CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s045

Trade Name:	KEYTRUDA
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp & Dohme Corp.
Approval Date:	December 19, 2018
Indication:	KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated: **Melanoma** • for the treatment of patients with unresectable or metastatic melanoma. (1.1) **Non-Small Cell Lung Cancer (NSCLC)** • in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.2) • in combination with carboplatin and either paclitaxel or nabpaclitaxel, as first-line treatment of patients with metastatic squamous NSCLC. (1.2) • as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by an FDAapproved test, with no EGFR or ALK genomic tumor aberrations. (1.2)

MERCK EX1174
Merck Sharp & Dohme LLC v. The Johns Hopkins University
IPR2024-00647

- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) 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. (1.2)

Head and Neck Squamous Cell Cancer (HNSCC)

- for the the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.[1] (1.3)

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.[1] (1.4)

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.[1] (1.5)
- Limitation of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[1] (1.6)
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.6)

Microsatellite Instability-High Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
  - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options,[1] or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1] (1.7)
- Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. (1.7)

Gastric Cancer

- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1] (1.8)

Cervical Cancer

- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA approved test.[1] (1.9)

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC who have been previously treated with sorafenib.[1] (1.10)

Merkel Cell Carcinoma (MCC)

for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1] (1.11)

[1] 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.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s045

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-45

ACCELERATED APPROVAL

Merck Sharp & Dohme Corp.
Attention: Victoria Demby, Ph.D.
Director, Global Regulatory Affairs
351 N. Sumneytown Pike, P.O. Box 1000
UG2CDS-015
North Wales, PA 19454

Dear Dr. Demby:

Please refer to your Supplemental Biologics License Application (sBLA), dated June 29, 2018, received June 29, 2018, and your amendments, submitted under section 351 of the Public Health Service Act for KEYTRUDA® (pembrolizumab) injection, for intravenous use.

This Prior Approval supplemental biologics application adds a new indication for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. 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 trial.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.40), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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

CONTENT OF LABELING

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

identical to the enclosed labeling text for the Prescribing Information and Medication Guide and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 November 27, 2018. 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:

3546-1 Conduct and submit the results of a multicenter clinical trial to confirm the clinical benefit of pembrolizumab in patients with locally advanced or metastatic Merkel cell carcinoma (MCC) who have not received prior systemic therapies for metastatic MCC. The trial will enroll at least 50 patients to be followed for a minimum of 12 months to establish the objective response rate and characterize the durability of response. Overall survival, which is a secondary endpoint, will be followed to maturity until at least 70% of patients have died, or for an additional two years beyond the primary data analysis cut-off, to characterize effects on survival.

Interim Report:	12/2023
Trial Completion:	06/2032
Final Report Submission:	12/2032

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 (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

PROMOTIONAL MATERIALS

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

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information (PI)/Medication Guide/Patient Package Insert (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 Sharon Sickafuse, Senior Regulatory Health Project Manager, at 301-796-2320 or email sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.P.H.
Associate Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Prescribing Information
Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ASHLEY F WARD on behalf of STEVEN J LEMERY
12/19/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s045

<u>LABELING</u>

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)	12/2018
Dosage and Administration (2)	12/2018
Warnings and Precautions (5)	08/2018

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

KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated:

Melanoma
- for the treatment of patients with unresectable or metastatic melanoma. (1.1)

Non-Small Cell Lung Cancer (NSCLC)
- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.2)
- in combination with carboplatin and either paclitaxel or nab-paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC. (1.2)
- as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. (1.2)
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) 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. (1.2)

Head and Neck Squamous Cell Cancer (HNSCC)
- for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.[1] (1.3)

Classical Hodgkin Lymphoma (cHL)
- for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.[1] (1.4)

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.[1] (1.5)
- Limitation of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[1] (1.6)
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.6)

Microsatellite Instability-High Cancer
- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
  - o solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options,[1] or
  - o colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1] (1.7)
- Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. (1.7)

Gastric Cancer
- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1] (1.8)

Cervical Cancer
- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.[1] (1.9)

Hepatocellular Carcinoma (HCC)
- for the treatment of patients with HCC who have been previously treated with sorafenib.[1] (1.10)

Merkel Cell Carcinoma (MCC)
- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1] (1.11)

[1] 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.

---------- DOSAGE AND ADMINISTRATION ----------
- Melanoma: 200 mg every 3 weeks. (2.2)
- NSCLC: 200 mg every 3 weeks. (2.3)
- HNSCC: 200 mg every 3 weeks. (2.4)
- cHL or PMBCL: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.5, 2.6)
- Urothelial Carcinoma: 200 mg every 3 weeks. (2.7)
- MSI-H Cancer: 200 mg every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for children. (2.8)
- Gastric Cancer: 200 mg every 3 weeks. (2.9)
- Cervical Cancer: 200 mg every 3 weeks. (2.10)
- HCC: 200 mg every 3 weeks. (2.11)
- MCC: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.12)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

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

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

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Immune-mediated pneumonitis: Withhold for moderate, and permanently discontinue for severe, 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):
  - o Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  - o Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or life-threatening hyperthyroidism.
  - o 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)

- Immune-mediated skin adverse reactions including, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): Withhold for severe and permanently discontinue for life-threatening skin reactions. (5.6)
- Other immune-mediated adverse reactions: In organ transplant recipients, consider the benefit of treatment with KEYTRUDA versus the risk of poss ble organ rejection. (5.7)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.8)
- Complications of allogeneic HSCT (5.9):
  - Allogeneic HSCT after treatment with KEYTRUDA: Monitor for hepatic veno-occlusive disease, grade 3-4 acute GVHD including hyperacute GVHD, steroid-requiring febrile syndrome, and other immune-mediated adverse reactions. Transplant-related mortality has occurred.
  - Allogeneic HSCT prior to treatment with KEYTRUDA: In patients with a history of allogeneic HSCT, consider the benefit of treatment with KEYTRUDA versus the risk of GVHD.
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking ant body in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.10)
- Embryo-Fetal toxicity: KEYTRUDA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.11)

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

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

- KEYTRUDA as a single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. (6.1)
- KEYTRUDA in combination with chemotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, and peripheral neuropathy. (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: 12/2018

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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, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.2)]*.

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC *[see Clinical Studies (14.2)]*.

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.2)]*.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) 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)]*.

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.

1.4 Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy *[see Clinical Studies (14.4)]*.

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

1.5 Primary Mediastinal Large B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy *[see Clinical Studies (14.5)]*.

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

Limitation of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

1.6 Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status *[see Clinical Studies (14.6)].*

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

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.6)].*

1.7 Microsatellite Instability-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan *[see Clinical Studies (14.7)]*.

This indication is approved under accelerated approval based on 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.

Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

1.8 Gastric Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy *[see Clinical Studies (14.8)]*.

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.

1.9 Cervical Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test *[see Clinical Studies (14.9)]*.

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.

1.10 Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib *[see Clinical Studies (14.10)].*

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.

1.11 Merkel Cell Carcinoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC) *[see Clinical Studies (14.11)]*.

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 for Treatment of NSCLC, Urothelial Carcinoma, Gastric Cancer, or Cervical Cancer

Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in:

- metastatic NSCLC *[see Clinical Studies (14.2)]*.
- metastatic urothelial carcinoma *[see Clinical Studies (14.6)].*
- metastatic gastric cancer *[see Clinical Studies (14.8)]*. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.
- recurrent or metastatic cervical cancer *[see Clinical Studies (14.9)].*

Information on FDA-approved tests for the detection of PD-L1 expression in NSCLC, urothelial carcinoma, gastric cancer, or cervical cancer is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage for Melanoma

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*.

2.3 Recommended Dosage for NSCLC

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 (14.2)]*.

When administering KEYTRUDA in combination with chemotherapy, KEYTRUDA should be administered prior to chemotherapy when given on the same day *[see Clinical Studies (14.2)]*. See also the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA, as appropriate.

2.4 Recommended Dosage for HNSCC

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)]*.

2.5 Recommended Dosage for cHL

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.4)]*.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.6 Recommended Dosage for PMBCL

The recommended dose of KEYTRUDA in adults 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 (14.5)]*.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.7 Recommended Dosage for Urothelial Carcinoma

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression *[see Clinical Studies (14.6)]*.

2.8 Recommended Dosage for MSI-H Cancer

The recommended dose of KEYTRUDA in adults 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 (14.7)].*

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.9 Recommended Dosage for Gastric 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 (14.8)].*

2.10 Recommended Dosage for Cervical 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 (14.9)].*

2.11 Recommended Dosage for HCC

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 (14.10)]*.

2.12 Recommended Dosage for MCC

The recommended dose of KEYTRUDA in adults 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 (14.11)].*

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.13 Dose Modifications

No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage adverse reactions as described in Table 1.

Table 1: Recommended Dose Modifications for Adverse Reactions
[see Warnings and Precautions (5.1-5.9)]

Adverse Reaction	Severity*	Dose Modification for KEYTRUDA
Immune-mediated pneumonitis	Grade 2	Withhold†
	Grades 3 or 4 or recurrent Grade 2	Permanently discontinue
Immune-mediated colitis	Grades 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Immune-mediated hepatitis in patients with HCC	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 5 times upper limit of normal (ULN) if baseline less than 2 times ULN; AST or ALT greater than 3 times baseline if baseline greater than or equal to 2 times ULN Total bilirubin greater than 2.0 mg/dL if baseline less than 1.5 mg/dL; or Total bilirubin greater than 3.0 mg/dL, regardless of baseline levels	Withhold‡
	ALT or AST greater than 10 times ULN; or Child-Pugh score greater than or equal to 9 points; Gastrointestinal bleeding suggestive of portal hypertension; or New onset of clinically detectable ascites; or encephalopathy	Permanently discontinue
Immune-mediated hepatitis in patients without HCC	AST or ALT greater than 3 but no more than 5 times the ULN or total bilirubin greater than 1.5 but no more than 3 times the ULN	Withhold†
	In patients without liver metastases, AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN In patients with liver metastasis and Grade 2 AST or ALT at baseline, with an increase in AST or ALT of 50% or more relative to baseline that persists for at least 1 week	Permanently discontinue
Immune-mediated endocrinopathies	Grades 3 or 4	Withhold until clinically stable
Immune-mediated nephritis	Grade 2	Withhold†
	Grades 3 or 4	Permanently discontinue
Immune-mediated skin adverse reactions	Grade 3 or suspected Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
Other immune-mediated adverse reactions	Grades 2 or 3 based on the severity and type of reaction	Withhold†

Adverse Reaction	Severity*	Dose Modification for KEYTRUDA
	Grade 3 based on the severity and type of reaction or Grade 4	Permanently discontinue
Recurrent immune-mediated adverse reactions	Recurrent Grade 2 pneumonitis Recurrent Grades 3 or 4	Permanently discontinue
Inability to taper corticosteroid	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks after last dose of KEYTRUDA	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathy)	Grades 2 or 3 adverse reactions lasting 12 weeks or longer after last dose of KEYTRUDA	Permanently discontinue
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue

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

† Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper.

‡ Resume in HCC patients when AST or ALT and total bilirubin recover to Grades 0-1 or to baseline.

2.14 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-dose vial for reconstitution
- Injection: 100 mg/4 mL (25 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. 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 (2.13) and Adverse Reactions (6.1)].*

Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), Grade 2 (1.3%), Grade 3 (0.9%), Grade 4 (0.3%), and Grade 5 (0.1%) pneumonitis. The median time to onset was 3.3 months (range: 2 days to 19.3 months), and the median duration was 1.5 months (range: 1 day to 17.2+ months). Sixty-three (67%) of the 94 patients received systemic corticosteroids, with 50 of the 63 receiving high-dose corticosteroids for a median duration of 8 days (range: 1 day to 10.1 months) followed by a corticosteroid taper. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation (2.9%). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 (59%) of the 94 patients.

5.2 Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis. 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 (2.13) and Adverse Reactions (6.1)].*

Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.4%), Grade 3 (1.1%), and Grade 4 (<0.1%) colitis. The median time to onset was 3.5 months (range: 10 days to 16.2 months), and the median duration was 1.3 months (range: 1 day to 8.7+ months). Thirty-three (69%) of the 48 patients received systemic corticosteroids, with 27 of the 33 requiring high-dose corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 (85%) of the 48 patients.

5.3 Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. 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 (2.13) and Adverse Reactions (6.1)].*

Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.4%), and Grade 4 (<0.1%) hepatitis. The median time to onset was 1.3 months (range: 8 days to 21.4 months), and the median duration was 1.8 months (range: 8 days to 20.9+ months). Thirteen (68%) of the 19 patients received systemic corticosteroids, with 12 of the 13 receiving high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 (79%) of the 19 patients.

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

KEYTRUDA can cause hypophysitis. 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 (2.13) and Adverse Reactions (6.1)].*

Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), Grade 3 (0.3%), and Grade 4 (<0.1%) hypophysitis. The median time to onset was 3.7 months (range: 1 day to 11.9 months), and the median duration was 4.7 months (range: 8+ days to 12.7+ months). Sixteen (94%) of the 17 patients received systemic corticosteroids, with 6 of the 16 receiving high-dose corticosteroids. Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 (41%) of the 17 patients.

Thyroid Disorders

KEYTRUDA can cause thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis. 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 (2.13) and Adverse Reactions (6.1)].*

Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months), and the median duration was 2.1 months (range: 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 (74%) of the 96 patients.

Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and Grade 3 (0.1%) hypothyroidism. The median time to onset was 3.5 months (range: 1 day to 18.9 months), and the median duration was not reached (range: 2 days to 27.7+ months). Hypothyroidism led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Hypothyroidism resolved in 48 (20%) of the 237 patients. The incidence of new or worsening hypothyroidism was higher in patients with HNSCC occurring in 28 (15%) of 192 patients receiving KEYTRUDA, including Grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of hypothyroidism.

Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. The median time of onset was 1.2 months (range: 0.5 to 3.5 months).

Type 1 Diabetes mellitus
KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. 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 (2.13) and Adverse Reactions (6.1)]*.

5.5 Immune-Mediated Nephritis and Renal Dysfunction
KEYTRUDA can cause immune-mediated nephritis. 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 (2.13) and Adverse Reactions (6.1)].*

Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis. The median time to onset was 5.1 months (range: 12 days to 12.8 months), and the median duration was 3.3 months (range: 12 days to 8.9+ months). Eight (89%) of the 9 patients received systemic corticosteroids, with 7 of the 8 receiving high-dose corticosteroids for a median duration of 15 days (range: 3 days to 4.0 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 (56%) of the 9 patients. Nephritis occurred in 1.7% of 405 patients receiving KEYTRUDA in combination with pemetrexed and platinum in the KEYNOTE-189 study, including Grade 3 (1%) and Grade 4 (0.5%) nephritis. The median time to onset was 3.2 months (range: 16 days to 11.1 months) and the duration ranged from 1.6 to 16.8+ months. Six (86%) of the 7 patients received systemic corticosteroids, with all 6 receiving high-dose corticosteroids for a median duration of 3 days (range: 1 to 17 days) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 5 (1.2%) patients. Nephritis resolved in 2 (29%) of the 7 patients.

5.6 Immune-Mediated Skin Adverse Reactions
Immune-mediated rashes, including SJS, TEN (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. *[See Dosage and Administration (2.13).]*

5.7 Other Immune-Mediated Adverse Reactions
Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving KEYTRUDA. While immune-mediated adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, they may occur after discontinuation of treatment.

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

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients treated with KEYTRUDA: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and

encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials, including cHL, and post-marketing use.

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA versus the risk of possible organ rejection in these patients.

5.8 Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. 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 (2.13)]*.

5.9 Complications of Allogeneic HSCT

Allogeneic HSCT after treatment with KEYTRUDA

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA. Of 23 patients with cHL who proceeded to allogeneic HSCT after treatment with KEYTRUDA on any trial, 6 patients (26%) developed graft-versus-host-disease (GVHD), one of which was fatal, and 2 patients (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning, one of which was fatal. Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

Allogeneic HSCT prior to treatment with KEYTRUDA

In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with KEYTRUDA. Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with KEYTRUDA. Consider the benefit of treatment with KEYTRUDA versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

5.10 Increased Mortality in Patients with Multiple Myeloma when KEYTRUDA is Added to a Thalidomide Analogue and Dexamethasone

In two randomized clinical trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

5.11 Embryo-Fetal 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)]*.
- Immune-mediated skin adverse reactions *[see Warnings and Precautions (5.6)]*.
- Other immune-mediated adverse reactions *[see Warnings and Precautions (5.7)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.8)].*

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 as a single agent in 2799 patients in three randomized, open-label, active-controlled clinical trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001), which enrolled 655 patients with melanoma and 550 patients with NSCLC. In addition, these data reflect exposure to KEYTRUDA as a single agent in a non-randomized, open-label, multi-cohort trial (KEYNOTE-012), which enrolled 192 patients with HNSCC and in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087), which enrolled 241 patients with cHL; in combination with chemotherapy in a randomized, active-controlled trial (KEYNOTE-189), which enrolled 405 patients with nonsquamous NSCLC; and in post-marketing use. Across all trials, 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 the 2799 patients, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

The data described in this section were obtained in six randomized, controlled clinical trials (KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-045, KEYNOTE-189, and KEYNOTE-407) in which KEYTRUDA was administered to 912 patients with melanoma, 1188 patients with NSCLC, and 542 patients with urothelial carcinoma, and eight non-randomized, open-label trials (KEYNOTE-012, KEYNOTE-087, KEYNOTE-170, KEYNOTE-052, KEYNOTE-059, KEYNOTE-158, KEYNOTE-224, and KEYNOTE-017) in which KEYTRUDA was administered to 192 patients with HNSCC, 210 patients with cHL, 53 patients with PMBCL, 370 patients with urothelial carcinoma, 259 patients with gastric cancer, 98 patients with cervical cancer, 104 patients with HCC, and 50 patients with MCC. 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

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 Study KEYNOTE-006. KEYNOTE-006 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 systemic therapy which included a BRAF inhibitor (15%), chemotherapy (13%), and immunotherapy (6%).

In KEYNOTE-006, 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 2 and Table 3 summarize the incidence of selected adverse reactions and laboratory abnormalities that occurred in patients receiving KEYTRUDA.

Table 2: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-006

Adverse Reaction	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
	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 3: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-006

Laboratory Test†	KEYTRUDA 10 mg/kg every 2 or 3 weeks		Ipilimumab	
	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

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 Study KEYNOTE-002. KEYNOTE-002 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 KEYNOTE-002, 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 4 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 4: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-002

Adverse Reaction	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks n=357		Chemotherapy† n=171	
	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 5: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-002

Laboratory Test†	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks		Chemotherapy	
	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

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The safety of KEYTRUDA in combination with pemetrexed and investigator's choice of platinum (either carboplatin or cisplatin) was investigated in Study KEYNOTE-189, a multicenter, double-blind, randomized (2:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations. A total of 607 patients received KEYTRUDA 200 mg, pemetrexed and platinum every 3 weeks for 4 cycles followed by KEYTRUDA and pemetrexed (n=405) or placebo, pemetrexed, and platinum every 3 weeks for 4 cycles followed by placebo and pemetrexed (n=202). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible *[see Clinical Studies (14.2)]*.

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 7.2 months (range: 1 day to 20.1 months). Sixty percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months.

Seventy-two percent of patients received carboplatin. The study population characteristics were: median age of 64 years (range: 34 to 84), 49% age 65 years or older, 59% male, 94% White and 3% Asian, and 18% with history of brain metastases at baseline.

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 53% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (13%), asthenia/fatigue (7%), anemia (7%), thrombocytopenia (5%), diarrhea (4%), pneumonia (4%), increased blood creatinine (3%), dyspnea (2%), febrile neutropenia (2%), upper respiratory tract infection (2%), increased ALT (2%), and pyrexia (2%).

Table 6 summarizes the adverse reactions that occurred in at least 20% of patients treated with KEYTRUDA.

Table 6: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE-189

Adverse Reaction	KEYTRUDA Pemetrexed Platinum Chemotherapy n=405		Placebo Pemetrexed Platinum Chemotherapy n=202	
	All Grades* (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal Disorders				
Nausea	56	3.5	52	3.5
Constipation	35	1.0	32	0.5
Diarrhea	31	5	21	3.0
Vomiting	24	3.7	23	3.0
General Disorders				
Fatigue†	56	12	58	6
Pyrexia	20	0.2	15	0
Metabolism and Nutrition Disorders				
Decreased appetite	28	1.5	30	0.5
Skin and Subcutaneous Tissue Disorders				
Rash‡	25	2.0	17	2.5
Respiratory, Thoracic and Mediastinal Disorders				
Cough	21	0	28	0
Dyspnea	21	3.7	26	5

* Graded per NCI CTCAE v4.03
† Includes asthenia and fatigue
‡ Includes genital rash, rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

Table 7 summarizes the laboratory abnormalities that worsened from baseline in at least 20% of patients treated with KEYTRUDA.

Table 7: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-189

Laboratory Test*	KEYTRUDA Pemetrexed Platinum Chemotherapy		Placebo Pemetrexed Platinum Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	63	9	60	7
Increased ALT	47	3.8	42	2.6
Increased AST	47	2.8	40	1.0
Hypoalbuminemia	39	2.8	39	1.1
Increased creatinine	37	4.2	25	1.0
Hyponatremia	32	7	23	6
Hypophosphatemia	30	10	28	14
Increased alkaline phosphatase	26	1.8	29	2.1
Hypocalcemia	24	2.8	17	0.5
Hyperkalemia	24	2.8	19	3.1
Hypokalemia	21	5	20	5
Hematology				
Anemia	85	17	81	18
Lymphopenia	64	22	64	25
Neutropenia	48	20	41	19
Thrombocytopenia	30	12	29	8

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/pemetrexed/platinum chemotherapy (range: 381 to 401 patients) and placebo/pemetrexed/platinum chemotherapy (range: 184 to 197 patients).

† Graded per NCI CTCAE v4.03

First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy

The safety of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in 558 patients with previously untreated, metastatic squamous NSCLC. Safety data are available for the first 203 patients who received KEYTRUDA and chemotherapy (n=101) or placebo and chemotherapy (n=102). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible *[see Clinical Studies (14.2)]*.

The median duration of exposure to KEYTRUDA was 7 months (range: 1 day to 12 months). Sixty-one percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months. A total of 139 of 203 patients (68%) received paclitaxel and 64 patients (32%) received nab-paclitaxel in combination with carboplatin. The study population characteristics were: median age of 65 years (range: 40 to 83); 52% age 65 or older; 78% male; 83% White; and 9% with history of brain metastases.

KEYTRUDA was discontinued for adverse reactions in 15% of patients, with no single type of adverse reaction accounting for the majority. Adverse reactions leading to interruption of KEYTRUDA occurred in 43% of patients; the most common (≥2%) were thrombocytopenia (20%), neutropenia (11%), anemia (6%), asthenia (2%), and diarrhea (2%). The most frequent (≥2%) serious adverse reactions were febrile neutropenia (6%), pneumonia (6%), and urinary tract infection (3%).

The adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs. 36%) and peripheral neuropathy (31% vs. 25%) were observed in the KEYTRUDA and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.

Previously Treated NSCLC

The safety of KEYTRUDA was investigated in Study KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations. A total of 991 patients received KEYTRUDA 2 mg/kg (n=339) or 10 mg/kg (n=343) every 3 weeks or docetaxel (n=309) at 75 mg/m^2 every 3 weeks. Patients with autoimmune disease, medical conditions that required systemic corticosteroids or other immunosuppressive medication, or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.5 months (range: 1 day to 22.4 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 3.5 months (range 1 day to 20.8 months). The data described below reflect exposure to KEYTRUDA 2 mg/kg in 31% of patients exposed to KEYTRUDA for ≥6 months. In the KEYTRUDA 10 mg/kg arm, 34% of patients were exposed to KEYTRUDA for ≥6 months.

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 years or older, 61% male, 72% white and 21% Asian, 8% with advanced localized disease, 91% with metastatic disease, and 15% with history of brain metastases. Twenty-nine percent received two or more prior systemic treatments for advanced or metastatic disease.

In KEYNOTE-010, the adverse reaction profile was similar for the 2 mg/kg and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=682). Treatment was discontinued for adverse reactions in 8% of patients receiving KEYTRUDA. The most common adverse events resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.8%). Adverse reactions leading to interruption of KEYTRUDA occurred in 23% of patients; the most common (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%).

Table 8 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA.

Table 8: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-010

Adverse Reaction	KEYTRUDA 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m^2 every 3 weeks n=309	
	All Grades† (%)	Grade 3-4 (%)	All Grades† (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased appetite	25	1.5	23	2.6
Gastrointestinal Disorders				
Nausea	20	1.3	18	0.6
Constipation	15	0.6	12	0.6
Vomiting	13	0.9	10	0.6
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	23	3.7	20	2.6
Cough	19	0.6	14	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	11	1.0	9	0.3
Back pain	11	1.5	8	0.3
Skin and Subcutaneous Tissue Disorders				
Rash‡	17	0.4	8	0
Pruritus	11	0	3	0.3

* Adverse reactions occurring at same or higher incidence than in docetaxel arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (25%), diarrhea (14%), asthenia (11%) and pyrexia (11%).

Table 9 summarizes the laboratory abnormalities that worsened from baseline in at least 20% of patients treated with KEYTRUDA.

Table 9: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving KEYTRUDA in KEYNOTE-010

Laboratory Test†	KEYTRUDA 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Chemistry				
Hyponatremia	32	8	27	2.9
Alkaline phosphatase increased	28	3.0	16	0.7
Aspartate aminotransferase increased	26	1.6	12	0.7
Alanine aminotransferase increased	22	2.7	9	0.4

* Laboratory abnormalities occurring at same or higher incidence than in docetaxel 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: 631 to 638 patients) and docetaxel (range: 274 to 277 patients).
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were hyperglycemia (44% all Grades; 4.1% Grades 3-4), anemia (37% all Grades; 3.8% Grades 3-4), hypertriglyceridemia (36% all Grades; 1.8% Grades 3-4), lymphopenia (35% all Grades; 9% Grades 3-4), hypoalbuminemia (34% all Grades; 1.6% Grades 3-4), and hypercholesterolemia (20% all Grades; 0.7% Grades 3-4).

HNSCC
Among the 192 patients with HNSCC enrolled in Study KEYNOTE-012, 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 KEYNOTE-012.

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)]*.

cHL
Among the 210 patients with cHL enrolled in Study KEYNOTE-087 *[see Clinical Studies (14.4)]*, the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). KEYTRUDA was discontinued due to adverse reactions in 5% of patients, and treatment was interrupted due to adverse reactions in 26%. Fifteen percent (15%) of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, pyrexia, dyspnea, graft versus host disease and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

Table 10 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA.

Table 10: Adverse Reactions in ≥10% of Patients with cHL in KEYNOTE-087

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=210	
	All Grades* (%)	Grade 3 (%)
General Disorders and Administration Site Conditions		
Fatigue[†]	26	1.0
Pyrexia	24	1.0
Respiratory, Thoracic and Mediastinal Disorders		
Cough[‡]	24	0.5
Dyspnea[§]	11	1.0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[¶]	21	1.0
Arthralgia	10	0.5
Gastrointestinal Disorders		
Diarrhea[#]	20	1.4
Vomiting	15	0
Nausea	13	0
Skin and Subcutaneous Tissue Disorders		
Rash[Þ]	20	0.5
Pruritus	11	0
Endocrine Disorders		
Hypothyroidism	14	0.5
Infections and Infestations		
Upper respiratory tract infection	13	0
Nervous System Disorders		
Headache	11	0.5
Peripheral neuropathy[β]	10	0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes cough, productive cough
§ Includes dyspnea, dyspnea exertional, wheezing
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
\# Includes diarrhea, gastroenteritis, colitis, enterocolitis
Þ Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, dermatitis acneiform, dermatitis contact, rash erythematous, rash macular, rash papular, rash pruritic, seborrhoeic dermatitis, dermatitis psoriasiform
β Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

Other clinically important adverse reactions that occurred in less than 10% of patients on KEYNOTE-087 included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), and myelitis and myocarditis (0.5% each).

Table 11: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of cHL Patients Receiving KEYTRUDA in KEYNOTE-087

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grade 3-4 (%)
Chemistry		
Hypertransaminasemia‡	34	2
A kaline phosphatase increased	17	0
Creatinine increased	15	0.5
Hematology		
Anemia	30	6
Thrombocytopenia	27	4
Neutropenia	24	7

* 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: 208 to 209 patients)
† Graded per NCI CTCAE v4.0
‡ Includes elevation of AST or ALT

Hyperbilirubinemia occurred in less than 15% of patients on KEYNOTE-087 (10% all Grades, 2.4% Grade 3-4).

PMBCL
Among the 53 patients with PMBCL treated in KEYNOTE-170 *[see Clinical Studies (14.5)],* the median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 22.8 months). KEYTRUDA was discontinued due to adverse reactions in 8% of patients, and treatment was interrupted due to adverse reactions in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 26% of patients, and included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment.

Table 12 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA. Table 13 summarizes the incidence of laboratory abnormalities that occurred in at least 15% of patients receiving KEYTRUDA.

Table 12: Adverse Reactions in ≥10% of Patients with PMBCL in KEYNOTE-170

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=53	
	All Grades* (%)	Grade 3-4 (%)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain†	30	0
Infections and Infestations		
Upper respiratory tract infection‡	28	0
General Disorders and Administration Site Conditions		
Pyrexia	28	0
Fatigue§	23	2
Respiratory, Thoracic and Mediastinal Disorders		
Cough¶	26	2
Dyspnea	21	11
Gastrointestinal Disorders		
Diarrhea#	13	2
Abdominal pain Þ	13	0
Nausea	11	0
Cardiac Disorders		
Arrhythmia β	11	4
Nervous System Disorders		
Headache	11	0

* Graded per NCI CTCAE v4.0
† Includes arthralgia, back pain, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, bone pain, neck pain, non-cardiac chest pain
‡ Includes nasopharyngitis, pharyngitis, rhinorrhea, rhinitis, sinusitis, upper respiratory tract infection
§ Includes fatigue, asthenia
¶ Includes allergic cough, cough, productive cough
\# Includes diarrhea, gastroenteritis
Þ Includes abdominal pain, abdominal pain upper
β Includes atrial fibrillation, sinus tachycardia, supraventricular tachycardia, tachycardia

Other clinically important adverse reactions that occurred in less than 10% of patients in KEYNOTE-170 included hypothyroidism (8%), hyperthyroidism and pericarditis (4% each), and thyroiditis, pericardial effusion, pneumonitis, arthritis and acute kidney injury (2% each).

Table 13: Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of PMBCL Patients Receiving KEYTRUDA in KEYNOTE-170

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grade 3-4 (%)
Chemistry		
Hyperglycemia	38	4
Hypophosphatemia	29	10
Hypertransaminasemia‡	27	4
Hypoglycemia	19	0
A kaline phosphatase increased	17	0
Creatinine increased	17	0
Hypocalcemia	15	4
Hypokalemia	15	4
Hematology		
Anemia	47	0
Leukopenia	35	9
Lymphopenia	32	18
Neutropenia	30	11

* 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: 44 to 48 patients)
† Graded per NCI CTCAE v4.0
‡ Includes elevation of AST or ALT

Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The safety of KEYTRUDA was investigated in Study KEYNOTE-052, a single-arm trial that enrolled 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression. The median duration of exposure to KEYTRUDA was 2.8 months (range: 1 day to 15.8 months).

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, decreased appetite, constipation, rash and diarrhea. KEYTRUDA was discontinued due to adverse reactions in 11% of patients. Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with KEYTRUDA experienced sepsis which led to death, and three patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

Immune-related adverse reactions that required systemic glucocorticoids occurred in 8% of patients, use of hormonal supplementation due to an immune-related adverse reaction occurred in 8% of patients, and 5% of patients required at least one steroid dose ≥40 mg oral prednisone equivalent.

Table 14 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 14: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=370	
	All Grades* (%)	Grades 3 – 4 (%)
All Adverse Reactions	96	49
Blood and Lymphatic System Disorders		
Anemia	17	7
Gastrointestinal Disorders		
Constipation	21	1.1
Diarrhea[†]	20	2.4
Nausea	18	1.1
Abdominal pain[‡]	18	2.7
Elevated LFTs[§]	13	3.5
Vomiting	12	0
General Disorders and Administration Site Conditions		
Fatigue[¶]	38	6
Pyrexia	11	0.5
Weight decreased	10	0
Infections and Infestations		
Urinary tract infection	19	9
Metabolism and Nutrition Disorders		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[#]	24	4.9
Arthralgia	10	1.1
Renal and Urinary Disorders		
Blood creatinine increased	11	1.1
Hematuria	13	3.0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	14	0
Dyspnea	11	0.5
Skin and Subcutaneous Tissue Disorders		
Rash[Þ]	21	0.5
Pruritus	19	0.3
Edema peripheral	14	1.1

* Graded per NCI CTCAE v4.0

† Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements

‡ Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper

§ Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, transaminases increased, hyperbilirubinemia, blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzymes increased, liver function tests increased

¶ Includes fatigue, asthenia

\# Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain

Þ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneiform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized

Previously Treated Urothelial Carcinoma

The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in

Study KEYNOTE-045. KEYNOTE-045 was a multicenter, open-label, randomized (1:1), active-controlled trial in which 266 patients received KEYTRUDA 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) *[see Clinical Studies (14.6)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. The median duration of exposure was 3.5 months (range: 1 day to 20 months) in patients who received KEYTRUDA and 1.5 months (range: 1 day to 14 months) in patients who received chemotherapy.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). The most common adverse reactions (occurring in at least 20% of patients who received KEYTRUDA) were fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea and rash. Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis.

Table 15 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA. Table 16 summarizes the incidence of laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 15: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=266		Chemotherapy* n=255	
	All Grades† (%)	Grade 3-4 (%)	All Grades† (%)	Grade 3-4 (%)
Gastrointestinal Disorders				
Nausea	21	1.1	29	1.6
Constipation	19	1.1	32	3.1
Diarrhea‡	18	2.3	19	1.6
Vomiting	15	0.4	13	0.4
Abdominal pain	13	1.1	13	2.7
General Disorders and Administration Site Conditions				
Fatigue§	38	4.5	56	11
Pyrexia	14	0.8	13	1.2
Infections and Infestations				
Urinary tract infection	15	4.9	14	4.3
Metabolism and Nutrition Disorders				
Decreased appetite	21	3.8	21	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain¶	32	3.0	27	2.0
Renal and Urinary Disorders				
Hematuria#	12	2.3	8	1.6
Respiratory, Thoracic and Mediastinal Disorders				
Cough Þ	15	0.4	9	0
Dyspnea ß	14	1.9	12	1.2
Skin and Subcutaneous Tissue Disorders				
Pruritus	23	0	6	0.4
Rash à	20	0.4	13	0.4

* Chemotherapy: paclitaxel, docetaxel, or vinflunine
† Graded per NCI CTCAE v4.0
‡ Includes diarrhea, gastroenteritis, colitis, enterocolitis
§ Includes asthenia, fatigue, malaise lethargy
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
\# Includes blood urine present, hematuria, chromaturia
Þ Includes cough, productive cough
ß Includes dyspnea, dyspnea exertional, wheezing
à Includes rash maculo-papular, rash genital rash, rash erythematous, rash papular, rash pruritic, rash pustular, erythema, drug eruption, eczema, eczema asteatotic, dermatitis contact, dermatitis acneiform, dermatitis, seborrhoeic keratosis, lichenoid keratosis

Table 16: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Glucose increased	52	8	60	7
Hemoglobin decreased	52	13	68	18
Lymphocytes decreased	45	15	53	25
Albumin decreased	43	1.7	50	3.8
Sodium decreased	37	9	47	13
Alkaline phosphatase increased	37	7	33	4.9
Creatinine increased	35	4.4	28	2.9
Phosphate decreased	29	8	34	14
Aspartate aminotransferase increased	28	4.1	20	2.5
Potassium increased	28	0.8	27	6
Calcium decreased	26	1.6	34	2.1

* 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: 240 to 248 patients) and chemotherapy (range: 238 to 244 patients); phosphate decreased: KEYTRUDA n=232 and chemotherapy n=222.

† Graded per NCI CTCAE v4.0

Gastric Cancer

Among the 259 patients with gastric cancer enrolled in Study KEYNOTE-059, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 21.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression or with clinical evidence of ascites by physical exam were ineligible. Adverse reactions occurring in patients with gastric cancer were similar to those occurring in patients with melanoma or NSCLC.

Cervical Cancer

Among the 98 patients with cervical cancer enrolled in Cohort E of Study KEYNOTE-158, the median duration of exposure to KEYTRUDA was 2.9 months (range: 1 day to 22.1 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%).

Table 17 summarizes the adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 17: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=98	
	All Grades* (%)	Grades 3 – 4 (%)
General Disorders and Administration Site Conditions		
Fatigue[†]	43	5
Pain[‡]	22	2.0
Pyrexia	19	1.0
Edema peripheral[§]	15	2.0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[¶]	27	5
Gastrointestinal Disorders		
Diarrhea[#]	23	2.0
Abdominal pain[Þ]	22	3.1
Nausea	19	0
Vomiting	19	1.0
Constipation	14	0
Metabolism and Nutrition Disorders		
Decreased appetite	21	0
Vascular Disorders		
Hemorrhage[ß]	19	5
Infections and Infestations		
UTI[à]	18	6
Infection (except UTI)[è]	16	4.1
Skin and Subcutaneous Tissue Disorders		
Rash[ð]	17	2.0
Endocrine Disorders		
Hypothyroidism	11	0
Nervous System Disorders		
Headache	11	2.0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	10	1.0

* Graded per NCI CTCAE v4.0

† Includes asthenia, fatigue, lethargy, malaise

‡ Includes breast pain, cancer pain, dysesthesia, dysuria, ear pain, gingival pain, groin pain, lymph node pain, oropharyngeal pain, pain, pain of skin, pelvic pain, radicular pain, stoma site pain, toothache

§ Includes edema peripheral, peripheral swelling

¶ Includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, myositis, neck pain, non-cardiac chest pain, pain in extremity

\# Includes colitis, diarrhea, gastroenteritis

Þ Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper

ß Includes epistaxis, hematuria, hemoptysis, metrorrhagia, rectal hemorrhage, uterine hemorrhage, vaginal hemorrhage

à Includes bacterial pyelonephritis, pyelonephritis acute, urinary tract infection, urinary tract infection bacterial, urinary tract infection pseudomonal, urosepsis

è Includes cellulitis, clostridium difficile infection, device-related infection, empyema, erysipelas, herpes virus infection, infected neoplasm, infection, influenza, lower respiratory tract congestion, lung infection, oral candidiasis, oral fungal infection, osteomyelitis, pseudomonas infection, respiratory tract infection, tooth abscess, upper respiratory tract infection, uterine abscess, vulvovaginal candidiasis

ð Includes dermatitis, drug eruption, eczema, erythema, palmar-plantar erythrodysesthesia syndrome, rash, rash generalized, rash maculo-papular

Table 18 summarizes the laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 18: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with Cervical Cancer in KEYNOTE-158

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grade 3-4 (%)
Chemistry		
Hypoalbuminemia	44	5
A kaline phosphatase increased	42	2.6
Hyponatremia	38	13
Hyperglycemia	38	1.3
Aspartate aminotransferase increased	34	3.9
Creatinine increased	32	5
Hypocalcemia	27	0
Alanine aminotransferase increased	21	3.9
Hypokalemia	20	6
Hematology		
Anemia	54	24
Lymphocyte count decreased	47	9

* 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: 76 to 79 patients)

† Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥10% of patients receiving KEYTRUDA were hypophosphatemia (19% all Grades; 6% Grades 3-4), INR increased (19% all Grades; 0% Grades 3-4), hypercalcemia (14% all Grades; 2.6% Grades 3-4), platelet count decreased (14% all Grades; 1.3% Grades 3-4), activated partial thromboplastin time prolonged (14% all Grades; 0% Grades 3-4), hypoglycemia (13% all Grades; 1.3% Grades 3-4), white blood cell decreased (13% all Grades; 2.6% Grades 3-4), and hyperkalemia (13% all Grades; 1.3% Grades 3-4).

HCC

Among the 104 patients with HCC who received KEYTRUDA in Study KEYNOTE-224, the median duration of exposure to KEYTRUDA was 4.2 months (range: 1 day to 1.5 years). Adverse reactions occurring in patients with HCC were generally similar to those in patients with melanoma or NSCLC, with the exception of increased incidences of ascites (8% Grades 3-4) and immune-mediated hepatitis (2.9%). Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (20%), ALT (9%), and hyperbilirubinemia (10%).

MCC

Among the 50 patients with MCC enrolled in Study KEYNOTE-017, the median duration of exposure to KEYTRUDA was 6.6 months (range 1 day to 23.6 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MCC were similar to those occurring in patients with melanoma or NSCLC. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (11%) and hyperglycemia (19%).

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. 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 pembrolizumab in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

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 2 or 3 weeks, 27 (2.1%) of 1289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies of whom six (0.5%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding antibody development.

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 (5.11) 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

There is limited experience with KEYTRUDA in pediatric patients. In a study, 40 pediatric patients (16 children ages 2 years to less than 12 years and 24 adolescents ages 12 years to 18 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumors were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range: 1-17 doses), with 34 patients (85%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The safety profile in these pediatric patients was similar to that seen in adults treated with pembrolizumab; toxicities that occurred at a higher rate (≥15% difference) in pediatric patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), hypertransaminasemia (28%) and hyponatremia (18%).

Efficacy for pediatric patients with cHL, PMBCL, MSI-H cancers, or MCC is extrapolated from the results in the respective adult populations *[see Clinical Studies (14.4, 14.5, 14.7, 14.11)].*

8.5 Geriatric Use

Of 3991 patients with melanoma, NSCLC, HNSCC, cHL or urothelial carcinoma who were treated with KEYTRUDA in clinical studies, 46% were 65 years and over and 16% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

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. Pembrolizumab is produced in recombinant Chinese hamster ovary (CHO) cells.

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-dose 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.

12.2 Pharmacodynamics

Based on dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks in patients with melanoma or NSCLC.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2993 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] at steady state than that after the first dose [252 mL/day (37%)]; this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for volume of distribution at steady state is 6.0 L (20%) and for terminal half-life ($t_{1/2}$) is 22 days (32%).

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-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 (89% 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. Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients (2 to 17 years) are comparable to those of adults at the same dose.

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

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-006 (NCT01866319), 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 10 mg/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; 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, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ]). 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 19 and Figure 1).

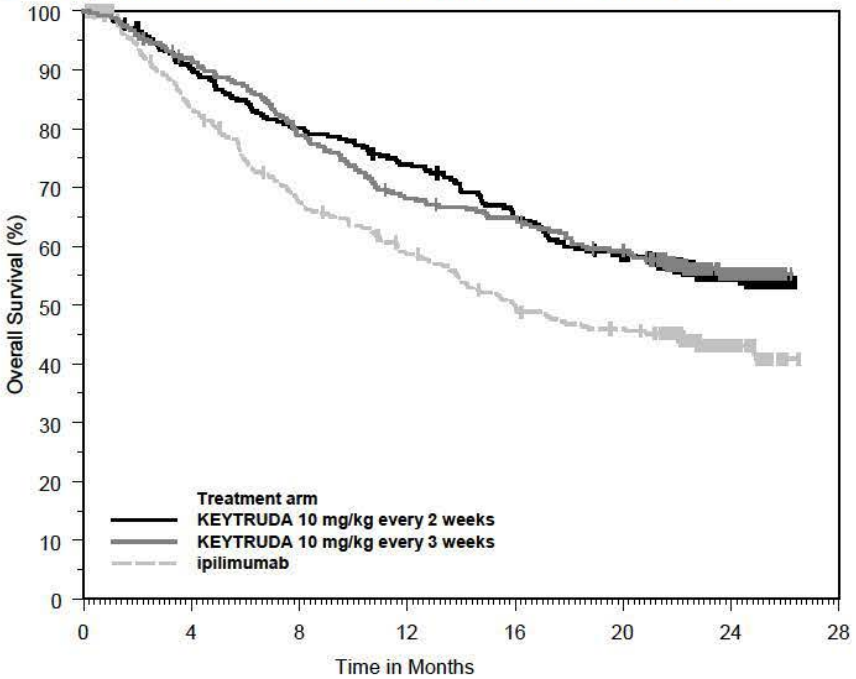
Table 19: Efficacy Results in KEYNOTE-006

	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 rate	6%	5%	1%
Partial response rate	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 KEYNOTE-006*



Number at Risk								
KEYTRUDA 10 mg/kg every 2 weeks:	279	249	221	202	176	156	44	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	251	215	184	174	156	43	0
ipilimumab:	278	213	170	145	122	110	28	0

**based on the final analysis with an additional follow-up of 9 months (total of 383 deaths as pre-specified in the protocol)*

Ipilimumab-Refractory Melanoma

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-002 (NCT01704287), 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, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and overall survival (OS). Additional efficacy outcome measures were confirmed overall response rate (ORR)

as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, 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 20). There was no statistically significant difference between KEYTRUDA 2 mg/kg and chemotherapy or between KEYTRUDA 10 mg/kg and chemotherapy in the OS analysis in which 55% of the patients who had been randomized to receive chemotherapy had crossed over to receive KEYTRUDA.

Table 20: Efficacy Results in KEYNOTE-002

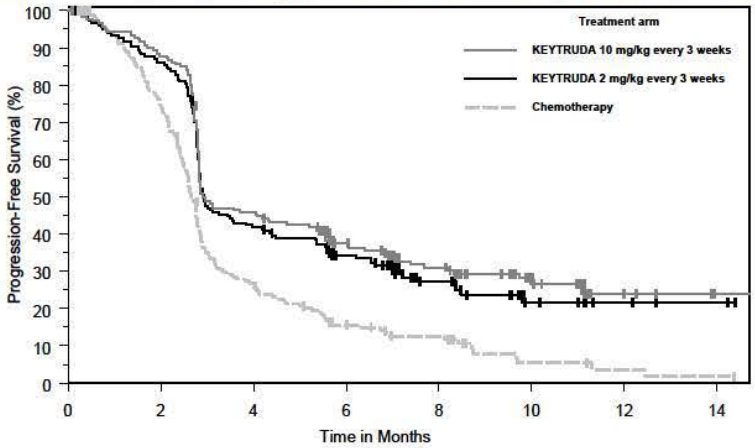
	KEYTRUDA 2 mg/kg every 3 weeks n=180	**KEYTRUDA 10 mg/kg every 3 weeks n=181**	**Chemotherapy n=179**
Progression-Free Survival			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (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)	---
Overall Survival[†]			
Deaths (%)	123 (68%)	117 (65%)	128 (72%)
Hazard ratio* (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value (stratified log-rank)	0.117	0.011[‡]	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Objective Response Rate			
ORR (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response rate	2%	3%	0%
Partial response rate	19%	23%	4%

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

† With additional follow-up of 18 months after the PFS analysis

‡ Not statistically significant compared to multiplicity adjusted significance level of 0.01

Figure 2: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-002



Number at Risk								
KEYTRUDA 10 mg/kg:	181	158	82	55	39	15	5	1
KEYTRUDA 2 mg/kg:	180	153	74	53	26	9	4	2
Chemotherapy:	179	128	43	22	15	4	2	1

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

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in Study KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). Patients were randomized (2:1) to one of the following treatment arms:

- KEYTRUDA 200 mg, pemetrexed 500 mg/m^2, and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Placebo, pemetrexed 500 mg/m^2, and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously on Day 1 of each 21-day cycle for 4 cycles followed by placebo and pemetrexed 500 mg/m^2 intravenously every 3 weeks.

Treatment with KEYTRUDA continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator.

Patients randomized to placebo and chemotherapy were offered KEYTRUDA as a single agent at the time of disease progression.

Assessment of tumor status was performed at Week 6, Week 12, and then every 9 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR and duration of response, as assessed by the BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

A total of 616 patients were randomized: 410 patients to the KEYTRUDA and chemotherapy arm and 206 to the placebo and chemotherapy arm. The study population characteristics were: median age of 64 years (range: 34 to 84); 49% age 65 or older; 59% male; 94% White and 3% Asian; 56% ECOG performance status of 1; and 18% with history of brain metastases. Thirty-one percent had tumor PD-L1 expression TPS <1% [negative]. Seventy-two percent received carboplatin and 12% were never smokers. A total of 85 patients in the placebo and chemotherapy arm received an anti-PD-1/PD-L1 monoclonal antibody at the time of disease progression.

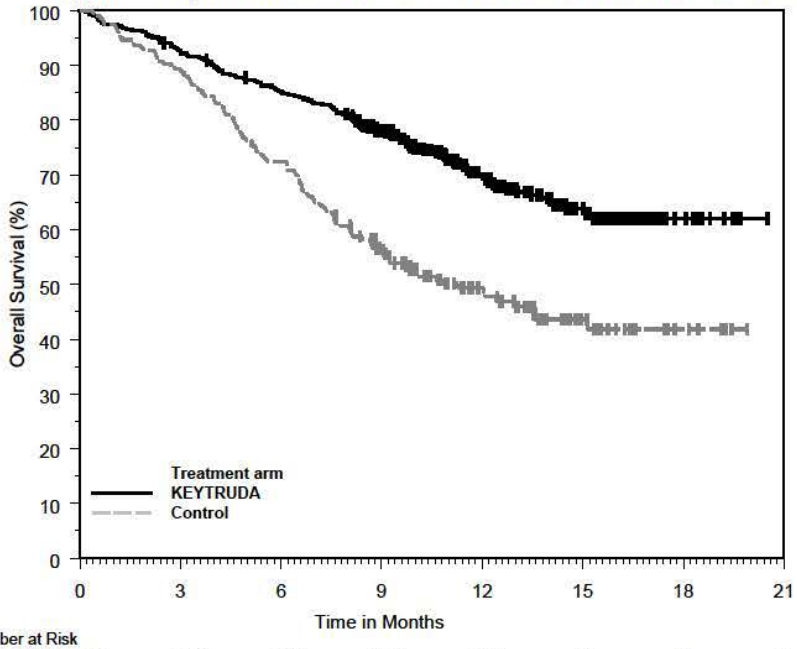
The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 21 and Figure 3 summarize the key efficacy measures for KEYNOTE-189.

Table 21: Efficacy Results in KEYNOTE-189

Endpoint	**KEYTRUDA Pemetrexed Platinum Chemotherapy n=410**	**Placebo Pemetrexed Platinum Chemotherapy n=206**
OS		
Number (%) of patients with event	127 (31%)	108 (52%)
Median in months (95% CI)	NR (NR, NR)	11.3 (8.7, 15.1)
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.00001	
PFS		
Number of patients with event (%)	244 (60%)	166 (81%)
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.00001	
ORR		
Overall response rate‡ (95% CI)	48% (43, 53)	19% (14, 25)
Complete response	0.5%	0.5%
Partial response	47%	18%
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test.
‡ Response: Best objective response as confirmed complete response or partial response
§ Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy and smoking status
NR = not reached

Figure 3: Kaplan-Meier Curve for Overall Survival in KEYNOTE-189



Number at Risk								
KEYTRUDA:	410	377	347	278	163	71	18	0
Control:	206	183	149	104	59	25	8	0

First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy

The efficacy of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial conducted in patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%), choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- KEYTRUDA 200 mg and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Placebo and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo every 3 weeks.

Treatment with KEYTRUDA and chemotherapy or placebo and chemotherapy continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

Patients randomized to the placebo and chemotherapy arm were offered KEYTRUDA as a single agent at the time of disease progression.

Assessment of tumor status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter. The main efficacy outcome measures were PFS and ORR as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. An additional efficacy outcome measure was DOR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

A total of 559 patients were randomized: 278 patients to the KEYTRUDA and chemotherapy arm and 281 to the placebo and chemotherapy arm. The study population characteristics were: median age of 65 years (range: 29 to 88); 55% age 65 or older; 81% male; 77% White; 71% ECOG performance status of 1; and 8% with a history of brain metastases. Thirty-five percent had tumor PD-L1 expression TPS <1%; 19% were from the East Asian region; and 60% received paclitaxel.

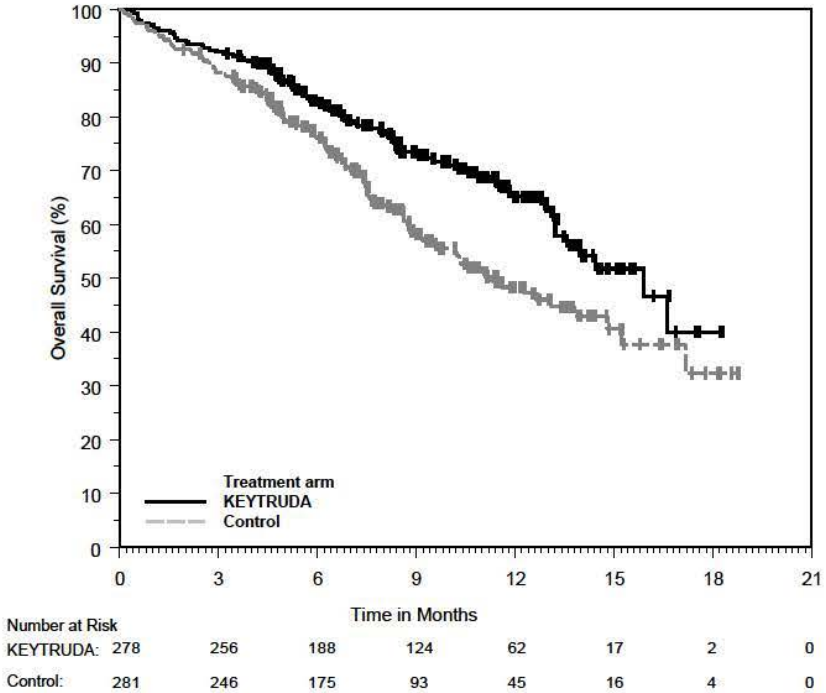
The trial demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy compared with patients randomized to placebo with carboplatin and either paclitaxel or nab-paclitaxel chemotherapy. Table 22 and Figure 4 summarize the key efficacy measures for KEYNOTE-407.

Table 22: Efficacy Results in KEYNOTE-407

Endpoint	**KEYTRUDA Carboplatin Paclitaxel/Nab-paclitaxel**	**Placebo Carboplatin Paclitaxel/Nab-paclitaxel**
	n=278	**n=281**
OS		
Number of events (%)	85 (31%)	120 (43%)
Median in months (95% CI)	15.9 (13.2, NE)	11.3 (9.5, 14.8)
Hazard ratio* (95% CI)	0.64 (0.49, 0.85)	
p-Value†	0.0017	
PFS		
Number of events (%)	152 (55%)	197 (70%)
Median in months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.3, 5.7)
Hazard ratio* (95% CI)	0.56 (0.45, 0.70)	
p-Value†	<0.0001	
	n=101	**n=103**
Overall Response Rate‡		
Overall response rate (95% CI)	58% (48, 68)	35% (26, 45)
Difference (95% CI)	23.6% (9.9, 36.4)	
p-Value§	0.0008	
Duration of Response‡		
Median duration of response in months (range)	7.2 (2.4, 12.4+)	4.9 (2.0, 12.4+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ ORR primary analysis and DOR analysis were conducted with the first 204 patients enrolled.
§ Based on a stratified Miettinen-Nurminen test
NE = not estimable

Figure 4: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407



First-line treatment of metastatic NSCLC as a single agent

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-024 (NCT02142738), a randomized, multicenter, open-label, active-controlled trial in patients with metastatic NSCLC, whose tumors had high PD-L1 expression [tumor proportion score (TPS) of 50% or greater] by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx Kit, and had not received prior systemic treatment for metastatic NSCLC. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. Randomization was stratified by ECOG performance status (0 vs. 1), histology (squamous vs. nonsquamous), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of any of the following platinum-containing chemotherapy regimens:

- Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m^2 on Days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for nonsquamous histologies).

Treatment with KEYTRUDA continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by an independent radiology committee, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression.

Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measure was PFS as assessed by a blinded independent central radiologists' (BICR) review according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were OS and ORR as assessed by the BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

A total of 305 patients were randomized: 154 patients to the KEYTRUDA arm and 151 to the chemotherapy arm. The study population characteristics were: median age of 65 years (range: 33 to 90), 54% age 65 or older; 61% male; 82% white and 15% Asian; 65% ECOG performance status of 1; 18% with squamous and 82% with nonsquamous histology and 9% with history of brain metastases. A total of 66 patients in the chemotherapy arm received KEYTRUDA at the time of disease progression.

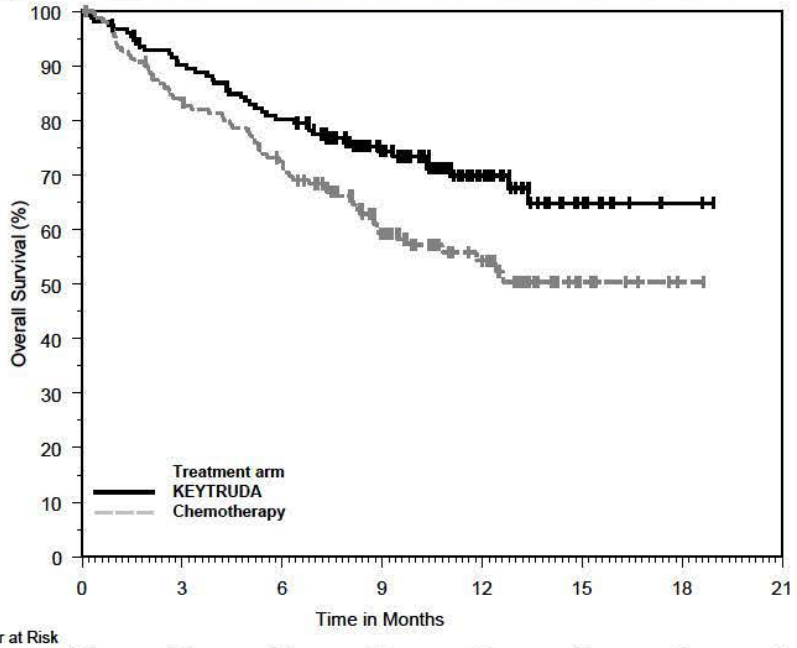
The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared with chemotherapy. Additionally, a pre-specified interim OS analysis at 108 events (64% of the events needed for final analysis) also demonstrated statistically significant improvement of OS for patients randomized to KEYTRUDA as compared with chemotherapy. Table 23 summarizes key efficacy measures for KEYNOTE-024.

Table 23: Efficacy Results in KEYNOTE-024

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=154**	**Chemotherapy n=151**
PFS		
Number (%) of patients with event	73 (47%)	116 (77%)
Median in months (95% CI)	10.3 (6.7, NR)	6.0 (4.2, 6.2)
Hazard ratio* (95% CI)	0.50 (0.37, 0.68)	
p-Value (stratified log-rank)	<0.001	
OS		
Number (%) of patients with event	44 (29%)	64 (42%)
Median in months (95% CI)	NR (NR, NR)	NR (9.4, NR)
Hazard ratio* (95% CI)	0.60 (0.41, 0.89)	
p-Value (stratified log-rank)	0.005†	
Objective Response Rate		
ORR (95% CI)	45% (37, 53)	28% (21, 36)
Complete response rate	4%	1%
Partial response rate	41%	27%
p-Value (Miettinen-Nurminen)	0.001	
Median duration of response in months (range)	NR (1.9+, 14.5+)	6.3 (2.1+, 12.6+)

* Based on the stratified Cox proportional hazard model
† p-Value is compared with 0.0118 of the allocated alpha for this interim analysis.
NR = not reached

Figure 5: Kaplan-Meier Curve for Overall Survival in KEYNOTE-024



Number at Risk								
KEYTRUDA:	154	136	121	82	39	11	2	0
Chemotherapy:	151	123	106	64	34	7	1	0

Previously treated NSCLC

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx Kit. 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. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS=1-49%), ECOG performance scale (0 vs. 1), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1:1) to receive KEYTRUDA 2 mg/kg intravenously every 3 weeks, KEYTRUDA 10 mg/kg intravenously every 3 weeks or docetaxel intravenously 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue until disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or confirmation of progression at 4 to 6 weeks with repeat imaging or for up to 24 months without disease progression.

Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measures were OS and PFS as assessed by the BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%. Additional efficacy outcome measures were ORR and response duration in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%.

A total of 1033 patients were randomized: 344 to the KEYTRUDA 2 mg/kg arm, 346 patients to the KEYTRUDA 10 mg/kg arm, and 343 patients to the docetaxel arm. The study population characteristics were: median age 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG performance status 1; 43% with high PD-L1 tumor expression; 21% with

squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease.

Tables 24 and 25 summarize key efficacy measures in the subgroup with TPS ≥50% population and in all patients, respectively. The Kaplan-Meier curve for OS (TPS ≥1%) is shown in Figure 6.

Table 24: Efficacy Results of the Subgroup of Patients with TPS ≥50% in KEYNOTE-010

Endpoint	**KEYTRUDA 2 mg/kg every 3 weeks n=139**	**KEYTRUDA 10 mg/kg every 3 weeks n=151**	**Docetaxel 75 mg/m^2 every 3 weeks n=152**
OS			
Deaths (%)	58 (42%)	60 (40%)	86 (57%)
Median in months (95% CI)	14.9 (10.4, NR)	17.3 (11.8, NR)	8.2 (6.4, 10.7)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	89 (64%)	97 (64%)	118 (78%)
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Objective response rate			
ORR† (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 16.8+)	NR (2.1+, 17.8+)	8.1 (2.1+, 8.8+)

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

† All responses were partial responses

NR = not reached

Table 25: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

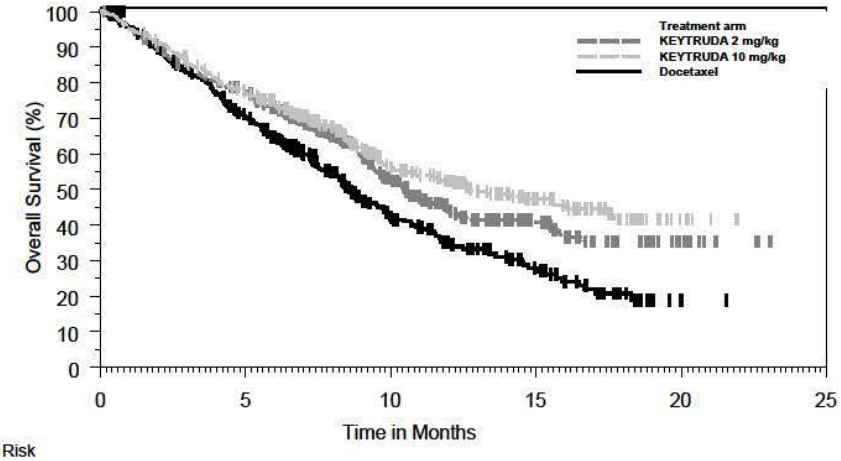
Endpoint	**KEYTRUDA 2 mg/kg every 3 weeks n=344**	**KEYTRUDA 10 mg/kg every 3 weeks n=346**	**Docetaxel 75 mg/m^2 every 3 weeks n=343**
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	266 (77%)	255 (74%)	257 (75%)
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value (stratified log-rank)	0.068	0.005	---
Objective response rate			
ORR† (95% CI)	18% (14, 23)	19% (15, 23)	9% (7, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 20.1+)	NR (2.1+, 17.8+)	6.2 (1.4+, 8.8+)

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

† All responses were partial responses

NR = not reached

Figure 6: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-010 (TPS ≥1%)



Number at Risk						
KEYTRUDA 2 mg/kg:	344	259	115	49	12	0
KEYTRUDA 10 mg/kg:	346	255	124	56	6	0
Docetaxel:	343	212	79	33	1	0

14.3 Head and Neck Cancer

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-012 (NCT01848834), a multicenter, non-randomized, 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 v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, 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.

14.4 Classical Hodgkin Lymphoma

The efficacy of KEYTRUDA was investigated in 210 patients with relapsed or refractory cHL, enrolled in a multicenter, non-randomized, open-label study (KEYNOTE-087; NCT02453594). Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or greater than 5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Patients received KEYTRUDA at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months in patients who did not progress. Disease assessment was performed every 12 weeks. The major efficacy outcome measures (ORR, CRR, and duration of response) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria.

Among the 210 patients, the baseline characteristics were: median age of 35 years (range: 18 to 76), 9% age 65 or older; 54% male; 88% White; 49% had an ECOG performance status (PS) of 0 and 51% had an ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range: 1 to 12). Fifty-eight percent were refractory to the last prior therapy, including 35% with primary refractory disease and 14% whose disease was chemo-refractory to all prior regimens. Sixty-one percent of patients had undergone prior auto-HSCT, 83% had received prior brentuximab vedotin and 36% of patients had prior radiation therapy.

Efficacy results for KEYNOTE-087 are summarized in Table 26.

Table 26: Efficacy Results in KEYNOTE-087

	KEYNOTE-087*
Endpoint	N=210
Overall Response Rate	
ORR (95% CI)	69% (62, 75)
Complete response	22%
Partial response	47%
Response Duration	
Median in months (range)	11.1 (0.0+, 11.1) †

* Median follow-up time of 9.4 months
† Based on patients (n=145) with a response by independent review

14.5 Primary Mediastinal Large B-Cell Lymphoma

The efficacy of KEYTRUDA was investigated in 53 patients with relapsed or refractory PMBCL enrolled in a multicenter, open-label, single-arm trial (Study KEYNOTE-170; NCT02576990). Patients were not eligible if they had active non-infectious pneumonitis, allogeneic HSCT within the past 5 years (or greater than 5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy. The patients were treated with KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months for patients who did not progress. Disease assessments were performed every 12 weeks and assessed by blinded independent central review according to the 2007 revised IWG criteria.

Among the 53 patients accrued, the baseline characteristics were: median age 33 years (range: 20 to 61 years), 43% male; 92% White; 43% had an ECOG performance status (PS) of 0 and 57% had an ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of PMBCL was 3 (range 2 to 8). Thirty-six percent had primary refractory disease, 49% had relapsed disease refractory to the last prior therapy, and 15% had untreated relapse. Twenty-six percent of patients had undergone prior autologous HSCT, and 32% of patients had prior radiation therapy. All patients had received rituximab as part of a prior line of therapy.

Efficacy was based on overall response rate (ORR) and duration of response. The efficacy results for KEYNOTE-170 are summarized in Table 27. For the 24 responders, the median time to first objective response (complete or partial response) was 2.8 months (range 2.1 to 8.5 months).

Table 27: Efficacy Results in KEYNOTE-170

Endpoint	KEYNOTE-170*
	N=53
Overall Response Rate	
ORR (95% CI)	45% (32, 60)
Complete response	11%
Partial response	34%
Response Duration	
Median in months (range)	NR (1.1+, 19.2+)†

* Median follow-up time of 9.7 months
† Based on patients (n=24) with a response by independent review
NR = not reached

14.6 Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-052 (NCT02335424), a multicenter, open-label, single-arm trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Tumor response assessments were performed at 9 weeks after the first dose, then every 6 weeks for the first year, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ as assessed by independent radiology review, and duration of response.

In this trial, the median age was 74 years, 77% were male, and 89% were White. Eighty-seven percent had M1 disease, and 13% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 19% of patients had a primary tumor in the upper tract. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Reasons for cisplatin ineligibility included: 50% with baseline creatinine clearance of <60 mL/min, 32% with ECOG performance status of 2, 9% with ECOG 2 and baseline creatinine clearance of <60 mL/min, and 9% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

Among the 370 patients, 30% (n = 110) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. The baseline characteristics of these 110 patients were: median age 73 years, 68% male, and 87% White. Eighty-two percent had M1 disease, and 18% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 18% of patients had a primary tumor in the upper tract. Seventy-six percent of patients had visceral metastases, including 11% with liver metastases. Reasons for cisplatin ineligibility included: 45% with baseline creatinine clearance of <60 mL/min, 37% with ECOG performance status of 2, 10% with ECOG 2 and baseline creatinine clearance of <60 mL/min, and 8% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

The median follow-up time for 370 patients treated with KEYTRUDA was 7.8 months (range 0.1 to 20 months). Efficacy results are summarized in Table 28.

Table 28: Efficacy Results in KEYNOTE-052

Endpoint	KEYTRUDA 200 mg every 3 weeks		
	All Subjects n=370	**PD-L1 CPS <10 n=260***	**PD-L1 CPS ≥10 n=110**
Objective Response Rate			
ORR (95% CI)	29% (24, 34)	21% (16, 26)	47% (38, 57)
Complete response rate	7%	3%	15%
Partial response rate	22%	18%	32%
Duration of Response			
Median in months (range)	NR (1.4+, 17.8+)	NR (1.4+, 16.3+)	NR (1.4+, 17.8+)

* Includes 9 subjects with unknown PD-L1 status
\+ Denotes ongoing
NR = not reached

Previously Untreated Urothelial Carcinoma
KEYNOTE-361 (NCT02853305) is an ongoing, multicenter, randomized study in previously untreated patients with metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy. The study compares KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. The trial also enrolled a third arm of monotherapy with KEYTRUDA to compare to platinum-based chemotherapy alone. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and found that in patients classified as having low PD-L1 expression (CPS <10), those treated with KEYTRUDA monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The iDMC recommended to stop further accrual of patients with low PD-L1 expression in the monotherapy arm, however, no other changes were recommended, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm.

Previously Treated Urothelial Carcinoma
The efficacy of KEYTRUDA was evaluated in Study KEYNOTE-045 (NCT02256436), a multicenter, randomized (1:1), active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients were randomized to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (n=87). Treatment continued until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed at 9 weeks after randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and duration of response.

Among the 542 randomized patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 42% ECOG status of 0 and 56% ECOG performance status of 1; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had

a primary tumor in the lower tract and 14% had a primary tumor in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

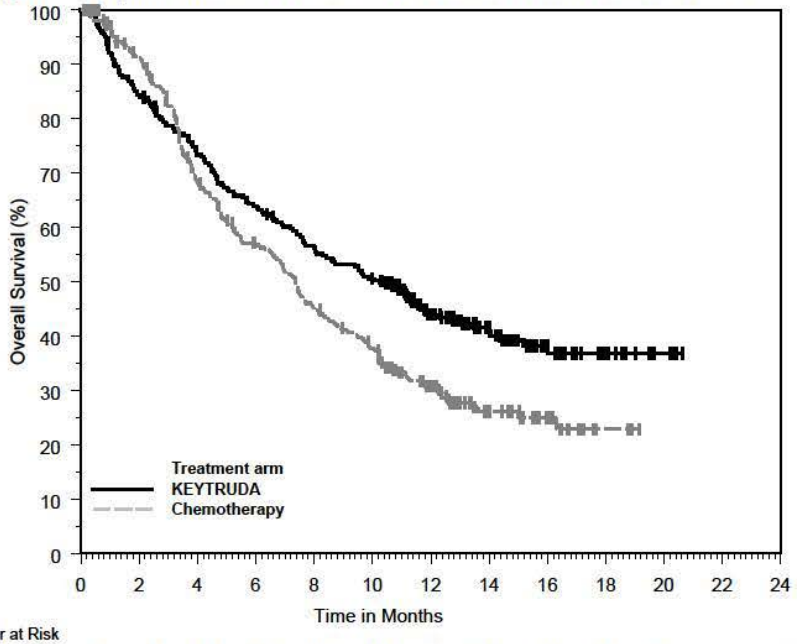
Table 29 and Figure 7 summarize the key efficacy measures for KEYNOTE-045. The study demonstrated statistically significant improvements in OS and ORR for patients randomized to KEYTRUDA as compared to chemotherapy. There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. The median follow-up time for this trial was 9.0 months (range: 0.2 to 20.8 months).

Table 29: Efficacy Results in KEYNOTE-045

	KEYTRUDA 200 mg every 3 weeks n=270	**Chemotherapy n=272**
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
Hazard ratio* (95% CI)	0.98 (0.81, 1.19)	
p-Value (stratified log-rank)	0.833	
Objective Response Rate		
ORR (95% CI)	21% (16, 27)	11% (8, 16)
Complete response rate	7%	3%
Partial response rate	14%	8%
p-Value (Miettinen-Nurminen)	0.002	
Median duration of response in months (range)	NR (1.6+, 15.6+)	4.3 (1.4+, 15.4+)

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model
\+ Denotes ongoing
NR = not reached

Figure 7: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



Number at Risk													
KEYTRUDA:	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemo herapy:	272	232	171	138	109	89	55	27	14	3	0	0	0

14.7 Microsatellite Instability-High Cancer

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by blinded independent central radiologists' (BICR) review according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and duration of response.

Table 30: MSI-H Trials

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

A total of 149 patients with MSI-H or dMMR cancers were identified across the five clinical trials. Among these 149 patients, the baseline characteristics were: median age 55 years (36% age 65 or older); 56% male; 77% White, 19% Asian, 2% Black; and ECOG PS 0 (36%) or 1 (64%). Ninety-eight percent of patients had metastatic disease and 2% had locally advanced, unresectable disease. The median number of prior therapies for metastatic or unresectable disease was two. Eighty-four percent of patients with metastatic CRC and 53% of patients with other solid tumors received two or more prior lines of therapy.

The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.

Efficacy results are summarized in Table 31.

Table 31: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	n=149
Objective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4%
Partial response rate	32.2%
Response duration	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

NR = not reached

Table 32: Response by Tumor Type

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

14.8 Gastric Cancer

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-059 (NCT02335411), a multicenter, non-randomized, open-label multi-cohort trial that enrolled 259 patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma who progressed on at least 2 prior systemic treatments for advanced disease. Previous treatment must have included a fluoropyrimidine and platinum doublet. HER2/neu positive patients must have previously received treatment with approved HER2/neu-targeted therapy. Patients with active autoimmune disease or a medical condition that required immunosuppression or with clinical evidence of ascites by physical exam were ineligible.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, 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. Assessment of tumor status was performed every 6 to 9 weeks. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by blinded independent central review, and duration of response.

Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. The baseline

characteristics of these 143 patients were: median age 64 years (47% age 65 or older); 77% male; 82% White, 11% Asian; and ECOG PS of 0 (43%) and 1 (57%). Eighty-five percent had M1 disease and 7% had M0 disease. Fifty-one percent had two and 49% had three or more prior lines of therapy in the recurrent or metastatic setting.

For the 143 patients, the ORR was 13.3% (95% CI: 8.2, 20.0); 1.4% had a complete response and 11.9% had a partial response. Among the 19 responding patients, the duration of response ranged from 2.8+ to 19.4+ months, with 11 patients (58%) having responses of 6 months or longer and 5 patients (26%) having responses of 12 months or longer.

Among the 259 patients enrolled in KEYNOTE-059, 7 (3%) had tumors that were determined to be MSI-H. An objective response was observed in 4 patients, including 1 complete response. The duration of response ranged from 5.3+ to 14.1+ months.

14.9 Cervical Cancer

The efficacy of KEYTRUDA was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort (Cohort E) in Study KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients were treated with KEYTRUDA intravenously at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by blinded independent central review, and duration of response.

Among the 98 patients in Cohort E, 77 (79%) had tumors that expressed PD-L1 with a CPS ≥ 1 and received at least one line of chemotherapy in the metastatic setting. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. The baseline characteristics of these 77 patients were: median age was 45 years (range: 27 to 75 years); 81% were White, 14% Asian, 3% Black; ECOG PS was 0 (32%) or 1 (68%); 92% had squamous cell carcinoma, 6% adenocarcinoma, and 1% adenosquamous histology; 95% had M1 disease and 5% had recurrent disease; 35% had one and 65% had two or more prior lines of therapy in the recurrent or metastatic setting.

No responses were observed in patients whose tumors did not have PD-L1 expression (CPS <1).

Efficacy results are summarized in Table 33.

Table 33: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158

Endpoint	n=77*
Objective response rate	
ORR (95% CI)	14.3% (7.4, 24.1)
Complete response rate	2.6%
Partial response rate	11.7%
Response duration	
Median in months (range)	NR (4.1, 18.6+)[†]
% with duration ≥6 months	91%

* Median follow-up time of 11.7 months (range 0.6 to 22.7 months)
† Based on patients (n=11) with a response by independent review
\+ Denotes ongoing
NR = not reached

14.10 Hepatocellular Carcinoma

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-224 (NCT02702414), a single-arm, multicenter trial in patients with HCC who had disease progression on or after sorafenib or were intolerant to sorafenib; had measurable disease; and Child-Pugh class A liver impairment. Patients with active autoimmune disease, greater than one etiology of hepatitis, a medical condition that required immunosuppression, or clinical evidence of ascites by physical exam were ineligible for the trial.

Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity, investigator-assessed confirmed disease progression (based on repeat scan at least 4 weeks from the initial scan showing progression), or completion of 24 months of KEYTRUDA. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR and duration of response according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by blinded independent central review committee (BICR).

A total of 104 patients were enrolled. The baseline characteristics were: median age 68 years (67% age 65 or older); 83% male; 81% White; 14% Asian; ECOG PS of 0 (61%) or 1 (39%). Child-Pugh class and score were A5 for 72%, A6 for 22%, B7 for 5%, and B8 for 1% of patients. Twenty-one percent of the patients were HBV seropositive and 25% HCV seropositive. There were 9 patients (9%) who were seropositive for both HBV and HCV. For these 9 patients, all of the HBV cases and three of the HCV cases were inactive. Sixty-four percent (64%) of patients had extrahepatic disease, 17% had vascular invasion, and 9% had both. Thirty-eight percent (38%) of patients had alpha-fetoprotein (AFP) levels ≥400 µg/L. All patients received prior sorafenib; of whom 20% were unable to tolerate sorafenib. No patient received more than one prior systemic therapy (sorafenib).

Efficacy results are summarized in Table 34.

Table 34: Efficacy Results in KEYNOTE-224

Endpoint	n=104
BICR-Assessed Objective Response Rate (RECIST v1.1*)	
ORR (95% CI)[†]	17% (11, 26)
Complete response rate	1%
Partial response rate	16%
BICR-Assessed Response Duration	
% with duration ≥6 months	89%
% with duration ≥12 months	56%

* Modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ

† Based on patients (n=18) with a confirmed response by independent review.

14.11 Merkel Cell Carcinoma

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-017 (NCT02267603), a multicenter, non-randomized, open-label trial that enrolled 50 patients with recurrent locally advanced or metastatic MCC who had not received prior systemic therapy for their advanced disease. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 2 mg/kg every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, 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. Assessment of tumor status was performed at 13 weeks followed by every 9 weeks for the first year and every 12 weeks thereafter. The major efficacy outcome measures were ORR and duration of response as assessed by BICR per RECIST v1.1.

Among the 50 patients, the median age was 71 years (range: 46 to 91 years), with 80% age 65 or older; 68% male; 90% White; and ECOG performance score was 0 (48%) and 1 (52%). Fourteen percent had stage IIIB disease and 86% had stage IV. Eighty-four percent of patients had prior surgery and 70% had prior radiation therapy.

Efficacy results are summarized in Table 35.

Table 35: Efficacy Results in KEYNOTE-017

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=50
Objective Response Rate	
ORR (95% CI)	56% (41, 70)
Complete response (CR) rate (95% CI)	24% (13, 38)
Partial response (PR) rate (95% CI)	32% (20, 47)
Duration of Response	
Range in months*	5.9-34.5+
Patients with duration ≥6 months, n (%)	27 (96%)
Patients with duration ≥12 months, n (%)	15 (54%)

* The median duration of response was not reached

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

KEYTRUDA injection (clear to slightly opalescent, colorless to slightly yellow solution): carton containing one 100 mg/4 mL (25 mg/mL), single-dose 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 be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA. These reactions may include:
  - 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)]*.
  - Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN *[see Warnings and Precautions (5.6)]*.
  - Other immune-mediated adverse reactions: Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms *[see Warnings and Precautions (5.7)]*.
- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.8)]*.
- Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection *[see Warnings and Precautions (5.7)]*.
- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.9)].*
- 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 females that KEYTRUDA can cause fetal harm. Instruct females of reproductive potential to use highly effective contraception during and for 4 months after the last dose of KEYTRUDA *[see Warnings and Precautions (5.11) 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:
MSD International GmbH,
County Cork, Ireland

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

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

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uspi-mk3475-iv-1812r021

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 certain cancers by working with your immune system. KEYTRUDA can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. These problems may happen anytime during treatment or even after your treatment has ended.

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

Skin problems. Signs of skin problems may include:
- rash
- itching
- blisters, peeling or skin sores
- painful sores or ulcers in your mouth or in your nose, throat, or genital area

Problems in other organs. Signs and symptoms of these problems may include:
- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness
- low red blood cells (anemia)
- swollen lymph nodes, rash or tender lumps on skin, cough, shortness of breath, vision changes, or eye pain

(sarcoidosis)
- confusion, fever, muscle weakness, balance problems, nausea, vomiting, stiff neck, memory problems, or seizures (encephalitis)
- shortness of breath, irregular heartbeat, feeling tired, or chest pain (myocarditis)

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

Rejection of a transplanted organ. People who have had an organ transplant may have an increased risk of organ transplant rejection. Your doctor should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.

Complications, including graft-versus-host-disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be severe and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with KEYTRUDA. Your doctor will monitor you for the following signs and symptoms: skin rash, liver inflammation, stomach-area (abdominal) pain, and diarrhea.

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 that 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 with the chemotherapy medicines pemetrexed and a platinum as your first treatment when your lung cancer:
    - has spread (advanced NSCLC), **and**
    - is a type called “nonsquamous”, **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
  - KEYTRUDA may be used with the chemotherapy medicines carboplatin and either paclitaxel or nab-paclitaxel as your first treatment when your lung cancer:
    - has spread (advanced NSCLC), **and**
    - is a type called “squamous”.
  - KEYTRUDA may be used alone when your lung cancer:
    - has spread (advanced NSCLC) **and,**
    - tests positive for “PD-L1” **and,**
      - as your first treatment if you have not received chemotherapy to treat your advanced NSCLC and your tumor does not have an abnormal “EGFR” or “ALK” gene,

      or
      - you have received chemotherapy that contains platinum to treat your advanced NSCLC, and it did not work or it is no longer working, **and**
      - if your tumor has an abnormal “EGFR” or “ALK” gene, you have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.
- a kind of cancer called head and neck squamous cell cancer (HNSCC) that:
  - has returned or spread **and**
  - you have received chemotherapy that contains platinum and it did not work or is no longer working.
- a kind of cancer called classical Hodgkin lymphoma (cHL) in adults and children when:
  - you have tried a treatment and it did not work **or**
  - your cHL has returned after you received 3 or more types of treatment.
- a kind of cancer called primary mediastinal B-cell lymphoma (PMBCL) in adults and children when:
  - you have tried a treatment and it did not work **or**

- your PMBCL has returned after you received 2 or more types of treatment.

- a kind of bladder and urinary tract cancer called urothelial carcinoma. KEYTRUDA may be used when your bladder or urinary tract cancer:
  - has spread or cannot be removed by surgery (advanced urothelial cancer) **and**,
  - you are not able to receive chemotherapy that contains a medicine called cisplatin, and your tumor tests positive for PD-L1, **or**
  - you are not able to receive a medicine called cisplatin or carboplatin, **or**
  - you have received chemotherapy that contains platinum, and it did not work or is no longer working.
- a kind of cancer that is shown by a laboratory test to be a microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumor. KEYTRUDA may be used in adults and children to treat:
  - cancer that has spread or cannot be removed by surgery (advanced cancer), **and**
  - has progressed following treatment, and you have no satisfactory treatment options, **or**
  - you have colon or rectal cancer, and you have received chemotherapy with fluoropyrimidine, oxaliplatin, and irinotecan but it did not work or is no longer working.

  It is not known if KEYTRUDA is safe and effective in children with MSI-H cancers of the brain or spinal cord (central nervous system cancers).
- a kind of stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma that tests positive for "PD-L1." KEYTRUDA may be used when your stomach cancer:
  - has returned or spread (advanced gastric cancer), **and**
  - you have received 2 or more types of chemotherapy including fluoropyrimidine and chemotherapy that contains platinum, and it did not work or is no longer working, **and**
  - if your tumor has an abnormal "HER2/neu" gene, you also received a HER2/neu-targeted medicine and it did not work or is no longer working.
- a kind of cancer called cervical cancer that tests positive for "PD-L1." KEYTRUDA may be used when your cervical cancer:
  - has returned, or has spread or cannot be removed by surgery (advanced cervical cancer), **and**
  - you have received chemotherapy, and it did not work or is no longer working.
- a kind of liver cancer called hepatocellular carcinoma, after you have received the medicine sorafenib.
- a kind of skin cancer called Merkel cell carcinoma (MCC) in adults and children. KEYTRUDA may be used to treat your skin cancer when it has spread or returned.

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 received an organ transplant, such as a kidney or liver
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- 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 when used alone include: feeling tired, pain, including pain in muscles, bones or joints and stomach-area (abdominal) pain, decreased appetite, itching, diarrhea, nausea, rash, fever, cough, shortness of breath, and constipation.

Common side effects of KEYTRUDA when given with certain chemotherapy medicines include: feeling tired or weak, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, trouble breathing, fever, hair loss, and inflammation of the nerves that may cause pain, weakness, and paralysis in the arms and legs.

In children, feeling tired, vomiting and stomach-area (abdominal) pain, and increased levels of liver enzymes and decreased levels of salt (sodium) in the blood are more common than in adults.

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:
MSD International GmbH, County Cork, Ireland
For KEYTRUDA injection, at:
MSD Ireland (Carlow), County Carlow, Ireland
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s045

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sBLA
Application Number	125514/S-45
Priority or Standard	Priority
Submit Date	June 29, 2018
Received Date	June 29, 2018
PDUFA Goal Date	December 28, 2018
Division/Office	DOP2/OHOP
Review Completion Date	December 19, 2018
Established Name	pembrolizumab
Trade Name	Keytruda
Pharmacologic Class	Programmed Death-Receptor-1 (PD-1) Blocking Antibody
Applicant	Merck Sharp & Dohme Corp.
Formulations	For injection: 50 mg lyophilized powder single dose vials; 100 mg/4 mL (25 mg/mL) solution in single dose vials
Dosing Regimen	200 mg over 30 minutes every 3 weeks
Applicant Proposed Indication	Treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.
Recommendation on Regulatory Action	Approval (Accelerated)
Recommended Indication	Treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.

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Additional Reviewers of Application

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OPDP=Office of Prescription Drug Promotion

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Pembrolizumab is a monoclonal antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with programmed death ligand-1 (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 multiple solid tumors, including indications for melanoma, non-small cell lung cancer, *head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite-high cancer, gastric cancer, cervical cancer, and hepatocellular carcinoma*[1].

1.2. Conclusions on the Substantial Evidence of Effectiveness

It is recommended that approval for pembrolizumab be granted under the provisions of accelerated approval delineated in 21 CFR 601, Subpart E, for the treatment of patients with locally advanced or metastatic Merkel cell carcinoma (MCC) who have not received systemic therapy for their advanced disease. All primary scientific disciplines participating in the review of this application and I concur with this recommendation.

The primary evidence of effectiveness supporting this supplemental BLA is from KEYNOTE-017, a multi-center, non-randomized open-label trial of pembrolizumab in 50 patients with the indicated disease. The assessment of efficacy is based on the endpoints of confirmed objective response rate (ORR) and duration of response (DOR) as determined by a blinded independent central review (BICR). Among the 50 participants in the trial, 28 achieved a confirmed objective response (CR or PR), resulting in an ORR of 56% (95% CI: 41.3, 70.0). Twelve participants (24%) (95% CI: 13.1, 38.2) achieved a complete response (CR), and 16 participants (32%) (95% CI: 19.5, 46.7) achieved a partial response (PR). The median DOR was not reached, and the duration of response ranged from 5.9 to 34.5 months.

The Applicant is seeking approval under the Subpart E Accelerated Approval regulations. Durable objective response rate of sufficient magnitude is an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., improved survival) for patients with locally advanced or metastatic MCC. The effect size of pembrolizumab on ORR and DOR demonstrated in KEYNOTE-017 represents substantial evidence of effectiveness and is an acceptable surrogate for clinical benefit. The results from KEYNOTE-017 compare favorably with off-label use of chemotherapy that produces nondurable response rates and no improvement in overall survival. A trial to evaluate the effect on overall survival and confirm the clinical

[1] The indications in italics were approved under the Accelerated Approval regulations, 21 CFR 601 Subpart E

benefit of pembrolizumab in patients with recurrent locally advanced or metastatic MCC will be required.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin, which can be distinguished from other cutaneous malignancies by its expression of cytokeratin 20 (CK20) and an association with the Merkel cell polyomavirus (MCV) in the majority (approximately 80%) of patients. The 5-year survival rates for patients with MCC are 75%, 59%, and 25% for primary localized tumors, tumors with regional lymph node metastases (or local recurrences), and tumors with distant metastases, respectively (Becker, 2010). More than 30% of patients will develop distant metastatic disease (Voog, 1999). There are no large prospective studies reporting outcomes for patients with purely distant metastatic disease as many studies pool patients with locoregional and distant metastatic disease.

The findings of effectiveness demonstrating the benefits of pembrolizumab in the indicated population of patients are stated above and will not be repeated here.

Serious risks of pembrolizumab are like those of other monoclonal antibodies acting on the PD -1/PD-L1 pathway, including the risk of serious and fatal immune-related adverse reactions. The safety of pembrolizumab in patients with MCC in Study KEYNOTE-017 was compared to the safety in a large pooled population of patients (n=2799) in trials KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010 with various advanced solid tumors who received pembrolizumab at a dose of 10 mg/kg every two to three weeks. The safety profile, evaluated by incidences of adverse events, serious adverse events, adverse events of special interest, and laboratory evaluations, indicated that the safety of pembrolizumab in patients with MCC is comparable to the previously established safety profile for this drug. Specific differences in the incidence of certain adverse events in the primary safety population compared to the pooled population are discussed in detail by the primary clinical reviewer in Section 8.2 of this review, and do not reflect a meaningful difference in the safety of pembrolizumab in the relevant safety population studied for this application.

The benefits of treatment with pembrolizumab for patients with locally advanced or metastatic Merkel cell carcinoma (MCC) who had not received systemic therapy for their advanced disease outweigh the risks of treatment in this serious and life-threatening disease in the setting of limited treatment options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin, which can be distinguished from other skin cancers by its expression of cytokeratin 20 (CK20) and an association with the Merkel cell polyomavirus (MCV) • Factors associated with increased risk for developing MCC include ultraviolet (UV) radiation exposure, infection with MCV, advanced age, and immunosuppression, although most patients with MCC are immunocompetent. The mean age at presentation is approximately 75 years • The 5-year survival rate for patients with MCC is 25% for tumors with distant metastases. More than 30% of patients will develop distant metastatic disease	Metastatic MCC is incurable and represents a disease with only one FDA-approved therapy, therefore, there is a high unmet medical need and a need for additional drugs proven to be effective for the disease.
Current Treatment Options	• Avelumab • The most common drugs used off-label are cisplatin or carboplatin in combination with etoposide, single agent topotecan, and cyclophosphamide, doxorubicin, and vincristine (CAV) • MCC is generally a chemo-sensitive tumor with response rates between 50-60% for patients with newly diagnosed metastatic MCC; however, responses are not durable (median duration of 85 days from reports in the published literature), and chemotherapy has not been shown to improve OS in patients with metastatic disease	There are few treatment options for patients with metastatic MCC and only one approved drug, avelumab. Avelumab was approved under the accelerated approval regulations and confirmation of clinical benefit has not yet been demonstrated. Existing chemotherapy regimens offer limited benefit in terms of duration of responses, when responses are observed. Furthermore, there is no evidence that these treatments prolong survival or result in clinically meaningful delays in disease progression.
Benefit	• The primary evidence of effectiveness supporting this supplemental BLA is from KEYNOTE-017, a multi-center, non-randomized open-label trial of pembrolizumab in 50 patients with the indicated disease.	KEYNOTE-017 was a well-conducted trial demonstrating a clinically meaningful response rate for a serious and life threatening rare disease and with significantly longer response

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The assessment of efficacy is based on the endpoints of confirmed objective response rate (ORR) and duration of response (DOR) as determined by a blinded independent central review (BICR). • Among the 50 participants in the trial, 28 achieved a confirmed objective response (CR or PR), resulting in an ORR of 56% (95% CI: 41.3, 70.0). • Twelve participants (24%) (95% CI: 13.1, 38.2) achieved a complete response (CR), and 16 participants (32%) (95% CI: 19.5, 46.7) achieved a partial response (PR). • The median DOR was not reached, and the range of responses were 5.9 to 34.5 months.	durations observed or reported with chemotherapy. In addition, the data observed for pembrolizumab in the relevant patient population compares favorably to those of the only drug approved for this indication. Because both pembrolizumab and avelumab will have been approved under the accelerated approval regulations, confirmation of the clinical benefit for both drugs is pending.
Risk and Risk Management	• The size of the pooled safety database was considered adequate to characterize the safety profile of pembrolizumab. • In KEYNOTE-017, there were no fatal AEs that were clearly pembrolizumab-related • Forty-four percent of patients experienced at least one SAE, comparable to the pooled safety database (37.2%). • Fourteen patients (28%) experienced 21 adverse events of special interest, including immune-mediated events as well as infusion-related reactions. The frequency of these adverse events was like that of the pooled safety population (21.2%). • Nine patients (18%) discontinued pembrolizumab due to adverse events. • Serious risks of pembrolizumab are like those of other monoclonal antibodies acting on the PD -1/PD-L1 pathway, including the risk of serious and fatal immune-related adverse reactions. There were no fatal immune-related adverse reactions during KEYNOTE-017 and there were 0.3% fatal immune-related adverse reactions in the pooled safety database. • Overall, the safety of pembrolizumab is consistent with the expected toxicity profile of immunologically-mediated anticancer therapies.	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. The incidence and severity of immune-mediated adverse reactions in KEYNOTE-017 is like that reported in the pooled safety database for pembrolizumab administered as a single agent. Significant and serious adverse reactions, including immune-mediated adverse reactions, are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There is a favorable benefit-risk assessment for pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic MCC.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

					Section where discussed, if applicable
□	The patient experience data that was submitted as part of the application, include:				
	□	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
X	Patient experience data was not submitted in the application.				

Suzanne Demko
Cross-Disciplinary Team Leader

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2 Therapeutic Context

2.1. Analysis of Condition

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin, which can be distinguished from other cutaneous malignancies by its expression of cytokeratin 20 (CK20) and an association with the Merkel cell polyomavirus (MCV) in the majority (approximately 80%) of patients. The name of the tumor is taken from the Merkel cell which is located in the basal layer of the epidermis and characterized by neuroendocrine granules and CK20 expression. These shared characteristics have led to the common thinking that MCC originates from Merkel cells; however, the cell of origin is not definitive and the pathogenesis not completely understood (Becker, 2010).

MCC is a rare disease with an estimated 1,600 new patients diagnosed each year in the U.S.; however, the annual incidence rate is increasing. Data from the Surveillance, Epidemiology and End Results (SEER) Program database estimated the annual incidence rate in 2011 as 0.79 per 100,000 persons. Factors associated with increased risk for developing MCC include ultraviolet (UV) radiation exposure, infection with the MCV, advanced age, and immunosuppression, although the majority of patients with MCC are immunocompetent. The mean age at presentation is approximately 75 years (Schadendorf, 2017).

MCC usually presents as a firm, painless, rapidly enlarging, dome-shaped cutaneous nodule located in a sun-exposed area such as the head, neck or upper extremities (Heath, 2008). Wide local excision with at least a 2-3cm minimum margin is the standard of care for localized MCC. Depending on the tumor location and the excision margins, adjuvant radiation may be administered following resection. For patients with disease present in local lymph nodes, the resection may include a wider dissection with lymphadenectomy, and adjuvant radiation is often administered (Becker, 2010; Porceddu, 2015). For patients with distant metastatic disease, chemotherapy regimens similar to those used for small cell lung cancer are utilized, the most common being cisplatin or carboplatin in combination with etoposide. However, chemotherapy is generally tailored to the individual patient's age and baseline comorbidities, and the National Comprehensive Cancer Network (NCCN) guidelines suggest that a clinical trial, when available, is an appropriate first option, as well as anti-PD-1/ PD-L1 antibodies (avelumab, pembrolizumab, nivolumab) (NCCN, 2018). Although MCC tends to be a chemosensitive tumor, responses are not durable, and chemotherapy has not been shown to improve overall survival in patients with metastatic disease (Cassler, 2016; Hughes, 2014). Chemotherapy is also associated with risk of severe toxicity and toxic death, particularly among older patients. Voog et al. performed a retrospective review of 107 patients with MCC who received chemotherapy for locally advanced or metastatic MCC between 1980 and 1995 and found an 8% risk of chemotherapy-related death during front-line treatment (Voog, 1999).

The 5-year survival rates for patients with MCC are 75%, 59%, and 25% for primary localized tumors, tumors with regional lymph node metastases (or local recurrences), and tumors with distant metastases, respectively (Becker, 2010). More than 30% of patients will develop distant metastatic disease (Voog, 1999). There are no large prospective studies reporting outcomes for patients with purely distant metastatic disease as many studies pool patients with locoregional and distant metastatic disease. A retrospective analysis of the treatment outcomes of 62 patients with MCC with distant metastases treated with chemotherapy demonstrated a median OS from start of chemotherapy for all patients of 9.5 months. The ORR with front-line chemotherapy was 55% (34/62). The median DOR from onset of response for first-line chemotherapy was 85 days (range 12–942 days). For the 30 patients who received salvage chemotherapy at recurrence, the ORR was 23% (7/30) with a median DOR of 101 days (range 6-226 days). In this case series, no patients died due to direct toxicity from chemotherapy; however, 7% of patients experienced febrile neutropenia and 5% of patients had septic events (Iyer, 2016).

2.2. Analysis of Current Treatment Options

Avelumab was granted accelerated approval by the FDA in 2017 for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma. The efficacy and safety of avelumab was demonstrated in the JAVELIN Merkel 200 trial (NCT02155647), an open-label, single-arm, multi-center study conducted in patients with histologically confirmed metastatic MCC whose disease had progressed on or after chemotherapy administered for metastatic disease. Patients received avelumab 10 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by a blinded independent central review committee (IRC) and IRC-assessed duration of response (DOR). The overall response rate among 88 enrolled patients was 33.0% (95% confidence interval [CI] 23.3, 43.8), with a DOR of 2.8 – 23.3+ months. Eighty-six percent of patients had a DOR ≥ 6 months, and 45% of patients had a DOR ≥ 12 months. Per the product labeling, warnings and precautions with the use of avelumab include immune-mediated adverse reactions (hepatitis, pneumonitis, colitis, endocrinopathies, and nephritis and renal dysfunction) and infusion-related reactions. The most common adverse events observed in patients receiving avelumab (in ≥ 20% of patients) were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema.

Off-label use of chemotherapy regimens similar to those used for small cell lung cancer may also be employed in the frontline setting. The most common regimens are cisplatin or carboplatin in combination with etoposide, single agent topotecan, and cyclophosphamide, doxorubicin, and vincristine (CAV), although CAV is used less than the other regimens due to increased risk for toxicity. MCC is generally a chemo-sensitive tumor with response rates between 50-60% in newly diagnosed metastatic MCC; however, responses are not durable, and chemotherapy has not been shown to improve OS in patients with metastatic disease (NCCN, 2018; Cassler, 2016; Voog, 1999).

There are published case reports and small case series of partial responses to kinase inhibitors including imatinib, cabozantinib, pazopanib and mTOR inhibitors in patients with metastatic MCC; however, no large prospective clinical trials have demonstrated evidence of effectiveness for any of these agents to date. Other drug classes under early investigation for metastatic MCC include cytokines, adoptive T-cell therapy, toll-like receptor 4 agonists, and somatostatin analogues (Schadendorf, 2017).

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pembrolizumab is approved in the U.S. for multiple indications. As of July 10, 2018, pembrolizumb is indicated in:

- Melanoma
  - for the treatment of patients with unresectable or metastatic melanoma.
- Non-Small Cell Lung Cancer (NSCLC)
  - in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
  - as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
  - as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) 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.
  - in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC.
- Head and Neck Squamous Cell Cancer (HNSCC)
  - for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.*
- Classical Hodgkin Lymphoma (cHL)
  - for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.*
- Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
  - for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.*
    - Limitation of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy
- Urothelial Carcinoma
  - for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10], or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.*

    - for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- Microsatellite Instability-High Cancer
    - for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
        - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.*
        - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.*
        - Limitation of Use: The safety and effectiveness of pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established.
- Gastric Cancer
    - for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinumcontaining chemotherapy and if appropriate, HER2/neu-targeted therapy.*
- Cervical Cancer
    - for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.*

*These indications are approved under accelerated approval based on tumor response rate and durability of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

3.2. Summary of Presubmission/Submission Regulatory Activity

- On August 27, 2014, IND 123618, investigating pembrolizumab in patients with advanced Merkel Cell Carcinoma, was allowed to proceed.

- On December 28, 2016, FDA granted Orphan Drug Designation to pembrolizumab for the treatment of MCC.

- On July 21, 2017, FDA granted Breakthrough Therapy Designation to pembrolizumab for the treatment of MCC. A Breakthrough Therapy meeting was held on October 3, 2017. During that meeting, FDA requested that Merck submit, in a pre-sBLA meeting package, a minimum of 6 months of follow-up data from the onset of an independently confirmed response for all patients to characterize the durability of response. In

addition, FDA requested that Merck submit a proposal for a post-marketing requirement confirmatory study in at least 50 patients.

- On October 3, 2017, a Type B Breakthrough meeting teleconference was held with Merck and the FDA to discuss the development program for the treatment of (b) (4) [redacted]. FDA advised that a minimum follow-up of 6 months from the onset of an independently confirmed response would be required to conclude that the observed overall response rate is reasonably likely to predict clinical benefit. FDA also advised that the confirmatory trial should include patients with MCC who will be followed for a minimum of 12 months from onset of response to establish the ORR and the DOR. Patients should also be followed for OS until at least 70% of patients have died to characterize effects on survival. FDA strongly encouraged enrollment of pediatric patients to capture safety outcomes and responses in this population. FDA agreed that a 120-day safety update would not be required for the proposed sBLA.

- On December 21, 2017, (b) (4) [redacted] On February 22, 2018, FDA advised Merck (b) (4) [redacted]

- On March 15, 2018, Merck submitted a meeting request (SDN 71) to discuss a proposed sBLA, to be submitted under the provisions of 21 CFR 610.41, intended to support a new indication for pembrolizumab for the treatment of (b) (4) [redacted] based on the results from Protocol 017/Cancer Immunotherapy Trials Network-09, "A Phase 2 Study of MK-3475 in Patients with Advanced Merkel Cell Carcinoma", conducted under an IND sponsored by NCI.

- The pre-sBLA meeting was conducted on June 14, 2018. Merck presented data from 50 patients in Study P017, with a duration of follow up of at least 6 months from the onset of an independently confirmed response. FDA agreed that the study demonstrated a durable overall response rate in patients with MCC receiving pembrolizumab and could potentially permit a substantive review for an application seeking accelerated approval under 21 CFR 601 Subpart E. FDA noted that the confirmatory study should be underway at the time of the sBLA submission.

- During this meeting, FDA referred to advice conveyed during the October 3, 2017, teleconference. FDA stated that submission of an sBLA for the proposed indication should include all relevant portions of an application required to conduct a comprehensive review, including but not limited to the datasets to support the analyses provided in the CSR, the Summaries of Safety and Efficacy, the clinical summary and overview, and narratives of serious adverse events, deaths and adverse events of special interest. FDA requested that the following be included in the sBLA: 1) SAS programs that produced all efficacy results, 2) all raw as well as derived variables in .xpt format, 3) SAS programs by which the derived variables were produced from the raw variables, and 4) the results of any interim analysis, if performed.

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

4.1. Office of Scientific Investigations (OSI)

The need for inspections was discussed with the Office of Scientific Investigations. The independent radiology review facility was recently inspected, and a repeat inspection was not deemed necessary. No inspections were conducted specifically for this supplemental application.

4.2. Product Quality

Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

Not applicable. Nonclinical did not conduct a review of this supplemental application given the prior approval of pembrolizumab in multiple indications.

6 Clinical Pharmacology

Not applicable. Given the prior approval of pembrolizumab in multiple other indications, Clinical Pharmacology did not conduct a review of this supplemental application.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 1 lists the clinical trials included in the original BLA submission. The primary evidence to support the clinical efficacy and safety of pembrolizumab in patients with metastatic MCC is from 50 patients enrolled in Study CITN-009. A pooled population (N=2799) comprised of patients with various advanced solid tumors who received pembrolizumab at a dose of 1-10 mg/kg every 2 – 3 weeks in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010 was analyzed to support the safety review.

Table 1: Listing of Relevant Clinical Trials

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety							
KEYNOTE-017	Single arm, open label, multicenter study to assess efficacy, safety and PK	Pembrolizumab 2 mg/kg Q3 W for up to 2 years	-Confirmed ORR by central review according to RECIST 1.1 -DOR -PFS -OS	Up to 2 years/until disease progression or the start of new anticancer therapy	50 (as of data cut-off, January 2018)	Patients with metastatic MCC	12 US sites
Studies to Support Safety							
Reference Data Set: KEYNOTE-001, -002, -006, and -010 (N=2799)							
KEYNOTE-001	Open-label, nonrandomized Phase 1 study of IV MK-3475	Pembrolizumab 1, 2, 3, and 10 mg/kg IV Q2W or Q3W	-Safety, tolerability -ORR according to RECIST 1.1	Until disease progression or unacceptable toxicity/ median follow-up 14.8 months	~1187 Melanoma DB cutoff: 18-SEP-2015 NSCLC DB cutoff: 23-JAN-2015	Males/females Age: 18 or older Participants with progressive, locally advanced or metastatic carcinoma, especially melanoma and NSCLC	Australia, Canada, France, Italy, Norway, South Korea, Spain, Taiwan, UK, US

KEYNOTE-002	Randomized, Phase 2 study of MK-3475 versus chemotherapy. MK-3475 dose is blinded to the investigator, and participant, and Applicant	Pembrolizumab 2 or 10 mg/kg IV Q3W versus choice of chemotherapy (paclitaxel plus carboplatin, paclitaxel alone, dacarbazine, or oral temozolomide)	-PFS -OS -ORR	Until disease progression or unacceptable toxicity/ median follow-up 19.5 months	540 DB cutoff: 16-NOV-2015	Males/females Age: 18 or older Participants with advanced melanoma refractory to ipilimumab (IPI)	Australia, Canada, France, Italy, Norway, South Korea, Spain, Taiwan, UK, US
KEYNOTE-006	Randomized, controlled, openlabel, 3-arm pivotal study of 2 dosing regimens of MK-3475 versus IPI	Pembrolizumab 10 mg/kg IV Q2W or Q3W versus IPI 3 mg/kg IV Q3W for 4 doses	-PFS -OS -ORR	Up to 2 years/ median follow-up 13.8 months	834 DB cutoff: 03-DEC-2015	Males/females Age: 18 or older Participants with diagnosed unresectable or metastatic melanoma who have not received treatment with IPI 834 DB cutoff: 03-DEC-2015	Austria, Belgium, Canada, Chile, Colombia, France, Germany, Israel, Netherlands, New Zealand, Norway, Spain, Sweden, UK, US

KEYNOTE-010	Multi-center, worldwide, randomized, adaptively designed Phase 2/3 study of MK-3475 at 2 dosing schedules versus docetaxel	Pembrolizumab 2 mg/kg IV Q3W versus pembrolizumab 10 mg/kg IV Q3W versus docetaxel at 75 mg/m2 Q3W	-OS -PFS -ORR	Up to 2 years/ median follow-up 13 months	Multi-center, worldwide, randomized, adaptively designed Phase 2/3 study of MK-3475 at 2 dosing schedules versus docetaxel	Males/females Age: 18 or older Participants with NSCLC with PD-L1 positive tumors who have progressed after platinum-based therapy	Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Lithuania, Netherlands, Portugal, Russia, South Africa, South Korea, Spain, Taiwan, UK, US

7.2. Review Strategy

The FDA statistical and clinical sBLA review team consisted of one primary statistical reviewer of efficacy and one primary clinical reviewer of safety and efficacy.

The sBLA submission contained data from one single-arm, multicenter trial entitled "A Phase II, MK-3475 in Patients with Advanced Merkel cell carcinoma" as primary support for the proposed indication.

The statistical and clinical review of safety and efficacy included the following:

- Review of the current literature on MCC epidemiology and treatment and the Applicant's background materials
- Review of Study CITN-009, including the clinical study report (CSR), protocol, protocol amendments, SAP and SAP amendments
- Review and assessment of Applicant analyses of pembrolizumab safety and efficacy in the clinical study reports and the ISS
- Review of datasets submitted as SAS transport files
- Review of patient narratives of SAEs, deaths, and adverse events of special interest (AESI)
- Review of minutes of key meetings conducted during the pembrolizumab development program for MCC
- Review and assessment of the Module 2 summaries including the Summary of Clinical Efficacy (SCE) and the Summary of Clinical Safety (SCS)
- Review of Applicant responses to multiple FDA requests for additional analyses and clarifications throughout the review
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

Data Sources

The electronic submission including protocols and protocol amendments, SAP, CSRs, clinical summaries, patient listings, case report forms, supporting literature, SAS transport datasets in legacy, SDTM, and ADAM format, and SAS codes for the sBLA submission are located at the following network paths:
Original submission: Application 125514 - Sequence 0562 - 0562 (1990) 06/29/2018 SUPPL-45 (Efficacy) /Multiple Categories/Subcategories

Data and Analysis Quality

The submission contained all the required components of the electronic Common Technical Document (eCTD) and was of adequate quality and integrity to allow for review of the clinical trial data supporting the proposed indication. The primary analysis dataset was reproducible, and FDA was able to confirm the Applicant's analyses of the primary and secondary endpoints.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CITN-009/KEYNOTE-017

Trial Design and Endpoints

Study CITN-009 was a Phase 2, multicenter, nonrandomized, open-label, single arm clinical study to evaluate the efficacy and safety of pembrolizumab in patients with recurrent locally advanced or metastatic MCC who have not received prior systemic chemotherapy for advanced MCC. The study was conducted by the NCI.

Patients were eligible to participate in the study if they had biopsy-proven metastatic MCC or locoregional MCC that had recurred following standard locoregional therapy with surgery and/or radiation therapy. If administered, prior radiation therapy must have occurred more than 2 weeks prior to the beginning of study treatment. Patient disease had to be measurable per RECIST 1.1 and assessed by CT imaging, except for skin lesions not measurable by CT scan, in which case measurements with a caliper or flexible ruler were permitted. Patients who had received prior systemic therapy for MCC, or who had participated in a study of an investigational systemic agent to treat MCC, were not eligible.

Patients received pembrolizumab 2 mg/kg every 3 weeks intravenously for 2 years, or until progressive disease or unacceptable toxicity. Imaging assessments were performed at week 13, then every 9 weeks during the first year, and then every 12 weeks during the second year of treatment.

The primary endpoint was overall response rate (ORR) as per RECIST 1.1 as determined by Blinded Independent Committee Review (BICR). The secondary endpoints included duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

Statistical Analysis Plan

The All-Subjects-as-Treated (ASaT) population served as the primary population for the analysis of efficacy and safety data in this study. The ASaT population was defined as all participants who received at least 1 dose of pembrolizumab.

The primary endpoint of the study was overall response rate (ORR) assessed by BICR as per RECIST 1.1, defined as the proportion of participants who had a confirmed complete response (CR) or partial response (PR). The secondary endpoints of the study included duration of response (DOR), progression-free survival (PFS), and overall survival (OS). DOR was defined as the time from the first documented evidence of confirmed CR or PR until progressive disease (PD). PFS was defined as the time from allocation in the study to the first documented evidence

of progressive disease as per RECIST 1.1 or death due to any cause. OS was defined as the time from allocation to death due to any cause.

The primary endpoint of ORR was described using a point estimate of response rate and 95% confidence interval (CI) based on the Clopper-Pearson methods for the exact binomial distribution. For the secondary endpoints of DOR, PFS, and OS, the survival curve and median time were estimated using the Kaplan-Meier (KM) method. Participants who were alive at the time of analysis were censored at the database cutoff date for OS analysis, and DOR and PFS were censored at the last assessment date.

If a substantial amount of primary endpoint data was missing (at least 1 value missing from more than 20% of participants), analyses of the ORR would be performed using parametric generalized linear models fit by maximum likelihood. A generalized linear model for the ORR would use a binomial error distribution and include all available baseline predictors of the missing outcomes as covariates.

The sponsor assumed a historical ORR of 55% as the null hypothesis. No multiplicity adjustment was proposed for this study.

Protocol Amendments

The original protocol for this study was approved on August 28, 2014. As of the database cutoff date (February 6, 2018), the protocol had been amended 5 times. The original protocol and protocol amendments 2, 4, 5, 6, and 7 are summarized in Table 2. There were 2 other proposed protocol amendments (1 and 3) authored by Cancer Immunotherapy Trials Network (CITN) that were not approved by the Cancer Therapy Evaluation Program (CTEP), and therefore were not submitted to any regulatory agencies or IRBs or distributed to sites. Protocol amendment 7 dated December 27, 2017 was approved by CTEP; at the time of database cutoff, 3 sites had received IRB approval.

Table 2: Protocol Amendments for Study CITN-09/ KEYNOTE-017

Amendment Date	Major changes introduced into the protocol
Amendment 2 April 20, 2015	• Deleted redundant inclusion criterion for prior systemic therapy and updated exclusion criterion to allow patients who received adjuvant chemotherapy more than 6 months before beginning treatment to enroll in the study • Simplified the inclusion criterion for measurable disease and allowed caliper and flexible ruler assessments in addition to CT scans for eligibility • Clarified the inclusion criterion for thyroid stimulating hormone (TSH) for values outside the normal range • Deleted the inclusion criterion and requirement for study measurements for coagulation factors (international normalized ratio, prothrombin time, and activated partial thromboplastin time) • Clarified the inclusion criterion for tumor tissue such that if archival tissue was not available, tumor biopsies were collected and that a newly-obtained biopsy was preferable • Added rationale and criteria for continuing pembrolizumab treatment after confirmed PD for clinically stable participants, including during the 4-week period after initial evidence of PD was reported and before central radiological confirmation • Specified that pembrolizumab treatment was discontinued if alternative anticancer therapy was warranted or ≥25% increase in tumor burden following confirmation of PD • Clarified that systemic corticosteroids may be approved after consultation with the investigator • Specified that biopsies near the time of initial identification of PD and at end of treatment were optional • Clarified that exploratory analyses (immune cell infiltrate, MCPyV, and gene expression) were performed on baseline biopsy samples and on optional samples collected when PD was confirmed and added testing laboratories for tumor tissue samples • Clarified the time point for beginning follow-up phone contact for OS • Added windows for treatment administration and CT scans • Incorporated an Oncology Patient Enrollment Network registration system
Amendment 4 January 29, 2016	• Specified that the initial phase of study enrollment completed and increased the total number of participants to be enrolled in the study to 50 • Increased the estimated time required for enrolling participants and thus the overall duration of the study • Clarified the inclusion criterion for skin lesions that lesions not measurable by CT scan may be measured using a flexible ruler, in addition to a caliper
Amendment 5 June 16, 2016	• Provided an explanation for enrolling 2 additional participants per protocol

Amendment Date	Major changes introduced into the protocol
	• Updated preliminary clinical data from the study and added new references • Added an exclusion criterion for active noninfectious pneumonitis • Revised the inclusion criterion for serum creatinine from ≤1.5×ULN to ≤2.5×ULN and creatinine clearance from 60 mL/min to ≥30 mL/min for patients with creatinine levels >2.5×ULN • Updated potential risks with pembrolizumab administration associated information with updated Comprehensive Adverse Events and Potential Risks (CAEPR) list • Added an optional biopsy, if safe and feasible, in participants who had not achieved a CR, but who were responding to treatment, were stable, or who had progressing lesions • Added a visit at Cycle 2, Day 1, and a new study calendar for Year 2, including assessment windows for follow-up visits • Added exploratory immunologic analyses on pre- and post-treatment biopsy tissue samples and specified that baseline biopsy tissue may be archival or fresh • Clarified that correlative blood samples will be collected at Week 4 and throughout Year 1, but not during Year 2, except for upon discontinuation of pembrolizumab treatment and at the end of treatment
Amendment 6 August 17, 2017	• Updated potential risks with pembrolizumab administration associated information with updated CAEPR • Added option for participants to receive pembrolizumab beyond 2 years under exceptional circumstances • Added option for participants with confirmed SD or PR who completed 2 years of pembrolizumab study treatment to be retreated • Specified that end of treatment visit assessments can be performed on the same day as last dose if permanent treatment discontinuation is anticipated • Clarified requirements for post-treatment follow-up of participants who discontinued treatment without documented disease progression • Clarified that participants who withdraw from the study due to unacceptable drug-related AEs will be monitored for disease status by radiologic imaging • Clarified post-treatment requirements for AEs occurring within 30 days after the last dose of pembrolizumab and SAEs for 90 days after the last dose of pembrolizumab as well as for radiologic imaging
Amendment 7 December 27, 2017	• Updated information about ordering of NCI-supplied agents by eligible participating investigators or their authorized designee at each participating institution

Amendment Date	Major changes introduced into the protocol
	• Clarified the requirements for access to CTEP's Pharmaceutical Management Branch (PMB) Online Agent Order Processing (OAOP) application • Updated the links for the following: - NCI-CTEP Investigator Registration - CTEP Identity and Access Management (IAM) account - CTEP Associate Registration and IAM account

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated the following: "This study was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding IEC review, informed consent, and the protection of human participants in biomedical research." (Module 5.3.5.2)

Financial Disclosure

In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in module 1.3.4. The document includes a table listing all investigators who participated in the three covered studies supporting sBLA 125512 S045. NCI collected financial disclosure forms annually and provided the sites at which any investigator answered "Yes" with regards to financial interests. Merck conducted due diligence of each investigator at each site and determined that 3 investigators had provided a "Yes" response and one investigator was uncertain. It was determined that one of the investigators had financial interests not affiliated with Merck.

The financial interests reported for each investigator were included in Section 1.3.4. These included 1) a grant payment to the university which did not include research involving pembrolizumab, 2) an academic industry collaboration between the institution and Merck, and 3) payment to the institution from Merck in support of investigator-initiated studies.

Patient Disposition

As of the database cutoff date, 50 participants were enrolled and received treatment. Patients who were consented but did not meet eligibility criteria and did not receive treatment were not entered into the clinical database; thus, the number of screen failures is not available.

Disposition	Pembrolizumab n (%)
Number receiving at least one dose of pembrolizumab	50 (100)
Treatment ongoing at data cutoff	10 (20)
Completed treatment by data cutoff	6 (12)
Off treatment at data cutoff	34 (68)
Reasons for treatment discontinuation prior to data cutoff	
Progressive disease	19 (38)
Adverse event	10 (20)
Physician decision	2 (4)
Death	2 (4)
Withdrawal by patient	1 (2)
Patients in post-treatment follow-up at cutoff	23 (46)

AEs prompting drug withdrawal: alanine aminotransferase and alkaline phosphatase increase, inflammatory arthritis, pancreatitis, colitis, adrenal insufficiency, pneumonitis, nephritis, lichen planus, myocarditis.

Protocol Violations/Deviations

A protocol deviation was defined as is any change, divergence, or departure from the study design or procedures defined in an approved protocol. An "important" protocol deviation was defined by the applicant as a protocol deviation that may have significantly impacted the quality (i.e., completeness, accuracy, and reliability) or integrity of key study data; or that may have significantly affected a participant's rights, safety, or well-being.

A total of 37 major deviations (defined as deviations from the IRB-approved protocol that may affect a participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data) were reported based on an assessment by CITN and the investigator at each site. All protocol deviations reported by CITN were reviewed by the applicant to accurately assess their clinical significance and potential impact on the outcome of the study. Based on the clinical review conducted by applicant following standard processes and ICH E3 guidelines for the assessment of protocol deviations, a total of 49 important protocol deviations were identified in enrolled patients. These deviations included three major categories, with specific examples provided below.

- Trial procedures:
  - Failure to conduct major/significant protocol-specified efficacy and/or safety evaluations (missed follow-up visits, some due to patient 'opting out' and others unexplained)
  - Cycle 1 research blood collected prior to timestamp of eligibility confirmation
  - Patient did not meet eligibility criteria

  - Patient had a silent myocardial infarction 5.7 months prior to study entry, while exclusion criterion 3.2.30 stated that patients with a recent MI (within the last 6 months) were excluded.
- Safety reporting:
  - Reportable safety event not reported within timeline outlined in protocol
- Informed consent deviations:
  - Patient was not reconsented in a timely manner following IRB approval of an updated informed consent document.
  - Documentation to confirm that a patient was reconsented to protocol amendment version 5 was not available. When the deviation was found, the patient could not be reconsented, and the data were sanctioned.

Reviewer comment: These protocol deviations were clearly described in a response to an information request and do not substantially impact the integrity of the study or the reliability of the study results for conducting the safety and efficacy reviews.

Table of Demographic Characteristics

Participants in the ASaT population were primarily male (68.0%) and white (90.0%), with a median age of 70.5 years. The Reference Safety Database (RSD) was also predominantly male (59.3%) and White (88.4%). The RSD population differed in geographic region (45% from US, vs. 100% from US in Study CITN-09/KEYNOTE-017) and age (median age of 61.0 years).

Table 3: Demographic characteristics of all enrolled patients

Demographic Characteristics	Pembrolizumab (N=50) Median or n (%)
Age	70.5
Age < 65 years	10 (20.0%)
Age ≥ 65 years	40 (80.0%)
Sex	
Male	34 (68.0%)
Female	16 (32.0%)
Race	
White	45 (90.0%)
Asian	1 (2.0%)
Unknown	4 (8.0%)

ECOG	
0	24 (48.0%)
1	26 (52.0%)

Source: Reviewer generated from Applicant submitted data (adsl.xpt)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The majority of patients had distant metastatic disease (86%), while the minority had locally advanced disease (Stage IIIB,14%). Eighty-four percent of patients had prior surgery, 70% had prior radiation. Eighty-six percent of patients had no prior medical therapy; of the remaining patients, 8% had intratumoral therapy and 6% had prior adjuvant therapy. Intratumoral therapy consisted of glucopyranosyl lipid A, interleukin-12 plasmid DNA vaccine, and interleukin-12 plasmid DNA vaccine, interferon alpha, and interferon beta-1b. Adjuvant therapy consisted of cisplatin and etoposide for all patients.

PD-L1 status was determined using a prototype assay performed at [redacted] (b) (4) [redacted]. "Positive" was defined as 1% staining which included tumor cells and contiguous immune cells. The majority of patients were classified as PD-L1 positive (68%), with 28% PD-L1 negative, and the remaining 4% had unknown status.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was not analyzed because pembrolizumab was administered as an intravenous infusion at the clinic. Use of rescue medication is not applicable to the study treatment mechanism of action.

Efficacy Results – Primary Endpoint

Overall Response Rate

The database cutoff date for the submitted Clinical Study Report (CSR) was February 6, 2018. Table 4 provides the BICR-assessed confirmed overall response rate for participants in the ASaT population and the duration of response among responders.

Table 4. Results of Response and Duration of Response

Efficacy Parameter	Pembrolizumab 2mg/kg Q3W N = 50
Overall Response Rate (CR + PR)	
Number of responses, n	28
% (95% CI)[1]	56 (41, 70)
Complete responses, n (%)	12 (24)

Partial responses, n (%)	16 (32)
Duration of Response	
Median in months [2]	NR
Min, Max	5.9, 34.5+

Abbreviations: CR, complete response; PR, partial responses; n, number of responses; CI, confidence interval; NR, not reached
[1]Based on the exact binomial distribution
[2]Based on the Kaplan-Meier method
+Ongoing response as of database cutoff date
Source: Reviewer generated from Applicant submitted data (adsl.xpt, adrs.xpt, adtte.xpt)

Based on the BICR assessment, among the 50 participants in the ASaT population, 28 achieved a confirmed objective response (CR or PR), resulting in an ORR of 56% (95% CI: 41, 70). Twelve participants (24%) (95% CI: 13, 38) achieved a CR, and 16 participants (32%) (95% CI: 20, 47) achieved a PR.

Subgroup Analyses of Overall Response Rate

The results of the subgroup analyses of BICR-confirmed ORR per RECIST 1.1 by age, gender, and baseline ECOG performance status are presented in Table 5. The results of the subgroup analyses are consistent with the overall results. The subgroup data should be interpreted with caution, since the sample size of the subgroups was small.

Table 5. Subgroup Analysis of ORR by Age, Gender, and ECOG Performance Status

	# Objective Responses (CR+PR) /N of Patients	ORR % (95% CI)[1]
Overall	28/50	56 (41, 70)
Age		
<65 years	4/10	40 (12, 74)
>=65 years	24/40	60 (43, 75)
Gender		
Male	18/34	53 (35, 70)
Female	10/16	63 (35, 85)
ECOG Performance Status		
0	15/24	63 (41, 81)
1	13/26	50 (30, 70)

[1] Based on the binomial exact confidence interval method
Source: Reviewer generated from Applicant submitted data (adsl.xpt, adrs.xpt)

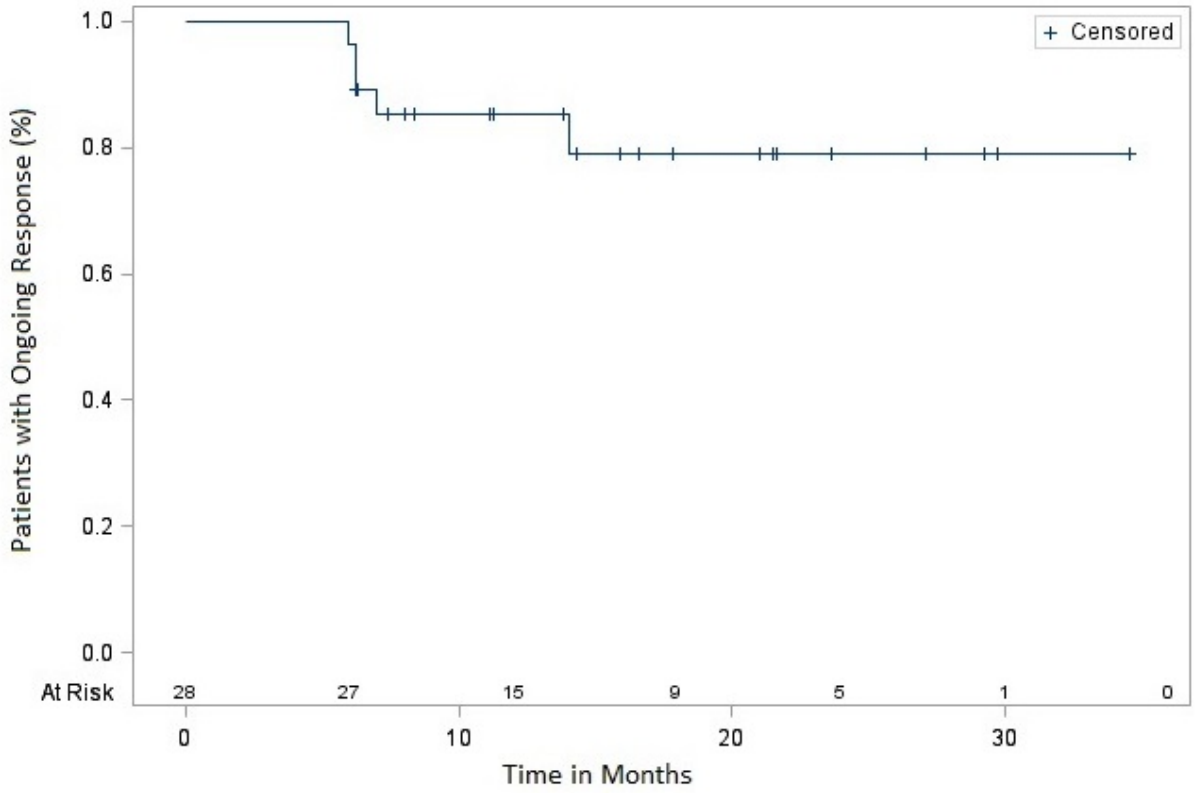
Efficacy Results – Secondary and other relevant endpoints

Duration of Response

The Kaplan-Meier estimate of the median duration of response was not reached (NR) among the 28 responders with BICR-assessed confirmed objective response. The range of duration of response was 5.9-34.5 months (ongoing). As of the database cutoff date of February 06, 2018, 20/28 (71%) of the responses were ongoing.

Among the responders, the median time to response was 2.8 months with a range of 1.5-9.7 months. The Kaplan-Meier curves of response duration among the responders with BICR-confirmed responses are presented in Figure 1.

Figure 1. Kaplan-Meier Estimates of Response Duration among Responders based on BICR-assessed Confirmed Responses per RECIST 1.1



Source: Reviewer generated from Applicant submitted data (adsl.xpt, adrs.xpt, adtte.xpt)

Among the 28 responders, the number of patients observed with a duration of response greater than 6 months was 27 (96%), greater than 12 months was 15 (4%), greater than 18 months was 9 (32%), and greater than 24 months was 5 (18%).

Progression-free Survival and Overall Survival

Progression-free survival (PFS) and overall survival (OS) were secondary endpoints in this study. However, time-to-event endpoints are difficult to interpret in a single arm study. Therefore, the results of these endpoints are not reported in this review.

Dose/Dose Response

Patients in Study CITN-09/KEYNOTE-017 received the same dose of pembrolizumab, 2 mg/kg IV every 3 weeks. The applicant proposes that the indication for this supplement include flat dosing of 200 mg IV every 3 weeks, based on prior pharmacokinetic simulation studies demonstrating similar control of PK variability for the fixed dose relative to a weight-based regimen, and exposures similar to, or slightly higher than those obtained at the weight-based dose of 2 mg/kg every 3 weeks.

Persistence of Effect

Treatment was ongoing for 20% (n=10) of patients as of the data cut-off, and 46% (n=23) of patients were in post-treatment follow-up. An analysis of persistence of effect was not performed given the relatively small number of patients available for this analysis and the immaturity of the data.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

See discussion in section 8.1.4.

8.1.3. Assessment of Efficacy Across Trials

The supplemental application relied upon data from a single study, thus this section is not applicable.

Primary Endpoints

8.1.4. Integrated Assessment of Effectiveness

Data from a single trial were submitted as the primary support for efficacy for this sBLA. The effectiveness of pembrolizumab in patients with recurrent locally advanced or metastatic MCC

is based upon the results of CITN-09/KEYNOTE-017, a multi-center, single-arm trial of pembrolizumab in 50 patients with locally advanced or metastatic MCC who had not received systemic therapy for their advanced disease.

The assessment of efficacy in this application is based on the endpoints of confirmed ORR and DOR according to RECIST 1.1 and as determined by BICR. Among the 50 participants in the ASaT population, 28 achieved a confirmed objective response (CR or PR), resulting in an ORR of 56.0% (95% CI: 41.3, 70.0). Twelve participants (24.0%) (95% CI: 13.1, 38.2) achieved a CR, and 16 participants (32.0%) (95% CI: 19.5, 46.7) achieved a PR.

The Applicant is seeking approval of pembrolizumab for patients with recurrent locally advanced or metastatic MCC under the Accelerated Approval regulations. Durable objective response rate of sufficient magnitude is an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., improved survival) in patients with locally advanced or metastatic MCC. The effect size of pembrolizumab on ORR and DOR demonstrated in Study CITN-09/KEYNOTE-017 represents substantial evidence of effectiveness and clinical benefit over off-label use of chemotherapy which produces nondurable response rates and no improvement in overall survival. A confirmatory trial of pembrolizumab in patients with recurrent locally advanced or metastatic MCC will be performed to evaluate the effect on overall survival.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of pembrolizumab was primarily evaluated in 50 patients with locally advanced or metastatic MCC that recurred following locoregional therapy with surgery and/or radiation therapy. All patients received at least one dose of pembrolizumab 2 mg/kg IV, and the safety monitoring period was from the time the patient signed the informed consent through 30 days after the end of treatment. Serious adverse events were collected for 90 days after the end of treatment. The primary safety analysis was performed with a database cutoff date of February 6, 2018. A pooled population (N=2799) comprised of patients with various advanced solid tumors, largely melanoma, who received pembrolizumab at a dose of 1-10 mg/kg every 2 – 3 weeks in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010 was analyzed to support the safety review.

8.2.2. Review of the Safety Database

Overall Exposure

All patients in Study CITN-09/KEYNOTE-017 received at least one dose of pembrolizumab 2 mg/kg intravenously over 30 minutes. The treatment plan called for study drug administration in clinic every three weeks. At the primary analysis data cut-off date, the median duration of treatment was 6.6 months (range 0.03 – 23.6 months), with patients receiving a median of 10.5 infusions. In the pooled safety population, the median exposure for the subset of patients who

received pembrolizumab at the 2 mg/kg dose at the data cut-off date was 4.2 months (range 0.03 – 30.4 months), with patients receiving a median of 7.0 infusions. Table 4 summarizes pembrolizumab exposure in Study CITN-09 and the pooled population.

Table 4: Exposure Summary, primary analysis

	Study CITN-09 N=50	Pooled Population N= 2799
Duration of treatment in months		
Median	6.6	4.17
Mean	9.0	6.5
Range	1 day – 23.6 months	1 day – 30.4 months
Number of infusions		
Median	10.5	7
Mean	13.5	11.1
Range	1-35	1-59

Relevant characteristics of the safety population:

The safety population of Study CITN-09/KEYNOTE-017 was comprised of patients with metastatic or locally advanced MCC that recurred following locoregional therapy with surgery and/or radiation therapy. Consistent with the epidemiology and natural history of MCC, the median age was 70.5 years. Eighty percent of patients were over the age of 65. The Reference Safety Database (RSD) was also predominantly male (59.3%) and White (88.4%) with baseline ECOG performance status of 0 (51.7%) or 1 (48.1%). The RSD population differed in geographic region (55.3% ex-US, vs. 100% US in Study CITN-09/KEYNOTE-017) and age, with a median age of 61.0 years, and 43.3% of patients being 65 years or older. The Applicant provided subgroup safety analyses to evaluate the impact of age on adverse event frequency in Study CITN/09-KEYNOTE-017 and the pooled population. Additional exploratory analyses were conducted based on gender and race. Limitations of these subgroup analyses are the small sample sizes in Study CITN/09-KEYNOTE-017 and lack of internal control.

Adequacy of the safety database:

Overall, the safety database submitted by the Applicant was adequate. No major deficiencies were identified. The median duration of treatment in Study CITN-09 (6.6 months) was longer that that observed in the RSD (4.17 months). The size of the safety database was sufficient to identify adverse events that occur at an incidence of approximately 1%.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted was well-organized and the quality was adequate to perform a complete review of the safety of pembrolizumab in patients with MCC. Multiple information requests were sent to the Applicant during the review of safety to confirm data, request additional data, or clarify minor discrepancies in the pooled database. The Applicant provided sufficient responses including additional analyses and clarifications as required.

Categorization of Adverse Events

AEs were graded according to the NCI CTCAE, Version 4.0. In all AE tables, participants were counted once for a specific AE term by the worst severity recorded. MedDRA version 20.1 was used in the generation of all tables in this document. The MedDRA preferred terms (PTs) "neoplasm progression," "malignant neoplasm progression," and "disease progression," not related to pembrolizumab were excluded from the AE tables, as disease

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Routine Clinical Tests

Routine hematology and core chemistry laboratory assessments were performed within 28 days of enrollment and every three weeks prior to pembrolizumab administrations. Vital signs, physical examination and performance score assessments were performed prior to each cycle. Free thyroxine (free T4) and thyroid stimulating hormone (TSH) were collected at screening and every 6 cycles and as medically indicated. Merkel Cell polyomavirus (MCPyV) antibody levels were measured prior to pembrolizumab initiation, prior to cycle 5, then every 9 weeks during year one and every 12 weeks during year two. A 12-lead ECG was assessed at screening, prior to infusion and 30 minutes post-infusion for cycle 1 and cycle 8.

8.2.4. Safety Results

Deaths

At the time of the primary analysis for Study CITN-09/KEYNOTE-017, 16 patients (32%) had died; 14 died from progressive disease, and one patient died to due cardiac arrest >100 days after the last dose of study treatment. One patient died due to an adverse event within 90 days after the last dose. The narrative for the patient who died due to an adverse event is provided below:

(b) (6): A 73-year-old male with Stage IIIB MCC and history of atrial fibrillation developed a Grade 3 pleural effusion and Grade 2 pericardial effusion on study day 2; progressive metastatic disease in the thorax, which included multiple pleural metastases, was identified at that time. The patient died due to progressive disease with suspected worsening pleural effusion on study day 12. The investigator assessed the pleural effusion as related to study medication.

Reviewer assessment: The event of pleural effusion is confounded by the presence of pleural metastases and disease progression, which could account for the patient's death. Pleural effusions have also been reported in patients receiving pembrolizumab. This reviewer agrees

Reference ID: 4365657

with the Applicant's assessment that the event was unlikely related to pembrolizumab and likely related to underlying disease.

Serious Adverse Events

Forty-four percent of patients in Study CITN-09/KEYNOTE-017 experienced at least one SAE, comparable to the RSD (37.2%). The most frequently reported SAE aside from disease progression was dehydration (4 [8.0%] participants). SAEs of AST increased and embolism were each reported for 3 (6.0%) participants, compared to 6 (0.2%) and 9 (0.3%) participants, respectively in the RSD. In CITN-09/KEYNOTE-017, all other SAEs were each reported for ≤2 (4.0%) participants.

Reviewer note: The events of elevated AST were reviewed, with narratives provided in Table 6 *below. Two of three events were significantly confounded by 1) anti-tuberculous therapy and 2) progressive metastatic hepatic disease, and are assessed by this reviewer as unlikely to be related to pembrolizumab. The third event, a Grade 4 AST elevation which responded to corticosteroid therapy, is consistent with immune-mediated hepatitis, a known adverse effect of pembrolizumab. Additional events of AST increase not reported as serious adverse events are discussed with Laboratory Findings.*

Table 5: Serious Adverse Events in Study CITN-09/KEYNOTE-017 and Reference Safety Database

	Study CITN-09/ KEYNOTE-017 (N=50)				Reference Safety Dataset (N=2799)			
Preferred Term	All Grades	All Grades %	Grades 3- 5	Grades 3 - 5 %	All Grades	All Grades %	Grades 3- 5	Grades 3 - 5%
Disease progression	8	16%	8	16%	2	0%	2	0%
Dehydration	4	8%	4	8%	27	1%	24	1%
Aspartate aminotransferase increased	3	6%	3	6%	7	0%	6	0%
Embolism	3	6%	3	6%	8	0%	6	0%
Alanine aminotransferase increased	2	4%	2	4%	5	0%	5	0%
Fatigue	2	4%	2	4%	12	0%	8	0%
Hematoma	2	4%	2	4%	2	0%	2	0%
Hyperglycemia	2	4%	2	4%	3	0%	3	0%
Pneumonitis	2	4%	1	2%	32	1%	23	1%
Pyrexia	2	4%	0	0%	41	1%	10	0%

Rash maculo-papular	2	4%	1	2%	2	0%	1	0%
Small intestinal hemorrhage	2	4%	2	4%	1	0%	1	0%
Upper gastrointestinal hemorrhage	2	4%	2	4%	3	0%	3	0%
Abdominal pain	1	2%	0	0%	30	1%	17	1%
Acidosis	1	2%	1	2%	0	0%	0	0%
Acute kidney injury	1	2%	1	2%	21	1%	14	1%
Anemia	1	2%	1	2%	41	1%	32	1%
Atrial fibrillation	1	2%	1	2%	13	0%	8	0%
Blood alkaline phosphatase increased	1	2%	1	2%	0	0%	0	0%
Blood bilirubin increased	1	2%	1	2%	4	0%	3	0%
Cancer pain	1	2%	0	0%	5	0%	4	0%
Chills	1	2%	0	0%	3	0%	0	0%
Colitis	1	2%	1	2%	45	2%	38	1%
Decreased appetite	1	2%	1	2%	3	0%	2	0%
Delirium	1	2%	1	2%	4	0%	4	0%
Dysphagia	1	2%	0	0%	4	0%	3	0%
Dyspnoea	1	2%	1	2%	52	2%	40	1%
Epistaxis	1	2%	0	0%	2	0%	2	0%
Gastroesophageal reflux disease	1	2%	0	0%	1	0%	0	0%
Hypercalcemia	1	2%	1	2%	10	0%	9	0%
Hypernatremia	1	2%	0	0%	0	0%	0	0%
Hyperuricemia	1	2%	0	0%	2	0%	2	0%
Hypotension	1	2%	1	2%	8	0%	6	0%
Hypoxia	1	2%	1	2%	14	1%	8	0%
Lichenoid keratosis	1	2%	1	2%	1	0%	1	0%
Lung infection	1	2%	0	0%	9	0%	6	0%
Malaise	1	2%	0	0%	5	0%	2	0%
Mastitis	1	2%	1	2%	1	0%	1	0%
Muscular weakness	1	2%	1	2%	8	0%	4	0%
Myocarditis	1	2%	1	2%	0	0%	0	0%

Pain of skin	1	2%	1	2%	0	0%	0	0%
Paraneoplastic syndrome	1	2%	1	2%	0	0%	0	0%
Pericardial effusion	1	2%	0	0%	12	0%	9	0%
Pleural effusion	1	2%	1	2%	55	2%	36	1%
Sepsis	1	2%	1	2%	21	1%	20	1%
Sialoadenitis	1	2%	1	2%	0	0%	0	0%
Sinus bradycardia	1	2%	1	2%	0	0%	0	0%
Small intestinal obstruction	1	2%	1	2%	12	0%	11	0%
Streptococcal bacteremia	1	2%	1	2%	0	0%	0	0%
Tuberculosis	1	2%	1	2%	1	0%	0	0%
Tumor pain	1	2%	1	2%	14	1%	11	0%
Urinary tract infection	1	2%	1	2%	20	1%	11	0%
Ventricular arrhythmia	1	2%	1	2%	0	0%	0	0%

Eleven patients (22%) experienced a treatment-related SAE in CITN-09/KEYNOTE-017, which was higher than observed in the RSD (10%). In CITN-09/KEYNOTE-017, the most frequently reported treatment-related SAEs were AST increased and pneumonitis, each reported in 2 (4.0%) participants, compared to 4 (0.1%) and 44 (1.6%) participants, respectively in the RSD. All other treatment-related SAEs were reported for 1 participant each. Narratives for drug-related serious adverse events are provided in Table 6.

Table 6: Drug-Related Serious Adverse Events, Study CITN-09/KEYNOTE-017

Patient ID	AE	Event Summary
(b) (6)	Grade 4 AST/ALT increase	A 72-year-old male with Stage IV MCC developed Grade 4 asparate aminotranserfase (AST) and alanine aminotransferase (ALT) elevation, as well as Grade 2 blood alkaline phosphatase elevation and Grade 2 bilirubin elevation; laboratory results were first abnormal 43 days after initiating treatment with pembrolizumab and peaked on day 50. Corticosteroids were initiated and the patient rapidly improved, with complete resolution by day 77.

(b) (6)	Grade 3 colitis and Grade 3 pancreatitis	A 73-year-old with Stage IV MCC developed pancreatitis and colitis first identified 45 days after initiating treatment with pembrolizumab. Corticosteroid treatment was initiated. Subsequently, on day 57, the patient was admitted for treatment of colitis and diagnosed with *Clostridium difficile*. Pembrolizumab was permanently discontinued, and the events were noted as resolved on day 86. The patient developed a second event of colitis (Grade 2) on day 182.
(b) (6)	Grade 3 dehydration, Grade 1 pyrexia and chills; Grade 3 increased bilirubin and ALT; Grade 2 lung infection	An 83-year-old male with Stage IV MCC developed several SAEs. The patient developed Grade 3 elevated bilirubin and ALT after cycle 12; this was attributed to the patient's recent treatment with anti-tuberculosis medications. The patient also developed Grade 2 lung infection after cycle 18 (unclear etiology), pyrexia and chills during cycle 17, and dehydration in cycle 19. The investigator assessed the events of pyrexia, chills, and dehydration as related to study medication. *Reviewer note: The patient experienced multiple serious and non-serious adverse events. A rationale for assessment as related to the study product is not provided, but the patient's diagnosis of tuberculosis, tuberculosis treatment, and progressive malignancy could account for the observed adverse events and in the opinion of the reviewer, is more likely.*
(b) (6)	Grade 3 fatigue	A 61-year-old male with Stage IV MCC and a history of type 2 diabetes mellitus was admitted to the hospital for diabetic ketoacidosis 74 days after initiation of treatment. The patient had diffuse metastatic disease in the abdomen at the time of admission and discontinued study medication due to progression. The event of fatigue was related to the study medication per the investigator.
(b) (6)	Grade 3 Rash maculopapular	A 91-year-old female with Stage IV MCC developed a drug-related SAE and AESI of maculopapular rash on day 190 (worsening to Grade 3 on study day 379). The patient was treated with corticosteroids and later withdrew from the study.
(b) (6)	Grade 3 pneumonitis	A 65-year-old with Stage IV MCC was diagnosed with a drug-related SAE and AESI of Grade 3 pneumonitis on study day 327 after discontinuing study medication on study day 281 due to the development of brain metastases. The patient was treated with antibiotics, steroids, as well as enoxaparin given a concomitant

		pulmonary embolism. The SAE was assessed as related to study medication.
(b) (6)	Grade 2 pneumonitis, Grade 3 dyspnea	A 70-year-old male with Stage IIIB MCC developed Grade 2 pneumonitis on day 35 of the study. Bronchoscopy and bronchoalveolar lavage were performed, and cultures did not reveal an infectious cause. The patient was treated with antibiotics and corticosteroids, and the study medication was discontinued. The event of dyspnea occurred in association with a lung infection experienced on day 83 of the study, which was deemed to be of infectious etiology.
(b) (6)	Grade 3 lichenoid keratosis	A 67-year-old female with Stage IV MCC developed lichenoid keratosis on day 300, which worsened to Grade 3 on day 412. The patient was treated with topical and systemic corticosteroids. The investigator assessed the event as related to the investigational therapy. *Reviewer note: Multiple dermatologic adverse reactions have been reported in association with anti-PD-1 or anti-PD-L1 antibodies. A retrospective review of patients with melanoma treated with anti-PD-1 therapies found that 17% of patients developed lichenoid reactions and eczema. (Hwang, 2016) This reviewer therefore agrees with the assessment of this event as potentially related to pembrolizumab.*
(b) (6)	Grade 3 AST increased	A 74-year-old male with Stage IV MCC, including liver metastases, and baseline Grade 1 AST and ALT elevation developed Grade 3 AST increase on day 73 of treatment with pembrolizumab. The patient developed Grade 3 AST elevation and Grade 2 alkaline phosphatase and ALT elevation. Imaging performed at that time demonstrated an increase in size and number of hepatic metastases; hepatology assessed the hepatic abnormalities as consistent with a mixed cholestatic rather than hepatocellular heptatits. The patient improved without steroid administration. AST, ALT and alkaline phosphatase again increased on day 87 following initiation of treatment, and imaging demonstrated progressive disease in the liver. The patient discontinued pembrolizumab and died nearly a year later of progressive disease. The investigator assessed the event as related to the investigational product. *Reviewer assessment: The case is clearly confounded by progressive hepatic metastases; the improvement without*

		corticosteroids and correlation with imaging findings of progression argue against the contribution of pembrolizumab, however a possible relationship with pembrolizumab cannot be ruled out.
(b) (6)	Grade 4 myocarditis (AESI), Grade 3 ventricular arrhythmia, Grade 4 hyperglycemia, Grade 4 small intestinal hemorrhage	A 67-year-old male with Stage IIIB MCC developed a ventricular arrhythmia and myocarditis on day 26 of the study. The patient presented with pallor, fatigue and weakness to a scheduled study visit, and had increased liver enzymes, CPK, and an ejection fraction of <25%. The patient was treated with corticosteroids in addition to antibiotics and anticoagulation; the patient developed hyperglycemia. Following an intensive care unit stay marked by intubation and multiple resuscitations, the patient developed a small intestinal hemorrhage. Ultimately the patient was discharged on day 53 following initiation of treatment. In the opinion of the investigator, the SAEs of myocarditis, ventricular arrhythmia, hyperglycemia, and small intestinal hemorrhage were related to study medication. In the opinion of the Sponsor, myocarditis was an AEOSI.

Dropouts and/or Discontinuations Due to Adverse Effects

Nine patients (18%) discontinued pembrolizumab due to adverse events. The most common reason for discontinuation was pancreatitis in 2 patients, followed by one event each of the following: adrenal insufficiency, blood alkaline phosphatase increased, colitis, myocarditis, paraneoplastic syndrome, pneumonitis, polyarthritis, and tuberculosis. Adverse event narratives for patients (b) (6) and (b) (6) are included in the above table of SAE narratives.

Table 7: Discontinuations Due to Adverse Events, Study CITN-09/KEYNOTE-017

(b) (6)	Grade 2	A 76-year-old female with Stage IV MCC and a history of osteoarthritis and gout developed Grade 2 polyarthritis on day 631 after initiating treatment with pembrolizumab. The patient had received 28 doses of pembrolizumab prior to the event, and was treated with prednisone. In the opinion of the investigator, the event of polyarthritis was related to study medication.
(b) (6)	Grade 2 Pancreatitis (AEOSI)	A 61-year-old with Stage IV MCC developed Grade 2 pancreatitis on day 274 after beginning therapy with pembrolizumab. After receiving 13 doses of pembrolizumab, the patient was found to have elevated lipase after presenting with abdominal pain. Pembrolizumab was discontinued. The investigator assessed the

		event as related to the investigational product. In the opinion of the Sponsor, myocarditis was an AEOSI.
(b) (6)	Grade 3 paraneoplastic syndrome	A 72-year-old female with Stage IV MCC developed Grade 3 paraneoplastic syndrome on day 409 after beginning therapy with pembrolizumab. The patient developed progressive double vision and downbeat nystagmus; a serum paraneoplastic panel was positive for anti-ZIC4 antibodies. The patient was treated with corticosteroid and subsequently plasmapheresis, and pembrolizumab was discontinued. The investigator assessed that the SAE of paraneoplastic syndrome was not related to study medication.
(b) (6)	Grade 2 adrenal insufficiency (AEOSI)	A 71-year-old male with Stage IV MCC developed Grade 2 adrenal insufficiency on day 330 after beginning therapy with pembrolizumab. Details are not provided, but the patient started treatment with hydrocortisone, and pembrolizumab was discontinued. In the opinion of the investigator, the AE of adrenal insufficiency was related to study medication. In the opinion of the Sponsor, adrenal insufficiency was an AEOSI.

Significant Adverse Events

Fourteen patients (28%) experienced 21 adverse events of special interest (AEOSIs) on Study CITN-09/KEYNOTE-017. The preferred terms included in the definition of AEOSI were provided in the Applicant's submission, and included standard terms describing potential immune-mediated events as well as infusion-related reactions. AEOSIs included events of adrenal insufficiency, colitis, hyperthyroidism, hypothyroidism, infusion reactions, myocarditis, pancreatitis, pneumonitis, severe skin reactions, and thyroiditis. The most commonly reported AEOSI were hypothyroidism (n=3, 6%) and pneumonitis (n=3, 6%). Pancreatitis and rash maculopapular were each reported in 2 (4%) of patients. Of the 5 participants with Grade 3 or 4 AEOSI, 1 (2.0%) participant experienced Grade 4 myocarditis, 1 (2.0%) participant experienced Grade 3 colitis and pancreatitis, 1 (2.0%) participant experienced Grade 3 pneumonitis, and 2 (4.0%) participants experienced Grade 3 rash maculo-papular. All of these AEOSI resolved. Five patients had an AEOSI that was not resolved as of the database cutoff date (hypothyroidism in 3 patients; adrenal insufficiency, hyperthyroidism, and pneumonitis each in 1 patients). There were no Grade 5 AEOSI. Seven events in 6 patients resulted in discontinuation of the study medication.

The frequency of AEOSI in CITN-09/KEYNOTE-017 was similar to the RSD (594 patients or 21.2% in the RSD). The incidence of particular AEOSI were similar to those observed in the RSD, with less than 2% difference in incidence, with the exception of myocarditis (1 case [2%] vs. 0 cases

[0%] in the RSD), pneumonitis (3 cases [6%] vs. 94 cases [3.4%] in the RSD), pancreatitis (2 cases [4%] vs. 9 cases [0.3%] in the RSD) and severe skin reactions (2 cases [4%] vs. 38 cases [1.4%] in the RSD). The discrepancy in the percentages of these events may be due to the extremely small numbers of events given the limited population in Study CITN-09/KEYNOTE-017. In addition, patients in Study CITN-09/KEYNOTE-017 received a longer median duration of treatment than those in the RSD.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent adverse events (TEAEs) which occurred in > 20% of patients included fatigue (58%), anemia (32%), constipation (28%), hyperglycemia (26%), upper respiratory tract infection (26%), decreased appetite (22%), alanine aminotransferase increased (22%), rash and pruritis (22% each).

TEAEs which occurred in Study CITN-09/KEYNOTE-017 with greater frequency (by >10%) than the RSD included anemia (32% vs. 14%), fatigue (58% vs. 39%), upper respiratory tract infection (26% vs. 7%), alanine aminotransferase increased (22% vs. 6%) and aspartate aminotransferase increased (18% vs. 6%), hyperglycemia (26% vs. 5%), hypocalcemia (14% vs. 2%), hyponatremia (20% vs. 5%), and rash maculo-papular (16% vs. 4%).

Reviewer note: Among non-laboratory-based AEs, fatigue, maculopapular rash and upper respiratory tract infection are notable for being reported with higher incidence in Study CITN-09; some of these differences, such as fatigue and URI, may be related to the older patient population in this study.

Review of laboratory analysis data is better characterized by the review of the laboratory dataset (see Table 9: Laboratory Abnormalities, Study CITN-09/KEYNOTE-017 vs. Reference Safety Database*). There were differences in the incidence of hyperglycemia and aspartate aminotransferase between Study CITN-09/KEYNOTE-017 and the RSD, but these differences are smaller when evaluated by laboratory-based CTCAE grade rather than the data reported as an adverse event. Thus, the larger differences observed in these values likely largely represents differences in reporting of laboratory AEs.*

Table 8: Treatment-Emergent Adverse Events in ≥ 5% of Patients, Study CITN-09/KEYNOTE-017 and Reference Safety Database

	Study CITN-09/KEYNOTE-017 (N=50)				Reference Safety Database (N=2799)			
Preferred Term	Any Grade	Any Grade %	Grades 3-5	Grade 3-5 %	Any Grade	Any Grades %	Grades 3-5 2	Grades 3-5 %
Blood and lymphatic system disorders								
Anemia	16	32%	3	6%	399	14%	116	4%
Leukocytosis	3	6%	0	0%	30	1%	9	0%
Endocrine disorders								
Hypothyroidism	3	6%	0	0%	199	7%	3	0%
Gastrointestinal disorders								
Abdominal discomfort	3	6%	0	0%	49	2%	0	0%
Abdominal pain	6	12%	0	0%	311	11%	37	1%
Constipation	14	28%	0	0%	503	18%	13	0%
Diarrhea	11	22%	0	0%	679	24%	48	2%
Gastroesophageal reflux disease	5	10%	0	0%	75	3%	0	0%
Nausea	10	20%	0	0%	720	26%	37	1%
Vomiting	5	10%	0	0%	406	15%	37	1%
General disorders and administration site conditions								
Chills	4	8%	0	0%	156	6%	0	0%
Disease progression	8	16%	8	16%	3	0%	2	0%
Fatigue	29	58%	2	4%	1085	39%	74	3%
Edema peripheral	4	8%	0	0%	283	10%	12	0%
Peripheral swelling	4	8%	0	0%	46	2%	1	0%
Pyrexia	9	18%	0	0%	351	13%	11	0%
Infections and infestations								
Cellulitis	3	6%	0	0%	40	1%	18	1%
Herpes zoster	4	8%	0	0%	19	1%	1	0%
Nasopharyngitis	3	6%	0	0%	184	7%	0	0%
Oral candidiasis	3	6%	0	0%	38	1%	1	0%
Sinusitis	3	6%	0	0%	68	2%	3	0%
Upper respiratory tract infection	13	26%	0	0%	188	7%	2	0%

Urinary tract infection	6	12%	1	2%	187	7%	19	1%
Injury, poisoning and procedural complications								
Contusion	3	6%	0	0%	32	1%	0	0%
Fall	3	6%	0	0%	62	2%	2	0%
Investigations								
Alanine aminotransferase increased	11	22%	3	6%	160	6%	25	1%
Aspartate aminotransferase increased	9	18%	5	10%	167	6%	26	1%
Blood alkaline phosphatase increased	7	14%	2	4%	105	4%	12	0%
Blood bilirubin increased	4	8%	1	2%	58	2%	15	1%
Blood creatinine increased	6	12%	0	0%	94	3%	2	0%
Lymphocyte count decreased	7	14%	1	2%	54	2%	16	1%
Weight decreased	5	10%	0	0%	196	7%	7	0%
White blood cell count decreased	5	10%	0	0%	36	1%	7	0%
Metabolism and nutrition disorders								
Decreased appetite	11	22%	1	2%	577	21%	21	1%
Dehydration	5	10%	4	8%	113	4%	31	1%
Hyperglycemia	13	26%	7	14%	132	5%	24	1%
Hyperkalemia	4	8%	0	0%	58	2%	5	0%
Hypoalbuminemia	4	8%	0	0%	105	4%	16	1%
Hypocalcemia	7	14%	0	0%	52	2%	2	0%
Hypokalemia	5	10%	0	0%	132	5%	23	1%
Hyponatremia	10	20%	4	8%	152	5%	59	2%
Musculoskeletal and connective tissue disorders								
Arthralgia	7	14%	0	0%	501	18%	15	1%
Back pain	4	8%	0	0%	345	12%	35	1%
Muscular weakness	6	12%	1	2%	100	4%	13	0%

Musculoskeletal pain	3	6%	0	0%	197	7%	11	0%
Myalgia	6	12%	0	0%	252	9%	11	0%
Pain in extremity	3	6%	0	0%	242	9%	15	1%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Squamous cell carcinoma	3	6%	0	0%	23	1%	8	0%
Nervous system disorders								
Dizziness	8	16%	0	0%	243	9%	8	0%
Dysgeusia	4	8%	0	0%	77	3%	0	0%
Headache	10	20%	0	0%	430	15%	14	1%
Hypoesthesia	3	6%	0	0%	50	2%	0	0%
Paresthesia	3	6%	0	0%	92	3%	3	0%
Sciatica	3	6%	0	0%	33	1%	2	0%
Psychiatric disorders								
Sleep disorder	4	8%	0	0%	15	1%	0	0%
Renal and urinary disorders								
Hematuria	3	6%	0	0%	42	2%	0	0%
Reproductive system and breast disorders								
Breast pain	3	6%	0	0%	15	1%	0	0%
Respiratory, thoracic and mediastinal disorders								
Cough	11	22%	0	0%	575	21%	3	0%
Dysphonia	4	8%	0	0%	49	2%	2	0%
Dyspnea	9	18%	1	2%	465	17%	69	2%
Nasal congestion	8	16%	0	0%	83	3%	0	0%
Oropharyngeal pain	3	6%	0	0%	83	3%	0	0%
Pneumonitis	3	6%	1	2%	62	2%	23	1%
Skin and subcutaneous tissue disorders								
Actinic keratosis	3	6%	0	0%	21	1%	0	0%
Pruritus	11	22%	0	0%	598	21%	7	0%
Rash	11	22%	0	0%	486	17%	12	0%
Rash maculo-papular	8	16%	2	4%	102	4%	8	0%
Vascular disorders								

Embolism	4	8%	4	8%	17	1%	8	0%
Hematoma	3	6%	2	4%	15	1%	2	0%
Hot flush	5	10%	0	0%	50	2%	0	0%
Hypertension	6	12%	3	6%	97	3%	25	1%
Hypotension	5	10%	1	2%	62	2%	11	0%

Laboratory Findings

Routine hematology and core chemistry laboratory assessments were performed within 28 days of enrollment and every three weeks prior to pembrolizumab administrations. Free thyroxine (free T4) and thyroid stimulating hormone (TSH) were collected at screening and every 6 cycles and as medically indicated.

The Applicant provided an analysis of common laboratory abnormalities occurring in Study CITN-09/KEYNOTE-017 and the RSD considering on-treatment worsening. This analysis reports incidence rates based on a denominator that includes all patients who had non-missing baseline and on-treatment values and only includes patients who experienced a laboratory abnormality that was worse than their baseline abnormality (if present). Therefore, grade 1 anemia events, for example, would not be counted if the patient had a baseline grade 1 anemia at study entry. Overall, increases in laboratory values from baseline observed in Study CITN-09/KEYNOTE-017 were typically consistent with the incidence observed in the RSD. The incidence of Grade 3 – 4 elevated AST was higher in Study CITN-09 compared to the RSD (10.6% vs. 2.0%), but Grade 3 – 4 elevations in ALT and total bilirubin were not observed at significantly increased frequency. Three of five events of Grade 3 – 4 AST increase occurred in patients with liver metastases, and two of these had elevated liver enzymes at baseline. One patient had elevated liver enzymes attributed to anti-tuberculous medications. Four of five events of Grade 3 – 4 AST increase in Study CITN-009 recovered; the remaining case was a patient with Grade 3 AST increased who had progressive liver metastases.

Reviewer note: The majority of cases of AST elevation in Study CITN-09 were confounded by baseline liver dysfunction, hepatic metastases, or concomitant hepatotoxic medications. The increased incidence of increased AST observed in this study is thus unlikely to represent an increased risk of hepatic injury related to pembrolizumab in this patient population.

The incidence of Grade 3 – 4 hyperglycemia was also greater in Study CITN-09 compared to the RSD (18.8% vs. 4.4%). All patients who experienced Grade 3 – 4 hyperglycemia on Study CITN-09 had baseline type 2 diabetes mellitus (n=8) or impaired glucose tolerance (n=1). A comparison of on-treatment worsening of laboratory values, adapted from the submission, is provided in Table 9 below.

Table 9: Laboratory Abnormalities, Study CITN-09/KEYNOTE-017 vs. Reference Safety Database

Laboratory Test	CITN-09/KEYNOTE-017 (N=50*)		Reference Safety Database (N=2799*)	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Chemistry				
Increased serum creatinine	10 (23)	0 (0.0)	417 (16.0)	19 (0.7)
Hyperglycemia	30 (62.5)	9 (18.8)	1237 (49.0)	111 (4.4)
Increased amylase	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Increased alanine aminotransferase	17 (34.7)	2 (4.1)	617 (23.8)	58 (2.2)
Increased aspartate aminotransferase	12 (25.5)	5(10.6)	709 (27.4)	52 (2.0)
Increased alkaline phosphatase	8 (16.3)	2 (4.2)	904 (35.1)	37 (1.4)
Increased bilirubin	8 (16.3)	0 (0.0)	239 (9.2)	41 (1.6)
Hematology				
Anemia	27 (55.1)	3 (6.1)	1112 (42.4)	117 (4.5)
Leukopenia	17 (34.7)	2 (4.1)	317 (12.1)	11 (0.4)
Neutropenia	5 (11.1)	2 (4.4)	152 (6.7)	28 (1.2)
Thrombocytopenia	10 (20.4)	1 (2.0)	306 (11.7)	36 (1.4)

Source: Table 5.3.4.3.3-mccl: 30, ISS
*Note: Percentages provided use the denominator of patients with post-baseline assessments

Vital Signs

Vital signs were assessed and recorded at baseline and every three weeks in clinic on the day of the pembrolizumab infusion. Vital sign changes during an infusion reaction were captured as part of the infusion reaction AE. The dataset was analyzed for significant vital sign derangements, including patients who experienced an increase in heart rate of more than 40 BPM, a systolic blood pressure of 160 mm Hg or higher with an increase of at least 20 mm Hg from baseline, or a respiratory rate > 20 breaths per minute during the treatment phase. Seven patients had a systolic blood pressure of 160 mm Hg or higher with an increase of at least 20 mm Hg from baseline and did not have an adverse event of hypertension recorded. Instances of significant tachypnea and tachycardia as defined above were not associated with any physical exam findings or coincide with any reported adverse events. Fever was not commonly observed during vital sign evaluations (n=2) during study visit 6 and study visit 15; the timing relative to infusion is not provided in the advs.xpt dataset. The applicant provided tables demonstrating

the mean change and standard deviation compared to baseline in vital sign parameters over time, and no significant trends were observed.

One patient demonstrated a Grade 2 infusion reaction on day 71 of the study; the outcome is reported as resolved. The patient did not receive further study treatments, and the reason for discontinuation is listed as death due to progressive disease.

Electrocardiograms (ECGs)

In Study CITN-09/KEYNOTE-017, ECGs were obtained at baseline, within 30 minutes of the end of infusion on day 1 of cycles 1 and 8, and at the end of treatment. Adverse events related to arrhythmias or abnormal ECGs included tachycardia (n=1) and the following adverse events in a patient who experienced myocarditis: left bundle branch block, ventricular arrhythmia, atrial fibrillation. The latter patient also experienced cardiac failure acute and acute myocardial infarction; all cardiac AEs for this patient were assessed as related to study medication. There were no other arrhythmias or abnormal ECG findings attributed to treatment with pembrolizumab.

QT

A QT study was not submitted as part of this supplemental application. As per the clinical and clinical pharmacology reviews of the original BLA, no dedicated QTc studies were conducted, and no large change (i.e., >20 ms) in the QTc interval was detected when pembrolizumab was administered up to 10 mg/kg Q3 weeks.

Immunogenicity

The prevalence of anti-pembrolizumab antibodies was not assessed in Study CITN-09/KEYNOTE-017. Therefore, an analysis of immunogenicity was not provided in the supplemental BLA as part of the CSR or ISS. The following is an excerpt from the FDA Clinical Pharmacology BLA review of the original BLA:

> Immunogenicity data included 2063 samples from 480 patients in study P001 (Parts A, B, C and D) as of the data cut-off date December 31, 2013, among which 449 patients with at least one post-dose sample were defined as evaluable patients. A bridging electrochemiluminescent (ECL) assay was developed for the detection of APA in human serum using a typical 3-tiered assay approach. In the 153 patients treated with dose of 2 mg/kg Q3W, 97 of these patients had a concentration of pembrolizumab in the last post dose sample below the drug tolerance level of the anti-product antibody assay. None of these 97 patients tested positive for treatment emergent anti-pembrolizumab antibodies in an ECL based assay. One patient had a pre-treatment sample tested positive for anti-pembrolizumab antibodies, then the post dose samples were tested negative. Overall, 129 of 449 patients, who treated with doses of 1 to 10 mg/kg, Q2W or Q3W, had a concentration of pembrolizumab in the last post sample below the drug

tolerance. One patient given 10 mg/kg, Q3W had a post-dose sample that tested positive for treatment emergent anti-pembrolizumab antibodies. This patient did not develop any clinical hypersensitivity events such as anaphylaxis, urticaria, angioedema or injection site reactions.

Reviewer note: There is no apparent reason why immunogenicity would be markedly different in this patient population compared to other populations in which the use of pembrolizumab is approved, such as melanoma.

8.2.5. Analysis of Submission-Specific Safety Issues

Immune-mediated Adverse Reactions

Adverse Events of Special Interest (AEOSI) are discussed in section 8.3.4 under Significant Adverse Events.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Ten patients (20%) were less than 65 years of age, and 40 patients (80%) were 65 years of age or older. There were differences in the incidence of adverse events according to age, but given the small numbers of patients in each group this is likely not significant.

Table 10: Adverse events in CITN-09/KEYNOTE-017 by Age group

Adverse Event	Age < 65 (n=10)	Age < 65 %	Age ≥ 65 (n=40)	Age ≥ 65 %
Gastrointestinal disorders				
Constipation	4	40%	10	25%
Diarrhea	2	20%	9	23%
Nausea	3	30%	7	18%
Abdominal pain	2	20%	4	10%
Gastroesophageal reflux disease	0	0%	5	13%
Vomiting	1	10%	4	10%

Metabolism and nutrition disorders				
Hyperglycemia	3	30%	10	25%
Decreased appetite	1	10%	10	25%
Hyponatremia	2	20%	8	20%
Hypocalcemia	1	10%	6	15%
Hypoalbuminemia	0	0%	4	10%
General disorders and administration site conditions				
Fatigue	5	50%	24	60%
Pyrexia	5	50%	4	10%
Disease progression	3	30%	5	13%
Chills	0	0%	4	10%
Investigations				
Alanine aminotransferase increased	2	20%	9	23%
Aspartate aminotransferase increased	2	20%	7	18%
Blood alkaline phosphatase increased	1	10%	6	15%
Lymphocyte count decreased	2	20%	5	13%
Blood creatinine increased	1	10%	5	13%
Weight decreased	1	10%	4	10%
White blood cell count decreased	1	10%	4	10%
Blood bilirubin increased	0	0%	4	10%
Infections and infestations				
Upper respiratory tract infection	3	30%	10	25%
Urinary tract infection	2	20%	4	10%
Herpes zoster	0	0%	4	10%
Skin and subcutaneous tissue disorders				
Pruritus	1	10%	10	25%

Rash	2	20%	9	23%
Rash maculo-papular	2	20%	6	15%
Respiratory, thoracic and mediastinal disorders				
Cough	4	40%	7	18%
Dyspnea	3	30%	6	15%
Nasal congestion	2	20%	6	15%
Dysphonia	0	0%	4	10%
Nervous system disorders				
Headache	3	30%	7	18%
Dizziness	1	10%	7	18%
Dysgeusia	0	0%	4	10%
Musculoskeletal and connective tissue disorders				
Arthralgia	1	10%	6	15%
Muscular weakness	2	20%	4	10%
Myalgia	1	10%	5	13%
Blood and lymphatic system disorders				
Anemia	3	30%	13	33%
Vascular disorders				
Hypertension	1	10%	5	13%
Hypotension	1	10%	4	10%

Thirty-four patients (68%) were male, and 16 were female (32%). All patients experienced at least one adverse event. The majority of patients experienced at least one Grade 3 – 5 event regardless of gender, including 62.5% (n=10) of females and 53% (n=18) of males. The incidence of adverse events by race was significantly limited by the small numbers of non-white patients enrolled. Forty-five patients (90%) were white, one patient (2%) was Asian, and 4 patients' (8%) race was unknown. Three patients with unknown race (75%) experienced at least one Grade 3 – 5 event; the only Asian patient experienced a Grade 3 event, and 24 (53%) white patients experienced at least one Grade 3 – 5 event. For all subgroups, these analyses are exploratory, and the small number of patients included in each subgroup precludes any meaningful

conclusions about differences in safety between these groups.

8.2.8. Specific Safety Studies/Clinical Trials

None.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct carcinogenicity studies.

Human Reproduction and Pregnancy

Fertility studies have not been conducted with pembrolizumab.

Pediatrics and Assessment of Effects on Growth

CITN-09/KEYNOTE-017 did not include pediatric patients. The proposed indication includes pediatric patients based on extrapolation of pharmacokinetics and target exposures from the adult to the pediatric population, as established in KEYNOTE-051.

KEYNOTE-051 enrolled patients between 6 months and < 18 years of age with locally advanced or metastatic solid tumors or lymphoma who had failed prior therapy, had no available standard therapy, or were not eligible for standard therapy. One-hundred forty-four patients were treated for a median of 44 days (range, 1-646 days) and had a median follow-up of 5.8 months (range 0-33.3 months). Overall, 79 (54.9%) of pediatric participants experienced drug-related AEs and 10 (6.9%) experienced Grade 3 to 5 drug-related AEs. Two patients (1.4%) discontinued pembrolizumab due to a drug-related AE (one due to increased AST, and one due to treatment-related pulmonary edema). Potentially immune-mediated AEs were reported in 26 patients (18.1%), comparable to that reported in the established safety profile of pembrolizumab (21.2%). Immunogenicity was observed in 1.9% of pediatric patients, similar to adult patients (1.9%).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No studies have been conducted to evaluate the abuse potential with pembrolizumab. There is no evidence that suggests a risk for dependence on pembrolizumab. No cases of withdrawal symptoms were reported during human clinical trials.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Pembrolizumab is being approved under the regulations in section 601 subpart E (accelerated approval); therefore, confirmatory trial(s) are required to verify and describe the clinical benefit

of pembrolizumab in the proposed population, i.e., patients with metastatic Merkel cell carcinoma.

Expectations on Safety in the Postmarket Setting

Pembrolizumab is approved in multiple indications, and the safety profile is well characterized. This reviewer believes that the pooled safety database is adequate to evaluate safety concerns associated with pembrolizumab. A clinical post-marketing requirement to confirm the efficacy of pembrolizumab in patients with Merkel cell carcinoma is described in Section 13: Postmarketing Requirements and Commitment.

8.2.11. Integrated Assessment of Safety

The evaluation of the safety of pembrolizumab in patients with recurrent locally advanced or metastatic MCC was primarily based on Study CITN-09/KEYNOTE-017, an open-label, multicenter, single arm trial in 50 patients who had not received prior systemic therapy for their advanced disease. A pooled population of patients from Study CITN-009/KEYNOTE-017 and patients from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010 (n=2799) with various advanced solid tumors who received pembrolizumab at a dose of 10 mg/kg every two – three weeks was also analyzed to support the safety review. The size of the pooled safety database was considered adequate to characterize the safety profile of pembrolizumab.

In Study CITN-09/KEYNOTE-017, there were no fatal AEs that were clearly pembrolizumab-related (see Section 8.2.4). Forty-four percent of patients in Study CITN-09/KEYNOTE-017 experienced at least one SAE, comparable to the RSD (37.2%). Fourteen patients (28%) experienced 21 adverse events of special interest (AEOSIs), which included immune-mediated events as well as infusion-related reactions on Study CITN-09/KEYNOTE-017. The frequency of AEOSI in CITN-09/KEYNOTE-017 was similar to the RSD (594 patients or 21.2% in the RSD). Nine patients (18%) discontinued pembrolizumab due to adverse events.

Serious risks of pembrolizumab are similar to those of other monoclonal antibodies acting in the PD -1/PD-L1 pathway, including the risk of serious and fatal immune-related adverse reactions (imARs). There were no fatal imARs during Study CITN-09/KEYNOTE-017, 8 (0.3%) fatal imARs were observed in the pooled safety database.

Overall, the safety of pembrolizumab is consistent with the expected toxicity profile of immunologically-mediated anticancer therapies. The safety data from Study CITN-09/KEYNOTE-017 and the larger pooled database do not change the favorable benefit-risk assessment for pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic MCC.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

There are no outstanding statistical issues with the study design, statistical analysis plan, or efficacy results of Study CITN-009. The proposed indication of pembrolizumab as the first systemic intervention for patients with locally advanced or metastatic Merkel cell carcinoma (MCC) is mainly supported by this non-randomized study in 50 patients. No statistical comparison was conducted in Study CITN-009 and therefore no statistical inference can be drawn from the study.

8.4. Conclusions and Recommendations

Patients with unresectable locally advanced or metastatic MCC represent a population with a serious and life-threatening rare disease. Although MCC is known to be a chemosensitive disease, off-label use of cytotoxic chemotherapy does not provide durable responses and has not demonstrated improvement in overall survival. One other immunotherapeutic, avelumab, has been granted accelerated approval for the treatment of patients ages 12 years and older with metastatic MCC.

Reviewer note: This reviewer recommends approval in pediatric patients, rather than pediatric patients ages 12 and older. As discussed in Section 10, there is pediatric experience with pembrolizumab including a recommended pediatric dose; in contrast, there was not adequate experience with avelumab in pediatric patients less than 12 years of age at the time of the approval. The approval in pediatric patients is based on extrapolation of efficacy data given the expected similarity in the disease process in pediatric patients; further, a study in pediatric patients with MCC would be highly impracticable given the extreme rarity of this disease in the pediatric population.

The clinical benefit of pembrolizumab for patients with unresectable locally advanced or metastatic MCC is based on the experience with 50 patients treated in Study CITN-09/KEYNOTE-017. Efficacy analyses demonstrated a confirmed, centrally reviewed ORR per RECIST 1.1 of 56.0% (95% CI: 41.3, 70.0), including 12 patients with CR (24%, 95% CI: 31.1, 38.2) and 16 patients with a PR (32.0%, 95% CI: 19.5, 46.7). The median DOR was not reached among the responders with confirmed CR or PR, with a range of 5.9 – 34.5+ months. Twenty-seven of 28 confirmed responders (96.4%) demonstrated responses of 6 months or greater, and 15 responders (53.6%) demonstrated responses of 12 months or greater.

Reviewer note: The indication proposed for approval includes patients with locally advanced disease who did not previously receive treatment; this indication reflects the population of study KEYNOTE-017, which included patients with Stage IIIB disease.

Serious risks of pembrolizumab are similar to those of other monoclonal antibodies acting in the PD -1/PD-L1 pathway, including the risk of serious and fatal immune-related adverse reactions (imARs). The safety of pembrolizumab in patients with MCC in Study CITN-09 was compared to the safety in a large pooled population of patients (n=2799). The safety profile, evaluated by incidences of adverse events, serious adverse events, adverse events of special

interest, and laboratory evaluations indicated that the safety of pembrolizumab in patients with MCC is comparable to the previously established safety profile. Twenty-eight percent of patients enrolled on Study CITN-09 experienced AEOSI, which was similar to the incidence observed in the RSD (594 patients or 21.2% in the RSD). Specific differences in the incidence of certain adverse events in the primary safety population compared to the RSD are discussed in detail in Section 8.2 and, in the opinion of this reviewer, do not reflect a significant difference in the safety of pembrolizumab in this patient population.

The reviewers recommend accelerated approval under Subpart E (21CFR601.41) for pembrolizumab for the treatment of (b) (6) at a dose of 200 mg IV every 2 weeks. Accelerated approval is recommended given the uncertainty of the relation of ORR and DOR to ultimate outcomes of clinical benefit including overall survival data. Confirmatory evidence of clinical benefit will be based on a demonstration of a clinically meaningful improvement in overall survival, as well as confirmation of overall response rate and duration of response, in patients with unresectable locally advanced or metastatic MCC. Depending on the demonstrated effect size, these data may be sufficient to support granting regular approval for this indication.

Susan Jin	Pallavi Mishra-Kalyani
Primary Statistical Reviewer	Statistical Team Leader
Diana Bradford	Suzanne Demko
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

10 Pediatrics

CITN-09/KEYNOTE-017 did not include pediatric patients. The proposed indication includes pediatric patients based on extrapolation of pharmacokinetics and target exposures from the adult to the pediatric population, as established in KEYNOTE-051.

KEYNOTE-051 enrolled patients between 6 months and < 18 years of age with locally advanced or metastatic solid tumors or lymphoma who had failed prior therapy, had no available standard therapy, or were not eligible for standard therapy. One-hundred forty-four patients were treated for a median of 44 days (range, 1-646 days) and had a median follow-up of 5.8 months (range 0-33.3 months). Overall, 79 (54.9%) of pediatric participants experienced drug-related AEs and 10 (6.9%) experienced Grade 3 to 5 drug-related AEs. Two patients (1.4%) discontinued pembrolizumab due to a drug-related AE (one due to increased AST, and one due to treatment-related pulmonary edema). Potentially immune-mediated AEs were reported in 26 patients (18.1%), comparable to that reported in the established safety profile of pembrolizumab (21.2%). Immunogenicity was observed in 1.9% of pediatric patients, similar to adult patients (1.9%).

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
(b) (4) Indications and Usage	For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. 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 a confirmatory trial.	Same as proposed by applicant
(b) (4) Dosage and Administation	The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to 200 mg) every 3 weeks weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.	Same as proposed by applicant
6.1 Clinical Trials Experience	*MCC* Among the 50 patients with MCC enrolled in Study KEYNOTE-017, the median duration of exposure to KEYTRUDA was 6.6 months (range 1 day to 23.6 months). Patients with autoimmune disease or a medical condition	Same as proposed by applicant

	that required immunosuppression were Ineligible. Adverse reactions occurring in patients with MCC were similar to those occurring in patients with melanoma or NSCLC.	
8.4 Pediatric Use	(b) (4) [redacted]	(b) (4) [redacted]
(b) (4) Merkel Cell Carcinoma	The efficacy of KEYTRUDA was (b) (4) in Study KEYNOTE-017 (NCT02267603), a multicenter, non-randomized, open-label trial that enrolled 50 patients with recurrent locally advanced or metastatic MCC who had not received prior systemic therapy for their advanced disease. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 2 mg/kg every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, 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. Assessment of tumor status was performed at 13 weeks followed by every 9 weeks for the first year and every 12 weeks thereafter. The major efficacy outcome measures were	(b) (4) [redacted] Eighty-four percent of patients had prior surgery and 70% had prior radiation therapy.

	ORR and duration of response as assessed by BICR per RECIST 1.1. Among the 50 patients, the median age was 71 years (range: 46 to 91 years), with 80% age 65 or older; 68% male; 90% White; and ECOG performance score was 0 (48%) and 1 (52%). Fourteen percent had stage IIIB disease and 86% had stage IV. (b) (4) [redacted] 84% had prior surgery and 70% had prior radiation therapy. Efficacy results are summarized in Table (b) (4).	

Changes to the product label were made in Sections 1, 2, 6, 8, and 14 as noted above. Negotiations with the sponsor regarding the proposed changes are noted in the table.

12 Risk Evaluation and Mitigation Strategies (REMS)

Pembrolizumab has been previously approved for multiple indications. The product label includes listings of immune-related reactions that have been observed across the class as well as dose modifications and treatment for these events. The reviewer does not recommend a risk evaluation and mitigation strategy (REMS) be implemented for pembrolizumab. Recommendations for safe and effective use of pembrolizumab will be addressed in the product label.

13 Postmarketing Requirements and Commitment

The supplemental Application was approved with one Accelerated Approval requirement to confirm clinical benefit. The data provided in the Application, including a robust and durable response rate, are sufficient to support approval of pembrolizumab as a treatment for patients with recurrent locally advanced or metastatic Merkel cell carcinoma who have not received prior systemic chemotherapy for their advanced disease, however, data on overall survival is required to confirm clinical benefit. Given the demonstrated efficacy of pembrolizumab in many other indications, and the robust and durable response rate observed in previously untreated patients in this study, a modest number of patients were chosen to confirm clinical benefit.

The postmarketing requirement is as follows:

Accelerated Approval PMR under 21 CFR 601.41 Subpart E

Conduct and submit the results of a multicenter clinical trial confirming the clinical benefit of pembrolizumab in patients with locally advanced or metastatic Merkel cell carcinoma (MCC) who have not received prior systemic therapies for metastatic MCC. The trial will enroll at least 50 patients to be followed for a minimum of 12 months to establish the objective response rate and characterize the durability of response. Overall survival, which is a secondary endpoint, will be followed to maturity until at least 70% of patients have died, or for an additional two years beyond the primary data analysis cut-off, to characterize effects on survival.

The Applicant estimates that the analysis for overall survival will occur after 13 years. In order to provide timely information regarding overall survival in patients with MCC treated with pembrolizumab, an interim analysis will be requested after 5 years.

14 Associate Division Director (OB)

Kun He

15 Associate Division Director (Clinical)

Steven Lemery

16 Appendices

16.1. References

Becker, J, 2010, Merkel cell carcinoma, Ann Oncol, 21 Suppl 7:81-5

Schadendorf, D, C Lebbe, A Haussen, et al., 2017, Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs, Eur J Cancer, 71:53-69

Heath, M, N Jaimes, B Lemos, et al., 2008, Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features, J Am Acad Dermatol, 58(3):375-81

Hwang SJE, Carlos G, Wakade D, et al., 2016, Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: A single-institution cohort. Journal of the American Academy of Dermatology, 74 (3) 455 – 461.

Porceddu, S, M Beness and A Guminski, 2015, Nonmelanoma cutaneous head and neck cancer and Merkel cell carcinoma: current concepts, advances, and controversies, J Clin Oncol, 33(29):3338-45

NCCN Clinical Practice Guidelines in Oncology, Merkel Cell Carcinoma, Version 1.2019. Last updated 31 August 2018.

Cassler, N, D Merrill, C Bichakjian, and I Brownell, 2016, Merkel cell carcinoma therapeutic update, Curr. Treat. Options in Oncol, 17:36

Hughes. M, M Hardee, L Cornelius, et al., 2014, Merkel cell carcinoma: Epidemiology, target, and therapy, Curr Dermatol Rep, 3:46-53

Voog, E, P Biron, J Martin, et al., 1999, Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma, Cancer, 85(12):2589-95

Iyer, J, A Blom, R Doumani, et al., 2016, Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma, Cancer Medicine, 5(9):2294-301

16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): CITN-09/KEYNOTE-017

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 41		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 03		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant) The study was conducted by NCI, who required financial disclosure by investigators. NCI, per policy, could not transfer the investigator names to the Applicant, thus the Applicant conducted independent due diligence.
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 (see above)		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IDARA UDOH
12/19/2018

SUSAN S JIN
12/19/2018

PALLAVI S MISHRA-KALYANI
12/19/2018

KUN HE
12/19/2018

DIANA L BRADFORD
12/19/2018

SUZANNE G DEMKO
12/19/2018

ASHLEY F WARD on behalf of STEVEN J LEMERY
12/19/2018
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s045

PRODUCT QUALITY REVIEW(S)

Memorandum of Review:

Submission Tracking Number (STN):	BLA 125514/SUPPL-45, 47
Subject:	Efficacy supplements
Primary Reviewer:	Shadia Zaman, Ph.D., DBRR1/OBP/OPQ/CDER
Secondary Reviewer:	Jennifer Swisher, Ph.D., TL, DBRR1/OBP/OPQ/CDER
RBPM:	Andrew Shiber
Consults:	None
Applicant:	Merck Sharp & Dohme Corp
Product:	Pembrolizumab
Indication:	Multiple indications

- **Recommendation: I recommend approval of these supplements from a CMC perspective.**

- **Future Inspection Items: None**

- **Executive Summary:** This memo is for efficacy supplements 45 (for approval in patients with advanced merkel cell carcinoma) and 47 (for expansion of the NSCLC indication). A categorical exclusion from environmental assessment per 21 CFR 25.31(c) were claimed for these supplements and were found to be acceptable.

- **Review:**

Reviewer comments are in italicized text.

1.12.14 Environmental Analysis

A categorical exclusion from an environmental assessment was claimed under 21 CFR 25.31(c) because approval of the application does not significantly alter the concentration or distribution of the substance, its metabolites or degradation products in the environment. In addition, extraordinary circumstances as referred to in §21 CFR 25.21 do not apply.

Reviewer comment: *This is acceptable.*

Shadia Zaman

Digitally signed by Shadia Zaman
Date: 9/11/2018 12:53:20PM
GUID: 583dce940076eea0edb730e401622d6d

Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 9/11/2018 01:16:16PM
GUID: 508da6d7000262dc015dcdc5f6541612

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s045

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	December 4, 2018
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:	Ruth Lidoshore, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	KEYTRUDA (pembrolizumab) for injection, for intravenous use KEYTRUDA (pembrolizumab) injection, for intravenous use
Application Type/Number:	BLA 125514
Supplement Number:	S-045
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On June 29, 2018, Merck Sharp & Dohme Corp. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved Biologics License Application (BLA) 125514/S-045 for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection. With this supplement, the Applicant proposes to add a new indication for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on July 10, 2018, for DMPP and OPDP 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 KEYTRUDA (pembrolizumab) injection MG received on June 29, 2018, and received by DMPP and OPDP on November 27, 2018.
- Draft KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection Prescribing Information (PI) received on June 29, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 27, 2018.
- Approved KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection labeling dated November 9, 2018.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

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

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RUTH I LIDOSHORE
12/04/2018

NAZIA FATIMA
12/04/2018

BARBARA A FULLER
12/04/2018

LASHAWN M GRIFFITHS
12/06/2018