response (CR), had been treated for at least 24 weeks with pembrolizumab, and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. If such a patient then experienced disease progression while off pembrolizumab therapy, that patient could be eligible for up to 1 year of additional treatment with pembrolizumab at the discretion of the investigator.

Tumor imaging was obtained every 8 weeks from the first dose of study therapy and assessed based on Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST 1.1). If imaging was determined to show PD, tumor assessment was to be repeated ≥4 weeks later in order to confirm PD, with the option of continuing treatment for clinically stable patients while awaiting confirmation of PD. Clinical stability was defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG PS
- Absence of rapid progression of disease

- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent medical intervention.

If repeat imaging confirmed PD, the patient would be discontinued from study therapy. If repeat imaging showed a reduction in tumor burden compared to the initial scan demonstrating PD, treatment could be continued. In addition, if a patient with confirmed PD was clinically stable or clinically improved per investigator assessment and there was no further increase in the tumor dimensions on the confirmatory scan, upon consultation with the Sponsor an exception could be considered to continue treatment. For patients who discontinued trial treatment for reasons other than PD, imaging was to be continued every 8 weeks until confirmed PD or the start of a new anti-neoplastic therapy.

Investigator assessment with site radiology reading was used to determine patient eligibility and for patient management. An Independent Imaging Review Charter (IRC) was established for independent central radiology review of all imaging time points for efficacy analyses.

Study Endpoints
The primary objectives for KEYNOTE 012 (per the final version of the protocol) were:

1) To determine the safety and tolerability of the 10 mg/kg Q2W dose of pembrolizumab in patients with PD-L1-positive advanced solid tumors enrolled in Cohorts A, B, C, and D.

2) To evaluate anti-tumor activity of the 10 mg/kg Q2W dose of pembrolizumab in patients with PD-L1-positive advanced solid tumors enrolled in Cohorts A, B, C, and D based on objective response rate (ORR) per RECIST 1.1 assessed by independent central radiology review.

3) To determine the safety and tolerability of the 200 mg Q3W dose of pembrolizumab in patients with advanced HNSCC enrolled into Cohort B2.

4) To evaluate anti-tumor activity of the 200 mg Q3W dose of pembrolizumab in patients with advanced HNSCC enrolled into Cohort B2 based on ORR per RECIST 1.1 assessed by independent central radiology review.

Secondary endpoints related to the HNSCC cohorts in KEYNOTE 012 included:
- ORR in patients in Cohort B with PD-L1-positive, HPV-positive HNSCC
- ORR in patients in Cohorts B and B2 with HNSCC previously treated with cetuximab and platinum
- ORR in each cohort using RECIST 1.1 per investigator assessment
- Assessment of the correlation between PD-L1 expression and anti-tumor activity of pembrolizumab in patients with HNSCC enrolled in Cohort B2

- Progression-free survival (PFS);
- Overall survival (OS)
- Duration of response (DOR)

The study also had one exploratory objective: to explore the PK profile of pembrolizumab in the advanced solid tumor population.

Statistical Analysis Plan

See the Statistical Review by Drs. Weishi Yuan and Kun He for detailed evaluation of the statistical analysis plan. The statistical methods used for the KEYNOTE 012 CSR and the ISE / SCE presented in the sBLA differed from the statistical analysis plan included in the KEYNOTE 012 protocol.

Statistical analysis plan per the protocol for KEYNOTE 012:

A patient that discontinues the trial for PD or a drug-related AE will not be replaced and will be counted in the evaluable population of patients for the respective cohort. Additional patients may be enrolled in a given cohort to ensure that the required number of evaluable patients in each cohort is achieved.

The primary population for analyses of efficacy data in KEYNOTE 012 will be the full analysis set (FAS) population, defined as all subjects with a baseline scan with measurable disease by independent central radiology review for each cohort and who either have a post baseline scan or discontinue the trial due to progressive disease or a drug-related AE. Supportive analyses of efficacy will be conducted in the all subjects as treated (ASaT) population, defined as all patients who received at least one dose of study treatment, and the FAS population by Investigator review. For each cohort, ORR will be used as the primary endpoint for efficacy assessment, and a 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for the response rate in each cohort. Table 5, abstracted from the final version of the protocol, presents an outline of the efficacy analysis strategy.

Table 5: Primary Analysis Strategy for Efficacy Endpoints (Applicant Table)

Endpoint/Variable‡ (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Overall RECIST 1.1 response rate based on independent central radiology review (Cohort A, Cohort B HPV negative subjects, Cohort C, and Cohort D evaluated separately)	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Overall RECIST 1.1 response rate based on independent central radiology review for subjects in Cohort B2	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Secondary:			
Overall RECIST1.1 response rate based on independent central radiology review, Cohort B HPV positive subjects,	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Overall RECIST 1.1 response rate based on independent central radiology review, Cohort D AP subjects.	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Overall RECIST 1.1 response rate based on based on independent central radiology review, for subjects previously treated with cetuximab and platinum in Cohorts B and B2	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Overall RECIST 1.1 response rate based on investigator assessment for cohorts A,B, C and D	Exact methods for binomial parameter	FAS	Subjects with missing data are considered non-responders
Overall RECIST 1.1 response rate based on investigator assessment for Cohort B2	Exact methods for binomial parameter	FAS	Subjects with missing data are considered non-responders
Progression-free survival	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Overall survival	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Response duration	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
‡ For Cohort D, the analyses for the Asia Pacific (AP) population will be performed as appropriate.			

Power and sample size:

- Cohort B (HNSCC patients): HPV-negative HNSCC patients will be evaluated separately from HPV-positive head and neck cancer subjects. With a maximum of 22 evaluable PD-L1 positive subjects with HPV-negative head and neck cancer, the study has approximately 80% power to detect a 25% difference in ORR under the null hypothesis of ORR=10% with a type I error rate of 2.5% if the true ORR is 35%. Success for this hypothesis requires at least 6/22 responses. With a maximum of 12 evaluable PD-L1 positive patients with HPV-positive HNSCC, the study has approximately 73% power to detect a 35% difference in ORR under the null ORR=20% with a type I error rate of 5% if the true ORR is 55%. Success for this hypothesis requires at least 6 responses.

- Cohort B2 (HNSCC patients, expansion cohort): With 100 evaluable patients in Cohort B2, the study provides >99% power to detect a 15% difference in ORR under the null hypothesis of ORR=5% with a type I error rate of 2.5% if the true ORR is 20%. Success for this hypothesis requires at least 11/100 responses.

- Cohorts B and B2 previously treated with cetuximab and platinum: With 60 evaluable HNSCC patients previously treated with cetuximab and platinum, the study has 93% power to detect a 15% difference in ORR under the null hypothesis of ORR=5% with a type I error rate of 2.5% if the true ORR is 20%. Success for this hypothesis requires at least 8/60 responses.

No interim analyses were planned for Cohort B2. An interim analysis for Cohort B could be performed if the rate of enrollment was much slower than anticipated during the course of the trial.

The ASaT population was to be used for the analysis of safety data.

The statistical methods used by the Applicant for analysis of the data presented in the sBLA:

The primary efficacy analyses are based on the ASaT population, defined as all patients who received at least one dose of study treatment. ORR as assessed per independent central radiology review was the primary efficacy endpoint. The RECIST 1.1 response rate, exact Clopper-Pearson 95% confidence interval, and p-value for the hypothesis test of whether the RECIST 1.1 response rate was greater than the historical control response rate (when specified) were analyzed using the exact binomial distribution.

Patients in the primary analysis population without response data were counted as non-responders. For DOR, PFS, and OS endpoints, Kaplan-Meier curves and median estimates from the Kaplan-Meier curves were provided. Patients without efficacy evaluation data or without survival data were censored at Day 1.

Analyses are provided for the following three populations based on patients' prior treatment:

- 110 patients who had PD after prior treatment with cetuximab and platinum therapy, received either concurrently or sequentially
- 64 patients who had PD after prior treatment with platinum but without prior cetuximab exposure
- these 2 populations of patients combined (n=174), the total efficacy population

Analysis of the efficacy endpoints of ORR, DOR, PFS, and OS are also presented for the following populations:

- All patients in Cohort B and B2 combined (n=192)
- All patients in Cohort B (n=60)
- All patients in Cohort B2 (n=132)

ORRs are also presented for the following subgroups (from the entire HNSCC population of 192 patients): age, ECOG PS, HPV status, PD-L1 status, and gender.

Protocol Amendments

Key changes are described for the following protocol amendments relevant to this application:

Amendment 2 (April 7, 2014):

- Added new cohort, Cohort B2, to assess pembrolizumab 200 mg Q3W in 110 patients with recurrent or metastatic HNSCC with any PD-L1 status.
- Added two new primary objectives: 3) to determine the safety and tolerability of the 200 mg Q3W dose of pembrolizumab in patients enrolled in Cohort B2 and 4) to evaluate the clinical activity of pembrolizumab at the 200 mg Q3W dose in patients with PD-L1-negative advanced head and neck cancer enrolled into Cohort B2 based on RECIST 1.1 as determined by the Investigator.

Amendment 3 (May 26, 2015):

- Modified primary objective #4 to evaluation of anti-tumor activity of pembrolizumab 200 mg Q3W in all patients in Cohort B2 regardless of PD-L1 status.
- Changed the method of efficacy assessment for primary endpoints from investigator assessment to independent central radiology review.
- Added a new secondary objective: to evaluate the anti-tumor activity of pembrolizumab in patients with advanced HNSCC previously treated with cetuximab and platinum enrolled in Cohort B or Cohort B2 based on RECIST 1.1 as assessed by independent central radiology review.

Amendment 4 (October 13, 2015):

- Changed the term for one of the analysis populations to be used for supportive analyses of efficacy from the intention-to-treat population to the ASaT population, the same population to be used for safety analyses.

5.3.2 KEYNOTE 055

Trial Design and Treatment Plan

The protocol design for KEYNOTE 055 is a non-randomized, open-label, single arm study of pembrolizumab 200 mg Q3W in patients with recurrent or metastatic HNSCC with progression of disease on or after platinum and cetuximab therapy. Planned enrollment is approximately 150 patients. The primary efficacy endpoint is ORR assessed using RECIST 1.1 per independent central radiology review. Assessment of the safety and tolerability of pembrolizumab 200 mg Q3W is also a primary objective.

Eligibility criteria were consistent with those used in KEYNOTE 012 with the following exceptions:

- Inclusion requires a diagnosis of histologically or cytologically confirmed recurrent or metastatic HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx considered incurable by local therapies and resistant to platinum (either cisplatin or carboplatin) and cetuximab. Resistance is defined as tumor progression or recurrence within 6 months of the last dose of platinum and cetuximab therapy in the adjuvant (e.g. with radiation after surgery), primary (e.g. with radiation), recurrent, or metastatic setting. Patients must be resistant to both platinum and cetuximab. Platinum and cetuximab do not need to be given concurrently (i.e. can be given with sequential regimens) however the patient must have recurred within 6 months of the last dose for each of these therapies. Any number of previous systemic regimens given for recurrent and/or metastatic disease is allowed.
- Inclusion requires measurable disease based on RECIST 1.1 as determined by independent central radiology review.
- Exclusion criterion related to previous treatment with antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways is limited to prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

Treatment consists of pembrolizumab 200 mg Q3W administered as a 30-minute intravenous infusion and per protocol is to be administered for up to 24 months. Dose modification guidelines, supportive care guidelines, prohibited concomitant medications, and guidelines related to radiation therapy are similar to those in KEYNOTE 012. The duration of treatment and protocol-specified reasons for early discontinuation are the same as in KEYNOTE 012, as are the guidelines for optional discontinuation of study therapy after CR.

Tumor imaging is to be obtained 9 weeks from the first dose of trial treatment and then every 6 weeks through the first year of treatment; patients who remain on treatment for

one year will subsequently have imaging performed every 9 weeks. Guidelines for imaging and treatment after first radiologic evidence of PD are the same as in KEYNOTE 012.

Study Endpoints

The primary objectives for KEYNOTE 055 (per the most recent version of the protocol prior to sBLA submission, Amendment 2):

1) To determine the safety and tolerability of 200 mg Q3W dose of pembrolizumab in patients with recurrent or metastatic HNSCC who have progressed on platinum and cetuximab therapy.

2) To evaluate anti-tumor activity of pembrolizumab by ORR using RECIST 1.1 assessed by independent radiology review in patients with recurrent or metastatic HNSCC who have progressed on platinum and cetuximab therapy.

3) To evaluate anti-tumor activity of pembrolizumab by ORR using RECIST 1.1 assessed by independent radiology review in subjects with PD-L1 strong positive recurrent or metastatic HNSCC who have progressed on platinum and cetuximab therapy.

Secondary endpoints include:

- ORR by RECIST 1.1 in patients with PD-L1-positive tumors
- DOR in all patients receiving pembrolizumab
- DOR in patients with PD-L1 strong positive tumors
- ORR by modified RECIST 1.1 (all patients, PD-L1 strong positive, PD-L1-positive)
- ORR by RECIST 1.1 in patients with HPV-positive tumors
- PFS (all patients, PD-L1 strong positive, PD-L1-positive)
- OS (all patients, PD-L1 strong positive, PD-L1-positive)

Statistical Analysis Plan

The statistical analysis plan included in the protocol for KEYNOTE 055 is not relevant to the clinical review of the current sBLA. This sBLA only includes efficacy and safety data from an interim analysis of the first 50 treated patients with follow-up of ≥6 months from KEYNOTE 055, submitted as supportive data.

The primary efficacy endpoint analyzed was ORR per RECIST 1.1 as assessed by independent central radiology review. Supportive analyses of ORR were performed based on investigator assessments using RECIST 1.1. Other efficacy endpoints presented include DOR, PFS, and OS. The primary safety endpoints were AEs graded using CTCAE (Version 4.0) criteria. Safety was assessed by quantifying the toxicities and grades experienced by subjects who had received pembrolizumab. Other safety

endpoints included laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

This is an interim report, so no protocol-specified hypothesis testing was performed. Point estimates and 95% confidence intervals were provided for the evaluation of ORR. Descriptive and graphical summaries, including Kaplan-Meier plots, were provided for the evaluation of DOR, PFS and OS.

Although the FAS population was the primary population for the analysis of efficacy data per the protocol, the ASaT population was used as the primary population for efficacy data analysis for this interim report. The ASaT population and FAS population are identical, as patients were required to have baseline measurable disease by independent radiology review.

Protocol Amendments
As initially designed, the protocol included a 3rd primary objective, to evaluate anti-tumor activity by ORR in patients with PD-L1-positive tumors.

Amendment 2 (April 28, 2015):
Modified primary objective #3 to include only patients with "PD-L1 strong positive" tumors (defined as TPS ≥50% by IHC), and ORR in patients with PD-L1-positive tumors (defined as TPS exceeding 0% by IHC) was changed to a secondary objective.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Merck proposed the following indication for pembrolizumab in the sBLA submission:

"For the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy."

6.1.1 Methods

KEYNOTE 012 is a non-randomized, open-label, multi-cohort study, which included two cohorts of patients with recurrent or metastatic HNSCC. Cohort B consisted of patients with PD-L1-positive HNSCC treated with pembrolizumab at a dose of 10 mg/kg Q2W, while Cohort B2 consisted of patients with HNSCC regardless of PD-L1 status treated with pembrolizumab at a fixed dose of 200 mg Q3W. See Section 5.3.1 for detailed discussion of the study design.

The primary efficacy population considered for this review consists of 174 patients treated with pembrolizumab, across Cohorts B and B2 of KEYNOTE 012, with recurrent or metastatic HNSCC who had disease progression on or after treatment with platinum-containing chemotherapy. Of the 192 HNSCC patients treated in KEYNOTE 012, 18 patients who had never received platinum-containing chemotherapy were excluded from the efficacy population. Unless otherwise noted, the results presented here are based on the data cut-off of used for KEYNOTE 012 in the updated SCE (February 19, 2016). Efficacy data from the first 50 patients with ≥6 months of follow-up treated on KEYNOTE 055 is presented as supportive data (Section 6.1.10). All data presented for both studies are based on confirmed responses as per IRC assessment using RECIST 1.1, unless otherwise noted. Demographic, tumor characteristics, and prior treatment data for both study populations are presented in Tables 6, 7, and 8 in Section 6.1.2.

6.1.2 Demographics

Table 6: Demographic Characteristics of Patients in KEYNOTE 012 and KEYNOTE 055 (Reviewer Table)

Patient Characteristic	KEYNOTE 012 (n=174)	KEYNOTE 055 (n=50)
Age (years)		
Mean (SD)	60 (25-84)	60 (45-90)
≥65 years (%)	55 (32%)	15 (30%)
Gender		
Female (%)	31 (18%)	10 (20%)
Male (%)	143 (82%)	40 (80%)
Race		
White (%)	131 (75%)	43 (86%)
Asian (%)	27 (16%)	2 (4%)
Black (%)	10 (6%)	4 (8%)
Other (%)	6 (3%)	1 (0.2%)
Region		
USA (%)	134 (77%)	--
Europe (%)	16 (9%)	--
Asia (%)	24 (14%)	--
ECOG Performance Status		
0 (%)	51 (29%)	17 (34%)
1 (%)	123 (71%)	32 (64%)
Smoking Status		
Never smoker (%)	47 (27%)	22 (44%)
Ex-smoker (%)	111 (64%)	23 (46%)
Current smoker (%)	16 (9%)	5 (10%)

One patient in KEYNOTE 055 had ECOG PS 2

Table 7: Baseline Disease Characteristics for Patients in KEYNOTE 012 and KEYNOTE 055 (Reviewer Table)

Disease Characteristic	KEYNOTE 012 (n=174)	KEYNOTE 055 (n=50)
Locoregional vs distant		
M0 (%)	21 (12%)	6 (12%)
M1 (%)	152 (87%)	44 (88%)
HPV status		
Positive (%)	58 (33%)	16 (32%)
Negative (%)	115 (66%)	8 (16%)
Unknown (%)	1 (0.6%)	26 (52%)
Primary tumor site		
Oral cavity (%)	25 (14%)	6 (12%)
Oropharynx (%)	40 (23%)	14 (28%)
Tongue (%)	35 (20%)	13 (26%)
Pharynx (%)	7 (4%)	--
Hypopharynx (%)	11 (6%)	2 (4%)
Larynx (%)	15 (9%)	13 (26%)
Nasopharynx (%)	8 (5%)	--
Nasal Cavity (%)	11 (6%)	--
Maxilla (%)	2 (1%)	--
Unknown Primary (%)	6 (3%)	--
Other (%)	14 (8%)	2 (4%)

Disease status classified as Mx for one patient in KEYNOTE 012

Table 8: Prior Treatment for Patients in KEYNOTE 012 and KEYNOTE 055 (Reviewer Table)

Prior Treatment	KEYNOTE 012 (n=174)	KEYNOTE 055 (n=50)
Adjuvant/neoadjuvant (%)	85 (49%)	15 (30%)
Systemic therapy for recurrent/metastatic disease		
Median number of therapies	2	2
0 (%)	26 (15%)	1 (2%)
1 (%)	37 (21%)	7 (14%)
2 (%)	41 (24%)	23 (46%)
≥3 (%)	70 (40%)	19 (38%)
Specific chemotherapy		
Prior platinum & cetuximab (%)	110 (63%)	50 (100%)
Prior platinum without cetuximab (%)	64 (37%)	--
Prior taxane (%)	125 (72%)	39 (78%)
Radiation	166 (95%)	46 (92%)

Of the 26 patients in KEYNOTE 012 who had not received prior systemic therapy for recurrent or metastatic disease, all had received platinum as part of either induction (n=5), concurrent (n=10), or adjuvant (n=11) chemotherapy. Of these 26 patients, 14 had PD within 6 months of multimodality platinum-containing chemotherapy, while 12 had PD >6 months after completion of therapy.

6.1.3 Subject Disposition

At the time of the data cut-off used for KEYNOTE 012 in the updated SCE (February 19, 2016), 18 of 174 patients (10%) were still receiving treatment, while 119 patients (68%) had died. A total of 150 patients (86%) had discontinued treatment, including 5 patients (3%) in Cohort B who had completed 24 months of treatment without evidence of PD and had not restarted therapy at the time of data cut-off (see Section 6.1.9 of this review for further discussion of these patients). The majority of treatment discontinuations were due to PD (111 patients [64%]), while 22 patients (13%) discontinued due to AE. The reasons reported for treatment discontinuation for the remaining patients were withdrawal by subject (n=10), death (n=5), physician decision (n=1), and excluded medication (n=1). The median duration of follow-up was 8.9 months (range 0.2 to 30 months).

For both KEYNOTE 012 and KEYNOTE 055, a major protocol deviation was defined as any protocol deviation which may significantly/adversely impact the completeness,

accuracy, or reliability of the trial data or that may significantly or adversely affect a patient's rights, safety or well-being, while a clinically relevant major protocol deviation was defined as those that either affected a primary endpoint or a safety assessment. There were 55 major protocol deviations on Study KEYNOTE 012; see the Appendix of this review (Section 9.5) for list of protocol deviations provided by the Applicant. Only 3 of these deviations were assessed by the Applicant as clinically relevant deviations:

- Missing image assessment (imaging not acquired) - Week 32 (due 5/29/14), Week 64 (due 1/8/15), and Week 72 (due 3/5/15) scans were not performed. Partial response (PR) was documented beginning at Week 8 and continuing through Week 48 (imaging done 9/5/14). Tumor assessment not performed again until 5/19/15, at which time CR was noted. Patient had discontinued treatment due to an AE on 4/2/15.

- Patient discontinued inappropriately from the trial - Tumor response was assessed as CR by site review in Dec 2014. CR was confirmed by site review with next imaging assessment in Feb 2015, and patient was discontinued from study treatment due to confirmed CR. The Dec 2014 site response assessment was later updated to PR (July 2015). Study treatment was not resumed as the patient had died in April 2015 due to worsening congestive heart failure.

- Patient entered that did not satisfy the inclusion/exclusion criteria as stated in the protocol - Upon review of the patient's study biopsy, it was determined that the lesion biopsied was not a metastasis from the patient's laryngeal cancer but a new pancreatic malignancy. The patient received 1 cycle of treatment and was discontinued from study.

There were 16 protocol deviations related to failure to obtain appropriate informed consent; the majority of these were related to timing of signatures or failure to re-consent with modified informed consent form in a timely manner.

Reviewer comment: Details of the protocol deviations, provided in the CSR for KEYNOTE 012, were reviewed. Based on the information provided, this reviewer agrees with the Applicant's classification of the deviations determined to be not clinically relevant. While the 3 protocol deviations detailed above could be considered clinically relevant, taken together these would not be expected to have a significant impact on assessments of safety or primary and key secondary endpoints.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for the clinical review of this application is the confirmed ORR by RECIST 1.1 as assessed by independent central radiology review in the ASaT population of 174 patients treated with pembrolizumab across Cohorts B and B2 of

KEYNOTE 012 with recurrent or metastatic HNSCC who had disease progression on or after treatment with platinum-containing chemotherapy.

There were 28 patients with responses per RECIST 1.1, resulting in an ORR of 16.1% (95% CI: 11.0, 22.4). This included 8 CR (4.6%) and 20 PR (11.5%).

6.1.5 Analysis of Secondary Endpoints(s)

Duration of response (DOR) is considered a key secondary endpoint for this clinical review. The median time to response was 2.9 months (range 1.6 to 16.7 months); there were several delayed responses, including 1 CR and 1 PR after 10 months and 2 CRs after 15 months. Among the 28 responders, response duration ranged from 2.4+ months to 27.7+ months (with "+" indicating ongoing response), and the median duration of response had not been reached. Duration of response was ≥6 months for 82% of responders and ≥12 months for 73% of responders.

The lower end of the DOR range, 2.4+ months, is the result of a patient who withdrew April 28, 2015, two weeks after confirmation of PR (initial PR noted at 25.3 weeks, confirmed at 35.4 weeks) due to the inconvenience of traveling across country for study visits. The patient withdrew from further disease assessment follow-up but continues to be followed for survival. As of December 4, 2015, the patient was alive and had not initiated any new anti-cancer therapy.

There were 148 PFS events reported (85%), and median PFS was 2.0 months (95% CI: 1.9, 2.1). At the time of data cut-off, 119 patients (68%) had died, and median OS was 8.5 months (95% CI: 6.2, 10.2).

Confirmed ORR using RECIST 1.1 as assessed by investigator was 18.4% (95% CI: 12.9, 25.0) in the ASaT population.

6.1.6 Other Endpoints

The ORR per immune-related RECIST criteria as assessed by independent central radiology review was identical to ORR per RECIST 1.1 at 16.1% (95% CI 11, 22.4).

6.1.7 Subpopulations

Table 9: ORR and DOR by Prior Treatment (Platinum Only vs Platinum-Cetuximab) (Reviewer Table)

	Platinum only (n=64)	Platinum-cetuximab (n=110)	All (n=174)
ORR, %	20.3	13.6	16.1
95% CI	11.3, 32.2	7.8, 21.5	11.0, 22.4
CR, %	4.7	4.5	4.6
PR, %	15.6	9.1	11.5
Responders	N=13	N=15	N=28
DOR range, months	4.3, 27.7+	2.4+, 24.0+	2.4+, 27.7+
DOR ≥6 months	85%	80%	82%

Median DOR not reached in either group. CR, complete response; PR, partial response

Reviewer comment: The platinum only subgroup likely represents a less heavily pretreated population of patients, in which case a higher ORR would not be unexpected. While the point estimate of ORR was higher for the group of patients not previously treated with cetuximab, the confidence intervals for the subgroups in Table 9 overlap. Importantly, prolonged durations of response were observed in the platinum only subgroup and the platinum-cetuximab subgroup, with upper range of DOR >24 months in both. In addition, a similar proportion of patients in each subgroup experienced DOR ≥6 months and ≥12 months.

Table 10: ORR and DOR by HPV status (Reviewer Table)

	HPV-negative (n=115)	HPV-positive (n=58)
ORR, %	15.7	17.2
95% CI	9.6, 23.6	8.6, 29.4
DOR range, months	2.4+, 24.0+	4.2, 27.7+

One patient with HPV status unknown not included in table

Reviewer comment: ORR was similar for patients with HPV-negative and HPV-positive tumors, with upper range of DOR >24 months observed in both subgroups.

Table 11: Subgroup Analyses of ORR (Reviewer Table)

	N	ORR, % (95% CI)
ASaT	174	16.1 (11, 22.4)
Age		
<65 years	119	16.0 (9.9, 23.8)
≥65 years	55	16.4 (7.8, 28.8)
Gender		
Male	143	15.4 (9.9, 22.4)
Female	31	19.4 (7.5, 37.5)
Race		
White	131	16.0 (10.2, 23.5)
Non-white	40	17.5 (7.3, 32.8)
ECOG PS		
0	51	31.4 (19.1, 45.9)
1	123	9.8 (5.1, 16.4)
Smoking status		
Current or ex-smoker	127	18.1 (11.8, 25.9)
Never smoker	47	10.6 (3.5, 23.1)
Locoregional vs distant		
M0	21	9.5 (1.2, 30.4)
M1	152	17.1 (11.5, 24.1)
Prior systemic therapy for recurrent or metastatic disease		
Yes	148	15.5 (10.1, 22.4)
No	26	19.2 (6.6, 39.4)

Non-white includes Asian, Black, Multi-racial, or American Indian/Alaskan Native
3 patients who did not report race are not included in race subgroup analyses; 1 patient with baseline stage Mx is not included in locoregional/distant subgroup analyses

Reviewer comment: In general, ORR was similar across subgroups, with overlapping confidence intervals. The exception to this was ECOG PS, with a higher ORR observed in patients with ECOG PS 0 (31.4%) versus ECOG PS 1 (9.8%). While the 95% CI of the ORR for patients with ECOG PS 0 is wide, confidence intervals for these two subgroups do not overlap. This prompted additional analyses for this group during this review.

The duration of treatment for the subgroup of patients with ECOG PS 0 (mean 43.6 weeks [range 0.1 to 107.0]) was significantly longer than for the ECOG PS 1 subgroup (mean 18.4 weeks [range 0.1 to 121.1]), with mean number of infusions for the ECOG PS 0 subgroup 17 (range 1-52) versus 8 (range 1-56) for the ECOG PS 1 subgroup.

Reviewer comment: The differing durations of treatment are at least partially explained by an increased rate in the ECOG PS 1 subgroup of dose modification due to AE (48%

vs 20%) and discontinuation of pembrolizumab treatment due to AE (24% vs 4%; assessed as drug-related, 9% vs 2%). See Table 28 in Section 7.5.3 of this review. In addition, if the symptoms leading to a classification of ECOG PS 1 are related to significant locoregional tumor burden, as is likely the case for some patients, such patients may be more likely to experience rapid symptomatic disease progression.

Table 12: ORR and DOR by ECOG Performance Status (Reviewer Table)

	ECOG PS 0 (n=51)	**ECOG PS 1 (n=123)**	**All (n=174)**
ORR, %	31.4	9.8	16.1
95% CI	19.1, 45.9	5.1, 16.4	11.0, 22.4
Responders	N=16	N=12	N=28
DOR range, months	5.8, 27.7+	2.4+, 24.0+	2.4+, 27.7+
DOR ≥6 months	94%	67%	82%

Median DOR not reached in either group.

Reviewer comment: Median DOR was not reached in either subgroup, and prolonged DOR were observed in both subgroups, including DOR ranging from 2.4+ to 24.0+ months in the ECOG PS 1 subgroup (with the low end of the range for a non-ongoing DOR 4.2 months). Of the responding patients in the ECOG PS 1 subgroup, more than half had response lasting ≥6 months. These findings regarding duration of response suggest that pembrolizumab therapy may still have significant benefit in the population of HNSCC patients with ECOG PS 1 despite a lower ORR. These findings will need to be confirmed when data from the ongoing randomized study, KEYNOTE 040, is submitted for review.

ORR by PD-L1 status as assessed by TPS was presented by the Applicant for all 192 patients with HNSCC enrolled in KEYNOTE 012 and is presented in Table X.

Table 13: ORR by PD-L1 status (Reviewer Table)

N=192	**PD-L1 negative**	**PD-L1 positive**	
	TPS = 0% (n=63)	**1% ≤ TPS < 50% (n=71)**	**TPS ≥ 50% (n=53)**
ORR, %	17.5	14.1	22.6
95% CI	9.1, 29.1	7.0, 24.4	12.3, 36.2

5 patients with TPS unknown (ORR 20%) not included in table

Exploratory analyses of ORR by PD-L1 status as assessed by CPS were also presented by the Applicant but are not relevant to this review, as the utility of this scoring system is still being evaluated by the Applicant.

Reviewer comment: Responses were observed in patients with PD-L1 negative tumors and PD-L1 positive tumors, with overlapping confidence intervals for ORR across three subgroups defined by TPS.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosage regimens used in Cohorts B and B2 of KEYNOTE 012 resulted in different levels of exposure to pembrolizumab, with exposure approximately 4-fold higher for the 10 mg/kg Q2W dosage regimen (see Section 4.4.3 of this review). Demographic characteristics were similar across these cohorts, with the exception of a higher percentage of white (85% vs 71%) and black patients (11% vs 3%) and a lower percentage of Asian patients (2% vs 22%) in Cohort B compared to Cohort B2. There was a higher proportion of patients with HPV-positive tumors in Cohort B (42% vs 30%), but a lower proportion of never smokers (15% vs 32%). A higher proportion of patients in Cohort B had received ≥2 prior systemic therapies for recurrent or metastatic disease (71% vs 61%), both prior platinum and cetuximab (72% vs 60%), and prior taxane (76% vs 70%).

ORR and DOR are presented by cohort and by prior treatment (platinum only or platinum-cetuximab) in Table 14.

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Table 14: ORR and DOR by Cohort and Prior Treatment (Reviewer Table)

	Cohort B (10 mg/kg Q2W)	**Cohort B2 (200 mg Q3W)**	**Cohorts B+B2**
Platinum only, n	15	49	64
ORR	26.7%	18.4%	20.3%
95% CI	7.8, 55.1	8.8, 32.0	11.3, 32.2
DOR range, months	7.6, 27.7	4.3, 15.2	4.3, 27.7
Median f/u, months	22.3	9.1	10.6
Platinum-cetuximab, n	38	72	110
ORR	13.2%	14.9%	13.6%
95% CI	4.4, 28.1	6.9, 24.1	7.8, 21.5
DOR range, months	4.2, 24.0	2.4, 15.0	2.4, 24.0
Median f/u, months	7.2	6.4	6.6
Combined, n	**53**	**121**	**174**
ORR	**17.0%**	**15.7%**	**16.1%**
95% CI	**8.1, 29.8**	**9.7, 23.4**	**11.0, 22.4**
DOR range, months	**4.2, 27.7**	**2.4, 15.2**	**2.4, 27.7**
Median f/u, months	**9.6**	**8.5**	**8.9**

Reviewer comment: In the efficacy population for KEYNOTE 012 (n=174), ORR was similar for the different dosage regimens used in Cohort B (ORR 17.0%) vs Cohort B2 (ORR 15.7%). Given the small number of patients in the platinum only group in Cohort B (n=15), this ORR, with its wide confidence interval, cannot be interpreted as superior to the ORR in a similar population in Cohort B2. Durations of response >12 months were observed in both Cohort B and B2. Cohort B was initiated over 1 year prior to the addition of Cohort B2 to KEYNOTE 012 (initial submission of protocol February 2013, amendment to add Cohort B2 May 2014), which is the most likely reason for the higher upper range of DOR observed in Cohort B vs B2.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See Section 6.1.5 of this review for duration of response data. Per protocol, for both KEYNOTE 012 and KEYNOTE 055, treatment with pembrolizumab was to continue until confirmed radiologic PD, unacceptable toxicity, or completion of 24 months of study therapy. Six of the 60 patients in Cohort B of KEYNOTE 012 completed 24 months of treatment with pembrolizumab without evidence of PD; all stopped treatment as per protocol. Of these 6 patients, 5 were alive and still off treatment at the time of the updated data cut-off date. One patient who had stable disease at completion of 24

months of therapy had PD by site assessment documented 8 weeks after discontinuation of pembrolizumab. This patient restarted pembrolizumab on November 24, 2015, and was still receiving treatment with pembrolizumab as of the data cut-off date of February 19, 2016 (12 weeks). As of February 19, 2016, for the 5 patients who remained off treatment, 3 were documented as in CR, 2 as in PR, and 1 as having stable disease. These patients had been off treatment ranging from approximately 19 weeks to 27 weeks.

While discontinuation of pembrolizumab following complete response was allowed per protocol, this was only done in one patient ((b) (6)), who was later determined not to have achieved CR. This patient had PR initially reported on Day 51 of treatment and CR per site assessment initially reported on Day 505, with confirmation by site assessment on Day 561. Pembrolizumab was discontinued in the setting of presumed confirmed CR, with last dose received on Day 588. However, CR was not confirmed by central radiology assessment, with findings assessed as still consistent with PR. The patient had a pre-existing diagnosis of congestive heart failure and died 39 days after receiving his last dose pembrolizumab (day 626) due to worsening congestive heart failure, assessed by investigator as not related to study treatment (see Section 7.3.1 of this review).

A discussion of tolerance effects is not applicable to this review.

6.1.10 Additional Efficacy Issues/Analyses

KEYNOTE 055

For KEYNOTE 055, all data provided in the CSR are based on the cut-off date of November 25, 2015, which was ≥ 6 months after the 50th enrolled subject was initially treated with pembrolizumab. The first patient was enrolled (signed informed consent) in the study on October 24, 2014, and the last patient included in this partial dataset was enrolled on May 6, 2015. The data included from KEYNOTE 055 in the updated SCE is based on a cut-off date of January 29, 2016.

Demographic, tumor characteristic, and prior treatment data for the patients in KEYNOTE 055 are presented in Tables 6, 7, and 8 in Section 6.1.2 of this review. At the time of the data cut-off used for KEYNOTE 055 in the updated SCE, 7 of 50 patients (14%) were still receiving treatment. A total of 43 patients (86%) had discontinued treatment. The majority of treatment discontinuations were due to PD (31 patients [62%]), while 3 patients (6%) discontinued due to AE. The reasons reported for treatment discontinuation for the remaining patients were clinical progression (n=7), physician decision (n=1), and excluded medication (n=1). All patients were still alive at the time of data cut-off. The median duration of follow-up was 8.4 months (range 0 to 14.2 months).

There were 18 major protocol deviations among the relevant 50 patients from KEYNOTE 055; see the Appendix of this review (Section 9.5) for list of protocol deviations provided by the Applicant. Only one deviation was considered clinically relevant by the Applicant:

- Patient entered that did not satisfy the inclusion/exclusion criteria as stated in the protocol – Per eligibility criteria, the patient did not have HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx. Patient had a diagnosis of HNSCC of the right maxillary sinus. This patient is included in the safety and efficacy analyses.

Reviewer comment: Details of the protocol deviations, provided in the CSR for KEYNOTE 055, were reviewed. Based on the information provided, this reviewer agrees with the Applicant's classification of the deviations determined to be not clinically relevant. The single protocol deviation detailed above could be considered clinically relevant but would not be expected to have a significant impact on assessments of safety or primary and key secondary endpoints.

For the 50 patients with efficacy data reported from KEYNOTE 055, the confirmed ORR by RECIST 1.1 as assessed by independent central radiology review was 18% (95% CI: 8.6, 31.4), with all 9 responses categorized as PR. The median time to response was 2.1 months (range 2.0 to 3.3 months). The median duration of response was 6.9 months, with response durations ranging from 3.0 months to 8.3+ months.

Reviewer comment: The ORR observed to date for KEYNOTE 055 is similar to that reported for KEYNOTE 012. The difference in duration of response in KEYNOTE 055 compared to KEYNOTE 012 is most likely attributable to the difference in duration of follow-up between the trials, with a maximum follow-up duration of 8.3 months for KEYNOTE 055 versus 30 months in KEYNOTE 012.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

For a discussion of the review strategy for this sBLA, see Section 5.2 of this review. The clinical reviewer confirmed the Applicant's safety analyses of KEYNOTE 012 and KEYNOTE 055, conducting analyses of primary data using the MAED program. For analysis of the safety data from KEYNOTE 012, the datasets used for this review were the updated datasets submitted with the SCS – Safety Update Report. Safety data was

not updated for KEYNOTE 055, so safety assessments for this study are based on the CSR and datasets with a cut-off date of November 25, 2015.

In this review, major safety results (Section 7.3) are presented for KEYNOTE 012 and KEYNOTE 055, unless otherwise noted. Supportive safety results (Section 7.4) are presented for KEYNOTE 012, with the exception of common AEs (Section 7.4.1) which are presented for both studies. Pooled safety data, as reported by the Applicant, from 2799 clinical trial patients with NSCLC (treated in KEYNOTE 001 and 010) or melanoma (treated in KEYNOTE 001, 002, and 006), referred to as "pooled melanoma and NSCLC population" is considered to represent the known safety profile of pembrolizumab and is used for purposes of comparison in this review.

7.1.2 Categorization of Adverse Events

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 was used to grade adverse events. The Applicant presents adverse events using MedDRA's system organ class hierarchy. This creates a "splitting" effect for some AE terms such as cough and productive cough, fatigue and asthenia, and face edema and swelling face. Listings provided by the Applicant included all AEs occurring from Day 1 through 30 days after the last dose of pembrolizumab, serious AEs (SAEs) occurring from Day 1 through 90 days after the last dose of pembrolizumab, and AEs resulting in death occurring up to 90 days after the last dose of pembrolizumab.

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

Pooled safety data from 2799 clinical trial patients with NSCLC (treated in KEYNOTE 001 and 010) or melanoma (treated in KEYNOTE 001, 002, and 006), referred to as "pooled melanoma and NSCLC population", is used for purposes of comparison in this review.

7.2 Adequacy of Safety Assessments

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

The primary safety analysis presented by the Applicant for pembrolizumab for patients with recurrent or metastatic HNSCC includes 192 patients from KEYNOTE 012; of these, 132 patients (69%) received pembrolizumab at the dose being recommended for the currently proposed HNSCC indication, a fixed dose of 200 mg Q3W. Exposure information by cohort is presented in Table X.

Table 15: Extent of Exposure for Cohort B and Cohort B2 (Reviewer Table)

	Cohort B 10 mg/kg Q2W (n=60)	**Cohort B2 200 mg Q3W (n=132)**	**Total (n=192)**
Weeks on therapy			
Mean	29.9	23.8	25.7
Median	14.4	12.6	14.2
Standard deviation	34.2	25.9	28.8
Range	0.1, 121.1	0.1, 85.1	0.1, 121.1
Number of doses			
Mean	15.0	8.5	10.5
Median	8	5	6
Standard deviation	15.8	8.3	11.6
Range	1, 56	1, 28	1, 56
% exposed for ≥6 months	32%	33%	32%
% exposed for ≥12 months	20%	18%	19%

Patient and disease characteristics for the 192 patients included in the safety population for KEYNOTE 012 were similar to those for the 174 patients included in the primary efficacy population.

Extensive safety information is available related to the use of pembrolizumab at similar or higher doses for other indications, including the approved melanoma and NSCLC indications.

7.2.2 Explorations for Dose Response

The exposure with the 10 mg/kg Q2W dosage regimen is approximately 4-fold higher than the exposure with the 200 mg Q3W fixed dose (see Section 4.4.3 of this review).

Only 25% of patients (43/174) in the KEYNOTE 012 HNSCC efficacy population had PK data available, so analysis of the exposure-response relationship in this population is inconclusive. However, the ORRs observed using the two dosage regimens are similar. See the FDA Clinical Pharmacology review and Section 6.1.8 of this review.

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 tests conducted as part of routine clinical testing and the frequency of such testing are detailed in the Study Flow Charts included in Sections 9.4 of this review. The safety assessment methods and time points described in the protocols seem adequate for the population, disease, and indication being investigated.

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 nivolumab, immune-mediated adverse reactions have been observed in patients treated with pembrolizumab. The safety information submitted by the Applicant includes evaluation of adverse events of special interest (AEOSI), which include immune-mediated AEs (irAEs) and infusion reactions. These AEs are discussed in Section 7.3.5 of this review.

7.3 Major Safety Results

7.3.1 Deaths

Deaths reported include those occurring up to 90 days after the last dose of pembrolizumab. A total of 19 deaths (10%) within this period were reported among the 192 HNSCC patients in KEYNOTE 012, with 8 deaths (13%) in Cohort B and 11 deaths (8%) in Cohort B2. Six deaths were attributed to malignant neoplasm progression, while 10 deaths were considered related to an AE and 3 deaths were reported as due to unknown cause.

A grade 5 AE with preferred term other than “death” was reported for 14 of these 19 patients: 3 cases of aspiration pneumonia or pneumonia (2 in Cohort B, 1 in Cohort B2), 3 cases of respiratory failure (all in Cohort B), and 1 case each of dyspnea, respiratory

distress, tumor hemorrhage, post-procedural hemorrhage, cardiac arrest, congestive cardiac failure, arterial injury, and pulmonary embolism. None of these grade 5 AEs were considered related to study drug per investigator assessment. Additional details are presented in this section.

Reviewer comment: Review of the details of these deaths does not raise any new safety concerns relative to the safety profile of pembrolizumab reflected in the current USPI (see additional reviewer comments in this section).

Aspiration pneumonia, pneumonia

- (b) (6) (Cohort B2): This 73 year old man started pembrolizumab (b) (6) and received 2 doses; disease sites at study entry were oral cavity and lymph node. The last dose of pembrolizumab was given (b) (6); on this same day, chest x-ray showed bronchiectasis and ill-defined nodules, as well as ground-glass opacity in bilateral lower lobes. Two days later, he presented with increased cough, sputum, and intermittent dyspnea and was assessed as having grade 3 aspiration pneumonia. Cycle 3 dose of pembrolizumab was held (b) (6), and he was admitted for further evaluation and treatment. CT showed variable change of metastatic lymph nodes, with decreased size in right side of neck but increased size in left parotid area and parapharyngeal space. Bronchoalveolar lavage (BAL) ((b) (6)) results were consistent with aspiration pneumonia, with purulent thick secretions from RML and RLL bronchi; Gram stain showed Enterobacter cloacae and Staphylococcus aureus. He was treated with antibiotics; high dose steroids were not given. BAL cultures reported MRSA on (b) (6). CT scan (b) (6) showed increase in right lung consolidation. He was transferred to a local hospital (b) (6) with aspiration pneumonia ongoing. He died (b) (6)

- (b) (6) (Cohort B): This 68 year old man started pembrolizumab (b) (6) and received 6 doses; disease sites at study entry were oropharynx, tonsils, lymph nodes, and right parapharyngeal space. Past medical history included aspiration pneumonia. Last dose of pembrolizumab was given on (b) (6). He presented (b) (6) with shortness of breath, cough, altered mental status, and increased secretions and was hospitalized in ICU with diagnosis of “respiratory distress”. The same day he was diagnosed with non-serious AEs of nausea and vomiting (both grade 2 and considered drug-related) and the following non-serious AEs considered not related to study drug: aspiration pneumonia (grade 3), dehydration, altered mental status, worsening hypokalemia, constipation, atrial fibrillation, ventricular fibrillation, cough, and hypotension. Chest x-ray showed “persistent, re-developing infiltration in the left lower lung”. CT scan was reported as showing developing bilateral upper lobe and progressive bilateral lower lobe infiltration/consolidation and/or sub-segmental atelectasis. He received antibiotics for treatment of aspiration pneumonia; high dose steroids were not administered. On (b) (6), he developed rapid ventricular

response and began to desaturate, then developed asystole. Cardiac life support was initiated, including defibrillation for ventricular fibrillation, but the patient died.

- (b) (6) (Cohort B): This 62 year old man started pembrolizumab (b) (6) and received 4 doses; disease sites at study entry were right pharyngo-epiglottic fold, tongue base, bone, liver, lymph node, and lung. Last dose of pembrolizumab was given on (b) (6). On (b) (6), he experienced a syncopal episode at home. On (b) (6), he collapsed and was unresponsive, which led to hospitalization the same day for diagnosis of post-obstructive pneumonia. In addition to grade 3 pneumonia, SAE of grade 4 anemia was reported. He was placed on BiPAP. Chest x-ray showed pneumonia in right upper lobe, while CT showed fluid in the abdomen. He was transfused 2 units of blood; bleeding was thought to likely be due to erosion of cancer into a vessel. He received antibiotics for pneumonia; he was not treated with high dose steroids. On (b) (6), the CT scan showed opacities in right upper & middle lobes, pleural effusion, and metastases, as well as hemoperitoneum; findings were assessed as consistent with progressive disease. He was discharged with (b) (6) and described as recovered from pneumonia; anemia was considered likely due to bleeding liver metastasis. Four days later, (b) (6), he visited ER for lightheadedness & dizziness, attributed to dehydration, along with chronic cough and was hospitalized; SAE of grade 3 pneumonia was again reported. He was treated with IVF and antibiotics. Chest x-ray showed right upper lobe and left basilar airspace opacities. He also had altered mental status attributed to hypoglycemia, dehydration, and hypercalcemia. He was discharged the same day to hospice. Chest x-ray (b) (6) showed interval worsening of bilateral airspace disease, and he died on (b) (6).

Reviewer comment: Pneumonia, particularly aspiration pneumonia, is a common occurrence in the advanced HNSCC patient population and is not unexpected as a cause of death. There are no details in the above cases to raise suspicion for immune-mediated pneumonitis.

<u>Respiratory failure, dyspnea, and respiratory distress</u>

- (b) (6) (Cohort B): This 76 year old man started pembrolizumab in (b) (6) 2013 and received 46 doses; disease sites at study entry were tonsil and lymph nodes. Dosing was interrupted between (b) (6) and (b) (6) due to weakness and respiratory failure and between (b) (6) and (b) (6) due to pneumonia. He received his last dose of pembrolizumab on (b) (6), at which point treatment was discontinued due to completion of 2 years of treatment. On (b) (6), approximately 4 weeks after last dose of pembrolizumab, he presented with coughing and difficulty breathing and was admitted to the hospital with a diagnosis of acute hypoxic respiratory failure. Oxygen saturation was 70%, and he was placed on BiPAP; he was subsequently intubated, and antibiotics were started due to concern for

pneumonia. The CRF contained no mention of corticosteroid use, indicating pneumonitis was not considered a likely diagnosis. He died on (b) (6).

- (b) (6) (Cohort B): This 57 year old man started pembrolizumab (b) (6) and received 3 doses prior to discontinuation for PD; disease sites at study entry were tongue and lung. Last dose of pembrolizumab was given on (b) (6). He presented on (b) (6) with wheezing, assessed by investigator as grade 2, related to study drug, and immune-related; this represented worsening of baseline wheezing. Chest x-ray showed potential interstitial pneumonitis, and he was started on high-dose steroids (prednisone 60 mg daily). Repeat x-ray on (b) (6), after approximately1 week of steroid treatment, showed no improvement. CT scan done (b) (6) showed left base of tongue mass decreased in size, numerous pulmonary nodules and extensive mediastinal adenopathy consistent with metastatic disease, as well as new, potentially necrotic lymphadenopathy in the left lower neck. At the end-of-treatment visit on (b) (6), he reported 2 days of worsening productive cough, non-cardiac chest pain, inability to speak, and rattling in the lungs. CT scan done (b) (6) showed PD with a new laryngeal mass displacing the right vocal cords, resulting in airway stenosis just above the vocal cords. He was admitted to the hospital, and he died the following day with hypoxic respiratory failure reported as a grade 5 AE. The discharge diagnosis was death due to malignant neoplasm progression.

- (b) (6) (Cohort B): This 69 year old man started pembrolizumab (b) (6) and received 9 doses; disease sites at study entry were pharynx, neck, lymph nodes, supraglottic larynx, hypopharynx, and lung. Last dose of pembrolizumab was given on (b) (6). On (b) (6), he was admitted to the hospital with grade 3 hemoptysis from tracheostomy site. Laryngoscopy showed bleeding from tumor site. He was transfused red blood cells; hemoptysis resolved (b) (6). On (b) (6), during visit to ENT clinic, he was being suctioned when he suddenly became limp without a pulse. Chest compressions were started, and spontaneous circulation returned, and he was transferred to ICU. He subsequently became bradycardic, desaturated, and hypotensive. He was assessed for orotracheal intubation, but a large laryngeal mass inferior to the epiglottis was seen on direct laryngoscopy. Chest x-ray revealed near complete collapse of the right lung, and bronchoscopy showed a large mass obstructing the right mainstem bronchus near the carina and adherent to the proximal trachea. After consultation with his family, DNR/DNI orders were issued and comfort care was initiated; he died the same day, with cause of death reported as respiratory failure.

- (b) (6) (Cohort B2): This 56 year old man started pembrolizumab (b) (6) and received 2 doses; disease sites at study entry were larynx, lung, bone, and kidney. Last dose of pembrolizumab was given on (b) (6). He was admitted to the hospital on (b) (6) for treatment of grade 3 hypercalcemia and was treated with zolendronic acid and IV fluids. Grade 1 acute kidney injury, worsening grade 2

hyponatremia, and grade 2 fatigue were reported on (b) (6). CT scan (b) (6) demonstrated thickening of the wall of a cavitary lesion, reportedly indicative of progressive disease. Calcium levels had returned to baseline, and he was discharged on (b) (6). On (b) (6), his spouse contacted the clinical site to report that the patient was confused and had an exacerbation of dyspnea. He presented to the ER already on BiPAP. Due to minimal improvement with BiPAP, he was intubated, but he died shortly after the removal of BiPAP, prior to intubation. The primary cause of death was reported as malignant neoplasm progression.

- (b) (6) (Cohort B2): This 60 year old man started pembrolizumab (b) (6) 4 and received 2 doses; disease sites at study entry were tonsil and lymph nodes. Last dose of pembrolizumab was given on (b) (6). On (b) (6), he was found unresponsive at home. He was taken to local emergency department, where he was intubated. A tracheostomy tube could not be placed due to large tumor involvement at the possible tracheostomy site. He died the same day with cause of death reported as malignant neoplasm progression.

Reviewer comment: For 4 of these 5 cases, including one patient ((b) (6)) who had an AE of pneumonitis reported, details are consistent with death due to underlying malignancy. In the remaining case ((b) (6)), the patient was treated for pneumonia; he had also been previously hospitalized for pneumonia approximately 1 month earlier. There is no evidence from review of the narrative or the CRF that he received steroids as part of treatment during this hospitalization, indicating that immune-mediated pneumonitis was not suspected, and the investigator assessed the SAE of acute hypoxic respiratory failure as not related to study medication. As previously noted, pneumonia is a common occurrence in the advanced HNSCC patient population and not unexpected as a potential cause of death.

Tumor hemorrhage

(b) (6) (Cohort B2): This 62 year old man started pembrolizumab (b) (6) and received 2 doses; disease sites at study entry were hypopharynx, lymph nodes, and sub cutis. The last dose of pembrolizumab was given (b) (6). He had a history of bleeding from subcutaneous metastasis (grade 1). On (b) (6), he experienced worsening of tumor hemorrhage (grade 2). He was hospitalized on (b) (6) due to worsening of bleeding from subcutaneous metastasis. An astriction (details unknown) was performed, and the bleeding was transiently stopped. On (b) (6), glycerin (+) zinc chloride (MOHU) ointment was applied in addition to astriction, and study treatment was temporarily stopped due to bleeding. CT scan showed that the tumor did not invade the internal or external carotid artery. On (b) (6), study treatment was resumed, and he completed Cycle 2 without any untoward effects. On an unknown date, the tumor partially peeled off from the cervical skin. On (b) (6),CT scan showed that the internal cervical artery was exposed on the surface of the neck lesion due to shedding of the tumor. On (b) (6), his hemoglobin dropped to 6.9 g/dl (baseline 14.5 g/dL) due

to hemorrhage at the tumor site; he was transfused blood. On (b) (6), the internal carotid artery ruptured due to tumor metastasis, and he died.

Post-procedural hemorrhage

(b) (6) (Cohort B2): This 72 year old man started pembrolizumab (b) (6) and received 13 doses; disease sites at study entry were thyroid, lymph node, and lung. The last dose of pembrolizumab was given (b) (6). He presented (b) (6) with complaint of intermittent tracheostomy site bleed; this was classified as grade 1 from (b) (6) to (b) (6). He presented to the hospital (b) (6) with severe hemoptysis from tracheostomy site bleed; decision was made to focus on comfort care only, and he died the same day.

Cardiac arrest

(b) (6) (Cohort B): This 48 year old woman started pembrolizumab (b) (6) and received 8 doses; disease sites at study entry were tongue and lymph nodes. Last dose of pembrolizumab was given on (b) (6). On (b) (6), she experienced cardiac arrest and was found unresponsive and bleeding by family members at home. ACLS interventions were initiated, and she was transported to local emergency department. The source of bleeding was not specified in the records. Resuscitation efforts were unsuccessful. The cause of death was reported as cardiac arrest. Per investigator, this cardiac arrest was considered as not related to pembrolizumab.

Congestive cardiac failure

(b) (6) (Cohort B): This 83 year old man started pembrolizumab (b) (6) and received 41 doses prior to discontinuation for PD; disease sites at study entry were neck, lung, and skin. Past medical history included atrial fibrillation, coronary artery disease, and congestive heart failure (CHF). Last dose of pembrolizumab was given on (b) (6). On (b) (6), prior to starting treatment with pembrolizumab, his ECG showed AV dual-paced rhythm with occasional ventricular-paced complexes. He was hospitalized (b) (6) for exacerbation of CHF. On (b) (6), pembrolizumab was discontinued, reportedly for complete response (per site assessment). The patient's wife communicated to the investigator that the patient had decided to no longer receive treatment for his CHF, and the patient transitioned to comfort care. His CHF worsened, resulting in his death on (b) (6) due to worsening CHF.

Arterial injury

(b) (6) (Cohort B2): This 60 year old man started pembrolizumab (b) (6) and received 2 doses; disease sites at study entry were neck lymph node and lung. Last dose of pembrolizumab was given (b) (6). On (b) (6) he reportedly experienced SAE of injury to the carotid artery at home; he died the same day. His last study visit prior to death was for his 2nd dose of study medication; he reportedly had extensive disease in the neck.

Pulmonary embolism
(b) (6) (Cohort B2): This 67 year old man started pembrolizumab (b) (6) and received 2 doses; disease sites at study entry were tongue, lymph node, neck, bone, and lung. The last dose of pembrolizumab was given (b) (6) On (b) (6) pulmonary embolism (PE, grade 4) was diagnosed. CTshowed probable PE in segmental pulmonary arteries of the RLL; probable metastases in the RLL, lower mediastinum, and LLL were larger compared to the prior examination. He was taken off trial due to increasing fatigue and dyspnea. On an unspecified date, he became dsypneic while sitting in his chair with oxygen saturation 73% while receiving oxygen via nasal cannula; he was started on non-rebreather mask with high flow oxygen after which his oxygen saturation increased to 100%, although he still reported significant dyspnea. He never received treatment with high dose steroids. On (b) (6), he was given morphine for symptoms of dyspnea; he was reportedly given naloxone the same day. Lung auscultation revealed poor airflow bilaterally with mild diffuse wheezing. His code status was DNR/DNI; he died the same day. AE of pulmonary embolism was reported as fatal (grade 5), but cause of death was reported as respiratory distress and respiratory failure from disease progression.

The following synopses are based on review of available information for the 5 patients reported as having grade 5 AE of “death”:

- (b) (6) (Cohort B, 10 mg/kg Q2W): This 50 year old man started pembrolizumab (b) (6) and received 20 doses; disease sites at study entry were tongue, lymph node, lung, and soft tissue mass. Last dose of pembrolizumab was given (b) (6). Pembrolizumab was held for SAE of left perimandibular space abscess (reported initially (b) (6) and then (b) (6)), which reportedly resolved by (b) (6). Starting (b) (6), he reported occasional bloody sputum. He was found unresponsive at home (b) (6). The site investigator reported that patient had been doing well and had been responding to treatment with no recent toxicities except for an enlarging left mandibular fistula since (b) (6) where necrotic tumor appeared to be responding to treatment.

- (b) (6) (Cohort B2, 200 mg Q3W): This 65 year old man started pembrolizumab (b) (6) and received 5 doses; disease sites at study entry were tongue, lymph node, and lung. The last dose of pembrolizumab was given (b) (6). On (b) (6), while traveling, he stated he felt weak and went to bed. He died in his sleep early in the morning of (b) (6). It was not known if autopsy was performed. The only reported AE for this patient was grade 1 nausea.

- (b) (6) (Cohort B2, 200 mg Q3W): This 44 year old man started pembrolizumab (b) (6) and received 1 dose; disease sites at study entry were lymph node, nasal cavity, pharynx, bone, and maxilla. The only dose of pembrolizumab was given (b) (6). He died at home in his sleep on (b) (6) with cause of death reported as unknown. The only available significant information was that his abdominal pain had

increased recently, but he had not sought medical attention. According to his wife, he had not experienced any diarrhea or bleeding and continued to move bowels daily; he had no shortness of breath and no fever, as far as she was aware.

- (b) (6) (Cohort B2, 200 mg Q3W): This 44 year old woman started pembrolizumab (b) (6) and received 1 dose; disease sites at study entry were oral cavity, liver, and lung. Only dose of pembrolizumab was given on (b) (6). On (b) (6) she was reportedly diagnosed with grade 3 pneumonitis. She presented with hypoxia (oxygen saturation 76%) and reported shortness of breath and cough for 3 to 4 weeks. Chest x-ray showed new partially cavitary RML mass with superimposed moderate pleural effusion and interval increased atelectasis/consolidation. CT showed RML mass increased in size and cavitated; RLL consolidation/atelectasis; new lingular consolidation; and RUL consolidation. Oxygen saturation improved to 91% with 2 liters oxygen. She was treated with antibiotic and antifungal. She was not treated with steroids. On (b) (6), bronchoscopy with BAL revealed copious upper airway secretions and large endobronchial mass in the RLL consistent with broncholith. BAL cultures grew Candida parapsilosis. CT scan (b) (6) showed unchanged cavitary RML mass, improving lingular consolidation and patchy peribronchiolar nodular opacities particularly in the LLL, and bi-apical ground-glass opacities. She was discontinued from study, reportedly due to SAE of pneumonitis, and she opted for palliative care. Last contact with patient was (b) (6). Although discharge diagnosis was pneumonitis, results of cultures and discharge summary suggested infectious etiology co-existed with pneumonitis. She died on (b) (6), approximately 1 week after last contact with site. Autopsy was not performed. Grade 3 pneumonitis was reported by investigator as immune-related and an event of clinical interest; cause of death was reported as unknown.

  Reviewer comment: Although grade 3 pneumonitis was reported in this case, there is no indication the patient received treatment with high dose steroids. Based on the reported findings on CT scans and bronchoscopy, her presentation and death were more likely due to infectious pneumonia and/or underlying malignancy.

- (b) (6) (Cohort B2, 200 mg Q3W): This 60 year old man started pembrolizumab (b) (6) and received 7 doses; disease sites at study entry were oropharynx, lung, subcutaneous chest wall, and neck. Last dose of pembrolizumab was given on (b) (6). Approximately 10 days after this last dose of pembrolizumab, he withdrew from the study to enroll in hospice. The following non-serious AEs were ongoing at the time of his withdrawal from study: worsening autonomic postural hypotension, increased shortness of breath, right lower extremity pain, worsening dysphagia, pain below left chest wall mass, chronic pain, and worsening insomnia. He died (b) (6), with cause of death reported as unknown.

Reviewer comment: Investigators assessed these 5 deaths as not related to study drug.

Information for 2 of the 5 patients ([redacted] and [redacted]) classified as having "unknown cause of death" suggests death due to underlying malignancy but is not adequate to rule out the possibility that death was related to study treatment. The death of patient [redacted] was most likely related to infectious pneumonia and/or underlying malignancy. For the remaining 2 patients, cause of death is truly unknown.

KEYNOTE 055

Narratives were provided in the updated SCS for a total of 25 deaths occurring on KEYNOTE 055; of these, 12 deaths were reported as due to malignant neoplasm progression. For the other 13 deaths, the following grade 5 AEs were reported: aspiration pneumonia or pneumonia Staphylococcal (4 patients), pneumonia/septic shock/cerebrovascular accident (all for 1 patient), respiratory failure (2 patients), cardiac arrest (2 patients), and myocardial infarction, hyperglycemia, suicide, and death (from narrative appears related to sepsis in setting of open wound) in 1 patient each. According to investigator (and Sponsor) assessments, none of these grade 5 AEs were considered drug-related. One grade 5 AE of pneumonitis ([redacted]), considered drug-related by investigator, was reported in KEYNOTE 055 CSR but not listed in updated SCS. The other two grade 5 AEs reported in the CSR (respiratory failure and cardiac arrest) were included in the updated SCS.

Reviewer comment: Narratives were reviewed for KEYNOTE 055 deaths. Review of the details of these deaths does not raise any new safety concerns.

7.3.2 Nonfatal Serious Adverse Events

SAEs were reported in 45% of the 192 HNSCC patients in KEYNOTE 012. The most frequently reported SAEs (including fatal AEs reported in Section 7.1.3) by preferred term were pneumonia (3.6%), dyspnea (3.1%), confusional state (2.6%); vomiting, pleural effusion, and respiratory failure (2.1% each); anemia, hypercalcemia, tumor hemorrhage, syncope, stoma site infection, aspiration pneumonia, and respiratory distress (1.6% each). Other SAEs occurred in only 1 patient each. There were no notable differences in non-fatal SAEs between Cohort B and Cohort B2. The most frequently reported SAEs considered drug-related were pneumonitis, face edema, and face swelling (1% each).

SAEs were reported in 50% of the 50 patients from KEYNOTE 055. The most frequently reported SAEs were pneumonia and dehydration, each occurring in 3 patients (6%); and dysphagia, hypercalcemia, syncope, pleural effusion, pneumonitis, pulmonary embolism, and respiratory failure, each occurring in 2 patients (4%).

7.3.3 Dropouts and/or Discontinuations

A total of 33 patients (17%) of the 192 HNSCC patients in KEYNOTE 012 discontinued study treatment due to AE, with AE(s) leading to discontinuation considered related to pembrolizumab (per investigators assessment) in 12 patients (6.3%). AEs leading to treatment discontinuation in >1 patient were: alanine aminotransferase increased (1.6%), aspartate aminotransferase increased (1.6%), dyspnea (1.0%), aspiration pneumonia (1.0%), pneumonitis (1.0%), and swelling face (1.0%).

The number of patients who discontinued due to an AE listed in the disposition tables for KEYNOTE 012 (23 patients [12%]) is less than the number of AEs leading to discontinuation in the overall AE summary (33 patients [17%]). Per the Applicant, this discrepancy is due to 10 patients, including some patients in the primary efficacy population, with clinical progression but without radiological assessment that were counted as having PD in the disposition table but who had an outcome for AE recorded as “study medication discontinued” in the AE summary.

The AEs leading to treatment discontinuation which were considered to be related to pembrolizumab per investigator assessment were: alanine aminotransferase increased, aspartate aminotransferase increased, and pneumonitis or interstitial lung disease occurring in 3 patients each (1.6%) and swelling face in 2 patients (1.0%). The remaining AEs were reported in 1 patient each: immune thrombocytopenic purpura, atrial fibrillation, colitis, blood alkaline phosphatase increased, and type 1 diabetes mellitus.

Amon the 50 patients from KEYNOTE 055, 3 patients (6%) discontinued treatment due to an AE. These AEs, occurring in 1 patient (2%) each, were cardiac arrest, aspartate aminotransferase increased, and pneumonitis. The AE of cardiac arrest was not considered related to pembrolizumab, while the other two AEs were assessed by investigators as related to pembrolizumab.

7.3.4 Significant Adverse Events

AEs that occurred at toxicity grade 3 or higher in ≥2% of the 192 HNSCC patients in KEYNOTE 012 are listed in Table 16.

Table 16: Grade 3-5 AEs Occurring in ≥2% of HNSCC Patients in KEYNOTE 012 (Reviewer Table)

Preferred Term	N=192
Pneumonia	4.2%
Pneumonia aspiration	3.1%
Fatigue	3.1%
Dyspnea	3.1%
Respiratory distress	2.6%
Abdominal pain	2.6%
Dehydration	2.6%
Dysphagia	2.1%
Respiratory failure	2.1%

Grade 3-5 AEs occurring in ≥3 patients (≥5% of patients) in KEYNOTE 055 were pneumonia (8%), dehydration (6%), dysphagia (6%), and fatigue (6%). Details for grade 5 AEs from both studies are provided in Section 7.3.1 of this review.

7.3.5 Submission Specific Primary Safety Concerns

Immune-mediated AEs

Data on AEOSI are presented here for the 192 patients with HNSCC representing the safety population from KEYNOTE 012. A total of 22 AEOSI categories were identified by the Applicant with a predefined list of preferred AE terms potentially associated with immune etiology. Of these, 11 AEOSI had no reported events: Guillain-Barré Syndrome, hematologic, hypophysitis, myasthenic syndrome, myocarditis, neuropathy, pancreatitis, pericarditis, renal, uveitis and vasculitis.

AEOSI were reported in 43 patients (22%). The AEOSI of hepatic, hyperthyroidism, and myositis events were reported in 1 patient each (0.5%). The majority of these events were grades 1-2, with a 5% incidence of grade 3-4 AEOSI and no grade 5 AEOSI. There were 8 AEOSI which occurred in >1 patient or were considered a serious event: adrenal insufficiency, colitis, hypothyroidism, infusion reactions, pneumonitis, severe skin reactions, thyroiditis, and Type 1 diabetes mellitus. Grade 3 AEOSI were skin toxicity (decubitus ulcer, papule, rash, rash macular) in 4 patients, hypothyroidism in 2 patients and colitis, drug-induced liver injury, diabetes mellitus, and pneumonitis in 1 patient each. There was 1 grade 4 AEOSI reported, diabetic ketoacidosis. Infusion reactions were reported in 2 HNSCC patients (1.0%) treated in KEYNOTE 012; neither infusion reaction was Grade ≥3. Table 17 presents a comparison of potentially immune-mediated AEs reported in KEYNOTE 012 and in the pooled melanoma + NSCLSC population as presented by the Applicant.

Table 17: Potentially Immune-Mediated Adverse Events (Reviewer Table)

	Keynote 012 (n=192)	Pooled melanoma + NSCLC (n=2799)
Pneumonitis/ILD	2.6%	3.4%
Colitis	0.5%	1.6%
Hepatitis	0.5%	0.7%
Hypophysitis	0	0.3%
Adrenal insufficiency	1.0%	0.8%
Hypothyroidism	14.6%	8.5%
Hyperthyroidism	0.5%	3.4%
Thyroiditis	1.6%	0.6%
Diabetes mellitus	0.5%	0.2%
Nephritis	0	0.1%
Skin toxicity	2.1%	1.6%
Myositis	0.5%	0.4%

ILD, interstitial lung disease

For KEYNOTE 055, 11 potentially immune-mediated AEs were reported, consisting of 7 cases of hypothyroidism (14.0%), 1 case of hepatitis (2.0%), and 3 events of pneumonitis (occurring in 2 patients and including 1 fatal AE of pneumonitis). The majority of events were grade 2; the exceptions were one grade 5 pneumonitis event and one grade 3 hepatitis event.

Reviewer comment: The reported incidence of potentially immune-mediated events was similar overall for HNSCC patients in KEYNOTE 012 compared to the pooled population, except for a higher incidence of hypothyroidism in HNSCC patients, which will be further discussed.

Hypothyroidism

Hypothyroidism is a common finding among HNSCC patients, commonly related to prior radiation therapy. According to the updated SCS, 27 of the 28 patients (14.6%) in the KEYNOTE 012 HNSCC population with the reported AE of hypothyroidism had received radiation, and a history of hypothyroidism was reported for 7 patients. Per information received in response to an information request sent to the Applicant, 15 of these 28 patients did not have a past medical history of hypothyroidism, prior thyroid replacement medication use, or an elevated baseline thyroid stimulating hormone (TSH) at study entry. Of the 7 patients with a past medical history of hypothyroidism, 6 also had an elevated TSH at baseline, while one had a normal TSH. One additional patient reported prior thyroid medication use and had an elevated TSH at baseline, although hypothyroidism was not reported in the past medical history. The remaining 5 patients had elevated TSH prior to study treatment without a reported history of hypothyroidism.

Reviewer comment: Based on the available information, a more accurate estimate of

the incidence of potentially immune-mediated hypothyroidism among HNSCC patients treated with pembrolizumab is 8% (15 of 192 patients), which is consistent with the incidence reported in the pooled melanoma + NSCLC population.

Potential HNSCC specific safety issues
The reviewer assessed the incidence of several potential HNSCC specific safety issues, presented in Table 18.

Table 18: Potential HNSCC Specific Safety Issues (Reviewer Table)

Preferred term	**KEYNOTE 012 (n=192)**		**KEYNOTE 055 (n=50)**	
	All	**Grade 3-4**	**All**	**Grade 3-4**
Dysphagia	11%	2.1%	22%	6%
Face edema + swelling face	10%	2.1%	6%	0
Tongue or palatal edema	1.6%	0.5%	0	0
Laryngeal edema	1.0%	0.5%	0	0

Reviewer comment: Incidences of tongue, palatal, and laryngeal edema were low. Dysphagia was reported more frequently than in the pooled melanoma + NSCLC cohort, where the incidence was 2.1%. However, dysphagia is a common symptom for HNSCC patients and is usually related to underlying tumor or effects of prior treatment, particularly prior head and neck surgery or radiation. This increased incidence is most likely attributable to the underlying disease, rather than a differential toxicity related to pembrolizumab. Facial edema, which was a rare event in the pooled population (0.6%), was a relatively common AE in the HNSCC population. While facial edema may occur in patients with HNSCC in relation to underlying disease, there is also the potential for facial edema to be the result of an inflammatory or immune-mediated reaction related to treatment; therefore, this AE is further discussed in this review.

In the CSRs for KEYNOTE 012 and KEYNOTE 055, the Sponsor presented analyses of head/neck edema events. This was done because the Sponsor noted during the course of the trial that many AEs of localized edema were reported. A defined list of terms was selected by the Sponsor in an attempt to capture events of head/neck edema in order to undertake a formal review of these events. Head/neck edema AEs were reported in 26 patients (14%) among the 192 HNSCC patients in KEYNOTE 012, and a general summary of these events is presented in Table 19.

Table 19: Head/Neck Edema AEs in HNSCC Patients from KEYNOTE 012 (n=192) (Reviewer Table)

	All events	Drug-related[a] events
Number of patients (%)	26 (14%)	12 (6%)
Grade 3-4	9 (4.7%)	5 (2.6%)
Serious adverse events	7 (3.6%)	5 (2.6%)
Dose modification due to AE	6 (3.1%)	---
Discontinuation due to AE	3 (1.6%)	2 (1.0%)

[a]Assessed as related to study drug per investigator assessment

The most common head/neck edema AEs reported were face edema and swelling face (10% all grade and 2.1% grade 3-4 for combined terms, see Table 18). Local swelling and localized edema were reported in 3 patients each, and laryngeal edema was reported in 2 patients. The remaining head/neck edema AEs reported occurred in 1 patient each and included: ear swelling, lip swelling, mouth swelling, palatal edema, swollen tongue, and tongue edema. Swelling face was the preferred term for both AEs leading to discontinuation of pembrolizumab and assessed as drug-related.

The Sponsor also assessed concomitant use of corticosteroids for head/neck edema episodes. Only 4 of 29 (14%) total episodes of grade 1-2 head/neck edema, were treated with corticosteroids (starting dose low for 1 patient, high for 3 patients). Of 10 grade 3-4 head/neck edema events, 50% were treated with corticosteroids (starting dose low for 1 patient, high for 4 patients). Among the 26 patients with head/neck edema AEs reported, the AE was reported as resolved for 7 (27%), resolving for 5 (19%), and not resolved for 14 (54%) at the time of the data cut-off for the CSR.

For KEYNOTE 055, among the 50 patients included in the CSR, 4 head/neck edema AEs were reported, for an incidence of 8%; the AE was considered drug-related in 2 patients (4%). Two of these AEs were grade 1 and two were grade 2. No head/neck edema events were considered a SAE and none led to dose modification or discontinuation of pembrolizumab. The reported head/neck edema AEs were face edema in 2 patients and swelling face and localized edema in 1 patient each. Only 1 patient (25%) received treatment with systemic corticosteroids for a head/neck edema AE; this patient received high dose steroids.

Reviewer comment: While facial edema is not an unexpected occurrence in patients with advanced HNSCC, many of whom have persistent tumor in the head and neck area, facial edema could also be a manifestation of an immune-mediated reaction associated with pembrolizumab treatment. Since the available safety data is from single arm trials, it is difficult to determine to what extent, if any, facial edema is related to pembrolizumab treatment. Investigators assessed these events in KEYNOTE 012 as drug-related in almost half of the 26 patients experiencing these events, and these AEs resulted in pembrolizumab dose modification for 6 of these 26 patients (23%). Two patients were discontinued from treatment due to AE of swelling face considered drug-

related by investigator. In addition, half of patients experiencing grade 3-4 events were treated with corticosteroids, suggesting some concern by investigators for potential immune-mediated etiology. Given the currently available information, facial edema should be included in the USPI for pembrolizumab as a potential adverse reaction in HNSCC patients treated with pembrolizumab. This issue will be re-assessed when data from the ongoing randomized study, KEYNOTE 040, is submitted for review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse reactions (reported for ≥20% of patients) for pembrolizumab in the KEYNOTE 012 HNSCC population were fatigue, decreased appetite, and dyspnea. Treatment-emergent AEs occurring in ≥10% of HNSCC patients from KEYNOTE 012 are presented in Table 20, with data on incidence of these AEs (all grades) also presented for the 50 patients from KEYNOTE 055 as supportive data and for the pooled melanoma + NSCLC population for purposes of comparison. For a listing of grade 3-5 AEs occurring in ≥2% of HNSCC patients in KEYNOTE 012, see Table 16 in Section 7.3.4 of this review.

Reviewer comment: The Applicant reported fatigue and asthenia separately, while the reviewer determined that it would be more appropriate to report these as a composite term "fatigue". Similarly, the Applicant reported cough and productive cough separately, while the reviewer determined that it would be more appropriate to report these as a composite term "cough". Percentages for all grade TEAEs from KEYNOTE 012 and KEYNOTE 055 are based on reviewer's analyses using MAED, while percentages for grade 3-4 TEAEs in Table 20 are based on Applicant tables included in the updated SCS.

Table 20: Adverse Reactions Occurring in ≥10% (All Grades) of HNSCC Patients from KEYNOTE 012 (Reviewer Table)

Preferred or Composite Term	KEYNOTE 012 (n=174)		KEYNOTE 055 (n=50)	Pooled melanoma + NSCLC (n=2799)
	All Grades (%)	Grades 3-4 (%)	All Grades	All Grades
Fatigue[a]	52	3.1	40	50
Decreased appetite	23	1.6	14	23
Dyspnea	20	3.1[d]	14	19
Cough[b]	20	0.5	16	27
Nausea	19	0.5	22	25
Constipation	19	0.5	24	18
Pyrexia	19	0	4	13
Weight decreased	18	0.5	18	8
Diarrhea	15	1.0	10	22
Rash	15	0.5	10	18
Vomiting	15	1.6	14	14
Arthralgia	14	0	8	18
Headache	13	0.5	2	14
Facial edema[c]	12	2.1	6	0.6
Pruritis	11	0	4	20
Back pain	11	1.0	6	13
Dysphagia	11	2.1	22	2

[a]Includes fatigue and asthenia
[b]Includes cough and productive cough
[c]Includes face edema and swelling face
[d]Includes one Grade 5 event

Reviewer comment: For the most common AEs occurring in HNSCC patients in KEYNOTE 012, the majority of events were grades 1-2. Hypothyroidism is not included in this section, as the best estimate of treatment-emergent hypothyroidism is approximately 8% in the KEYNOTE 012 HNSCC population (see Section 7.3.5 of this review). With the exceptions of facial edema and dysphagia, the incidences of these AEs do not differ significantly compared to incidences in the pooled melanoma + NSCLC population or compared to information currently included in the USPI for pembrolizumab.

7.4.2 Laboratory Findings

These findings are based on review of data presented by the Applicant. Data on incidence of these laboratory abnormalities (all grades) is also presented for the pooled melanoma + NSCLC population for purposes of comparison

Table 21: Laboratory Abnormalities Worsened from Baseline in ≥20% of HNSCC Patients in KEYNOTE 012 (Reviewer Table)

Laboratory Abnormality	KEYNOTE 012 (n=174)		Pooled melanoma + NSCLC (n=2799)
	All Grades (%)	Grades 3-4 (%)	All Grades (%)
Hyperglycemia	52	3.6	46
Lymphopenia	51	27.6	29
Anemia	44	12.5	39
Hypoalbuminemia	42	0	32
Hyponatremia	35	7.8	33
Hypophosphatemia	23	3.6	18

Additional grade 3-4 laboratory abnormalities occurring in ≥2% of HNSCC patients in KEYNOTE 012 were hypokalemia (4.2%), hypercalcemia (3.1%), hypocalcemia (2.6%), neutrophils decreased (2.6%), and increased aspartate aminotransferase (2.1%).

7.4.3 Vital Signs

Vital signs were obtained at screening and during each follow up visit. No clinically meaningful vital sign changes were observed in the KEYNOTE 012 HNSCC patient population based on mean change in vital sign measurements from baseline over time.

7.4.4 Electrocardiograms (ECGs)

ECGs were not obtained as part of routine clinical testing.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies/clinical trials conducted with pembrolizumab.

7.4.6 Immunogenicity

The following is an excerpt from the US Prescribing Information (USPI) for pembrolizumab current at the time of this review:

"As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg Q3W or 10 mg/kg every two or three weeks, 1 (0.3%) of 392 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies and confirmed positive in the neutralizing assay."

The Applicant has updated this information in the proposed label submitted with this sBLA, adding reference to the 200 mg Q3W dose and updating numbers based on additional data - "20 (1.7%) of 1149 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies". The phrase "…and confirmed positive in the neutralizing assay" has been removed. The following sentence has been added, "There was no evidence of an altered pharmacokinetic (b) (6) profile with anti-pembrolizumab binding antibody development."

See the FDA Clinical Pharmacology Review of the current sBLA submission for details and for FDA labeling recommendations regarding this section of the USPI.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Table 22: Adverse Event Summary for HNSCC Patients from KEYNOTE 012 by Cohort (Reviewer Table)

KEYNOTE 012	Cohort B 10 mg/kg Q2W (n=60)	Cohort B2 200 mg Q3W (n=132)
All grade AEs	97%	99%
Grade ≥3 AEs	63%	54%
Serious AEs	45%	45%
Deaths	13%	8%
Treatment interruption due to AE	27%	23%
Discontinued due to AE	20%	16%

Reviewer comment: Drug-relatedness as determined by investigator is not included in Table 22 for comparison between cohorts. Cohort B2 was added to the trial over 1 year after initiation of KEYNOTE 012, by which time additional information regarding the safety profile of pembrolizumab was available, which may have influenced investigators' determinations of drug-relatedness. The incidence of grade ≥3 AEs was greater in Cohort B; the rates of treatment interruption due to AE and discontinuations due to AE

were also slightly higher in Cohort B2. These findings are not unexpected given the differential exposure with the two dosage regimens used (see Section 4.4.3 of this review). A higher percentage of deaths was also reported in Cohort B compared to Cohort B2, but these deaths are not clearly related to the use of pembrolizumab. See Section 7.3.1 of this review for details regarding these deaths.

7.5.2 Time Dependency for Adverse Events

Table 23 presents time to onset of AEOSI occurring in the KEYNOTE 012 HNSCC population, with data for the pooled melanoma + NSCLC population included for reference. This table is based on information provided in the ISS, which includes all AEOSI with the exception of one case of hypothyroidism reported in the updated SCS.

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Table 23: Time to Onset for AEOSI (Reviewer Table)

Time to Onset, weeks	KEYNOTE 012 (n=192)	Pooled melanoma + NSCLC population (n=2799)
Pneumonitis, n	5	94
Mean (Std)	6.6 (2.8)	19.7 (16.3)
Median (range)	7.6 (3.6, 9.3)	14.2 (0.3, 84.0)
Colitis, # of patients	1	49
Mean (Std)	23.6	18.4 (14.2)
Median (range)	23.6	15.3 (1.3, 70.6)
Adrenal insufficiency, n	2	22
Mean (Std)	30.2 (2.7)	27.4 (18.2)
Median (range)	30.2 (28.3, 32.1)	22.9 (3.7, 72.1)
Hypothyroidism, n	27	237
Mean (Std)	14.5 (8.7)	17.7 (12.7)
Median (range)	10.9 (0.1, 36.9)	15.1 (0.1, 82.3)
Thyroiditis, n	3	16
Mean (Std)	17.2 (10.6)	6.8 (4.3)
Median (range)	18.4 (6.0, 27.1)	5.1 (2.1, 15.1)
Type I diabetes mellitus, n	1	6
Mean (Std)	8.3	20.2 (18.6)
Median (range)	8.3	16.6 (4.4, 55.1)
Severe skin reaction, n	4	46
Mean (Std)	8.3 (8.4)	20.9 (22.0)
Median (range)	7.8 (0.1, 17.3)	15.2 (0.6, 93.3)
Infusion reaction, n	2	70
Mean (Std)	16.1 (13.1)	14.4 (17.3)
Median (range)	16.1 (6.9, 25.4)	6.1 (0.1, 74.4)

n = number of patients with AEOSI; Std, standard deviation;

For the AEOSI of hypothyroidism, 13 of 28 patients had a past medical history of hypothyroidism, prior thyroid replacement medication use, or an elevated baseline thyroid stimulating hormone (TSH) at study entry (see Section 7.3.5 of this review for additional details).

Reviewer comment: Direct comparison of time to onset is not appropriate given the small number of events and the relatively limited duration of follow-up in the KEYNOTE 012 HNSCC population. The time of onset data from the KEYNOTE 012 HNSCC population is consistent with the previously noted finding that potentially immune-mediated AEs may occur early or late in the course of treatment.

7.5.3 Drug-Demographic Interactions

The following tables present AE summaries by subgroup for demographic and patient characteristics of age, gender, region, and ECOG PS. These tables are based on information provided in the ISS (data cut-off date September 1, 2015).

Table 24: AE Summary for HNSCC Patients from KEYNOTE 012 by Age (Reviewer Table)

KEYNOTE 012	**Age <65 (n=125)**	**Age ≥65 (n=67)**
All grade AEs	98%	99%
Drug-related[a]	62%	67%
Grade ≥3 AEs	53%	60%
Drug-related[a]	9%	18%
Serious AEs	39%	51%
Drug-related[a]	6%	13%
Deaths	8%	10%
Due to drug-related AE[a]	0	0
Discontinued due to AE	13%	25%
Drug-related[a]	5%	9%

[a]Assessed as related to study drug per investigator assessment

Reviewer comment: There was a slightly higher incidence of grade ≥3 AEs in patients age ≥65, with the incidence of grade ≥3 AEs assessed by investigator as drug-related double that reported in patients age <65. SAEs (all and drug-related) and discontinuations due to AE (all and drug-related) occurred more frequently in the group of patients age ≥65. These findings are not unexpected as, as older patients may have more comorbidities and less functional reserve, increasing the likelihood of experiencing higher grade or serious AEs.

Table 25: AE Summary for HNSCC Patients from KEYNOTE 012 by Gender (Reviewer Table)

KEYNOTE 012	Male (n=159)	Female (n=33)
All grade AEs	98%	97%
Drug-related[a]	60%	79%
Grade ≥3 AEs	55%	55%
Drug-related[a]	11%	15%
Serious AEs	43%	46%
Drug-related[a]	8%	12%
Deaths	9%	6%
Due to drug-related AE[a]	0	0
Discontinued due to AE	18%	15%
Drug-related[a]	6%	9%

[a]Assessed as related to study drug per investigator assessment

Reviewer comment: There were no major differences in incidence of overall events by gender, but AEs occurring in females were more frequently assessed as related to study drug.

Table 26: AE Summary for HNSCC Patients from KEYNOTE 012 by Region (Reviewer Table)

KEYNOTE 012	United States (n=150)	Outside United States (n=42)
All grade AEs	97%	100%
Drug-related[a]	66%	55%
Grade ≥3 AEs	56%	52%
Drug-related[a]	13%	10%
Serious AEs	42%	48%
Drug-related[a]	9%	7%
Deaths	9%	7%
Due to drug-related AE[a]	0	0
Discontinued due to AE	17%	17%
Drug-related[a]	7%	2%

[a]Assessed as related to study drug per investigator assessment

Reviewer comment: There were no major differences in incidence of overall events reported in patients treated at sites in the U.S. versus outside the U.S. AEs leading to discontinuation of study drug were more frequently assessed as related to study drug for patients treated at sites in the U.S.

Table 27: AE Summary for HNSCC Patients from KEYNOTE 012 by ECOG PS (Reviewer Table)

KEYNOTE 012	ECOG PS 0 (n=57)	ECOG PS 1 (n=135)
All grade AEs	98%	99%
Drug-related[a]	70%	61%
Grade ≥3 AEs	30%	66%
Drug-related[a]	4%	16%
Serious AEs	16%	55%
Drug-related[a]	0%	13%
Deaths	0%	13%
Due to drug-related AE[a]	0	0
Discontinued due to AE	5%	22%
Drug-related[a]	2%	8%

[a]Assessed as related to study drug per investigator assessment

Table 28 presents an AE summary by ECOG PS for the 174 HNSCC patients comprising the efficacy population from KEYNOTE 012 (based on the cut-off date used for the updated SCS).

Table 28: AE Summary for HNSCC Patients from Efficacy Population in KEYNOTE 012 by ECOG PS (Reviewer Table)

KEYNOTE 012 Efficacy Population	ECOG PS 0 (n=51)	ECOG PS 1 (n=123)
All grade AEs	98%	98%
Drug-related[a]	67%	62%
Grade ≥3 AEs	35%	65%
Drug-related[a]	4%	16%
Serious AEs	18%	58%
Drug-related[a]	0%	13%
Deaths	2%	17%
Due to drug-related AE[a]	0	0
Dose modification due to AE[a]	20%	48%
Discontinued due to AE	4%	24%
Drug-related[a]	2%	9%

[a]Assessed as related to study drug per investigator assessment

Reviewer comment: Grade 3 AEs (all and drug-related), SAEs (all and drug-related), and discontinuations due to AE (all and drug-related) were significantly higher in the subgroup of patients with ECOG PS 1. By definition, patients with ECOG PS 1 have baseline symptomatic disease, and in HNSCC patients the symptoms leading to a classification of ECOG PS 1 are frequently related to locoregional disease. With this

background, it is not unexpected to observe a higher incidence of AEs in this subgroup of patients. All but one reported death in the KEYNOTE 012 HNSCC population occurred in the ECOG PS 1 subgroup. None of these deaths were assessed by investigators as due to drug-related AE, and the increased incidence of death may be related to increased disease burden, either locoregionally or at distant sites, at the start of treatment for some patients with ECOG PS 1. Review of the death narratives suggests this may be the case for several of the reported deaths occurring early in the course of treatment (i.e., patients who received ≤4 doses of pembrolizumab). See Section 7.3.1 of this review for details regarding these deaths. Determination of whether the increased rate of AEs observed in the ECOG PS 1 subgroup is particular to pembrolizumab, rather than likely with any systemic anti-cancer therapy, is not possible as there is no randomized control arm for comparison. This issue will be re-assessed when data from the ongoing randomized study, KEYNOTE 040, is submitted for review. Based on the data available at the time of this review, specifically information related to duration of response (see Section 6.1.7 of this review), it appears the risk-benefit profile for pembrolizumab is favorable in the subgroup of HNSCC patients with ECOG PS 1 despite an increased incidence of AEs in this subgroup.

7.5.4 Drug-Disease Interactions

Table 29 presents an AE summary for HNSCC patients from KEYNOTE 012 and for the pooled melanoma + NSCLC population as reported by the Applicant.

Table 29: Adverse Event Summary for HNSCC Patients from KEYNOTE 012 and for Pooled Melanoma + NSCLC Population (Reviewer Table)

	KEYNOTE 012 (n=192)	**Pooled melanoma + NSCLC population (n=2799)**
All grade AEs	98%	97%
Drug-related[a]	64%	74%
Grade ≥3 AEs	57%	46%
Drug-related[a]	12%	14%
Serious AEs	45%	37%
Drug-related[a]	9%	10%
Deaths	10%	4%
Due to drug-related AE[a]	0	0.4%
Treatment interruption due to AE	25%	22%
Discontinued due to AE	17%	12%
Drug-related[a]	6%	5%

[a]Assessed as related to study drug per investigator assessment

Reviewer comment: Grade ≥3 AEs, SAEs, and treatment discontinuation due to AE were reported at a higher incidence for the KEYNOTE 012 HNSCC population compared to the melanoma + NSCLC population but were in a similar range. The

percentage of deaths reported in KEYNOTE 012 was more than double that reported for the pooled melanoma + NSCLC population, but none of the deaths in the KEYNOTE 012 HNSCC population were assessed as due to drug-related AE. Based upon my review of the death narratives for this application, it does not appear that HNSCC patients are at an increased risk of death related to the use of pembrolizumab compared to NSCLC and melanoma patients. See Section 7.3.1 of this review for details regarding these deaths.

For comparisons of incidence of common AEs reported in the HNSCC population of KEYNOTE 012 versus the pooled melanoma + NSCLC population, see Section 7.4.1 of this review. Significant differences in incidence were observed for facial edema and dysphagia in the HNSCC populations from KEYNOTE 012 and KEYNOTE 055. See Section 7.3.5 for additional discussion of these findings.

7.5.5 Drug-Drug Interactions

No formal PK drug interaction studies have been conducted with pembrolizumab. See the FDA Clinical Pharmacology review for details.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No studies have been performed to test the potential of pembrolizumab for carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Females of reproductive potential are advised to use effective contraception during treatment with pembrolizumab and for at least 4 months following the final dose. For additional details, see the FDA Pharmacology/Toxicology Review from the original BLA submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness of pembrolizumab have not been established in pediatric patients. This subsection has limited relevance for this sBLA, as HNSCC is extremely rare in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Pembrolizumab received accelerated approval for the treatment of patients with unresectable or metastatic melanoma in September 2014 and for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 in October 2015. The safety profile for pembrolizumab was summarized in the first Periodic Safety Update Report covering the period September 4, 2014 through September 3, 2015. There was no additional new safety information regarding known important identified/potential risks that was analyzed during the reporting interval. The previously identified immune-mediated important potential risks of hypophysitis (including hypopituitarism and secondary adrenal insufficiency), nephritis, uveitis, type 1 diabetes mellitus, severe skin reactions, myositis, and pancreatitis were confirmed. The previously identified important potential risk of infusion-related reactions was also confirmed. A fatal case of pneumonitis was identified in the NSCLC population and characterized in product labeling. Guillan Barré syndrome was characterized as a new important identified risk under the heading of “Other Immune-mediated Adverse Reactions – Guillain Barré Syndrome”. These adverse reactions are all discussed in the USPI for pembrolizumab current at the time of this review.

There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling includes the addition of the HNSCC indication. The labeling negotiations were ongoing at the time of finalization of this review.

Key recommendations included:

Highlights of Prescribing Information, Adverse Reactions

- Include a listing of the most common adverse reactions (reported in ≥20% of patients) observed for HNSCC patients (based on KEYNOTE 012 data): fatigue, decreased appetite, and dyspnea.

Section 2.2 (Recommended Dosing)

- The proposed dosage regimen for HNSCC, 200 mg administered as an intravenous infusion every 3 weeks, is acceptable.
- Modify recommended duration of treatment from "until disease progression or unacceptable toxicity" to "until disease progression, unacceptable toxicity, or a maximum of 24 months in patients with response or stable disease."

Section 5.4 (Warnings and Precautions, Immune-Mediated Endocrinopathies)
- If data regarding the incidence of hypothyroidism observed in the HNSCC population from KEYNOTE 012 is added to this section, include information on the percentage of these patients with or without a prior history of hypothyroidism.

Section 6.1 (Adverse Reactions, Clinical Trials Experience), new subsection for HNSCC
- Include specific information related to serious adverse reactions.
- (b) (4). The following (or similar) statement should be included in this section: "Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, with the exception of increased incidence of facial edema (10% all Grades; 2.1% Grades 3-4)."

Section 14 (Clinical Studies), new subsection for Head and Neck Cancer
- Add subsection 14.3, Head and Neck Cancer.
- Demographic / tumor characteristic information and efficacy data should be presented for the total HNSCC efficacy population from KEYNOTE 012 (n=174) (b) (4)
- Proportion of patients with response durations of ≥6 months should be reported as the actual percentage of patients, (b) (4)

9.3 Advisory Committee Meeting

There was no advisory committee meeting for this application because the safety profile of pembrolizumab is acceptable for the treatment of patients with recurrent or metastatic HNSCC who have progressed on platinum-containing chemotherapy, the application did not raise significant public health questions regarding the role of pembrolizumab for this indication, and outside expertise was not necessary as there were no controversial issues that could benefit from an Advisory Committee discussion.

9.4 Study Flow Charts

Study flow charts relevant to Cohorts B and B2 in KEYNOTE 012.

6.1 Study Flow Chart for Cohorts A, B, C and D (10 mg/kg Q2W dosing)

Trial Period:	Screening Phase		Treatment Cycles[a]								End of Treatment	Post-Treatment		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)[b]	Main Study Screening (Visit 2)[c]	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days)[f]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Administrative Procedures														
Pre-screening Consent	X[g]													
Informed Consent		X[h]												
Informed Consent for Future Biomedical Research		X[i]												
Inclusion/Exclusion Criteria		X												
Subject Identification Card		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X[j]	X	X	X	X	X	X	X	X	X	X[j]		
Trial Treatment Administration			X	X	X	X	X	X	X	X				
Post-study anticancer therapy status													X	X
Survival Status														X
Clinical Procedures/Assessments														
Review Adverse Events[k]		X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	
Full Physical Examination		X					X[m]							
Directed Physical Examination			X	X	X	X		X[n]	X[n]	X[n]	X			
Vital Signs and Weight[n]		X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status		X	X	X	X	X	X	X[gg]	X[gg]	X[gg]	X			
Laboratory Procedures/Assessments: analysis performed by local laboratory														
Pregnancy Test – Urine or Serum □-HCGo		X												
PT/INR and aPTT[p]		X[q]												
CBC with Differential[r]		X[q]		X	X	X	X	X	X	X	X	X[s]		
Comprehensive Chemistry Panel[r]		X[q]		X	X	X	X	X	X	X	X	X[s]		
Urinalysis[r]		X[q]					X[m]					X[s]		

Trial Period:	Screening Phase		Treatment Cycles[a]								End of Treatment	Post-Treatment		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)[b]	Main Study Screening (Visit 2)[c]	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days)[f]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
T3, FT4 and TSH[r]		X[q]					X[m]					X[s]		
Laboratory Procedures/Assessments: analysis performed by central laboratory														
Anti-MK-3475 Antibodies[t]			X[t]	X[t]			X[t]					X[t]		
Pharmacokinetics[t]			X[t,u]	X[t]			X[t]					X[t]		
Blood for Future Biomedical Research[v]			X											
Efficacy Measurements														
Tumor Imaging[w,x]		X					X				X[y]		X[d]	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Archival Tissue Collection[z]	X[aa]													
Cohort B (H/N) and Cohort D (gastric cancer) Tumor Tissue Collection[z]		X[aa,bb]					X[bb]				X[cc]			
Cohort A (TNBC) and Cohort C (urothelial tract cancer) Tumor Tissue Collection[z]		X[aa,dd]					X[dd]				X[cc]			
Correlative Studies Blood Collection			X[ee]				X[ee]				X[ee]			

Trial Period:	Screening Phase		Treatment Cycles[a]								End of Treatment	Post-Treatment		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)[b]	Main Study Screening (Visit 2)[c]	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days)[f]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 2 weeks. Imaging should always be performed every 8 weeks (56 days ± 7 days) regardless of any treatment delays.
b. At the pre-screening visit, subjects will sign the pre-screening consent and submit an archival sample for PD-L1 characterization.
c. Subjects who submit an archival tumor sample at the prescreening visit and are found to be PD-L1 positive will continue to the screening portion of the study. Subjects who do not have an archival sample will go directly to the screening phase of the study.
d. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging[x] every 8 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
e. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone every 12 weeks to assess for survival status.
f. In general, the window for each visit is ± 3 days unless otherwise noted.
g. Pre-screening informed consent must be obtained prior to sending an archival sample to the lab for characterization. Subjects that do not have archival tissue available to send must sign the main study consent prior to undergoing a newly obtained biopsy.
h. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
i. Signing the informed consent for future biomedical research (FBR) samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
j. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
k. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
l. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
m. To be repeated every 4 cycles after cycle 5.
n. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 2 only.
o. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
p. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

Trial Period:	Screening Phase		Treatment Cycles[a]								End of Treatment	Post-Treatment		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)[b]	Main Study Screening (Visit 2)[c]	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days)[f]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks

q. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
r. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
s. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
t. Pre-dose trough and post-dose peak PK samples will be collected at Cycles 1 and 2. Pre-dose trough samples only will be collected every 4 cycles starting with Cycle 5 and through Cycle 37, 30 days after discontinuation of study drug, and 3 months and 6 months after discontinuation of study drug (or until the subject starts new anti-neoplastic therapy). All trough samples should be drawn within 24 hours before infusion of MK-3475. All peak samples should be drawn within 30 minutes after the end of the infusion. Anti-MK-3475 antibodies should be drawn with all pre-dose trough PK samples, the 30 day discontinuation draw and 3 months and 6 months after discontinuation of study drug (or until the subject starts new anti-neoplastic therapy). Procedures for sample collection are described in the Procedures Manual.
u. An additional single PK sample should be drawn between 24 to 96 hours after Cycle 1 dosing.
v. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
w. The initial tumor imaging will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. On-study imaging will be performed every 8 weeks (± 7 days) after the first dose of trial treatment or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management; Sponsor will collect radiological assessments for retrospective analysis by an independent central radiology review vendor. The processes for image collection and transmission to the independent central radiology reviewl vendor are in the Site Imaging Manual.
x. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be performed at a minimum of 4 weeks later in order to confirm progressive disease as described in Section 4.2.3.1. Please refer to the Procedure Manual for additional details on modifications to RECIST.
y. In subjects who discontinue study therapy without confirmed disease progression, a radiological evaluation should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.
z. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
aa. Baseline tumor tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy (FNA not adequate) of a tumor lesion not previously irradiated must be provided and received by the independent central radiology reviewl vendor before enrollment for characterization of PD-L1 status. These samples are not required to be obtained within 28 days of enrollment. Subjects with H/N cancer may provide tissue from a previously irradiated lesion.

Trial Period:	Screening Phase		Treatment Cycles[a]								End of Treatment	Post-Treatment		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)[b]	Main Study Screening (Visit 2)[c]	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up	Follow Up Visits[d]	Survival Follow-Up[e]
Scheduling Window (Days)[f]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks

bb. Newly obtained tumor biopsy is required for subjects enrolled into Cohort B (H/N cancer) and Cohort D (gastric cancer) of the study. Tumor biopsies that are inaccessible or contraindicated due to subject safety concerns are exempt from this requirement. The pre-dose newly obtained biopsy is not required for PD-L1 characterization and may be performed just prior to the first dose of study treatment after all eligibility criteria has been met.
cc. Tumor biopsy for clinically stable subjects at treatment discontinuation is highly encouraged.
dd. Tumor biopsy is highly encouraged for all subjects. If activity within the Cohort is observed (at least 2 responders within the Cohort) the tumor biopsy will become mandatory. Tumor biopsies that are inaccessible or contraindicated due to subject safety concerns are exempt from this requirement. The pre-dose newly obtained biopsy is not required for PD-L1 characterization and may be performed just prior to the first dose of study treatment after all eligibility criteria has been met
ee. Blood for correlative studies should be collected prior to Cycle 1, at Cycle 5 and again at treatment discontinuation.
ff. Following Cycle 8, the directed physical exam is only required at Cycle 11, 15, 19, and every 4 cycles thereafter.
gg. Following Cycle 8, the ECOG performance status should be determined only in conjunction with a protocol-specified full or directed physical exam (Cycle 9, 11, 13, 15, 17, 19 and every 2 cycles thereafter.

6.2 Study Flow Chart for Cohort B2 (200 mg Q3W dosing)

Trial Period:	Screening Phase	Treatment Cycles[a]						End of Treatment	Post-Treatment		
					To be repeated beyond 6 cycles						
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	5	6	Discon	Post-Treatment Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up[c]
Scheduling Window (Days)[d]:	-28 to -1		± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks
Informed Consent	X[e]										
Informed Consent for Future Biomedical Research	X[f]										
Inclusion/Exclusion Criteria	X										
Subject Identification Card	X										
Demographics and Medical History	X										
Prior and Concomitant Medication Review	X[g]	X	X	X	X	X	X	X	X[g]		
Trial Treatment Administration		X	X	X	X	X	X				
Post-study anticancer therapy status										X	X
Survival Status											X
Review Adverse Events[h]	X	X	X	X	X	X	X	X	X[i]	X[i]	
Full Physical Examination	X				X[j]						
Directed Physical Examination		X	X	X		X[k]	X[k]	X			
Vital Signs and Weight[l]	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X[m]	X[m]	X			
Pregnancy Test – Urine or Serum β-HCG[n]	X										
PT/INR and aPTT[o]	X[p]										
CBC with Differential[q]	X[p]		X	X	X	X	X	X	X[r]		
Comprehensive Chemistry Panel[q]	X[p]		X	X	X	X	X	X	X[r]		
Urinalysis[q]	X[p]				X[j]				X[r]		
T3, FT4 and TSH[q]	X[p]				X[j]				X[r]		
Blood for Future Biomedical Research[s]		X									
Tumor Imaging[t,u]	X				X			X[v]		X[b]	
Archival Tissue Collection[w]	X[x]										
Newly Obtained Biopsy Collection[w]	X[y]			X[y]				X[z]			
Correlative Studies Blood Collection		X[aa]		X[aa]				X[aa]			

Trial Period:	Screening Phase	Treatment Cycles[a]						End of Treatment	Post-Treatment		
					To be repeated beyond 6 cycles						
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	5	6	Discon	Post-Treatment Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up[c]
Scheduling Window (Days)[d]:	-28 to -1		± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks; Imaging should always be performed every 8 weeks (56 days ± 7 days) regardless of any treatment delays.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging[a] every 8 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone every 12 weeks to assess for survival status.
d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research (FBR) samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
h. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
i. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
j. To be repeated every 3 cycles after cycle 4.
k. Following Cycle 6, the directed physical exam is only required as clinically appropriate as long as a physical exam is performed every 6 weeks.
l. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at the screening visit (visit 2) only.
m. Following Cycle 6, the ECOG performance status should be determined only in conjunction with a protocol-specified full or directed physical exam.
n. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
o. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
p. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
q. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
r. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

Trial Period:	Screening Phase	Treatment Cycles[a]						End of Treatment	Post-Treatment		
					To be repeated beyond 6 cycles						
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	5	6	Discon	Post-Treatment Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up[c]
Scheduling Window (Days)[d]:	-28 to -1		± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 8 weeks post discon	Every 12 weeks

s. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
t. The initial tumor imaging will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. On-study imaging will be performed every 8 weeks (± 7 days) after the first dose of trial treatment or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management; Sponsor will collect radiological assessments for retrospective analysis by an independent central radiology review vendor. The processes for image collection and transmission to the independent central radiology review vendor are in the Site Imaging Manual.
u. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be performed at a minimum of 4 weeks later in order to confirm progressive disease as described in Section 4.2.3.1. Please refer to the Procedure Manual for additional details on modifications to RECIST.
v. In subjects who discontinue study therapy without confirmed disease progression, a radiological evaluation should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.
w. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
x. Baseline tumor tissue for biomarker analysis from an archival tissue sample of a tumor lesion must be provided and submitted to the independent central radiology review vendor before enrollment These samples are not required to be obtained within 28 days of enrollment. . Exceptions to the archival tissue requirement may be granted after discussion with the Sponsor if a newly obtained biopsy is performed at baseline.
y. Newly obtained tumor biopsies are mandatory for subjects prior to Cycle 1 initiation of MK-3475 and again at Cycle 3. Exemptions to the tumor biopsy require Sponsor approval and appropriate justification..
z. Tumor biopsy for clinically stable subjects at treatment discontinuation is highly encouraged.
aa. Blood for correlative studies should be collected prior to Cycle 1, at Cycle 3 and again at treatment discontinuation.

Study flow chart for KEYNOTE 055.

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
	Screening (Visit 1)						To be repeated beyond 6 cycles		Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Treatment Cycle/Title:			1	2	3	4	5	6				
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Administrative Procedures												
Informed Consent	X[e]											
Informed Consent for Future Biomedical Research		X[f]										
Inclusion/Exclusion Criteria		X										
Subject Identification Card		X										
Demographics and Medical History		X										
Prior and Concomitant Medication Review[g]		X	X	X	X	X	X	X	X	X		
Trial Treatment Administration[h]			X	X	X	X	X	X				
Post-study Anticancer Therapy Status											X	X
Survival Status												X
Clinical Procedures/Assessments												
Review Adverse Events		X	X	X	X	X	X	X	X	X[i]	X[i]	
12-Lead ECG (Local)[k]		X										
Full Physical Examination[k]		X							X			
Directed Physical Examination			X	X	X	X	X	X				
Vital Signs and Weight[k]		X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Serum or Urine[l]		X										
PT/INR and aPTT[m]		X[n]										
CBC with Differential[o]		X[n]		X	X	X	X	X	X	X[p]		
Chemistry Panel[o]		X[n]		X	X	X	X	X	X	X[p]		
Urinalysis[o]		X[n]		X		X		X[j]		X[p]		
T3, FT4 and TSH[o]		X[n]		X		X		X[j]		X[p]		

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
	Screening (Visit 1)						To be repeated beyond 6 cycles		Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Treatment Cycle/Title:			1	2	3	4	5	6				
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
HPV Status[w]	X											
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory												
Pharmacokinetics[q]			X[q]	X[q]		X[q]				X[q]		
Anti-MK-3475 Antibodies[q]			X[q]	X[q]		X[q]				X[q]		
Correlative Blood Samples[r]			X	X	X				X			
Blood for Genetics[v]			X									
Efficacy Measurements												
Tumor Imaging		X[s]				X[t]		X[t]			X[o]	
Tumor Tissue Collection												
Newly Obtained Tissue Collection	X[u]											

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks. Imaging should be performed at 9 weeks after 1st dose and every 6 weeks thereafter (42 days ± 7 days) regardless of any treatment delays. After 1 year, imaging will occur every 9 weeks (± 7 days).
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 6 weeks (± 7 days) in the first year and every 9 weeks (± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) notified by the Sponsor, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone every 12 weeks to assess for survival status.
d. In general, the window for each visit is ± 3 days unless otherwise noted. Cycle 1 treatment must be given within 3-5 days of enrollment.
e. Written consent must be obtained prior to performing any protocol specified procedure. Please note that the window for acquiring the "newly obtained" tissue specimen is within 42 days of the first dose of study drug and written consent should be obtained prior to acquiring the specimen if a biopsy for the study is performed. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the window specified for screening procedures (e.g., within 28 days prior to the first dose of trial treatment for required lab tests). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research (FBR) sample is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the appendices of the Central Lab Manual and Section 12.2 of the Protocol.
g. Prior medications – Record all medications taken within 30 days of the screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
h. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The reason for any delay in infusion outside of the protocol specified window should be documented in the patient's chart and recorded on the eCRFs.
i. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.

j. To be repeated every 2 cycles after Cycle 6 up to 1 year.
k. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
l. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to first dose of trial treatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
m. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
n. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
o. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
p. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
q. Pre-dose trough PK and anti-pembrolizumab (MK-3475) antibody samples will be collected at Cycles 1, 2, 4, 8, and every 4 cycles thereafter, 30 days after discontinuation of study drug, and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab (MK-3475). Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab (MK-3475) infusion at Cycles 1 and 8. An **additional, single PK** sample should be drawn between 72 and 168 hours after Cycle 1 dosing.
r. Blood for correlative studies should be collected prior to Cycle 1, Cycle 2, Cycle 3 and again at treatment discontinuation.
s. The initial tumor imaging will be performed within 28 days prior to the first dose of trial treatment and must be sent to the central vendor to confirm measureable disease for study eligibility. Imaging should include the head, neck, chest, and abdomen; imaging of the pelvis is optional (refer to Section 7.1.2.6). Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality, meet the requirements specified by the protocol, and are performed within 28 days prior to the first dose of trial treatment.
t. The first on-study imaging time point will be performed at 9 weeks (± 7 days) after first dose of study treatment and then every 6 weeks (± 7 days) thereafter or more frequently if clinically indicated. After 1 year, imaging time point will occur every 9 weeks (± 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab (MK-3475) cycle frequencies. Imaging should include the head, neck, chest, and abdomen; imaging of the pelvis is optional (refer to Section 7.1.2.6). The same imaging technique should be used in a subject throughout the trial. On-study scans, including the baseline scans, should be submitted immediately to the central imaging vendor.
u. Baseline tumor tissue for biomarker analysis from a newly obtained core or excisional biopsy (FNA not adequate) must be provided to the central vendor for PD-L1 biomarker testing. Confirmation of tissue adequacy should be received from the central vendor prior to the first dose of trial treatment. A "newly obtained" sample may be obtained up to 42 days prior to treatment initiation. Tissue beyond the 42-day window may be considered with Sponsor approval as long as no intervening systemic therapy has been administered. Tissue that has been previously irradiated is acceptable. Detailed instructions for tissue collection, process and shipment are provided in the appendices of the Central Lab Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
v. This sample should be drawn for planned, exploratory genetic analysis of DNA unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the optional Future Biomedical Research consent.
w. Subjects with oropharynx cancer must have an assessment of HPV status from tumor tissue. Any prior HPV status included in the patient's medical history may be used..
x. In the event that a screening assessment is delayed due to a central vendor assessment (i.e. assessment of measureable disease by the central imaging vendor or assessment of tumor adequacy), Sponsor approval may be granted to allow testing outside of the visit window.

9.5 Protocol Deviations

KEYNOTE-012 Protocol Deviations Summary

Deviation Category	Deviation Description	Number of Deviations	Subject ID	Country	Site Number
Clinically Relevant Deviations					
Efficacy Assessment	Missing imaging assessment (imaging not acquired)	1	(b) (6)	USA	(b) (6)
Discontinuation Criteria	Subject discontinued inappropriately from the trial	1		USA	
Entry Criteria	Subjects entered that did not satisfy the inclusion/exclusion criteria as stated in the protocol	1		USA	
Other Major Protocol Deviations					
Discontinuation Criteria	Developed withdrawal criteria but not withdrawn from study	6	(b) (6)	USA USA USA USA USA USA	(b) (6)
Efficacy	Missing imaging	2		USA	

			(b) (6)		(b) (6)
Assessment	assessment (imaging not acquired)			USA	
Entry Criteria	Prohibited Medication	7		USA USA Israel South Korea USA USA USA	
Entry Criteria	Concurrent participation in another trial	4		USA USA USA USA	
Entry Criteria	No tissue was provided at baseline for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy.	2		USA USA	
Entry Criteria	The patient did not meet the requirement for hemoglobin count ≥9 g/dL or ≥5.6 mmol/L as patient's hemoglobin was 8.8 g/dL at Screening.	1		South Korea	
Entry Criteria	Screening labs conducted out of window.	1		USA	
Informed Consent	Subjects who did not give appropriate Informed Consent	16		USA USA USA USA USA USA USA USA USA USA USA USA USA USA USA USA USA USA	

Prohibited Medications	Disallowed Concomitant Medication: Steroids	1	(b) (6)		Israel
Safety Assessment	Subjects where Serious Adverse Events (SAE) / Adverse Events were not reported or not reported in a timely manner	12		*	USA
				*	USA
				*	USA
					USA
					USA
					USA
					USA
					USA
					USA
				**	USA
				**	USA
					USA
					USA

*3 separate safety assessment deviations for patient (b) (6)

** 2 separate safety assessment deviations for patient (b) (6)

KEYNOTE-055 Protocol Deviations Summary

Deviation Category	Deviation Description	Number of Deviations	Subject ID	Country	Site Number
Clinically Relevant Deviations					
Entry Criteria	Subjects entered that did not satisfy the inclusion/exclusion criteria as stated in the protocol	1	(b) (6)	USA	(b) (6)
Other Major Protocol Deviations					
Clinical Supplies	Subjects who received the wrong study treatment from what they were assigned (incorrect study therapy or an incorrect dose)	2		USA USA	
Discontinuation Criteria	Subjects discontinued inappropriately from the study by the investigator	1		USA	
Entry Criteria	Subjects entered that did not satisfy the inclusion/exclusion criteria as stated in the protocol	2		USA USA	
Informed Consent	Subjects who did not give appropriate Informed Consent	8		USA USA USA USA USA USA USA‡ USA‡	
Safety Assessment	Safety procedures are not performed at a protocol-specified timepoint	1		USA	
Safety Assessment	Subjects where Serious Adverse Events (SAE)/Adverse Events were not reported or not reported in a timely manner	4		USA USA USA USA	

‡ 2 separate informed consent deviations for patient (b) (6)

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/s/

ERIN A LARKINS
07/18/2016

GIDEON M BLUMENTHAL
07/18/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s009

PRODUCT QUALITY REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Biotechnology Review and Research I
Silver Spring, MD, 20993
Tel. 240-402-9446

Memorandum of Review

(Environmental Assessment)

Date: June 7, 2016

To: File for STN: 125514 SUPPL-9 (SD#547)

From: Mark Paciga, Ph.D., Product Quality Reviewer, DBRR I/OBP

Through: Linan Ha, Ph.D., Team Leader, DBRR I/OBP

Subject: 125514/SUPPL-9 Environmental Assessment

Applicant: Merck Sharp & Dohme Corp.

Product: pembrolizumab (Keytruda®)

Indication: Treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma

Received: February 9, 2016
Action Due Date: August 9, 2016

Review Recommendation: The claim of categorical exclusion from the environmental assessment is accepted.

1. FDA Regional Information
1.12. Other Correspondence
1.12.14. Environmental Analysis

Merck requests a categorical exclusion from the preparation of an 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 supplemental Biologics License Application. Under this regulation, an exclusion is provided if the substance comprises naturally occurring elements but has a sequence different from that of a naturally occurring substance, and when approval of the application does not significantly alter the concentration or distribution of the substance, its metabolites or degradation products in the environment.

Reviewer comment: *There is no information in this supplement indicating that any additional environmental information is warranted, and the claim of categorical exemption is accepted.*

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/s/

MARK PACIGA
06/07/2016

LINAN HA
06/07/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s009

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA Serial Number:	125514/ 09
Drug Name:	Keytruda (Pembrolizumab/MK-3475)
Indication(s):	Head and Neck Cancer
Applicant:	Merck
Submission Date:	02/09/2016
PDUFA Date:	08/09/2016
Review Priority:	Priority
Biometrics Division:	V
Statistical Reviewer:	Weishi Yuan
Concurring Reviewers:	Kun He, Team Leader Rajeshwari Sridhara, Division Director
Medical Division:	Oncology Products 2
Clinical Team:	Erin Larkins, Clinical Reviewer Gideon Blumenthal, Team Leader Patricia Keegan, Division Director
Project Manager:	Sharon Sickafuse
Keywords:	Objective Response Rate, Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC), Exact Method

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LIST OF TABLES

1. EXECUTIVE SUMMARY

The applicant submitted data and final study report of a single arm study to support approval for pembrolizumab (MK-3475) as the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. Pembrolizumab had previously received approval for unresectable or metastatic melanoma; and accelerated approval for metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

This application was based on a single arm study, Study P012V01 (KEYNOTE 012), titled "A Phase Ib Multi-Cohort Study of MK-3475 in Patients with Advanced Solid Tumors." The primary endpoint was objective response rate (ORR) per the RECIST 1.1 criteria by independent central radiology review.

A total of 174 patients were included in the final analysis for HNSCC. The ORR assessed by the independent review was 16.1% with 95% CI: (11.0%, 22.4%). The median duration of response was not reached, and duration ranged from 2.4 to 27.7 months. A total of 23 (85%) patients had response of 6.0 months or longer.

Based on the data and analyses, the results showed 16.1% ORR in pembrolizumab treated patients. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

2. INTRODUCTION

The applicant submitted data and final study report of a pivotal study to seek accelerated approval for a new indication for pembrolizumab. This application was based on the Study P012V01 (KEYNOTE 012), an open-label, multicenter, multi-cohort, single-arm study of pembrolizumab in patients with advanced solid tumors.

2.1 Overview

2.1.1. Class and Indication

Pembrolizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to block the interaction between programmed cell death 1 (PD-1) and its ligands, PD-L1 and (programmed cell death ligand 2 (PD-L2).

The applicant is seeking an indication as a treatment for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) on or after platinum-containing chemotherapy.

2.1.2. Regulatory History

Pembrolizumab had previously received approval for unresectable or metastatic melanoma; and accelerated approval for metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

In February 2013 the initial KEYNOTE 012 protocol was submitted to IND 110080. In July 2015 a Type B meeting was held to discuss the clinical program for pembrolizumab in HNSCC. Key points discussed related to HNSCC included importance of sufficient maturity of data from KEYNOTE 012 to obtain adequate information on durability of observed responses, acceptability of pooling data from KEYNOTE 012 Cohorts B and B2. In November 2015, a Type B pre-sBLA meeting was held to discuss the results from KEYNOTE 012 and to reach agreement on the content and format of the proposed sBLA.

The sBLA was submitted in on February 9, 2016.

2.1.3. Study Reviewed

KEYNOTE 012 was a multicenter, nonrandomized, multi-cohort trial of pembrolizumab in patients with advanced solid tumors. Patients were enrolled into Cohort A for triple negative breast cancer (TNBC), Cohort B as the initial HNSCC cancer cohort, Cohort B2 as the HNSCC cancer expansion cohort, Cohort C for urothelial tract cancer, or Cohort D for gastric cancer. Only patients with PD-L1 positive tumors were enrolled in cohorts A, B, C and D. Patients in Cohort B2 were enrolled regardless of PD-L1 status. Only data

from HNSCC Cohorts B and B2 are used to support for this indication and analyzed in this review.

Eligible patients enrolled in Cohorts B received pembrolizumab 10 mg/kg every 2 weeks; while patients enrolled in Cohort B2 received pembrolizumab 200 mg every 3 weeks. The primary objective of this study was to evaluate objective response rate (ORR) per RECIST1.1 criteria by the independent central radiology review. Secondary endpoints included ORR in patients who progressed following cetuximab and platinum therapy in Cohort B and Cohort B2.

A total 174 patients in Cohorts B and B2 combined who progressed on, or after, platinum therapy, regardless of cetuximab exposure were analyzed for efficacy. Trial is ongoing. All data presented in this review are from the HNSCC Cohorts B and B2 with a data cut-off date of February 19, 2016.

2.2 Data Sources

Data used for review is from the electronic submission received on February 9, 2016 and April 27, 2016. The network paths are

- \\CDSESUB1\evsprod\BLA125514\0225
- \\CDSESUB1\evsprod\BLA125514\0240

APPEARS THIS WAY
ON ORIGINAL

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data for both studies as well as the related SAS programs for analysis.

The reviewer was able to perform most of the analyses using the submitted data.

3.2 Evaluation of Efficacy

3.2.1. Study Design and Endpoints

The KEYNOTE-012 was a multicenter, nonrandomized, multi-cohort trial of pembrolizumab in patients with advanced solid tumors. Patients were enrolled into Cohort A for triple negative breast cancer (TNBC), Cohort B as the initial HNSCC cancer cohort, Cohort B2 as the HNSCC cancer expansion cohort, Cohort C for urothelial tract cancer, or Cohort D for gastric cancer. Only patients with PD-L1 positive tumors were enrolled in cohorts A, B, C and D. Patients in Cohort B2 were enrolled regardless of PD-L1 status. There were 165 patients enrolled in Cohorts A (32 patients), B (61 patients), C (33 patients) and D (39 patients). An additional 132 patients with HNSCC cancer were enrolled into Cohort B2 to study the safety and efficacy in the head and neck cancer population at a different dose and schedule of pembrolizumab; Cohort B2 included both PDL1 positive and negative patients. Patients enrolled in cohorts A, B, C and D received 10 mg/kg of pembrolizumab administered Q2W. Patients enrolled in Cohort B2 received 200 mg of pembrolizumab administered Q3W. Only data from HNSCC Cohorts B and B2 are used to support for this indication and analyzed in this review.

Patients were evaluated every 8 weeks (56 days ± 7 days) with radiographic imaging to assess response to treatment. Treatment with pembrolizumab continued until documented disease progression, unacceptable adverse events, inter-current illness that prevented further administration of treatment, investigator's decision to withdraw the patient, patient withdrew consent, pregnancy, noncompliance, completion of 24 months of treatment with pembrolizumab, or administrative reasons.

The primary objective of this study was to evaluate objective response rate (ORR) per RECIST1.1 criteria by central radiology review. Secondary endpoints included ORR in patients who progressed following cetuximab and platinum therapy in Cohort B and Cohort B2.

A total of 174 patients in Cohorts B and B2 combined who progressed on, or after, platinum therapy, regardless of cetuximab exposure were included in the efficacy analysis. The first patient enrolled in Cohort B was on June 7, 2013 and the last patient enrolled was on October 21, 2013. The first patient enrolled in Cohort B2 was June 12, 2014 and the last patient enrolled was on October 8, 2014.

Reviewer's Comment:

The original sBLA submission included report and data with a cut-off date of September 1, 2015. The applicant submitted an updated report based on data with cut-off date February 9, 2016 which had 5.5 months additional follow-up. This review used the updated data.

3.2.2. Efficacy Measures

The primary endpoint ORR was defined as the percentage of patients who have a complete response [CR] or partial response [PR] defined by RECIST 1.1 by independent central radiology review.

3.2.3. Sample Size Consideration

In the final KEYNOTE 012 study protocol for Cohort B, HPV negative head and neck cancer patients would be evaluated separately from HPV positive head and neck cancer subjects.

With 22 evaluable PD-L1 positive subjects with HPV negative head and neck cancer, the study has approximately 80% power to detect a 25% difference in ORR under the null hypothesis of ORR=10% with a type I error rate of 2.5% if the true ORR is 35%.

With 12 evaluable PD-L1 positive subjects with HPV positive head and neck cancer, the study has approximately 73% power to detect a 35% difference in ORR under the null ORR=20% with a type I error rate of 5% if the true ORR is 55%.

The efficacy analysis dataset of Cohort B included a total of 53 patients, of which 31 were HPV negative and 22 were HPV positive.

Reviewer's Comments:

In a single arm study, the point estimate and its 95% confidence interval will be used in decision making, instead of a formal testing with selected null hypothesis.

The protocol did not provide power analysis for the sample size calculation for Cohort B2.

3.2.4. Statistical Methodologies

The efficacy analysis dataset which included patients in the combined cohorts B and B2 who progressed after platinum therapy regardless of cetuximab exposure,.

The ORR was calculated as the percentage of patients who have a CR or PR defined by RECIST 1.1 by the independent centrally review. Patients without response data were

treated as non-responders. A 95% confidence interval (CI) was derived for the ORR using the exact Clopper-Pearson method.

3.2.5. Patient Disposition, Demographic and Baseline Characteristics

This trial was conducted at 16 centers, of which 8 were in the United States; 2 were in Japan; 2 were in Israel; 2 were in Korea, 1 was in Belgium; and 1 was in Taiwan. A total of 53 patients from Cohort B and 121 patients from Cohort B2 were combined to form the efficacy analyses set. The disposition of the patients are presented in the following table.

Table 1. Patient Disposition

Disposition	N (%)
Patients in Efficacy Analysis	174 (100)
Patients Discontinued Treatment	150 (86.2)
Adverse Event	22 (12.6)
Death	5 (2.9)
Excluded Medicine	1 (0.6)
Physician Decision	1 (0.6)
Disease Progression	111 (63.8)
Patient Withdrawn	10 (5.7)
Patients Completed 2 Years Treatment	6 (3.4)
Patients Ongoing Study	18 (10.3)

Demographic data at baseline are summarized in the following table.

Table 2. Patients Demographics

Demographics	N (%)
Patients in Efficacy Analysis	174 (100)
Age	
< 65	119 (68.4)
65	55 (31 6)
Sex	
Male	143 (82 2)
Female	31 (17 8)
Race	
White	131 (75 3)
Other	43 (24 7)
Region	
USA	134 (77 0)
Europe	16 (9 2)
Asia	24 (13.8)

Disease characteristics at baseline are summarized in the following table.

Table 3. Patients Baseline Characteristics

Baseline Characteristics	N (%)
Patients in Efficacy Analysis	174 (100)
ECOG Status	
0	51 (29.3)
1	123 (70.7)
HPV Status	
Positive	58 (33.3)
Negative	115 (66.1)
Unknown	1 (0.6)
Prior Cetuximab Therapy	
Yes	110 (63.2)
No	64 (36.8)
Metastatic Stage	
M0	21 (12.1)
M1	152 (87.4)
MX	1 (0.6)
Prior Systemic Therapy for Recurrent/Metastatic Disease	
0	26 (14.9)
>0	148 (85.1)

Reviewer's comments:

The demographic and baseline characteristics are from the 174 patients in the efficacy analysis population. More patients were Caucasians. About 30% of the patients were females. More patients were older than 65. Most patients were enrolled in the USA. Most patients had metastatic disease. Most patients had prior lines of therapies.

The 26 patients who did not receive systemic therapy for recurrent/metastatic disease received platinum as part of either induction (n=5), concurrent (n=10), or adjuvant (n=11) chemotherapy.

3.2.6. Results and Conclusions

Based on the 174 patients in the efficacy analysis population, there were a total of 74 responders per investigator's assessment, and 53 responders per central review. The following table summarizes the ORR results based on independent central radiology review.

Table 4. ORR Analysis Results

	N (%)	95 % CI
Patients in Efficacy Analysis	174 (100)	
CR+PR (%)	28 (16.2)	(11.0, 22.4)
CR	8 (4.6)	
PR	20 (11.5)	
SD	31 (17.8)	
PD	86 (48.4)	
NE	3 (1.7)	
Non-CR/Non-PD	7 (4.0)	
No Assessment	19 (10.9)	

The median of the duration of responses was not reached. The duration ranged from 2.4 to 27.7 months. There were 23 patients' responses were on-going at time of data cut-off. There were 23 patients who had longer than 6 months duration of responses.

Reviewer's Comments

The 7 non-CR/non-PD patients were enrolled based on assessment of measurable disease (presence of target lesions) based on investigator assessment but were classified as not having measurable disease at baseline by central radiology review.

The 19 no assessment patients did not have post-baseline response assessments. These patients had baseline imaging assessments but none of these patients obtained a scheduled post-baseline radiologic disease assessment, nor did any of these 19 patients have an unscheduled post-baseline imagining assessment.

3.3 Evaluation of Safety

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

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The following table summarizes the subgroup analysis of ORR.

Table 5. ORR Subgroup Analyses

	N	ORR (95% CI)	Range of DOR
Age			
< 65	119	16.0 (9.9, 23.8)	(2.4, 24.0)
≥ 65	55	16.4 (7.8, 28.8)	(4.3, 27.7)
Sex			
Male	143	15.4 (9.9, 22.4)	(2.4, 27.7)
Female	31	19.4 (7.5, 37.5)	(7.6, 20.5)
Race			
White	131	16.0 (10.2, 23.5)	(2.4, 27.7)
Other	43	17.5 (7.3, 32.8)	(5.8, 24.0)
Region			
USA	134	14.9 (9.4, 22.1)	(2.4, 27.7)
Europe	16	25 (7.3, 52.4)	(5.4, 15.0)
Asia	24	16.7 (4.7, 37.4)	(5.8, 14.6)

Reviewer's comments:

The analyses showed that there were no outliers.

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ON ORIGINAL

4.2 Other Subgroup Analysis

The following table summarizes the subgroup analyses of ORR by baseline characteristics.

Table 6. ORR Subgroup Analyses by Baseline Characteristics

	N	ORR (95% CI)	Range of DOR
ECOG Status			
0	51	31.4 (19.1, 45.9)	(5.8, 27.7)
1	123	9.8 (5.1, 16.4)	(2.4, 24.0)
HPV Status			
Positive	58	17.2 (8.6, 29.4)	(4.2, 27.7)
Negative	115	15.7 (9.6, 23.6)	(2.4, 24.0)
Prior Cetuximab Therapy			
Yes	110	13.6 (7.8, 21.5)	(2.4, 24.0)
No	64	20.3 (11.3, 32.2)	(4.3, 27.7)
Metastatic Stage			
M0	21	9.5 (1.2, 30.4)	(11,2 15.0)
M1	152	17.1 (11.5, 24.1)	(2.4, 27.7)
Prior Systemic Therapy for Recurrent/Metastatic Disease			
0	26	19.2 (6.6, 39.4)	(9.4, 24.0)
>0	148	15.5 (10.1, 22.4)	(2.4, 27.7)

Reviewer's comments:

No outlier was observed.

APPEARS THIS WAY
ON ORIGINAL

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The KEYNOTE 012 study included 174 patients in the efficacy analysis. The ORR assessed by the independent review was 16.1% with 95% CI: (11.0%, 22.4%). The median duration of response was not reached, and duration of response ranged from 2.4 to 27.7 months. A total of 23 (85%) patients had response of 6.0 months or longer.

5.2 Conclusions and Recommendations

Based on the data and analyses, the results showed a 16.1% ORR in pembrolizumab treated patients. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

5.3 Labeling Recommendations

1. The ORR results combined by data from Cohort B and B2 should be included in the label.
2. (b) (4)

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/s/

WEISHI YUAN
07/15/2016

KUN HE
07/15/2016

RAJESHWARI SRIDHARA
07/15/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
BLA (supplement)	125514 (S-9)
Submission Date:	February 9, 2016
PDUFA Date:	August 9, 2016
Brand Name:	Keytruda®
Generic Name:	Pembrolizumab
Formulation/Strength:	50 mg lyophilized powder in single-use vial for reconstitution
Sponsor:	Merck
Submission Type; Code:	Efficacy Supplement
Dosing regimen:	200 mg as a 30 minute intravenous (IV) infusion every 3 weeks
Approved Indications:	• Unresectable or metastatic melanoma. • Metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy
Proposed New Indication	• Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy
Pharmacometrics Reviewer	Chao Liu, Ph.D.
Pharmacometrics Team Leader	Jingyu Yu, Ph.D.
OCP Reviewer:	Sriram Subramaniam, Ph.D.
OCP Team Leader:	Hong Zhao, Ph.D.
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Oncology Products 2 (DOP2)

1 EXECUTIVE SUMMARY

Pembrolizumab (KEYTRUDA) is a programmed death receptor-1 (PD-1)-blocking antibody that received full FDA approval on December 18, 2015 for the treatment of unresectable or metastatic melanoma, and accelerated approval on October 2, 2015 for the treatment of programmed cell death 1 ligand 1 (PD-L1) positive, non-small cell lung cancer (NSCLC) patients with prior platinum-chemotherapy. The approved dosage regimen for Keytruda is 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks (Q3W).

The current Supplement 9 was submitted to support accelerated approval of a proposed indication with pembrolizumab for the treatment of patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) after platinum containing systemic therapy. The efficacy of pembrolizumab in the recurrent/metastatic HNSCC patients was investigated with two dosage regimens (10 mg/kg Q2W and fixed 200 mg Q3W) in non-randomized, multi-cohort Trial 012. In addition, supporting data from ongoing, non-randomized, single-cohort Trial P055 in recurrent/metastatic HNSCC patients at fixed dose of 200 mg Q3W was provided. The approved 2 mg/kg Q3W dosage regimen was not studied in Trial 012. Merck proposes the fixed 200 mg Q3W dosage regimen for recurrent/metastatic HNSCC patients with prior platinum-chemotherapy. The proposal of the use of the fixed pembrolizumab dosage regimen of 200 mg Q3W for recurrent/ metastatic HNSCC patients is acceptable based on the following supporting data:

- Updated population PK analyses by pooling data from Trial P012 and P055 with data from Trials 001, 002 and 006 from other solid tumors indicates that pharmacokinetic parameters are in similar range in HNSCC patients compared to patients with other solid

tumors, and the observed exposures for HNSCC patients at 200 mg Q3W dose are similar to prior data at 2 mg/kg Q3W and within the therapeutic exposure-range previously observed from 2 mg/kg Q3W to 10 mg/kg Q2W in melanoma and NSCLC patients.

- The dose-response analysis of data from Trials 012 and 055 that studied the efficacy of 10 mg/kg Q2W and 200 mg Q3W pembrolizumab dosage regimen in recurrent/metastatic HNSCC patients with prior platinum-chemotherapy, suggested a flat dose response relationship for efficacy between 10 mg/kg Q2W and 200 mg Q3W.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology (Division of Pharmacometrics and Division of Clinical Pharmacology V) has reviewed the information contained in Supplement 9 of BLA 125514 and concludes that efficacy data from Trials 012 and 055, and the dose-efficacy relationships support the use of the Keytruda dosage regimen of 200 mg Q3W for the proposed indication, treatment of recurrent/metastatic HNSCC patients who were previously treated with platinum-chemotherapy.

1.2 POST MARKETING REQUIREMENTS

None

Signatures:

Chao Liu, Ph.D. Pharmacometrics Reviewer (Primary) Division of Pharmacometrics	Jingyu Yu, Ph.D. Pharmacometrics Team Leader Division of Pharmacometrics
Sriram Subramaniam, Ph.D. Reviewer Division of Clinical Pharmacology V	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V

Cc: DOP2: CSO – S Sickafuse; DD – P Keegan; MTL – G Blumenthal; MO – E Larkins
DCPV: DDD - B Booth; DD - A Rahman

2 QUESTION BASED REVIEW

Keytruda was previously reviewed under BLA 125514 (approved 09/04/2014). This review will only address questions related to the current efficacy supplemental submission.

2.1 Is there exposure-response relationship (dose-response, concentration-response) data from the current supplement to support 200 mg Q3W dose for the indicated patient population?

Trial 012 did not investigate 2 mg/kg Q3W, the labeling recommended dosage regimen for the approved indications, instead studied pembrolizumab 10 mg/kg Q2W & fixed 200 mg Q3W dosing regimens in HNSCC patients with prior platinum-chemotherapy. In Trial 012, cohort B enrolled HNSCC patients with PD-L1 positive tumors ≥ 1%, treated with pembrolizumab 10 mg/kg Q2W (n=53), and cohort B2 enrolled HNSCC patients regardless of PD-L1 status, treated with pembrolizumab 200 mg Q3W (n=121). In addition, Trial 055 studied pembrolizumab at a fixed 200 mg Q3W dosing regimen in HNSCC patients who progressed on platinum and cetuximab therapy. Dose-response analysis using pooled data from Trials 012 and 055 showed similar efficacy [for tumor dynamics, objective response rate (ORR), progression free survival (PFS) and overall survival (OS)] between 10 mg/kg Q2W and 200 mg Q3W in HNSCC patients (**APPENDIX**: PHARMACOMETRICS REVIEW, **Figure 1**). In addition, multivariate analysis showed no significant dose-response relationship for ORR, PFS and OS (**APPENDIX**: PHARMACOMETRICS REVIEW, **Figure 2**).

2.2 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

As stated in Section 2.1, dose-response analysis in HNSCC patients suggested a flat relationship for efficacy between 10 mg/kg Q2W and 200 mg Q3W, which supports 200 mg Q3W dosing regimen. Further, a flat dose-response relationship for efficacy for pembrolizumab doses of 2 and 10 mg/kg Q3W and 10 mg Q2W was previously demonstrated in the melanoma population.

2.3 Is pharmacokinetics different between HNSCC patients and other solid tumor patients?

Updated population pharmacokinetic (PK) analysis (n=2878) after pooling data from Trials 012 and 055 in HNSCC patients with data from Trials 001, 002 and 006 in non-HNSCC patients suggested no major differences in PK parameters between HNSCC and non-HNSCC (melanoma or NSCLC) patients (**APPENDIX**: PHARMACOMETRICS REVIEW, **Table 1** and **Figure 5**). The estimated clearance and volume of distribution were in similar range for HNSCC patients compared to other solid tumor patient populations, In addition, the observed exposures (*i.e.*, AUC over 6 weeks at steady state) in the HNSCC patients administered 200 mg Q3W were similar to those in the melanoma and NSCLC patients administered 2 mg/kg Q3W. Also, the observed exposures at 200 mg Q3W are within the therapeutic exposure-range of 2 mg/kg Q3W and 10 mg/kg Q2W observed previously in the melanoma and NSCLC patients (**APPENDIX**: PHARMACOMETRICS REVIEW, Figure 6).

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

To investigate the immunogenicity potential of pembrolizumab, an integrated immunogenicity evaluation was performed using data from Trials 001, 002, 006, 010, 012 and 055 for all assessable[1] patients (at least one post-dose sample included for analysis). Immunogenicity reviewed in the original BLA supplement 6 showed that of the 1819 assessable patients in Trials 001, 002 and 006, 390 patients were evaluable[2]; of which only one was treatment-emergent positive for anti-pembrolizumab binding antibodies[3]. In current updated immunogenicity assessment, of the 3022 patients in Trials 001, 002, 006, 012 and 055, 2733 patients were assessable: 706 patients with melanoma and NSCLC at 2 mg/kg, 1926 patients with melanoma and NSCLC at 10 mg/kg, 56 patients with HNSCC at 10 mg/kg, and 45 patients with HNSCC at 200 mg (Table 1). Of the 2733 assessable patients, 1149 patients were evaluable. Of the 1149 evaluable patients, 32 patients showed a positive immunogenicity status, with 12 patients (4 Melanoma, 6 NSCLC and 2 HNSCC) identified as non-treatment emergent positive[4], and 20 patients (3 Melanoma, 16 NSCLC and 1 HNSCC) identified as treatment emergent positive (see table below). Impact of ADA on pembrolizumab exposure was not observed. For patients with HNSCC, there were 101 assessable patients in Trials 012 and 055, of which 62 were evaluable. Two patients were identified as non-treatment emergent positive, and only one was identified as treatment emergent positive.

Of the 20 patients that were treatment emergent positive, only 4 patients were tested for neutralizing antibodies, of which one was positive. Merck stated that during the course of the study, measurement of the ADA samples was transferred from original vendor (b) (4) to a new vendor (b) (4). Consequently, according to Merck, the neutralizing capacity of the remaining 16 confirmed positive ADA patients are still pending as the optimization of the neutralizing assay at the new vendor is not finalized yet. Per Merck, the results of this analysis will be provided to the FDA in a future update of the immunogenicity report.

Study/Cohorts	2 mg/kg		10 mg/kg			200 mg	Pooled
	Melanoma	NSCLC	Melanoma	NSCLC	HNSCC	HNSCC	
Assessable Patients	345	361	1190	736	56	45	**2733**
Evaluable Patients	221	349	213	304	17	45	**1149** (41.7%)
Negative	219	336	208	295	16	43	**1117** (97.2%)

[1] Assessable was defined as patients having received treatment and having a post-dose ADA sample available.
[2] Evaluable patients was defined as the total number of negative and positive patients (non-treatment emergent and treatment emergent). Negative refers to all pre-treatment and postdose samples negative in the confirmatory assay and the pembrolizumab concentration in the last postdose sample is below the drug tolerance level.
[3] Pre- treatment sample negative and at least one post-dose sample positive in the confirmatory assay, or pre-treatment and post-dose sample positive in the confirmatory assay with an increase in titer of ≥ 2-fold compared to baseline.
[4] Pre-treatment and post-dose sample negative in the confirmatory assay, or pre-treatment and post-dose sample positive in the confirmatory assay with an increase in titer of < 2-fold compared to baseline.

Non Treatment emergent positive	2	5	2	1	1	1	**12** (1.0%)
Treatment emergent positive	0	8	3	8	0	1	**20** (1.7%)

In conclusion, overall the observed incidence of treatment emergent ADA in evaluable pooled patients was low (1.7%: 20 of 1141 patients). No impact of ADA on pembrolizumab exposure was identified.

2.5 What bioanalytical methods are used to assess pembrolizumab concentrations?

The electrochemiluminescence (ECL) bioanalytical method was used to assess ADA in melanoma, NSCLC and HNSCC patients, and was reviewed in the original BLA. The history of the bioanalytical method was previously detailed in Supplements 4 and 6. The bioanalytical method validation was reviewed earlier as part of Supplements 4 and 6.

2.6 What methods are used to assess pembrolizumab anti-drug antibody (ADA)?

A validated bridging electrochemiluminescence (ECL) immunoassay was used for the detection of anti-pembrolizumab antibodies in human serum. Bioanalysis of pembrolizumab ADA was carried out using the standard 3-tiered assay approach that consisted of screening (Tier 1), confirmation (Tier 2) and antibody titer assessment (Tier 3). Only Tier 2 confirmed ADA positive samples moved to Tier 3 and were reported with a titer value. Tier 2 confirmed ADA positive samples were also assessed using a Nab assay based on the ability of ADA to block (neutralize) the critical first step in the pharmacological action of pembrolizumab, which is binding to PD-1, its *in vivo* target. Finally, Protein G depletion was used to confirm the presence of pembrolizumab NAbs.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The sponsor's proposed changes are underlined and proposed deletions have a strikethrough line. The reviewer's proposed changes are in blue and proposed deletions have a red strikethrough line.

2.2 Recommended Dosing

Head and Neck Cancer

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression (b) (4) (b) (4) unacceptable toxicity, or (b) (4) 24 months in patients (b) (4)

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every two or three weeks, 20~~1~~ (1.70~~.3~~%) of 1149~~392~~ evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies. Of 4 patients with treatment-emergent anti-pembrolizumab antibodies tested to date, 1 was positive for neutralizing antibodies. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding 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 KEYTRUDA with the incidences of antibodies to other products may be misleading.

Reviewer Comments: *Only 4 of 20 treatment emergent positive patients were further tested for neutralizing antibodies. Merck plans to test the rest of the 16 patients in future.*

~~**8.6 Renal Impairment**~~

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

~~**8.7 Hepatic Impairment**~~

~~Based on a population pharmacokinetic analysis, no dose adjustment is needed for patients with mild hepatic impairment [total bilirubin (TB) less than or equal to ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST].~~
~~KEYTRUDA has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*.~~

Reviewer Comments: *Sections 8.6 and 8.7 deleted as no action is recommended and the information for renal and hepatic impairment is included under Specific Populations subsection in Section 12.3 Pharmacokinetics.*

(b) (4)

12.2 Pharmacodynamics

Pembrolizumab exposure-response relationships and the time course of the pharmcodynamic response are unknown

Reviewer Comments: (b) (4)

12.3 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 2195 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analyses in patients with solid tumors, the geometric mean [% coefficient of variation (CV %)] for clearance, steady-state volume of distribution, and terminal half-life were 202 mL/day (38%), 7.38 L (19%) and 27 days (38%), respectively.

Steady-state concentrations of pembrolizumab were reached by 19 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.2-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Specific Populations: (b) (4) ~~The CL of pembrolizumab increased with increasing body weight; the resulting exposure differences were adequately addressed by the administration of a weight based dose~~. The following factors had no clinically important effect on the CL of pembrolizumab: age (range 158 to 94 years), (b) (4) sex, race (94% White), renal impairment (eGFR greater than or equal to 15 mL/min/1.73 m^2 (b) (4)), mild hepatic impairment (total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1 and 1.5 times ULN and any AST), (b) (4) or tumor burden. . (b) (4) There is insufficient information to determine whether there are clinically important differences in the CL of pembrolizumab in patients with moderate or severe hepatic impairment.

(b) (4)


(b) (4)

4 APPENDIX: PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	BLA125514S9
Compound	Pembrolizumab
Dosing regimen (route of administration)	200 mg every 3 weeks as an intravenous infusion over 30 minutes.
Indication	Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy
Clinical Division	Division of Oncology Products 2 (DOP2)
Primary PM Reviewer	Chao Liu, Ph.D.
PM Team Leader	Jingyu Yu, Ph.D.

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

Table of Contents

1 SUMMARY OF FINDINGS

1. The pembrolizumab pharmacokinetics in HNSCC patients is comparable to that in non-HNSCC (melanoma or NSCLC) patients.
2. There is no evidence indicating significant difference in efficacy between 200 mg Q3W and 10 mg/kg (approximately 750mg) Q2W.

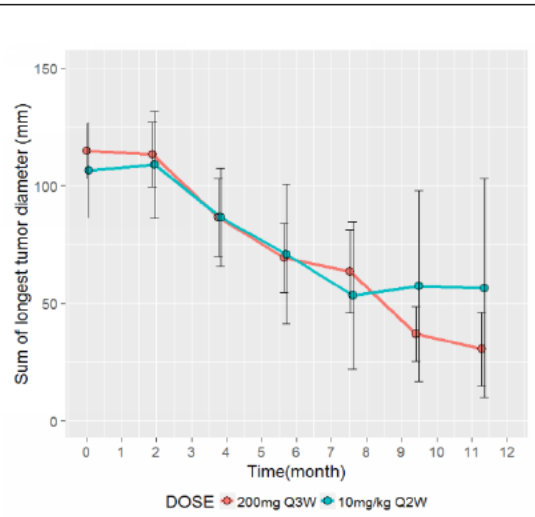
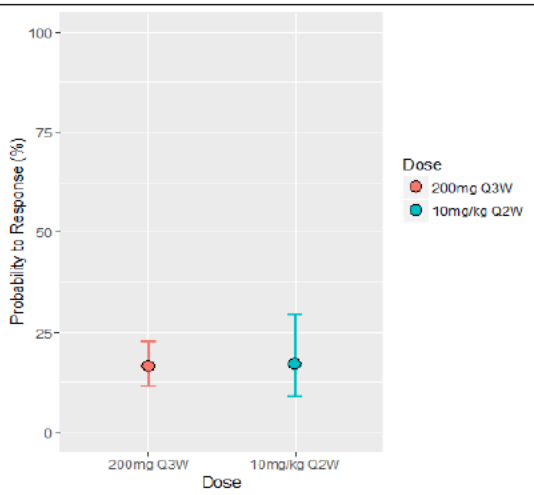
1.1 KEY REVIEW QUESTIONS

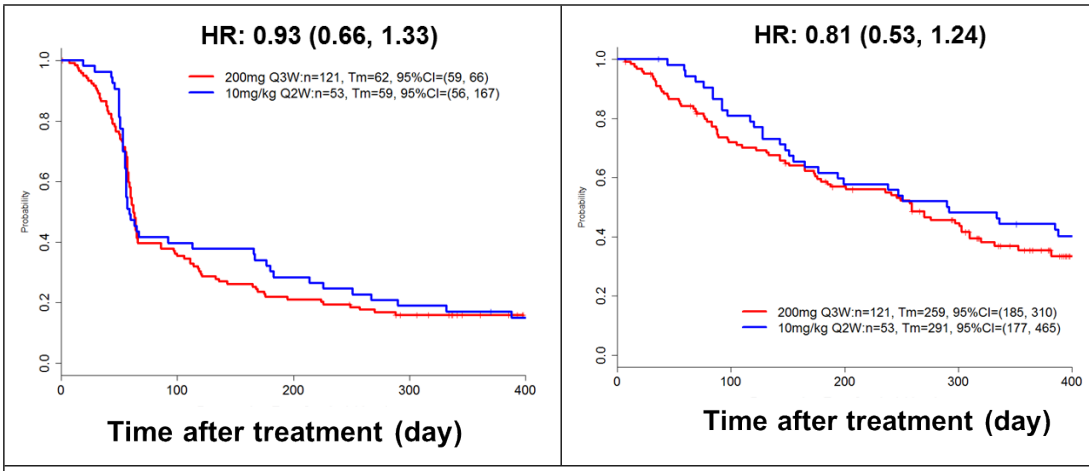
The purpose of this review is to address the following key questions.

Q1: Is there a significant difference in efficacy between 10 mg/kg Q2W dose and 200 mg Q3W dose based on dose-response relationship?

No. Dose-response analysis for tumor dynamics, objective response rate (ORR), progression free survival (PFS) and overall survival (OS) using the pooled data from study KEYNOTE-012 and KEYNOTE-055 suggests that there is no significant difference in efficacy between the two dosing regimens of pembrolizumab in HNSCC patients (**Figure 1**).

Figure 1: No trend of increase of responder rate or tumor suppression with the increase of dose in pembrolizumab treated patients

Tumor Dynamics	Objective Response Rate
	
Progression Free Survival	**Overall Survival**



Source: FDA reviewer's analysis

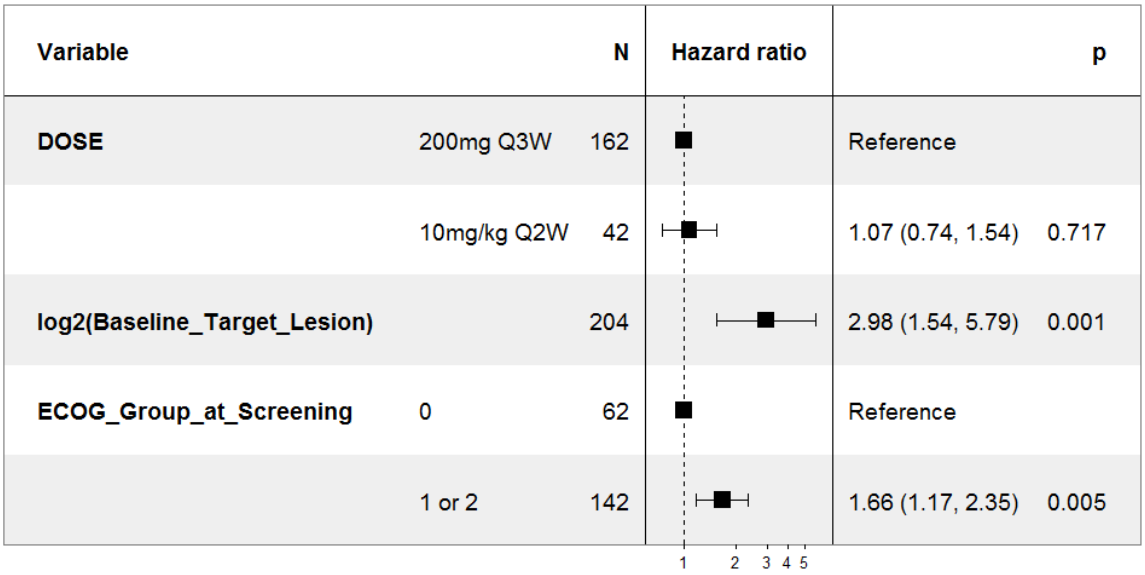
Due to the non-randomized nature of the trials, multivariate analysis was performed to adjust the potential confounding effects (**Figure 2, Figure 3 and Figure 4**). Consistent with univariate analysis, no significant dose-response relationship for ORR/PFS/OS was identified with multivariate analysis.

Figure 2: Multivariate Analysis for Objective Response Rate

Variable		N	Odds ratio	p
DOSE	200mg Q3W	162	Reference	
	10mg/kg Q2W	42	1.05 (0.40, 2.56)	0.911
log2(Baseline_Target_Lesion)		204	0.21 (0.05, 0.84)	0.028
ECOG_Group_at_Screening	0	62	Reference	
	1 or 2	142	0.36 (0.17, 0.77)	0.009

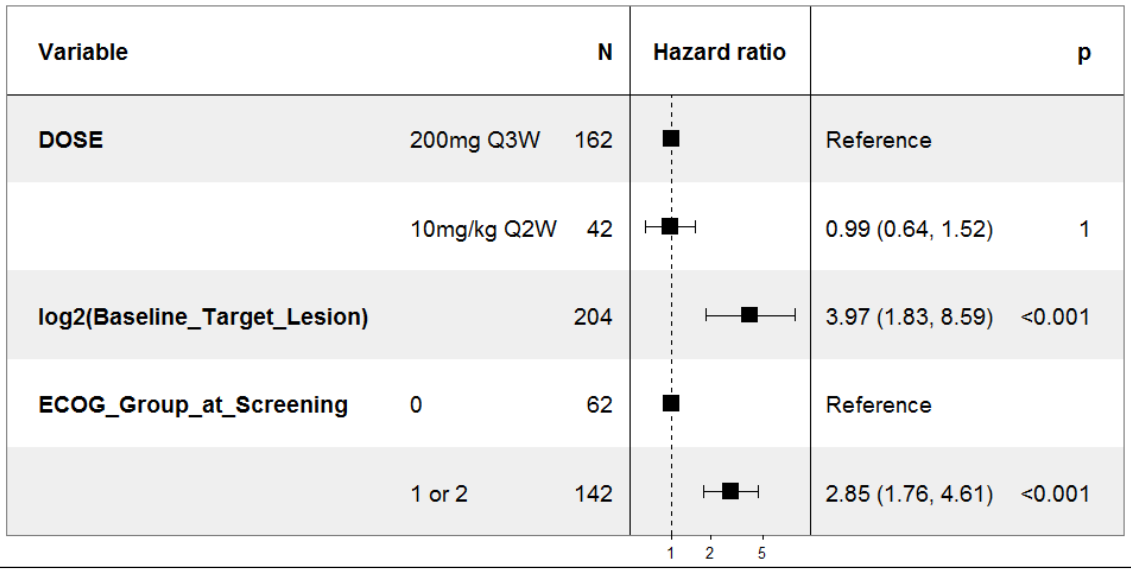
Source: FDA reviewer's analysis

Figure 3: Multivariate Analysis for Progression Free Survival



Source: FDA reviewer's analysis

Figure 4: Multivariate Analysis for Overall Survival



Source: FDA reviewer's analysis

ECOG performance group and baseline tumor size were identified as a significant covariate in the dose-response analysis for ORR/PFS/ OS.

Overall, there is no clear evidence supporting that there would be significant improvement in efficacy with 10 mg/kg Q2W as compared with 200 mg Q3W, even the exposure at 10 mg/kg is about five fold higher than that at 200 mg Q3W. However, there is a large uncertainty in estimated

odds ratio and hazard ratio between two dosing regimens due to the limited sample size in the clinical studies. In addition, as the trial was not randomized between the two dosing regimens, potential the dose -response may still be confounded even the observed risk factors were adjusted.

Q2. Are there any notable differences in pharmacokinetics between HNSCC patients and non-HNSCC patients based on the population PK analysis?

No. There were no clinically relevant new findings in pembrolizumab pharmacokinetics of HNSCC patients. The previously developed linear, 2-compartment, zero-order input intravenous (IV) infusion model was able to reasonably well describe the pembrolizumab concentration-time data. No major differences in PK parameters were identified between HNSCC and non-HNSCC (melanoma or NSCLC) patients (**Table 1** and **Figure 5**).

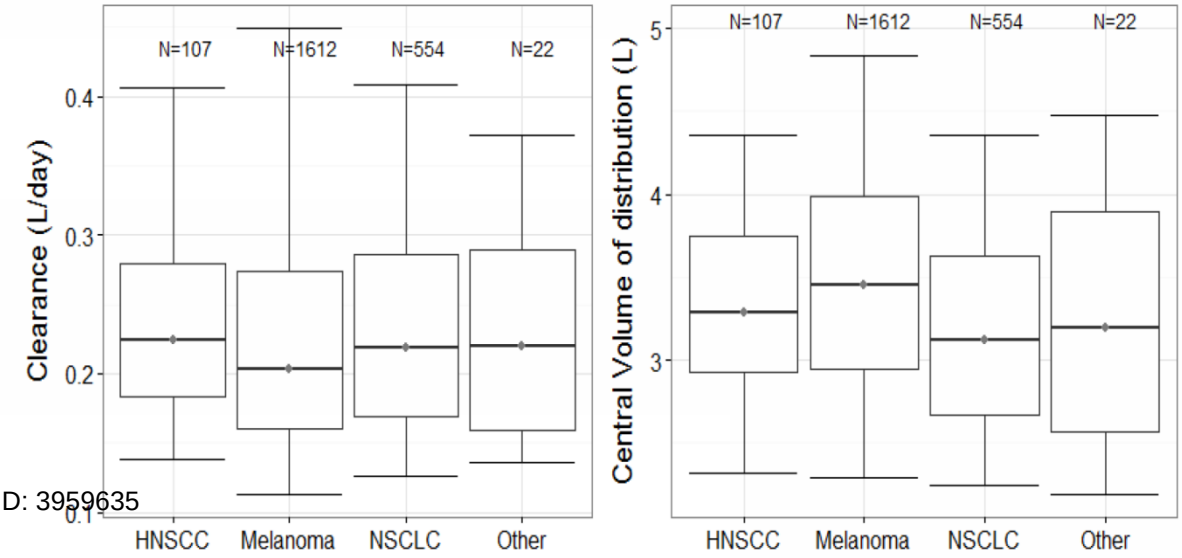
Table 1: Comparisons of descriptive statistics of individual PK parameters (CL, Vc) and derived parameters under 10 mg/kg Q2W between HNSCC and non-HNSCC patients

Parameter	HNSCC				Non-HNSCC			
	N	Mean	Median	SD	N	Mean	Median	SD
CL (L/day)	60	0.23	0.217	0.0798	660	0.222	0.197	0.108
Vc (L)	60	3.2	3.13	0.619	660	3.32	3.31	0.75
Cmax[a] (µg/mL)	53	221	213	37.1	604	236	230	44.7
Cmin[b] (µg/mL)	22	176	171	68.4	225	226	231	74.2
Half life (days)	60	24.8	23.3	7.52	660	27.9	27.4	8.2
AUCss (µg.h/mL)	60	9960	9890	3040	660	11900	11900	4070
Vdss (L)	60	7.01	6.81	1.3	660	7.37	7.34	1.49
Time to steady state (days)	60	124	117	37.6	660	140	137	41

[a] Cmax is concentration at time of peak sample in Cycle 1
[b] Cmin is trough concentration Cycle 8 through 12

Source: Sponsor's PPK analysis report, Summary

Figure 5: Comparison of CL and Vd Using the Individual Empirical Bayes Parameters by Indication



Source: Sponsor's PPK analysis report, page 33

1.2 RECOMMENDATIONS

Division of Pharmacometrics finds BLA 125514/S9 acceptable from a pharmacometrics perspective.

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 POPULATION PK ANALYSIS

The objectives of sponsor's population PK analysis were:

- Assess the population pharmacokinetics of pembrolizumab in patients with head & neck squamous cell carcinoma (HNSCC)
- Assess the similarity in pembrolizumab pharmacokinetics in HNSCC as compared to other tumor indications (melanoma, NSCLC)

2.1.1 Data

The definitive population PK model was developed by a pooled analysis of concentration data from PN001 (all data related to doses of 1 mg/kg and higher), PN002 and PN006. For this updated population PK evaluation, the model was estimated on an updated dataset from KN001, KN002 and KN006 and subsequently the data from HNSCC patients from studies PN012 and PN055 were added and the parameters from the existing population PK model were re-estimated to obtain *posthoc* parameters for all the individuals included in this pooled dataset.

2.1.2 Results

The population pharmacokinetics model was based on two compartment model with allometric scaling on the basis of body weight. The IIV was assumed to be log normally distributed, and both a shared IIV on CL and Q, and a shared IIV on Vc and Vp were used. The residual error model utilized an additive error on the log scale. Parameter estimates from previous model for KN001, KN002, KN006 and updated model with additional data from KN012 and KN055are presented in **Table 2**

Table 2: Comparison of Population Pharmacokinetic Parameters of Pembrolizumab (MK-3475) from the Previous Model with Non-HNSCC vs. Updated Model Including HNSCC Subjects

	The Definitive Population PK Model N=2188			Update Model N=2295 (107 out of 2295 HNSCC)		
Parts and Studies included in the analysis	**Melanoma/NSCLC;** A, A1, A2, B1, B2, B3, C, D, F1, F2 and F3 from KN001, KN002, KN006			**Melanoma/NSCLC;** A, A1, A2, B1, B2, B3, C, D and F1, F2, and F3 from KN001, KN002, KN006 **HNSCC;** KN012, KN055		
Data cut-off date	P001V01; 26-July-2013 P001V02; 18-April-2014 P001V03; 29-August-2014 P002V01; 12-May-2014 P006V01; 03-September-2014			P001V01; 26-July-2013 P001V02; 18-April-2014 P001V03; 29-August-2014 P002V01; 12-May-2014 P006V01; 03-September-2014 P012V01; 01-Sep-2015 P055V01; 25-Nov-2015		
Parameter	**Value**	**%RSE**	**%CV[a]**	**Value**	**%RSE**	**%CV[a]**
CL (L/day)	0.202	1.63	37.8	0.204	1.59	37.5
Vc (L)	3.47	0.892	20.6	3.47	0.85	20.6
Q (L/day)	0.794	4.03	37.8	0.817	3.75	37.5
Vp (L)	4.06	2.0	20.6	4.07	1.94	20.6
α for CL and Q	0.596	7.61		0.584	7.76	
α for Vc and Vpc	0.489	5.99		0.491	6.01	
Albumin on CL	-0.896	8.25		-0.904	8.06	
Bilirubin on CL	-0.0531	32.2		-0.0538	32.7	
eGFR on CL	0.127	21.5		0.13	22.2	
GENDER on CL	-0.159	10.2		-0.162	10.2	
Cancer Type (NSCLC vs Mel+HNSCC[b]+other) on CL	0.139	16.8		0.133	21.5	
Baseline ECOG on CL	0.0685	29.3		0.0704	29.8	
Baseline tumor size on CL	0.0884	12.1		0.0875	12.3	
IPI prior treatment status on CL	0.139	15.8		0.133	21.5	
Albumin on Vc	-0.208	20.6		-0.206	22.6	
GENDER Vc	-0.134	9.13		-0.135	9.13	
IPI prior treatment status on Vc	0.0735	22.5		0.0743	22.3	
Residual error	0.272	1.87		0.272	1.85	

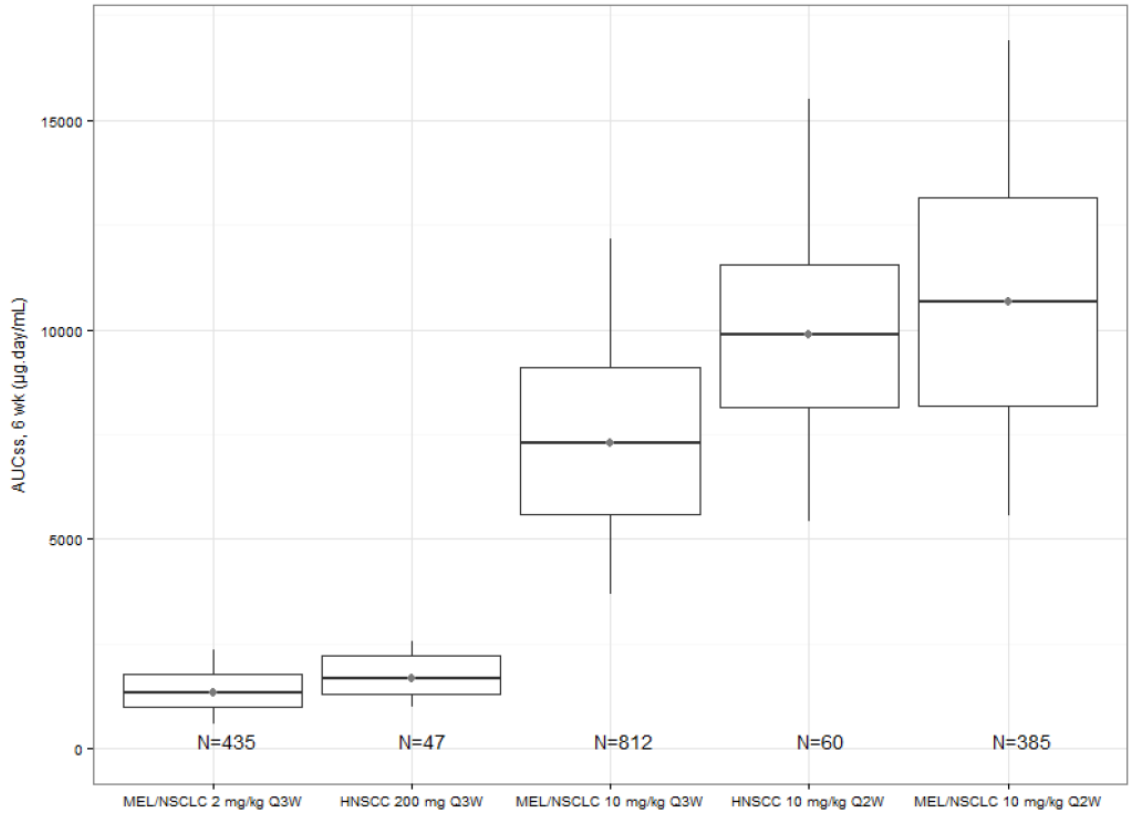
[a] %CV of residual error is related to estimate of between-subject variability on this parameter.
[b] HNSCC only included in update model.
Presented population parameter estimates exclude effects of covariates; therefore apply to a hypothetical typical patient with average characteristics. CL: clearance; Vc: central volume of distribution; Q: intercompartmental clearance; Vp: peripheral volume of distribution; Vd,ss: volume of distribution at steady state; t1/2: terminal half-life; %RSE: relative standard error (%); 95% CI: 95% confidence interval of parameter estimate based on bootstrap results; %CV: coefficient of variation of between-subject distributions of parameters; NA: not applicable.

Source: Synopsis of sponsor's population PK report for HNSCC

Table 2 presents summaries of descriptive statistics for posthoc estimates of CL, Vc as well as derived parameters for HNSCC and non-HNSCC populations. The pharmacokinetic model parameter estimates (e.g. CL and Vc) are in a similar range for HNSCC patients compared to other indications.
Additionally, the observed exposures for HNSCC subjects receiving the 200 mg Q3W regimen demonstrate no clinically meaningful difference in PK variability compared to weight-based dosing

(**Figure 6**) and are similar to prior data at 2 mg/kg Q3W and within the therapeutic window defined by the exposure-range previously observed from 2 mg/kg Q3W to 10 mg/kg Q2W in melanoma and NSCLC subjects.

Figure 6: Pembrolizumab (MK-3475) Exposure across Indications at Clinically Tested Dose Regimens



Source: Synopsis of sponsor's population PK report for HNSCC

Reviewer's comments:

- *Sponsor's population PK model is acceptable.*
- *The reviewer agrees with sponsor's conclusion that no significant difference in terms of PK in HNSCC patients as compared with non-HNSCC patients.*

3 RESULTS OF REVIEWER'S ANALYSIS

3.1 INTRODUCTION

The reviewer conducted an independent analysis to investigate if efficacy is similar between 10 mg/kg Q2W and 200 mg Q3W.

3.2 OBJECTIVES

Analysis objective is to address the potential imbalanced confounder distribution between 10 mg/kg Q2W and 200 mg Q3W by performing multivariate analysis.

3.3 DATA SETS

Data set are summarized in the following table:

Study #	Name	Link to EDR
012	adorr.xpt	\\cdsesub1\evsprod\bla125514\0225\m5\datasets\p012v01\analysis\legacy\datasets\adorr.xpt
055	adorr.xpt	\\cdsesub1\evsprod\bla125514\0225\m5\datasets\p055v01\analysis\legacy\datasets\adorr.xpt
012	adpfs.xpt	\\cdsesub1\evsprod\bla125514\0225\m5\datasets\p012v01\analysis\legacy\datasets\adpfs.xpt
055	adpfs.xpt	\\cdsesub1\evsprod\bla125514\0225\m5\datasets\p055v01\analysis\legacy\datasets\adpfs.xpt
012	ados.xpt	\\cdsesub1\evsprod\bla125514\0225\m5\datasets\p012v01\analysis\legacy\datasets\ados.xpt
055	ados.xpt	\\cdsesub1\evsprod\bla125514\0225\m5\datasets\p055v01\analysis\legacy\datasets\ados.xpt
012	adsl.xpt	\\cdsesub1\evsprod\bla125514\0225\m5\datasets\p012v01\analysis\legacy\datasets\adsl.xpt
055	adsl.xpt	\\cdsesub1\evsprod\bla125514\0225\m5\datasets\p055v01\analysis\legacy\datasets\adsl.xpt

3.4 SOFTWARE

R version 3.1.1 was used for data handling, visualization, and post-processing.

3.5 RESULTS AND DISCUSSIONS

The HNSCC patients from KEYNOTE-012 and KEYNOTE-055 were included in the multivariate dose-efficacy analysis. For ORR, multivariate regression was performed using logistic model and showed that there is no statistically significant different between 10 mg/kg Q2W and 200 mg Q3W doses. In addition, multivariate analysis was conducted for PFS and OS. There was no dose-response relationship identified between the two dosing regimens and the PFS/OS. (**Figure 2**, **Figure 3**, **Figure 4**)

3.6 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ER BLA125514 S9.R	Multivariate dose-response analysis for ORR/PFS/OS	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Pembrolizumab_BLA125514S9_CL\ER Analysis\

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/s/

SRIRAM SUBRAMANIAM
07/15/2016

CHAO LIU
07/15/2016

JINGYU YU
07/15/2016

HONG ZHAO
07/15/2016
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s009

OTHER REVIEW(S)

MEMORANDUM

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

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

Date: July 14, 2016

To: Sharon Sickafuse
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

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

Subject: OPDP Comments on BLA 125514
KEYTRUDA (pembrolizumab) injection, for intravenous use

OPDP has reviewed the proposed product labeling (PI) for KEYTRUDA (pembrolizumab) injection, for intravenous use (Keytruda) as requested in the consult dated February 18, 2016. The following comments, using the proposed substantially complete, marked-up version of the PI emailed to OPDP by Sharon Sickafuse on June 30, 2016, are provided below.

OPDP has no additional comments on the proposed Keytruda patient labeling at this time after reviewing DMPP's July 8, 2016, comments.

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

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

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/s/

NICHOLAS J SENIOR
07/14/2016

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

PATIENT LABELING REVIEW

Date:	July 8, 2016
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	KEYTRUDA (pembrolizumab)
Dosage Form and Route:	for injection, for intravenous use injection, for intravenous use
Application Type/Number:	BLA 125514
Supplement Number:	S-009
Applicant:	Merck Sharp and Dohme Corp.

1 INTRODUCTION

On February 9, 2016, Merck Sharp and Dohme Corp. submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved Biologics License Application (BLA) 125514/S-009 for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection. With this supplement the Applicant proposes a new indication for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection, for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Oncology Products 2 (DOP2) on February 18, 2016, to review the Applicant's proposed Medication Guide (MG) for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection.

2 MATERIAL REVIEWED

- Draft KEYTRUDA (pembrolizumab) for injection and injection MG received on February 9, 2016.
- Draft KEYTRUDA (pembrolizumab) for injection and injection Prescribing Information (PI) received on February 9, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on June 30, 2016.

3 REVIEW METHODS

In our focused review of the MG we:

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHARON R MILLS
07/08/2016

BARBARA A FULLER
07/08/2016

LASHAWN M GRIFFITHS
07/08/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 122325

MEETING MINUTES

Merck Sharp & Dohme Corporation
Attention: Margaret E. McCann, D.V.M., Ph.D.
Director, Global Regulatory Affairs
126 East Lincoln Avenue; P.O. Box 2000; RY34-B293
Rahway, NJ 07065-0900

Dear Dr. McCann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Keytruda (pembrolizumab; MK-3475)."

We also refer to the meeting between representatives of your firm and the FDA on November 23. 2015. The purpose of the meeting was to discuss the content and format of a submission of data from your KEYNOTE-012 study to a request for support accelerated approval for the proposed indication of treatment of (b) (4) .

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

If you have any questions, call me at (301) 796-4255.

Sincerely,

{See appended electronic signature page}

Norma Griffin
Lead Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	pre-sBLA
Meeting Date and Time:	Monday, November 23, 2015 / 12:00-1:00 PM (ET)
Meeting Location:	White Oak Building 22; Conference Room 1313
Application Number:	IND 122325
Product Name:	Keytruda (pembrolizumab; MK-3475)
Proposed Indication:	For the treatment of (b) (4)
Sponsor/Applicant Name:	Merck Sharp & Dohme Corporation
Meeting Chair:	Gideon Blumenthal
Meeting Recorder:	Norma Griffin

FDA ATTENDEES

Patricia Keegan	Division Director, DOP2
Gideon Blumenthal	Clinical Team Leader, DOP2
Erin Larkins	Clinical Reviewer, DOP2
Monica Hughes	Chief Project Management Staff, DOP2
Norma Griffin	Lead Regulatory Health Project Manager, DOP2
Hong Zhao	Clinical Pharmacology Team Leader, DCPV
Sriram Subramaniam	Clinical Pharmacology Reviewer, DCPV
Anshu Marathe	Pharmacometrics Reviewer, DPM
Kun He	Statistical Team Leader, DBV
Vivian Yuan	Statistical Reviewer, DBV

SPONSOR ATTENDEES

Peggy McCann	Director, Regulatory Affairs
Julie Lepin	Vice President, Regulatory Affairs
Jonathan Cheng	Executive Director, Clinical Research
Roger Dansey	Senior Vice President, Clinical Research
Christine Gause	Director, Biostatistics
Ellen Asam	Director, Statistical Programming
Keaven Anderson	Executive Director, Biostatistics
Shilpa Alekar	Senior Principal Scientist, Drug Safety
Mary Frances Schubert	Associate Vice President, Drug Safety

Kapil Mayawala	Principal Scientist, Quantitative Pharmacology and Pharmacometrics
Dinesh de Alwis	Executive Director, Quantitative Pharmacology and Pharmacometrics
Diana Chirovsky	Associate Director, Outcomes Research
Andrew Robertson	Director, Regulatory Affairs – Regulatory Policy

BACKGROUND

Pembrolizumab (MK-3475) is a humanized monoclonal antibody of the IgG4/kappa isotype that binds to the programmed death (PD)-1 molecule, thus blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2. KEYTRUDA (pembrolizumab) received accelerated approval in the U.S. on September 4, 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. KEYTRUDA also received approval in the U.S. on October 2, 2015 for the treatment of patients with metastatic, PD-L1 positive, non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.

Clinical Development Program in Head and Neck Squamous Cell Carcinoma (HNSCC)

The clinical development program of pembrolizumab in head and neck squamous cell carcinoma (HNSCC) is ongoing and includes the following studies: KEYNOTE (KN)-012 (cohorts B and B2), KN055, KN040 and KN048. KEYNOTE-012 is a phase Ib multi-cohort study of MK-3475 in subjects with advanced solid tumors. This multicenter, nonrandomized, multi-cohort trial of pembrolizumab included a total of 192 subjects with HNSCC enrolled in Cohort B and Cohort B2.

During the development of pembrolizumab in the HNSCC indication, regulatory guidance was obtained regarding cohorts B and B2 in Study KN012 under IND 110080; further development for this indication was conducted under IND 122325, to which Studies KN055, KN040 and KN048 have been submitted. A Type B meeting on June 30, 2015, was held under IND 122325 to discuss Merck's proposal to submit data from KN012 to support a request for accelerated approval for the proposed indication of treatment of (b) (4) . During the meeting, FDA stated that the data necessary to support an expanded labeling claim for this population would be based on the totality of evidence, including observed response rate and durability of response sufficient to show a meaningful advance over available therapy.

On September 25, 2015, to discuss and obtain FDA feedback regarding the adequacy of the proposed clinical program of KEYTRUDA to support approval of a proposed indication for the (b) (4) . In the meeting briefing package, Merck states their intent to submit a supplemental BLA at the end of December 2015, seeking accelerated approval under the provisions of 21CFR Part 601 Subpart E based upon demonstration of durable overall responses in patients with no available therapy (i.e.,

[redacted] (b) (4) in the KN012 trial. Merck intends to submit Study KN040 or Study KN048 as the confirmatory trial to verify clinical benefit predicted by the observed durable overall response rate (ORR). The preliminary results of the trial are summarized in the table below:

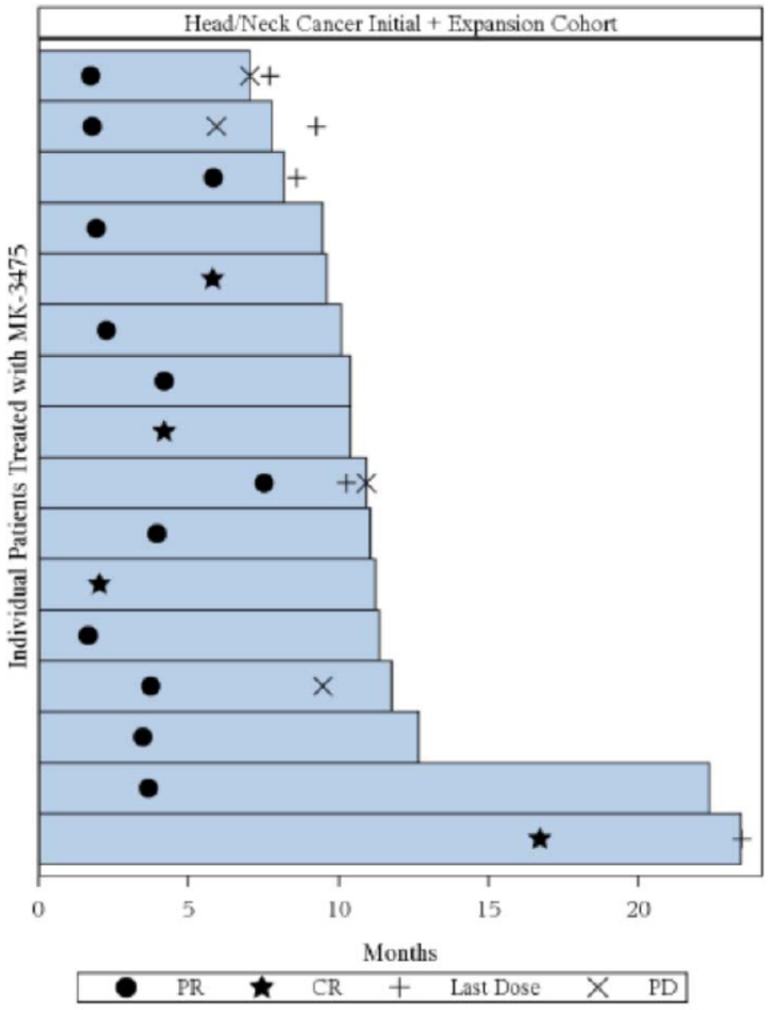
Response Rate by Independent Central Review for Cohorts B and B2 of KEYNOTE-012

	n	ORR, n (%)	95% CI
All patients	192	17.7	12.6, 23.9
Progressed after platinum	174	16.7	11.5, 23.1
Progressed after platinum and cetuximab	110	14.5	8.5, 22.5
Progressed after platinum but not cetuximab	64	20.3	11.3, 32.2

Among the 110 patients with recurrent disease (i.e., experienced progression of disease) during or following treatment with platinum and cetuximab, the median duration of response has not been reached. Of the 16 observed responses, 12 (75%) are ongoing; Merck states that based on Kaplan-Meier estimation of duration of response, 13 patients have a response duration of ≥6 months.

[redacted] APPEARS THIS WAY ON ORIGINAL

Swim Lane Plot – Head and Neck Cohort B + B2 Cetuximab and Platinum Progressed Subjects (Confirmed Responses by Independent Central Radiology Review) (ASaT)



APPEARS THIS WAY ON ORIGINAL

Proposed Confirmatory Trials
The following table summarizes key design elements of the proposed confirmatory trials: KEYNOTE 040 and KEYNOTE 048, and an additional trial evaluating the anti-tumor activity of pembrolizumab in patients with PD-L1 strongly expressing, platinum- and cetuximab-resistant, recurrent/metastatic HNSCC.

Protocol Number	Study Design	Co-Primary Efficacy Endpoints	Current enrollment/ planned enrollment
KEYNOTE 055	Single arm, study in patients with resistant[1] HNSCC that has progressed on or following platinum and cetuximab	• ORR in all subjects • ORR in PD-L1 strongly positive[2] HNSCC	51/150
KEYNOTE 040	Randomized (1:1), active-controlled, open-label trial comparing pembrolizumab with investigator's choice of (methotrexate, docetaxel, or cetuximab) in patients with R/M[3] HNSCC	• Progression-free survival (PFS) • Overall survival (OS) • PFS in PD-L1 strong positive • OS in PD-L1 strong positive	208/600
KEYNOTE 048	Randomized (1:1:1), 3-arm open-label trial, comparingpembrolizumab and pembrolizumab plus platinum and 5-FU with platinum, 5-FU, and cetuximab in patients with R/M[3] HNSCC	• Pairwise comparisons (pembrolizumab alone or with chemotherapy vs. chemotherapy) in PD-L1-strongly positive HNSCC subpopulation • Pairwise comparisons of PFS regardless of PD-L1 expression (ITT population)	100/780

[1]Resistant HNSCC is defined as tumor progression or recurrence within 6 months of platinum and cetuximab therapy in the adjuvant (e.g. with radiation after surgery), primary (e.g. with radiation), recurrent, or metastatic setting

[2]PD-L1 strongly positive: ≥50% of tumor cells with PD-L1 expression

[3]R/M HNSCC: recurrent is defined as disease progression following platinum and cetuximab therapy in either the adjuvant or metastatic setting

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

Clinical

See Company Position for Question 1 on Pages 15-25 of Merck's Meeting Background Package.

1. Data from KEYNOTE-012 cohorts B and B2 (N = 110), a heavily pretreated recurrent /metastatic HNSCC patient population whose disease has progressed following platinum andcetuximab-containing therapy, show that there is a meaningful response rate and a durable duration of response from pembrolizumab treatment.

   Does the agency agree that these data in a patient population with high unmet need and no effective treatment options (e.g. methotrexate) with a bleak prognosis are acceptable to enable an evaluation of the sBLA of pembrolizumab for the treatment of (b) (4) **?**

   FDA 11/19/2015 Response to Question 1:

   (b) (4) In order to provide a more accurate estimation of the treatment effect, Merck should also include response data on all patients enrolled in KN055 with at least 6 months follow-up. The adequacy of the data to support accelerated approval will be determined during the review of the sBLA.

   Merck 11/20/2015 Email Response: Merck would like to discuss FDA response to Question 1. Also see Merck's position as presented in their 11/23/2015 slide presentation.

   Discussion During 11/23/2015 Meeting: Merck stated that it would be possible to provide data on approximately 50 patients enrolled in KN-055 with at least 6 months of follow-up, where an interim CSR and datasets would be provided in the sBLA. FDA agreed that this would make a stronger application.

See Company Position for Question 2 on Pages 26-30 of Merck's Meeting Background Package.

2. (b) (4) a meaningful response rate and durable duration of response has also been demonstrated in (b) (4) 174 patients with recurrent / metastatic head and neck cancer whose disease has progressed following a platinum containing regimen.

Given the limited treatment options available for these patients, would the agency consider for review for accelerated approval a sBLA with data from this (b) (4) HNSCC patient population to support the following proposed indication: KEYTRUDA is indicated for the treatment of patients with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC) and disease progression on or following platinum-containing chemotherapy?

FDA 11/19/2015 Response to Question 2:

Based on the information provided in the pre-meeting briefing document, there may be insufficient data to support a conclusion that the centrally-confirmed response rate of 20.3% (95% CI: 11.3, 32.2) with pembrolizumab observed in patients with progressive disease after platinum but not cetuximab provides a meaningful therapeutic benefit over existing treatments, given the small absolute number of patients in cohorts B and B2 of KEYNOTE-012 in this population with observed responses (13 of 64 patients) and the wide confidence intervals around the observed ORR, which overlap the confidence intervals for the historical ORR of 11% (95% CI: 7, 15) observed with cetuximab in this patient population. In order to provide appropriate context for the observed response rate, submit duration of response data for the cetuximab-naïve patient population (n=64). Determination of whether or not the data is sufficient to support an expanded labeling claim under accelerated approval for this population would be made at the time of sBLA review and would be based on the totality of evidence, including observed response rate and durability of response sufficient to show a meaningful advantage over available therapy in the intended patient population.

Merck 11/20/2015 Email Response: Merck would like to discuss FDA response to Question 2. Also see Merck's position as presented in their 11/23/2015 slide presentation.

Discussion During 11/23/2015 Meeting: Determination of whether an approval would (b) (4) is a review issue that will consider the durability of responses observed in this population. Therefore, FDA agreed that it would be acceptable to submit updated information on duration of response at the 90 day safety update encompassing 174 patients.

See Company Position for Question 3 on Page 31 of Merck's Meeting Background Package.

3. The safety analysis for this sBLA will consist of the following components:

- Data from a total of 2799 patients from the pembrolizumab clinical program, including 1567 patients with melanoma treated with pembrolizumab in KN001, KN002, and KN006 and from 1232 NSCLC patients in KN001 and KN010.
- Data from 192 patients from KN012 cohorts B (10 mg/kg Q2W) and B2 (200 mg Q3W) with advanced HNSCC treated with pembrolizumab.

- A summary of the safety data for pembrolizumab received in the postmarketing environment.

A robust safety dataset from the entire completed pembrolizumab clinical program will be submitted and therefore the company proposes (b) (4)

Does the Agency agree with this approach for presenting safety data for pembrolizumab to support the sBLA?

FDA 11/19/2015 Response to Question 3:

FDA does not agree that it is necessary to submit datasets containing safety information for all 2799 patients exposed to pembrolizumab in ongoing and completed clinical trials. FDA agrees with the proposal to submit datasets from 192 patients enrolled in KN012 cohorts B (10 mg/kg Q2W) and B2 (200 mg Q3W) with advanced HNSCC who received at least one dose of pembrolizumab. Given the limited safety data available for pembrolizumab at the proposed dose (200 mg IV every 3 weeks) in patients with HNSCC from KEYNOTE 012 (n=132), Merck should also submit available safety data from ongoing HNSCC clinical trials (KN055, KN040, and KN048) consisting of narrative summaries for each serious adverse event (SAE) for events not currently listed in the prescribing information for pembrolizumab.

Merck 11/20/2015 Email Response: Merck would like to discuss FDA response to Question 3. Also see Merck's clarification as presented in their 11/23/2015 slide presentation.

Discussion During 11/23/2015 Meeting: FDA requested, and Merck agreed to provide, the datasets from KN-012 containing safety information for all 192 patients, narrative summaries for each serious adverse event (SAE) for events not currently listed in the prescribing information for pembrolizumab, and to present side by side tabular presentations of the KN-012 data and adverse reactions in other primary cancer sites with discussion of whether any new cancer sites have been identified. FDA agreed that it may not be necessary to update the Warnings & Precautions of product labeling given the small sample size in KN-012.

See Company Position for Question 4 on Page 32 of Merck's Meeting Background Package.

4. For the Safety Update Report to be submitted during review of the sBLA, the sponsor proposes to include updated safety data from KN012 cohorts B and B2. The Sponsor is targeting the sBLA submission for December 2015 and the initial data cut-off for the file (KN012 Last Patient Last Visit) is September 1, 2015. The SUR will be submitted approximately 90 days after the sBLA submission.

Does the Agency agree with the content and timing for the SUR submission?

FDA 11/19/2015 Response to Question 4:

FDA agrees with the proposed timing of the Safety Update Report; however in addition to the proposed information, Merck should also provide updated response durations for responding patients identified in Studies KN012 and KN055 in the BLA supplement.

Merck 11/20/2015 Email Response: Merck would like to discuss FDA response to Question 4.

Discussion During 11/23/2015 Meeting: FDA agreed that datasets for KN-012 and KN-055 submitted in the ISE do not need to be integrated.

See Company Position for Question 5 on Page 33 of Merck's Meeting Background Package.

5. **Does the Agency concur that a dossier consisting of the KEYNOTE-012** (b) (4) **would be acceptable to support review of the sBLA?**

FDA 11/19/2015 Response to Question 5:

FDA agrees that the content may be adequate to support review of the sBLA, provided that the additional information identified by FDA in response to Questions 1 and 4 is also included. (b) (4) .

Merck 11/20/2015 Email Response: Merck acknowledged and is in agreement with FDA's 11/19/2015 response to Question 5.

Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

See Company Position for Question 6 on Page 34 of Merck's Meeting Background Package.

6. The Sponsor intends to submit the KEYNOTE-012 dossier for approval under 21 CFR 601 Subpart E.

Does the Agency agree that Study KN040 "A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer" or Study KN048 "A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma" would suffice as the required confirmatory trial for such a submission?

FDA 11/19/2015 Response to Question 6:

FDA agrees that KEYNOTE 040 and KEYNOTE 048 are adequate in design to provide the data necessary to verify clinical benefit.

Merck 11/20/2015 Email Response: Merck acknowledged and is in agreement with FDA's 11/19/2015 response to Question 6.

Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

See Company Position for Question 7 on Page 35 of Merck's Meeting Background Package.

7. The background package contains the proposed table of contents for the Common Technical Document (CTD) modules. Does the Agency agree that the package as outlined will support an evaluation of the overall benefit/ risk assessment of pembrolizumab for the treatment of recurrent and/or metastatic head and neck squamous cell carcinoma in patients who have progressed following prior platinum therapy?

   Merck will provide two versions of Study Data Tabulation Model (SDTM) in Version (v) 3.1.3 and v3.1.1 formatted data. In accordance with the FDA Study Data Technical Conformance Guide:

   - M5 tabulation\legacy will include: SDTM v 3.1.1 SAS transport files; data definition with supporting files; and SDTM v 3.1.1 annotated CRF. These datasets support end to end traceability as they were the source for the analysis datasets.
   - M5 tabulation\sdtm will include: SDTM v3.1.3 SAS transport files, data definition with supporting files; SDTM v3.1.3 annotated CRF; and Study Data Reviewer's Guide.

   Does the Agency agree that this approach to provision of datasets will support an evaluation of the overall benefit/ risk assessment of pembrolizumab for the proposed indication?

   FDA 11/19/2015 Response to Question 7:

   No, the proposed approach is not acceptable. The analysis data should be derived from the SDTM datasets, instead of raw datasets that do not comply with the CDISC formats. FDA will accept one set of SDTM and ADam datasets that is sufficient for the review of the sBLA. Please submit the SAS programs for the data derivations and efficacy analyses.

   Merck 11/20/2015 Email Response: Merck would like to discuss FDA response to Question 7. Also see Merck's position as presented in their 11/23/2015 slide presentation.

Discussion During 11/23/2015 Meeting: FDA stated that it would be preferable to receive the data in a single CDISC compliant version and that version 3.1.1. is acceptable provided that there is a detailed define file with functioning hyperlinks and that raw and analyses datasets are clearly segregated in separate folders. FDA noted that in the past, when datasets were provided in two different versions of CDISC, the data were not concordant, leading to confusion as to the most appropriate dataset to use. FDA encouraged Merck to update their databases to the most recent version of CDISC for future submissions.

See Company Position for Question 8 on Page 36 of Merck's Meeting Background Package.

8. The Sponsor will provide the following to support the ISS analysis:

- Integrated ADSL dataset
- Integrated CM (Concomitant Medication) SDTM version 3.1.1 domain plus SUPPQUAL (CMPLUS)
- Integrated AE (Adverse Event) SDTM version 3.1.1 domain plus SUPPQUAL (AEPLUS)
- Integrated RELREC SDTM 3.1.1 domain

Does the Agency agree with the Sponsor's proposed integrated safety data set package consisting of KN001- melanoma; KN002 – melanoma; KN006 – melanoma; KN001 – lung; KN010 – lung; and KN012 – head and neck? In addition, source data used as input to generating the integrated ADSL will also be included. Does the Agency agree with this approach?

FDA 11/19/2015 Response to Question 8:

No, FDA does not agree. See FDA response to Question 3.

Merck 11/20/2015 Email Response: Merck acknowledged FDA's 11/19/2015 response to Question 8.

Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

See Company Position for Question 9 on Pages 37 - 38 of Merck's Meeting Background Package.

9. **Does the Agency agree with the Sponsor's proposed approach to include an Analysis Data Reviewers Guide (ADRG) and a separate analysis define document to facilitate the reproduction of topline efficacy and safety analyses?**

FDA 11/19/2015 Response to Question 9:

Yes. In the define file, please provide sufficient documentation for the definition and derivations of the variables. Provide hyperlinks that link back to the variable definitions, original locations in the CRF, etc. The documentation should be sufficient to facilitate review of the efficacy and safety analyses as well as data derivations.

Merck 11/20/2015 Email Response: Merck acknowledged and is in agreement with FDA's 11/19/2015 response to Question 9.

Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

See Company Position for Question 10 on Page 39 of Merck's Meeting Background Package.

10. Merck plans to provide site level datasets in the sBLA to aid Office of Scientific Investigation (OSI) in identifying clinical trial sites for inspections for the trial. Financial disclosure information will not be included in the summary level dataset since this information is sensitive and has extremely limited distribution within Merck. Note that this information is provided by a separate group within Merck and will be available within module 1.3.4 of the sBLA.

    Does the Agency agree that providing site level datasets with no financial disclosure information will satisfy OSI requirements?

    FDA 11/19/2015 Response to Question 10:

    Yes, it is acceptable to omit clinical investigator financial disclosure information from the OSI Requested (Part III) Summary Level Clinical Site Datasets.

    Merck 11/20/2015 Email Response: Merck acknowledged and is in agreement with FDA's 11/19/2015 response to Question 10.

    Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

See Company Position for Question 11 on Page 40 of Merck's Meeting Background Package.

11. The sponsor understands that as required by 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. As required by the Food and Drug Administration Safety and Innovation Act (FDASIA), the Sponsor submitted an Initial Pediatric Study Plan (iPSP) on August 8, 2014, which was received within 60 days of the June 11, 2104 End of Phase (EOP2)

meeting for the clinical development for pembrolizumab for the treatment of patients with head and neck squamous cell carcinoma.

Merck would like clarification of the agency timeline for completing review of the iPSP in light of the anticipated filing of the sBLA for pembrolizumab for the HNSCC indication in December, 2015.

FDA 11/19/2015 Response to Question 11:

FDA acknowledges submission of the iPSP on August 8, 2014, which remains under review. FDA anticipates providing its assessment of the iPSP no later than December 16, 2015.

Merck 11/20/2015 Email Response: Merck acknowledged and is in agreement with FDA's 11/19/2015 response to Question 11.

Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

Additional Comments

Clinical Pharmacology:

12. Submit bioanalytical methods and validation reports for analysis of PK samples in KEYNOTE 012.

Merck 11/20/2015 Email Response: Merck acknowledged FDA's 11/19/2015 Additional Comment 12.

Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

13. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations or patients that have been excluded from the analysis should be flagged and maintained in the datasets.

Merck 11/20/2015 Email Response: Merck acknowledged FDA's 11/19/2015 Additional Comment 13.

Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

14. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in the study reports.

Merck 11/20/2015 Email Response: Merck acknowledged FDA's 11/19/2015 Additional Comment 14.

Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

15. Provide the population analysis report.
Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for more information.

Merck 11/20/2015 Email Response: Merck acknowledged FDA's 11/19/2015 Additional Comment 15.

Discussion During 11/23/2015 Teleconference: No discussion occurred during the 11/23/2015 meeting.

16. Provide the exposure-response (ER) analysis reports for efficacy and safety endpoints. The report should include univariate and multivariate analyses that account for relevant risk factors for efficacy or safety. Submit associated datasets and scripts used to conduct the analysis. Data files should be submitted as SAS transport files.

Merck 11/20/2015 Email Response: Merck would like to discuss FDA Clinical Pharmacology Additional Comments 16. Also see Merck's clarification as presented in their 11/23/2015 slide presentation.

Discussion During 11/23/2015 Meeting: FDA confirmed that advice provided during the June 29, 2015 meeting is still applicable to this supplement.

PRESCRIBING INFORMATION

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

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

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

Office of Scientific Investigations (OSI) Requests

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

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

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

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

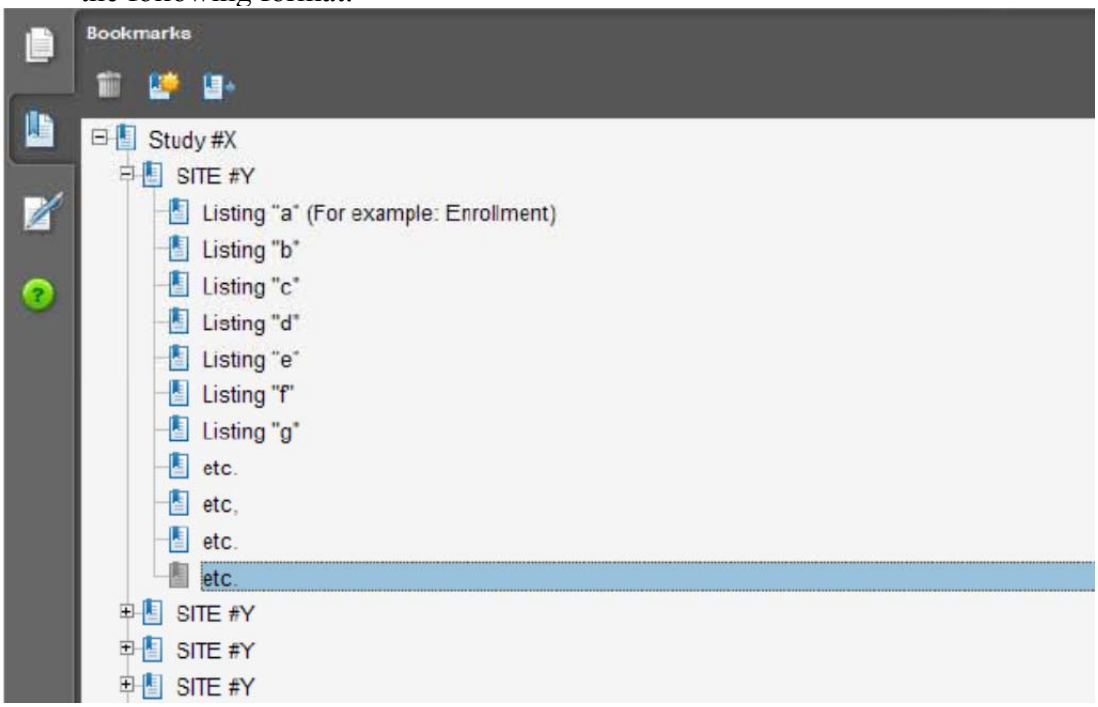
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing

Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

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

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

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

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

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

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

References:

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

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

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

ATTACHMENTS AND HANDOUTS

- OHOP's End-of-Phase 2 General Advice for Planned Marketing Applications
- Additional DOP2 CDISC Guidance
- Merck's PowerPoint Presentation "MK-3475/Pembrolizumab Pre sBLA - Head and Neck Meeting November 23, 2015"
- Meeting Participant List

OHOP's End-of-Phase 2
General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

FDA's methodology and submission structure for regulatory applications supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. Our methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. The sponsor/applicant should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications*). Study analyses datasets should be traceable to the tabulations datasets.

The *PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017* guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsors/Applicants should design and implement data standardization in all research protocols to be included in regulatory submissions, as required, based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. The sponsor/applicant should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (*CDASH*) standard for design and implementation of data collection instruments.

The *Study Data Specifications* provide the current specifications for submissions. The specifications provide the most conducive data content definition and structure for the review team. The review team assigned to the submission determines the acceptability. Therefore, you are encouraged to follow this best practice noted in the *Study Data Specifications*, "prior to submission, sponsors should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset and the organization of the data within the file".

In addition, please reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions. The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration.

Additional Links:

Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application.

These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application, we encourage you to provide justification and discuss it with us.

GENERAL

Special Protocol Assessment (SPA) Requests

1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.

SPA Requests for a Single Trial Intended to Support Marketing Approval

Note: You may also apply these concepts to a trial for which you are not seeking SPA agreement.

2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document:
   - Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. *See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products'*).
   - A description of your drug development plan, including each indication that is being (or has been) studied and a timetable for submission of the planned studies. You should also include information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.

Additional Content for SPA Request Submission

Note: You may also apply some of the concepts below to trials for which you are not seeking SPA agreement.

3) Please submit/address the items below in your SPA request.
   - The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
   - If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
   - If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
   - If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
   - If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:

- How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
- Applicability of comparator treatment or of disease characteristics to U.S. population

- Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot be performed. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on single arm trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)) in your SPA request and NDA/BLA submission. Under §314.510 and 601.41, confirmatory trials would usually be underway at the time of accelerated approval. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on the timing and number of confirmatory trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).
   - If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format

CLINICAL

1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.

2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.

3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure

4) All randomization lists and, if used, IVRS datasets (in SAS transport format)

5) All datasets used to track adjudications (in SAS transport format)

6) A Reviewers Guide to the data submission that includes, but is not limited to the following:
   a) description of files and documentation
   b) description of selected analysis datasets
   c) key variables of interest, including efficacy and safety variables
   d) SAS codes for sub-setting and combining datasets
   e) coding dictionary used
   f) methods of handling missing data
   g) list of variable contained in every dataset
   h) listing of raw data definitions
   i) analysis data definitions
   j) annotated CRF (the annotated CRF should contain links connecting to the document that defines

the variable name and lists the data sets that contain the specific item)

k) documentation of programs

7) Clinical study report(s) for all trials should follow the ICH E3 Structure and Content of Clinical Study Reports guidance: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf

8) Pediatric Studies:

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the FDA Pediatric Team at Pedsdrugs@fda.hhs.gov. You may also refer to the following FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

9) Quantitative Safety Analysis Plan (QSAP):

The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:

a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
b) Safety endpoints for Adverse Events of Special Interest (AERI)
c) Definition of Treatment Emergent Adverse Event (TEAE)
d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))
e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:

a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)
b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)

11) Perform the following Standard MedDRA Queries (SMQs) on the ISS adverse event data and include the results in your ISS report. Also, provide any additional SMQ that may be useful based

on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.
12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application
13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.
14) References: There should be active links from lists of references to the referenced article.
Studies, Data And Analyses
15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).
16) Provide a table with the following columns for each of the completed Phase 3 clinical trials: a) Site number b) Principle investigator c) Location: City State, Country d) Number of subjects screened e) Number of subjects randomized f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection) g) Number of protocol violations (Major, minor, including definition)
17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components: a) subject age and gender b) signs and symptoms related to the adverse event being discussed c) an assessment of the relationship of exposure duration to the development of the adverse event d) pertinent medical history e) concomitant medications with start dates relative to the adverse event f) pertinent physical exam findings g) pertinent test results (for example: lab data, ECG data, biopsy data) h) discussion of the diagnosis as supported by available clinical data i) a list of the differential diagnoses, for events without a definitive diagnosis j) treatment provided k) re-challenge and de-challenge results (if performed) l) outcomes and follow-up information

m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
b) Exposure-Response Relationships – important exposure-response assessments.
c) Less common adverse events (between 0.1% and 1%).
d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
f) Marked outliers and dropouts for laboratory abnormalities.
g) Analysis of vital signs focused on measures of central tendencies.
h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
l) Standard analyses and explorations of ECG data.
m) Overdose experience.

n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.

o) Explorations for:
   i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
   ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
   iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
   iv) Drug-demographic interactions
   v) Drug-disease interactions

p) Drug-drug interactions
   i) Dosing considerations for important drug-drug interactions.
   ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf .

Physician's Labeling Rule

1) Please refer to the PLR Requirements, Guidances, and Labeling Tools for Prescribing Information at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

2) Please utilize the Selective Requirements for Prescribing Information (SRPI) tool which is an interactive checklist of 42 important format items from labeling regulations and guidances. See: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

3) Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (http://www.cdisc.org/sdtm) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)

CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE,ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601

RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRESP, NTGRESP & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL

TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials[1]. RECIST (Response Evaluation Criteria in Solid Tumors)[2] has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification[3] in the assessment lymphomas, or, MacDonald Response[4] in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:
--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

(1) E.A. Eisenhauera,*, P. Therasseb, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247*
(2) RECIST Criteria - http://www.eortc.be/recist/
(3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology. Vol 25 Number 5 Feb 10 2007*
(4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology, Vol 8, 1277-1280*

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3. *x.x* …….. One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.

2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

   Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

   During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

   a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".

   b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).

   c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.

4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.

7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..*x x* …….. One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORRES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORRES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.

2. TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. “Percent Change From Nadir”) if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL=”INDEPENDENT ASSESSOR” and TREVALID=”RADIOLOGIST 1”. The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..*x x* ..... One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.

2. RSTESTCD / RSTEST values for this domain(this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. ***TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.***

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

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MEETING ATTENDANCE LIST

Meeting between Merck Sharp & Dohme (IND # 122325) and the Center for Drug Evaluation and Research.

DATE: November 23, 2015 TIME: 12:00-1:00 PM ET ROOM: WO22/Room 1313

NAME - Please print	AFFILIATION
Norma Griffin	FDA/CDER/OHOP/DOPZ
Ellen Asam	Merck
Julie Lepin	Merck
Peggy McCann	Merck
Jonathan Cheng	Merck
Roger Dansey	Merck.
Christine Gause	Merck
KAPIL MAYAWALA	Merck
Shilpa Alekar	Merck
Diana Chirovsky	Merck
Keaven Anderson	Merck
Mary Frances Schubert	Merck
Dinesh de Alwis	Merck
ANDREW ROBERTSON	Merck
Erin Larkins	FDA/CDER/OHOP/DOPZ
Hong Zhao	FDA/OCP/DCPV
SRIRAM SUBRAMANIAN	FDA/OCP/DCPV
ANSHU MARATHE	FDA/OCP/DPM
Kun He	FDA
PATRICIA KEEGAN	FDA/CDER/OND/OHOP/DOPZ
Blumenthal	"
Vivian Yuan	FDA/CDER/OND/D
Monica Hughes	FDA/CDER/OND/OHOP/DOPZ

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/s/

NORMA S GRIFFIN
11/25/2015