CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s034

Trade Name:	KEYTRUDA
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp & Dohme Corp.
Approval Date:	June 12, 2018
Indication:	Keytruda is a programmed death receptor-1 (PD-1)-blocking antibody indicated in: Melanoma • for the treatment of patients with unresectable or metastatic melanoma. Non-Small Cell Lung Cancer (NSCLC) • 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, and is: • 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. • in combination with pemetrexed and carboplatin, as first-

line treatment of patients with metastatic nonsquamous NSCLC.[1]

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.[2]

Classical Hodgkins 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.[2]

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.[2]
- 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 neodjuvant 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,[2] or
    - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[2]
- Limitations of Use: The safety and effectiveness of KEYTRUDA 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) $\geq$1] as determined by an

FDA-approved test, with disease progression on or after 2 or more prior lines ot therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[2]

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 $\geq$1) as determined by an FDA-approved test.[2]

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

2 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:

125514Orig1s034

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-034

SUPPLEMENT APPROVAL

Merck Sharp and Dohme Corp.
Attention: Lynn May Brown, PhD
Director, Global Regulatory Affairs
1 Merck Drive, P.O. Box 100
Whitehouse Station, NJ 08889

Dear Dr. Brown:

Please refer to your Supplemental Biologics License Application (sBLA), dated December 28, 2017, received December 28, 2017, submitted under section 351(a) of the Public Health Service Act for Keytruda®(pembrolizumab) powder for solution for infusion/solution for infusion, 50 mg and 100 mg.

This Prior Approval supplemental biologics application proposes the addition of a new indication for treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS $\geq$1) as determined by an FDA-approved test.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

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

CONTENT OF LABELING

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

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

The SPL will be accessible via publicly available labeling repositories.

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

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If the postmarketing trial fails to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated June 6, 2018. This requirement, along with required completion dates, is listed below.

PMR 3427-1 Conduct clinical trial KEYNOTE-826 (KN-826) in cervical cancer for Progression Free Survival (PFS)-Overall Survival (OS), entitled "A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy vs. Chemotherapy Plus Placebo for the First-line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer". Submit analyses and datasets with final report for PFS and OS.

Final Protocol Submission:	06/2018
Trial Completion:	pending final protocol
Final Report Submission:	pending final protocol

In addition, under 21 CFR 601.70 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.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable because pediatric cervical cancer is extremely rare.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC 3427-2	Submit the median Duration of Response (DOR) analyses and datasets with the final report of clinical trial Keynote 158 (Cohort E), entitled; "A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors"

The timetable you submitted on June 6, 2018, states that you will conduct this study according to the following schedule:

Trial Completion:	08/2019
Final Report Submission:	02/2020

Submit clinical protocols to your IND 126191 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Fatima Rizvi, Regulatory Project Manager, at (240) 402-7426.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

JULIA A BEAVER
06/12/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s034

LABELING

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

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

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

Indications and Usage (1)	06/2018
Dosage and Administration (2)	06/2018
Warnings and Precautions (5)	06/2018

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

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

Melanoma

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

Non-Small Cell Lung Cancer (NSCLC)

- 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)
- in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC.[1] (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.[2] (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.[2] (1.4)

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.[2] (1.5)
- 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. (1.5)

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,[2] or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[2] (1.6)
- Limitation of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. (1.6)

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.[2] (1.7)

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.[2] (1.8)

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

[2] 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: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.5)
- Urothelial Carcinoma: 200 mg every 3 weeks. (2.6)
- MSI-H Cancer: 200 mg every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for children. (2.7)
- Gastric Cancer: 200 mg every 3 weeks. (2.8)
- Cervical Cancer: 200 mg every 3 weeks. (2.9)

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):
  - Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  - Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or life-threatening hyperthyroidism.
  - Type 1 diabetes mellitus: Monitor for hyperglycemia. Withhold KEYTRUDA in cases of severe hyperglycemia.
- Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis. (5.5)
- 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 after 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. (5.9)
- 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)
- Embryofetal 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 fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. (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: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

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

1.2 Non-Small Cell Lung Cancer

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (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)]*.

KEYTRUDA, in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with metastatic nonsquamous NSCLC *[see Clinical Studies (14.2)]*. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.3 Head and Neck Cancer

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

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

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 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 *[see Clinical Studies (14.5)].*

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 (14.5)].*

1.6 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 (14.6)]*.

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.

1.7 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 (14.7)]*.

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.

1.8 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 (14.8)]*.

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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of NSCLC, 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 gastric cancer *[see Clinical Studies (14.7)]*. 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 (14.8)]*

Information on FDA-approved tests for the detection of PD-L1 expression in NSCLC, 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 pemetrexed and carboplatin.

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 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 (14.5)]*.

2.7 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 (14.6)].*

The recommended dose of KEYTRUDA in children 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.

2.8 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 (14.7)].*

2.9 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 (14.8)].*

2.10 Dose Modifications

Withhold KEYTRUDA for any of the following:

- Grade 2 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 2 or 3 colitis *[see Warnings and Precautions (5.2)]*
- Grade 3 or 4 endocrinopathies *[see Warnings and Precautions (5.4)]*
- Grade 4 hematological toxicity in cHL patients
- Grade 2 nephritis *[see Warnings and Precautions (5.5)]*
- Grade 3 severe skin reactions or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) *[see Warnings and Precautions (5.6)]*
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction *[see Warnings and Precautions (5.7)]*

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

Permanently discontinue KEYTRUDA for any of the following:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy, or hematological toxicity in patients with cHL)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity *[see Warnings and Precautions (5.1)]*
- Grade 3 or 4 nephritis *[see Warnings and Precautions (5.5)]*
- Grade 4 severe skin reactions or confirmed SJS or TEN *[see Warnings and Precautions (5.6)]*
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions *[see Warnings and Precautions (5.8)]*
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- Any severe or Grade 3 treatment-related adverse reaction that recurs *[see Warnings and Precautions (5.7)]*

2.11 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) 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 (2.10) 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 (2.10) 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 (2.10) 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 (2.10) 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 (2.10) 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 (2.10) 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 (2.10) 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.

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 (2.10).]*

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 (2.10) 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, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. 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 (2.10)]*.

5.9 Complications of Allogeneic HSCT after 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.

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 Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA *[see Use in Specific Populations (8.1, 8.3)].*

6 ADVERSE REACTIONS

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

- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)].*
- Immune-mediated colitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated hepatitis *[see Warnings and Precautions (5.3)]*.
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.4)]*.
- Immune-mediated nephritis and renal dysfunction *[see Warnings and Precautions (5.5)]*.
- 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 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 in a non-randomized, open-label, multi-cohort trial (KEYNOTE-012) which enrolled 192 patients with HNSCC and 241 cHL patients in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087). Across all studies, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among 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 five randomized, open-label, active-controlled clinical trials (KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-021, and KEYNOTE-045) in which KEYTRUDA was administered to 912 patients with melanoma, 741 patients with NSCLC, and 542 patients with urothelial carcinoma, and five non-randomized, open-label trials (KEYNOTE-012, KEYNOTE-087, KEYNOTE-052, KEYNOTE-059, and KEYNOTE-158) in which KEYTRUDA was administered to 192 patients with HNSCC, 210 patients with cHL, 370 patients with urothelial carcinoma, 259 patients with gastric cancer, and 98 patients with cervical cancer. 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 1 and Table 2 summarize the incidence of selected adverse reactions and laboratory abnormalities that occurred in patients receiving KEYTRUDA.

Table 1: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-006

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

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

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

Table 2: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-006

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

* Laboratory abnormalities occurring at same or higher incidence than in ipilimumab arm
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: KEYTRUDA n=429 and ipilimumab n=183; hypercholesterolemia: KEYTRUDA n=484 and ipilimumab n=205.
‡ Graded per NCI CTCAE v4.0

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

Ipilimumab-Refractory Melanoma

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

Table 3: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-002

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

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

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

Table 4: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-002

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

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

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

NSCLC

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

Table 5: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-010

	KEYTRUDA 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m^2 every 3 weeks n=309	
Adverse Reaction	**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 6: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving KEYTRUDA in KEYNOTE-010

	KEYTRUDA 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
Laboratory Test†	**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).

Previously Untreated Nonsquamous NSCLC, in Combination with Chemotherapy

The safety of KEYTRUDA in combination with pemetrexed and carboplatin was investigated in a randomized (1:1) open-label cohort in Study KEYNOTE-021. Patients with previously untreated, metastatic nonsquamous NSCLC received KEYTRUDA 200 mg with pemetrexed and carboplatin (n=59), or pemetrexed and carboplatin alone (n=62). 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 8 months (range: 1 day to 16 months). Sixty-eight percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA 200 mg for ≥6 months. The study population characteristics were: median age of 64 years (range: 37 to 80), 48% age 65 years or older, 39% male, 87% White and 8% Asian, 97% with metastatic disease, and 12% with brain metastases.

KEYTRUDA was discontinued for adverse reactions in 10% of patients. The most common adverse reaction resulting in discontinuation of KEYTRUDA (≥2%) was acute kidney injury (3.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 39% of patients; the most common (≥2%) were fatigue (8%), neutrophil count decreased (8%), anemia (5%), dyspnea (3.4%), and pneumonitis (3.4%).

Table 7 summarizes the adverse reactions that occurred in at least 20% of patients treated with KEYTRUDA. KEYNOTE-021 was not designed to demonstrate a statistically significant difference in adverse reaction rates for pembrolizumab plus chemotherapy, as compared to chemotherapy alone, for any specified adverse reaction listed in Table 7.

Table 7: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE-021

	KEYTRUDA Pemetrexed Carboplatin n=59		Pemetrexed Carboplatin n=62	
Adverse Reaction	**All Grades* (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	71	3.4	50	0
Peripheral edema	22	0	18	0
Gastrointestinal Disorders				
Nausea	68	1.7	56	0
Constipation	51	0	37	1.6
Vomiting	39	1.7	27	0
Diarrhea	37	1.7	23	1.6
Skin and Subcutaneous Tissue Disorders				
Rash†	42	1.7	21	1.6
Pruritus	24	0	4.8	0
Alopecia	20	0	3.2	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	39	3.4	21	0
Cough	24	0	18	0
Metabolism and Nutrition Disorders				
Decreased appetite	31	0	23	0
Nervous System Disorders				
Headache	31	0	16	1.6
Dizziness	24	0	16	0
Dysgeusia	20	0	11	0
Psychiatric Disorders				
Insomnia	24	0	15	0
Infections and Infestations				
Upper respiratory tract infection	20	0	3.2	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	15	0	24	1.6

* Graded per NCI CTCAE v4.0

† Includes rash, rash generalized, rash macular, rash maculo-papular, and rash pruritic.

Table 8: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients in KEYNOTE-021

	KEYTRUDA Pemetrexed Carboplatin		Pemetrexed Carboplatin	
Laboratory Test*	**All Grades† %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	74	9	61	5
Lymphocytes decreased	53	23	60	28
Aspartate aminotransferase increased	51	3.5	46	1.7
Hypertriglyceridemia	50	0	43	0
Alanine aminotransferase increased	40	3.5	32	1.7
Creatinine increased	34	3.4	19	1.7
Hyponatremia	33	5	35	3.5
Hypoalbuminemia	32	0	31	0
Hypocalcemia	30	5	19	1.7
Hypokalemia	29	5	22	1.7
Hypophosphatemia	29	5	24	11
Alkaline phosphatase increased	28	0	9	0
Hematology				
Hemoglobin decreased	83	17	84	19
Neutrophils decreased	47	14	43	8
Platelets decreased	24	9	36	10

* 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 carboplatin (range: 56 to 58 patients) and pemetrexed carboplatin (range: 55 to 61 patients).

† Graded per NCI CTCAE v4.0

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

Table 9: Adverse Reactions in ≥10% of Patients with cHL in KEYNOTE-087

	KEYTRUDA 200 mg every 3 weeks N=210	
Adverse Reaction	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), myelitis and myocarditis (0.5% each).

Table 10: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of cHL Patients Receiving KEYTRUDA in KEYNOTE-087

	KEYTRUDA 200 mg every 3 weeks	
Laboratory Test*	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).

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

Table 11: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

	KEYTRUDA 200 mg every 3 weeks N=370	
Adverse Reaction	**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		
Rashᵇ	21	0.5
Pruritis	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

ᵇ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneform, 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 (14.5)]*. 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 12 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA. Table 13 summarizes the incidence of laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 12: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

	KEYTRUDA 200 mg every 3 weeks n=266		Chemotherapy* n=255	
Adverse Reaction	**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				
Coughᵖ	15	0.4	9	0
Dyspneaß	14	1.9	12	1.2
Skin and Subcutaneous Tissue Disorders				
Pruritus	23	0	6	0.4
Rashà	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
ᵖ 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 13: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045

	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
Laboratory Test*	**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 14 summarizes the adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 14: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158

	KEYTRUDA 200 mg every 3 weeks N=98	
Adverse Reaction	**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 15 summarizes the laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 15: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with Cervical Cancer in KEYNOTE-158

	KEYTRUDA 200 mg every 3 weeks	
Laboratory Test*	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).

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 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.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to KEYTRUDA with the incidences of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development, but an assessment of the effects on reproduction was provided. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.11) 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 or MSI-H cancers is extrapolated from the results in the respective adult populations *[see Clinical Studies (14.4, 14.6)].*

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.

10 OVERDOSAGE

There is no information on overdosage with KEYTRUDA.

11 DESCRIPTION

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

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-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 safety and efficacy of KEYTRUDA were evaluated 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 10mg/kg every 3 weeks as an intravenous infusion until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg every 3 weeks as an intravenous infusion for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors [RECIST v1.1]). Additional efficacy outcome measures were overall response rate (ORR) and response duration.

A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study population characteristics were: median age of 62 years (range: 18 to 89 years), 60% male, 98% White, 66% had no prior systemic therapy for metastatic disease, 69% ECOG PS of 0, 80% had PD-L1 positive

melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay, 65% had M1c stage disease, 68% with normal LDH, 36% with reported BRAF mutation-positive melanoma, and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor.

The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab (Table 16 and Figure 1).

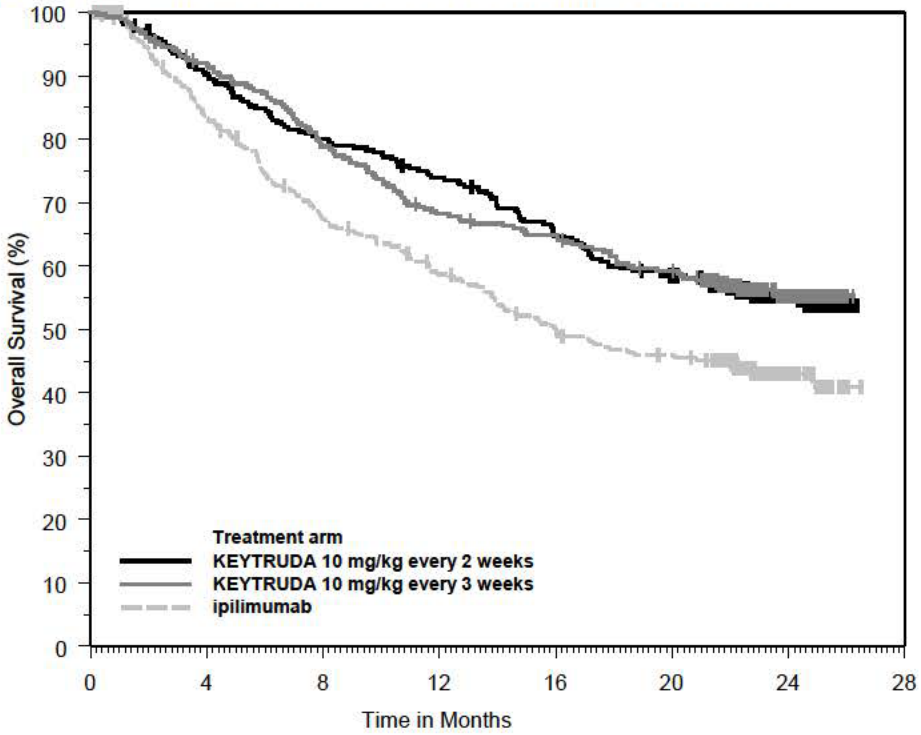
Table 16: Efficacy Results in KEYNOTE-006

	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 safety and efficacy of KEYTRUDA were evaluated 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 and overall survival (OS). Additional efficacy outcome measures were confirmed overall response rate (ORR) as assessed by BICR per RECIST v1.1 and duration of response.

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

The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm (Table 17). 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 17: Efficacy Results in KEYNOTE-002

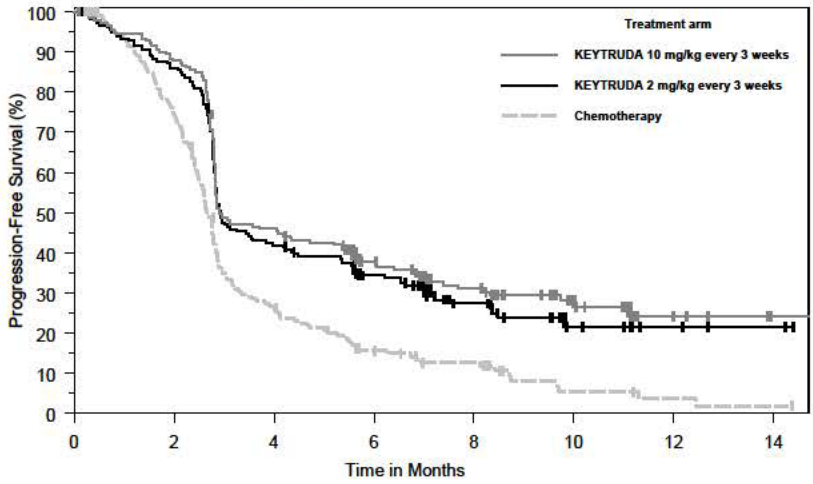
	KEYTRUDA 2 mg/kg every 3 weeks n=180	**KEYTRUDA 10 mg/kg every 3 weeks n=181**	**Chemotherapy n=179**
Progression-Free Survival			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (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 NSCLC as a single agent

Study KEYNOTE-024 (NCT02142738) was 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 1.1-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 1.1. Additional efficacy outcome measures were OS and ORR as assessed by the BICR according to RECIST 1.1.

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 18 summarizes key efficacy measures for KEYNOTE-024.

Table 18: Efficacy Results in KEYNOTE-024

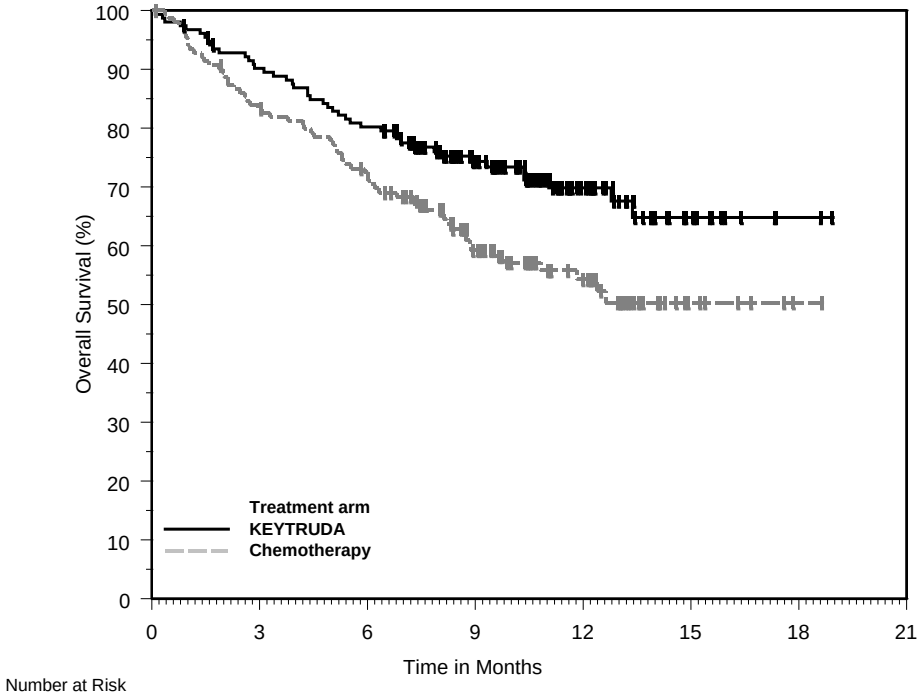
Endpoint	**KEYTRUDA 200 mg every 3 weeks n=154**	**Chemotherapy n=151**
PFS		
Number (%) of patients with event	73 (47%)	116 (77%)
Median in months (95% CI)	10.3 (6.7, NR)	6.0 (4.2, 6.2)
Hazard ratio* (95% CI)	0.50 (0.37, 0.68)	
p-Value (stratified log-rank)	<0.001	
OS		
Number (%) of patients with event	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 3: 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

First-line treatment of metastatic nonsquamous NSCLC in combination with pemetrexed and carboplatin
The efficacy of KEYTRUDA was investigated in patients enrolled in an open-label, multicenter, multi-cohort study, Study KEYNOTE-021 (NCT02039674); the efficacy data are limited to patients with metastatic nonsquamous NSCLC randomized within a single cohort (Cohort G1). The key eligibility criteria for this cohort were locally advanced or metastatic nonsquamous NSCLC, regardless of tumor PD-L1 expression status, and no prior systemic treatment 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 PD-L1 tumor expression (TPS <1% vs. TPS ≥1%). Patients were randomized (1:1) to one of the following treatment arms:

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

At the investigator's discretion, maintenance pemetrexed 500 mg/m^2 every 3 weeks was permitted in both treatment arms.

Treatment with KEYTRUDA continued until RECIST 1.1-defined progression of disease as determined by blinded independent central review (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 on chemotherapy 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 and every 9 weeks thereafter. The major efficacy outcome measure was objective response rate (ORR) as assessed by BICR using RECIST 1.1. Additional efficacy outcome measures were progression-free survival (PFS) as assessed by BICR using RECIST 1.1, duration of response, and overall survival (OS).

A total of 123 patients were randomized: 60 patients to the KEYTRUDA and chemotherapy arm and 63 to the chemotherapy arm. The study population characteristics were: median age of 64 years (range: 37 to 80); 48% age 65 or older; 39% male; 87% White and 8% Asian; ECOG performance status of 0 (41%) and 1 (56%); 97% had metastatic disease; and 12% had brain metastases. Thirty-six percent had tumor PD-L1 expression TPS <1%; no patients had sensitizing EGFR or ALK genomic aberrations. A total of 20 (32%) patients in the chemotherapy arm received KEYTRUDA at the time of disease progression and 12 (19%) additional patients received a checkpoint inhibitor as subsequent therapy.

In Cohort G1 of KEYNOTE-021, there was a statistically significant improvement in ORR in patients randomized to KEYTRUDA in combination with pemetrexed and carboplatin compared with pemetrexed and carboplatin alone (see Table 19).

Table 19: Efficacy Results in Cohort G1 of KEYNOTE-021

Endpoint	KEYTRUDA Pemetrexed Carboplatin n=60	Pemetrexed Carboplatin n=63
Overall Response Rate		
Overall response rate	55%	29%
(95% CI)	(42, 68)	(18, 41)
Complete response	0%	0%
Partial response	55%	29%
p-Value*	0.0032	
Duration of Response		
% with duration ≥ 6 months†	93%	81%
Range (months)	1.4+ to 13.0+	1.4+ to 15.2+
PFS		
Number of events (%)	23 (38%)	33 (52%)
Progressive disease	15 (25%)	27 (43%)
Death	8 (13%)	6 (10%)
Median in months (95% CI)	13.0 (8.3, NE)	8.9 (4.4, 10.3)
Hazard ratio‡ (95% CI)	0.53 (0.31, 0.91)	
p-Value§	0.0205	

* Based on Miettinen-Nurminen method stratified by PD-L1 status (TPS <1% vs. TPS ≥1%).
† Based on Kaplan-Meier estimation
‡ Based on the Cox proportional hazard model stratified by PD-L1 status (TPS <1% vs. TPS ≥1%).
§ Based on the log-rank test stratified by PD-L1 status (TPS <1% vs. TPS ≥1%).
NE = not estimable

Exploratory analyses for ORR were conducted in subgroups defined by the stratification variable, PD-L1 tumor expression (TPS <1% and TPS ≥1%). In the TPS <1% subgroup, the ORR was 57% in the KEYTRUDA-containing arm and 13.0% in the chemotherapy arm. In the TPS ≥1% subgroup, the ORR was 54% in the KEYTRUDA-containing arm and 38% in the chemotherapy arm.

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 1.1 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 20 and 21 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 4.

Table 20: 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 21: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

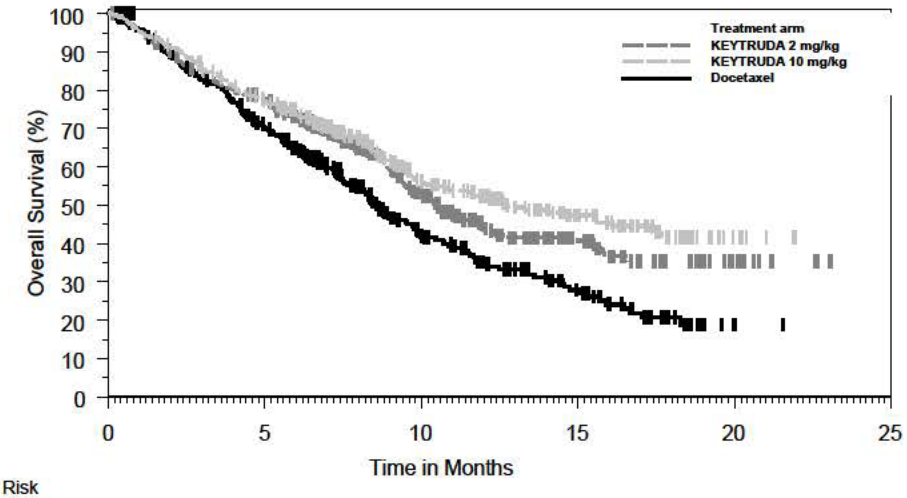
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
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 4: 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 1.1, as assessed by blinded independent central review, and duration of response.

Among the 174 patients, the baseline characteristics were median age 60 years (32% age 65 or older); 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumors; 63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; and the median number of prior lines of therapy administered for the treatment of HNSCC was 2.

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

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 that 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 22.

Table 22: Efficacy Results in KEYNOTE-087

	KEYNOTE-087*
Endpoint	N=210
Overall Response Rate	
ORR (95% CI)	69% (62, 75)
Complete remission	22%
Partial remission	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 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 1.1 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.

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 23.

Table 23: Efficacy Results in KEYNOTE-052

Endpoint	KEYTRUDA 200 mg every 3 weeks n=370
Objective Response Rate	
ORR (95% CI)	29% (24, 34)
Complete response rate	7%
Partial response rate	22%
Duration of Response	
Median in months (range)	NR (1.4+, 17.8+)

\+ Denotes ongoing
NR = not reached

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 1.1. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST 1.1 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 24 and Figure 5 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 24: Efficacy Results in KEYNOTE-045

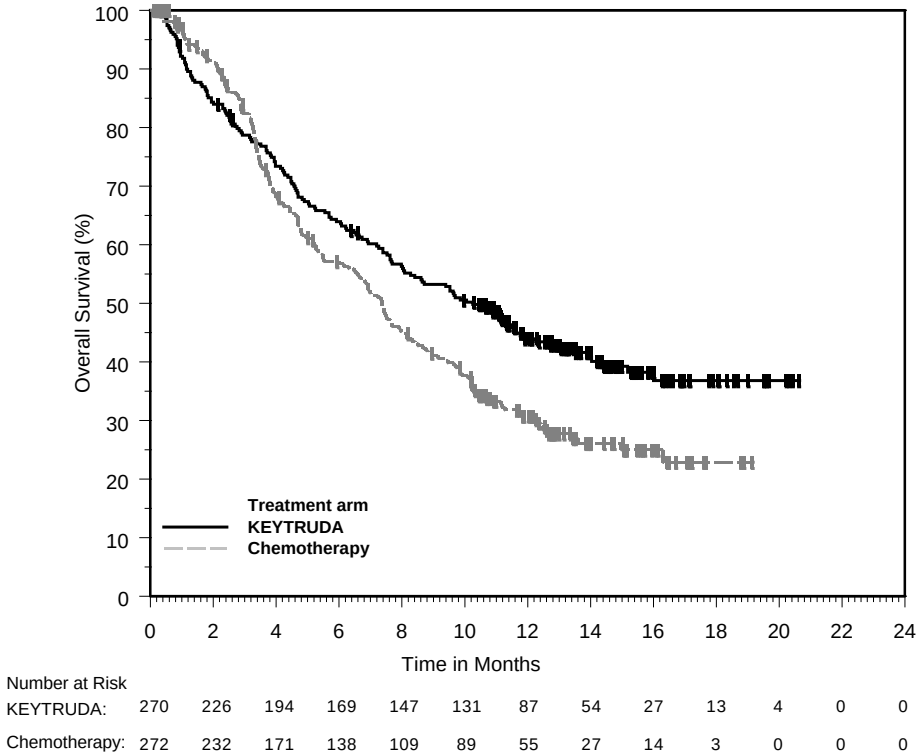
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (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 5: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



14.6 Microsatellite Instability-High Cancer

The efficacy of KEYTRUDA was evaluated 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 1.1 and duration of response.

Table 25: 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 26.

Table 26: 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 27: Response by Tumor Type

	N	**Objective response rate**		**DOR range** (months)
		n (%)	**95% CI**	
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

14.7 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 1.1, 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.

14.8 Cervical Cancer

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 1.1, 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 28.

Table 28: 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

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 (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)]*.

- 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

uspi-mk3475-iv-1806r015

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

- 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 if they are treated with KEYTRUDA. 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 of stem cell transplantation that uses donor stem cells (allogeneic) after treatment with KEYTRUDA. These complications can be severe and can lead to death. Your doctor will monitor you for signs of complications if you are an allogeneic stem cell transplant recipient.

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 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.
  - KEYTRUDA may be used with the chemotherapy medicines pemetrexed and carboplatin as your first treatment when your lung cancer:
    - has spread (advanced NSCLC) **and**
    - is a type of lung cancer called “nonsquamous”.
- 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 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, **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.

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have any other medical problems
- are pregnant or plan to become pregnant
  - KEYTRUDA can harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during and for at least 4 months after the final dose of KEYTRUDA. Talk to your doctor about birth control methods that you can use during this time.
  - Tell your doctor right away if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed.
  - It is not known if KEYTRUDA passes into your breast milk.
  - Do not breastfeed during treatment with KEYTRUDA and for 4 months after your final dose of KEYTRUDA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive KEYTRUDA?

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

What are the possible side effects of KEYTRUDA?

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

Common side effects of KEYTRUDA 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.

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 U.S. License No. 0002 For patent informa ion: www.merck.com/product/patent/home.html usmg-mk3475-iv-1806r013

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: June 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s034

OFFICER/EMPLOYEE LIST

Officer/ Employee List
Application: BLA 125514 / SE1-034
Keytruda® (pembrolizumab)

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

1. Julia Beaver
2. Sanjeeve Balasubramaniam
3. Gwynn Ison
4. Shaily Arora
5. Lijun Zhang
6. Joyce Cheng
7. Jason Schroeder
8. Pengfei Song
9. Huiming Xia
10. Shadia Zaman
11. Barbara Fuller
12. Sharon Mills
13. Fatima Rizvi
14. Trung-Hieu Tran
15. LaShawn Griffiths
16. Katherine Fedenko
17. William Pierce
18. Alice Kacuba
19. Sherry Hou
20. Leyish Minie
21. Shyam Kalavar

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s034

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	BLA
Application Number(s)	125514
Priority or Standard	Priority
Submit Date(s)	December 28, 2017
Received Date(s)	December 28, 2017
PDUFA Goal Date	June 28, 2018
Division/Office	DOP1
Review Completion Date	June 11, 2018
Established Name	Pembrolizumab
(Proposed) Trade Name	Keytruda
Pharmacologic Class	Monoclonal antibody blocking PD-1
Code name	Not applicable
Applicant	Merck
Formulation(s)	Intravenous infusion
Dosing Regimen	200 mg as an intravenous infusion every 3 weeks
Applicant Proposed Indication(s)/Population(s)	Pembrolizumab is indicated for the treatment of patients with advanced cervical cancer with disease progression on or after chemotherapy
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Pembrolizumab 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.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Fatima Rizvi
Nonclinical Reviewer	N/A
Nonclinical Team Leader	N/A
Office of Clinical Pharmacology Reviewer(s)	Huiming Xia
Office of Clinical Pharmacology Team Leader(s)	Pengfei Song
Clinical Reviewer	Gwynn Ison (efficacy) Shaily Arora (safety)
Clinical Team Leader	Sanjeeve Balasubramaniam
Statistical Reviewer	Joyce Cheng
Statistical Team Leader	Lijun Zhang
Associate Director for Labeling	William Pierce
Cross-Disciplinary Team Leader	Sanjeeve Balasubramaniam
Division Director (DHOT)	N/A
Division Director (OCP)	N/A
Associate Division Director (OB)	Jason Schroeder
Division Director (OHOP)	Julia Beaver
Office Director (or designated signatory authority)	N/A

Additional Reviewers of Application

OBP	Shadia Zaman, Jennifer Swisher
Microbiology	N/A
OPDP	Nazia Fatima
OSI	Lauren Iacono-Connor
OSE/DEPI	N/A
OSE/DMEPA	Tingting Gao / Chi-Ming Tu
OSE/DRISK	N/A
Other- DMPP	Sharon Mills / Barbara Fuller

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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 (KEYTRUDA®) is a humanized monoclonal antibody that blocks the interaction between programmed death receptor (PD-1) and its ligands, PD-L1 and PD-L2. Blocking of this interaction between PD-1 and its ligands can release PD-1 mediated inhibition of the immune response, including anti-tumor immune response. In mouse models, blocking PD-1 activity resulted in decreased tumor growth.

The applicant's proposed indication at the time of supplemental BLA submission on December 28, 2017, was:

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

- for the treatment of patients with advanced cervical cancer with disease progression on or after chemotherapy.

The recommended indication for accelerated approval is:

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

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.

The recommended dose for pembrolizumab is 200 mg as an intravenous infusion every 3 weeks.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Pembrolizumab has been approved in multiple indications since its initial approval on September 4, 2014, for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The current application seeks licensure of pembrolizumab in cervical cancer. The recommendation for the approval of pembrolizumab per 21 CFR Part 601.41[1] is based on the efficacy and safety data from Cohort E of the phase 2, non-randomized, open-label, multicenter, single cohort basket trial, KEYNOTE-158 (KN-158). Ninety-eight (n=98) patients with advanced, metastatic cervical cancer who had received one or more lines of standard therapy were eligible and were treated with pembrolizumab 200 mg by intravenous administration every 3 weeks until disease progression, death, unacceptable toxicity, or for a maximum of 2 years (35 administrations). Patients had to provide an evaluable tissue sample for biomarker analysis, including PD-L1 status by immunohistochemical assay (IHC) from a tumor lesion not previously irradiated. Archived samples were acceptable for this purpose. A tumor sample was considered PD-L1-positive (PD-L1+) when microscopic analysis revealed a (prespecified) combined proportion score (CPS) ≥ 1 as demonstrated by the IHC assay.

Of the 98 patients enrolled, 82 had tumors that were determined to be PD-L1+ by the assay. Overall, 77 patients had PD-L1+ tumors and had received at least one line of systemic chemotherapy for metastatic disease; this comprised the primary efficacy population. The confirmed ORR by RECIST 1.1 in these patients was 14.3% (95% CI: 7.4%, 24.1%) per Central Radiology Assessment (IRC). This consisted of 2 complete responses (CRs, 2.6%) and 9 partial responses (PRs, 11.7%). The median duration of response (DOR) was not reached (range: 4.1 to 18.6 months) after a median study follow-up time of 11.7 months (range: 0.6 to 22.7 months). Pembrolizumab for the recommended indication is considered an improvement over available therapy: currently, there are no approved agents for this setting. While single-agent chemotherapies are comparable to the 14.3% objective response rate, responses with pembrolizumab are more durable, with the median not yet reached. Toxicity with pembrolizumab also is favorable when compared against single agent chemotherapies, especially in the context of multiple prior cytotoxic regimens.

The safety profile of pembrolizumab in this population was consistent with the known safety profile of pembrolizumab in other advanced cancer settings, aside from specific adverse events that may be attributed to the natural history of cervical cancer: its development in the central pelvis and primary treatment with chemoradiotherapy, including fistulas and gastrointestinal bleeding.

Overall, the benefit-risk profile is favorable to support accelerated approval of pembrolizumab 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.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pembrolizumab (Keytruda®) is a programmed death receptor-1 (PD-1)-blocking antibody recommended for approval 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. Pembrolizumab has been approved in multiple indications since its initial approval on September 4, 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The current application seeks licensure of pembrolizumab in cervical cancer.

In 2015, there were an estimated 12,990 new cases of cancers of the uterine cervix and an estimated 4,120 deaths in the US. Incidence has fallen dramatically since the introduction of screening; however, for those who develop this cancer, treatment is traditionally chemoradiotherapy for all but the most locally confined disease presentations. For those women who develop recurrent disease, bevacizumab plus a platinum doublet is standard-of-care; beyond this initial therapy, single-agent chemotherapies are used, with generally single-digit response rates and short durations of response. On top of these fairly limited treatment options, the natural history of advanced cervical cancer is particularly challenging, with pelvic pain and fistula formation, as well as distal gastrointestinal toxicity from radiation, resulting in significant and unrelenting morbidity in this patient population.

The efficacy of pembrolizumab in patients with cervical cancer was explored in Cohort E of the phase 2, non-randomized, open-label, multicenter, single cohort basket trial, KEYNOTE-158 (KN-158). Ninety-eight (n=98) patients with advanced, metastatic cervical cancer who had received one or more lines of standard therapy were eligible and were treated with pembrolizumab 200 mg by intravenous administration every 3 weeks until disease progression, death, unacceptable toxicity, or for a maximum of 2 years (35 administrations). Despite the largely international patient population enrolled on this trial, patient characteristics were generalizable to the US population.

Of the 98 patients enrolled, there were 77 patients who had PD-L1+ tumors and who had received at least one line of systemic chemotherapy for metastatic disease. The confirmed ORR by RECIST 1.1 was 14.3% (95% CI: 7.4%, 24.1%) per Central Radiology Assessment (IRC) in these 77 patients. This consisted of 2 complete responses (CRs, 2.6%) and 9 partial responses (PRs, 11.7%).

Median time to response was 2.2 months (range: 1.6 to 4.1 months), and the median duration of response (DOR) was not reached (range: 4.1 to 18.6

months) after a median study follow-up time of 11.7 months (range: 0.6 to 22.7 months). For the 11 patients with confirmed response, the majority (8/11, 72.7%) had ongoing responses at the time of data cutoff and 3 (27.3%) subsequently experienced PD. Also, most had extended response durations: 10/11 (90.9%) had duration ≥6 months, 9/11 (81.8%) had duration ≥9 months, 7/11 (63.6%) had duration ≥12 months, and 5/11 (45.5%) had duration ≥15 months. There were no responses (CR or PR) observed in the 16 patients with tumors that were PD-L1- or unknown.

Safety was evaluated in 98 patients from KEYNOTE-158, where the median duration of exposure was 2.9 months (range: 1 day to 22.1 months). Pembrolizumab was discontinued due to adverse reactions in 8% of patients; serious adverse reactions occurred in 39% of patients. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%). Findings did not differ from the known safety profile of pembrolizumab for other disease indications, other than those attributable to the natural history of advanced cervical cancer and its treatment. These specific events include fistula formation and rectal bleeding, which can be attributed to both the tumor as well as exposure of the pelvic organs to radiation included in the standard up-front therapy algorithm. Analyses of interactions between history of radiation and pembrolizumab exposure did not suggest any increase in adverse events as compared to no radiation and pembrolizumab exposure, but the sample size was small for this type of analysis.

Overall, pembrolizumab demonstrated efficacy in the PD-L1 positive population based on the totality of the evidence from one key study in patients who have an advanced, life-threatening malignancy and unmet medical need with few effective therapies currently available. The safety profile is acceptable in the population indicated. Pembrolizumab for the recommended indication is considered an improvement over available therapy: currently, there are no approved agents for women with recurrent or metastatic cervical cancer who have disease progression on or after systemic chemotherapy, and response rates with standard-of-care single-agent chemotherapies, while comparable to the 14.3% objective response rate, responses with pembrolizumab demonstrate substantially prolonged durations of response, with the median not yet reached. Toxicity with pembrolizumab also is favorable when compared against single agent chemotherapies, especially in the context of multiple prior cytotoxic regimens.

The benefit: risk profile is favorable to support approval of pembrolizumab 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. No risk mitigation other than accurate labeling and routine oncology care is required. There is one postmarketing requirement, for the conduct and submission of OS and PFS results of a phase 3 trial to confirm clinical benefit per accelerated approval regulations, and one post-marketing commitment, to provide the median duration of response analyses of trial KEYNOTE-158.

Based on the totality of the evidence, the recommendation is for accelerated approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cervical cancer (carcinoma of the uterine cervix) is the fourth most common cancer in women worldwide, with 85% of cases occurring in developing countries. In developing countries, cervical cancer is a leading cause of cancer death in women. Persistent infection with human papilloma virus (HPV) is the most important factor in the development of cervical cancer and immunization to protect against the common types of HPV infection are expected to prevent specific HPV cancer in women. The most common histologic types of cervical cancer are squamous cell (69%) and adenocarcinoma (25%). • In 2015, there were an estimated 12,990 new cases of cancer of the uterine cervix and an estimated 4,120 deaths in the US.	**Recurrent, metastatic cervical cancer is serious, life-threatening, and incurable. There is an unmet need to develop effective therapies that can deliver prolonged durations of response for patients with these cancers.**
Current Treatment Options	• Single-agent chemotherapy is the mainstay of treatment for women with recurrent cervical cancer, where response rates and response durations are generally low.	**Patients with recurrent or metastatic cervical cancer who have been treated with at least one line of systemic chemotherapy can benefit from treatment with an agent that provides a more favorable response rate and prolonged duration of response compared to available therapy.**
Benefit	• The confirmed ORR by RECIST 1.1 was 14.3% (95% CI: 7.4%, 24.1%) per Central Radiology Assessment in these 77 patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1). • The median duration of response (DOR) was not reached (range: 4.1 to 18.6 months) after a median study follow-up time of 11.7 months (range: 0.6 to 22.7 months).	**Evidence of effectiveness was supported by an objective response rate not typically seen with cytotoxic chemotherapy in this disease setting, and was also supported by a clinically meaningful duration of response.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety profile of pembrolizumab in the treatment population is similar to the known safety profile from extensive clinical experience with bevacizumab since its initial approval in 2014. • Pembrolizumab is intended to be prescribed by oncologists. • Oncologists are well versed in the identification and management of toxicities associated with bevacizumab.	**The overall safety profile of pembrolizumab for the treatment of patients with recurrent or metastatic cervical cancer is consistent with the known safety profile of pembrolizumab, and current risk mitigation strategies are sufficient.** **The safe use of pembrolizumab can be managed through accurate labeling and routine oncology care. No REMS is indicated.**

1.4. Patient Experience Data

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

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	PRO assessment via the EuroQol EQ-5D and EORTC QLQ-C30 questionnaires were included as exploratory endpoints and discussed in Section 8.2.6.
			□	Observer reported outcome (ObsRO)	
			X	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	
	□	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)	
□	Patient experience data that was not submitted in the application, but was considered in this review.		

Sanjeeve Balasubramaniam, MD, MPH
Clinical Team Leader,
Division of Oncology Products 1

Cross-Disciplinary Team Leader

2 Therapeutic Context

Analysis of Condition

Cervical cancer (carcinoma of the uterine cervix) is the fourth most common cancer in women worldwide, with 85% of cases occurring in developing countries. In developing countries, cervical cancer is a leading cause of cancer death in women.[2-5] In 2015, there were an estimated 12,990 new cases of cancers of the uterine cervix and an estimated 4,120 deaths in the US.[6] Persistent infection with human papilloma virus (HPV) is the most important factor in the development of cervical cancer and immunization to protect against the common types of HPV infection are expected to prevent specific HPV cancer in women.[7-9] The most common histologic types of cervical cancer are squamous cell (69%) and adenocarcinoma (25%).[10]

2.2. Analysis of Current Treatment Options

The initial management of cervical cancer depends upon staging, which initially is clinical staging by pelvic exam and pathology. Patients with smaller tumors confined to the cervix (Stage IA) are treated with surgery alone or, if they are not surgical candidates, with radiation therapy. Patients who have locally-advanced disease at presentation (which includes Stage IB2-IVA) are typically managed with primary chemoradiation, and this often includes a regimen of either cisplatin alone during XRT or a combination of cisplatin+ 5FU during XRT.

It is uncommon, especially in the US, for patients to present with *de novo* metastatic disease. However, anywhere from 15-60% of patients will develop metastatic disease, and this usually occurs within the first 2 years after primary therapy. For select patients with recurrence in the central pelvis, surgical total pelvic exenteration is still the treatment of choice, and can potentially be curative.

In the setting of metastatic disease that is not amenable to surgery or radiation, chemotherapy is used. In the first-line metastatic setting, the treatment of choice in the US, is platinum-based chemotherapy with bevacizumab. Bevacizumab (in combination with chemotherapy) gained FDA approval for the treatment of recurrent, persistent, or metastatic carcinoma of the cervix in August 2014. This approval was based upon the GOG-0240 study which showed a 3.7 month improvement in median overall survival (HR 0.74) for chemotherapy + bevacizumab versus chemotherapy alone[11].

For women who have progressed after first line treatment, there are no approved therapies, and single agent chemotherapy is commonly used. An analysis was conducted by both the applicant and the FDA to assess the activity of available chemotherapy options in the proposed therapeutic space including patients with metastatic cervical cancer who have received at least

one prior line of chemotherapy (second-line setting and beyond). The FDA's assessment is shown in Table 1. These studies included over 300 patients.

Table 1 Available therapy for 2L cervical cancer

	Ref.	Agent	No. treated	No. Prior lines chemotherapy included	ORR	Median DOR/ TTP	Comments
1	Sutton[12] 1989	ifosfamide	30	Recurrent after XRT+ surgery; "refractory to first line"	**11%** (3 PR)	**Range 10-16 m** (median not reported)	Duration of response unclear, reported range seems long, but not further information provided
2	Irvin[13] 1998	irinotecan	16	Second line, platinum resistant	**0**	N/A	
3	Verschr-aegen[14] 1997	irinotecan	42	"Refractory" first-line chemotherapy; up to 4 lines	**21%** (1 CR, 2 PR)	**3 m**	Unclear why ORR for this irinotecan trial differs from the Irvin, et al. trial
4	Coronel [15] 2009	topotecan	22	≥1 prior line; all had 1-2 prior lines	**0**	N/A	27.7% SD
5	Fiorica[16] 2009	topotecan	27	1 prior line +/- radiosensitizer with chemoradiation	**0**	N/A	40% SD
6	Lorusso [17] 2011	topotecan	21	1 prior line; could include only chemoradiation	**0**	N/A	
7	Garcia[18] 2007	docetaxel	27 (23 evaluable)	Not more than 1 prior line	**8.7%** (2 PR)	TTP **3.8 m** (range 1.2-11.7 mos)	Study closed due to low response rate
8	Lorusso [19] 2010	pemetrexed	43	1 prior platinum based chemotherapy +/- XRT	**13.9%** (6 PR)	**1.75 m**	Response duration negligible
9	Miller[20] 2008	pemetrexed	29	1 prior line	**15%** (4 PR)	**4.4 m**	ORR 25% non-radiated vs 7% previously irradiated
10	Monk[21] 2009	bevacizumab	46	1-2 prior lines (73% one prior chemo)	**11%** (5 PR)	**6.2 m**	
11	Alberts[22] 2012	Nab-paclitaxel	37 (35 evaluable)	1 prior line (excluded patients who had received prior paclitaxel)	**28.6%** (10 PR)	**6 m** (range 1.5- 9.2m)	Applicant excluded this reference due to study's exclusion of patients receiving prior paclitaxel, however included for FDA analysis

Reviewer comment: The review team did not include agents (e.g., topotecan and irinotecan) with no response rates as "available therapies". Therefore, when considering agents with clinical activity (e.g., response rate > 0) in the setting of second-line metastatic cervical cancer, response rates for available chemotherapy agents range from 8-29%. More importantly, response durations for these agents tend to be short, with median durations ranging from <2 months to approximately 6 months, for most agents likely to be used in clinical practice. When considering a new agent for accelerated approval based on response rate, where the metric is to be "better than available therapy", the duration of response and toxicity profile in conjunction with overall response rate needs to be considered.

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pembrolizumab has been approved for multiple indications by the FDA and is currently marketed for the following indications in the United States:

Table 2: Approvals for Pembrolizumab in the United States by Indication

September 2014	Accelerated approval was granted for treatment of patients with advanced or unresectable melanoma who are no longer responding to other therapies.
October 2015	Accelerated approval was granted for treatment of patients with advanced (metastatic) non-small cell lung cancer whose disease progressed after other treatments and with tumors that express PD-L1 protein.
December 2015	Approved for an expanded indication, to include the first line treatment of patients with unresectable or metastatic melanoma.
August 2016	Approved for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy.
August 2016	Approved for the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors have high PD-L1 expression as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
March 2017	Accelerated approval was granted for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma, or those who have relapsed after three or more prior lines of therapy.
May 2017	Accelerated approval was granted for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.
May 2017	Accelerated approval was granted for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
November 2017	Accelerated approval was granted 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.

3.2. Summary of Presubmission/Submission Regulatory Activity

Major regulatory activities with FDA are summarized in Table 3 below. This summary focuses on activities relevant to the development program for pembrolizumab in cervical cancer only.

Table 3: Key Regulatory Activities During Clinical Development Of Pembrolizumab In Advanced, Metastatic Cervical Cancer Who Have Received One Or More Lines Of Therapy

April 2015	Meeting held to discuss the preliminary results of study KEYNOTE-028 and proposal to conduct KEYNOTE-158
December 2017	Correspondence between Merck and FDA regarding trial data, data presentation and 90-day safety update report.
December 2017	Pre-sNDA meeting for IND 126191 held to discuss data to be included in the sBLA for accelerated approval of pembrolizumab for cervical cancer.
December 2017	Merck presented overall strategy and status of KEYNOTE-158 at oncology rounds.
December 2017	Submission of this sBLA

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

4.1. Office of Scientific Investigations (OSI)

The clinical team selected one site for inspection by the Office of Scientific Investigations (OSI). The primary efficacy endpoint was objective response rate (ORR) per RECIST 1.1, as determined by an Independent Review Committee (IRC). The IRC assessment from KN-158 (Study 3475-158) was conducted by the Contract Research Organization (CRO) (b) (4) The inspection findings are shown in Table 4.

Table 4 OSI Clinical Inspection Summary

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Dates	Final Classification
CRO: (b) (4) Independent Review Center for imaging/ clinical data assessment) (b) (4)	Protocol: 3475-158 98 subjects (Group E: Cervical Carcinoma)	(b) (4)	Final Classification NAI

Key to Compliance Classifications
NAI= No deviation from regulations
VAI= Deviation(s) from regulations
OAI= Significant deviations from regulations. Data unreliable.
Pending: Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

The overall conclusion conveyed in the Inspection Summary was that there were no discrepancies discovered in review of data listings and image readings performed by the CRO radiologists; there was no evidence of CRO non-compliance with the Radiology Charter.

4.2. Product Quality

There were no product quality data reviewed for this supplement.

4.3. Clinical Microbiology

There were no clinical microbiology data reviewed for this supplement.

4.4. Devices and Companion Diagnostic Issues

A supplemental PMA for the PD-L1 IHC assay was submitted to CDRH on 1/27/18.

Effectiveness of the of PD-L1 IHC 22C3 pharmDx is based on clinical performance and the benefit to patients with advanced cervical cancer. This was assessed in study KN-158, which was conducted to evaluate the safety and the efficacy of single-agent pembrolizumab in these patients who had at least one line of chemotherapy in the metastatic setting. In this single-arm study, PD-L1 IHC 22C3 pharmDx was used to determine patient PD-L1 status. Out of the 98 patients enrolled in KN-158, 97 had evaluable tissue. Eighty-two (83.7%) were PD-L1 positive and 15 (15.3%) were PD-L1 negative. The sites of the tumor samples were as follows: 62 (63.2%) patients provided primary tumors, 36 (36.7%) provided metastatic tumors. The sampling procedure was as follows: 53 (54.1%) had biopsy and 45 (45.9%) had resections. Based on the testing with this device, pembrolizumab demonstrated a significant improvement in ORR for cervical cancer patients who had tumors that expressed PD-L1 with a CPS ≥ 1 and received at least one line of chemotherapy in the metastatic setting compared to cervical cancer patients whose tumors did not express PD-L1(CPS < 1). The data supports the performance of this device in identifying cervical cancer patients who will benefit from the therapeutic when used in accordance with the instructions for use. The performance of the PD-L1 IHC 22C3 pharmDx in cervical cancer was also supported by the analytical validation studies.

Based upon review of the data submitted to CDRH, in conjunction with the review team's assessment of the pembrolizumab sBLA application, there will be contemporaneous approval of the PD-L1 IHC 22C3 pharmDx assay as a companion diagnostic for selection of cervical cancer patients who may be appropriate for treatment with pembrolizumab therapy.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There were no nonclinical studies submitted with this supplement, so this section is omitted.

5.2. Referenced NDAs, BLAs, DMFs

There were no nonclinical studies submitted with this supplement, so this section is omitted.

5.3. Pharmacology

There were no nonclinical studies submitted with this supplement, so this section is omitted.

5.4. ADME/PK

There were no nonclinical studies submitted with this supplement, so this section is omitted.

5.5. Toxicology

There were no nonclinical studies submitted with this supplement, so this section is omitted.

5.5.1. General Toxicology

There were no nonclinical studies submitted with this supplement, so this section is omitted.

5.5.2. Genetic Toxicology

There were no nonclinical studies submitted with this supplement, so this section is omitted.

5.5.3. Carcinogenicity

There were no nonclinical studies submitted with this supplement, so this section is omitted.

5.5.4. Reproductive and Developmental Toxicology

There were no nonclinical studies submitted with this supplement, so this section is omitted.

5.5.5. Other Toxicology Studies

There were no nonclinical studies submitted with this supplement, so this section is omitted.

6 Clinical Pharmacology

6.1. Executive Summary

No significant clinical pharmacology related issues were identified in the current submission. No clinical pharmacology pertinent labeling changes are made in this submission.

The proposed dose is the previously approved dose (200 mg Q3W, as an intravenous infusion over 30 minutes), which was supported by the clinical safety and efficacy results in trial KEYNOTE 158. No PK, PD or immunogenicity analyses were conducted for the same dose of this well-studied drug in the proposed indication, though blood samples were collected only for potential future exploration.

Huiming Xia Pengfei Song

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

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Table 5 Clinical study

Trial identity	Trial design	Regimen/ schedule/ route	Primary endpoint	Treatment duration/ follow-up	No. patients enrolled	Study population	No. of centers and countries
MK-3475-158 KEYNOTE-158 Group E	Phase 2, non-randomized, open-label, multicenter, single cohort trial.	Pembrolizumab 200 mg IV q 3 weeks	ORR by blinded IRC	Until disease progression, death, unacceptable toxicity, or up to a maximum of 35 administrations (2 years).	98	Advanced, metastatic cervical cancer who have received one or more lines of standard therapy.	42 centers in 17 countries

7.2. Review Strategy

Data Sources

The electronic submission, including the KN-158 clinical protocol, statistical analysis plan (SAP), clinical study report (CSR), and SAS transport datasets in SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) formats, for the sBLA submission was utilized to conduct the clinical and statistical analyses for this application.

The EDR location for the original sBLA, submitted 12/28/17, including protocol, study reports, analysis datasets, narratives and case report forms is:

\\CDSESUB1\evsprod\BLA125514\0469.

Updated SDTM datasets for IA7 were subsequently provided in the safety update submitted 3/27/18 (\\CDSESUB1\evsprod\BLA125514\0500) and updated ADaM datasets for IA7 were submitted 4/9/18 (\\CDSESUB1\evsprod\BLA125514\0512) per FDA information request. Additional FDA requested datasets to better characterize prior therapy were submitted 4/23/18 (\\CDSESUB1\evsprod\BLA125514\0516).

Data Quality and Integrity

The original sBLA submission included efficacy and safety results for cohort E of trial KN-158, based upon a database cutoff of 8/23/17 (termed IA6, by the Applicant). There were several changes in efficacy assessments reported by the Applicant, during the course of the review. These changes were based on findings at a preplanned interim efficacy analysis (IA7, with a database cutoff of 1/15/18). A summary of the key changes, which were reported to the FDA in a general correspondence letter on 3/28/18, are described in Table 6.

Additionally, on 4/23/18, the Sponsor provided updated information regarding prior lines of therapy in all 98 patients, and confirmed that 6 of the 98 subjects had received no prior treatment for metastatic cervical cancer prior to enrolling on KN-158. Instead, all 6 had received only definitive or neoadjuvant/adjuvant therapy for cervical cancer prior to enrolling. Since the eligibility criteria for the cervical cohort on KN-158 indicated that patients were supposed to have received at least one line of systemic therapy for advanced/metastatic disease, it was determined that only 92 of the patients enrolled had met that criterion. Of these 92 patients, 77 had tumors expressing PD-L1.

Table 6 IA7 Interim analysis and changes to study populations

Date of submission	Details of submission
3/23/18	IA7- Preplanned interim efficacy analysis; database cutoff 1/15/18.
	1) Outcome of the IRC review determined that one subject ((b) (6)), who had originally been assessed to have

	a PR as best overall response by IRC in the IA6 interim analysis, was subsequently changed to have a best overall response by IRC of SD at the preplanned IA7 interim efficacy analysis (data cutoff 1/15/18). 2) One patient ((b) (6)) was changed from having PD-L1- disease to having PD-L1+ disease, taking the overall number of patients with PD-L1+ disease to n=82 out of 98 patients in the cohort.
4/23/18	Response to Agency information request on prior lines of therapy indicated that 6 of the 98 patients treated had received no prior therapy for metastatic disease prior to enrollment. Of these 92 patients, 77 had tumors that were PD-L1+, and these 77 patients were analyzed separately in the efficacy assessments, since they most closely approximate the subset for whom pembrolizumab monotherapy appears to yield tumor response.

Reviewer comment: Throughout the review, the team sent multiple information requests to the applicant, in an attempt to obtain additional information on patients treated on the clinical trial, due to missing and/or poorly presented information in the analysis datasets. In some cases, the applicant continued to find errors in previously reported analyses and performed repeated updates on details including patient demographics, disease characteristics, and prior therapies. The repeated updates from the applicant, including those described in Table 6*, required the review team to further scrutinize the clinical trial data and prompted multiple information requests in order to verify the applicant's findings.*

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. KEYNOTE-158 (KN-158)

Trial Design

KEYNOTE-158 is an ongoing, non-randomized, Phase 2, multicohort (basket) study to assess pembrolizumab in advanced (unresectable and/or metastatic) rare cancers, analyzed for predictive biomarkers. Patients with the following tumor types may be enrolled into the trial, and the cohort of interest in the current application is Cohort E (cervical carcinoma):

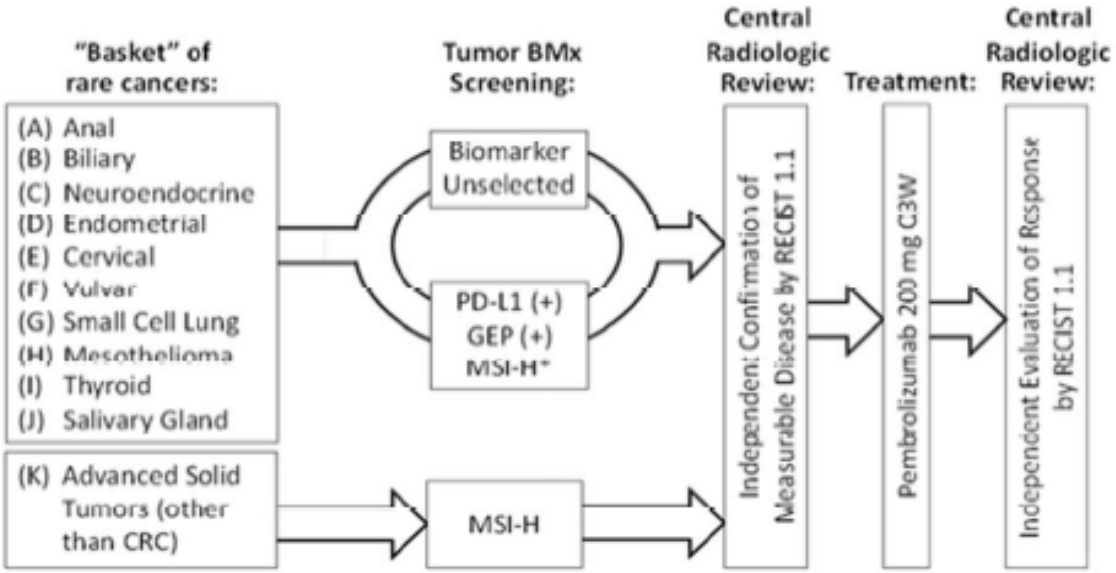

Figure 1 KN-158 Trial Design

Source: Sponsor p158mk3475 protocol amendment No. 7 4-17-17

Key inclusion criteria

1) Patients with histologically or cytologically documented advanced (metastatic and/or unresectable) solid tumor that is incurable and for which prior standard first-line treatment has failed. Patients must have progressed on or been intolerant to therapies known to provide clinical benefit. No limit to number of prior regimens.

Note: Prior neoadjuvant or adjuvant therapy included in initial treatment may not be considered first- or later line standard of care treatment unless such treatments were completed less than 12 months prior to the current tumor recurrence.

Reviewer comment: For the current review, considering the proposed indication in patients with advanced/metastatic cervical cancer, the applicant' (b) (4) *, was deemed to be unacceptable by the review team. Cervical cancer is managed with surgery and/or chemoradiation in the non-metastatic setting, even in some cases with multiple local relapses. Combination platinum-based chemotherapy (with or without bevacizumab) is the standard of care regimen in the first-line advanced or metastatic setting in the US, and there is no time frame that is used as a marker for chemotherapy sensitivity or resistance as is used in ovarian cancer. Given these factors, it was determined that the most clearly-defined cervical cancer population on KEYNOTE-158 would be patients who had recurred/progressed after at least one line of systemic therapy in the advanced setting.*

2) Have cervical squamous cell carcinoma.

3) Have submitted evaluable tissue sample for biomarker analysis from a tumor lesion not previously irradiated (exceptions may be considered with approval from applicant). Tumor tissue submitted for analysis must be from a single tumor tissue specimen and of sufficient quantity and quality to allow assessment of ALL required primary biomarkers (PD-L1 expression, GEP score, and MSI-H status).

4) If enrollment has moved to biomarker enrichment, have a tumor that is positive for one or more of the prespecified primary biomarker(s), as assessed by the central laboratory. These enrichment biomarkers may be PD-L1 expression by IHC (at a percentage to be prespecified), a positive tumor RNA GEP score (at a prespecified cut-off), and/or tumor MSI-H.

5) Have radiologically measurable disease based on RECIST 1.1. Independent central radiologic review must confirm presence of radiologically measurable disease based on RECIST 1.1 for the patient to be eligible to participate in the trial. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

6) ECOG 0-1.

7) Life expectancy of at least 3 months.

8) Adequate organ function as defined:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin (Hgb)	≥9.0 g/dL or ≥5.6 mmol/L, without recent transfusion (defined as a transfusion that has occurred within 2 weeks of the Hgb measurement)
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or creatinine clearance)	≤1.5xULN **OR** ≥60.0 mL/min for subject with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN **OR** ≤5xULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

Source: Sponsor Table 6 p158v01mk3475-protocol

9) Adequate contraception, as defined in the protocol.

Key exclusion criteria

1) Currently participating and receiving study therapy or received study therapy or used an investigational device within 4 weeks of first dose of treatment.

2) Has a diagnosis of immunodeficiency or is receiving systemic steroids or any other form of immunosuppressive therapy within 7 days prior. Physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

3) Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) or treatment with drugs (e.g. neomercazol, carbmazole, etc.) that functions to decrease the generation of thyroid hormone by a hyperfunctioning thyroid gland (e.g. in Graves' disease) is not considered a form of systemic treatment of an autoimmune disease.

4) Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from an AE due to mAbs administered more than 4 weeks earlier.

5) Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered from an AE due to previously administered agent.

6) Has a known additional malignancy within 2 years prior to enrollment except curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or curatively resected in situ cancers.

7) Has known active CNS metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided these brain metastases are stable (without evidence of progression by imaging over a period of at least 4 weeks and any neurologic symptoms have returned to baseline), then have no evidence of new or enlarging brain metastases (confirmed by imaging within 28 days of the first dose of trial treatment) and they are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

8) Known glioblastoma multiforme of the brainstem.

9) Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

10) Active infection requiring systemic therapy.

11) Known psychiatric or substance abuse disorder that would interfere with cooperation with the trial.

12) Pregnant or breastfeeding or expecting to conceive or father a child during the trial or within 120 days after last dose of treatment.

13) Previously participated in any other pembrolizumab trial or received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or any other immune modulating mAb (including ipilimumab or other checkpoint inhibitors).

14) Known HIV infection.

15) Known active Hepatitis B (HBsAg positive) or Hepatitis C (HCV RNA is detected).

16) Received live vaccine within 30 days.

Study treatment:
The treatment used is as follows:

Drug	Dose/Potency	Dose Regimen*	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV	Day 1 of each 3 week cycle	Experimental
*Pembrolizumab (MK-3475) doses may be withheld due to toxicity as described in Section 5.2.1.2.					

Source: Applicant p158v01m3475 protocol

Dose modifications:
Pembrolizumab was to be withheld for drug-related toxicities and severe or life-threatening AEs as per the Table 8. Dosing interruptions were permitted in the case of medical/surgical events not related to study therapy (e.g., elective surgery, unrelated medical events, holidays). Patients were to be put back on therapy within 3 weeks of the interruption, unless otherwise noted.

Supportive care guidelines:
Patients were to receive appropriate supportive care measures as necessary. Suggested measures for specific adverse events are described below. Where appropriate, the guidelines included the use of oral or IV corticosteroids and other anti-inflammatory agents. For each AE, attempts were to be made to rule out other causes, such as disease progression or infection.

Pneumonitis

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade 3 or 4 events, immediately treat with IV steroids. Administer anti-inflammatory measures as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/ Colitis
Carefully monitor for signs and symptoms of enterocolitis and of bowel perforation.

- All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral intake is not feasible, fluid and electrolytes should be administered via IV infusion. For Grade 2 or higher diarrhea, consider gastroenterology consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhea/colitis, administer oral corticosteroids
- For Grade 3 or 4 diarrhea/colitis, treat with IV steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type I diabetes mellitus [if new onset, including diabetic ketoacidosis [DKA] or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)]

- For T1DM or Grade 3-4 Hyperglycemia
    - Insulin replacement is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis

- For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as steroid dose is tapered.

Hyperthyroidism or Hypothyroidism

Monitor patients for changes in thyroid function (at start of treatment and periodically during treatment) and for signs and symptoms of thyroid disorders.

- Grade 2 hyperthyroidism events and Grade 2-4 hypothyroidism
    - In hyperthyroidism, non-selective beta blockers are suggested as initial therapy
    - In hypothyroidism, thyroid replacement hormone therapy is levothyroxine is indicated as per SOC
- Grade 3-4 hyperthyroidism
    - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as steroid dose is tapered.

Hepatic

- For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly)
- For Grade 3-4 events, treat with IV corticosteroids

Renal Failure/ Nephritis

- For Grade 2 events, treat with corticosteroids
- For Grade 3-4 events, treat with systemic corticosteroids
- When symptoms improve to Grade 1 or less, steroid taper and continue over no less than 4 weeks.

Management of Infusion Reactions

Signs and symptoms of infusion reactions were to be managed as shown in Table 7.

Table 7 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Table 8 Dose Modification Guidelines for Drug-Related Adverse Events

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

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

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

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to **Table 9 – Infusion Reaction Treatment Guidelines** for further management details.

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

Source: Applicant p158v01m3475 protocol

Sample Size

The KEYNOTE-158 study, as a whole, will enroll a minimum of 200 and a maximum of approximately 1350 patients over a period of approximately 60 months. The intent is to initially enroll approximately 50 biomarker unselected patients for the ten tumor types in Groups A-J and approximately 50 additional patients in each of those tumor types either regardless of primary biomarker status or based on tumor expression of selected primary biomarker(s). Additionally, Group K may enroll up to 350 patients.

No power calculations were incorporated into the design of KEYNOTE-158. However, for Group E, the applicant estimates that 100 patients provide 87% power to find that the ORR is >10% assuming a true ORR of 20% with a one-sided significance level of alpha=0.025.

Analysis Populations

The primary efficacy and safety analysis were planned to be conducted in the All Subjects as Treated (ASaT) population.

Study Endpoints

The primary endpoint was objective response rate (ORR) defined as the proportion of patients with a confirmed CR or PR assessed by independent central radiologic review (IRC) per RECIST 1.1 at any time during the study.

Secondary endpoints included the following:

- Duration of response (DOR) defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause (whichever occurs first).
- Progression-free survival (PFS) defined as the time from allocation to the first documented disease progression per RECIST 1.1 or death due to any cause (whichever occurs first). For patients without documented date of progression or death at the time of analysis, PFS was censored at the date of the last adequate assessment.
- Overall survival (OS) defined as the time from allocation to death due to any cause. For patients without documented death at the time of analysis, OS was censored at the date of last known contact.

Statistical Analysis Plan

The KEYNOTE-158 basket trial incorporates an adaptive design in which multiple interim analyses may be performed with accrual and efficacy/safety data reviewed in an ongoing manner. The first interim analysis was planned for when approximately 200 patients are enrolled (regardless of biomarker status) across all tumor types and are followed for response/progression for at least 18 weeks. There was originally a cap for all-comers within

each tumor type of 50 patients with a plan for biomarker enrichment using interim analyses results, but this was not conducted due to fast enrollment. Additional interim analyses were planned on an approximately quarterly basis, including groups of patients across all tumor types that have been followed for response/progression for at least a certain number of weeks, and a final analysis will be conducted when all patients have been enrolled >45 weeks.

At each interim analysis, ORR and DOR will be evaluated and summarized in the following populations:

1. All comers (i.e. patients without biomarker selection) pooled across all tumor types
2. Biomarker-selected patients pooled across all tumor types
3. All comers within an individual tumor type
4. Biomarker-selected patients within an individual tumor type

The applicant has general guidance specified in the supplemental SAP for evaluating interim analyses to determine whether to proceed with a regulatory submission. This submission is based off an interim analysis (IA7) for the cervical cohort (Group E).

The primary analysis of the primary efficacy endpoint of ORR by central radiologic assessment (IRC) per RECIST 1.1 was conducted in the ASaT population using an exact test of binomial parameter with 95% confidence interval (CI) calculated using the Clopper-Pearson method.

The time-to-event secondary endpoints of DOR by central radiologic assessment per RECIST 1.1, PFS by central radiologic assessment per RECIST 1.1, and OS were all summarized using the Kaplan-Meier method. All analyses were conducted in the ASaT population except DOR, which was assessed only for the responders. The censoring rules employed for DOR are shown in Table 9.

Table 9: Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥ 2 missed adequate disease assessments	Last adequate disease assessment prior to the after ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed adequate disease assessments	PD or death	End of response (Event)
Patients are considered to have an ongoing response if censored, alive, have not progressed, and have not started a new anti-cancer therapy and have not been lost to follow-up (ie, Situation 1 in the first row of the table)		

[Source: CSR Table 9-4]

<u>Reviewer Comment:</u> In single arm trials, FDA does not use inferential procedures to evaluate

trial results. Instead, the efficacy evaluation is based on the magnitude of response rate and adequate duration of response. Additionally, we note that time-to-event endpoints are uninterpretable without a comparator arm.

Protocol and SAP Amendments

The original protocol was amended seven times. Amendments may have applied to all or some of the cohorts within KN-158, with the cervical cohort being relevant to the current application. The details of each protocol amendment are shown in Table 10.

Table 10 KN-158 protocol amendments

Amendment No. and Date	Key changes
Original protocol - 9/11/15	
Amendment 1 - 11/5/15	Clarified groups and 2L treatment based on FDA feedback
Amendment 2 - 11/23/15	Allowed archival tissue collection based on FDA feedback
Amendment 3 – 12/10/15	UK- added 120 day followup for live vaccine administration and monthly pregnancy testing due to CTFG guidance
Amendment 4- 1/25/16	France- clarified risk/benefit language and exclusion of GBM of the brainstem
Amendment 5- 3/29/16	Clarified whole blood collection for all patients and added inclusion criterion of life expectancy of at least 3 months.
Amendment 6- 5/20/16	Updated exclusion criteria related to pneumonitis
Amendment 7- 4/17/17	Increased enrollment to up to 350 patients in Group K and added mandatory tissue submission in Group K for retrospective central MSI analysis.

[Source: CSR 16.1.1. Protocol and Amendments]

The statistical analysis plan (SAP) is in the trial protocol section 8. The supplemental statistical analysis plan (sSAP), which provides additional details, was amended once with the following changes: analysis plan for patient reported outcomes was provided, and interim analyses section was updated to reflect that biomarker enrichment was not implemented due to fast enrollment.

8.1.2. Study Results

The entire cervical cancer cohort (Cohort E) on KN-158 included 98 patients who were enrolled and treated, comprising the all patients as treated (ASaT) population. Of the 98 patients, 82 (84%) of them had tumors that expressed PD-L1 at a CPS ≥ 1%, while 16 (16%) were negative for PD-L1 expression (tumors that were PD-L1 “not evaluable” were considered to be PD-L1 negative; one of the 16 patients had a tumor that was PD-L1 “not evaluable”). There were no responses observed in the 16 patients with tumors that were negative/not evaluable for PD-L1 expression (PD-L1 negative). Most of the efficacy analyses in this review will include

assessments for the ASaT population (n=98), the PD-L1 positive population (n=82), and the PD-L1 negative population (n=16); the PD-L1 negative cohort is not described in some analyses since none were responders to pembrolizumab. In addition, as noted previously, the patients (n=77) who were confirmed to have received at least one prior line of therapy for advanced/metastatic disease and who had tumors that expressed PD-L1 were analyzed separately in this review. This (n=77) group is referred to as the "1L+ in metastatic setting" cohort in this review, and these patients will comprise FDA's primary efficacy analysis population. Finally, there were 11 patients with confirmed response (CR or PR) by IRC assessment, so the characteristics of these 11 patients (Responders) are also described separately in most analyses.

Compliance with Good Clinical Practices

The clinical study was conducted worldwide and was patient to Quality Control and Quality Assurance oversight, including independent audits by the company. The Sponsor's Code of Conduct was described and the trial was monitored to ensure compliance with Good Clinical Practices.

Financial Disclosure

Financial disclosure information for KN-158 is discussed in section 19.2 of this review.

Patient Disposition

The disposition for the various groups within the cervical cancer cohort, including the all subjects treated (ASaT) population are shown in Table 11. Most patients discontinued therapy due to progressive disease, including clinical progression.

Table 11 Patient disposition

Disposition	ASaT N=98 (%)	PD-L1+ N=82 (%)	PD-L1+ and 1L+ in metastatic setting N=77 (%)	PD-L1+ and 1L+ in met setting, Responders N=11 (%)
Treated	98 (100)	82 (100)	77 (100)	11 (100)
Treatment ongoing at data cutoff	10 (10)	10 (12)	10 (13)	7 (64)
Discontinued from treatment	88 (90)	72 (88)	67 (87)	4 (36)
Primary reason for discontinuation				
Adverse event	7 (7)	6 (7)	5 (6)	1 (9)
Progressive disease	64 (65)	52 (63)	49 (64)	1 (9)

Physician decision (including clinical progression)	15 (15)	12 (15)	12 (16)	2 (18)
Withdrawal by subject	2 (2)	2 (2)	1 (1)	0

[Source: Disposition data based on IA07 with data cut off 1/15/18. DS dataset SDTM format and ADSL dataset ADaM format].

Reviewer comment: Of the 11 responders, 4 had discontinued from treatment at the time of data cutoff. Two of these patients ((b) (6) and (b) (6)) discontinued due to clinical progression by investigator assessment. These patients had best response to therapy by investigator assessment of stable disease (SD), but were considered to have partial response by IRC assessment. In both cases, they received treatment beyond radiologic progression (by IRC and INV assessments), but eventually developed further clinical progression by INV assessment and discontinued study therapy.

Protocol Violations/Deviations

Information on major protocol deviations was reported by the Sponsor in tabular form, without an analysis dataset. There were 75 major protocol violations in the 98 patients treated in the cervical cancer cohort. The major categories are shown in Table 12.

Table 12 Major protocol deviations

Major protocol deviations	N=98 (%)
Any major protocol deviation	75 (77)
Failure to meet entry criteria[1]	30 (31)
Receipt of prohibited medications[2]	14 (14)
Efficacy assessment deviation[3]	11 (11)
Clinical supplies	3 (3)
Discontinuation criteria[4]	2 (2)
GCP non-compliance	2 (2)

[Source: CSR 16.2.2]

[1]One patient with adenocarcinoma histology, several with ECOG status not documented, tumor measurements for baseline outside of window, lab assessments outside of window, steroids within 5 days of screening, tumor bloc from previously irradiated area; (b) (6) – measurable disease not confirmed.

[2]All events were administration of steroids (most cases were for cancer pain or for premedication for radiology); one patient (b) (6) received XRT while on study.

[3]Scans conducted outside of window or missing; one patient (b) (6) had a previously irradiated lesion chosen as a target lesion.

[4]One patient (b) (6) experienced RECIST PD, but was not taken off study, follow up scan confirmed progression, but INV continued patient on therapy without notifying Sponsor. Patient was discontinued after the next cycle and INV was retrained on protocol guidelines. Second patient (b) (6) had confirmed RECIST PD per irRECIST, but INV did not discontinue therapy until Sponsor mandated it.

Reviewer comment: The number of protocol deviations is relatively high, but there did not appear to be an excess number of violations in any category. Review of specific details of violations did not indicate that the violations were likely to have affected the trial efficacy or safety results in an unacceptable way.

Demographic Characteristics

The baseline demographics for the different groups within the cervical cancer cohort are shown in Table 13. The majority of patients were white and had an ECOG of 0-1. Only 11 of the patients enrolled came from the US.

Table 13 Baseline demographics

Demographic	ASaT N= 98 (%)	PD-L1+ N=82 (%)	PD-L1- N=16 (%)	PD-L1+ and 1L+ in met setting N=77 (%)	PD-L1+ and 1L+ in met setting, Responders N=11 (%)
Age (years)					
Mean (SD)	48 (11)	47 (11)	52 (10)	48 (11)	54 (14)
Median	46	45	48	45	59
Range (min, max)	24,75	24, 75	41, 72	27, 75	27, 75
≥ 65 years	8 (8)	5 (6)	3 (19)	5 (6)	3 (27)
≥ 75 years	1 (1)	1 (1)	0	1 (1)	1 (9)
Race					
White	78 (80)	64 (78)	14 (88)	62 (81)	8 (73)
Asian	14 (14)	12 (15)	2 (13)	11 (14)	3 (27)
Black	2 (2)	2 (2)	0	2 (3)	0
American Indian/Alaska Native	1 (1)	1 (1)	0	1 (1)	0
Hawaiian/Pacific Islander	1 (1)	1 (1)	0	0	0
Other*	2 (2)	1 (1)	0	1 (1)	0
Ethnicity					
Hispanic	3 (3)	2 (2)	1 (6)	2 (3)	0
Non-Hispanic	86 (88)	73 (89)	13 (81)	70 (91)	11 (100)
Unknown	9 (9)	7 (9)	2 (13)	5 (6)	0
ECOG					
0	34 (35)	28 (34)	6 (38)	25 (32)	5 (45)
1	64 (65)	54 (66)	10 (62)	52 (68)	6 (55)
Country of enrollment					
US	11 (11)	11 (13)	0	11 (14)	1 (9)
Non-US Western**	68 (69)	56 (68)	12 (75)	51 (66)	6 (55)
Non-US Non-Western***	19 (19)	15 (18)	4 (25)	15 (19)	4 (36)

[Source: DM SDTM dataset clinical safety update 3/27/18 and ADSL ADaM dataset 4/23/18]
*Other includes multiple and missing designations.
**Non-US Western countries include: France, Israel, Netherlands, Italy, Canada, Australia, Denmark, Spain, Germany, Norway.

***Non-US Non-Western countries include: Korea, Russia, Japan, Taiwan, Brazil

Reviewer comment: The median age for the 11 responders was older than the other groups, although the significance of this is unclear. In addition, only one responder, patient (b) (6) *, came from the US. She was also one of the 2 responders who had received prior therapy with bevacizumab, and this is depicted in Table 15 below.*

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

Disease characteristics

Disease characteristics including tumor histology and stage at initial diagnosis are shown in Table 14. Most patients had disease with squamous histology, which is typical for a primary cervical tumor. Over 80% of the patients enrolled had PD-L1-positive tumors. The breakdown for stage at initial diagnosis in the 11 patients from the US shows that a slightly higher percentage have Stage IV disease at diagnosis, despite the numbers being small. Otherwise, the groups were similar with regard to tumor location and histology.

Table 14 Disease characteristics

Disease characteristics	ASaT n= 98 (%)	PD-L1 + N=82 (%)	PD-L1- N=16 (%)	PD-L1+ and 1L+ in met setting N=77 (%)	PD-L1+ and 1L+ in met setting, Responders N=11** (%)
Tumor type/location					
Cervical	93 (95)	77 (94)	16 (100)	72 (94)	11 (100)
Endometrial*	5 (5)	5(6)	0	5 (6)	0
Histology at diagnosis					
Squamous	92 (94)	76 (93)	16 (100)	71 (92)	10 (91)
Adenocarcinoma	5 (5)	5 (6)	0	5 (6)	1 (9)
Adenosquamous	1 (1)	1 (1)	0	1 (1)	0
Overall TNM stage at diagnosis					
I	1 (1)	1 (1)	0	0	0
IB (includes IB1 and IB2)	21 (21)	20 (25)	1 (6)	19 (25)	0
II	4 (4)	1 (1)	3 (19)	1 (1)	0
IIA	7 (7)	6 (7)	1 (6)	6 (8)	1 (9)
IIB	24 (25)	22 (27)	2 (13)	19 (25)	5 (45)
III$^{\infty}$	1 (1)	0	1 (6)	0	0
IIIB	10 (10)	7 (9)	3 (19)	7 (9)	1 (9)
IVA	2 (2)	1 (1)	1 (6)	1 (1)	0
IVB	28 (29)	24 (29)	4 (25)	24 (31)	4 (37)
Metastatic disease at study entry (prior therapy in the metastatic setting)					
Yes	92 (94)	77 (94)	15 (94)	77 (100)	11 (100)
No	6 (6)	5 (6)	1 (6)	0	0
Brain metastases					
Yes**	1 (1)	1 (1)	0	1 (1)	1 (9)
No	97 (99)	81 (99)	16 (100)	76 (99)	10 (91)
PD-L1 status					

Positive	82 (84)	82 (100)	0	77 (100)	11 (100)
Negative	16 (16)	0	16 (100)	0	0

[Source: MI SDTM dataset submitted 3/27/18, ADSL and ADPRIOR ADaM datasets submitted 4/23/18.]

* All 5 endometrial carcinoma patients had squamous histology, which is consistent with cervical carcinoma rather than true endometrial carcinoma, which is typically adenocarcinoma. These 5 patients were: (b) (6) .
None of these were responders to pembrolizumab.

**Patient (b) (6) had brain metastases according to the ADSL dataset and was a responder (PR), but there is no documentation in the lesion datasets that any brain metastases were recorded as target/non-target lesions, nor was it documented whether she had response in any of the brain metastases.

ᵓNo patients had stage IIIA at initial diagnosis.

Reviewer comment: The analysis of the overall disease stage for patients at diagnosis, rather than at study entry was difficult to conduct, as this was not reported in the initial submission by the applicant, and the information was only provided late in the review, after several attempts made by the review team. When further analyzing overall stage, as reported by the applicant, in comparison to the stage according to the TNM staging system, there was not always consistency in the Applicant's reported staging for patients. The staging reported in Table 14 *was per FDA assessment of data reported in the analysis datasets, but utilizing the TNM staging system. Although the majority of patients had metastatic disease at study entry, most did not have metastatic disease at diagnosis.*

An overview of prior therapies, including radiation and number of lines chemotherapy is shown in Table 15.

Table 15 Prior therapies

	ASaT N=98 (%)	**PD-L1 + N=82 (%)**	**PD-L1- N=16 (%)**	**PD-L1+ and 1L+ in met setting N=77 (%)**	**PD-L1+ and 1L+ in met setting, Responders N=11 (%)**
Prior radiation therapy					
Yes	85 (87)	70 (85)	15 (94)	65 (84)	9 (82)
No	13 (13)	12 (15)	1 (6)	12 (16)	2 (18)
Adjuvant/neoadjuvant therapy					
Yes	21 (21)	16 (20)	5 (31)	13 (17)	2 (18)*
No	77 (79)	66 (80)	11 (69)	64 (83)	9 (82)
Prior lines of systemic chemotherapy					
Adjuvant/neoadjuvant only	4 (4)	3 (4)	1 (6)	0	0
1	30 (31)	29 (35)	1 (6)	27 (35)	5 (45)
2	34 (35)	26 (32)	8 (50)	26 (34)	4 (36)

3	16 (16)	12 (15)	4 (25)	12 (16)	0
4	10 (10)	8 (10)	2 (13)	8 (10)	1 (9)
5+	4 (4)	4 (5)	0	4 (5)	1 (9)
Prior bevacizumab					
Yes	41 (42)	34 (41)	7 (44)	34 (44)	2 (18)**
No	57 (58)	48 (59)	9 (56)	43 (56)	9 (82)

[Source: ADSL and ADPRIOR ADaM datasets submitted 4/23/18]

* The 2 responders who received prior adj/neoadj were (b) (6) and (b) (6)

**The 2 responders who had received prior bevacizumab were (b) (6) and (b) (6)

Reviewer comment: Most patients had prior radiation therapy. Prior number of systemic chemotherapy regimens varied, with most having either 1 or 2 prior regimens. The information on prior lines of therapy was difficult to extract from the analysis datasets, and it required several information requests before an appropriate dataset could be obtained to conduct the analysis. It is still unclear whether these numbers are accurate. Nevertheless, this analysis revealed that only 77 of the patients enrolled in the cervical cancer cohort on KN-158 had received at least one line of therapy for metastatic disease and had tumors expressing PD-L1. In addition, although approximately 40% of patients in the ASaT population (n=98) had received prior bevacizumab, which is approved for metastatic cervical cancer in the US, only 2 of the 11 responders (18%) to pembrolizumab received prior bevacizumab. It is unknown whether prior therapy with bevacizumab affects the likelihood of response to pembrolizumab therapy, but this may be important to characterize, given that patients in the US will likely have received bevacizumab before becoming candidates for pembrolizumab in the later line.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Pembrolizumab was administered in the clinic by qualified site personnel. Compliance with pembrolizumab administration was to be measured by patients receiving unscheduled infusions and/or missing an infusion. There were no specific reports by the Applicant of non-compliance with study medication administration.

Based upon the propensity for pembrolizumab to cause immune-mediated adverse events which can be managed, in some cases, by corticosteroid use, an analysis of steroid administration in patients treated on KN-158 was conducted. The results are shown in the safety review in Table 30. Concomitant use of other anticancer agents was prohibited, and was described in the discussion on protocol deviations in Table 12, a 14% of patients did receive prohibited steroid therapy during the study. These were documented as protocol deviations.

Efficacy Results – Primary Endpoint

Results from the FDA's analysis of confirmed ORR (IRC) based upon IA7 data cutoff date 15 January 2018 are shown in Table 16. The confirmed ORR by RECIST 1.1 was 14.3% (95% CI:

7.4%, 24.1%) per Central Radiology Assessment (IRC) in the 77 patients with tumors that were PD-L1 positive and who had received at least one prior line of systemic chemotherapy for metastatic cervical cancer. This consisted of 2 complete responses (CRs, 2.6%) and 9 partial responses (PRs, 11.7%). There were 29 subjects whose assessments required adjudication.

Among the responders, median time to response was 2.2 months (range: 1.6 to 4.1 months), and the Kaplan-Meier estimated median duration of response (DOR) was not reached (range: 4.1 to 18.6 months) after a median study follow-up time of 11.7 months (range: 0.6 to 22.7 months). For the 11 patients with confirmed response (CR or PR), the majority (8/11, 72.7%) had ongoing responses at the time of data cutoff and 3 (27.3%) subsequently experienced PD. Also, most had extended response durations: 10/11 (90.9%) had duration ≥6 months, 9/11 (81.8%) had duration ≥9 months, 7/11 (63.6%) had duration ≥12 months, and 5/11 (45.5%) had duration ≥15 months.

Table 16: Primary Analysis of ORR by Central Radiology Assessment (IRC)

	PD-L1+ and 1L+ in Metastatic Setting N=77
Confirmed ORR, n (%, [95% CI])	11 (14.3, [7.4, 24.1])
Complete Response (CR), n (%, [95% CI])	2 (2.6 [0.3, 9.1])
Partial Response (PR), n (%, [95% CI])	9 (11.7 [5.5, 21.0])
Stable Disease (SD), n (%, [95% CI])	13 (16.9 [9.3, 27.1])
Progressive Disease (PD), n (%, [95% CI])	42 (54.5 [42.8, 65.9])
Non-evaluable (NE), n (%, [95% CI])	4 (5.2 [1.4, 12.8])
No Assessment, n (%, [95% CI])	7 (9.1 [3.7, 17.8])
Duration of Response (months)	
Median[1] (range)	NR (4.1, 18.6+)
Duration ≥6 months, n (%)	10 (90.9)
Duration ≥9 months, n (%)	9 (81.8)
Duration ≥12 months, n (%)	7 (63.6)
Duration ≥15 months, n (%)	5 (45.5)
Time to Response (months)	
Median (range)	2.2 (1.6, 4.1)

[1] Kaplan-Meier Estimate
CI = confidence interval, NR = not reached, + denotes ongoing
[Source: RS SDTM dataset submitted 3/27/18, ADRS and ADTTE ADaM datasets submitted 4/9/18]

Additionally, the confirmed ORR was 12.2% (12/98, 95% CI: 6.5%, 20.4%) in the 98 all comers and 14.6% (12/82, 95% CI: 7.8%, 24.2%) in the 82 patients with tumors that were PD-L1+. There were no responses (CR or PR) observed in the 16 patients with tumors that were PD-L1- or unknown.

Reviewer comment: The applicant initially conducted the primary efficacy analysis of ORR based upon IRC assessment in the ASaT population (n=98), but the FDA assessment focused on the 77 patients with tumors that were PD-L1 positive and who had received at least one prior line of systemic chemotherapy for metastatic cervical cancer. The results of the primary efficacy analysis support the hypothesis that pembrolizumab has antitumor activity in cervical cancer patients with tumors expressing PD-L1 (PD-L1+). Given that none of the patients with tumors lacking PD-L1 expression (PD-L1-) responded to therapy, the consideration that pembrolizumab could be approved for all patients with advanced cervical cancer regardless of PD-L1 expression is not supported by the current study results.

Investigator-assessed Confirmed ORR by RECIST 1.1

The confirmed ORR by investigator assessment by RECIST 1.1 was 18.2% (95% CI: 10.3%, 28.6%) in the 77 patients with tumors that were PD-L1+ who had received at least one prior line of systemic chemotherapy for metastatic cervical cancer, including 3 CRs (3.9%) and 11 PRs (14.3%). Among the responders, median time to response was 2.1 months (range: 1.6 to 10.5 months), and the Kaplan-Meier estimated median duration of response (DOR) was 10.4 months (range 4.6 to 16.7 months) after a median study follow-up time of 11.7 months (range 0.6 to 22.7 months).

Table 17 shows the concordance between confirmed response determined by central radiology assessment compared to by investigator. Note that both central review and investigator had 7 patients with no assessment meaning they had a baseline assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan. Of the remaining 70 patients, there were 37 patients (52.9%) whose responses were agreed upon completely by both central review and investigator.

Of the 11 patients with confirmed response (CR or PR) by central review, 9 (81.8%) also had confirmed response (CR or PR) by investigator, the other two (18.2%) were considered to have SD by investigator. Of 14 patients with confirmed response (CR or PR) by investigator, 9 also had confirmed response (CR or PR) by central review, but the remaining 5 were considered SD (one patient) and PD (four patients).

Table 17: Concordance between Central Review and Investigator Assessment

	By Investigator						
By Central Review	CR	PR	SD	PD	NE	Not Assessed	Total
CR	0	2	0	0	0	0	2
PR	3	4	2	0	0	0	9
SD	0	1	9	3	0	0	13
PD	0	4	13	24	1	0	42
NE	0	0	2	2	0	0	4

Not Assessed	0	0	0	0	0	7	7
Total	3	11	26	29	1	7	77

[Source: RS SDTM dataset submitted 3/27/18, ADRS ADaM dataset submitted 4/9/18]

Reviewer comment: The concordance, particularly between the IRC and INV assessment of the 11 responders (primary IRC analysis), was quite good, and reinforces the overall assessment that there are some patients with PD-L1 positive cervical cancer who may achieve a tumor response to therapy with pembrolizumab, making this a reasonable therapeutic option for carefully selected patients.

FDA analysis of disease burden in IRC responders

An analysis of the baseline tumor burden for the 11 confirmed responders (IRC) was conducted. The results of the analysis of tumor burden for each patient, according to IRC and INV assessment, is shown in Table 18.

Table 18 Responder analysis: Baseline tumor burden by IRC and INV assessment and best overall response

	Patient ID	Date of baseline scan/ measurement	Target lesions by IRC	Non-target lesions by IRC	Best overall response and date by IRC	Target lesions by INV	Non-target lesions by INV	Best overall response and date by INV
1	(b) (6)	(b) (6)	1) 15.5 mm lesion 2) 15.5 mm lesion Sum longest diam: 31 mm	6	**CR** (b) (6) C6	1) 15 mm lesion	1	**PR** (b) (6) C6
2	(b) (6)	(b) (6)	1) 13.1 mm 2) 1 target lesion "present"	0	**CR** (b) (6) Follow-up Day 30 *Patient came off therapy (b) (6) d/t G3 ALT and AST elevation Had f/u IRC assessement	1) 10 mm 2) 10.5 mm	1	**PR** (b) (6) Follow up day 30 *Patient came off therapy (b) (6) d/t G3 ALT and AST elevation Had f/u INV assessments (b) (6) **(PR)**,

					s (b) (6) **(CR)**, (b) (6) **(CR)** and (b) (6) **(CR)**			then **PD** on (b) (6)
3	(b) (6)	(b) (6)	1) 38.5 mm 2) 19.8 mm 3) 21.4 mm 4) 26.4 mm Sum longest diam: 106.1 mm	6	**PR** (b) (6) C6 Then **PD** by IRC (b) (6) C22	Both spiral CT and MRI reported: 1) bulky subcarinal nodal mass 2) extranodal mass abd cavity inferior to L renal artery 3) R abd wall 4) large mass involving cervix, uterus, vagina, rectum 5) SQ lesion R arm Measurements for 5 lesions (location not specified) 1) 22 mm 2) 23 mm 3) 34 mm 4) 75 mm 5) 37 mm	1) LUL lung nodule 2) pleural effusion 3) bulky R mediastinal mass 4) R axillary lymph node 5) extensive RP adenopathy 6) pelvic ascites 7) R hilar node 8) internal iliac nodes 9) R arm brachial chain adenopathy 10) gastrohepatic node	**SD** C3 and C6 (confirmed), then PR on C9 (b) (6), <u>but not confirmed-</u> SD at next assessment C12. Then **PD** by INV (b) (6) C15.
4	(b) (6)	(b) (6)	1) 19.3 mm (sum of diam only reported) 2) 1 target lesion "present"	1	**PR** (b) (6) C6	1) 21.6 mm	1	**PR** (b) (6) C6
5	(b) (6)	(b) (6)	1) 16.9 mm 2) 16.8 mm 3) 18.8 mm 4) 16.1 mm Sum longest diam 68.6 mm	5	**PR** (b) (6) C3 Then PD (b) (6) C9	1) 16 mm 2) 18 mm 3) 19 mm	2	**SD** since PR not confirmed (PR (b) (6) C3, then PD (b) (6) C6)

6	(b) (6)	(b) (6)	1) 71.8 mm 2) 48.4 mm 3) 26.7 mm 4) 19.5 mm 5) 19.8 mm 6) 15.9 mm Sum of diam 202.1 mm	1	**PR** (b) (6) C6 Continued with PR through C22 (b) (6)	1) 69 mm 2) 18 mm 3) 24 mm 4) 44 mm 5) 17 mm 6) 16 mm	2	**PR** (b) (6) C6 Continued with PR through C22 (b) (6)
7	(b) (6)	(b) (6)	1) 13.7 mm 2) 13.3 mm 3) 11.7 mm 4) 11.1 mm 5) 36.5 mm Sum of diam 86.3 mm	6	**PR** (b) (6) C4 IRC still called PR C18 (b) (6)	1) 15 mm	1	**CR** (b) (6) C10 (SD prior to this) INV called PD C18 (b) (6) based on NEW lesion
8	(b) (6)	(b) (6)	1) 15.2 mm 2) 25.8 mm Sum longest diam 41 mm	2	**PR** (b) (6) C3 confirmed	1) 45 mm 2) 17 mm Sum longest diam 62 mm	1	**CR** (b) (6) C10 Confirmed
9	(b) (6)	(b) (6) (INV) (b) (6) IRC	1) 45 mm 2) 13.9 mm Sum of diam 58.9 mm	1	**PR** (b) (6) C3 Lasted till C18 (b) (6)	1) 42 mm 2) 11 mm	2	**PR** (b) (6) C3 Lasted till C18 (b) (6)
10	(b) (6)	(b) (6) (INV) (b) (6) (IRC)	1) 20.8 mm 2) 19.4 mm 3) 21.1 mm 4) 26.4 mm Sum of diam 87.7 mm	2	**PR** (b) (6) C3 Lasted till C18 (b) (6)	1) 20 mm 2) 23 mm 3) 15 mm	1	**PR** (b) (6) C3 Lasted till C18 (b) (6)
11	(b) (6)	(b) (6) (INV) (b) (6) (IRC)	1) 29.3 mm Sum of diam 29.3 mm	1	**PR** (b) (6) (C4) Lasted till C19 (b) (6)	1) 24.2 mm	-	**CR** (b) (6) C18 (Had PR starting C3 (b) (6))

[Source: TR and TU SDTM datasets 12/28/17 and ADRS ADaM dataset 12/28/17]

Reviewer comment: One concern was whether response to pembrolizumab was isolated to patients with minimal/negligible disease burden, and that the responses may have occurred only in patients who were not in need of therapy, based upon tumor burden. Things to note from the table above include that there seemed to be fairly good concordance between disease burden at baseline according to IRC assessment and INV assessment, with a few exceptions.

Also, although there were some patients ([redacted], [redacted], [redacted]) who had smaller disease burden, based upon target lesion summation, there were also several patients ([redacted], [redacted], [redacted]) who had more substantial lesions documented, who also achieved responses to therapy. This observation is encouraging and supports the proposal to make pembrolizumab a therapeutic option for select patients with metastatic cervical cancer whose tumors express PD-L1.

Treatment beyond INV progression

Treatment beyond initial assessment of progressive disease by investigator was allowed in the protocol due to the hypothesis that immunotherapies, such as pembrolizumab, may produce antitumor effects by potentiating endogenous anti-cancer immune responses, and that these response patterns may not follow the same time course as is seen with cytotoxic agents. Because of potential for a response to occur after an initial apparent increase in tumor burden (pseudoprogression) or the appearance of new lesions, the ir-RECIST assessment was employed in KN-158. Patients who had an initial radiologic progression (PD by RECIST 1.1) as determined by the investigator, could continue study treatment until repeat imaging (ir-RECIST), provided they were clinically stable, as defined in the protocol. These patients could continue pembrolizumab and have a subsequent image-based assessment ≥ 4 weeks later to reassess PD per investigator assessment. If PD was confirmed on repeat imaging, patients had to discontinue therapy.

A breakdown of all patients, by subgroup, who received treatment beyond initial INV assessed progression is shown in Table 19. It is notable that both of these patients had best overall response by INV assessment of stable disease, but were deemed to have partial responses by IRC assessment.

Table 19 Treatment beyond initial INV progression

	ASaT N=98 (%)	PD-L1+ N=82 (%)	PDL1+ and 1L+ in metastatic setting N=77	PD-L1+ and 1L+ in met setting, Responders N=11 (%)
Patients who received treatment beyond INV progression	28	22	22	2

Reviewer comment: Of the 11 responders, one of the patients treated beyond INV progression ([redacted]) had a partial response by IRC and SD by INV assessment (as best response). She continued on therapy for approximately 8 months beyond initial assessment of PD by INV. The other patient ([redacted]) also achieved a best response by INV of SD, compared with PR by IRC assessment. She was treated for approximately 10 months beyond the initial assessment of INV progression. Given these long durations of clinical stability on

therapy, even upon initial progression by standard radiologic criteria, it is reasonable to allow investigators to use clinical judgment in deciding to continue therapy in some patients who may be deemed to be benefitting from therapy by more subjective criteria.

Exploratory Subgroup Analyses

Exploratory subgroup analyses of confirmed ORR by central radiology assessment (IRC) were assessed by age, race, region, prior bevacizumab, and prior radiation therapy. Results are shown in Table 20.

Table 20: Exploratory Subgroup Analyses

	N	# Responders	Confirmed ORR (95% CI)
Overall	77	11	14.3 (7.4, 24.1)
Age Group			
<65	72	8	11.1 (4.9, 20.7)
≥65	5	3	60.0 (14.7, 94.7)
Race Group			
White	62	8	12.9 (5.7, 23.9)
Non-White	15	3	20.0 (4.3, 48.1)
Region			
US	11	1	9.1 (0.2, 41.3)
Non-US	66	10	15.2 (7.5, 26.1)
Prior Bevacizumab			
Yes	34	2	5.9 (0.7, 19.7)
No	43	9	20.9 (10.0, 36.0)
Prior Radiation Therapy			
Yes	65	9	13.8 (6.5, 24.7)
No	12	2	16.7 (2.1, 48.4)

[Source: RS SDTM dataset submitted 3/27/18, ADRS ADaM dataset submitted 4/9/18, ADSL ADaM dataset submitted 4/23/18]

Reviewer's Comment: The higher response rate seen in patients age ≥65 is likely attributed to the subgroup's small sample size (n=5) and we note that the confidence interval is very wide. Otherwise, no outlier subgroups were observed. All subgroup analyses presented are considered exploratory or hypothesis generating and no formal inference can be drawn.

Efficacy Results – Secondary and other relevant endpoints

PFS and OS results are summarized below for the 77 patients with tumors that were PD-L1+ who had received at least one prior line of systemic chemotherapy for metastatic cervical cancer.

Progression-free Survival (PFS)
By Central Radiology Assessment, 65 (84.4%) patients had a PFS event with a median PFS time of 2.1 months (95% CI: 2.1, 2.3). By investigator assessment, 68 (88.3%) patients had a PFS event with a median PFS time of 3.6 months (95% CI: 2.2, 6.1).

Overall Survival (OS)
By the 15 January 2018 data cutoff, there were 50 deaths (64.9%) with a median survival time of 11.0 months (95% CI: 9.2, 14.2).

Reviewer's Comment: Again, time-to-event endpoints are uninterpretable without a comparator arm.

Durability of Response

Duration of response (DOR) is discussed with the assessment of the primary endpoint, ORR. This analysis is shown in Table 16. As is shown, there were responses that were durable, indicating that a small number of patients can experience prolonged benefit from therapy with pembrolizumab.

In addition, an analysis of the individual response duration for the 11 responders (IRC assessment) was conducted and is shown in Table 21.

Table 21 Individual DOR for responders

	Patient ID	IRC Best overall response	IRC DOR in days	INV Best overall response	INV DOR in days	Treatment beyond INV PD? Y/N
1	(b) (6)	CR	566 (no PD)	CR	504 (no PD)	N
2		CR	246 (no PD)	PR	162	N
3		PR	338	SD -PD #1- (b) (6) (C15) -PD#2- (b) (6) (C26)	N/A	Y D/C treatment (b) (6)
4		PR	424	PR	424	N
5		PR	126	SD PD (b) (6)	N/A	Y D/C treatment (b) (6)
6		PR	507 (no PD)	PR	507 (no PD)	N

	(b) (6)					
7		PR	308 (no PD)	CR	189	N
8		PR	427 (no PD)	CR	427 (no PD)	N
9		PR	478 (no PD)	PR	478 (no PD)	N
10		PR	487 (no PD)	PR	487 (no PD)	N
11		PR	484 (no PD)	CR	484 (no PD)	N

Reviewer comment: This analysis also indicates that several of the responders experienced prolonged response durations, and this was not necessarily limited to the patients with lower disease burden, as was also shown in Table 18.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient reported outcomes (PROs) were included as exploratory endpoints in the basket trial but were not analyzed by the applicant in this interim analysis for the cervical cancer cohort. The FDA analysis of the PRO data that were submitted is described in Section 8.2.6.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

The KEYNOTE-028 (KN-028) study was a Phase 1B, single arm, open-label, multicenter, multicenter study of pembrolizumab. Patients with histologically confirmed cervical cancer with PD-L1 positive (IHC) were enrolled and treated on cohort B4 of this trial. The pembrolizumab dose utilized on KN-028 differed from KN-158, and was 10 mg/kg IV every 2 weeks. KN028 enrolled 24 patients onto cohort B4, and according to the Sponsor, the investigator assessed ORR was 16.7% (4 patients with confirmed PR), and central radiology assessed ORR was 10% (2 of 20 patients with confirmed PR). These data provided proof of concept to conduct additional assessments of efficacy and safety of pembrolizumab in patients with advanced cervical cancer, and supported the rationale for KN158. Due to the difference in the trial designs, pembrolizumab dose, and the study populations between KN158 and KN028, efficacy data for the two trials was not integrated, and an analysis of the efficacy data from KN028 was not conducted by the review team. KN158 was the single trial used to support the efficacy of pembrolizumab 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).

Primary Endpoints

Not applicable.

Secondary and Other Endpoints

Not applicable.

Subpopulations

Not applicable.

Additional Efficacy Considerations

Not applicable.

8.1.4. Integrated Assessment of Effectiveness

As described in 8.1.3, the only study designated to support the effectiveness of pembrolizumab in the treatment of advanced, metastatic cervical cancer was KN-158. No integration of efficacy data was conducted in this review.

8.2. Review of Safety

Safety Review Approach

The review of safety relies primarily upon data from KEYNOTE-158 (Group E, N=98) based on a data cut-off date of January 15, 2018. The evaluation of safety will be based upon incidence of adverse events (AEs) and laboratory values, graded according to NCI CTCAE, version 4.0, and observed during treatment with pembrolizumab (i.e., from the first dose of pembrolizumab until treatment was stopped), and up to 30 days after last dose was administered for non-serious adverse events and up to 90 days for serious adverse events.

KEYNOTE-028 (Cohort B4) cervical cancer (N=24), provided proof-of concept data for the KEYNOTE-158 submission, for patients with cervical cancer who have progressed on or after chemotherapy. Due to the difference in the trial design and the study population, between KN158 and KN028, safety data was not integrated.

The safety results of the analyses of KEYNOTE-158 data are compared to the safety findings from the pembrolizumab reference safety dataset (RSD; N=2799) which consists of pooled data from four clinical studies (KN001, KN002, KN006 and KN010) evaluating pembrolizumab for the treatment of melanoma and non-small cell lung cancer (NSCLC), which comprised the first and second approved indications for pembrolizumab, respectively. Per the Applicant, the RSD reflects the established safety profile for pembrolizumab.

The Applicant mapped and coded verbatim adverse event (AE) terms for KEYNOTE-158 using MedDRA version 20.0.

Reviewer comment: There were no obvious discrepancies identified between the dataset and the information provided in the Clinical Study Report. The applicant's categorization of data and coding methods were appropriate. The preferred terms (PTs) listed in the dataset adequately represented the investigator-recorded term and did not raise any apparent issues. A random audit of 5% of the AE case report forms to assess the completeness and verify the accuracy of the raw AE datasets did not raise any issues.

The size of the safety population is different from the size of the efficacy population for this single arm trial. The safety population consists of all patients who received at least one dose of pembrolizumab (ITT; n=98), whereas the efficacy population comprises of PDL1 positive patients who had received at least 1 prior line of chemotherapy (n = 77). The safety analyses were performed for both populations to ensure consistency of the safety profile.

While reviewing AEs and safety information for KN158 (Cohort E), FDA compiled a table to aggregate similar AEs for calculating and tabulating adverse events observed in this study. The applicant accepted these pooled terms (refer to appendix section 19.5 for the list of PTs that were used for safety analysis).

8.2.2. Review of the Safety Database

Overall Exposure

Study KEYNOTE-158 (Group E) is ongoing. The data cutoff date for this review was January 15, 2018. For the intention to treat population (ITT; n=98), the median number of doses received was 5 (range: 1 to 33) and the median time on therapy was 2.91 months (range: 0.03 to 22.1). A total of 48 (49%) patients received pembrolizumab for at least 3 months, and 25 (25.5%) patients for at least 6 months. Sixteen patients (16.3%) were exposed to pembrolizumab for 1 year or longer. Median duration of follow-up was 10 months (range: 0.6 to 22.7).

For the PDL1 positive patients who had received at least 1 prior line of chemotherapy (n=77), the median number of doses received was 6 (range: 1 to 33) and the median time on therapy was 3.5 months (range: 0.03 to 22.1). A total of 41 (53%) patients received pembrolizumab for at least 3 months, and 22 (29%) patients for at least 6 months. Sixteen patients (21%) were exposed to pembrolizumab for 1 year or longer. Median duration of follow-up was 11.7 months (range: 0.6 to 22.7).

Table 22: Duration of exposure

KEYNOTE-158 (Group E) [1,2,3]

Duration	ITT population (n=98)	PDL1 Positive with at least 1 prior line of chemotherapy (n=77)
Months (m)	Number of patients (%)	Number of patients (%)
>0 m	98 (100)	77 (100)
≥ 1 m	85 (86.7)	68 (88.3)
≥ 3 m	48 (49)	41 (53.2)
≥ 6 m	25 (25.5)	22 (28.6)
≥ 12 m	16 (16.3)	16 (20.8)

[1] *Duration of exposure was calculated as last dose date – first dose date + 1.*
[2] Database Cutoff date: January 15, 2018
[3] ADSL Dataset.

Table 23: Time on therapy

KEYNOTE-158 (Group E) [1,2,3]		
Time on therapy (months)	**ITT population (n=98)**	**PDL1 Positive with at least 1 prior line of chemotherapy (n=77)**
Mean	5.5	6.2
Median	2.9	3.5
SD	6.03	6.5
Range	0.03 to 22.1	0.03 to 22.1
Number of administrations	**ITT population (n=98)**	**PDL1 Positive with at least 1 prior line of chemotherapy (n=77)**
Mean	8.7	9.6
Median	5.0	6.0
SD	8.6	9.2
Range	1 to 33	1 to 33

[1] *Duration of exposure was calculated as last dose date – first dose date + 1.*
[2] Database Cutoff date: January 15, 2018
[3] ADSL Dataset.

<u>Reviewer comment:</u> The safety population consists of all patients who received at least one dose of pembrolizumab (ITT; n=98). For this review, the size of this safety population and the extent of exposure were adequate to allow for sufficient characterization of AEs associated with pembrolizumab in the study population. We note that checkpoint inhibitors may have delayed immune-mediated toxicities, but the study follow-up was adequate to capture these events.

Relevant characteristics of the safety population:

Of the 98 patients with cervical cancer (ITT population), most were non-U.S. (87/98; 88.8%) and median age of patient on study was 46 years. All 98 patients had metastatic and/or

unresectable disease. Most patients (92/98; 93.9%) had a histology of squamous cell carcinoma and nearly 65% had a baseline Eastern Cooperative Oncology Group (ECOG) Performance Status of 1. Patients were pre-treated and 62% had received 2 or more prior lines of therapy. Patients were enrolled regardless of tumor PD-L1 expression. Eighty-five patients (86.7%) had received prior radiation therapy. Of the 98 patients, microsatellite instability (MSI) status was reported for 87 patients, with 85 MSI-stable patients and 2 with MSI-high status.

Reviewer comment: The median age of patients on study was 46, which is close to the median age of onset of cervical cancer in the general population. Approximately 92% of the patients enrolled in the trial were younger than 65 years of age.

Adequacy of the safety database:

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The following issues arose during the safety review:

1. Upon review of adverse events in the analysis datasets ADAE and ADCM, we noted corticosteroids (CS) administered for immune-related AEs not classified as AESIs for eight patients. Two of the eight patients who received CS experienced immune-related AEs that should be classified as AESIs. The Table 30 lists the events requiring CS in these patients.
2. Upon review of laboratory values in the analysis dataset ADLBGRD, we noted that patients in the study were missing baseline lab analysis flag (ABLFL) but still had certain baseline variables populated.

Reviewer comment: During this review, multiple information requests (IR) were sent to the applicant regarding missing data/ discrepancies presented in the datasets. On several occasions, our IRs led to discovery of errors in the datasets. IRs prompting updated information after discovery of inconsistencies led to repetition of data analysis on multiple occasions during the review process.

Categorization of Adverse Events

Safety and tolerability assessment was based on the frequency of deaths, AEs, serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to interruptions, select AEs, clinical laboratory assessments (hematology, serum chemistry, liver, kidney and thyroid function tests), and vital sign measurements. AEs were coded using the MedDRA version 20.0. AEs and laboratory values were graded for severity using the NCI CTCAE version 4.0. Adverse events were categorized by System Organ Class (SOC) and Preferred Term (PT).

The Applicant pre-specified adverse events of special interest (AESIs) based on Event of Clinical Interest Guidance. For this application, AESIs comprised of immune-mediated events and

infusion-related reactions associated with pembrolizumab. Patients were assessed for possible immune related adverse events before each dose. Patients who developed an AEs considered to be immune-related by the investigator were further evaluated to rule out other causes. If no other cause was found, then the event was assumed to be immune-related.

Reviewer comment: The applicant's definition of AESI was pre-defined and adequate to evaluate these AEs. The PT listed in the dataset adequately represented the investigator-recorded term and did not raise any significant issues. To review the AE datasets, preferred terms (PTs) were pooled, so as not to underestimate the incidence of these AEs, which were accepted by the applicant (see Appendix). Our review of the ADAE and ADCM datasets identified two additional AESIs compared to the AESIs identified by the applicant (Table 29).

Routine Clinical Tests

The following assessments were planned starting on Cycle 1 Day 1 and continued at regular intervals as pre-specified in the protocol:

- Vital signs including temperature, blood pressure, heart rate, and respiratory rate.
- AEs continuously throughout the study.
- Directed physical examination and physical measurements including weight and ECOG performance status.
- CBCs with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count (results were to be obtained and acceptable prior to dosing on infusion days).
- Serum chemistry tests (blood urea nitrogen, uric acid, total protein, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, and specific gravity), (results were to be obtained and acceptable prior to dosing on infusion days).
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin (results were to be obtained and acceptable prior to dosing on infusion days).
- Thyroid function testing including TSH and free T3 and T4.
- Radiographic disease assessments after 9 weeks from the first dose of trial treatment, then every 9 weeks, more frequently as clinically indicated. For patients who remained on study > 1 year, imaging performed every 12 weeks.
- Pregnancy screening for women of childbearing potential every cycle.

A 12 lead ECKG was done at screening and then as clinically necessary. Full physical examination was done at screening and then at the time of discontinuation. A coagulation panel was done at screening and urinalysis was done every 2 cycles while on treatment.

Patients were assessed for toxicity prior to each dose. All visits had to occur within 3 days of the next scheduled dose date. All SAEs were collected up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever came first. A mandatory safety follow up visit was conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever came first. Once the patient

stopped receiving trial treatment, patients were followed for survival every 12 weeks and were contacted by telephone to assess for survival status, until death, withdrawal of consent, or end of study, whichever occurred first.

Reviewer comment: *Routine clinical testing of patients enrolled in the trial are adequate. Patients were followed closely for SAEs for 90 days, which is likely sufficient to determine late-onset immune-mediated AEs*.

8.2.4. Safety Results

Deaths

There were 17 deaths (17.3%) in the overall safety population of 98 patients that received 200mg of pembrolizumab every 3 weeks. The majority (14/17, 82.4%) of deaths were reported due to malignant neoplasm progression. Three patients (n=3, 3.1%) in the KEYNOTE-158 population, experienced AEs that led to death. The AEs leading to death were death (n=2, 2.0%), and intestinal obstruction (n=1, 1.0%). For the 2 AEs leading to death reported as "death," the underlying cause of death was unknown. Table 24 summarizes the narratives for the three patients who died for reasons other than progression of disease.

Table 24: Narratives Reports of Deaths due to Causes Other than Disease Progression

Subject ID	PDL1 status	Narrative	Reviewer's Comments
(b) (6)	Positive	Primary Reported Cause of Death: Unknown 48-year-old female with metastatic cervical cancer (metastasis to liver, bone, lymph node). Her PMH included diabetes, neuropathy, back pain, anxiety and insomnia. Concomitant medications included lorazepam, hydromorphone, warfarin, metformin, methadone, eszopiclone, furosemide, ondansetron and carisoprodol. She had received four prior lines of therapy including radiation prior to initiating pembrolizumab on (b) (6). She received 3 doses of pembrolizumab and experienced headache, worsening back pain and fatigue during the treatment. Per family, the patient felt weak with loss of appetite, leg edema and difficulty urinating. The patient died on (b) (6), at home and no further details were provided.	*The primary cause of death is unknown. AEs may have contributed but not enough information was provided for detailed assessment.*

Subject ID	PDL1 status	Narrative	Reviewer's Comments
(b) (6)	Negative	Primary Reported Cause of Death: Unknown 46-year-old female with metastatic cervical cancer (metastasis to bladder). Her PMH included retinal failure (eye disorder), back pain, and hypothyroidism. Concomitant medications included fentanyl patch, parnaparin, pregabalin, citalopram, trazodone, levothyroxine, amitriptyline and lansoprazole. She had received four prior lines of therapy including radiation prior to initiating pembrolizumab on (b) (6). She received 4 doses of pembrolizumab and experienced diarrhea, dehydration, hypokalemia, hypocalcemia, hyperuricemia, increase in serum creatinine and hematuria during the treatment. The patient experienced progression of the disease and pembrolizumab was discontinued on (b) (6). She died on (b) (6) and no further details were provided.	*The primary cause of death is unknown. Not enough information available for detailed assessment. Likely that the patient died due to disease progression.*
(b) (6)	Negative	Primary Reported Cause of Death: Intestinal obstruction 47-year-old female with metastatic cervical cancer (metastasis to abdominal cavity). Her PMH included obesity, sacral pain, leg pain and generalized weakness. Information on concomitant medications was not provided. She had received neoadjuvant and adjuvant chemotherapy and radiation before initiating pembrolizumab on (b) (6). On (b) (6), the patient was admitted to the hospital with acute bowel obstruction. The patient underwent colostomy and was in the ICU but died on (b) (6) due to multiple organ failure as a consequence of acute bowel obstruction.	*It is not uncommon for intestinal obstruction to develop in patients with metastatic cervical cancer and it is likely that patient did not die due to an AE of pembrolizumab treatment.*

Serious Adverse Events

Regardless of causality, 83 SAE events were experienced by 51 (52.0%) patients in the group of all ITT population (n=98). Excluding malignant neoplasm progression (16.3%), SAEs occurred in 38 (39%) patients, with anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%) reported most frequently.

In PDL1 positive patients with at least 1 prior line of chemotherapy (n=77), anemia (6.5%), fistula (5.2%), and hemorrhage (4%), continued to be the most frequently reported SAEs. The remaining SAEs, in both groups, occurred in ≤ 4% of patients. The SAEs by maximum toxicity grade and frequency are listed in Table 25 and Table 26 respectively. Reports of malignant neoplasm progression were excluded from our analysis.

Table 25: Subjects with Serious Adverse Events by Maximum Toxicity Grade

SAE by Max toxicity grade	ITT population (n=98)	PDL1 Positive with at least 1 prior line of chemotherapy (n=77)
Total Events	57	44
Grade 1	2	2
Grade 2	7	5
Grade 3	43	34
Grade 4	2	2
Grade 5	3*	1†

Source: ADAE Dataset.
*A total of 17 deaths occurred. However, 14/17(82.4%) of deaths were due to malignant neoplasm progression.
†A total of 11 deaths occurred in this group. However, 10/11(91%) of deaths were due to malignant neoplasm progression.

Table 26: Serious Adverse Events by Preferred Term Experienced In ≥ 2% of Cervical Cancer Patients

SOC PT	ITT Population (n=98)	PDL1 Positive with at least 1 prior line of chemotherapy (n=77)
	All grades* (%)	
Patients with any SAEs	38 (39)	28 (36.4)
Blood and Lymphatic system disorder		
Anaemia	6 (6.1)	5 (6.5)
Haemorrhage†	4 (4.1)	3 (3.9)
Infections and infestations		
Infection (except UTI)††	5 (5.1)	3 (3.9)
Urinary Tract Infection (UTI)¶	3 (3.1)	2 (2.6)
Gastrointestinal disorders		
Diarrhea‡	3 (3.1)	1 (1.3)
Fistula§	4 (4.1)	5 (5.2)
Intestinal Obstruction	3 (3.1)	2 (2.6)
Abdominal Pain||	2 (2)	2 (2.6)

SOC PT	**ITT Population (n=98)**	**PDL1 Positive with at least 1 prior line of chemotherapy (n=77)**
	All grades* (%)	
Renal and urinary disorders		
Hydronephrosis	3 (3.1)	3 (3.9)
Musculoskeletal and connective tissue disorders		
Musculoskeletal Pain**	1 (1)	1 (1.3)
General disorders and administration site conditions		
Death	2 (2)	1 (1.3)
Cancer Pain	1 (1)	1 (1.3)
Respiratory, thoracic and mediastinal disorders		
Pleural Effusion	2 (2)	1 (1.3)

Source: ADAE and ADSL Dataset.
*Graded per NCI CTCAE v4.0
†Includes epistaxis, hematuria, hemoptysis, metrorrhagia, rectal hemorrhage, uterine hemorrhage, vaginal hemorrhage
†† 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
¶ Includes bacterial pyelonephritis, pyelonephritis acute, urinary tract infection, urinary tract infection bacterial, urinary tract infection pseudomonal, urosepsis
‡ Includes colitis, diarrhea, gastroenteritis
§ Includes colonic fistula, vaginal fistula, enterovesical fistula, female genital tract fistula and fistula of small intestine
|| Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal distension, abdominal discomfort
** Includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, myositis, neck pain, non-cardiac chest pain, pain in extremity

<u>Reviewer comment:</u> We compared the safety results of our analyses to the safety findings from the pembrolizumab reference safety dataset (RSD; N=2799; data from melanoma and NSCLC trials), which per the applicant reflects the established safety profile for pembrolizumab.

Though not combined in the applicant's submission, the reviewer pooled several PTs, resulting in infections (except UTIs), hemorrhages and fistulas being frequent SAEs. The incidence of these SAE (hemorrhages and fistulas) was much lower in the RSD, which may be due to differences in the underlying disease state. Overall, when examining the SAEs in the ITT population compared to the PDL1 positive population with at least 1 prior line of chemotherapy (n=77), the numbers are similar, with a slightly higher percentage of the most frequent SAEs in the ITT population.

Interruptions and/or Discontinuations Due to Adverse Effects

Adverse events (AEs) that led to treatment interruption, regardless of causality, occurred in 29 (29.6%) patients in the ITT and 23 (29.9%) patients in the PDL1 positive population with at least 1 prior line of chemotherapy respectively. AEs that led to treatment interruption most frequently were elevated LFTs, UTIs, musculoskeletal, chest and abdominal pain in both groups (see Table 27). Median times to discontinuation due to AE were similar for patients in both groups (5.9 and 6.7 months, respectively).

Table 27: Adverse Events Resulting in Dose Interruption of Pembrolizumab in ≥ 2% of Patients

Pooled AEs leading to dose interruption*	**ITT Population (n=98)**	**PDL1 Positive with at least 1 prior line of chemotherapy (n=77)**
	N (%)	
Any AE leading to dose interruption	**29 (29.6)**	**23 (29.9)**
Elevated LFTs	9 (9.2)	4 (5.2)
UTIs	4 (4.1)	3 (3.9)
Chest pain	3 (3.1)	3 (3.9)
Musculoskeletal Pain	3 (3.1)	3 (3.9)
Abdominal Pain	2 (2)	2 (2.6)
Anemia	2 (2)	2 (2.6)
Fatigue	2 (2)	2 (2.6)
Fistula	2 (2)	2 (2.6)
Rash	2 (2)	1 (1.3)

Source: ADAE and ADSL Dataset.
*See appendix 19.5 for the list of pooled PTs

Overall, 8 patients (8.2%) in the ITT population and 7 patients (9.1%) in the PDL1 positive population with at least 1 prior line of chemotherapy discontinued therapy due to an AE other than malignant disease progression. Table 28 provides information on these patients.

Table 28:Adverse Events Resulting in Permanent Discontinuation of Pembrolizumab

Subject Identifier	**PDL1 Status**	**AE leading to discontinuation**	**Toxicity grade**
(b) (6)	Positive	Elevated LFTs	3
	Positive	Vaginal Hemorrhage	4
	Positive	Elevated LFTs	4
	Positive	Death	5
	Negative	Intestinal Obstruction	5
	Positive	Colonic Fistula	3
	Positive	Mucosal Inflammation	2
	Positive	Diarrhea	3

Source: ADAE and ADSL Dataset.

Reviewer comment: Though not combined in the applicant's submission, the reviewer pooled several preferred terms (PTs) resulting in elevated LFTs being the most frequent AE leading to drug interruption. There were no notable differences among the ITT population and the PDL1 positive population with at least 1 prior line of chemotherapy, in terms of treatment interruption or discontinuation.

Significant Adverse Events

Adverse events of special interest (AESIs) were pre-specified as immune-mediated events and infusion-related events considered to be identified risks (adverse drug reactions) or potential risks for pembrolizumab. There were 25 (25.5%) patients with 1 or more AESIs (34 total AESIs). Of the 34 AESIs, 31 events were Grade 1 and 2, and 3 were Grade 3. The most common AESIs identified were hypothyroidism (11 patients, 11.2%), hyperthyroidism (9 patients, 9.2%), infusion related reactions (3 patients, 6 events; 3.1%), colitis (2 patients, 2.04%), rash (2 patients, 2.04%), and one event each of adrenal insufficiency, drug eruption, myositis, pneumonitis, and uveitis (1% each). Per the applicant, corticosteroids were used in 4 patients for 6 AESIs including infusion related reaction (2 patients;3 events), rash (1 patient), adrenal insufficiency and hypothyroidism (1 patient).

Table 29:Additional Patients identified During Review as AESIs

Subject Identifier	Event requiring CS	Outcome
(b) (6)	CTCAE grade 3 ALT/AST elevations	Resolved
	CTCAE grade 4 ALT and grade 3 AST elevations	Resolved

* Potential hepatitis
Source: ADAE and ADSL Dataset.

Table 30:Corticosteroid use and AESIs in KEYNOTE-158

	ITT population (n=98)		PDL1 Positive with at least 1 prior line of chemotherapy (n=77)	
	Events	N (%)	Events	N (%)
Corticosteroid administered for any AE	34	25 (25.5)	26	19 (24.7)
AESI†				
• Total	34	25 (25.5)	22	18 (23.4)
• Requiring steroids	8	6 (6.1)	3	2 (2.6)

Source: ADAE and ADSL Dataset.

Reviewer comment: Our review of the ADAE and ADCM datasets identified two additional AESIs in two patients (see Table 29). Both patients required corticosteroids for AEs. Moreover, our analysis indicated that corticosteroids were use in 6 patients for AESIs (summarized in Table 30). Request to update the dataset was sent to the applicant and updated dataset was submitted on

Treatment Emergent Adverse Events and Adverse Reactions

For the ITT population (n=98), the most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, decreased appetite, pain, constipation, abdominal pain and diarrhea. The most common Grade 3 and 4 events (occurring in >3% of patients) were UTIs, fatigue, infections (except UTIs), musculoskeletal pain, abdominal pain, and hemorrhage. Similar trends in AEs were observed in the PDL1 positive population with at least 1 prior line of chemotherapy.

Table 31:Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer

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	ITT Population (n=98)		PDL1 Positive with at least 1 prior line of chemotherapy (n=77)	
Adverse Reaction	**All Grades* (%)**	**Grades 3 – 4 (%)**	**All Grades* (%)**	**Grades 3 – 4 (%)**
General Disorders and Administration Site Conditions				
Fatigue†	42.9	5.1	37.7	6.5
Pain‡	22	2.0	19.5	2.6
Pyrexia	19.4	1.0	15.6	1.3
Edema peripheral§	15.3	2.0	18.2	2.6
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain¶	27.6	5.1	28.6	6.5
Gastrointestinal Disorders				
Diarrhea#	23.5	2.0	23.4	1.3
Abdominal painÞ	22.4	3.1	20.8	3.9
Nausea	19.4	0	19.5	0
Vomiting	19.4	1.0	18.2	1.3
Constipation	14.3	0	13.0	0
Metabolism and Nutrition Disorders				
Decreased appetite	21.4	0	18.2	0
Vascular Disorders				
Hemorrhageß	20.4	5.1	20.8	5.2
Infections and Infestations				
UTIà	18.4	6.1	19.5	5.2
Infection (except UTI)è	20.5	5.1	26	5.2
Skin and Subcutaneous Tissue Disorders				
Rashð	17	2.0	11.7	1.3
Endocrine Disorders				
Hypothyroidism	11.2	0	9.1	0
Nervous System Disorders				
Headache	11.2	2.0	11.7	2.6
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	10.2	1.0	9.1	1.3

* Graded per NCI CTCAE v4.0
Source: ADAE and ADSL Dataset.
† 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

Reviewer comment: *The most common Grade 3-4 AEs in the ITT population were fatigue, musculoskeletal pain, hemorrhage, UTI, infections (except UTI), and abdominal pain. In the PDL1 positive population with at least 1 prior line of chemotherapy (n=77), the numbers are similar, with a slightly higher percentage of the most frequent Grade 3-4 AEs.*

We compared the safety results of our analyses to the safety findings from the pembrolizumab RSD. The incidence of these certain TEAEs (UTIs, hemorrhages and fistulas) was much lower in the RSD, which may be due to differences in the underlying disease process. Overall, the incidence of adverse events with pembrolizumab in KEYNOTE-152 was similar to that observed in prior trials with this drug.

Laboratory Findings

All laboratory abnormalities were graded based on their CTCAE grade. An analysis of shifts from baseline in the CTCAE grade, based on the highest CTCAE grade for a given laboratory test during the trial, was performed. The most frequently (≥20%) reported laboratory values that showed worsening in CTCAE grade from baseline, were anemia (54%), decreased lymphocytes (47%) and decreased albumin (44%).

Most laboratory abnormalities consisted of abnormal electrolytes, increased creatinine levels, and elevated transaminases. Please refer to Table 32 for the most common Grade 3 and 4 laboratory abnormalities that occurred in > 2% of patients.

Table 32: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with Cervical Cancer in ITT Population (n=98)

Laboratory Test*	All Grades† (%)	Grade 3-4 (%)
Chemistry		
Hypoalbuminemia	44	5
Alkaline phosphatase increased	42	2.6
Hyponatremia	38	13
Hyperglycemia	38	1.3
Aspartate aminotransferase increased	34	3.9

Laboratory Test*	All Grades† (%)	Grade 3-4 (%)
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
† Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥10% of patients receiving pembrolizumab 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).

Reviewer comment: The review of lab data was challenging as several patients in the study were missing baseline lab analysis flag (ABLFL) but still had certain baseline variables populated.

Electrocardiograms (ECGs)

A standard 12-lead ECG was performed using local standard procedures once at screening and then as clinically indicated. Clinically significant abnormal findings were recorded as medical history.

QT

No new QT clinical trials were conducted for pembrolizumab for this indication. This dose and schedule of pembrolizumab has been approved for different indications in the past.

Immunogenicity

Adapted from the label

Pembrolizumab being a therapeutic protein has the potential for immunogenicity. No new immunogenicity data were submitted as part of this sBLA.

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 with the incidences of antibodies to other products may be misleading.

8.2.5. Analysis of Submission-Specific Safety Issues

Immune-mediated Adverse Events

Class effects associated with anti-PD-1/anti-PD-L1 drugs, are primarily immune-related and include pneumonitis, hepatitis, colitis, hypophysitis, immune-mediated nephritis, and endocrine abnormalities such as hyper-/hypothyroidism, adrenal insufficiency, and diabetes mellitus.

In KEYNOTE-158, for the ITT population, 34 immune-mediated adverse events occurred in 25 out of 98 patients (25.5%) and for PDL1 positive with at least 1 prior line of chemotherapy, 22 events occurred in 18 out of 77 patients (23.4%). Table 33 summarizes the most common immune mediated AEs.]

Table 33: Common Immune-mediated Adverse Events in KEYNOTE-158 (Group E)

Immune-mediated Adverse Event	ITT Population (n=98)	PDL1 Positive with at least 1 prior line of chemotherapy (n=77)
	N (%)	
Hypothyroidism	11.2	9.1
Hyperthyroidism	9.2	7.8
Diarrhea	2	1.3
Elevated LFTs (Hepatitis)	2	-
Rash	2	1.3
Adrenal Insufficiency	1	-
Musculoskeletal Pain	1	1.3
Pneumonitis	1	-
Uveitis	1	-

Source: ADAE, ADSL dataset
*Some patients may have experienced more than one adverse event

Reviewer comment: The immune-mediated adverse event profile of pembrolizumab in this study was similar to that seen with prior indications, and with other immunotherapy agents of the same class. No new safety signals were identified.

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

The applicant collected patient reported outcomes (PROs) using the EQ-5D-3L and EORTC QLQ-C30 questionnaires at pre-specified time points while on treatment and 30 days following treatment discontinuation. The PRO data collection schedule was at C1 (week 0), C2 (week 3),

C3 (week 6), C4 (week 9), C7 (week 18), C10 (week 27), C14 (week 39), then every 4 cycles (after 9 months), as well as at the discontinuation visit and at the follow-up visit.

EQ-5D-3L
The EQ-5D-3L instrument is self-administered and consists of 2 parts. The first part is comprised of 5 descriptors of current health state including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The patient rates each state on a 3-level scale (1=no problem, 2=some problem, 3=extreme problem). The second part of this instrument assesses general health status, and is measured by a visual analog scale called the EQ-5D VAS. This scale measures the patient's self-rated health status on a scale from 0 (worse imaginable health state) to 100 (best imaginable health state).

Reviewer comment: The EQ-5D-3L is a composite that incorporates self-reported ability to function, pain, and general health status as filled out by the patient. This instrument is a generic preference based measure intended to provide a health utility index value for use in economic analyses and lacks content validity for use in estimating clinical benefit for the purposes of labeling claims, though we acknowledge that this instrument is often used by other regulatory authorities and/or payers.

EORTC QLQ-C30
The EORTC QLQ-C30 is a 30-item questionnaire that is composed of the following:

- A global quality of life domain
- 5 multi-item functional domains that include physical, role, emotional, cognitive and social functioning
- 3 multi-item symptom domains that include fatigue, nausea/vomiting, and pain
- 6 single item symptom questions that assess other cancer-related symptoms which include dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact of cancer

The questionnaire has 28 items with 4-point responses from "Not at all" to "Very much" which are used to assess functioning and symptoms, and 2 items that use 7-point scales for assessing global health and overall quality of life. The EORTC QLQ-C30 measures were scored per the EORTC Scoring Manual. If more than 50% of the constituent items were completed for a multi-item domain in the EORTC QLQ-C30, a transformed score was computed, and for domains with less than 50% of the items completed, the domain was considered missing as stated in the manual. The transformed score for each domain ranges from 0 to 100. For functional domains, higher transformed scores indicate better status; and for symptom domains, higher transformed scores indicate more severe symptoms.

Reviewer Comment: The EORTC QLQ-C30 instrument assesses a variety of factors that affect patients on treatment. The 30 items do encompass a reasonable amount of issues that are pertinent to a patient's daily level of functioning, but this questionnaire is limited in its ability to

ascertain the cause of any decreased level of functioning or quality of life for an individual patient.

FDA analyses of the PROs focused on the physical function subscale of the EORTC QLQ-C30. Completion rates for this measure were greater than approximately 88% at all cycles where PRO data were scheduled to be collected. Figure 2 shows the mean change from baseline in physical function score over the scheduled assessments. There appears to be minimal to no improvement in physical function score from baseline.

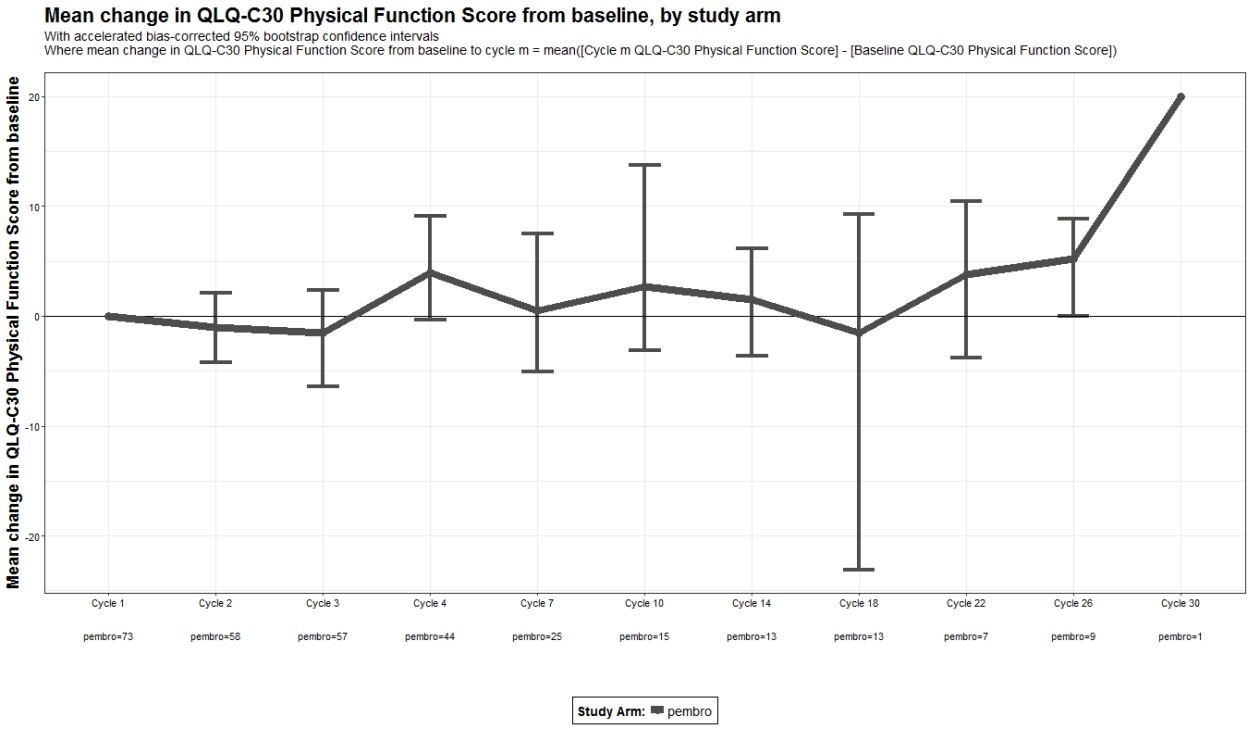

Figure 2: Mean change in QLQ-C30 Physical Function Score from baseline

8.2.7. Safety Analyses by Demographic Subgroups

A subgroup analyses based on gender was not performed as the study population was entirely (100%) female. Subgroup analyses based on age are shown in Table 34 below.

Table 34: Overall Summary of TEAEs by Age groups for ITT Population (N=98)

	Age >65 (n=8)	Age ≤65 (n=90)
Any TEAEs	8 (100)	89 (98.9)
SAEs	1 (12.5)	37 (41.1)
Grade 3-4 TEAEs	1 (12.5)	45 (50)

	Age >65 (n=8)	Age ≤65 (n=90)
TEAE with an outcome of death	0	3 (3.3)
TEAE leading to discontinuation	0	8 (8.9)
TEAE leading to treatment interruption	3 (37.5)	26 (28.9)

Source: ADAE, ADSL dataset

Reviewer Comment: The majority of the patients (91.8%) in this study were less than 65 years of age. Due to the small population of patients who were >65 years of age in KEYNOTE-158, a meaningful comparison is difficult to make. However, it is noteworthy that patients older than 65 had more SAEs, Grade 3-4 TEAEs and treatment interruptions compared to the less than 65 age group. Moreover, all deaths and treatment discontinuations also occurred in older than 65 age group. Eighty-seven of the patients in the study were from outside the U.S. The subgroups of races represented in the ovarian cancer safety population were White (79.6%), Asian (14.3%), Black or African American (2%) and other/multiple/ Alaskan native/missing (1% each).

8.2.8. Specific Safety Studies/Clinical Trials

No further studies were performed to address specific safety concerns.

8.2.9. Additional Safety Explorations

Safety Analyses by Exposure to Bevacizumab and Radiation Therapy

An exploratory analysis was performed to compare AEs in patients who had received prior treatment with bevacizumab and/or radiation (data cut-off date August 23, 2017). Student t-tests were performed to compare patients who had received patients who received both bevacizumab and radiation (n=35) versus all other patients (n=63) and for patients who had received radiation (85) versus no radiation (n=13) and bevacizumab (n=40) versus no bevacizumab (n=58).

Table 35: Exploratory Analysis

Pooled AEs	Radiation and Bevacizumab (n=35)	Other (n=63)	p-value
	N (%)	N (%)	
UTI	5 (14.3)	15 (23.8)	0.24
Pelvic pain	0	4 (6.4)	0.04
Intestinal obstruction	3 (8.6)	1 (1.6)	0.17
Elevated LFTs	6 (17.1)	9 (14.3)	0.72
Renal AEs	6 (17.1)	12 (19.1)	0.85
Hemorrhages	7 (20)	10 (15.9)	0.62
Fistulas	1 (2.9)	4 (6.4)	0.41

Pooled AEs	Radiation and Bevacizumab (n=35)	Other (n=63)	p-value
Anemia	13 (37.1)	11 (17.5)	**0.04**

Source: ADAE, ADSL dataset

Table 36: Exploratory Analysis

Pooled AEs	RT (+)	RT (-)	Total	T-test (RT+ vs RT-)	T-test (Bev+ vs Bev-)
UTI					
Bev (+)	5 (14.29)	2 (40)	7 (17.5)		
Bev (-)	12 (24)	1 (12.5)	13 (22.41)		
Total	17 (20)	3 (23.08)	20 (20.41)	0.82	0.55
Pelvic pain					
Bev (+)	0 (0)	0 (0)	0 (0)		
Bev (-)	3 (6)	1 (12.5)	4 (6.9)		
Total	3 (3.53)	1 (7.69)	4 (4.08)	0.61	0.04
Intestinal obstruction					
Bev (+)	3 (8.57)	0 (0)	3 (7.5)		
Bev (-)	1 (2)	0 (0)	1 (1.72)		
Total	4 (4.71)	0 (0)	4 (4.08)	0.04	0.21
Elevated LFTs					
Bev (+)	6 (17.14)	0 (0)	6 (15)		
Bev (-)	8 (16)	1 (12.5)	9 (15.52)		
Total	14 (16.47)	1 (7.69)	15 (15.31)	0.33	0.94
Renal AEs					
Bev (+)	6 (17.14)	0 (0)	6 (15)		
Bev (-)	9 (18)	3 (37.5)	12 (20.69)		
Total	15 (17.65)	3 (23.08)	18 (18.37)	0.68	0.47
Hemorrhages					
Bev (+)	7 (20)	2 (40)	9 (22.5)		
Bev (-)	8 (16)	0 (0)	8 (13.79)		
Total	15 (17.65)	2 (15.38)	17 (17.35)	0.84	0.29
Fistulas					
Bev (+)	1 (2.86)	1 (20)	2 (5)		
Bev (-)	3 (6)	0 (0)	3 (5.17)		
Total	4 (4.71)	1 (7.69)	5 (5.1)	0.72	0.97

Source: ADAE, ADSL dataset
Patients who received radiation therapy are abbreviated as RT+
Patients who did not receive radiation therapy are abbreviated as RT-

Patients who received bevacizumab therapy are abbreviated as Bev+
Patients who did not receive bevacizumab therapy are abbreviated as Bev-

Reviewer comment: Due to the small number of patients in each of the subgroups, no meaningful conclusion can be drawn, however it is noteworthy that statistical significance (p-value of 0.04) was observed for anemia between the subgroup that had received both bevacizumab and radiation therapies versus all other patients.

Analysis of Patients with Complete Response Lost to Follow-up

During review of this application we noted that 2 out of 3 patients with complete response (CR), were lost to follow-up. Those two responders had a duration of response (DOR) of 4.1 months and the other having CR with DOR of 3.7 months before being lost to follow up. A detailed review of the case report forms for the 2 patients was performed, Table 37 summarizes these two patients.

Table 37: Patients with Complete Response Lost to Follow-up

Subject ID	PDL1 status	Narrative	Reviewer's Comments
(b) (6) (Foreign)	Positive	61-year-old Asian female with metastatic cervical cancer (metastasis to lung). She initiated the study drug on (b) (6) and received the second dose on (b) (6). After the 2 doses, patient experienced several AEs and permanently discontinued the study drug due to Grade 3 elevations in AST, ALT on (b) (6). The survival follow-up summary reports that the patient was alive and had stable disease (last date of contact (b) (6)).	*The patient experienced several AEs which led to the discontinuation of the drug. Although not described in detail, patient was reported to have disease progression at last survival follow-up.*
(b) (6) (Foreign)	Positive	51-year-old female with metastatic cervical cancer (metastasis to lymph nodes, peritoneum). She initiated the study drug on (b) (6) and received the drug for 3 cycles (last dose on (b) (6)), discontinuing the treatment on (b) (6). The follow-up status on (b) (6) was reported as "Lost to Follow-Up".	*The patient experienced several AEs (asthenia and rash not resolved; headaches and myalgia resolved) which led to the discontinuation of the drug. The case report form states that the "subject judged inacceptable toxicities and wanted to stop study treatment. However, she's okay to continue with the follow up visit scheduled by protocol" but was eventually lost to follow-up shortly after drug discontinuation.*

Human Carcinogenicity or Tumor Development

This sBLA did not contain carcinogenicity studies.

Human Reproduction and Pregnancy

Adapted from the label

Based on its mechanism of action, pembrolizumab 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. Per the pembrolizumab label, women of reproductive potential should be advised to use highly effective contraception during treatment and for at least 4 months after the last dose of pembrolizumab.

Pediatrics and Assessment of Effects on Growth

Pembrolizumab has not been studied in a pediatric population. The Applicant has been granted a waiver of pediatric studies based on the low incidence of cervical cancer in the pediatric population (as of 5/9/18).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

For the purposes of the KEYNOTE-158 trial, any patient infused with 20% or more than the intended dose of pembrolizumab was reported as an overdose. No drug overdoses are noted to have occurred in this study. Also, no reports of drug abuse, withdrawal or rebound effects were observed with pembrolizumab use.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The periodic adverse experience report (PAER) covering period June 4, 2017 to September 3, 2017 (submitted September 26, 2017) was reviewed for the purposes of this application. During this report period, a total of 784 initial 15-day cases were submitted. Of these, follow-up information was submitted for 351 initial 15-day cases. In addition, 255 follow-up 15-day cases were submitted for cases initially submitted during a prior reporting period.

During the reporting period, the information related to severe skin reactions including Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) labeling changes were made to the U.S. label and the U.S. Medication Guide.

Expectations on Safety in the Postmarket Setting

Pembrolizumab has been marketed in the U.S. since 2014 and its safety profile is well understood. FDA will continue post-marketing safety surveillance.

8.2.11. Integrated Assessment of Safety

The safety profile of pembrolizumab in patients with recurrent or metastatic cervical cancer was assessed in all patients who received at least one dose of pembrolizumab. To ensure consistency of the safety profile, a safety analysis was also performed for PDL1 positive patients who had received at least 1 prior line of chemotherapy (efficacy population). For this review, the size of this safety population and the extent of exposure were adequate to allow for sufficient characterization of the safety of pembrolizumab for treatment of this serious and life-threatening condition.

Notable toxicities included a high incidence of fatigue, musculoskeletal pain, infections – both UTIs and non-UTI, although this is difficult to interpret the results in the disease setting of a single-arm trial. Immune-mediated adverse events have been observed and well characterized with use of checkpoint inhibitors such as pembrolizumab. Thyroid abnormalities, hepatitis, and diarrhea/colitis, were some of the commonly reported immune-mediated adverse events in this study.

This reviewer does not recommend a Risk Evaluation and Mitigation Strategy (REMS) given the current safety profile of pembrolizumab and the experience of the medical community in managing immune-mediated adverse reactions, based on use of this product and other FDA-approved immune checkpoint inhibitors. Recommendations for safe and effective use of pembrolizumab, including monitoring for immune-mediated adverse events, have been included in the label. In summary, the safety profile of pembrolizumab is acceptable for the intended population.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

Generally, there were no notable statistical issues with the study design, statistical analysis plan, or efficacy results for the cervical cohort in KEYNOTE-158. The study showed a confirmed ORR of 14.3% (95% CI: 7.4%, 24.1%) in the FDA's primary analysis population of patients with tumors that were PD-L1 positive and who had received at least one prior line of systemic chemotherapy for metastatic cervical cancer. We reiterate that no inferential procedures were used to evaluate results from this single arm study. Instead, the efficacy evaluation was based on the magnitude of response rate and adequate duration of response. Additionally, although PFS and OS results were summarized, we noted that time-to-event endpoints are uninterpretable without a comparator arm.

8.4. Conclusions and Recommendations

The review team recommends accelerated approval for the following indication:

Pembrolizumab 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.

The recommendation is based primarily upon the review of the study results from KN-158 which was a study in which 98 patients with cervical cancer received pembrolizumab 200 mg IV every 3 weeks until disease progression, death, or unacceptable toxicity.

Joyce Cheng
Primary Statistical Reviewer

Lijun Zhang
Statistical Team Leader

Gwynn Ison
Shaily Arora
Primary Clinical Reviewers

Sanjeeve Balasubramaniam
Clinical Team Leader

APPEARS THIS WAY ON ORIGINAL

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

APPEARS THIS WAY ON ORIGINAL

10 Pediatrics

Included in the sBLA submission was a request for waiver for study in all pediatric age groups for the indication of pembrolizumab in the treatment of cervical cancer, with the rationale that 0.1% of cervical cancers occur in females < 20 years of age in the US. The OCE PeRC convened on 5/9/18 and granted a full pediatric waiver, based upon the Applicant' request and justification.

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11 Labeling Recommendations

11.1. Prescription Drug Labeling

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights		
See Full Prescribing Information (FPI) for information related to corresponding revisions made in the Highlights.		
Full Prescribing Inforamtion		
1. Indications and Usage	**1.8 Cervical Cancer** KEYTRUDA is indicated for the treatment of patients with advanced cervical cancer with disease progression on or after chemotherapy *[see Clinical Studies (14.8)].* …	FDA revised this subsection to: 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 (14.8)].*
2. Dosage and Administration	**2.1 Patient Selection for Treatment of NSCLC or Gastric Cancer** **…**	FDA agreed to reformat this section in a bulleted format and added a statement to select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression in recurrent or metastatic cervical cancer to be consistent with the indication and companion diagnostic labeling best practices.
2. Dosage and Administration	**2.9 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 (14.8)].*	FDA agreed with the addition of this subsection and the proposed labeling statements.
5. Warnings and	(b) (4)	FDA removed (b) (4)

Precautions	(b) (4) [redacted] .	(b) (4) [redacted] This information was revised and added to subsection 5.7 Other Immune-Mediated Adverse Reactions.
5. Warnings and Precautions	**5.7 Other Immune-Mediated Adverse Reactions** (b) (4) [redacted] …	FDA revised this to the following: "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." …
6. Adverse Reactions	**6.1 Clinical Trials Experience** …	FDA agreed to the proposed labeling revisions to add and describe cohort E from the KEYNOTE-158 trial. FDA removed (b) (4) [redacted] . To provide adequate safety data for cervical cancer indications, • FDA added: "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%)." • FDA added the adverse reactions table (Table 14), laboratory

		abnormalities table (Table 15), and other laboratory abnormalities text statements.
14. Clinical Studies	**14.8 Cervical Cancer** **…**	FDA revised the study description to clarify (b) (4) [redacted] FDA revised the demographic and baseline disease descriptions from (b) (4) [redacted] to the patients that expressed PD-L1 with a CPS ≥1 (n=77) and had at least one line of prior chemotherapy to be more consistent with the indicated population for KEYTRUDA. FDA added: "No responses were observed in patients whose tumors did not have PD-L1 expression (CPS <1)." FDA revised the efficacy results table (Table 28) from (b) (4) [redacted] to use only the patients that expressed PD-L1 with a CPS >1 and at least one prior line of chemotherapy (n=77) to be more consistent with the indicated population for KEYTRUDA.

11.2. Patient Labeling

The Medication Guide for KEYTRUDA was updated to add the new indication for cervical cancer to the "What is KEYTRUDA?" section and to update the adverse reactions in the "What are the possible side effects of KEYTRUDA?" section.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

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13 Postmarketing Requirements and Commitment

There is one post-marketing requirement and one post-marketing commitment associated with this approval. The following post-marketing requirements and commitments (PMR and PMC) have been conveyed to the Applicant, along with expected due dates.

PMR-1 (AA): Conduct clinical trial KEYNOTE-826 (KN-826) in cervical cancer for progression-free survival (PFS), overall survival (OS), entitled "A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy vs. Chemotherapy Plus Placebo for the First-line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer." Submit analyses and datasets with final report for PFS and OS.

PMR Milestones:

Final protocol submission: 06/2018
Trial completion: 11/2022
Final report submission: 5/2023

Reviewer comment: The KN-826 is designed to be the clinical trial that will confirm the clinical benefit of pembrolizumab in patients with advanced, metastatic cervical cancer. The potential to fulfill the accelerated approval requirements of confirmation of clinical benefit is contingent upon the conduct of this trial and its results.

PMC-1: Submit the median Duration of Response (DOR) analyses and datasets with the final report of clinical trial Keynote-158 (Cohort E), entitled: "A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors."

PMC Milestones:

Trial Completion: 8/2019
Final report submission: 2/2020

14 Division Director (DHOT)

Not Applicable.

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15 Division Director (OCP)

Not Applicable.

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16 Division Director (OB)

Jason Schroeder, PhD
Associate Director, Division of Biometrics 5
Office of Biostatistics

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17 Division Director (Clinical)

Julia Beaver, MD
Director, Division of Oncology Products 1

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18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Julia Beaver, MD

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19 Appendices

19.1. References

1. 21 Code of Federal Regulations, Part 601.41.

2. Cervical Cancer: Estimated Incidence, Mortality, and Prevalence Worldwide in 2012. International Agency for Research on Cancer and World Health Organization; 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

3. Parkin DM, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-7108.

4. Kamanger F, et al. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006; 24: 2137-2150.

5. Jemal A, et al. Global cancer statistics. CA Cancer J Clin 2011: 62: 69-90.

6. Siegel R, et al. Cancer statistics, 2016. CA Cancer J Clin 2016: 66(1): 7-30.

7. Villa LL, et al. Prophylactic quadrivalent human papilloma virus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicenter phase II efficacy trial. Lancet Oncol 2005; 6: 271-278.

8. Ault KA. Effect of prophylactic human papilloma virus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomized clinical trials. Lancet 2007; 369: 1861-1868.

9. Quadrivalent vaccine against human papilloma virus to prevent high-grade cervical lesions. N Engl J Med 2007; 356: 1915-1927.

10. Ries LAG, et al. SEER Cancer Statistics Review, 1975-2004. National Cancer Institute; Bethesda, MD 2007.

11. Tewari, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014; 370 (8): 734-43.

12. Sutton, et al. Phase II study of ifosfamide and mesna in patients with previously-treated carcinoma of the cervix. A gynecologic oncology group study. Invest New Drugs. 1989 Nov; 7 (4): 341-3.

13. Irvin, et al. A phase II study of irinotecan (CPT-11) in patients with advanced squamous cell

carcinoma of the cervix. Cancer. 1998 Jan 15; 82(2): 328-33.

14. Verschraegen, et al. Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. J Clin Oncol. 1997 Feb; 15(2): 625-31.

15. Coronel, et al. Weekly topotecan as second- or third-line treatment in patients with recurrent or metastatic cervical cancer. Med Oncol. 2009; 26(2): 210-4.

16. Fiorica, et al. A Phase II evaluation of weekly topotecan as a single agent second line therapy in persistent or recurrent carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol. 2009 Nov; 115(2): 285-9.

17. Lorusso, et al. Phase II study on weekly bolus topotecan in advanced or recurrent cervical cancer. Oncology. 2011; 80(5-6): 390-4.

18. Garcia, et al. Phase II clinical trial of docetaxel in refractory squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Am J Clin Oncol. 2007 Aug; 30(4): 428-31.

19. Lorusso, et al. Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. Ann Oncol. 2010 Jan; 21(1): 61-6.

20. Miller, et al. Gynecologic Oncology Group. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol. 2008 Jul; 110(1): 65-70.

21. Monk, et al. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2009 Mar 1; 27(7): 1069-74.

22. Alberts, et al. Phase II trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer: A gynecologic oncology group study. Gynecol Oncol. 2012 Dec; 127(3): 451-5.

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19.2. Financial Disclosure

Disclosure of financial interests of the investigators who conducted the clinical trial (KN-158) supporting this s-BLA, including statements of due diligence in cases where the applicant was unable to obtain the signed form from the investigators, was submitted in the FDA form 3454. There were no investigators or subinvestigators who reported financial interests requiring disclosure. Details are summarized below.

Covered Clinical Study (Name and/or Number): KN-158

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators/ subinvestigators identified: **814**		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 9		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

Not Applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

Not Applicable.

19.5. Pooled Terms Used for Safety Analyses

[To review the AE datasets, the following terms, as shown in table below were pooled for this review. These pooled terms are used for safety analysis.]

Pooled Term	Preferred Term (PT)
Abdominal pain	Abdominal pain
	Abdominal pain lower
	Abdominal pain upper
	Abdominal distension
	Abdominal discomfort
Acute kidney injury	Acute kidney injury
	Renal failure
Haemorrhage	Vaginal haemorrhage
	Metrorrhagia
	Haematuria
	Rectal haemorrhage
	Haemoptysis
	Epistaxis
	Uterine haemorrhage
Diarrhea	Diarrhoea
	Gastroenteritis

Pooled Term	Preferred Term (PT)
	Colitis
Elevated LFTs	Alanine aminotransferase increased
	Gamma-glutamyltransferase increased
	Aspartate aminotransferase increased
	Blood alkaline phosphatase increased
	Blood bilirubin increased
Fatigue	Asthenia
	Fatigue
	Malaise
	Lethargy
Fistula	Colonic fistula

Pooled Term	Preferred Term (PT)
	Vaginal fistula
	Enterovesical fistula
	Female genital tract fistula
	Fistula of small intestine
Infection	Empyema
	Uterine abscess
	Infection
	Device related infection
	Clostridium difficile infection
	Osteomyelitis
	Respiratory tract infection
	Bacterial pyelonephritis
	Lung infection
	Upper respiratory tract infection
	Cellulitis
	Pseudomonas infection
	Tooth abscess
	Influenza
	Erysipelas
	Lower respiratory tract congestion
	Oral fungal infection
	Herpes virus infection
	Viral upper respiratory tract infection
	Oral candidiasis
	Viral upper respiratory tract infection
	Influenza
	Infected neoplasm
Infusion Related Reaction	Infusion related reaction
	Infusion site extravasation
	Infusion site erythema
	Infusion site oedema
Musculoskeletal Pain	Musculoskeletal chest pain
	Back pain

Pooled Term	Preferred Term (PT)
	Arthralgia
	Breast pain
	Pain in extremity
	Myositis
	Musculoskeletal pain
	Neck pain
	Myalgia
	Non-cardiac chest pain
Pain	Cancer pain
	Groin pain
	Ear pain
	Dysuria
	Stoma site pain
	Pain in extremity
	Dysaesthesia
	Pelvic pain
	Lymph node pain
	Pain
	Pain of skin
	Toothache
	Radicular pain
	Oropharyngeal pain
	Gingival pain
Rash	Rash maculo-papular
	Drug eruption
	Palmar-plantar erythrodysaesthesia syndrome
	Eczema
	Rash
	Erythema
	Rash generalised
	Dermatitis
Thromboembolism	Pulmonary embolism
	Deep vein thrombosis
	Portal vein thrombosis
	Venous thrombosis
UTI	Urosepsis
	Urinary tract infection
	Pyelonephritis acute

Pooled Term	Preferred Term (PT)
	Urinary tract infection bacterial
	Urinary tract infection pseudomonal
	White blood cells urine positive
	Vulvovaginal candidiasis
Vulvovaginal Pain	Vulvovaginal discomfort
	Vulvovaginal inflammation
	Vulvovaginal pain
	Vulvovaginal pruritus
	Vulvovaginal burning sensation

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/s/

FATIMA M RIZVI
06/11/2018

HUIMING XIA
06/11/2018

PENGFEI SONG
06/11/2018

JOYCE H CHENG
06/11/2018

LIJUN ZHANG
06/11/2018

ROBERT J SCHROEDER
06/11/2018

SHAILY ARORA
06/11/2018

GWYNN ISON
06/11/2018

SANJEEVE BALASUBRAMANIAM
06/11/2018

JULIA A BEAVER
06/11/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s034

PRODUCT QUALITY REVIEW(S)

Memorandum of Review:

Submission Tracking Number (STN):	BLA 125514/SUPPL-34
Subject:	(b) (4)
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 (KEYTRUDA)
Indication:	Advanced cervical cancer
Filing Action Date:	2/26/18
Action Due Date:	6/28/18

- **Recommendation: I recommend approval of this supplement.**

- **Future Inspection Items: None**

- **Executive Summary: This efficacy supplement is to support the use of pembrolizumab for a new indication (b) (4) The anti-drug antibody assay and neutralizing antibody assay that have been approved at (b) (4) were transferred to (b) (4) in (b) (4) and complete validations of these assays were performed at (b) (4). A statistical equivalence test showed no statistical significant difference in the drug tolerance values obtained at (b) (4), (b) (4), and (b) (4) and therefore, it was determined that the drug tolerances determined at (b) (4) would be the reported values for all three testing sites. However, the anti-drug antibody assay has high variability. As a caution, for the ADA screening assay, any data generated going forward using the ADA assay at the (b) (4) site should be determined inconclusive in the presence of ≥98 µg/mL of drug. A categorical exclusion from environmental assessment per 21 CFR 25.31(c) was claimed and is acceptable.**

- **Review:**

Reviewer comments are in italicized text. Unless otherwise noted, tables and figures are copied from the submission.

Introduction

The assays for determination of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were fully validated at (b) (4) in (b) (4) due to (b) (4) The assay

drug tolerance results at [redacted] were compared to the results obtained at the approved testing sites, [redacted] and [redacted] and the results showed that there was no statistical difference between the three labs. These assay validations and the statistical analysis comparing the sites are reviewed here.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

04RX2P – MK-3475 ADA Drug Tolerance Stat Memo – Comparison of Drug Tolerance by Lab

The MK-3475 ADA assay method has been validated at [redacted]. The drug tolerance was independently determined for each lab. Each lab performed three experimental runs and the final drug tolerance was calculated as the average of the three runs (Table 1).

Table 1: Summary drug tolerance at 250 ng/ml and 500 ng/ml anti-MK-3475 ADA.

Anti-MK-3475 ADA Concentration (ng/ml)	Lab	Lab Specific Drug Tolerance (µg/ml MK-3475)[2]	Recommended Uniform ADA Drug Tolerance Value[1] (µg/ml MK-3475)
250 ng/ml	[redacted]	[redacted]	124[1]
500 ng/ml			158[1]

[1]The recommended uniform drug tolerance level is based on the drug tolerance determined by [redacted], first lab to bring the MK-3475 ADA assay on-line).

[2]The calculated 95% confidence intervals for drug tolerance are based on an ANOVA analysis. The details on the calculation of the confidence interval can be found in the following section.

A statistical comparison was performed for ADA positive controls of 250 ng/mL and 500 ng/mL. Two complementary approaches were taken to analyze the data, which are described below.

First, a one-way analysis of variance (ANOVA) was performed using the individual drug tolerance estimates (Table 2, not copied here). The p-value for equivalence of drug tolerance across labs was 0.716 at ADA concentration of 250 ng/mL and 0.860 at ADA concentration of 500 ng/mL, indicating that the null hypothesis that the drug tolerance is equal across the labs cannot be rejected. This analysis showed that the difference in drug tolerance estimations were not statistically significant across labs.

Second, a linear mixed model was used to validate the observations of the ANOVA analysis: individual signal-to-noise values were modeled as a function of lab and drug concentration levels. Statistical tests were performed assuming the drug tolerance were at the 124 µg/mL and 158 µg/mL at 250 ng/mL and 500 ng/mL, respectively (the values at [redacted]). Table 3 (not copied here) reports the drug tolerance estimates by lab, the 95% confidence interval for the drug tolerance estimate, and the p-value for a t-test to test the equivalence of the estimated drug tolerance value from [redacted] and [redacted] against the [redacted] reported value. The p-values were all >0.05, which meant that the null hypothesis that the assay response at the [redacted] reported drug tolerance value is equal to the lab-specific cut-point could not be rejected. Thus, this test did

not find that the difference between the drug tolerance at (b) (4) and (b) (4) compared to the values estimated at (b) (4) to be statistically significant.

Conclusions

As a result of this analysis, the sponsor will be using a uniform drug tolerance level of 124 µg/mL MK-3475 at 250 ng/ml MK-3475 ADA and 158 µg/mL of MK-3475 at 500 ng/mL MK-3475 ADA. These were the drug tolerance values determine by (b) (4).

Reviewer comment: *The statistical analyses demonstrated that there was no statistical difference between the drug tolerance results at the three sites; therefore, the results determined at (b) (4) will be reported as the drug tolerance of the ADA assay. This is acceptable.*

Validation of an Electrochemiluminescence Immunoassay for the Detection of Anti-MK-3475 Antibodies in Human Serum Using Meso Scale Discovery Sector Imager 6000 Analyzer – Validation Report 15BAS0090 at (b) (4)

Principle of the Method

The ADA assay is an electrochemiluminescent (ECL) assay. Samples are 10% diluted (minimum required dilution) in acid to dissociate the antibody complex and incubated with biotin-labeled MK-3475, sulfo-TAG-labeled MK-3475, and drug (specificity/confirmatory assay only). Anti-MK-3475 antibodies forms a bridge between the labeled MK-3475, which are captured on MSD streptavidin-coated microtiter plate. Using the MSD 6000 plate reader, an electric current introduced across the plate-associated electrodes results in a series of electrically induced oxidation-reduction reactions involving ruthenium leading to a luminescent signal, which is quantified. The positive control used in the assay is a rabbit anti-MK-3475 anti-idiotype antibody, CDR-enriched affinity purified from (b) (4). The validation control samples were prepared at 4.5 ng/mL (LPC), 500 ng/mL (HPC), and 100 µg/mL (DPC). The assay negative control (NC) is pooled human matrix that was pre-screened for background.

Determination of anti-MK-3475 Screening Cut-Point

Screening cut-point was determined from analysis of 60 drug naïve healthy human serum samples in six different assay runs by three analysts (Table 3). Outlier evaluation was performed on the calculated signal/noise (S/N = mean response [test sample]/median NC response) ratios using Tukey's Outlier Test and five statistical outliers were removed. The S/N ratio of each population was rank ordered separately. The cut-point was determined from the 95th percentile of the rank order and was 1.22 for healthy human population. From this analysis, there were 18 non-confirmed positive responses of the 355 acceptable responses that were above the cut-point factor yielding a putative false positive rate of 5%. Samples that are above the screening cut-point in the Tier 1 screening assay are evaluated in the Tier 2 confirmatory assay.

Reviewer comment: *Determination of screening cut-point is acceptable.*

Determination of anti-MK-3475 Confirmatory Cut-Point

Confirmatory cut-point was determined by addition of a final concentration of 250 µg/mL unlabeled MK-3475 to the incubation mixture containing Biotin-MK-3475 and sulfo-TAG-MK-3475. A duplicate determination is made without addition of the unlabeled MK-3475. The cut-point was determined from analysis of 60 drug naïve healthy human serum samples in six different assay runs by three analysts. The percent inhibition for each sample was calculated. Outlier evaluation was performed on the percent inhibition data using Tukey's Outlier Test and

eight statistical outliers were removed. The percent inhibition of each population was rank ordered separately. The cut-point was determined from the 99th percentile of the rank order and was determined to be 25.7%. Samples with percent inhibition greater than the confirmatory cut-point will be considered positive for anti-MK-3475 antibodies and additional antibody specificity will be determined in Tier 3 testing.

Reviewer comment: *Determination of confirmatory cut-point is acceptable.*

Relative Sensitivity and LPC Determination for the Screening Assay
Screening sensitivity was determined from six runs performed by four analysts (Table 5). The anti-MK3475 positive control was 1:2 diluted starting from a concentration of 10 ng/mL and ending at a concentration of 0.078 ng/mL. Assay sensitivity was determined as mean concentration + (1.645 SD), which gave a sensitivity of 0.81 ng/mL. The LPC was determined to be 1.01 ng/mL (mean concentration + (t0.99 SD)).

Relative Sensitivity and LPC Determination for the Confirmatory Assay
Assay sensitivity for the confirmatory assay was determined from six runs performed by four different analysts (Table 6). The positive control was diluted as described above. Assay sensitivity was determined as mean concentration + (2.326 SD), which gave a sensitivity of 1.01 ng/mL. The LPC was determined to be 1.18 ng/mL (mean concentration + (t0.99 SD)).

Determination of Low Positive Controls
LPCs of 1.5 ng/mL and 4.5 ng/mL were evaluated in the assessment of assay precision and selectivity. The 1.5 ng/mL control met the assay acceptance criteria for selectivity but did not meet the criteria for precision. The 4.5 ng/mL control met the assay acceptance criteria for both precision and selectivity. Therefore, 4.5 ng/mL was used as the LPC in all tier testing and for future assays.

Reviewer comment: *The sensitivity of the screening and confirmatory assay was appropriately determined. A 4.5 ng/mL control will be used as the LPC for all assays because it passed the acceptance criteria for precision and selectivity, which is acceptable.*

Precision for Screening Assay
Intra-assay precision had %CV of ≤ 19.1% (range 1.6 – 19.1%) for HPC, ≤7.0% (range 1.9 – 7.0%) for LPC of 1.5 ng/mL, and ≤14.5% (range 3.1 – 14.5%) for LPC of 4.5 ng/mL. Inter-assay precision had %CV of 15.4% for HPC, 13.3% for LPC of 1.5 ng/mL, and 16.4% for LPC of 4.5 ng/mL.

Precision for Confirmatory Assay
Intra-assay precision had %CV of ≤ 0.1% (range 0.0 – 0.1%) for HPC, ≤31.0% (range 7.4 – 31.0%) for LPC of 1.5 ng/mL, and ≤5.7% (range 1.1 – 5.7%) for LPC of 4.5 ng/mL. Inter-assay precision had %CV of 0.1% for HPC, 37.7% for LPC of 1.5 ng/mL, and 13.0% for LPC of 4.5 ng/mL.

Reviewer comment: *LPC of 1.5 ng/mL did not pass the criteria for precision. As described above in "Determination of Low Positive Controls," because the 4.5 ng/mL LPC passed all the criteria, it will be used as the LPC for all future studies.*

Matrix Selectivity

Selectivity was assessed by testing human serum samples obtained from 10 healthy human donors, 10 hemolyzed samples, and 1 lipemic sample. Disease matrices included 10 individual samples each from patients with NSCLC, melanoma, and gastric cancer. The results demonstrated that at least 90% of the samples tested (healthy donor, NSCLC, melanoma, and gastric matrices) were positive in the screening assay when fortified at the HPC and LPC (pages 16 – 17 of the report and Table 9). In lipemic serum, the non-fortified sample was negative whereas the fortified samples, at HPC and both LPCs, were positive. For hemolyzed sera (prepared from one healthy human serum sample), the non-fortified sample tested positive whereas the fortified samples tested positive. Repeat analysis with hemolyzed sample showed that 10 non-fortified samples were negative and 10 fortified samples at HPC and 4.5 ng/mL LPC were positive but 8/10 fortified samples at 1.5 ng/mL LPC were positive. The 10 fortified samples were further confirmatory repeated in two additional runs for 1.5 ng/mL LPC and 10 fortified samples were confirmed positive for two times in the confirmatory repeat runs.

Reviewer comment: *Matrix selectivity is acceptable for the assay. There may be matrix interference in hemolyzed samples that will interfere with detection of low concentrations of ADA (1.5 ng/mL).*

Drug Tolerance

Drug tolerance was for ADA concentrations of 0 – 500 ng/mL were tested in the presence of 0 – 400 µg/mL of drug in three separate runs by two analysts. From this analysis, drug tolerances are reported to be (b) (4) and (b) (4) for ADA concentrations of 250 ng/mL and 500 ng/mL, respectively. The data are shown in Table 10.

Reviewer comment: *Review of data in Table 10 (page 44) shows that for the three tests performed, ADA concentration of 250 ng/mL is detected in the presence of 50 µg/mL drug in 3/3 tests, in the presence of 100 µg/mL drug in 1/3 tests, and in the presence of 200 µg/mL drug in 1/3 tests. Although, review of the three tests shows that the worst-case drug tolerance was 50 µg/mL, the forecasted drug tolerances were calculated to be (b) (4) µg/mL for the three tests. Similarly, ADA concentration of 500 ng/mL is detected in the presence of 50 µg/mL drug in 3/3 tests, in the presence of 100 µg/mL drug in 1/3 tests, and in the presence of 200 µg/mL drug in 1/3 tests. Again, although the worst-case drug tolerance was 50 µg/mL, the forecasted drug tolerances were calculated to be (b) (4) µg/mL. The final drug tolerance reported is the mean of the results from the three tests. The individual test results demonstrate that the assay has high variability. This is of concern because the sponsor performed a statistical equivalence test using (b) (4) and (b) (4) to show that the drug tolerance was not statistically different between (b) (4) (new site for ADA assay) and (b) (4) (current approved site for ADA assay), and as a result, the sponsor is proposing to use the drug tolerance values obtained at (b) (4), which is 250 ng/mL ADA is detectable in the presence of 124 µg/mL of drug and 500 ng/mL ADA is detectable in the presence of 158 µg/mL drug, as the values for the (b) (4) site.*

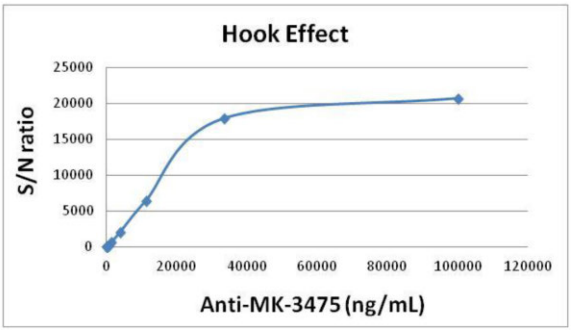
An IR was sent to the sponsor on April 24, 2018, requesting the raw data and signal to noise ratios for each of the runs performed during method validation of the ADA assay at (b) (4) to allow us to independently evaluate how the drug tolerances were determined at (b) (4) and whether the method of determining statistical equivalence between the different sites appeared reasonable. In the IR response (received May 1, 2018), the sponsor provided the raw data in Appendix 1 for drug tolerance experiments performed at (b) (4). In the three tests runs performed at (b) (4), the drug tolerances for ADA concentration of 250 ng/mL were 171, 154, and 47.5

µg/mL. The drug tolerances for ADA concentration of 500 ng/mL were 232, 173, and 68.6 µg/mL. These data show that the assay had high variability for determination of drug tolerance at (b) (4) *and the range of drug tolerance obtained at* (b) (4) *was comparable to the drug tolerance range obtained at* (b) (4)*. Therefore, use of the* (b) (4) *drug tolerance values because of the demonstration of statistical equivalence in the drug tolerances at the different sites is acceptable. However, as a caution, any data generated going forward using this assay at the* (b) (4) *site should be determined inconclusive in the presence of ≥98 µg/mL of drug.*

Prozone (Hook) Effect

Hook effect was examined for up to 100,000 ng/mL of anti-MK3475 antibodies and none was observed (Figure 1).

Figure 1 Prozone Effect of the Anti-MK-3475 Antibody Assay



Specificity

Assay specificity was tested by adding PD-L1, PD-L2, and human IgG4 at the same concentration as the drug in the confirmatory assay (250 µg/well) to the positive (HPC and LPC) and negative controls. None of the tested agents abrogated the response of the anti-MK-3475 antibody above the confirmatory cut-point of 25.7%.

Stability Studies

Stability studies were performed to test short-term stability of positive control in human serum at room temperature and 2-8°C, freeze/thaw stability of positive control in human serum, long-term stability of positive control in human serum stored at -80°C (study ongoing, data available for up to 3 months), long-term stability of positive control in human serum stored at -20°C (study ongoing, data available for up to 3 months), and long-term stability of labeled reagents stored at -80°C (study ongoing, data available for up to 12 months). The data demonstrate that anti-MK-3475 antibody and labeled reagents are stable at the tested conditions.

Conclusion

Reviewer comment: *The sponsor has performed a complete validation of the ADA assay at* (b) (4)*. The assay has a sensitivity of 0.81 ng/mL. An LPC of 4.5 ng/mL is detectable using the assay with high precision, selectivity, and specificity. Drug tolerance studies demonstrate that ADAs of 250 ng/mL and 500 ng/mL can be consistently detected in the presence 50 µg/mL drug; however, the sponsor reported the drug tolerance to be* (b) (4) *and* (b) (4) *for ADA concentrations of 250 ng/mL and 500 ng/mL, respectively.*

Validation of a Non-Cell-Based Ligand Binding Assay for the Detection of Anti-MK-3475 Neutralizing Antibodies in Human Serum by Electrochemiluminescence (ECL) Immunoassay – Validation Report 16BAS0338 at (b) (4)

Principle of the Method

The neutralizing antibody (NAb) assay is a bridging assay format. Biotinylated MK-3475 and soluble ruthenylated drug target PD-1 chimera Fc are used as the capture and detection agents, respectively. In the absence of anti-MK-3475 NAb, the biotinylated MK-3475 complexes with ruthenylated PD-1 resulting in an ECL signal. In the presence of NAb, the biotinylated MK-3475 cannot form a bridge with ruthenylated PD-1, resulting in decrease in ECL signal. The positive control used in the assay is a rabbit anti-MK-3475 anti-idiotype antibody, CDR-enriched affinity purified from (b) (4). The validation control samples were prepared at 52.8 ng/mL (LPC) and 500 ng/mL (HPC). The assay negative control (NC) is pooled human matrix that was pre-screened for background. No minimum required dilution (MRD) is required for the assay. However, the final sample dilution after addition of reagents is 1:2.4.

Determination of Assay Cut-Point

Assay cut-point was determined from analysis of 50 individual lots of normal human serum in six different assay runs performed by three analysts on three different days resulting in a total of 150 data points (Table 3 and Appendix 4). Signal-to-noise (S/N) values was calculated as the ratio of the sample determination to the mean negative control. The data was evaluated for outliers and normality by panel (2 assay runs per panel). Outlier evaluation using Tukey's method identified two outliers in panel 3, which were removed from further analysis resulting in 148 net observations. Shapiro-Wilk test for normality showed the null hypothesis of normality could not be rejected. Levene's test for equal variances showed that the null hypothesis of equal variances had to be rejected. One-way ANOVA analysis to test for equality of means showed that the null hypothesis for equality of means had to be rejected. The cut-point was calculated with a false positive rate of 1% and was determined to be 0.92.

Reviewer comment: *The cut-point was appropriately determined. However, there is no discussion on if this cut-point is going to be used as a floating or fixed cut-point. An IR was sent to the sponsor on April 24, 2018 to clarify if the cut-point is a fixed or a floating cut-point and how the normalization factor will be determined. In the IR response received on May 1, 2018, the sponsor stated the following:*

For the report in question, 04RYS4, and NAb assays conducted at (b) (4), the application of Normalization Cut Point Factor (NCPF) of 0.92 was used to calculate a floating cut-point for the NAb assay. The performance of the assay background or a Negative Control (NC) on a given day for a given run (96-well plate) is factored into the calculation for determining floating cut-point as: Plate Cut Point = Mean NC x NCPF. The Sponsor confirms that when NAb data from (b) (4) laboratories are submitted, a floating cut point is used to account for the run-to-run variability of the assay.

This response is acceptable.

Relative Sensitivity and LPC Determination for the Screening Assay

Sensitivity was determined from six runs performed by 3 analysts over 3 days. MK-3475 ADA was serially diluted in pooled normal human serum. The ADA concentration range was 500 ng/mL – 0.47 ng/mL. Assay sensitivity was calculated by linear interpolation of the ADA concentration across adjacent serial diluted samples that surround the assay cut-point (Table 2 in Appendix 4). The calculated mean sensitivity from the six runs was 16.0 ng/mL. The LPC was calculated as mean sensitivity value + $t_{0.99,df=5}$ * (standard deviation of sensitivity values) and was 52.8 ng/mL.

Reviewer comment: *The assay sensitivity and LPC were appropriately determined.*

Precision

Intra-assay precision had %CV of ≤ 17.3% (range 7.7 – 17.3%) for HPC and ≤12.5% (range 3.9 – 12.5%) for LPC. Inter-assay precision had %CV of 13.9% for HPC, 7.7% for LPC.

Reviewer comment: *Assay precision is acceptable.*

Matrix Selectivity

Selectivity was assessed by testing human serum samples obtained from 10 healthy human donors, 5 hemolyzed samples, and 5 lipemic samples. Disease matrices included 10 individual samples each from patients with NSCLC, melanoma, and gastric cancer. The results demonstrated that at least 90% of the samples tested had a result of negative (S/N > cut-point) and 100% of spiked samples had a result of HPC<LPC≤cut-point (Table 6).

Reviewer comment: *No matrix interference was observed for any of the samples tested, including hemolyzed and lipemic samples.*

Drug Tolerance

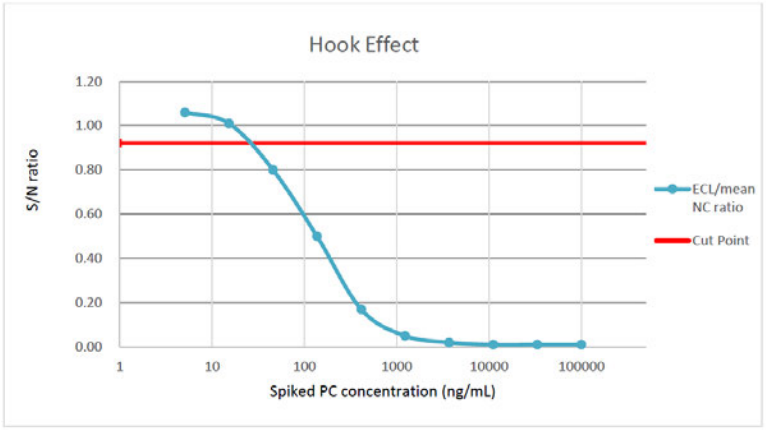
Drug tolerance for ADA concentrations of 0 – 500 ng/mL were tested in the presence of 0 – 250 µg/mL of drug in six separate runs performed by three analysts. Drug tolerance was determined by linear interpolation of the drug concentration across adjacent samples that bracketed the assay cut-point and the drug tolerances from six runs were averaged (Appendix 5 – Merck's Biostatistical Report "Memo of Drug Tolerance"). From this analysis, drug tolerance was determined to be 22.8 µg/mL of drug for 500 ng/mL ADA.

Reviewer comment: *Review of data in Table 7 shows that ADA concentration of 500 ng/mL is detected consistently in the presence of 16 µg/mL drug in 6/6 runs and it is not detectable in the presence of 40.0 µg/mL drug 6/6 runs. Therefore, the drug tolerance for the NAb assay is acceptable.*

Prozone (Hook) Effect

Hook effect was examined for up to 100,000 ng/mL of anti-MK3475 antibodies and no hook effect was observed (Figure 1).

Figure 1 Prozone Effect of the Anti-MK-3475 Antibody Assay



Stability Studies

Stability studies were performed to test short-term stability of positive control in human serum at room temperature and 2-8°C and freeze/thaw stability of positive control in human serum. The data demonstrate that anti-MK-3475 antibody are stable at the tested conditions. Analyses of long-term stability of positive control in human serum stored at -80°C and long-term stability of positive control in human serum stored at -20°C was removed from the NAb assay validation by a plan amendment due to sponsor's new departmental policy.

Conclusion

Reviewer comment: *The sponsor has performed a complete validation of the NAb assay at* (b) (4)*. The assay has a sensitivity of 16 ng/mL in pooled serum. LPC was estimated to be 52.8 ng/mL. Drug tolerance was determined to be 22.8 µg/mL of drug for 500 ng/mL ADA.*

Validation of an ECL Method for the Detection of Anti-MK3475 Antibodies in Human Serum 04RYS6 – RCZO9 – (b) (4) **Immunogenicity Report Addendum 6**

This addendum demonstrated the qualification of MSD 600 platform according to an approved method validation plan under Project Code "RCZ09." Intra-assay precision was evaluated for each positive control pool (LPC and HPC) by multiple analyses (n = 6) of each pool in each run. Intra-assay precision had %CV of 3.44% for LPC (uninhibited), 6.62% for HPC (uninhibited), 9.39% for LPC (inhibited), and 7.74% for HPC (inhibited). Inter-assay precision was calculated from the controls in multiple validation runs. Inter-assay precision had %CV of 5.19% for LPC (uninhibited), 4.61% for HPC (uninhibited), 6.14% for LPC (inhibited), and 4.89% for HPC (inhibited). Both intra-assay and inter-assay precision met the pre-defined acceptance criteria. Therefore, the MSD SECTOR S 600 plate reader was qualified for use in the ADA assay.

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: 5/11/2018 02:31:57PM
GUID: 583dce940076eea0edb730e401622d6d

Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 5/12/2018 03:39:13PM
GUID: 508da6d7000262dc015dcdc5f6541612

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s034

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: Friday, June 1, 2018

To: Fatima Rizvi
Regulatory Project Manger
Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products (OHOP)

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for Keytruda® (pembrolizumab) for injection

BLA: 125514/Supplement-034

In response to DOP1 consult request dated January 24, 2018, OPDP has reviewed the proposed product labeling (PI) and Medication Guide (MG) for the original BLA submission for Keytruda® (pembrolizumab) for injection (Keytruda). This supplement (SE-034) proposes a new indication for the treatment of certain patients with recurrent or metastatic cervical cancer.

OPDP's comments on the proposed labeling are based on the draft PI and MG received by electronic mail from DOP1 on May 22, 2018. OPDP has reviewed the draft PI for Keytruda and has no comments. A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed MG will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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

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/s/

NAZIA FATIMA
06/01/2018

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:	June 1, 2018
To:	Julia Beaver, MD Director **Division of Oncology Products 1 (DOP 1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** 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 injection KEYTRUDA (pembrolizumab) injection, for intravenous use
Application Type/Number:	BLA 125514
Supplement Number:	S-034
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On December 28, 2017, 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-034 for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection. With this supplement, the Applicant proposes a new indication for the treatment of patients with advanced cervical cancer who have received at least one line of prior therapy, based on data from the cervical cancer cohort (Group E) from study KEYNOTE 158 (KN158), *"A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors (KEYNOTE 158)."*

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 1 (DOP 1) on January 24, 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 December 28, 2017 and revised on May 18, 2018, and received by DMPP and OPDP on May 22, 2018.
- Draft KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection Prescribing Information (PI) received on December 28, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 22, 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.

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/s/

SHARON R MILLS
06/01/2018

NAZIA FATIMA
06/01/2018

LASHAWN M GRIFFITHS
06/01/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 12, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 125514/S-034
Product Name and Strength:	Keytruda (pembrolizumab) for Injection, 50 mg/vial Keytruda (pembrolizumab) Injection, 100 mg/4mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck Sharp & Dohme Corp
FDA Received Date:	December 28, 2017
OSE RCM #:	2018-544
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Merck submitted an Efficacy Supplement with updated Keytruda Prescribing Information (PI) to propose an additional indication for the treatment of patients with advanced cervical cancer who have received at least one line of prior therapy.

This review responds to a DOP1 consult for DMEPA to evaluate the proposed Keytruda PI to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Keytruda PI and noted that the newly proposed section "2.9 Recommended Dosage for Cervical Cancer" contains the same dosage (200 mg every 3 weeks) and language as the approved melanoma and several other indications. Therefore, the proposed addition to the Dosage and Administration section is acceptable from a medication error perspective. There are no other changes to the Dosage and Administration section, Dosage Forms and Strengths, How Supplied/Storage and Handling, and Patient Counseling Information sections of the Keytruda PI. Therefore, we have no recommendations for the proposed Keytruda PI from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The proposed Keytruda PI is acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Keytruda received on December 28, 2018 from Merck.

Table 2. Relevant Product Information for Keytruda	
Initial Approval Date	9/4/2014
Active Ingredient	pembrolizumab
Indication	**Melanoma** • for the treatment of patients with unresectable or metastatic melanoma. **Non-Small Cell Lung Cancer (NSCLC)** • 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 KEYTRUDA. • 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. 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) **Urothelial Carcinoma** • for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. • 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 o solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or o colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Table 2. Relevant Product Information for Keytruda	
	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. **Cervical Cancer[a]** • for the treatment of patients with advanced cervical cancer with disease progression on or after chemotherapy.
Route of Administration	Intravenous
Dosage Form	For injection and Injection
Strength	For injection: 50 mg/vial Injection: 100 mg/4 mL (25 mg/mL)
Dose and Frequency	Melanoma: 200 mg every 3 weeks. NSCLC: 200 mg every 3 weeks. HNSCC: 200 mg every 3 weeks. cHL: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. Urothelial Carcinoma: 200 mg every 3 weeks. MSI H Cancer: 200 mg every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for children. Gastric Cancer: 200 mg every 3 weeks. Cervical Cancer: 200 mg every 3 weeks.
How Supplied	For injection (lyophilized powder): carton containing one 50 mg single-dose vial. Injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial
Storage	**For Injection:** Store vials under refrigeration at 2°C to 8°C (36°F to 46°F). **Injection:** 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.
Container Closure	**For Injection:** 15 mL (b) (4) glass tubing vial, a (b) (4) stopper and a (b) (4) seal. Injection: **Injection:** 10-mL (b) (4) glass tubing vial, a (b) (4), and a (b) (4) seal.

[a] Highlighted in yellow is the proposed addition to the current approved indication.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 4, 2018, we searched DMEPA's previous reviews using the terms, Keytruda. Our search identified 1 previous review[b] since January 18, 2018[c], and we confirmed that our previous recommendations were implemented.

APPEARS THIS WAY ON ORIGINAL

[b] Ogbonna, C. Label and Labeling Review for Keytruda (BLA 125514/S-030). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 18. RCM No.: 2017-2038.

[c] February 13, 2017 is the date of our last search in L:drive and AIMS for Keytruda as stated in Ogbonna, C. Label and Labeling Review for Keytruda (BLA 125514/S-030). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 18. RCM No.: 2017-2038.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 4, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community
Search Strategy and Terms	Match Exact Word or Phrase: Keytruda

D.2 Results

The search retrieved no articles relevant to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Keytruda labels and labeling submitted by Merck.

- Prescribing Information (Image not shown) received on December 28, 2018

G.2 Label and Labeling Images

N/A

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TINGTING N GAO
04/12/2018

CHI-MING TU
04/12/2018

Clinical Inspection Summary

Date	March 30, 2018
From	Lauren Iacono-Connors, Ph.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation
To	Fatima Rizvi, Regulatory Project Manager Gwynn Ison, Clinical Reviewer Shaily Arora, Clinical Reviewer Division of Oncology Products 1
sBLA #	125514 S-034
Applicant	Merck Sharp & Dohme Corp.
Drug	Keytruda® (pembrolizumab)
NME	No
Therapeutic Classification	Priority
Proposed Indication	Treatment of patients with advanced cervical cancer with disease progression during or following chemotherapy.
Consultation Request Date	February 6, 2018
Summary Goal Date	May 15, 2018
Action Goal Date	June 28, 2017
PDUFA Date	June 28, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study 3475-158 were submitted to the Agency in support of sBLA 125514 S-034. One CRO, (b) (4) was selected for audit.

The primary efficacy endpoint, Objective Response (OR) per RECIST 1.1 as determined by an Independent Review Center (IRC), performed by CRO (b) (4) was verifiable with the source records generated by the IRC. There were no significant inspectional findings for CRO (b) (4)

The data from Study 3475-158 submitted to the Agency in support of sBLA 125514 S-034, appear reliable based on available information.

II. BACKGROUND

Merck Sharp & Dohme Corp., seeks approval to market Keytruda® (pembrolizumab) for the treatment of patients with advanced cervical cancer with disease progression during or following chemotherapy.

Data from Study 3475-158, specifically Group E subjects (cervical carcinoma cohort) support the proposed indication.

The following overview of the Study 3475-158 is intended as background context for interpreting the inspectional findings.

Study 3475-158, is entitled "A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors (KEYNOTE 158)". A minimum of 200 and maximum of 1350 subjects were to be enrolled into 1 of 11 solid tumor groups (Groups A-K). Subjects with advanced cervical cancer were enrolled into Group E, with a planned enrollment of approximately 100 subjects. Study 3475-158 screened 157 subjects and enrolled 98 subjects with advanced cervical cancer (Group E) at 42 clinical centers in 17 countries. The Group E subject cohort is the focus for this CRO inspection.

Study Period: Study completion date: Ongoing
Data cutoff date for analysis: August 23, 2017
Primary efficacy endpoint: Independently assessed Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).
Objectives of Inspections:

a. Verify the efficacy response data generated by the CRO for all subjects (98) treated in Group/Cohort E (Cervical Carcinoma).
b. Verify all contracted sponsor-related responsibilities to the CRO to perform a blinded central review of imaging for efficacy assessment, and their conduct of those responsibilities.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
(b) (4)	Protocol: 3475-158 98 subjects (Group E: Cervical Carcinoma)	(b) (4)	Preliminary Classification NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. CRO: (b) (4). (Independent Review Center for imaging/clinical data assessment)

This inspection was issued to review the conduct of one clinical study (3475-158)performed in support of sBLA 125514 S-034. The inspection focused primarily on assessing the accuracy of the tumor response and disease progression source records as it pertains to the contractual obligations of the CRO. Subject source documents/records generated by the CRO for all 98 subjects (Group E: Cervical Carcinoma Cohort) were compared to the data listings submitted to the application. The CRO reviewed a total of 373 imaging timepoints (including baseline) for all 98 subjects from 42 clinical sites. Assessment of (b) (4)'s conduct of the Charter-Specified CRO responsibilities included training, education, and qualifications of radiologists, correspondence with clinical sites/sponsor, intra- and inter-reader quality plan and findings, software review, data collection and management, and Independent Review Charter review and adherence.

All reviewed subjects' image readings performed by the CRO radiologists were verified against the data listings submitted to the application. There were no discrepancies. There was no evidence of CRO non-compliance with the Charter.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., Team Leader, acting for
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. sBLA #125514 S-034
DOP1/Division Director (Acting)/Julia Beaver
DOP1/Clinical Team Leader/Sanjeeve Balasubramaniam
DOP1/Project Manager/Fatima Rizvi
DOP1/Medical Officer/Gwynn Ison
DOP1/Medical Officer/Shaily Arora
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

LAUREN C IACONO-CONNORS
03/30/2018

SUSAN D THOMPSON
03/30/2018