CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s056

Trade Name:	KEYTRUDA
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp & Dohme Corp.
Approval Date:	July 30, 2019
Indication:	KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated: Melanoma • for the treatment of patients with unresectable or metastatic melanoma. • for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. Non-Small Cell Lung Cancer (NSCLC) • in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC. • as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations and is:

    - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
    - metastatic.
- 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 profression 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.

Small Cell Lung Cancer (SCLC)

- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[1]

Head and Neck Squamous Cell Cancer (HNSCC)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS)≥1] as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

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.[1]

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

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

Urothelial Carcinoma

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

Microsatellite Instability-High Cancer

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

Gastric Cancer

- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS)≥1] as determined by an FDA-aproved test with disease progression on or ater 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotheraoy and if appropriate, HER2/neu-targeted therapy.[1]

Esophageal Cancer

- for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

Cervical Cancer

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

Hepatocellular Carcinoma (HCC)

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

Merkel Cell Cancer MCC

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

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of patients with advanced RCC.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

125514Orig1s056

CONTENTS

Reviews / Information Included in this BLA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s056

APPROVAL LETTER

BLA 125514/S-55 and S-56

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp.
Attention: Michael D. Miller, Ph.D., Executive Director, Global Regulatory Affairs
Robert Kester, Director, Global Regulatory Affairs
351 N. Sumneytown Pike, P.O. Box 1000
UG2C-50
North Wales, PA 19454

Dear Dr. Miller and Mr. Kester:

Please refer to your supplemental biologics license applications (sBLAs), dated January 30, 2019, received January 30, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for KEYTRUDA® (pembrolizumab) for injection, for intravenous use, 50 mg and for KEYTRUDA® (pembrolizumab) injection, for intravenous use, 100 mg/4 mL.

These Prior Approval supplemental biologics applications provide for a new indication for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling text for the Prescribing Information

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

PROMOTIONAL MATERIALS

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

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

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

If you have any questions, please call Sharon Sickafuse, Senior Regulatory Health Project Manager, at 301-796-2320 or email sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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

/s/

PATRICIA KEEGAN
07/30/2019 06:59:16 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s056

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)	07/2019
Dosage and Administration (2)	07/2019
Warnings and Precautions (5)	06/2019

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

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

Melanoma

- for the treatment of patients with unresectable or metastatic melanoma. (1.1)
- for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. (1.1)

Non-Small Cell Lung Cancer (NSCLC)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.2)
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC. (1.2)
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic. (1.2, 2.1)
- 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, 2.1)

Small Cell Lung Cancer (SCLC)

- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[1] (1.3)

Head and Neck Squamous Cell Cancer (HNSCC)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC. (1.4)
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test. (1.4, 2.1)
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. (1.4)

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.[1] (1.5)

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.[1] (1.6)
- Limitations of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not elig ble for any platinum-containing chemotherapy regardless of PD-L1 status.[1] (1.7, 2.1)
- 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. (1.7)

Microsatellite Instability-High Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
  - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options,[1] or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1] (1.8)
- Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. (1.8)

Gastric Cancer

- 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 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1] (1.9, 2.1)

Esophageal Cancer

- for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy. (1.10, 2.1)

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 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.[1] (1.11, 2.1)

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC who have been previously treated with sorafenib.[1] (1.12)

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1] (1.13)

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of patients with advanced RCC. (1.14)

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

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

- Melanoma: 200 mg every 3 weeks. (2.2)
- NSCLC: 200 mg every 3 weeks. (2.3)
- SCLC: 200 mg every 3 weeks (2.4)
- HNSCC: 200 mg every 3 weeks. (2.5)
- cHL or PMBCL: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.6, 2.7)
- Urothelial Carcinoma: 200 mg every 3 weeks. (2.8)
- MSI-H Cancer: 200 mg every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.9)
- Gastric Cancer: 200 mg every 3 weeks. (2.10)
- Esophageal Cancer: 200 mg every 3 weeks. (2.11)
- Cervical Cancer: 200 mg every 3 weeks. (2.12)
- HCC: 200 mg every 3 weeks. (2.13)
- MCC: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.14)
- RCC: 200 mg every 3 weeks with axitinib 5 mg orally twice daily. (2.15)

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 (KEYTRUDA) and hepatotoxicity (KEYTRUDA in combination with axitinib): Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA, axitinib, or KEYTRUDA and axitin b. Consider corticosteroid therapy. (2.16, 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 possible organ rejection. (5.7)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.8)
- Complications of allogeneic HSCT (5.9):
  - Allogeneic HSCT after treatment with KEYTRUDA: Monitor for hepatic veno-occlusive disease, grade 3-4 acute GVHD including hyperacute GVHD, steroid-requiring febrile syndrome, and other immune-mediated adverse reactions. Transplant-related mortality has occurred.
  - Allogeneic HSCT prior to treatment with KEYTRUDA: In patients with a history of allogeneic HSCT, consider the benefit of treatment with KEYTRUDA versus the risk of GVHD.
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking ant body in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.10)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective method of contraception. (5.11, 8.1, 8.3)

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

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

- KEYTRUDA as a single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. (6.1)
- KEYTRUDA in combination with chemotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, and stomatitis. (6.1)
- KEYTRUDA in combination with axitin b: diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. (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: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2019

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.

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

1.2 Non-Small Cell Lung Cancer

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

KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with no EGFR or ALK genomic tumor aberrations, and is:

- stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
- metastatic.

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 *[see Dosage and Administration (2.1)]*, 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.

1.3 Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.4 Head and Neck Squamous Cell Cancer

KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

1.5 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.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.5)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.6 Primary Mediastinal Large B-Cell Lymphoma

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

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.6)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

1.7 Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14.7)]*. 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.

1.8 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.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.8)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

1.9 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 (CPS ≥1) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.9)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.10 Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥10) as determined by

an FDA-approved test *[see Dosage and Administration (2.1)]*, with disease progression after one or more prior lines of systemic therapy.

1.11 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 Dosage and Administration (2.1)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.11)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.12 Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.12)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.13 Merkel Cell Carcinoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.13)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.14 Renal Cell Carcinoma

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, or Cervical Cancer

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

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.2)]*.
- metastatic NSCLC *[see Clinical Studies (14.2)].*
- first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.4)]*.
- metastatic urothelial carcinoma *[see Clinical Studies (14.7)]*.
- metastatic gastric cancer *[see Clinical Studies (14.9)]*. 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.
- metastatic esophageal cancer *[see Clinical Studies (14.10)]*.
- recurrent or metastatic cervical cancer *[see Clinical Studies (14.11)]*.

Information on FDA-approved tests for the detection of PD-L1 expression for these indications is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage for Melanoma

The recommended dose of KEYTRUDA in patients with unresectable or metastatic melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease recurrence, unacceptable toxicity, or for up to 12 months in patients without disease recurrence.

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.

When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

2.4 Recommended Dosage for SCLC

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.

2.5 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.

When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

2.6 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.

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

2.7 Recommended Dosage for PMBCL

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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.

2.8 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.

2.9 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.

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.

2.10 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.

2.11 Recommended Dosage for Esophageal 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.

2.12 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.

2.13 Recommended Dosage for HCC

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

2.14 Recommended Dosage for MCC

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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.

2.15 Recommended Dosage for RCC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with 5 mg axitinib orally twice daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months in patients without disease progression. When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer. See also the Prescribing Information for recommended axitinib dosing information.

2.16 Dose Modifications

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

Table 1: Recommended Dose Modifications for Adverse Reactions

[see Warnings and Precautions (5.1-5.9)]

Adverse Reaction	Severity*	Dose Modification for KEYTRUDA
Immune-mediated pneumonitis	Grade 2	Withhold†
	Grades 3 or 4 or recurrent Grade 2	Permanently discontinue
Immune-mediated colitis	Grades 2 or 3	Withhold†

Adverse Reaction	Severity*	Dose Modification for KEYTRUDA
	Grade 4	Permanently discontinue
Immune-mediated hepatitis in patients with HCC	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 5 times upper limit of normal (ULN) if baseline less than 2 times ULN; AST or ALT greater than 3 times baseline if baseline greater than or equal to 2 times ULN Total bilirubin greater than 2.0 mg/dL if baseline less than 1.5 mg/dL; or Total bilirubin greater than 3.0 mg/dL, regardless of baseline levels	Withhold‡
	ALT or AST greater than 10 times ULN; or Child-Pugh score greater than or equal to 9 points; Gastrointestinal bleeding suggestive of portal hypertension; or New onset of clinically detectable ascites; or encephalopathy	Permanently discontinue
Immune-mediated hepatitis in patients without HCC For liver enzyme elevations in RCC patients treated with combination therapy, see dosing guidelines following this table.	AST or ALT greater than 3 but no more than 5 times the ULN or total bilirubin greater than 1.5 but no more than 3 times the ULN	Withhold†
	In patients without liver metastases, AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN In patients with liver metastasis and Grade 2 AST or ALT at baseline, with an increase in AST or ALT of 50% or more relative to baseline that persists for at least 1 week	Permanently discontinue
Immune-mediated endocrinopathies	Grades 3 or 4	Withhold until clinically stable
Immune-mediated nephritis	Grade 2	Withhold†
	Grades 3 or 4	Permanently discontinue
Immune-mediated skin adverse reactions	Grade 3 or suspected Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
Other immune-mediated adverse reactions	Grades 2 or 3 based on the severity and type of reaction	Withhold†
	Grade 3 based on the severity and type of reaction or Grade 4	Permanently discontinue
Recurrent immune-mediated adverse reactions	Recurrent Grade 2 pneumonitis Recurrent Grades 3 or 4	Permanently discontinue
Inability to taper corticosteroid	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks after last dose of KEYTRUDA	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathy)	Grades 2 or 3 adverse reactions lasting 12 weeks or longer after last dose of KEYTRUDA	Permanently discontinue
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion

Adverse Reaction	Severity*	Dose Modification for KEYTRUDA
	Grades 3 or 4	Permanently discontinue

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4)
† Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper.
‡ Resume in HCC patients when AST or ALT and total bilirubin recover to Grades 0-1 or to baseline.

In patients with RCC being treated with KEYTRUDA in combination with axitinib:

- If ALT or AST ≥3 times ULN but <10 times ULN without concurrent total bilirubin ≥2 times ULN, withhold both KEYTRUDA and axitinib until these adverse reactions recover to Grades 0-1. Consider corticosteroid therapy. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib Prescribing Information.
- If ALT or AST ≥10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN, permanently discontinue both KEYTRUDA and axitinib and consider corticosteroid therapy.

2.17 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. 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 diluted solution, 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 diluted solution, 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.

Discard after 6 hours at room temperature or after 24 hours under refrigeration.

Do not freeze.

Administration

- Administer diluted 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 white to off-white lyophilized powder in a single-dose vial for reconstitution
- Injection: 100 mg/4 mL (25 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.16) and Adverse Reactions (6.1)].*

In clinical studies enrolling 2799 patients with various cancers who received KEYTRUDA as a single agent, pneumonitis occurred in 94 (3.4%) patients, 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.

In clinical studies enrolling 790 patients with NSCLC who received KEYTRUDA as a single agent as first-line therapy for advanced disease, pneumonitis occurred in 65 (8.2%) patients, including Grades 3-4 in 3.2% of patients. Forty-eight of the 65 patients received high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days). Pneumonitis occurred in 17% of patients with a history of prior thoracic radiation and 7.7% of patients who did not receive prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 29 (3.7%) patients. Pneumonitis resolved in 51% of the patients.

In KEYNOTE-048 enrolling 300 patients with HNSCC who received KEYTRUDA as a single agent pneumonitis occurred in 18 (6%) patients, including Grade 3 (1.3%), Grade 4 (0%), and Grade 5 (0.3%). Eight of the 18 patients received high-dose corticosteroids for a median duration of 14 days (range: 1 to 77 days). Pneumonitis led to discontinuation of KEYTRUDA in 2 (0.7%) patients. Pneumonitis resolved in 12 (66%) of the patients. Pneumonitis occurred in 15 (5.4%) patients of 276 patients with HNSCC receiving KEYTRUDA in combination with platinum and FU as first-line therapy for advanced disease, including Grade 3 (1.1%), Grade 4 (0%), and Grade 5 (0.4%) pneumonitis. Four of the 15 patients received high-dose corticosteroids for a median duration of 16 days (range: 2 to 32 days). Pneumonitis led to discontinuation of KEYTRUDA in 5 (1.8%) patients. Pneumonitis resolved in 12 (80%) of the 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 (2.16) 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) and Hepatotoxicity (KEYTRUDA in Combination with Axitinib)

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 (2.16) 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.

Hepatotoxicity in Combination with Axitinib

KEYTRUDA in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib and consider administering corticosteroids as needed *[see Dosage and Administration (2.16)]*.

With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. The median time to onset of increased ALT was 2.3 months (range: 7 days to 19.8 months). Sixty-one percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (3%) or axitinib (31%) administered as a single agent or with both (50%), 55% had no recurrence of ALT >3 times ULN.

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 (2.16) 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 (2.16) 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 1185 patients with HNSCC (16%) receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) 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 (2.16) 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 (2.16) and Adverse Reactions (6.1)].*

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

5.6 Immune-Mediated Skin Adverse Reactions

Immune-mediated rashes, including SJS, TEN (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA *[see Dosage and Administration (2.16)].*

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

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients treated with KEYTRUDA: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other 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 (2.16)]*.

5.9 Complications of Allogeneic HSCT

Allogeneic HSCT after treatment with KEYTRUDA

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

Allogeneic HSCT prior to treatment with KEYTRUDA

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

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

In two randomized 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 trials.

5.11 Embryo-Fetal Toxicity

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

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling.

- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)]*.
- Immune-mediated colitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated hepatitis (KEYTRUDA) and hepatotoxicity (KEYTRUDA in combination with axitinib) *[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 reflect exposure to KEYTRUDA as a single agent in 2799 patients in three randomized, open-label, active-controlled 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 to the 2799 patients, certain subsections in the WARNINGS AND PRECAUTIONS describe adverse reactions observed with exposure to KEYTRUDA as a single agent in two randomized, open-label, active-controlled clinical trials (KEYNOTE-042 and KEYNOTE-024), which enrolled 790 patients with NSCLC; in a non-randomized, open-label, multi-cohort trial (KEYNOTE-012), a non-randomized, open-label, single-cohort trial (KEYNOTE-055), and two randomized, open-label, active-controlled trials (KEYNOTE-040 and KEYNOTE-048 single agent arms), which enrolled 909 patients with HNSCC; in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087), which enrolled 241 patients with cHL; in combination with chemotherapy in a randomized, active-controlled trial (KEYNOTE-189), which enrolled 405 patients with nonsquamous NSCLC; in a randomized, open-label, active-controlled trial (KEYNOTE-048 combination arm), which enrolled 276 patients with HNSCC; in combination with axitinib in a randomized, active-controlled trial (KEYNOTE 426), which enrolled 429 patients with RCC; and in post-marketing use. Across all trials, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among the 2799 patients, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

The data described in this section were obtained in ten randomized, controlled trials (KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-042, KEYNOTE-045, KEYNOTE-048, KEYNOTE-189, KEYNOTE-407, KEYNOTE-181, and KEYNOTE-426) and nine non-randomized, open-label trials

(KEYNOTE-028, KEYNOTE-012, KEYNOTE-087, KEYNOTE-170, KEYNOTE-052, KEYNOTE-059, KEYNOTE-158, KEYNOTE-224, and KEYNOTE-017). The data described in this section also included a single randomized, double-blind, placebo-controlled trial (KEYNOTE-054) in which KEYTRUDA was administered for the adjuvant treatment of 509 patients with melanoma with involvement of lymph node(s) following complete surgical resection. 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 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); 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%). Tables 2 and 3 summarize selected adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-006.

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

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

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

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

Table 3: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-006

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

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

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were increased hypoalbuminemia (27% all Grades; 2.4% Grades 3-4), increased ALT (23% all Grades; 3.1% Grades 3-4), and increased alkaline phosphatase (21% all Grades, 2% 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 investigated in 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)]*. 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, were ineligible.

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). In the KEYTRUDA 2 mg/kg arm, 36% of patients were exposed to KEYTRUDA for ≥6 months and 4% were 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); 61% male; 98% White; 41% had an elevated LDH value at baseline; 83% had 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%). Tables 4 and 5 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-002.

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

Adverse Reaction	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks n=357		Chemotherapy† n=171	
	All Grades‡ (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Pruritus	28	0	8	0
Rash§	24	0.6	8	0
Gastrointestinal				
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				
Cough	18	0	16	0
General				
Pyrexia	14	0.3	9	0.6
Asthenia	10	2.0	9	1.8
Musculoskeletal and Connective Tissue				
Arthralgia	14	0.6	10	1.2

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

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

Table 5: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-002

Laboratory Test†	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks		Chemotherapy	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	49	6	44	6
Hypoalbuminemia	37	1.9	33	0.6
Hyponatremia	37	7	24	3.8
Hypertriglyceridemia	33	0	32	0.9
Increased alkaline phosphatase	26	3.1	18	1.9
Increased AST	24	2.2	16	0.6
Decreased bicarbonate	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; decreased bicarbonate: 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).

Adjuvant Treatment of Resected Melanoma

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-054, a randomized (1:1) double-blind trial in which 1019 patients with completely resected stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma received 200 mg of KEYTRUDA by intravenous infusion every 3 weeks (n=509) or placebo (n=502) for up to one year *[see Clinical Studies (14.1)]*. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Seventy-six percent of patients received KEYTRUDA for 6 months or longer.

The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had stage IIIA, 46% had stage IIIB, 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (≥4 positive lymph nodes).

Two patients treated with KEYTRUDA died from causes other than disease progression; causes of death were drug reaction with eosinophilia and systemic symptoms and autoimmune myositis with respiratory failure. Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. Adverse reactions leading to permanent discontinuation occurred in 14% of patients receiving KEYTRUDA; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 19% of patients; the most common (≥1%) were diarrhea (2.4%), pneumonitis (2%), increased ALT (1.4%), arthralgia (1.4%), increased AST (1.4%), dyspnea (1%), and fatigue (1%). Tables 6 and 7 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-054.

Table 6: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-054

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=509		Placebo n=502	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	28	1.2	26	1.2
Nausea	17	0.2	15	0
Skin and Subcutaneous Tissue				
Pruritus	19	0	12	0
Rash	13	0.2	9	0
Musculoskeletal and Connective Tissue				
Arthralgia	16	1.2	14	0
Endocrine				
Hypothyroidism	15	0	2.8	0
Hyperthyroidism	10	0.2	1.2	0
Respiratory, Thoracic and Mediastinal				
Cough	14	0	11	0
General				
Asthenia	11	0.2	8	0
Influenza like illness	11	0	8	0
Investigations				
Weight loss	11	0	8	0

* Adverse reactions occurring at same or higher incidence than in placebo arm
† Graded per NCI CTCAE v4.03

Table 7: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-054

Laboratory Test†	KEYTRUDA 200 mg every 3 weeks		Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Increased ALT	27	2.4	16	0.2
Increased AST	24	1.8	15	0.4
Hematology				
Lymphopenia	24	1	16	1.2

* Laboratory abnormalities occurring at same or higher incidence than placebo.
† 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: 503 to 507 patients) and placebo (range: 492 to 498 patients).
‡ Graded per NCI CTCAE v4.03

NSCLC

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

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

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

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

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 53% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (13%), asthenia/fatigue (7%), anemia (7%), thrombocytopenia (5%), diarrhea (4%), pneumonia (4%), increased blood creatinine (3%), dyspnea (2%), febrile neutropenia (2%), upper respiratory tract infection (2%), increased ALT (2%), and pyrexia (2%). Tables 8 and 9 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-189.

Table 8: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE-189

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=405		Placebo Pemetrexed Platinum Chemotherapy n=202	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	56	3.5	52	3.5
Constipation	35	1.0	32	0.5
Diarrhea	31	5	21	3.0
Vomiting	24	3.7	23	3.0
General				
Fatigue†	56	12	58	6
Pyrexia	20	0.2	15	0
Metabolism and Nutrition				
Decreased appetite	28	1.5	30	0.5
Skin and Subcutaneous Tissue				
Rash‡	25	2.0	17	2.5
Respiratory, Thoracic and Mediastinal				
Cough	21	0	28	0
Dyspnea	21	3.7	26	5

* Graded per NCI CTCAE v4.03

† Includes asthenia and fatigue

‡ Includes genital rash, rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

Table 9: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-189

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy		Placebo Pemetrexed Platinum Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Anemia	85	17	81	18
Lymphopenia	64	22	64	25
Neutropenia	48	20	41	19
Thrombocytopenia	30	12	29	8
Chemistry				
Hyperglycemia	63	9	60	7
Increased ALT	47	3.8	42	2.6
Increased AST	47	2.8	40	1.0
Hypoalbuminemia	39	2.8	39	1.1
Increased creatinine	37	4.2	25	1.0
Hyponatremia	32	7	23	6
Hypophosphatemia	30	10	28	14
Increased alkaline phosphatase	26	1.8	29	2.1
Hypocalcemia	24	2.8	17	0.5
Hyperkalemia	24	2.8	19	3.1
Hypokalemia	21	5	20	5

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

† Graded per NCI CTCAE v4.03

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

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

The median duration of exposure to KEYTRUDA was 7 months (range: 1 day to 12 months). Sixty-one percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months. A total of 139 of 203 patients (68%) received paclitaxel and 64 patients (32%) received paclitaxel protein-bound in combination with carboplatin.

The study population characteristics were: median age of 65 years (range: 40 to 83), 52% age 65 or older; 78% male; 83% White; and 9% with history of brain metastases.

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

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

Previously Untreated NSCLC

The safety of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, open-label, randomized (1:1), active-controlled trial in 1251 patients with PD-L1 expressing, previously untreated stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC *[see Clinical Studies (14.2)].* Patients received KEYTRUDA 200 mg every 3 weeks (n=636) or investigator's choice of chemotherapy (n=615), consisting of pemetrexed and carboplatin followed by optional pemetrexed (n=312) or paclitaxel and carboplatin followed by optional pemetrexed (n=303) every 3 weeks. 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 thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA was 5.6 months (range: 1 day to 27.3 months). Forty-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 63 years (range: 25 to 90), 45% age 65 or older; 71% male; and 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Eighty-seven percent had metastatic disease (stage IV), 13% had stage III disease (2% stage IIIA and 11% stage IIIB), and 5% had treated brain metastases at baseline.

KEYTRUDA was discontinued for adverse reactions in 19% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3.0%), death due to unknown cause (1.6%), and pneumonia (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 33% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were pneumonitis (3.1%), pneumonia (3.0%), hypothyroidism (2.2%), and increased ALT (2.0%). The most frequent (≥2%) serious adverse reactions were pneumonia (7%), pneumonitis (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%).

Tables 10 and 11 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-042.

Table 10: Adverse Reactions Occurring in ≥10% of Patients in KEYNOTE-042

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=636		Chemotherapy n=615	
	All Grades* (%)	Grades 3-5 (%)	All Grades (%)	Grades 3-5 (%)
General				
Fatigue†	25	3.1	33	3.9
Pyrexia	10	0.3	8	0
Metabolism and Nutrition				
Decreased appetite	17	1.7	21	1.5
Respiratory, Thoracic and Mediastinal				
Dyspnea	17	2.0	11	0.8
Cough	16	0.2	11	0.3
Skin and Subcutaneous Tissue				
Rash‡	15	1.3	8	0.2
Gastrointestinal				
Constipation	12	0	21	0.2
Diarrhea	12	0.8	12	0.5
Nausea	12	0.5	32	1.1
Endocrine				
Hypothyroidism	12	0.2	1.5	0
Infections				
Pneumonia	12	7	9	6
Investigations				
Weight loss	10	0.9	7	0.2

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

Table 11: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients in KEYNOTE-042

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	52	4.7	51	5
Increased ALT	33	4.8	34	2.9
Hypoalbuminemia	33	2.2	29	1.0
Increased AST	31	3.6	32	1.7
Hyponatremia	31	9	32	8
Increased alkaline phosphatase	29	2.3	29	0.3
Hypocalcemia	25	2.5	19	0.7
Hyperkalemia	23	3.0	20	2.2
Increased prothrombin INR	21	2.0	15	2.9
Hematology				
Anemia	43	4.4	79	19
Lymphopenia	30	7	41	13

* 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: 598 to 610 patients) and chemotherapy (range: 588 to 597 patients); increased prothrombin INR: KEYTRUDA n=203 and chemotherapy n=173.

† Graded per NCI CTCAE v4.03

Previously Treated NSCLC

The safety of KEYTRUDA was investigated in 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 *[see Clinical Studies (14.2)]*. 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 or older; 61% male; 72% White and 21% Asian; and 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%). Tables 12 and 13 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-010.

Table 12: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-010

Adverse Reaction	KEYTRUDA 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m^2 every 3 weeks n=309	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Metabolism and Nutrition				
Decreased appetite	25	1.5	23	2.6
Respiratory, Thoracic and Mediastinal				
Dyspnea	23	3.7	20	2.6
Cough	19	0.6	14	0
Gastrointestinal				
Nausea	20	1.3	18	0.6
Constipation	15	0.6	12	0.6
Vomiting	13	0.9	10	0.6
Skin and Subcutaneous Tissue				
Rash‡	17	0.4	8	0
Pruritus	11	0	3	0.3
Musculoskeletal and Connective Tissue				
Arthralgia	11	1.0	9	0.3
Back pain	11	1.5	8	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 13: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving KEYTRUDA in KEYNOTE-010

Laboratory Test†	KEYTRUDA 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Chemistry				
Hyponatremia	32	8	27	2.9
Increased alkaline phosphatase	28	3.0	16	0.7
Increased AST	26	1.6	12	0.7
Increased ALT	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).

SCLC

Among the 131 patients with previously treated SCLC who received KEYTRUDA in KEYNOTE-158 Cohort G (n=107) and KEYNOTE-028 Cohort C1 (n=24) *[see Clinical Studies (14.3)]*, the median duration of exposure to KEYTRUDA was 2 months (range: 1 day to 2.25 years). Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required

immunosuppression were ineligible. Adverse reactions occurring in patients with SCLC were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

HNSCC

First-line treatment of metastatic or unresectable, recurrent HNSCC

The safety of KEYTRUDA, as a single agent and in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, was investigated in KEYNOTE-048, a multicenter, open-label, randomized (1:1:1), active-controlled trial in patients with previously untreated, recurrent or metastatic HNSCC *[see Clinical Studies (14.4)]*. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. A total of 576 patients received KEYTRUDA 200 mg every 3 weeks either as a single agent (n=300) or in combination with platinum and FU (n=276) every 3 weeks for 6 cycles followed by KEYTRUDA, compared to 287 patients who received cetuximab weekly in combination with platinum and FU every 3 weeks for 6 cycles followed by cetuximab.

The median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 24.2 months) in the KEYTRUDA single agent arm and was 5.8 months (range: 3 days to 24.2 months) in the combination arm. Seventeen percent of patients in the KEYTRUDA single agent arm and 18% of patients in the combination arm were exposed to KEYTRUDA for ≥12 months. Fifty-seven percent of patients receiving KEYTRUDA in combination with chemotherapy started treatment with carboplatin.

KEYTRUDA was discontinued for adverse reactions in 12% of patients in the KEYTRUDA single agent arm. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were sepsis (1.7%) and pneumonia (1.3%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 31% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were pneumonia (2.3%), pneumonitis (2.3%), and hyponatremia (2%).

KEYTRUDA was discontinued for adverse reactions in 16% of patients in the combination arm. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 45% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (14%), thrombocytopenia (10%), anemia (6%), pneumonia (4.7%), and febrile neutropenia (2.9%).

Tables 14 and 15 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-048.

Table 14: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-048

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=300		KEYTRUDA 200 mg every 3 weeks Platinum FU n=276		Cetuximab Platinum FU n=287	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
General						
Fatigue[†]	33	4	49	11	48	8
Pyrexia	13	0.7	16	0.7	12	0
Mucosal inflammation	4.3	1.3	31	10	28	5
Gastrointestinal						
Constipation	20	0.3	37	0	33	1.4
Nausea	17	0	51	6	51	6
Diarrhea[‡]	16	0.7	29	3.3	35	3.1
Vomiting	11	0.3	32	3.6	28	2.8
Dysphagia	8	2.3	12	2.9	10	2.1
Stomatitis	3	0	26	8	28	3.5
Skin						
Rash[§]	20	2.3	17	0.7	70	8
Pruritus	11	0	8	0	10	0.3
Respiratory, Thoracic and Mediastinal						
Cough[¶]	18	0.3	22	0	15	0
Dyspnea[#]	14	2.0	10	1.8	8	1.0
Endocrine						
Hypothyroidism	18	0	15	0	6	0
Metabolism and Nutrition						
Decreased appetite	15	1.0	29	4.7	30	3.5
Weight loss	15	2	16	2.9	21	1.4
Infections						
Pneumonia[Þ]	12	7	19	11	13	6
Nervous System						
Headache	12	0.3	11	0.7	8	0.3
Dizziness	5	0.3	10	0.4	13	0.3
Peripheral sensory neuropathy[ß]	1	0	14	1.1	7	1
Musculoskeletal						
Myalgia[à]	12	1.0	13	0.4	11	0.3
Neck pain	6	0.7	10	1.1	7	0.7
Psychiatric						
Insomnia	7	0.7	10	0	8	0

* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

‡ Includes diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis

§ Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, pruritic rash, seborrheic dermatitis

¶ Includes cough, productive cough

Includes dyspnea, exertional dyspnea

Þ Includes pneumonia, atypical pneumonia, bacterial pneumonia, staphylococcal pneumonia, aspiration pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal

ß Includes peripheral sensory neuropathy, peripheral neuropathy, hypoesthesia, dysesthesia

à Includes back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia

Table 15: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-048

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		KEYTRUDA 200 mg every 3 weeks Platinum FU		Cetuximab Platinum FU	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology						
Lymphopenia	54	25	69	35	74	45
Anemia	52	7	89	28	78	19
Thrombocytopenia	12	3.8	73	18	76	18
Neutropenia	7	1.4	67	35	71	42
Chemistry						
Hyperglycemia	47	3.8	55	6	66	4.7
Hyponatremia	46	17	56	20	59	20
Hypoalbuminemia	44	3.2	47	4.0	49	1.1
Increased AST	28	3.1	24	2.0	37	3.6
Increased ALT	25	2.1	22	1.6	38	1.8
Increased alkaline phosphatase	25	2.1	27	1.2	33	1.1
Hypercalcemia	22	4.6	16	4.3	13	2.6
Hypocalcemia	22	1.1	32	4	58	7
Hyperkalemia	21	2.8	27	4.3	29	4.3
Hypophosphatemia	20	5	35	12	48	19
Hypokalemia	19	5	34	12	47	15
Increased creatinine	18	1.1	36	2.3	27	2.2
Hypomagnesemia	16	0.4	42	1.7	76	6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/chemotherapy (range: 235 to 266 patients), KEYTRUDA (range: 241 to 288 patients), cetuximab/chemotherapy (range: 249 to 282 patients).

† Graded per NCI CTCAE v4.0

Previously treated recurrent or metastatic HNSCC

Among the 192 patients with HNSCC enrolled in KEYNOTE-012 *[see Clinical Studies (14.4)]*, the median duration of exposure to KEYTRUDA was 3.3 months (range: 1 day to 27.9 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for KEYNOTE-012.

The study population characteristics were: median age of 60 years (range: 20 to 84), 35% age 65 or older; 83% male; and 77% White, 15% Asian, and 5% 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); therefore, summary safety results are provided in a pooled analysis. 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 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent, 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 KEYNOTE-087 *[see Clinical Studies (14.5)]*, 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. Tables 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-087.

Table 16: Adverse Reactions in ≥10% of Patients with cHL in KEYNOTE-087

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

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

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

Table 17: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of cHL Patients Receiving KEYTRUDA in KEYNOTE-087

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

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 208 to 209 patients)

† Graded per NCI CTCAE v4.0

‡ Includes elevation of AST or ALT

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

PMBCL

Among the 53 patients with PMBCL treated in KEYNOTE-170 *[see Clinical Studies (14.6)],* the median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 22.8 months).

KEYTRUDA was discontinued due to adverse reactions in 8% of patients, and treatment was interrupted due to adverse reactions in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 26% of patients, and included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment. Tables 18 and 19 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-170.

Table 18: Adverse Reactions in ≥10% of Patients with PMBCL in KEYNOTE-170

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

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

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

Table 19: Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of PMBCL Patients Receiving KEYTRUDA in KEYNOTE-170

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

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 44 to 48 patients)
† Graded per NCI CTCAE v4.0
‡ Includes elevation of AST or ALT

Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The safety of KEYTRUDA was investigated in 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 *[see Clinical Studies (14.7)]*. 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).

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 20 summarizes adverse reactions in patients on KEYTRUDA in KEYNOTE-052.

Table 20: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=370	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue[†¶]	38	6
Pyrexia	11	0.5
Weight loss	10	0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[‡]	24	4.9
Arthralgia	10	1.1
Metabolism and Nutrition		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
Gastrointestinal		
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
Skin and Subcutaneous Tissue		
Rash[Þ]	21	0.5
Pruritus	19	0.3
Edema peripheral	14	1.1
Infections		
Urinary tract infection	19	9
Blood and Lymphatic System		
Anemia	17	7
Respiratory, Thoracic, and Mediastinal		
Cough	14	0
Dyspnea	11	0.5
Renal and Urinary		
Increased blood creatinine	11	1.1
Hematuria	13	3.0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
§ 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, increased transaminases, hyperbilirubinemia, increased blood bilirubin, increased alanine aminotransferase, increased aspartate aminotransferase, increased hepatic enzymes, increased liver function tests
Þ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneiform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized

Previously Treated Urothelial Carcinoma

The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in 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 (14.7)]*. 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%). 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. Tables 21 and 22 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-045.

Table 21: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

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

* Chemotherapy: paclitaxel, docetaxel, or vinflunine
† Graded per NCI CTCAE v4.0
‡ Includes asthenia, fatigue, malaise, lethargy
§ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
¶ 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, seborrheic keratosis, lichenoid keratosis
# Includes diarrhea, gastroenteritis, colitis, enterocolitis
Þ Includes cough, productive cough
ß Includes dyspnea, dyspnea exertional, wheezing
à Includes blood urine present, hematuria, chromaturia

Table 22: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Hyperglycemia	52	8	60	7
Anemia	52	13	68	18
Lymphopenia	45	15	53	25
Hypoalbuminemia	43	1.7	50	3.8
Hyponatremia	37	9	47	13
Increased alkaline phosphatase	37	7	33	4.9
Increased creatinine	35	4.4	28	2.9
Hypophosphatemia	29	8	34	14
Increased AST	28	4.1	20	2.5
Hyperkalemia	28	0.8	27	6
Hypocalcemia	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 KEYNOTE-059 *[see Clinical Studies (14.9)]*, 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 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Esophageal Cancer

Among the 314 patients with esophageal cancer enrolled in KEYNOTE-181 *[see Clinical Studies (14.10)]* treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 24.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Cervical Cancer

Among the 98 patients with cervical cancer enrolled in Cohort E of KEYNOTE-158 *[see Clinical Studies (14.11)]*, 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%). Tables 23 and 24 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-158.

Table 23: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=98	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue[†]	43	5
Pain[‡]	22	2.0
Pyrexia	19	1.0
Edema peripheral[§]	15	2.0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[¶]	27	5
Gastrointestinal		
Diarrhea[#]	23	2.0
Abdominal pain[Þ]	22	3.1
Nausea	19	0
Vomiting	19	1.0
Constipation	14	0
Metabolism and Nutrition		
Decreased appetite	21	0
Vascular		
Hemorrhage[ß]	19	5
Infections		
UTI[à]	18	6
Infection (except UTI)[è]	16	4.1
Skin and Subcutaneous Tissue		
Rash[ð]	17	2.0
Endocrine		
Hypothyroidism	11	0
Nervous System		
Headache	11	2.0
Respiratory, Thoracic and Mediastinal		
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 24: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with Cervical Cancer in KEYNOTE-158

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Hematology		
Anemia	54	24
Lymphopenia	47	9
Chemistry		
Hypoalbuminemia	44	5
Increased alkaline phosphatase	42	2.6
Hyponatremia	38	13
Hyperglycemia	38	1.3
Increased AST	34	3.9
Increased creatinine	32	5
Hypocalcemia	27	0
Increased ALT	21	3.9
Hypokalemia	20	6

* 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), increased INR (19% all Grades; 0% Grades 3-4), hypercalcemia (14% all Grades; 2.6% Grades 3-4), platelet count decreased (14% all Grades; 1.3% Grades 3-4), activated partial thromboplastin time prolonged (14% all Grades; 0% Grades 3-4), hypoglycemia (13% all Grades; 1.3% Grades 3-4), white blood cell decreased (13% all Grades; 2.6% Grades 3-4), and hyperkalemia (13% all Grades; 1.3% Grades 3-4).

HCC

Among the 104 patients with HCC who received KEYTRUDA in KEYNOTE-224 *[see Clinical Studies (14.12)]*, the median duration of exposure to KEYTRUDA was 4.2 months (range: 1 day to 1.5 years). Adverse reactions occurring in patients with HCC were generally similar to those in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent, with the exception of increased incidences of ascites (8% Grades 3-4) and immune-mediated hepatitis (2.9%). Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (20%), ALT (9%), and hyperbilirubinemia (10%).

MCC

Among the 50 patients with MCC enrolled in KEYNOTE-017 *[see Clinical Studies (14.13)]*, the median duration of exposure to KEYTRUDA was 6.6 months (range 1 day to 23.6 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (11%) and hyperglycemia (19%).

RCC

The safety of KEYTRUDA in combination with axitinib was investigated in KEYNOTE-426 *[see Clinical Studies (14.14)]*. Patients with medical conditions that required systemic corticosteroids or other immunosuppressive medications or had a history of severe autoimmune disease other than type 1 diabetes, vitiligo, Sjogren's syndrome, and hypothyroidism stable on hormone replacement were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks and axitinib 5 mg orally twice daily, or sunitinib 50 mg once daily for 4 weeks and then off treatment for 2 weeks. The median duration of exposure to the combination therapy of KEYTRUDA and axitinib was 10.4 months (range: 1 day to 21.2 months).

The study population characteristics were: median age of 62 years (range: 30 to 89), 40% age 65 or older; 71% male; 80% White; and 80% Karnofsky Performance Status (KPS) of 90-100 and 20% KPS of 70-80.

Fatal adverse reactions occurred in 3.3% of patients receiving KEYTRUDA in combination with axitinib. These included 3 cases of cardiac arrest, 2 cases of pulmonary embolism and 1 case each of cardiac failure, death due to unknown cause, myasthenia gravis, myocarditis, Fournier's gangrene, plasma cell myeloma, pleural effusion, pneumonitis, and respiratory failure.

Serious adverse reactions occurred in 40% of patients receiving KEYTRUDA in combination with axitinib. Serious adverse reactions in ≥1% of patients receiving KEYTRUDA in combination with axitinib included hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (1%).

Permanent discontinuation due to an adverse reaction of either KEYTRUDA or axitinib occurred in 31% of patients; 13% KEYTRUDA only, 13% axitinib only, and 8% both drugs. The most common adverse reaction (>1%) resulting in permanent discontinuation of KEYTRUDA, axitinib, or the combination was hepatotoxicity (13%), diarrhea/colitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%).

Dose interruptions or reductions due to an adverse reaction, excluding temporary interruptions of KEYTRUDA infusions due to infusion-related reactions, occurred in 76% of patients receiving KEYTRUDA in combination with axitinib. This includes interruption of KEYTRUDA in 50% of patients. Axitinib was interrupted in 64% of patients and dose reduced in 22% of patients. The most common adverse reactions (>10%) resulting in interruption of KEYTRUDA were hepatotoxicity (14%) and diarrhea (11%), and the most common adverse reactions (>10%) resulting in either interruption or reduction of axitinib were hepatotoxicity (21%), diarrhea (19%), and hypertension (18%).

The most common adverse reactions (≥20%) in patients receiving KEYTRUDA and axitinib were diarrhea, fatigue/asthenia, hypertension, hypothyroidism, decreased appetite, hepatotoxicity, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation.

Twenty-seven percent (27%) of patients treated with KEYTRUDA in combination with axitinib received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction.

Tables 25 and 26 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in at least 20% of patients treated with KEYTRUDA and axitinib in KEYNOTE-426.

Table 25: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Axitinib n=429		Sunitinib n=425	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea†	56	11	45	5
Nausea	28	0.9	32	0.9
Constipation	21	0	15	0.2
General				
Fatigue/Asthenia	52	5	51	10
Vascular				
Hypertension‡	48	24	48	20
Hepatobiliary				
Hepatotoxicity§	39	20	25	4.9
Endocrine				
Hypothyroidism	35	0.2	32	0.2
Metabolism and Nutrition				
Decreased appetite	30	2.8	29	0.7
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysaesthesia syndrome	28	5	40	3.8
Stomatitis/Mucosal inflammation	27	1.6	41	4
Rash¶	25	1.4	21	0.7
Respiratory, Thoracic and Mediastinal				
Dysphonia	25	0.2	3.3	0
Cough	21	0.2	14	0.5

* Graded per NCI CTCAE v4.03

† Includes diarrhea, colitis, enterocolitis, gastroenteritis, enteritis, enterocolitis hemorrhagic

‡ Includes hypertension, blood pressure increased, hypertensive crisis, labile hypertension

§ Includes ALT increased, AST increased, autoimmune hepatitis, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis fulminant, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased

¶ Includes rash, butterfly rash, dermatitis, dermatitis acneform, dermatitis atopic, dermatitis bullous, dermatitis contact, exfoliative rash, genital rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, seborrhoeric dermatitis, skin discoloration, skin exfoliation, perineal rash

Table 26: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Axitinib		Sunitinib	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	62	9	54	3.2
Increased ALT	60	20	44	5
Increased AST	57	13	56	5
Increased creatinine	43	4.3	40	2.4
Hyponatremia	35	8	29	8
Hyperkalemia	34	6	22	1.7
Hypoalbuminemia	32	0.5	34	1.7
Hypercalcemia	27	0.7	15	1.9
Hypophosphatemia	26	6	49	17
Increased alkaline phosphatase	26	1.7	30	2.7
Hypocalcemia‡	22	0.2	29	0.7
Blood bilirubin increased	22	2.1	21	1.9
Activated partial thromboplastin time prolonged§	22	1.2	14	0
Hematology				
Lymphopenia	33	11	46	8
Anemia	29	2.1	65	8
Thrombocytopenia	27	1.4	78	14

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/axitinib (range: 342 to 425 patients) and sunitin b (range: 345 to 422 patients).
† Graded per NCI CTCAE v4.03
‡ Corrected for albumin
§ Two patients with a Grade 3 elevated activated partial thromboplastin time prolonged (aPTT) were also reported as having an adverse reaction of hepatotoxicity.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to pembrolizumab in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks, 27 (2.1%) of 1289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies of whom six (0.5%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding antibody development.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. There are no available human data informing the risk of embryo-fetal toxicity. 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. Advise 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. A literature-based assessment of the effects of the PD-1 pathway on reproduction demonstrated that 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

There are no data on the presence of pembrolizumab in either animal or human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with KEYTRUDA and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating KEYTRUDA *[see Use in Specific Populations (8.1)].*

Contraception

KEYTRUDA can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.11), 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

The safety and effectiveness of KEYTRUDA have been established in pediatric patients with cHL, PMBCL, and MSI-H cancer. Use of KEYTRUDA in pediatric patients with cHL, PMBCL, and MSI-H cancers is supported by evidence from adequate and well-controlled studies of KEYTRUDA in adults with additional pharmacokinetic and safety data in pediatric patients *[see Adverse Reactions (6.1), Clinical Studies (14.5, 14.6, 14.8), Clinical Pharmacology (12.3)]*.

There is limited experience with KEYTRUDA in pediatric patients. In a trial (NCT02332668), 40 pediatric patients (16 children ages 2 years to less than 12 years and 24 adolescents ages 12 years to 18 years) with various cancers, including unapproved usages, 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 safety profile in these pediatric patients was similar to that seen in adults; adverse reactions that occurred at a higher rate (≥15% difference) in pediatric patients when compared to adults <65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), increased transaminases (28%) and hyponatremia (18%).

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 and effectiveness of KEYTRUDA in pediatric patients have not been established in the other approved indications *[see Indications and Usage (1)]*.

8.5 Geriatric Use

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

11 DESCRIPTION

Pembrolizumab is a programmed death receptor-1 (PD 1)-blocking antibody. Pembrolizumab is a humanized monoclonal IgG4 kappa antibody with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in recombinant Chinese hamster ovary (CHO) cells.

KEYTRUDA (pembrolizumab) for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials for intravenous use. 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 (pembrolizumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. 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.

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.

Distribution

The geometric mean value (CV%) for volume of distribution at steady state is 6.0 L (20%).

Elimination

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 terminal half-life ($t_{1/2}$) is 22 days (32%).

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 ≥ 15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or tumor burden. The impact of moderate or severe hepatic impairment on the pharmacokinetics of pembrolizumab is unknown.

Pediatric Patients: Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients (2 to 17 years) are comparable to those of adults at the same dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

14 CLINICAL STUDIES

14.1 Melanoma

Ipilimumab-Naive Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-006 (NCT01866319), a randomized (1:1:1), open-label, multicenter, active-controlled trial in 834 patients. Patients were randomized to receive KEYTRUDA at a dose of 10 mg/kg intravenously every 2 weeks or 10 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent central review [BICR] using Response Evaluation Criteria in Solid

Tumors [RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ]). Additional efficacy outcome measures were objective response rate (ORR) and duration of response (DoR).

The study population characteristics were: median age of 62 years (range: 18 to 89); 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.

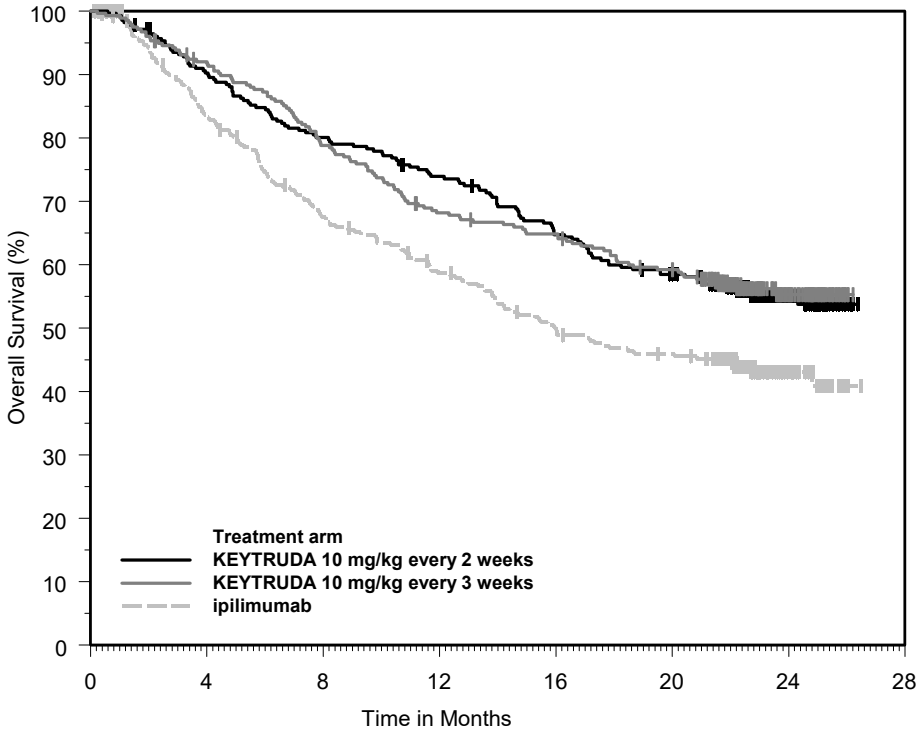
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to KEYTRUDA 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months. Efficacy results are summarized in Table 27 and Figure 1.

Table 27: Efficacy Results in KEYNOTE-006

Endpoint	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 objective 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

Figure 1: Kaplan-Meier Curve for Overall Survival in KEYNOTE-006*



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

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

Ipilimumab-Refractory Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-002 (NCT01704287), a multicenter, randomized (1:1:1), active-controlled trial in 540 patients 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 mg/mL/min intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 mg/mL/min 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 mg/mL/min intravenously every 3 weeks (8%). Randomization was stratified by ECOG PS (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 PFS as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. Additional efficacy outcome measures were confirmed ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The study population characteristics were: median age of 62 years (range: 15 to 89), 43% age 65 or older; 61% male; 98% White; and 55% ECOG PS of 0 and 45% ECOG PS of 1. 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. 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. 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. Efficacy results are summarized in Table 28.

Table 28: Efficacy Results in KEYNOTE-002

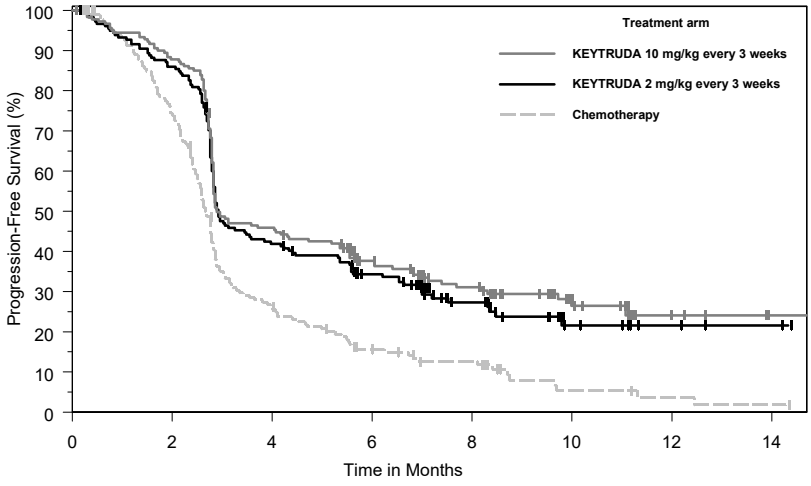
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 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)	---
OS†			
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

Adjuvant Treatment of Resected Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-054 (NCT02362594), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with completely resected stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma. Patients were randomized to KEYTRUDA 200 mg intravenously every three weeks or placebo for up to one year until disease recurrence or unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer 7th edition (AJCC) stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes) and geographic region (North America, European countries, Australia, and other countries as designated). Patients must have undergone lymph node dissection and, if indicated, radiotherapy within 13 weeks prior to starting treatment. The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1 positive tumors where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first two years, then every 6 months from year 3 to 5, and then annually.

The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had stage IIIA, 46% had stage IIIB, 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (≥4 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1% according to an IUO assay.

The trial demonstrated a statistically significant improvement in RFS for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 29 and Figure 3.

Table 29: Efficacy Results in KEYNOTE-054

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=514**	**Placebo n=505**
RFS		
Number (%) of patients with event	135 (26%)	216 (43%)
Median in months (95% CI)	NR	20.4 (16.2, NR)
Hazard ratio*† (95% CI)	0.57 (0.46, 0.70)	
p-Value† (log-rank)	<0.001±	

* Based on the stratified Cox proportional hazard model

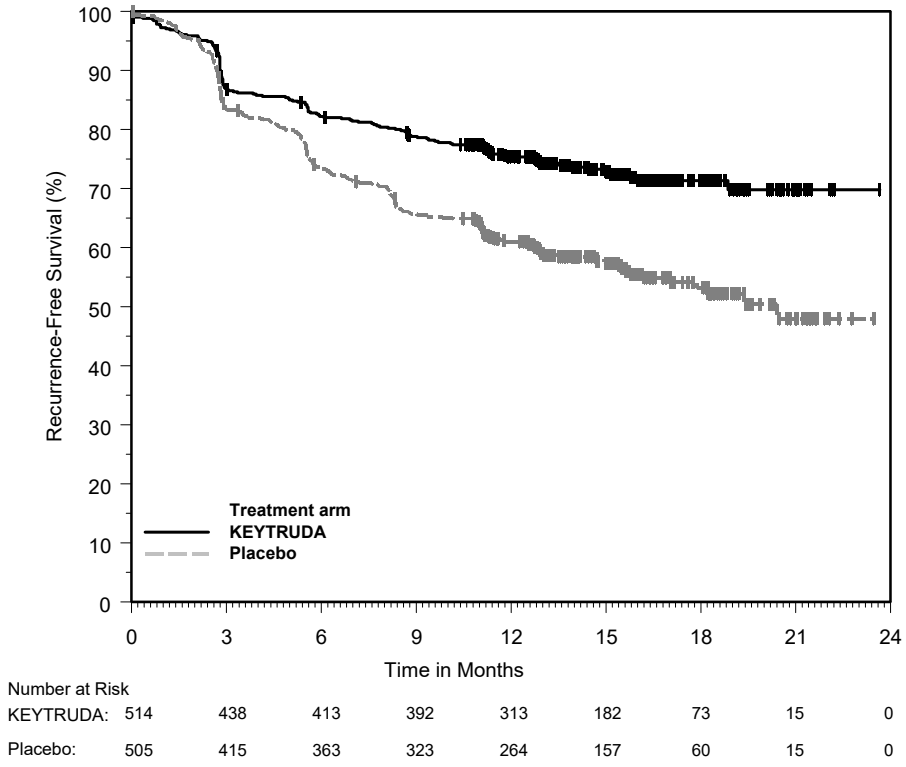
† Stratified by American Joint Committee on Cancer 7th edition (AJCC) stage

± p-Value is compared with 0.008 of the allocated alpha for this interim analysis.

NR = not reached

For patients with PD-L1 positive tumors, the HR was 0.54 (95% CI: 0.42, 0.69); p<0.001. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression.

Figure 3: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054



14.2 Non-Small Cell Lung Cancer

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

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). Patients were randomized (2:1) to one of the following treatment arms:

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

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

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

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

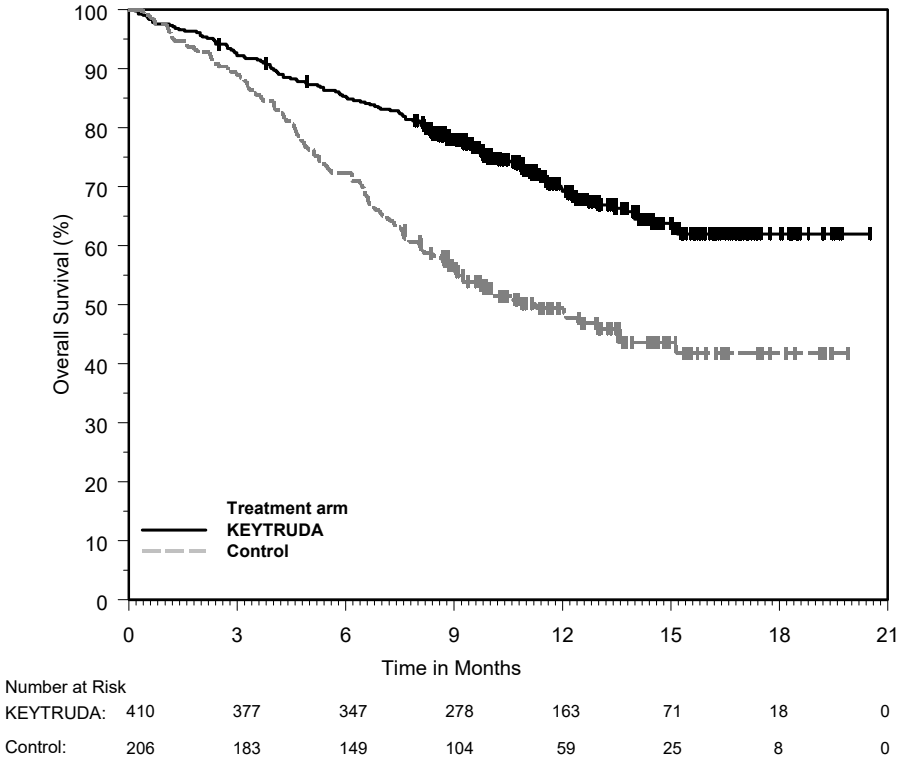
The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 30 and Figure 4 summarize the efficacy results for KEYNOTE-189.

Table 30: Efficacy Results in KEYNOTE-189

Endpoint	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=410	Placebo Pemetrexed Platinum Chemotherapy n=206
OS		
Number (%) of patients with event	127 (31%)	108 (52%)
Median in months (95% CI)	NR (NR, NR)	11.3 (8.7, 15.1)
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.0001	
PFS		
Number of patients with event (%)	244 (60%)	166 (81%)
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.0001	
Objective Response Rate		
ORR‡ (95% CI)	48% (43, 53)	19% (14, 25)
Complete response	0.5%	0.5%
Partial response	47%	18%
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)

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

Figure 4: Kaplan-Meier Curve for Overall Survival in KEYNOTE-189



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

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

The efficacy of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or paclitaxel protein-bound was investigated in KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial conducted in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%), choice of paclitaxel or paclitaxel protein-bound, and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

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

Treatment with KEYTRUDA and chemotherapy or placebo and chemotherapy continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Patients randomized to the placebo and chemotherapy arm were offered KEYTRUDA as a single agent at the time of disease progression. Assessment of tumor status was performed every 6 weeks through Week 18,

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

The study population characteristics were: median age of 65 years (range: 29 to 88), 55% age 65 or older; 81% male; 77% White; 71% ECOG PS of 1; and 8% with a history of brain metastases. Thirty-five percent had tumor PD-L1 expression TPS <1%; 19% were from the East Asian region; and 60% received paclitaxel.

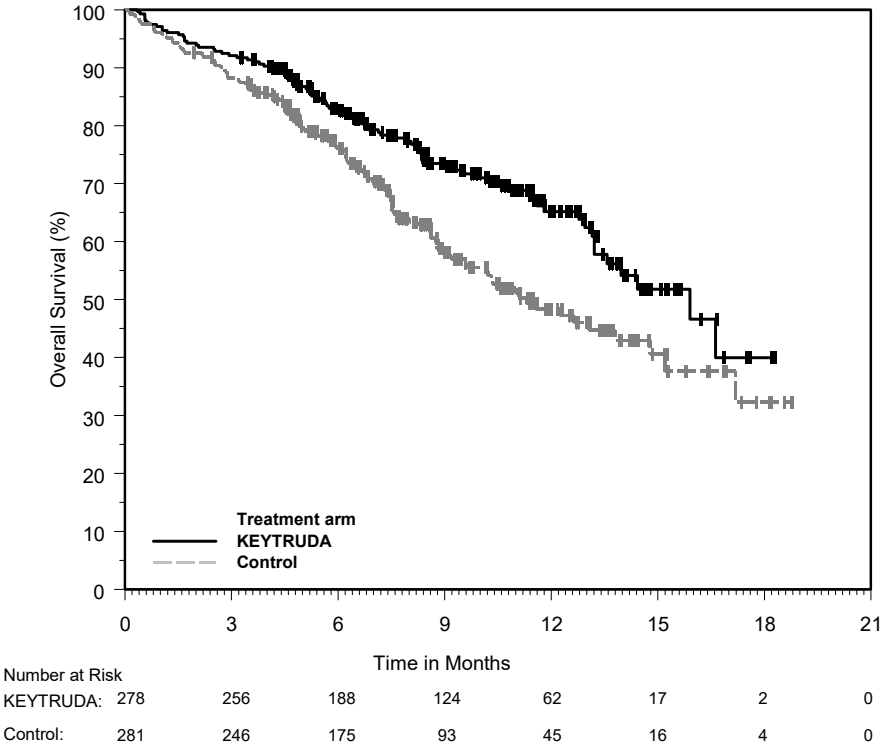
The trial demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy compared with patients randomized to placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy. Table 31 and Figure 5 summarize the efficacy results for KEYNOTE-407.

Table 31: Efficacy Results in KEYNOTE-407

Endpoint	**KEYTRUDA 200 mg every 3 weeks Carboplatin Paclitaxel/Paclitaxel protein-bound n=278**	**Placebo Carboplatin Paclitaxel/Paclitaxel protein-bound n=281**
OS		
Number of events (%)	85 (31%)	120 (43%)
Median in months (95% CI)	15.9 (13.2, NE)	11.3 (9.5, 14.8)
Hazard ratio* (95% CI)	0.64 (0.49, 0.85)	
p-Value†	0.0017	
PFS		
Number of events (%)	152 (55%)	197 (70%)
Median in months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.3, 5.7)
Hazard ratio* (95% CI)	0.56 (0.45, 0.70)	
p-Value†	<0.0001	
	n=101	**n=103**
Objective Response Rate‡		
ORR (95% CI)	58% (48, 68)	35% (26, 45)
Difference (95% CI)	23.6% (9.9, 36.4)	
p-Value§	0.0008	
Duration of Response‡		
Median duration of response in months (range)	7.2 (2.4, 12.4+)	4.9 (2.0, 12.4+)

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

Figure 5: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407



First-line treatment of metastatic NSCLC as a single agent

KEYNOTE-042

The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. 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 PS (0 vs. 1), histology (squamous vs. nonsquamous), geographic region (East Asia vs. non-East Asia), and PD-L1 expression (TPS ≥50% vs. TPS 1 to 49%). Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of either 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 a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies.

Treatment with KEYTRUDA continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease, 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. Treatment with KEYTRUDA could be reinitiated at the time of subsequent disease

progression and administered for up to 12 months. Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measure was OS in the subgroup of patients with TPS ≥50% NSCLC, the subgroup of patients with TPS ≥20% NSCLC, and the overall population with TPS ≥1% NSCLC. Additional efficacy outcome measures were PFS and ORR in the subgroup of patients with TPS ≥50% NSCLC, the subgroup of patients with TPS ≥20% NSCLC, and the overall population with TPS ≥1% NSCLC as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 63 years (range: 25 to 90), 45% age 65 or older; 71% male; and 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Sixty-nine percent had ECOG PS of 1; 39% with squamous and 61% with nonsquamous histology; 87% had M1 disease and 13% had Stage IIIA (2%) or Stage IIIB (11%) and who were not candidates for surgical resection or definitive chemoradiation per investigator assessment; and 5% with treated brain metastases at baseline. Forty-seven percent of patients had TPS ≥50% NSCLC and 53% had TPS 1 to 49% NSCLC.

The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to KEYTRUDA as compared with chemotherapy. Table 32 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%.

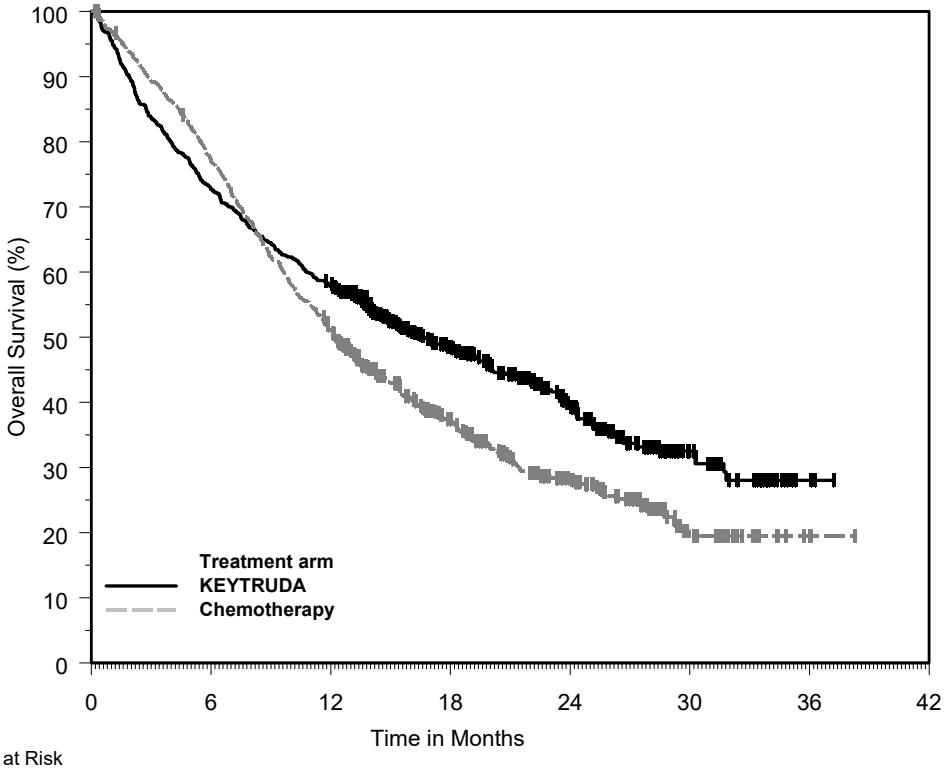
Table 32: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

	TPS ≥1%		**TPS ≥50%**	
Endpoint	**KEYTRUDA 200 mg every 3 weeks n=637**	**Chemotherapy n=637**	**KEYTRUDA 200 mg every 3 weeks n=299**	**Chemotherapy n=300**
OS				
Number of events (%)	371 (58%)	438 (69%)	157 (53%)	199 (66%)
Median in months (95% CI)	16.7 (13.9, 19.7)	12.1 (11.3, 13.3)	20.0 (15.4, 24.9)	12.2 (10.4, 14.2)
Hazard ratio* (95% CI)	0.81 (0.71, 0.93)		0.69 (0.56, 0.85)	
p-Value†	0.0036		0.0006	
PFS				
Number of events (%)	507 (80%)	506 (79%)	221 (74%)	233 (78%)
Median in months (95% CI)	5.4 (4.3, 6.2)	6.5 (6.3, 7.0)	7.1 (5.9, 9.0)	6.4 (6.1, 6.9)
Hazard ratio*,‡ (95% CI)	1.07 (0.94, 1.21)		0.81 (0.67, 0.99)	
p-Value†	-‡		NS§	
Objective Response Rate				
ORR‡ (95% CI)	27% (24, 31)	27% (23, 30)	39% (33.9, 45.3)	32% (26.8, 37.6)
Complete response rate	0.5%	0.5%	0.7%	0.3%
Partial response rate	27%	26%	39%	32%
Duration of Response				
% with duration ≥12 months¶	47%	16%	42%	17%
% with duration ≥18 months¶	26%	6%	25%	5%

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test; compared to a p-Value boundary of 0.0291
‡ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints
§ Not significant compared to a p-Value boundary of 0.0291
¶ Based on observed duration of response

The results of all efficacy outcome measures in the subgroup of patients with PD-L1 TPS ≥20% NSCLC were intermediate between the results of those with PD-L1 TPS ≥1% and those with PD-L1 TPS ≥50%. In a pre-specified exploratory subgroup analysis for patients with TPS 1-49% NSCLC, the median OS was 13.4 months (95% CI: 10.7, 18.2) for the pembrolizumab group and 12.1 months (95% CI: 11.0, 14.0) in the chemotherapy group, with an HR of 0.92 (95% CI: 0.77, 1.11).

Figure 6: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-042 (TPS ≥1%)



Number at Risk								
KEYTRUDA:	637	463	365	214	112	35	2	0
Chemotherapy:	637	485	316	166	88	24	1	0

KEYNOTE-024

The efficacy of KEYTRUDA was also investigated in KEYNOTE-024 (NCT02142738), a randomized, multicenter, open-label, active-controlled trial in 305 previously untreated patients with metastatic NSCLC. The study design was similar to that of KEYNOTE-042, except that only patients whose tumors had high PD-L1 expression (TPS of 50% or greater) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit were eligible. 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).

Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression.

The main efficacy outcome measure was PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were OS and ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

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% with ECOG PS 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 both PFS and OS for patients randomized to KEYTRUDA as compared with chemotherapy. Table 33 and Figure 7 summarize the efficacy results for KEYNOTE-024.

Table 33: 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)†	30.0 (18.3, NR)	14.2 (9.8, 19.0)
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+)

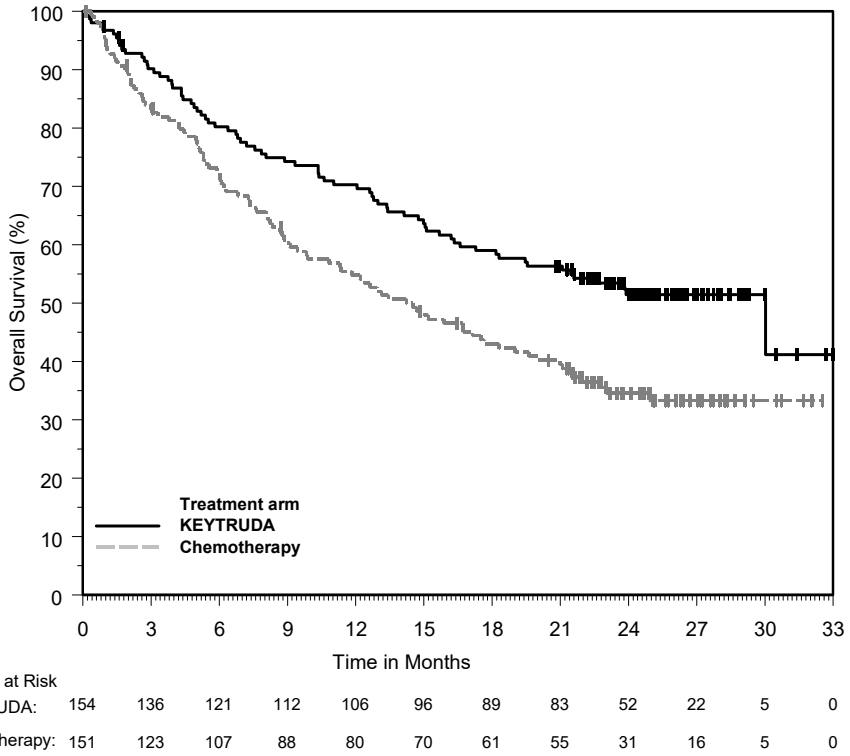
* Based on the stratified Cox proportional hazard model for the interim analysis

† Based on the protocol-specified final OS analysis conducted at 169 events, which occurred 14 months after the interim analysis.

‡ p-Value is compared with 0.0118 of the allocated alpha for the interim analysis

NR = not reached

Figure 7: Kaplan-Meier Curve for Overall Survival in KEYNOTE-024*



*Based on the protocol-specified final OS analysis conducted at 169 events, which occurred 14 months after the interim analysis.

Previously treated NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 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 PS (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 BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%. Additional efficacy outcome measures were ORR and DoR in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%.

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 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 34 and 35 and Figure 8 summarize efficacy results in the subgroup with TPS ≥50% population and in all patients, respectively.

Table 34: 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 35: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

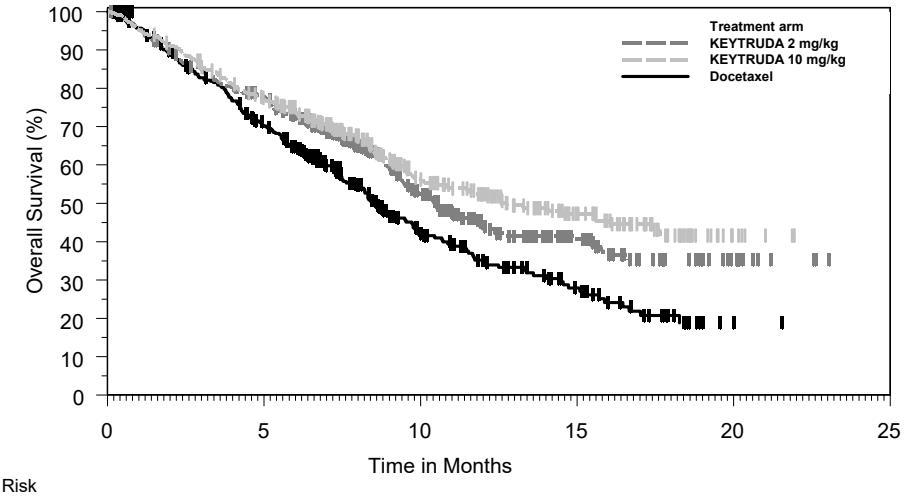
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
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 8: 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 Small Cell Lung Cancer

The efficacy of KEYTRUDA was investigated in 83 patients with SCLC who had disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy enrolled in one of two multicenter, multi-cohort, non-randomized, open label trials: KEYNOTE-028 (NCT02054806), Cohort C1, or KEYNOTE-158 (NCT02628067), Cohort G. The trials excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received either KEYTRUDA 200 mg intravenously every 3 weeks (n=64) or 10 mg/kg intravenously every 2 weeks (n=19). Treatment with KEYTRUDA continued until documented disease progression, unacceptable toxicity, or a maximum of 24 months. Patients with initial radiographic disease progression could receive additional doses of KEYTRUDA during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status.

Assessment of tumor status was performed every 8 weeks for the first 6 months in KEYNOTE-028, every 9 weeks for the first 12 months in KEYNOTE-158, and every 12 weeks thereafter for both studies. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 62 years (range: 24 to 84); 40% age 65 or older; 64% male; 63% White, 25% Asian, and 2% Black; 30% ECOG PS of 0 and 69% ECOG PS of 1; 7% had M0 disease and 93% had M1 disease; and 16% had a history of brain metastases. Sixty-four percent received two prior lines of therapy and 36% received three or more lines of therapy; 60% received prior thoracic radiation therapy; 51% received prior radiation therapy to the brain.

Efficacy results are summarized in Table 36.

Table 36: Efficacy Results in Patients with Small Cell Lung Cancer

Endpoint	KEYTRUDA n=83
Objective Response Rate	
ORR (95% CI)	19% (11, 29)
Complete response rate	2%
Partial response rate	17%
Duration of Response	n=16
Range (months)	4.1, 35.8+
% with duration ≥6 months	94%
% with duration ≥12 months	63%
% with duration ≥18 months	56%

\+ Denotes ongoing response

14.4 Head and Neck Squamous Cell Cancer

First-line treatment of metastatic or unresectable, recurrent HNSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS ≥50% or <50%) according to the PD-L1 IHC 22C3 pharmDx kit, HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs. 1). Patients were randomized 1:1:1 to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks
- KEYTRUDA 200 mg intravenously every 3 weeks, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m^2 intravenously every 3 weeks, and FU 1000 mg/m^2/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)
- Cetuximab 400 mg/m^2 intravenously as the initial dose then 250 mg/m^2 intravenously once weekly, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m^2 intravenously every 3 weeks, and FU 1000 mg/m^2/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)

Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months. A retrospective re-classification of patients' tumor PD-L1 status according to CPS using the PD-L1 IHC 22C3 pharmDx kit was conducted using the tumor specimens used for randomization.

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) sequentially tested in the subgroup of patients with CPS ≥20, the subgroup of patients with CPS ≥1, and the overall population.

The study population characteristics were: median age of 61 years (range: 20 to 94), 36% age 65 or older; 83% male; 73% White, 20% Asian and 2.4% Black; 61% had ECOG PS of 1; and 79% were former/current smokers. Twenty-two percent of patients' tumors were HPV-positive, 23% had PD-L1 TPS ≥50%, and 95% had Stage IV disease (Stage IVA 19%, Stage IVB 6%, and Stage IVC 70%). Eighty-five percent of patients' tumors had PD-L1 expression of CPS ≥1 and 43% had CPS ≥20.

The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA in combination with chemotherapy compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis in the overall population. The trial also demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 randomized to KEYTRUDA as a single agent compared to those randomized to cetuximab in combination with chemotherapy. At the time of the interim analysis, there was no significant difference in OS between the KEYTRUDA single agent arm and the control arm for the overall population. Table 37 and Figure 9 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

Table 37: Efficacy Results for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048

Endpoint	**KEYTRUDA 200 mg every 3 weeks Platinum FU n=281**	**Cetuximab Platinum FU n=278**
OS		
Number (%) of patients with event	197 (70%)	223 (80%)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
Hazard ratio* (95% CI)	0.77 (0.63, 0.93)	
p-Value†	0.0067	
PFS		
Number of patients with event (%)	244 (87%)	253 (91%)
Median in months (95% CI)	4.9 (4.7, 6.0)	5.1 (4.9, 6.0)
Hazard ratio* (95% CI)	0.92 (0.77, 1.10)	
p-Value†	0.3394	
Objective Response Rate		
ORR‡ (95% CI)	36% (30.0, 41.5)	36% (30.7, 42.3)
Complete response rate	6%	3%
Partial response rate	30%	33%
Duration of Response		
Median in months (range)	6.7 (1.6+, 30.4+)	4.3 (1.2+, 27.9+)

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response

In KEYNOTE-048, OS HRs for patients randomized to KEYTRUDA in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS ≥1 (HR 0.71, 95% CI: 0.57, 0.88), CPS ≥20 (HR 0.69, 95% CI:0.51, 0.94).

Figure 9: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048

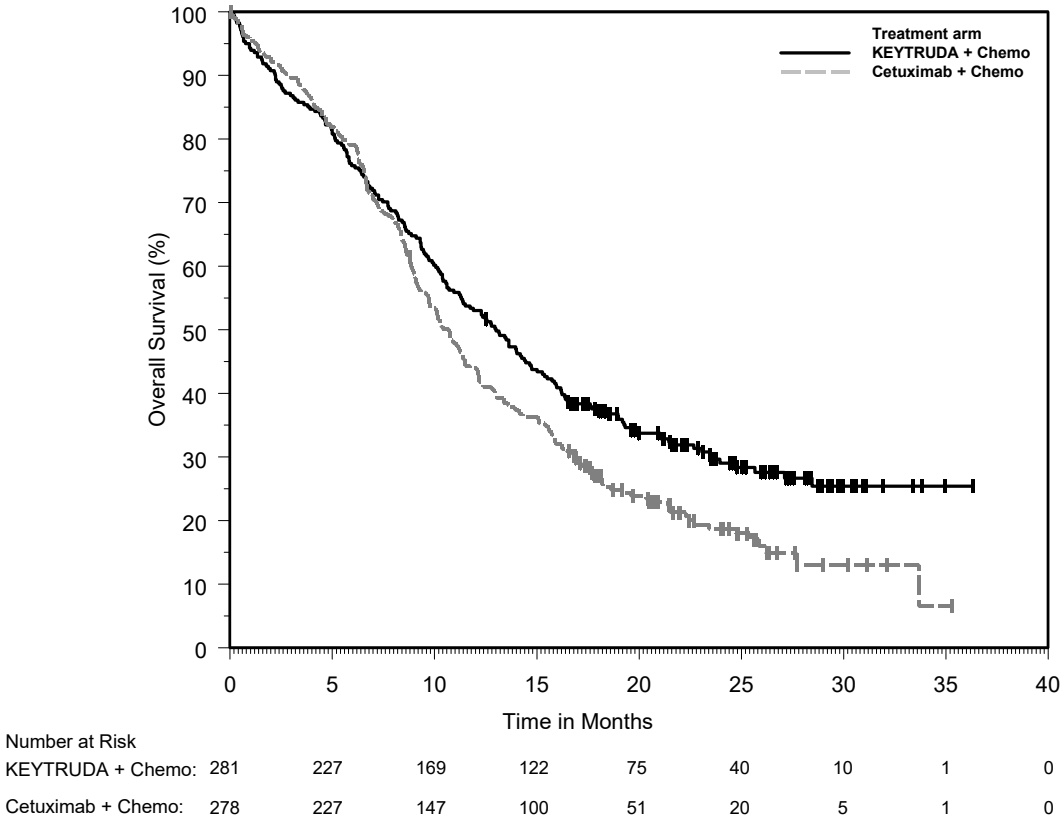


Table 38 summarizes efficacy results for KEYTRUDA as a single agent in the subgroups of patients with CPS ≥1 HNSCC and CPS ≥20 HNSCC. Figure 10 summarizes the OS results in the subgroup of patients with CPS ≥1 HNSCC.

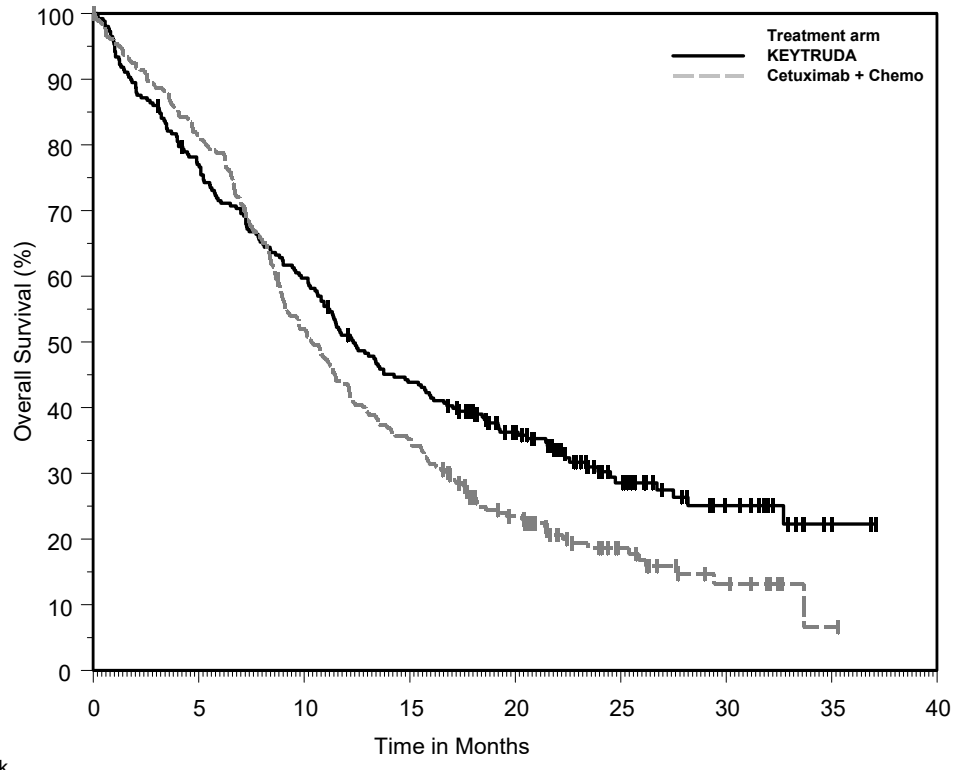
Table 38: Efficacy Results for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)

Endpoint	CPS ≥1		CPS ≥20	
	KEYTRUDA 200 mg every 3 weeks n=257	Cetuximab Platinum FU n=255	KEYTRUDA 200 mg every 3 weeks n=133	Cetuximab Platinum FU n=122
OS				
Number of events (%)	177 (69%)	206 (81%)	82 (62%)	95 (78%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0,11.5)	14.9 (11.6, 21.5)	10.7 (8.8, 12.8)
Hazard ratio* (95% CI)	0.78 (0.64, 0.96)		0.61 (0.45, 0.83)	
p-Value†	0.0171		0.0015	
PFS				
Number of events (%)	225 (88%)	231 (91%)	113 (85%)	111 (91%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 5.8)	3.4 (3.2, 3.8)	5.0 (4.8, 6.2)
Hazard ratio * (95% CI)	1.15(0.95, 1.38)		0.99 (0.75, 1.29)	
Objective Response Rate				
ORR‡ (95% CI)	19% (14.5, 24.4)	35% (29.1, 41.1)	23% (16.4, 31.4)	36% (27.6, 45.3)
Complete response rate	5%	3%	8%	3%
Partial response rate	14%	32%	16%	33%
Duration of Response				
Median in months (range)	20.9 (1.5+, 34.8+)	4.5 (1.2+, 28.6+)	20.9 (2.7, 34.8+)	4.2 (1.2+, 22.3+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC, the median OS was 10.8 months (95% CI: 9.0, 12.6) for KEYTRUDA as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.90 (95% CI: 0.68, 1.18).

Figure 10: Kaplan-Meier Curve for Overall Survival for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1)



Number at Risk									
KEYTRUDA:	257	196	152	110	74	34	17	2	0
Cetuximab + Chemo:	255	207	131	89	47	21	9	1	0

Previously treated recurrent or metastatic HNSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-012 (NCT01848834), a multicenter, non-randomized, open-label, multi-cohort study that enrolled 174 patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy. Patients with active autoimmune disease, a medical condition that required immunosuppression, evidence of interstitial lung disease, or ECOG PS ≥2 were ineligible.

Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=53) or 200 mg every 3 weeks (n=121) until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR, and DoR.

The study population characteristics were median age of 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 DoR had not been reached (range: 2.4+ to 27.7+ months), with 23 patients having responses of 6 months or longer. The ORR and DoR were similar irrespective of dosage regimen (10 mg/kg every 2 weeks or 200 mg every 3 weeks) or HPV status.

14.5 Classical Hodgkin Lymphoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-087 (NCT02453594), a multicenter, non-randomized, open-label trial in 210 patients with relapsed or refractory cHL. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or > 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 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months in patients who did not progress. Disease assessment was performed every 12 weeks. The major efficacy outcome measures (ORR, Complete Response Rate, and DoR) were assessed by BICR according to the 2007 revised International Working Group (IWG) criteria.

The study population characteristics were: median age of 35 years (range: 18 to 76), 9% age 65 or older; 54% male; 88% White; and 49% ECOG PS of 0 and 51% 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 39.

Table 39: Efficacy Results in KEYNOTE-087

Endpoint	KEYTRUDA 200 mg every 3 weeks n=210*
Objective Response Rate	
ORR (95% CI)	69% (62, 75)
Complete response rate	22%
Partial response rate	47%
Duration of Response	
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

14.6 Primary Mediastinal Large B-Cell Lymphoma

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

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

For the 24 responders, the median time to first objective response (complete or partial response) was 2.8 months (range 2.1 to 8.5 months). Efficacy results for KEYNOTE-170 are summarized in Table 40.

Table 40: Efficacy Results in KEYNOTE-170

Endpoint	KEYTRUDA 200 mg every 3 weeks n=53*
Objective Response Rate	
ORR (95% CI)	45% (32, 60)
Complete response rate	11%
Partial response rate	34%
Duration of Response	
Median in months (range)	NR (1.1+, 19.2+)†

* Median follow-up time of 9.7 months

† Based on patients (n=24) with a response by independent review

NR = not reached

14.7 Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-052 (NCT02335424), a multicenter, open-label, single-arm trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Tumor response assessments were performed at 9 weeks after the first dose, then every 6 weeks for the first year, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by independent radiology review, and DoR.

The study population characteristics were: median age of 74 years; 77% male; and 89% 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 PS of 2, 9% with ECOG PS of 2 and baseline creatinine clearance of <60 mL/min, and 9% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

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

The median follow-up time for 370 patients treated with KEYTRUDA was 7.8 months (range 0.1 to 20 months). Efficacy results are summarized in Table 41.

Table 41: Efficacy Results in KEYNOTE-052

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

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

Previously Untreated Urothelial Carcinoma

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

Previously Treated Urothelial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-045 (NCT02256436), a multicenter, randomized (1:1), active-controlled trial in 542 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=90), docetaxel 75 mg/m^2 (n=92), or vinflunine 320 mg/m^2 (n=90). Treatment continued until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed at 9 weeks after randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The study population characteristics were: median age of 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 42% ECOG PS of 0 and 56% ECOG PS 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.

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 42 and Figure 11 summarize the efficacy results for KEYNOTE-045.

Table 42: Efficacy Results in KEYNOTE-045

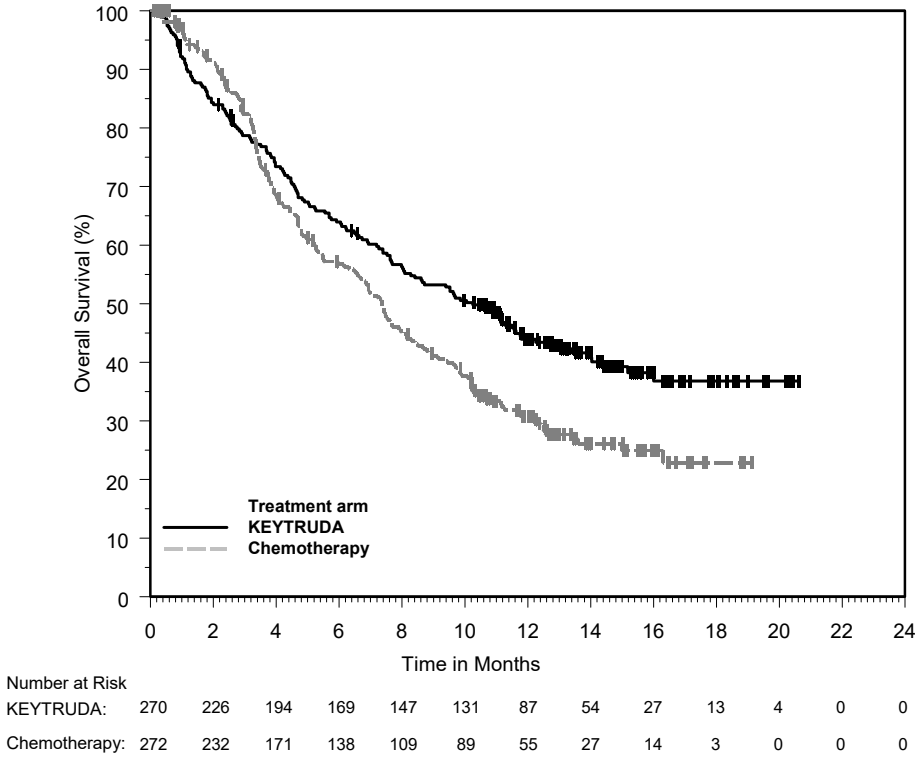
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (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 11: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



14.8 Microsatellite Instability-High Cancer

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

Table 43: MSI-H Trials

Study	Design and Patient Population	Number of Patients	MSI-H/dMMR Testing	Dosage	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 trials. Among these 149 patients, the baseline characteristics were: median age of 55 years, 36% age 65 or older; 56% male; 77% White, 19% Asian, and 2% Black; and 36% ECOG PS of 0 and 64% ECOG PS of 1. 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 Tables 44 and 45.

Table 44: Efficacy Results for Patients with MSI-H/dMMR Cancer

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

NR = not reached

Table 45: Response by Tumor Type

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

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

14.9 Gastric Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-059 (NCT02335411), a multicenter, non-randomized, open-label multi-cohort trial that enrolled 259 patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma who progressed on at least 2 prior systemic treatments for advanced disease. Previous treatment must have included a fluoropyrimidine and platinum doublet. HER2/neu positive patients must have previously received treatment with approved HER2/neu-targeted therapy. Patients with active autoimmune disease or a medical condition that required immunosuppression or with clinical evidence of ascites by physical exam were ineligible. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Assessment of tumor status was performed every 6 to 9 weeks. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR, and DoR.

Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a CPS ≥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 of 64 years, 47% age 65 or older; 77% male; 82% White and 11% Asian; and 43% ECOG PS of 0 and 57% ECOG PS of 1. 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 DoR 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 DoR ranged from 5.3+ to 14.1+ months.

14.10 Esophageal Cancer

KEYNOTE-181
The efficacy of KEYTRUDA was investigated in KEYNOTE-181 (NCT02564263), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. Patients with HER2/neu positive esophageal cancer were required to have received treatment with approved HER2/neu targeted therapy. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD L1 status was determined using the PD L1 IHC 22C3 pharmDx kit. Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive either KEYTRUDA 200 mg every 3 weeks or investigator's choice of any of the following chemotherapy regimens, all given intravenously: paclitaxel 80-100 mg/m^2 on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m^2 every 3 weeks, or irinotecan 180 mg/m^2 every 2 weeks. Randomization was stratified by tumor histology (esophageal squamous cell carcinoma [ESCC] vs. esophageal adenocarcinoma [EAC]/Siewert type I EAC of the gastroesophageal junction [GEJ]), and geographic region (Asia vs. ex-Asia). Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue beyond the first RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measure was OS evaluated in the following co-primary populations: patients with ESCC, patients with tumors expressing PD-L1 CPS ≥10, and all randomized patients. Additional efficacy outcome measures were PFS, ORR, and DoR, according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

A total of 628 patients were enrolled and randomized to KEYTRUDA (n=314) or investigator's treatment of choice (n=314). Of these 628 patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS ≥10. Of these 167 patients, 85 patients were randomized to KEYTRUDA and 82 patients to investigator's treatment of choice [paclitaxel (n=50), docetaxel (n=19), or irinotecan (n=13)]. The baseline characteristics of these 167 patients were: median age of 65 years (range: 33 to 80), 51% age 65 or older; 84% male; 32% White and 68% Asian; 38% had an ECOG PS of 0 and 62% had an ECOG PS of 1. Ninety percent had M1 disease and 10% had M0 disease. Prior to enrollment, 99% of patients had received platinum-based treatment and 84% had also received treatment with a fluoropyrimidine. Thirty-three percent of patients received prior treatment with a taxane.

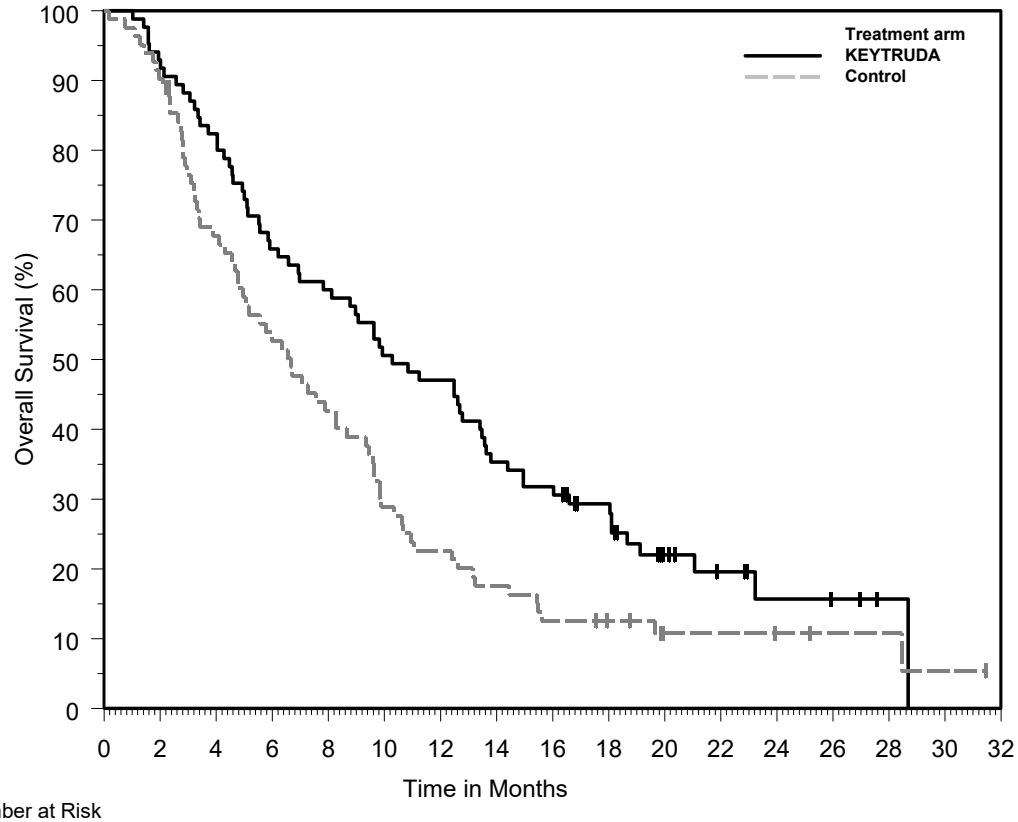
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 46 and Figure 12 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10.

Table 46: Efficacy Results in Patients with Recurrent or Metastatic ESCC (CPS ≥10) in KEYNOTE-181

Endpoint	KEYTRUDA 200 mg every 3 weeks n=85	Chemotherapy n=82
OS		
Number (%) of patients with event	68 (80%)	72 (88%)
Median in months (95% CI)	10.3 (7.0, 13.5)	6.7 (4.8, 8.6)
Hazard ratio* (95% CI)	0.64 (0.46, 0.90)	
PFS		
Number (%) of patients with event	76 (89%)	76 (93%)
Median in months (95% CI)	3.2 (2.1, 4.4)	2.3 (2.1, 3.4)
Hazard ratio* (95% CI)	0.66 (0.48, 0.92)	
Objective Response Rate		
ORR (95% CI)	22 (14, 33)	7 (3, 15)
Number (%) of complete responses	4 (5)	1 (1)
Number (%) of partial responses	15 (18)	5 (6)
Median duration of response in months (range)	9.3 (2.1+, 18.8+)	7.7 (4.3, 16.8+)

* Based on the Cox regression model stratified by geographic region (Asia vs. ex-Asia)

Figure 12: Kaplan-Meier Curve for Overall Survival in KEYNOTE-181 (ESCC CPS ≥10)



KEYNOTE-180

The efficacy of KEYTRUDA was investigated in KEYNOTE-180 (NCT02559687), a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after at least 2 prior systemic treatments for advanced disease. With the

exception of the number of prior lines of treatment, the eligibility criteria were similar to and the dosage regimen identical to KEYNOTE-181.

The major efficacy outcome measures were ORR and DoR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

Among the 121 patients enrolled, 29% (n=35) had ESCC that expressed PD-L1 CPS ≥10. The baseline characteristics of these 35 patients were: median age of 65 years (range: 47 to 81), 51% age 65 or older; 71% male; 26% White and 69% Asian; 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. One hundred percent had M1 disease.

The ORR in the 35 patients with ESCC expressing PD-L1 was 20% (95% CI: 8, 37). Among the 7 responding patients, the DoR ranged from 4.2 to 25.1+ months, with 5 patients (71%) having responses of 6 months or longer and 3 patients (57%) having responses of 12 months or longer.

14.11 Cervical Cancer

The efficacy of KEYTRUDA was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort (Cohort E) in 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 received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR, and DoR.

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 IHC 22C3 pharmDx kit. The baseline characteristics of these 77 patients were: median age of 45 years (range: 27 to 75); 81% White, 14% Asian, and 3% Black; 32% ECOG PS of 0 and 68% ECOG PS of 1; 92% had squamous cell carcinoma, 6% adenocarcinoma, and 1% adenosquamous histology; 95% had M1 disease and 5% had recurrent disease; and 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 47 for patients with PD-L1 expression (CPS ≥1).

Table 47: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158

Endpoint	KEYTRUDA 200 mg every 3 weeks n=77*
Objective Response Rate	
ORR (95% CI)	14.3% (7.4, 24.1)
Complete response rate	2.6%
Partial response rate	11.7%
Duration of Response	
Median in months (range)	NR (4.1, 18.6+)†
% with duration ≥6 months	91%

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

14.12 Hepatocellular Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-224 (NCT02702414), a single-arm, multicenter trial in 104 patients with HCC who had disease progression on or after sorafenib or were

intolerant to sorafenib; had measurable disease; and Child-Pugh class A liver impairment. Patients with active autoimmune disease, greater than one etiology of hepatitis, a medical condition that required immunosuppression, or clinical evidence of ascites by physical exam were ineligible for the trial. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity, investigator-assessed confirmed disease progression (based on repeat scan at least 4 weeks from the initial scan showing progression), or completion of 24 months of KEYTRUDA. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR and DoR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

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

Efficacy results are summarized in Table 48.

Table 48: Efficacy Results in KEYNOTE-224

Endpoint	KEYTRUDA 200 mg every 3 weeks n=104
BICR-Assessed Objective Response Rate (RECIST v1.1)	
ORR (95% CI)*	17% (11, 26)
Complete response rate	1%
Partial response rate	16%
BICR-Assessed Duration of Response	
% with duration ≥6 months	89%
% with duration ≥12 months	56%

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

14.13 Merkel Cell Carcinoma

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

Patients received KEYTRUDA 2 mg/kg every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Assessment of tumor status was performed at 13 weeks followed by every 9 weeks for the first year and every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR per RECIST v1.1.

The study population characteristics were: median age of 71 years (range: 46 to 91), 80% age 65 or older; 68% male; 90% White; and 48% ECOG PS of 0 and 52% ECOG PS of 1. Fourteen percent had stage IIIB disease and 86% had stage IV. Eighty-four percent of patients had prior surgery and 70% had prior radiation therapy.

Efficacy results are summarized in Table 49.

Table 49: Efficacy Results in KEYNOTE-017

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

* The median duration of response was not reached.

14.14 Renal Cell Carcinoma

The efficacy of KEYTRUDA in combination with axitinib was investigated in KEYNOTE-426 (NCT02853331), a randomized, multicenter, open-label trial conducted in 861 patients who had not received systemic therapy for advanced RCC. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease requiring systemic immunosuppression within the last 2 years were ineligible. Randomization was stratified by International Metastatic RCC Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of the World”).

Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks up to 24 months in combination with axitinib 5 mg orally, twice daily. Patients who tolerated axitinib 5 mg twice daily for 2 consecutive cycles (6 weeks) could increase to 7 mg and then subsequently to 10 mg twice daily. Axitinib could be interrupted or reduced to 3 mg twice daily and subsequently to 2 mg twice daily to manage toxicity.
- Sunitinib 50 mg orally, once daily for 4 weeks and then off treatment for 2 weeks.

Treatment with KEYTRUDA and axitinib continued until RECIST v1.1-defined progression of disease or unacceptable toxicity. Administration of KEYTRUDA and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at baseline, after randomization at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter.

The study population characteristics were: median age of 62 years (range: 26 to 90); 38% age 65 or older; 73% male; 79% White and 16% Asian; 19% and 80% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; and patient distribution by IMDC risk categories was 31% favorable, 56% intermediate and 13% poor.

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR, as assessed by BICR. A statistically significant improvement in OS was demonstrated at the pre-specified interim analysis in patients randomized to KEYTRUDA in combination with axitinib compared with sunitinib. The trial also demonstrated statistically significant improvements in PFS and ORR. Table 50 and Figure 13 summarize the efficacy results for KEYNOTE-426. The median follow-up time was 12.8 months (range 0.1 to 22.0 months). Consistent results were observed across pre-specified subgroups, IMDC risk categories and PD-L1 tumor expression status.

Table 50: Efficacy Results in KEYNOTE-426

Endpoint	KEYTRUDA 200 mg every 3 weeks and Axitinib n=432	Sunitinib n=429
OS		
Number of patients with event (%)	59 (14%)	97 (23%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.53 (0.38, 0.74)	
p-Value†	<0.0001‡	
12-month OS rate	90% (86, 92)	78% (74, 82)
PFS		
Number of patients with event (%)	183 (42%)	212 (49%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.1 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.57, 0.84)	
p-Value†	0.0001§	
ORR		
Overall confirmed response rate (95% CI)	59% (54, 64)	36% (31, 40)
Complete response rate	6%	2%
Partial response rate	53%	34%
p-Value¶	<0.0001	

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

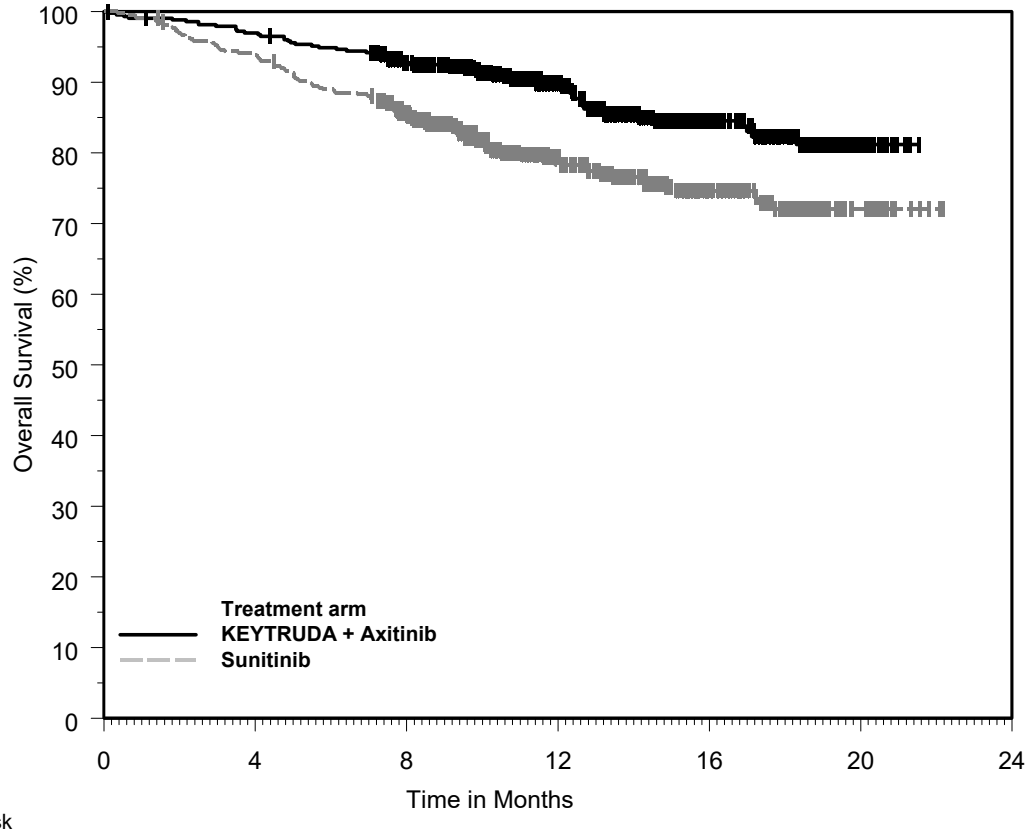
‡ p-Value (one-sided) is compared with the allocated alpha of 0.0001 for this interim analysis (with 39% of the planned number of events for final analysis).

§ p-Value (one-sided) is compared with the allocated alpha of 0.0013 for this interim analysis (with 81% of the planned number of events for final analysis).

¶ Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region

NR = not reached

Figure 13: Kaplan-Meier Curve for Overall Survival in KEYNOTE-426



Number at Risk							
KEYTRUDA + Axitin b:	432	417	378	256	136	18	0
Sunitinib:	429	401	341	211	110	20	0

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA for injection (white to off-white lyophilized powder):

Carton containing one 50 mg single-dose vial (NDC 0006-3029-02)
Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

KEYTRUDA injection (clear to slightly opalescent, colorless to slightly yellow solution):

Carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02)
Carton containing two 100 mg/4 mL (25 mg/mL), single-dose vials (NDC 0006-3026-04)
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).

Immune-Mediated Adverse Reactions

- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA. These reactions may include:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.

- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
- Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.
- Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.4)].*
- Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes *[see Warnings and Precautions (5.4)].*
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*.
- Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN *[see Warnings and Precautions (5.6)]*.
- Other immune-mediated adverse reactions:
  - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms *[see Warnings and Precautions (5.7)]*.
  - Advise patients 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)]*.

Infusion-Related Reactions

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.8)]*.

Complications of Allogeneic HSCT

- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.9)].*

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1, 8.3)].*
- Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for 4 months after the last dose *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1, 8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with KEYTRUDA and for 4 months after the final dose *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

- 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)]*.

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-1907r029

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, including hepatitis. Signs and symptoms of liver problems 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
- bleeding or bruising more easily than normal

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

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

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

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

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

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

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

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

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

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

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat:

- a kind of skin cancer called melanoma. KEYTRUDA may be used:
  - when your melanoma has spread or cannot be removed by surgery (advanced melanoma), **or**
  - to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.
- a kind of lung cancer called non-small cell lung cancer (NSCLC).
  - KEYTRUDA may be used with the chemotherapy medicines pemetrexed and a platinum as your first treatment when your lung cancer:
    - has spread (advanced NSCLC), **and**
    - is a type called “nonsquamous”, **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
  - KEYTRUDA may be used with the chemotherapy medicines carboplatin and either paclitaxel or paclitaxel protein-bound as your first treatment when your lung cancer:
    - has spread (advanced NSCLC), **and**
    - is a type called “squamous”.
  - KEYTRUDA may be used alone as your first treatment when your lung cancer:
    - has not spread outside your chest (stage III) and you cannot have surgery or chemotherapy with radiation **or**
    - your NSCLC has spread to other areas of your body (advanced NSCLC), **and**
    - your tumor tests positive for “PD-L1”, **and**
    - does not have an abnormal “EGFR” or “ALK” gene.
  - KEYTRUDA may also be used alone when:
    - you have received chemotherapy that contains platinum to treat your advanced NSCLC, and it did not work or it is no longer working, **and**
    - your tumor tests positive for “PD-L1”, **and**
    - if your tumor has an abnormal “EGFR” or “ALK” gene, you have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.
- a kind of lung cancer called small cell lung cancer (SCLC). KEYTRUDA may be used when your lung cancer:
  - has spread (advanced SCLC), **and**

- you have received 2 or more types of chemotherapy, including one that contains platinum, and it did not work or is no longer working.

- a kind of cancer called head and neck squamous cell cancer (HNSCC).
  - KEYTRUDA may be used with the chemotherapy medicines fluorouracil and a platinum as your first treatment when your head and neck cancer has spread or returned and cannot be removed by surgery.
  - KEYTRUDA may be used alone as your first treatment when your head and neck cancer:
    - has spread or returned and cannot be removed by surgery, **and**
    - your tumor tests positive for "PD-L1".
  - KEYTRUDA may be used alone when your head and neck cancer:
    - has spread or returned, **and**
    - you have received chemotherapy that contains platinum and it did not work or is no longer working.
- a kind of cancer called classical Hodgkin lymphoma (cHL) in adults and children when:
  - you have tried a treatment and it did not work **or**
  - your cHL has returned after you received 3 or more types of treatment.
- a kind of cancer called primary mediastinal B-cell lymphoma (PMBCL) in adults and children when:
  - you have tried a treatment and it did not work **or**
  - your PMBCL has returned after you received 2 or more types of treatment.
- a kind of bladder and urinary tract cancer called urothelial carcinoma. KEYTRUDA may be used when your bladder or urinary tract cancer:
  - has spread or cannot be removed by surgery (advanced urothelial cancer) **and**,
  - you are not able to receive chemotherapy that contains a medicine called cisplatin, and your tumor tests positive for "PD-L1", **or**
  - you are not able to receive a medicine called cisplatin or carboplatin, **or**
  - you have received chemotherapy that contains platinum, and it did not work or is no longer working.
- a kind of cancer that is shown by a laboratory test to be a microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumor. KEYTRUDA may be used in adults and children to treat:
  - cancer that has spread or cannot be removed by surgery (advanced cancer), **and**
  - has progressed following treatment, and you have no satisfactory treatment options, **or**
  - you have colon or rectal cancer, and you have received chemotherapy with fluoropyrimidine, oxaliplatin, and irinotecan but it did not work or is no longer working.

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

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant, such as a kidney or liver
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have lung or breathing problems
- have liver problems
- have any other medical problems

- are pregnant or plan to become pregnant
    - KEYTRUDA can harm your unborn baby.

  Females who are able to become pregnant:
    - Your doctor will give you a pregnancy test before you start treatment with KEYTRUDA.
    - You 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 think you may be pregnant or if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed.
    - It is not known if KEYTRUDA passes into your breast milk.
    - Do not breastfeed during treatment with KEYTRUDA and for 4 months after your final dose of KEYTRUDA.

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

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

How will I receive KEYTRUDA?

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

What are the possible side effects of KEYTRUDA?

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

Common side effects of KEYTRUDA when used alone include: feeling tired, pain, including pain in muscles, bones or joints and stomach-area (abdominal) pain, decreased appetite, itching, diarrhea, nausea, rash, fever, cough, shortness of breath, and constipation.

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

Common side effects of KEYTRUDA when given with axitinib include: diarrhea, feeling tired or weak, high blood pressure, liver problems, low levels of thyroid hormone, decreased appetite, blisters or rash on the palms of your hands and soles of your feet, nausea, mouth sores or swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina, hoarseness, rash, cough, 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 information: www.merck.com/product/patent/home.html

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: July 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s056

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

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	sBLA
Application Number	BLA 125514/S-56
Priority or Standard	Priority
Submit Date	January 30, 2019
Received Date	January 30, 2019
PDUFA Goal Date	July 30, 2019
Division/Office	DOP2/OHOP
Review Completion Date	July 30, 2019
Established Name	Pembrolizumab
Trade Name	Keytruda
Pharmacologic Class	Programmed Death-Receptor-1 (PD-1) Blocking Antibody
Code name	MK-3475
Applicant	Merck Sharp & Dohme Corp.
Formulations	For Injection: 50 mg lyophilized powder in single-dose vial Injection: 100 mg/4 mL (25 mg/mL) solution in single-dose vial
Dosing Regimen	200 mg over 30 minutes every 3 weeks
Applicant Proposed Indication	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication	Treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

Table of Contents

Table of Tables

Table of Figures

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OPDP=Office of Prescription Drug Promotion

Glossary

1L	first-line
2L	second-line
3L	third-line
5-FU	5-fluoropyrimidine
AC	advisory committee
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEOSI	adverse event of special interest
ALT	alanine aminotransferase
ASaT	all subjects as treated
AST	aspartate aminotransferase
BICR	blinded independent central review
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRAF	human gene that encodes a protein called B-Raf
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
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug-drug interactions
DILI	drug-induced liver injury
DMC	data monitoring committee
dMMR	mismatch repair deficient
DOP2	Division of Oncology Product

DOR	duration of response
EAC	esophageal adenocarcinoma
EC	esophageal cancer
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EGJ	esophagogastric junction
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQoL 5-dimension scale
ERC	Ethical Review Committee
ESCC	esophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
ETASU	elements to assure safe use
FA	final analysis
FAS	full analysis set
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
GE	gastroesophageal
GEP	gene expression profile
GI	gastrointestinal
GRMP	good review management practice
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HNSCC	head and neck squamous cell cancer
HR	hazard ratio
IA	interim analysis
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IHC	immunohistochemistry
IND	Investigational New Drug
irAE	immune-related adverse event
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors version 1.1
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system
KM	Kaplan-Meier
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MEL	melanoma
mITT	modified intent to treat
MRL	Merck Research Laboratories
MSI	microsatellite instability
MSI-H	microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCT	National Clinical Trial
NDA	new drug application
NME	new molecular entity
NSCLC	non-small cell lung cancer
OCE	Oncology Center of Excellence
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamics/progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetics
PMBCL	primary mediastinal large B-cell lymphoma
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PS	performance status
PSUR	Periodic Safety Update report

PT	preferred term
QA	quality assurance
Q2W	every 2 weeks
Q3W	every 3 weeks
Q9W	every 9 weeks
QLQ-C30	quality-of-life questionnaire core 30 items
QLQ-OES18	quality-of-life questionnaire esophageal cancer 18 module
QoL	quality of life
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
REMS	risk evaluation and mitigation strategy
RSD	Reference Safety Dataset
RTOR	Real Time Oncology Review
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental biologics license application
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TPS	tumor proportion score
UK	United Kingdom
US	United States
USPI	United States Prescribing Information
VAS	visual analog scale
WBC	white blood cell count

1 Executive Summary

1.1 Product Introduction

Pembrolizumab is a humanized monoclonal antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2), releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Pembrolizumab is approved for the treatment of multiple solid tumors, including refractory gastric and gastroesophageal cancer that expresses PD-L1 (CPS≥10), but has not previously been approved for the treatment of patients with microsatellite stable (MSS), mismatch-repair proficient esophageal cancer. For a listing of currently approved indications see Section 3.1 of this review.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends traditional approval of pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus (ESCC) whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy. The submitted data provide substantial evidence of the safety and effectiveness of pembrolizumab for this indication. This conclusion is based on demonstration of a clinically meaningful improvement in overall survival (OS) in patients randomized to receive pembrolizumab compared to those randomized to receive a systemic treatment of physicians' choice (TPC) in this subpopulation of patients who had received one prior line of systemic treatment in a single adequate and well-controlled randomized trial (KEYNOTE-181), and durable and clinically meaningful responses in this subpopulation in the third and later line setting in a single arm trial, KEYNOTE-180 (submitted to sBLA 125514/S-55, please see review of this supplement for additional details).

KEYNOTE-181 (NCT02564263) is a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD L1 status was determined using the PD L1 IHC 22C3 pharmDx kit. Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive either pembrolizumab 200 mg every 3 weeks or TPC consisting of one of the following chemotherapy regimens, all given intravenously: paclitaxel 80-

100 mg/m^2 on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m^2 every 3 weeks, or irinotecan 180 mg/m^2 every 2 weeks. Randomization was stratified by tumor histology (ESCC vs. esophageal adenocarcinoma [EAC]/Siewert type I EAC of the gastroesophageal junction [GEJ]), and geographic region (Asia vs. ex-Asia). Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomized to the pembrolizumab arm were permitted to continue treatment beyond the first RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with pembrolizumab without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks.

The prespecified outcome measure of KEYNOTE-181 was OS evaluated in the following co-primary populations: patients with ESCC, patients with tumors expressing PD-L1 CPS ≥10, and all randomized patients. Additional efficacy outcome measures were progression-free survival (PFS), overall response rate (ORR), and duration of response (DoR), according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

A total of 628 patients were enrolled and randomized to pembrolizumab (n=314) or TPC (n=314). Of these 628 patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS ≥10. Of these 167 patients, 85 patients were randomized to pembrolizumab and 82 patients to TPC [paclitaxel (n=50), docetaxel (n=19), or irinotecan (n=13)].

The trial did not meet the pre-specified threshold to demonstrate a statistically significant improvement in OS in any of the three pre-specified co-primary patient populations, with observed hazard ratios of 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. In an exploratory analysis conducted in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to pembrolizumab as compared with chemotherapy (HR=0.64 [95% CI:0.46,0.69]). Improved PFS [HR= 0.66 (95%CI: 0.48, 0.92)] and ORR (22% [95% CI: 14,33] vs. 7% [95% CI: 3,15]) were also observed in the ESCC CPS≥10 subpopulation randomized to pembrolizumab.

KEYNOTE-180 (NCT02559687) is a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after at least 2 prior systemic treatments for advanced disease. With the exception of the number of prior lines of treatment, the eligibility criteria were similar to the eligibility criteria in KEYNOTE-181, and the pembrolizumab dosage regimen was identical. The major efficacy outcome measures were ORR and DoR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

Among the 121 patients enrolled, 29% (n=35) had ESCC that expressed PD-L1 CPS ≥10. The ORR in the 35 patients with ESCC expressing PD-L1 was 20% (95% CI: 8, 37). Among the 7 responding patients, the DoR ranged from 4.2 to 25.1+ months, with 5 patients (71%) having responses of 6 months or longer and 3 patients (57%) having responses of 12 months or longer.

A key review issue during review of this sBLA was the lack of statistical significance for any of the pre-specified efficacy analyses of OS in KEYNOTE-181 and whether data from post-hoc subgroup analyses of OS in patients with ESCC whose tumors express PD-L1 with CPS ≥10 constitute substantial evidence of effectiveness of pembrolizumab in this patient population. The review team ultimately determined that the evidence provided in this sBLA, supported by the data submitted to sBLA 125514/S-55 (seeking approval of pembrolizumab in patients with (b) (4)) provide substantial evidence that pembrolizumab is effective and confers a clinically meaningful benefit to patients with locally advanced unresectable ESCC whose tumors express PD-L1 in the second-line setting and beyond, taking into account the following factors:

- The narrow difference between the calculated p-values derived from analysis of the pre-specified OS endpoints of KEYNOTE-181 and the thresholds for statistical significance, particularly for the ESCC and PD-L1 positive populations (Table 15)
- The magnitude of improvement in OS for the ESCC/CPS≥10 subgroup in the pembrolizumab arm over an active comparator in KEYNOTE-181, supported by favorable treatment effects in PFS and ORR in the pembrolizumab arm
- Increased efficacy in the ESCC/CPS ≥10 subgroup compared to the EAC and ESCC/PD-L1 negative subgroups in KEYNOTE-181, supported by data from the KEYNOTE-180 trial submitted to sBLA-125514/S-55 indicating that the majority of responses to pembrolizumab in the third- or later line setting were observed in this subgroup
- The totality of existing data from use of pembrolizumab in other cancers such as non-small cell lung cancer and gastric cancer for which increased efficacy was demonstrated in PD-L1-positive subpopulations
- Emerging knowledge regarding the biological differences between ESCC and EAC suggesting that underlying differences in tumor characteristic may confer differential susceptibility to PD-1 inhibition [25].

Taken together, the review team determined that the submitted evidence meets the statutory evidentiary standard for traditional approval of pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus (ESCC) whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

9

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Esophageal cancer (EC) is the sixth most fatal cancer worldwide [1]. In the US, esophageal cancer (EC) is an orphan disease; in the US in 2019, approximately 17,650 new cases of EC will be diagnosed and 16,080 people will die of their disease [24]. The 5-year survival rate of advanced unresectable or metastatic EC is 3.4% [2]. This poor prognosis highlights the need for new therapies to improve long-term outcomes after standard first-line therapies. The incidence and histological type of EC varies with geographic location. While the rate of esophageal squamous cell carcinoma (ESCC) exceeds esophageal adenocarcinoma (EAC) in more than 90% of all countries [3], EAC predominates in the US, accounting for 63.5% of all EC cases [4].

First-line treatment for advanced EC generally consists of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin), which confer moderate benefit. Although pembrolizumab is approved for the treatment of refractory microsatellite-high/mismatch repair-deficient (MSI-H/dMMR) solid tumors including EC, there are no approved treatments for the treatment of advanced microsatellite stable/mismatch repair proficient (MSS/pMMR) EC, including ESCC, in the second line setting and beyond and there are no randomized, well-controlled trials demonstrating an overall survival benefit for any drug or combination of drugs in the second-line or later treatment of EC. For second-line or subsequent therapy of MSS/pMMR proficient EC, ESMO and NCCN treatment guidelines [6] [5] recommend a variety of agents, including ramucirumab and paclitaxel for EAC, docetaxel, paclitaxel, irinotecan, and trifluridine and tipiracil (for third line or later treatment of EAC).

The safety and effectiveness of pembrolizumab for the treatment of with patients with PD-L1 positive (CPS≥10) ESCC who had received at least one prior line of systemic treatment was established by the results of a single adequate and well-controlled trial, KEYNOTE-181, demonstrating a clinically meaningful improvement in overall survival (OS) in this subpopulation favoring the pembrolizumab arm compared to a control arm consisting of single-agent chemotherapy of the physician's choice (TPC) selected prior to randomization. These results are supported by results of KEYNOTE-180, a single arm trial (submitted under sBLA 125514/S-55).

KEYNOTE-181 (NCT02564263) is a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic EC who progressed on or after one prior line of systemic treatment for advanced disease. All patients were

required to have tumor specimens for PD-L1 testing for advanced disease. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD L1 status was determined using the PD L1 IHC 22C3 pharmDx kit. Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive either pembrolizumab 200 mg every 3 weeks or TPC of any of the following chemotherapy regimens, all given intravenously: paclitaxel 80-100 mg/m^2 on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m^2 every 3 weeks, or irinotecan 180 mg/m^2 every 2 weeks. Randomization was stratified by tumor histology (ESCC vs. esophageal adenocarcinoma [EAC]/Siewert type I EAC of the gastroesophageal junction [GEJ]), and geographic region (Asia vs. ex-Asia). Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomized to Keytruda were permitted to continue beyond the first RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with pembrolizumab without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. The prespecified outcome measure of KEYNOTE-181 was OS evaluated in the following co-primary populations: patients with ESCC, patients with tumors expressing PD-L1 CPS ≥10, and all randomized patients. Additional efficacy outcome measures were progression-free survival (PFS), overall response rate (ORR), and duration of response (DoR), according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

A total of 628 patients were enrolled and randomized to pembrolizumab (n=314) or TPC (n=314). Of these 628 patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS ≥10. Of these 167 patients, 85 patients were randomized to pembrolizumab A and 82 patients to TPC [paclitaxel (n=50), docetaxel (n=19), or irinotecan (n=13)]. The trial did not meet the pre-specified threshold to demonstrate a statistically significant improvement in OS in any of the three pre-specified co-primary patient populations, with observed hazard ratios of 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients; however, in an exploratory analysis conducted in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to Keytruda as compared with chemotherapy (HR=0.64 [95% CI:0.46,0.69]). Improved PFS [HR= 0.66 (95%CI: 0.48, 0.92)] and ORR (22% [95% CI: 14,33] vs. 7% [95% CI: 3,15] were also observed in the ESCC CPS≥10 subpopulation randomized to pembrolizumab.

KEYNOTE-180 (NCT02559687) is a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced or metastatic EC who progressed on or after at least 2 prior systemic treatments for advanced disease. With the exception of the number of prior lines of treatment, the eligibility criteria were similar to and the dosage regimen identical to KEYNOTE-181. The major efficacy outcome measures were

ORR and duration of response (DoR) according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by blinded independent central review (BICR). Among the 121 patients enrolled, 29% (n=35) had ESCC that expressed PD-L1 CPS ≥10. The ORR in the 35 patients with ESCC expressing PD-L1 was 20% (95% CI: 8, 37). Among the 7 responding patients, the DoR ranged from 4.2 to 25.1+ months, with 5 patients (71%) having responses of 6 months or longer and 3 patients (57%) having responses of 12 months or longer.

The review of safety for this new indication was based primarily upon data from KEYNOTE-181. A total of 314 patients randomized to the pembrolizumab arm received at least one dose of pembrolizumab. The median duration of exposure to pembrolizumab was 2.1 months (range: 1 day to 24.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. The adverse reaction profile of pembrolizumab observed in patients with esophageal cancer was similar to the adverse reaction profile previously observed in the safety database of 2799 patients with melanoma or NSCLC treated with pembrolizumab as a single agent. Pembrolizumab was discontinued for adverse events in 13% of patients, compared to 14% of patients treated with single-agent systemic chemotherapy. Adverse reactions occurring in ≥ 20% of pembrolizumab-treated patients in KEYNOTE-181 were decreased appetite (25%) and fatigue (22%). Serious adverse events (SAE) occurred in 40% and 41% of patients in the pembrolizumab and control (TPC) arms, respectively. The most frequently reported SAE (≥2% incidence) in patients receiving pembrolizumab included pneumonia (4.5%), dysphagia (3.5%), aspiration pneumonia (3.5%), and pneumonitis (2.2%). The frequency of drug-related adverse events (AE) leading to death was low and also similar in both arms (1.6% in the pembrolizumab arm and 1.7% in the TPC arm). The fatal AE reported were consistent with the known safety profiles of pembrolizumab and chemotherapy. Five fatal AE in the pembrolizumab arm were considered drug-related by the investigator: pneumonitis (two patients), death, myocarditis, and esophageal hemorrhage (one patient each). The incidence of immune-mediated adverse reactions was similar to that seen in other patients with advanced solid tumors treated with pembrolizumab as a single agent.

The review team concluded that the overall risk:benefit assessment favored approval of pembrolizumab in patients with recurrent locally advanced or metastatic ESCC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test with disease progression after one or more prior lines of systemic therapy with disease progression after one or more prior lines of systemic therapy. ESCC is a serious and life-threatening disease with a poor prognosis and prior to this approval, there was no available therapy in the second line setting with a demonstrated improvement in overall survival, a measure of direct clinical benefit to patients and also a measure of safety. The demonstrated improvement in OS is clinically meaningful and supported by improvements in PFS and ORR over the active TPC comparator in KEYNOTE-181. The adverse reaction profile observed in patients with EC is consistent with the adverse reaction profile observed in the previously approved indications for pembrolizumab. These adverse reactions to pembrolizumab are largely manageable with dose interruption or treatment discontinuation and supportive care, and are acceptable considering the life-threatening nature of refractory advanced ESCC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Esophageal cancer (EC) is the sixth most fatal cancer worldwide [1]. • In the US, EC is considered an orphan disease. The American Cancer Society estimates that in the US in 2019, 17,650 new cases of EC will be diagnosed and 16,080 people will die of their disease [24] • The 5-year survival rate of advanced/metastatic EC is approximately 3.4% [2]. • The incidence and histological type of EC varies with geographic location. While the rate of esophageal squamous cell carcinoma (ESCC) exceeds esophageal adenocarcinoma (EAC) in more than 90% of all countries [3], EAC predominates in the US, accounting for 63.5% of all EC cases [4].	EC is a serious and life threatening disease, with a 5-year survival rate of 3.4%.
Current Treatment Options	• Cytotoxic chemotherapy is the mainstay of treatment for advanced esophageal cancer. • For initial treatment of unresectable locally advanced or metastatic EC,NCCN guidelines recommend the combination of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin), which confer moderate benefit [5] [6] [7] [8] [9]. Taxanes or epirubicin are sometimes used in combination with fluoropyrimidine and platinum agents [6] • There are no approved treatments for the treatment of advanced microsatellite stable/mismatch repair proficient EC, including ESCC, in the second line setting and beyond. • There are no randomized, well-controlled trials demonstrating an overall survival benefit for the second-line or later treatment of EC. For second-line or subsequent therapy of MSS/MMR proficient EC, ESMO and NCCN treatment guidelines [6] [5] recommend a variety of agents, including ramucirumab and paclitaxel for EAC, docetaxel,	There is an unmet medical for new effective therapies that improve survival in patients with unresectable or metastatic EC who are refractory to first-line cytotoxic chemotherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	paclitaxel, irinotecan, and trifluridine and tipiracil (for third line or later treatment of EAC) [10] [11], or participation in a clinical trial.	
Benefit	• A subgroup analysis of Study KEYNOTE-181 demonstrated that patients with recurrent locally advanced or metastatic ESCC whose tumors express PD-L1 (CPS ≥10) with disease progression after one prior lines of systemic therapy randomized to pembrolizumab had improved OS compared to patients randomized to a single-agent chemotherapy of their physician's choice (TPC; either paclitaxel 80-100 mg/m^2 intravenously (IV) on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m^2 IV every 3 weeks, or irinotecan 180 mg/m^2 IV every 2 weeks (HR=0.64 [95% CI:0.46,0.69]). • In KEYNOTE-181, improved PFS [HR= 0.66 (95%CI: 0.48, 0.92)] and ORR (22% [95% CI: 14,33] vs. 7% [95% CI: 3,15] were also observed in the ESCC CPS≥10 subpopulation randomized to pembrolizumab. • The results of KEYNOTE-181 were supported by KEYNOTE-180, in which an ORR of 20% (95% CI: 8, 37) was observed in a more refractory population of patients with recurrent locally advanced or metastatic ESCC whose tumors express PD-L1 (CPS ≥10), who had experienced disease progression after at least two prior lines of systemic therapy. These responses were durable, with 5 of 7 (71%) responding patients maintaining a response for at least 6 months and 3 patients (57%) having responses of 12 months or longer.	KEYNOTE-181 demonstrated clinically meaningful improvements in OS, PFS, and ORR compared to single-agent chemotherapy of the physician's choice in patients with recurrent locally advanced or metastatic ESCC whose tumors express PD-L1 (CPS ≥10) with disease progression after one prior lines of systemic therapy. These results were supported by observation of clinically meaningful and durable responses in patients with recurrent locally advanced or metastatic ESCC whose tumors express PD-L1 (CPS ≥10) who received pembrolizumab following receipt of at least two prior lines of systemic chemotherapy in Study KEYNOTE-180 (see FDA's review of sBLA 125514/S-56 for details).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety of pembrolizumab has been previously established for the treatment of patients with a variety of advanced/metastatic solid tumors, including melanoma, non-small cell lung cancer, and gastric cancer. • The observed safety profile of pembrolizumab in patients with EC enrolled in KEYNOTE-181 is consistent with the known safety profile of pembrolizumab. Additionally, this trial showed an OS benefit for patients with PD-L1+ (CPS≥10) ESCC, which further supports the safety of pembrolizumab in this patient population. • No new or unexpected adverse reactions were observed in patients with EC who received pembrolizumab in KEYNOTE-181. The incidence of immune-mediated adverse reactions was similar to that seen in other patients with advanced solid tumors treated with pembrolizumab as a single agent. • Adverse reactions occurring in ≥ 20% of pembrolizumab-treated patients in KEYNOTE-181 were decreased appetite (25%) and fatigue (22%). • Serious adverse events (SAE) occurred in 40% and 41% of patients in the pembrolizumab and control (TPC) arms, respectively. • The most frequently reported SAE (≥2% incidence) in patients receiving pembrolizumab included pneumonia (4.5%), dysphagia (3.5%), aspiration pneumonia (3.5%), and pneumonitis (2.2%). • The frequency of drug-related adverse events (AE) leading to death in KEYNOTE-181 was low and also similar in both arms (1.6% in the pembrolizumab arm and 1.7% in the TPC arm). Five fatal AE in the	The toxicity profile of pembrolizumab is acceptable when assessed in the context of the life-threatening nature of refractory ESCC and considering the demonstrated improvement in OS, which also reflects the safety of use of pembrolizumab in this patient population. No new significant safety concerned were identified during review of this supplemental application that would require a new risk management plan, including a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use. Significant and serious adverse reactions to pembrolizumab, including immune-mediated adverse reactions, are largely manageable through surveillance and timely dose interruption or discontinuation with supportive care. Additionally, oncologists who treat patients with ESCC are well trained in monitoring and treatment of the adverse reactions to pembrolizumab. The review team determined that standard postmarketing surveillance would be sufficient for continued assessment of the safety of cabozantinib in patients with unresectable HCC, and that a postmarketing requirement (PMR) under the Food and Drug Administration Amendments Act of 2007 (FDAAA) was not needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pembrolizumab arm were considered drug-related by the investigator: pneumonitis (two patients), death, myocarditis, and esophageal hemorrhage (one patient each).	

1.4 Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
		✓	☐	Patient reported outcome (PRO)	Section 7.2.6
			☐	Observer reported outcome (ObsRO)	
			☐	Clinician reported outcome (ClinRO)	
			☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	☐	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data			
	☐	Natural history studies			

	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.		

X _____

Martha Donoghue, M.D.
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:
Esophageal cancer is the sixth most fatal cancer worldwide [1]. In the US, EC is considered an orphan disease. The American Cancer Society estimates that in the US in 2019, 17,650 new cases of EC will be diagnosed and 16,080 people will die of their disease (https://www.cancer.org/cancer/esophagus-cancer/about/key-statistics.html). The 5-year survival rate of advanced/metastatic EC remains at 3.4% [2]. The poor prognosis of metastatic EC underscores the need for new therapies to improve long-term outcomes after standard first-line therapies.

The incidence and histological type of EC varies with geographic location. While the rate of ESCC exceeds EAC in more than 90% of all countries [3], EAC predominates in the US, accounting for 63.5% of all EC cases [4].

The FDA's Assessment:
FDA agrees with Merck's analysis of esophageal cancer, as described above.

2.2 Analysis of Current Treatment Options

The Applicant's Position:
Cytotoxic chemotherapies have remained the mainstay for treatment of metastatic EC for many years. Global guidelines provide recommendations on preferred 1L, 2L, and subsequent systemic treatment for patients with EC [5] [6] [7]. For previously untreated patients (1L), combination chemotherapies are routinely used. Although there are some differences among global guidelines, in general guidelines are consistent and recommend the combination of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin), which provides moderate benefit but high toxicity [5] [6] [7] [8] [9]. Taxanes or epirubicin are sometimes used in combination with fluoropyrimidine and platinum agents [6].

The role of 2L therapy in esophageal cancer is poorly defined because there are no randomized controlled Phase 3 studies demonstrating survival benefit in this setting, and recommended regimens are largely based on small Phase 2 study results or extrapolated data from gastric cancer studies [Table 1].

Several regimens were evaluated as 2L treatments for advanced or metastatic EC. The ESMO and NCCN treatment guidelines [6] [5] recommend docetaxel, paclitaxel, and irinotecan [10]

[11], which show marginal benefit (median OS ranging from 4.0 months to 8.1 months and median ORR ranging from 0% to 28.0%) [12] [13] [14] [15] [16] [17] [18] [19] [Table 1].

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Table 1
Summary of Treatments for Previously Treated Advanced/Metastatic ESCC or EAC

Product Name	Relevant Indication	Year and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments (Targeted Therapies)					
Pembrolizumab	Approved as a single agent for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	2017 (accelerated approval)	200 mg IV Q3W for adults and 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics.	A total of 149 participants with MSI-H or dMMR solid tumors who progressed following prior treatment enrolled in 1 of 5 uncontrolled, open-label, multi-cohort, multi-center, single-arm trials: 90 with colorectal cancer and 59 with other cancers, including 1 with esophageal cancer. ORR in the 9 participants with gastric or GEJ cancer was 56%, and the 1 patient with esophageal cancer had a partial response [20].	Warnings and Precautions for Pembrolizumab: Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis, thyroid disorders, Type 1 diabetes mellitus, and nephritis. Withhold or permanently discontinue based on severity.
Non-FDA Approved Treatments (Chemotherapy)					
Docetaxel	Not approved for 2L or beyond therapy or for EC. (Approved in combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received previous	Initial approval 1996 (full approval). Gastric indication approved in 2006 (full approval)	75 mg/m^2 followed by cisplatin 75 mg/m^2 (both on day 1 only) followed by fluorouracil 750 mg/m2 per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion	Heath, Urba 2002 [12]: Phase 2 study of docetaxel in participants with incurable adenocarcinoma of the esophagus. Docetaxel was administered at a dose of 75 mg/m^2 Q3W. A total of 22 participants were enrolled, including 7 who received previous chemotherapy (but not paclitaxel). Previously treated participants had a 0% response rate. There were no complete responses. Median PFS was 1.4 months and median OS was 4 months. Shirakawa, Kato 2014 [13]: A retrospective study of docetaxel (n=132) or	Warnings and Precautions for Docetaxel: Delayed myelodysplasia or myeloid leukemia, erythema of the extremities with edema followed by desquamation, paresthesia, dysesthesia, pain, severe asthenia, fetal harm can occur when administered to a pregnant woman.

	chemotherapy for advanced disease).			paclitaxel (n=31) in participants with advanced or recurrent esophageal squamous cell carcinoma who previously received fluoropyrimidine- and platinum-based chemotherapy. Docetaxel was administered 3-weekly at 70 mg/m^2. Paclitaxel was administered at 100 mg/m^2 weekly for 6 weeks, with 1 week's rest. Progression-free survival and median overall survival (OS) were 2.3 and 6.1 months, respectively, with paclitaxel and 2.3 and 5.5 months with docetaxel. Response rates were 19.4 % for paclitaxel and 5.3 % for docetaxel.	
				Metges, Hennequin 2001 [18]: Docetaxel as 2L treatment in 21 patients with ESCC and 10 with EAC previously treated with platinum and 5FU in a non-randomized interventional study. Docetaxel 100 mg/m2, IV infusion one day once every 3 weeks ORR was 28% with 3 complete responses, 4 partial responses, 10 stable disease, and 8 progressive disease	
				Yamazaki, Ono 2008 [19]: 2L chemotherapy for unresectable or recurrent squamous cell carcinoma of the esophagus refractory to chemotherapy with 5-fluorouracil plus platinum in 28 patients. Docetaxel 60 or 70 mg/m^2. ORR 18%, median survival 5.1 months, median PFS 2.1 months. 0% complete response.	
				Muro, Hamaguchi 2004 [14]: Non-randomized Phase 2 study of single-agent docetaxel in participants with histologically proven esophageal cancer, with measurable metastatic lesions who have received no more than 1 previous chemotherapy regimen. Ten of 49 evaluable patients showed a partial response. Of the 10 partial responses, six patients had received	

				previous platinum-based chemotherapy. Median survival time was 8.1 months and the 1-year survival rate was 35%.	
Irinotecan	Not approved for the treatment of advanced/metastatic ESCC or EAC. (Approved for first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum, and for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy).	Full approval for metastatic carcinoma of the colon and rectum (2L) 1998	In the study summarized in the adjacent column the dose used was 100 to 140 mg/m2 given on days 1, 8, and 15 every 4 weeks [15].	Burkart, Hartmann 2007 [15]: Non-randomized Phase 2 study of weekly single-agent irinotecan in participants with histologically proven, measurable metastatic or locally advanced esophageal adeno- or squamous cell carcinoma, with tumor progression during or after previous chemotherapy with cisplatin and 5-FU. In 13 evaluable patients, ORR was 15% with 0% complete responses and 15% partial responses. Median OS was 5 months and median PFS was 2 months.	Warnings and Precautions for Irinotecan: Diarrhea and cholinergic reactions, myelosuppression, increased risk for neutropenia in patients with reduced UGT1A1 activity, hypersensitivity, renal impairment/renal failure, pulmonary toxicity, embryofetal toxicity, and a greater likelihood of grade 3–4 neutropenia in patients with total bilirubin levels 1.0–2.0 mg/dL.
Paclitaxel	Not approved for the treatment of advanced/metastatic ESCC or EAC. (Approved for the treatment of advanced carcinoma of the ovary, adjuvant treatment of node-	Initial approval 1992 (full approval) for relapsed ovarian cancer	In the study summarized in the adjacent column the dose used in the paclitaxel alone arm, was 80 mg/m2 IV on	Cohen, Benson 2014 [16]: Randomized phase 2 study of paclitaxel with or without the anti-IGF-R antibody cixutumumab (IMC-A12) as 2L treatment for metastatic esophageal or GE junction cancer. 43 patients were evaluable in the paclitaxel arm. For patients given paclitaxel only the ORR 12%, median OS 6.5 months, median PFS 2.6 months.	Black Box Warning for Paclitaxel: Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2%-

	positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy, treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy).		days 1, 8, and 15 Q28 days [16].	Anderson, O'Reilly 2003 [17]: Non-randomized Phase 2 study of 96-hour paclitaxel in previously treated participants with advanced esophageal cancer. Paclitaxel was administered at 140mg/m^2 over 96 hours every 21 days. Among 14 evaluable participants, 5 had SD and 9 had PD.	4% of patients receiving paclitaxel in clinical trials. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel.
				Shirakawa, Kato 2014 [13]: A retrospective study of docetaxel (n=132) or paclitaxel (n=31) in participants with advanced or recurrent esophageal squamous cell carcinoma who previously received fluoropyrimidine- and platinum-based chemotherapy. Results described above.	

Abbreviations: EAC=esophageal adenocarcinoma; ESCC=esophageal squamous cell carcinoma; IGF-IR=insulin-like growth factor receptor; NR=not reported; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; TTP=time to progression.

[a] The data are for patients who received previous chemotherapy but not paclitaxel.

[b] This was a randomized Phase 2 study of paclitaxel with or without the anti-IGF-IR antibody cixutumumab. Median PFS and OS for the cixutumumab arm were 2.3 and 6.4 months, respectively. The response rate was 14%.

[c] Data are for the paclitaxel only arm.

The FDA's Assessment:

FDA agrees with Merck's assessment of the current standard of care for second and later line treatment of advanced or metastatic esophageal cancer. For most patients in the U.S., first-line treatment consists of a platinum and fluoropyrimidine combination. Although chemotherapy is considered standard of care for second line MSS advanced or metastatic esophageal cancer, the response rates and survival rates are poor and hence there remains a high unmet medical need in this population.

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3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:
KEYTRUDA® (BLA 125514) was first granted accelerated approval by the United States FDA 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 at a weight-based dose of 2 mg/kg Q3W. The initial accelerated approval granted on October 2, 2015 for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy was also at the weight-based dose of 2 mg/kg Q3W. These two weight-based dosing approvals were subsequently converted to the fixed dose of 200 mg Q3W on May 17, 2017 (melanoma) and October 24, 2016 (NSCLC).

As of January 22, 2019, KEYTRUDA® has received regular or accelerated approval in the US for a number of indications as summarized in [Table 2].

Table 2
Summary of FDA-approved Pembrolizumab Indications

Indication	Regular Approval	Accelerated Approval
Unresectable or metastatic melanoma	X	
Metastatic NSCLC (monotherapy based on PD-L1 TPS)	X	
Metastatic NSCLC (in combination with chemotherapy regardless of PD-L1 expression)	X	
Locally advanced or metastatic urothelial carcinoma with progression on or after platinum-containing chemotherapy	X	
Recurrent or metastatic HNSCC with progression during or after platinum-containing chemotherapy		X
Refractory classical HL, or who have relapsed after 3 or more prior lines of therapy		X
Refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy		X
Locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 CPS≥10 or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status		X
Unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed following prior treatment or CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan		X
Recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 CPS≥1 with disease progression on or after two or more previous lines of therapy		X
Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 CPS≥1		X

HCC that has been previously treated with sorafenib		X
Recurrent locally advanced or metastatic Merkel cell carcinoma		X

The FDA's Assessment:
FDA agrees with the approval history of pembrolizumab (BLA 125514) summarized above. Since the submission of this sBLA, pembrolizumab also received regular approval for renal cell carcinoma (RCC) in combination with axitinib, for the first-line treatment of patients with advanced RCC and accelerated approval in small cell lung cancer (SCLC) for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 3
Key Regulatory Interactions Related to KEYNOTE-181 Submitted to IND 123482

Date	Comments
21-NOV-2014	Merck submission of original IND 123482 for gastric cancer. IND opened with protocol KEYNOTE-059 (Serial No. 0000)
17-MAR-2015	Email communication from Ms. Tina Ennis of FDA to Dr. Chandrika Kumar (Merck) advising that submissions for the Esophageal Cancer indication be submitted to IND 123,482 which would cover all gastrointestinal (GI) malignancies and be reviewed by the same review team at the Division of Oncology Products (DOP2).
15-AUG-2015	Type B Meeting - End of Phase 2 meeting; discussion of Ph. 2 protocols KEYNOTE-180 (third-line esophageal cancer) and KEYNOTE-181 (second-line esophageal cancer), as confirmatory study for potential accelerated approval based on KEYNOTE-180.
28-AUG-2015	Receipt of FDA formal meeting minutes for August 15, 2015 Type B meeting
25-SEP-2015	Merck submission of Initial Pediatric Study Plan for esophageal cancer (Serial No. 0208)
30-SEP-2015	Merck submission of new protocol, KEYNOTE-181 for second-line esophageal cancer treatment (Serial No. 0209)

21-DEC-2015	Merck submission of a revised Pediatric Study Plan for esophageal cancer with additional information under Section 4 (Serial No. 0233)
21-MAR-2016	Submission of an agreed initial Pediatric Study Plan for esophageal cancer (Serial No. 0263)
27-FEB-2017	Receipt of preliminary comments for Type C Meeting Background Package for KEYNOTE-590
01-MAR-2017	Merck submission of request for Orphan Drug Designation
10-MAR-2017	Merck accepts Preliminary Comments as official meeting Minutes and cancels the Type C KEYNOTE-590 meeting (Serial No. 0349)
28-MAR-2017	Submission of new protocol, KEYNOTE-590 for first line esophageal cancer treatment (Serial No. 0404)
15-JUN-2017	FDA grants Orphan Drug Designation to pembrolizumab for treatment of "esophageal carcinoma" (Designation number #17-5787)
25-OCT-2017	Submission of a White Paper describing PD-L1 CPS10 biomarker selection for esophageal carcinoma in place of GEP (Serial No. 0463)
01-DEC-2017	Merck submission of request for FDA Advice on KEYNOTE-181 Amendment 04 (SAP) regarding change of IA timing to base the alpha spending at the interim analysis on the fraction of calendar time rather than on the fraction of events (Serial No. 0489)
02-JAN-2018	FDA email correspondence accepting Merck's proposal for IA timing for KEYNOTE-181 in the 12/01/17 Request for FDA Advice
26-JAN-2018	Merck submission of Request for FDA Advice inquiring about the need to provide MSI data on all subjects enrolled in KEYNOTE-181 and KEYNOTE-590 (Serial No. 0509)
16-FEB-2018	FDA response to Merck request for advice on MSI-H testing in KEYNOTE-181 and KEYNOTE-590
02-MAR-2018	Request for FDA Advice on KEYNOTE-181 Amendment 05 change of statistical testing for all subjects population to Max-Combo test
09-MAR-2018	Submission of KEYNOTE-181 protocol amendment 05 changing the statistical test for overall survival in all subjects to the Max-Combo test (Serial No. 0519)
16-MAR-2018	Merck submission of a Type B pre-sBLA Meeting request for KEYNOTE-181 (Serial No. 0521)
17-APR-2018	Merck withdrawal of pre-sBLA meeting request for KEYNOTE-181 (Serial No. 0528)
21-APR-2018	FDA Response to Question on KEYNOTE-181 Max-Combo amendment. FDA did not agree with Merck's proposal to test overall survival in all subjects with the Max-Combo test. FDA recommended that the log-rank test be retained as the primary analysis method and the Max-Combo test be used as a supportive analysis.

24-MAY-2018	Merck response to FDA comments regarding Max-Combo KEYNOTE-181-05 (Serial No. 0544). Merck agreed to conduct the log rank test in addition to the Max-Combo test in the assessment of survival curves in all subjects
07-NOV-2018	Merck submission of a Type B pre-sBLA Meeting Request for KEYNOTE-181 (Serial No. 0596)
27-NOV-2018	Receipt of a Meeting Request Granted letter for Type B pre-sBLA Meeting for KEYNOTE-181. Face to face meeting granted for January 25, 2019.
20-DEC-2018	Background package submitted to support the planned KEYNOTE-181 pre-sBLA meeting (Serial No. 606)
16-JAN-2019	Merck and FDA (CDER, CDRH, OCE) had telephone call to discuss use of the Real Time Oncology Review (RTOR) and Assessment Aid pilots for the KEYNOTE-181 sBLA. Agreement was reached on the planned submission timeline of the RTOR pre-submission package, sBLA submission, and Assessment Aid.
18-JAN-2019	Pre-submission package for KEYNOTE-181, including patient narratives and ISS datasets, was submitted.
23-JAN-2019	Receipt of FDA preliminary comments for KEYNOTE-181 pre-sBLA background package.
25-JAN-2019	Type B pre-sBLA meeting was held to discuss the preliminary comments issued on 23JAN2019. The discussion focused on the contents of the submission including an integrated assessment of efficacy, ISS, Summary of Clinical Safety and data packages to accompany the submission.

The FDA's Assessment:

FDA agrees with the pre-submission activity summarized above. In addition:

- FDA relayed the following key advice during the August 15, 2015 Type B EOP2 meeting:
  - FDA agreed with the proposed stratification factors for KEYNOTE-181 (histology and geographical region) and recommended that Merck add physician's choice of chemotherapy as a stratification factor.

  - FDA cautioned that both PFS and OS analyses are over powered in KEYNOTE-181, and a small but statistically significant improvement in PFS or OS may not be clinically meaningful.

- FDA recommended that Merck request a meeting with CDRH to discuss development of the gene expression profile (GEP) assay before the start of KEYNOTE-181.

- [redacted] (b) (4)

- [redacted] (b) (4)

- [redacted] (b) (4)

- On January 16, 2019, FDA held a teleconference with Merck to discuss the format and content of RTOR submissions for both pending supplements (S-55 and S-56)
  - Datasets and supportive information for RTOR of S-55 and S-66 were submitted on January 18, 2019.
  - sBLA 125514/S-55 and sBLA 125514/S-56 were formally submitted on January 30, 2019.

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

4.1 Office of Scientific Investigations (OSI)

Clinical site inspection was not requested for this efficacy supplement because the results of Study KEYNOTE-181 did not appear to be driven by any single site and since the primary endpoint of the trial was overall survival, an objective endpoint not prone to bias.

4.2 Product Quality

No new chemistry, manufacturing, and controls changes for pembrolizumab were proposed in this sBLA. 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.

The request for categorical exclusion was reviewed by the Division of Biotechnology Review and Research 1 (DBRR1), Office of Biotechnology Products and was deemed acceptable. Additionally, DBRR1 determined that additional studies to improve the drug tolerance of their binding anti-drug-antibody (ADA) assay were not needed to support the new indication.

Refer to the original biologics license application review for product quality information.

4.3 Clinical Microbiology

No clinical microbiology data were submitted in this sBLA. Refer to the original biologics license application review for product microbiology information.

4.4 Devices and Companion Diagnostic Issues

Contemporaneously with review of this sBLA, the Center for Devices and Radiological Health (CDRH) reviewed supplemental Premarket Approval Application (PMA) P150013/S016, submitted by Dako North America, Inc., for the PD-L1 IHC 22C3 pharm Dx test to include a expand the indication to include the detection of PD-L1 protein in ESCC. CDRH plans to approve this sPMA on July 30, 2019 for the following intended use by detection of a CPS ≥10:

PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying esophageal squamous cell cancer patients for treatment with KEYTRUDA® (pembrolizumab).
Please refer to the review by Dr. Jai Pandey for additional information on the companion diagnostic device and the sPMA. Also see section 7.1.1 for details on the device used in Study KEYNOTE-181.

5 Clinical Pharmacology

5.1 Executive Summary

The FDA's Assessment:
No clinical pharmacology data were submitted in this application.

5.2 Summary of Clinical Pharmacology Assessment

5.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:
The pharmacokinetic profiles and systemic exposures of pembrolizumab in study participants with esophageal cancer are consistent with those in participants with the approved indications (melanoma, NSCLC, HNSCC, classical HL, PMBCL, urothelial carcinoma, MSI-H cancer, cervical cancer, hepatocellular carcinoma, and recurrent locally advanced or metastatic gastric or EGJ adenocarcinoma). In addition, exposures of pembrolizumab were further investigated by stratifying the data by squamous cell carcinoma and adenocarcinoma tumor histology. The exposures in the 2 tumor histologies are similar in esophageal cancer.

The FDA's Assessment:
FDA agrees with the Merck's above description of regarding pharmacokinetics of pembrolizumab in patients with esophageal cancer.

5.2.2. General Dosing and Therapeutic Individualization

5.2.2.1. General Dosing

The Applicant's Position:
The proposed indication for this application based on KEYNOTE-181 is the following:

"KEYTRUDA® is indicated for the treatment of patients with (b) (4)
"

Pembrolizumab is approved globally at 2 mg/kg for pediatric indications and at 200 mg Q3W dosing regimen for multiple indications as noted in (2.5, Sec. 1.3). Overall, the clinical data in participants with metastatic esophageal cancer demonstrate efficacy at 200 mg Q3W and a similarity of clinical response over more than a 5-fold dose range (2 mg/kg or 200 mg to 10

mg/kg). Thus, the clinical data, in conjunction with an integrated body of evidence in previously approved indications, support the use of the 200 mg Q3W dose as the appropriate dose to support the above indication.

The FDA's Assessment:
FDA agrees with the Merck's statements above, with clarification that clinical responses over a more than a 5-fold dose range (2 mg/kg or 200 mg to 10 mg/kg) of pembrolizumab were observed previously-approved indications (other than esophageal cancer).

5.2.2.2. Therapeutic Individualization

The Applicant's Position:
A dosing regimen of 200 mg Q3W is recommended for pembrolizumab treatment in patients with esophageal cancer. The PK profiles and systemic exposures to pembrolizumab in this patient population with different histology, squamous cell carcinoma or adenocarcinoma are consistent with the approved indications; the clinical response observed in KEYNOTE-181 at 200 mg Q3W is favorable.

No dose adjustments are proposed based on intrinsic and extrinsic factors.

The FDA's Assessment:
FDA agrees that no dose adjustments are proposed based on intrinsic and extrinsic factors.

5.2.2.3. Outstanding Issues

The Applicant's Position:
There are no outstanding issues with regard to clinical pharmacology.

The FDA's Assessment:
FDA confirms that there are no clinical pharmacology pertinent outstanding issues.

5.3 Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
The pharmacokinetics of pembrolizumab have been characterized using a population PK approach by pooling PK data from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, and KEYNOTE-024 in both MEL and NSCLC indications, which serve as the PK reference dataset. See the current USPI [20] for more information on the clinical pharmacology of pembrolizumab. The PK profile of pembrolizumab in subjects with esophageal cancer, independent of histology, is consistent with the PK reference dataset.

The FDA's Assessment:
Merck's statements above are factually correct.

5.3.2. Clinical Pharmacology Questions

The Applicant's Position:
The clinical pharmacology program provides supportive evidence of effectiveness. Pembrolizumab PK and dose- / exposure-response have been extensively evaluated across studies using the data from multiple dosing paradigms: weight-based dosing of 2 mg/kg Q3W, 10 mg/kg Q2W and10 mg/kg Q3W, as well as 200 mg Q3W fixed dose. The proposed fixed-dose regimen of 200 mg Q3W for esophageal carcinoma is supported by the following:

- Flat dose-/exposure-response relationships across numerous tumor types, with similar efficacy and safety profiles over 5-fold exposure range between 2 mg/kg Q3W and 10 mg /kg Q2W
    - Exposures of fixed-dose of 200 mg Q3W are well within the exposure range of 2 mg/kg Q3W to 10 mg/kg Q2W
- Similarity in PK of pembrolizumab among tumor types and no effects of intrinsic and extrinsic factors on pembrolizumab PK profile were found.

Furthermore, alignment has been obtained with the US FDA that the population PK analysis conducted to date adequately characterizes pembrolizumab PK profile across indications [21].

The FDA's Assessment:
Merck's statements above are factually correct.

5.3.2.1. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:
The proposed dosing regimen is appropriate for the general patient population for which the indication is being sought. The pembrolizumab dose of 200 mg IV Q3W is approved for multiple other solid tumor indications and is supported by modeling and simulation.

The FDA's Assessment:
FDA agrees with the above position.

5.3.2.2. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:
No specific dosing modifications are required or recommended based on intrinsic factors.

The FDA's Assessment:
FDA agrees with the Merck's statement above.

5.3.2.3. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:
There are no clinically relevant food-drug or drug-drug interactions with pembrolizumab.

The FDA's Assessment:
FDA agrees with Merck's statement above.

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6 Sources of Clinical Data

6.1 Table of Clinical Studies

The Applicant's Position:

[Table 4] presents KEYNOTE-181 as a stand-alone study that supports efficacy and safety in the proposed indication with additional evidence of efficacy and safety from KEYNOTE-180 and KEYNOTE-028. KEYNOTE-028 (Cohort A4, n = 22) provided proof of concept data for the initiation of a pembrolizumab monotherapy program in esophageal cancer (KEYNOTE-028 CSR). KEYNOTE-180 is an ongoing, single-arm Phase 2 study of pembrolizumab in 121 participants with 3L+ advanced/metastatic esophageal cancer, regardless of histology or biomarker status (KEYNOTE-180 CSR).

Both KEYNOTE-180 and KEYNOTE-028 demonstrated clinically meaningful benefit of pembrolizumab in terms of tumor response and durability of response in the heavily treated advanced/metastatic esophageal cancer population. These results are consistent with KEYNOTE-181 results and show benefit of pembrolizumab across multiple studies of esophageal cancer.

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Table 4
List of Clinical Trials Relevant to this sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety and Efficacy								
KEYNOTE-181	NCT 02564263	Randomized (pembrolizumab vs investigator's choice), multi-center, open-label	Pembrolizumab: 200 mg IV Q3W or Investigator's choice: - Paclitaxel 80-100 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle, OR - Docetaxel 75 mg/m^2 Q3W, OR - Irinotecan 180 mg/m^2 Q2W	Primary endpoint: OS Secondary endpoints: PFS based on central imaging vendor assessments per RECIST 1.1; ORR (proportion of participants in the analysis population who have a CR or PR); Safety	Up to 2 years of treatment with pembrolizumab; until disease progression or other reason to discontinue chemotherapy treatment. All participants were followed for OS until death, withdrawal of consent, or end of the study.	628	Participants with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type I adenocarcinoma of the GEJ treated with 1 previous line of standard therapy	219 centers in 33 countries
KEYNOTE-180	NCT 02559687	Single-arm, open-label, multisite	Pembrolizumab 200 mg IV Q3W	Primary endpoint: The proportion of participants in the analysis population who have a CR or PR based upon central imaging vendor assessments per RECIST 1.1. Secondary endpoints: Safety and tolerability	Up to 2 years of treatment. All participants were followed up for OS until death, withdrawal of consent, or the end of the study.	121	Participants with previously treated (2 prior lines of therapy), advanced/ metastatic ESCC or EAC, including advanced/metastatic Siewert type I adenocarcinoma	43 centers in 10 countries

				of pembrolizumab, DOR, OS, and PFS, and an assessment of PD-L1 IHC in esophageal cancer for its utility to predict pembrolizumab efficacy.				
KEYNOTE-028	NCT 02054806	Phase 1b, multicenter, non-randomized, single-arm, multicohort	Pembrolizumab 10 mg/kg Q2W	Primary endpoints: ORR (proportion of participants in the analysis population who have a CR or PR based on investigator assessment and confirmed per RECIST 1.1); safety. Secondary endpoints: DOR, PFS, OS	Up to 2 years of treatment. All participants were followed up for OS until death, withdrawal of consent, or the end of the study.	23 (Cohort A4)	Participants with esophageal squamous cell carcinoma or adenocarcinoma (including GEJ) that has failed standard therapy, for which no standard therapy exists, or standard therapy is not considered appropriate	9 centers in 6 countries

The FDA's Assessment:
FDA agrees with the above summary of the design of the KEYNOTE-181 trial and supportive trials KEYNOTE-180 and KEYNOTE-028.

7 Statistical and Clinical Evaluation

7.1 Review of Relevant Individual Trials Used to Support Efficacy

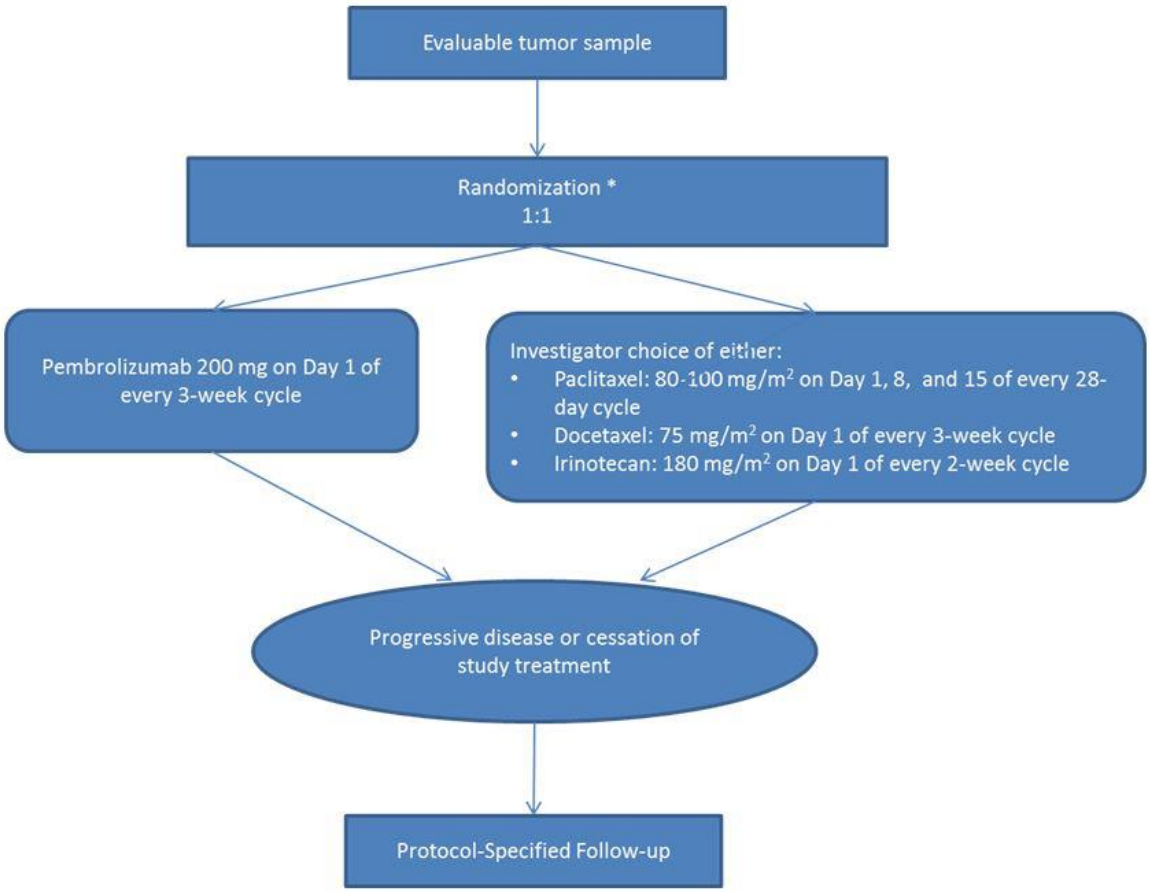
7.1.1. KEYNOTE-181

The Applicant's Position:

Trial Design

KEYNOTE-181 is an ongoing, randomized (1:1), multi-center, open-label, Phase 3 study of pembrolizumab vs SOC in participants with advanced/metastatic EAC or ESCC, or advanced/metastatic Siewert type I adenocarcinoma of the GEJ. Participants were required to have been previously treated with one line of chemotherapy (2L). Participants were stratified by tumor histology and geographic region (Asia vs. ex-Asia). Participants receiving SOC were not allowed to cross-over to the pembrolizumab arm during the trial. A summary of the study design is provided in [Figure 1].

Figure 1
KEYNOTE-181 Study Design Schematic



Summary of Key Entrance Criteria: Participants were required to have histologically or cytologically confirmed advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the GEJ, and experienced documented objective radiographic or clinical disease progression on 1 previous line of standard therapy. Measurable disease based on RECIST 1.1, as determined by local site investigator/radiology assessment, ECOG PS of 0 or 1, and demonstrated adequate organ function were also required as defined in the protocol (KEYNOTE-181-05 protocol, Sec. 5.1.2). Patients with active autoimmune disease requiring systemic treatment within the 2 years before the first dose of study treatment (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs), with a diagnosis of immunodeficiency or known history of HIV, with known active central nervous system metastases and/or carcinomatous meningitis, or with hepatitis B or C were excluded. Other entrance criteria are described in the protocol (KEYNOTE-181-05 protocol, Sec. 5.1).

Dose Selection: The planned dose of pembrolizumab for this trial was 200 mg Q3W. See [Section 5.3.2].

Treatment Allocation: Treatment randomization occurred centrally using an IVRS/IWRS. There were two treatment arms, with participants assigned randomly in a 1:1 ratio to pembrolizumab or investigator's choice of chemotherapy (i.e., paclitaxel, docetaxel, or irinotecan).

Concomitant Medications: Medications or vaccinations specifically prohibited in the exclusion criteria, such as live vaccines or anti-PD-1, anti-PD-L1, or anti-PD-L2 agents, were not allowed during the ongoing trial (KEYNOTE-181-05 protocol, Sec. 5.5).

Treatment Compliance: The instructions for preparing and administering pembrolizumab were provided in the Pharmacy Manual. Preparation and administration of paclitaxel, docetaxel, or irinotecan was to be completed as per the approved product label.

Dose Modification: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab were to be managed per regional prescribing information and are provided in the protocol (KEYNOTE-181-05 protocol, Sec. 5.2.1.2). Immune-related AEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most immune-related AEs are reversible and can be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. Dose modification of paclitaxel, docetaxel, or irinotecan was to be per the respective local labels or local standard of care.

Dose Discontinuation: Participants continued pembrolizumab until one or more of the discontinuation conditions, including confirmed radiographic disease progression, recurrent Grade 2 pneumonitis, and other criteria as listed in the protocol (KEYNOTE-181-05 protocol, Sec. 5.8), were met. Participants who discontinued study intervention for reasons other than PD had post-intervention follow-up for disease status until PD, initiation of a non-study cancer treatment, withdrawal of consent, or becoming lost to follow-up.

Study Procedures: [Table 5] the Trial Flow Chart, summarizes the trial procedures to be performed at each visit. Trial Flow Charts for treatment with paclitaxel, docetaxel, irinotecan, and retreatment with pembrolizumab in the Second Course Phase are in the protocol (KEYNOTE-181-05 protocol, Sec. 6.2 to Sec. 6.5).

Table 5
KEYNOTE-181 Trial Flow Chart – Initial Treatment Phase for Pembrolizumab Arm

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8 and Beyond	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up[a]
										At time of Discon	30 Days Post-discon	Every 9 Weeks Post-discon	Every 9 Weeks
Scheduling Window (Days)[b]	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures													
Informed Consent	X												
Informed Consent for Future Biomedical Research (optional)	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Post-study Anticancer Therapy Status												X	X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[c]	
Full Physical Examination	X									X			
Directed Physical Examination		X	X	X	X	X	X	X	X				
Height, Weight, and Vital Signs (T,P,RR,BP)[d]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram (Local)	X												
ECOG Performance Status	X[e]	X	X	X	X	X	X	X	X	X			
PROs (HRQoL Measures)[f]		X	X	X	X	X		X	X[f]	X	X		
Survival Status		<----------										---------->	X
Trial Treatment Administration													

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8 and Beyond	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up[a]
										At time of Discon	30 Days Post-discon	Every 9 Weeks Post-discon	Every 9 Weeks
Scheduling Window (Days)[b]	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Pembrolizumab Administration		X[b]	X	X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory													
Pregnancy Test[g]	X	X	X	X	X	X	X	X	X		X		
PT/INR and aPTT	X[e]												
CBC with Differential[h]	X[e]		X	X	X	X	X	X	X[h]	X	X		
Chemistry Panel[h]	X[e]		X	X	X	X	X	X	X[h]	X	X		
Urinalysis[h]	X[e]		X		X		X		X[h]	X			
T3, FT4, and TSH[h]	X[e]		X		X		X		X[h]	X	X		
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory													
Pembrolizumab Pharmacokinetics[i]		X[i]	X		X		X		X[i]				
Pembrolizumab Anti-Drug Antibodies (ADA)[i]		X	X		X		X		X[i]				
Blood for Genetics[j]		X											
Whole Blood for Correlative Studies (DNA and RNA)[k]		X	X	X						X			
Whole Blood for Biomarkers Studies (plasma and serum)[k]		X											

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8 and Beyond	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up[a]
										At time of Discon	30 Days Post-discon	Every 9 Weeks Post-discon	Every 9 Weeks
Scheduling Window (Days)[b]	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Tumor Tissue Collection													
Newly-Obtained Tumor Tissue[l]	X[l]												
Archival Tumor Tissue[m]	X												
Efficacy Measurements													
Tumor Imaging	X[n]	<----------X[o] ---------->								X[p]		X	

a. After centrally verified PD, or the start of new anticancer treatment; contacts are approximately every 9 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
b. Cycle 1 treatment must be given within 3 days of allocation. Trial treatment of pembrolizumab (administered on Day 1 of every 21-day [3-week] cycle) may be administered up to 3 days after randomization for Cycle 1 Day 1 due to administrative reasons or if the subject requires premedications. The window for each visit is ± 3 days unless otherwise noted.
c. SAEs will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.
d. Height will be measured at Visit 1 only.
e. ECOG Performance Status and Laboratory tests for screening are to be performed within 3 days before the first dose of trial treatment.
f. See KEYNOTE-181-05 protocol, Sec. 7.1.2.6 for details regarding administration of Patient Reported Outcomes (PROs). All PROs are to be performed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, and Cycle 7. After Cycle 7 (Week 18), PROs are to be performed every 3 cycles (e.g., Week 27, Week 36, Week 45). PROs are to be performed up to a year or End of Treatment, whichever comes first, and the 30-day post-treatment discontinuation follow-up visit. A visit window of ± 7 days will apply to PRO visit assessment.
g. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours before day 1 of each treatment cycle and 30 days post treatment. A serum test can be done if urine is not appropriate. Additionally, if urine test is positive or is not evaluable, a serum test is required. Subjects must be excluded/discontinued in the event of positive test results. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
h. Urinalysis and thyroid function tests to be performed every other cycle. CBC (Hematology) and Chemistry to be performed every cycle (excluding Cycle 1 Day 1).
i. Both PK and Anti-pembrolizumab-antibody Samples: pre-dose (trough) PK and anti-pembrolizumab antibody samples will be collected at within 24 hours before infusion at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter.
j. Detailed instructions for the collection and management of specimens are provided in the Central Lab Manual and in KEYNOTE-181-05 protocol, Sec. 7.1.3 Laboratory Procedure/Assessments.
k. Whole blood samples for biomarker studies (DNA and RNA) should be collected pre-dose on Day 1 of Cycle 1, Cycle 2, and Cycle 3, and again at treatment discontinuation. Whole blood for correlative studies (plasma and serum) to be collected pre-dose on Day 1 of Cycle 1 only. Leftover samples will be stored for FBR if the subject signs the FBR consent.
l. Newly-obtained tissue is preferred (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained and time of study enrollment). Formalin-fixed, paraffin-embedded (FFPE) block specimens are preferred to slides.
m. Archival tumor tissue will also be requested (where available) to assess the clinical utility of immune-related GEP assessment in newly obtained vs archived tissue samples.
n. Screening tumor imaging will be performed within 14 days before randomization. At sites where the local regulatory body and/or IRB/ERC will not permit a second tumor imaging within a 28-day period, an already available imaging scan obtained within 28 days before first dose may be used with the approval of the Sponsor Clinical Director. For all subjects, already available imaging scans performed as part of routine clinical management are acceptable if they are of diagnostic quality and performed within the acceptable timeframe.
o. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of allocation and will continue to be performed Q9W (63 days ± 7 days), or earlier if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts.
p. In order to follow irRECIST criteria, this protocol requires confirmation of disease progression by repeat imaging $\geq$ 4 weeks from initial disease progression. If a subject is discontinued from study therapy before PD being confirmed at the site then that subject should have tumor imaging performed at the time of treatment discontinuation. If previous tumor imaging was obtained within 4 weeks before the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.

Target tumors were monitored using RECIST 1.1 (modified by the Sponsor to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ; all mentions of RECIST 1.1 in this document refer to this definition), with on-study imaging assessments performed every 9 weeks. Imaging was continued until disease progression verified by central imaging vendor, unless the site PI elected to continue treatment and follow irRECIST. For a clinically stable participant with first radiologic evidence of PD, it was at the discretion of the site investigator to continue treating the participant with pembrolizumab until PD was confirmed at least 4 weeks from the date of the first tumor imaging suggesting PD. If radiologic PD was confirmed, the participant was to be discontinued from study intervention unless, in the opinion of the investigator, the participant was achieving a clinically meaningful benefit.

AEs were monitored throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute CTCAE version 4.0. After the end of study intervention, each participant was followed for 30 days for AE monitoring. SAEs were collected for 90 days after the end of study intervention or 30 days after the end of study intervention if the participant initiated new anticancer therapy, whichever was earlier.

The FDA's Assessment:

FDA agrees with Merck's summary of the design of KEYNOTE-181 above. Per the protocol, patients were to be discontinued from treatment but remain on study for continued monitoring for occurrence of any of the following:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Confirmed radiographic disease progression
- Unacceptable adverse experiences
- Progression of current malignancy or recurrence of previously treated malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to discontinue the subject
- Discontinuation of treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.
- Completed 35 cycles of pembrolizumab

In addition, per Merck's response to FDA's information request dated July 14, 2019, the selection of the treatment of physician's choice of chemotherapy administered to the patients in the trial was performed prior to randomization.

Study Endpoints

The Applicant's Position:

Primary Efficacy Endpoint:
The primary endpoint was OS, defined as the time from randomization to death due to any cause. The primary objectives were to compare pembrolizumab and SOC for OS in participants with ESCC, in participants with tumors expressing PD-L1 CPS ≥10, and in all participants.

Secondary Efficacy Endpoints:
The key secondary efficacy endpoints were:

- PFS in all participants, defined as the time from randomization to the first documented disease progression per modified RECIST 1.1 based on central imaging vendor review, or death due to any cause.

- ORR in all participants, defined as the proportion of the participants who have a CR or PR per RECIST 1.1 based on central imaging vendor review.

Additional secondary efficacy endpoints included PFS and ORR in the other two populations (participants with tumors expressing PD-L1 CPS ≥10 and participants with ESCC); DOR in all three populations (PD-L1 CPS ≥10, ESCC, and all); and safety and tolerability of pembrolizumab in all subjects compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.

Exploratory Efficacy Endpoints:
As part of the exploratory analyses, participants provided information regarding their health-related QoL via the following assessment tools: EORTC QLQ-C30, QLQ-OES18, and EQ-5D questionnaires.

PD-L1 Expression Analyses
Determination of PD-L1 CPS ≥10 as the biomarker for KEYNOTE-181 was made strictly outside of KEYNOTE-181, by using data from KEYNOTE-180 before conducting any efficacy analysis of KEYNOTE-181 as detailed in a White Paper submitted to the FDA on 25-OCT-2017 [22] (KEYNOTE-181 CSR, Sec. 9.5.4).

PD-L1 expression levels were measured in tumor tissue samples by immunohistochemistry using the Dako PD-L1 IHC 22C3 pharmDx. KEYNOTE-180 served as a training set for evaluating PD-L1 cut points that enriched for pembrolizumab responders relative to nonresponders in esophageal cancer. An interim analysis of KEYNOTE-180 from 17-JUL-2017 demonstrated that the selection of CPS ≥10 serves as an enriching cutoff for use in the esophageal cancer development program for pembrolizumab [22].

As detailed in [22], an interim analysis from KEYNOTE-180 informed selection of PD-L1 expression as a biomarker with an optimal cutoff of CPS ≥10. This decision was based on the data indicating positive predictive value, sensitivity, and prevalence evident with the CPS ≥10

cutpoint, and argue for further use of this assay and cutpoint in esophageal cancer trials with pembrolizumab.

The FDA's Assessment:
FDA agrees with Merck's statements regarding the diagnostic device above. For further details on the assay used for determination of PDL-1 status please refer to the CDRH review of the diagnostic device.

Statistical Analysis Plan and Amendments
The Applicant's Position:
The statistical analysis of the data obtained from this study was conducted by the Clinical Biostatistics department of the Sponsor. This trial is a randomized, open-label study, where unblinded interim analyses were conducted by an external unblinded statistician and the final analysis was conducted by the Clinical Biostatistics department after the database was locked. In addition, the central imaging vendor performed the central imaging review blinded to treatment group assignment.

Efficacy Analysis
The ITT population, which included all randomized subjects who received at least one dose of study treatment, served as the population for efficacy analysis. Subjects are included in the treatment group to which they are randomized.

A stratified maximum weighted log-rank (max-combo) test and a stratified log-rank test were used to test the hypotheses of treatment difference in OS and PFS in the overall ITT population, as the primary and supportive testing approaches specified in the protocol, respectively. Both tests use the same multiplicity strategy as outlined in the protocol. The stratified log-rank test was used to test the hypotheses of treatment differences in OS and PFS in participants with PD-L1 CPS ≥10 and in participants with ESCC. The magnitude of the treatment difference was estimated by the HR and 95% CI from a stratified Cox regression model. The KM method was used to estimate rates over time for each intervention group. The stratification factors used for randomization, histology (squamous cell carcinoma vs. adenocarcinoma/Siewert type 1 adenocarcinoma of the GEJ) and geographic region (Asia vs. ex-Asia), were applied to both the stratified log-rank test and stratified max-combo test, and the stratified Cox model, if applicable. For the OS analysis participants were censored at their last known alive date. For the PFS analysis, participants were censored at the date of last assessment. Details are provided in (KEYNOTE-181-05 protocol, Table 9). ORR was evaluated using a stratified Miettinen and Nurminen method.

The analysis strategy for the primary and secondary endpoints are described in [Table 6].

Table 6
Analysis Strategy for KEYNOTE-181 Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis #1			
OS in subjects with squamous cell carcinoma of the Esophagus.	Test: Stratified Log-rank test. Estimation: Stratified Cox model with Efron's tie handling method.	ITT in subjects with squamous cell carcinoma of the Esophagus.	Censored at last known alive date
Primary Hypothesis #2			
OS in subjects with PD-L1 CPS≥10.	Test: Stratified Log-rank test. Estimation: Stratified Cox model with Efron's tie handling method.	ITT in subjects with PD-L1 CPS≥10	Censored at last known alive date
Primary Hypothesis #3			
OS in all subjects	Test: Stratified Max-combo and stratified log-rank test. Estimation: Stratified Cox model with Efron's tie handling method.	ITT in all subjects	Censored at last known alive date
Key Secondary Endpoints			
PFS per RECIST 1.1 by central imaging vendor review in all subjects	Test: Stratified Max-combo Estimation: Stratified Cox model with Efron's tie handling method	ITT in all subjects	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in (KEYNOTE-181-05 protocol, Table 9)
ORR per RECIST 1.1 by central imaging vendor review in all subjects	Test: Stratified M & N method‡	ITT in all subjects	Subjects with missing data are considered non-responders

‡ Miettinen and Nurminen method [23]

One IA was performed in this study. Results were reviewed by an external data monitoring committee and the recommendation provided to the Sponsor was to continue the trial to the FA. The FA was performed at the protocol-specified timing for the trial. The boundary for the final analysis was adjusted according to the actual alpha spent at the IA and the actual number of events at the IA and FA.

Safety Analysis

The ASaT population was used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least 1 dose of study treatment.

Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Count and percentage of AEs will be provided.

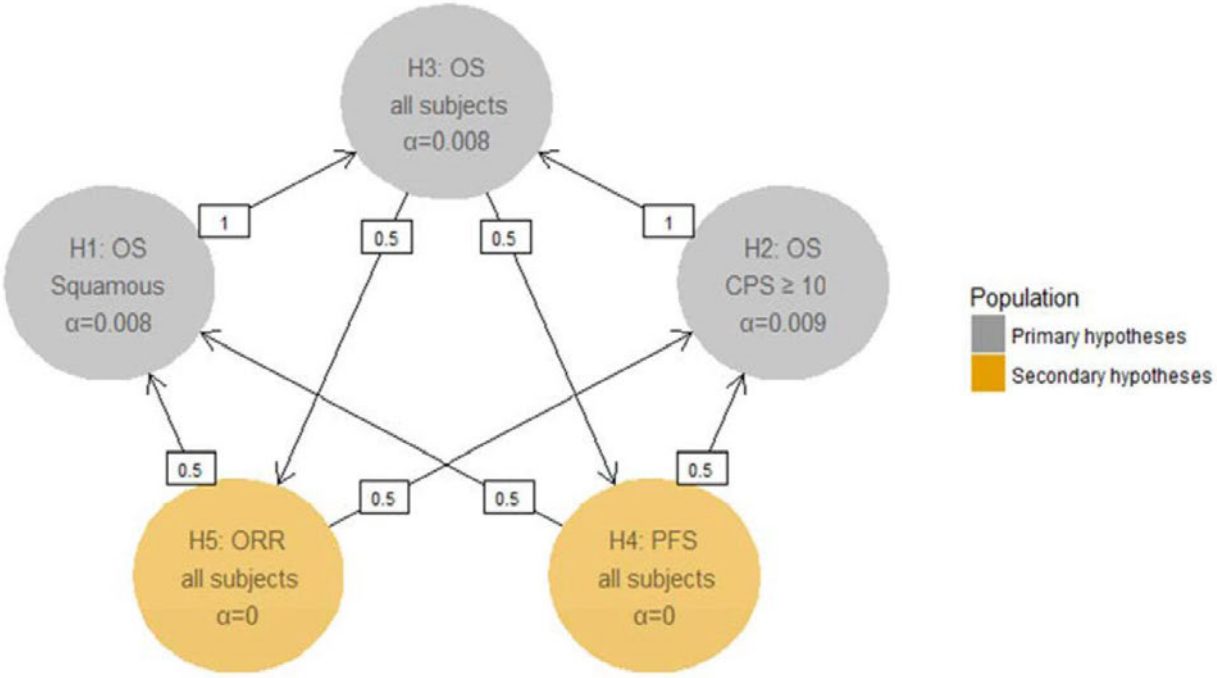
The FDA's Assessment:

FDA agrees with the summary of the design and statistical analysis plan of KEYNOTE-181

described by Merck above. FDA agrees that the choice of either docetaxel, paclitaxel or irinotecan in the control arm is appropriate as alternate second line therapy. Although FDA recommended that Merck consider adding the specific chemotherapy chosen as a stratification factor for randomization, Merck elected not to add this stratification factor.

Figure 2 provides Merck's multiple testing strategy for testing the three primary hypotheses to control the overall Type I error rate at one-sided 2.5%. Merck planned to use Lan-DeMets O'Brien-Fleming alpha spending function with specified calendar time fraction (76%) to construct group sequential boundaries at interim and final analyses for each hypothesis to control the Type I error rate.

Figure 2
KEYNOTE-181 Multiplicity Control Strategy



Source: Figure 4 on Page 112 in the MK-3475-181-05 Final Protocol.

Merck's sample size calculation was based on the following assumptions:

1) overall survival follows an exponential distribution with a median of 8 months in the control arm;
2) an enrollment period of 17 months and a minimum of 16 months follow-up after enrollment completion;
3) a yearly dropout rate of 2%.

The final OS analysis was prespecified to be performed after approximately 310 OS events and 473 OS events were observed among patients with ESCC and all patients, respectively, and 16 months after last patient was randomized. It was expected that approximately 213 OS events

would have been observed in patients with PD -L1 CPS ≥10 at the time of the final OS analysis. With 310/213/473 OS events in patients with ESCC/patients with PD-L1 CPS ≥10/all patients, the trial had at least 91.3%/90.9%/92.6% power to detect a hazard ratio of 0.65/0.6/0.7 at a one-sided alpha of 0.8%/0.9%/0.8%, respectively.

Reviewer Comments:

- *As stated in FDA's Advice/Information Request dated April 21, 2018, FDA does not agree with using the stratified maximum weighted log-rank (max-combo) test as the primary testing approach to test OS (as well as PFS) in all subjects. It is challenging to use weighted log-rank test given that the choice of parameters is not straightforward and subject to misspecification. In addition, there is limited prior knowledge in the literature describing the true distribution of OS in this disease setting. FDA's assessment for OS in the ITT population is based on the results of the stratified log-rank test, which is robust to random or unexpected data patterns. The results of the stratified maximum weighted log-rank test will be considered as supportive evidence.*

- *FDA also does not agree with Merck's calculation of alpha boundaries for the interim and final analyses of OS based on calendar time. FDA independently calculated the alpha boundaries by the Lan-DeMets approach based on the information time as calculated by the observed number of OS events at the interim analysis divided by the planned number of OS events at the final analysis.*

Protocol Amendments

The Applicant's Position:

The original protocol (181-00) was finalized on 25-AUG-2015 and amended 5 times. [Table 7] summarizes the key changes in the amendments.

Table 7
Summary of Key Changes to the KEYNOTE-181 Protocol

Protocol or Amendment	Key Changes
Protocol (25-AUG-2015)	Original Protocol
Amendment 01 (20-JUL-2016)	All sections were revised to describe the development of 2 GEP cutpoints to identify GEP low, intermediate, and high tumors; and/or to describe how the primary, secondary, and exploratory objectives and endpoints will be met and analyzed, respectively, based on these tumor designations.

Protocol or Amendment	Key Changes
Amendment 02 (09-DEC-2016)	Sections were revised to identify GEP low, intermediate, and high tumors; to describe the development of GEP cut-off "GEP intermediate or high" and/or to describe how the primary, secondary, and exploratory objectives and endpoints will be met and analyzed, respectively, based on these tumor designations.
Amendment 03 (29-MAR-2017)	A cohort of subjects to be enrolled in China was added to extend the enrollment period beyond the Global Cohort to achieve the required sample size in the China Cohort and the number of events to investigate efficacy and safety in Chinese 2L EC participants.
Amendment 04 (03-AUG-2017)	Primary objectives were changed from dual endpoints of OS and PFS to a single endpoint of OS. PFS was moved to secondary endpoint with multiplicity control. The timing of interim and final analyses were updated to be driven by the number of OS events and minimum follow-up time.
Amendment 05 (08-MAR-2018)	Information fraction was replaced by calendar time fraction in alpha spending. The stratified log-rank test was replaced with the stratified maximum weighted log rank test for testing the OS and PFS hypotheses in the all subjects population.

The FDA's Assessment:
FDA does not agree with the changes in Amendment 05 summarized above (see Reviewer Comments in The FDA's Assessment on Statistical Analysis Plan and Amendments above).

Additional Studies

The Applicant's Position:

KEYNOTE-180

Trial Design

KEYNOTE-180 was a single-arm, open-label, multisite study of pembrolizumab (200 mg IV every 3 weeks) in participants with histologically proven advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the GEJ (defined as adenocarcinomas of the lower esophagus with the center located within 1cm to 5cm above the anatomic GEJ) that had been previously treated with two lines of standard therapy.

Complete details of the study design are provided in the clinical study report (KEYNOTE-180 CSR).

KEYNOTE-028

KEYNOTE-028 was a multicenter, non-randomized, single arm, multicohort study of pembrolizumab in participants with PD-L1-positive advanced solid tumors. Cohort A4 (n = 22) provided proof of concept data for the initiation of a pembrolizumab monotherapy program in esophageal cancer.

Complete details of the study design are provided in the clinical study report (KEYNOTE-028 CSR).

7.1.2. KEYNOTE-181 Study Results

The Applicant's Position:

Compliance with Good Clinical Practices

KEYNOTE-181 study was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements and applicable country and/or local statutes and regulations regarding IEC review, informed consent and the protection of human participants in biomedical research (KEYNOTE-181 CSR, Sec. 5.2). The protocol and any amendments, information provided to participants and any recruitment materials were reviewed and approved by the IECs (also referred to as an IRB, ERC, or any other ethics committee) (KEYNOTE-181 CSR, Sec. 5.1). Informed consent was obtained from all participants before initiation of the study (KEYNOTE-181 CSR, Sec. 5.3).

Financial Disclosure

Disclosure of financial interests of the investigators who conducted the KEYNOTE-181 study has been obtained and submitted in the FDA Financial Disclosure Form 3454 (Module 1.3.4).

The FDA's Assessment:

FDA agrees with Merck's analysis above. Please also refer to the financial disclosure form at the end of this review for details.

Patient Disposition

Study enrollment was divided into two periods: global and China extension enrollment. Participants were enrolled (signed ICF) from 08-DEC-2015 to 16-JUN-2017 at 154 sites in 32 countries (KEYNOTE-181 CSR, Sec. 10.1). This application focuses on participants randomized during the global enrollment period. As of the data cutoff on 15-OCT-2018, 628 participants (314 participants in each arm) were randomized. Per the study protocol, only participants in the pembrolizumab arm who received 35 cycles of pembrolizumab are categorized as completed; 5 participants in the pembrolizumab arm received 35 cycles of intervention.

Median durations of follow-up were 7.1 months in the pembrolizumab arm and 6.9 months in the SOC arm (KEYNOTE-181 CSR, Table 14.1-5). Disposition was generally similar for overall population (KEYNOTE-181 CSR, Table 14.1-2) and participants with ESCC (KEYNOTE-181 CSR, Table 14.1-6).

There were 31 participants (4.9%) who received immune checkpoint inhibitors after progression (anti-PD-1 or anti-PD-L1): 1 in the pembrolizumab arm (0.3%) and 30 (9.5%) in the SOC arm (KEYNOTE-181 CSR, Sec. 16.2.4.5).

Most of the nonrandomized participants were screen failures (KEYNOTE-181 CSR, Table 14.1-3). The primary reason for screen failure was the inability to provide a tissue sample for intratumoral biomarker analysis (KEYNOTE-181 CSR, Table 14.1-4).

For PD-L1 CPS ≥10 population, treatment was ongoing in 5 (4.7%) participants in the pembrolizumab arm and no participants in the SOC arm. The most frequent reason for treatment discontinuation was progressive disease, with a discontinuation rate due to progressive disease of 68.2% for pembrolizumab and 63.2% for SOC [Table 8]. The rate of clinical progression resulting in treatment discontinuation was 7.5% for pembrolizumab and 13.2% for SOC.

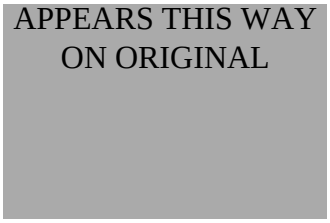


Table 8
Disposition of Subjects
(ITT Population, Subjects with PD-L1 CPS ≥10)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	107		115		222	
Status For Trial						
Discontinued	88	(82.2)	105	(91.3)	193	(86.9)
Adverse Event	10	(9.3)	12	(10.4)	22	(9.9)
Death	77	(72.0)	88	(76.5)	165	(74.3)
Withdrawal By Subject	1	(0.9)	5	(4.3)	6	(2.7)
Trial Ongoing	19	(17.8)	10	(8.7)	29	(13.1)
Status For Study Medication In Trial Segment Treatment						
Started	107		114		221	
Completed	1	(0.9)	0	(0.0)	1	(0.5)
Discontinued	101	(94.4)	114	(100.0)	215	(97.3)
Adverse Event	16	(15.0)	17	(14.9)	33	(14.9)
Clinical Progression	8	(7.5)	15	(13.2)	23	(10.4)
Physician Decision	0	(0.0)	2	(1.8)	2	(0.9)
Progressive Disease	73	(68.2)	72	(63.2)	145	(65.6)
Withdrawal By Subject	4	(3.7)	8	(7.0)	12	(5.4)
Treatment Ongoing	5	(4.7)	0	(0.0)	5	(2.3)
Database Cutoff Date: 15OCT2018.						

Source: [P181V01MK3475: adam-adsl; adpm]

The FDA's Assessment:

FDA agrees with Merck's analysis of disposition for patients with PD-L1 CPS ≥10 above. Of the patients in the overall ITT population randomized to the chemotherapy arm, 18 patients did not receive study treatment, as shown in Table 9 below. None of the 18 patients who did not receive their assigned chemotherapy had ESCC expressing PD-L1 (CPS ≥10); hence the lack of receipt of planned chemotherapy in these 18 patients did not affect the efficacy analysis in the subpopulation of patients with ESCC and CPS ≥ 10 in Study KEYNOTE-181.

Table 9
Disposition of Patients in Study KEYNOTE-181 (Overall ITT Population)

	Pembrolizumab 200mg	SOC	Total
Patients randomized (planned treatment) (ITT)	314	314	628
Patients received study treatment (actual treatment)	314	296	610
Patients who were randomized and did not receive treatment	0	18	18

Source: FDA reviewer analysis.

Table 10
Study Discontinuation Reason for the 18 Patients Who Did Not Receive Treatment in the SOC Arm

SUBJID	Study discontin-uation reason	Histology	PD-L1 Status	Event/ Censoring Description	Time to Event Start Date	Analysis Date
(b) (6)	DEATH	Squamous cell carcinoma	CPS <10	DEATH		(b) (6)
	DEATH	Squamous cell carcinoma	CPS <10	DEATH		
	NA[1]	Squamous cell carcinoma	CPS <10	Censored		
	ADVERSE EVENT	Squamous cell carcinoma	CPS <10	DEATH		
	DEATH	Squamous cell carcinoma	CPS <10	DEATH		
	DEATH	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		
	DEATH	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		
	WITHDRAWAL BY SUBJECT	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS ≥10	DEATH		
	WITHDRAWAL BY SUBJECT	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		
	WITHDRAWAL BY SUBJECT	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS<10	DEATH		

SUBJID	Study discontin-uation reason	Histology	PD-L1 Status	Event/ Censoring Description	Time to Event Start Date	Analysis Date
(b) (6)	DEATH	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		(b) (6)
	DEATH	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		
	DEATH	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		
	DEATH	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		
	WITHDRAWAL BY SUBJECT	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		
	WITHDRAWAL BY SUBJECT	Adenocarcinoma of esophagus and EGJ Siewert type I	Not Evaluable	DEATH		
	WITHDRAWAL BY SUBJECT	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		
	DEATH	Adenocarcinoma of esophagus and EGJ Siewert type I	CPS <10	DEATH		

[1] Discontinuation information was not provided for this patient.
Source: FDA reviewer analysis.

Protocol Violations/Deviations

The Applicant's Position:
Important deviations were reported for 70 participants (35 participants in each treatment arm) (KEYNOTE-181 CSR, Sec. 10.2).

The protocol deviations process is in line with ICH E3 Guidance on important protocol deviations. As detailed in the CSR, protocol deviations are classified as important (those that may significantly impact the quality or integrity of key study data or that may significantly affect a participant's rights, safety, or well-being) or not important. Upon reviewing each important deviation, the sponsor assessed whether there are any clinically important deviations that may have implications to the primary outcome of the trial.

There were no deviations deemed clinically important; therefore, no participant data were excluded from analyses.

The FDA's Assessment:

FDA agrees with Merck's analysis of protocol deviations. Major protocol deviations are outlined in Table 11 below.

Table 11
Major Protocol Deviations in KEYNOTE-181

Category	Sub-Category	Pembrolizumab 200mg N (%)	SOC N (%)
Discontinuation Criteria	Participants who develop trial specific discontinuation criteria but were not discontinued from the trial.	1 (0.3)	2 (0.6)
Inclusion/ Exclusion Criteria	Participants entered into the trial, i.e. progressed beyond screening, who did not meet key inclusion/exclusion criteria	4 (1.3)	9 (2.9)
Inclusion/ Exclusion Criteria	Randomization of a patient who did not meet the requirements for prior lines of therapy	11 (3.5)	4 (1.3)
Prohibited Medications	Antineoplastic systemic chemotherapy, biologic therapy, immunotherapy, other investigational agents given while on treatment (unless allowed per protocol).	1 (0.3)	0
Safety Reporting	Participants with reportable Safety Events and/or follow up Safety Event information that were not reported per the timelines outlined in the protocol.	17 (5.4)	14 (4.5)
Study Intervention	Participants who received incorrect study treatment and/or were administered improperly stored study treatment.	2 (0.6)	5 (1.6)
Trial Procedures	Participant with 2 consecutive missing imaging	3 (1.0)	1 (0.3)

Category	Sub-Category	Pembrolizumab 200mg N (%)	SOC N (%)
	assessments		

Source: ADSL, JMP

The FDA's Assessment:

In general, the protocol deviations were few in number and equally distributed between the arms, and are unlikely to have impacted the results of KEYNOTE-181.

As can be seen in
Table 11 above, the most common protocol deviation in the pembrolizumab arm was related to randomization of patients who did not meet the inclusion criterion requirements for prior lines of therapy. Fifteen participants did not meet the inclusion criteria regarding prior therapy (11 in the pembrolizumab arm and 4 in the SOC arm). Two participants previously only treated with neoadjuvant and adjuvant therapy had not experienced disease progression within the 6-month window allowed per study protocol eligibility criteria; for both of these participants, previous courses of treatment were not considered lines of therapy. Twelve participants experienced disease progression twice, and therefore it was considered that these participants already had two lines of prior therapy. One patient experienced disease progression three times on the same chemotherapy, and therefore it was considered that this participant had already had three prior lines of therapy. Although FDA does not agree that these protocol deviations were justified, given the limited activity of available treatments in EC, these deviations are not likely to materially affect the study results.

Table of Demographic Characteristics

The Applicant's Position:

The demographics and baseline characteristics were similar between treatment arms and were representative of participants with advanced/metastatic esophageal cancer who received previous therapy.

Demographics and baseline characteristics, including ECOG PS, of participants were generally similar between PD-L1 CPS ≥10, ESCC, and overall populations, though there were more Asian participants in the PD-L1 CPS ≥10 [Table 12] and ESCC (KEYNOTE-181 CSR, Table 14.1-10) populations and more participants in the ESCC population who were PD-L1 CPS ≥10 compared to the overall population (KEYNOTE-181 CSR, Table 10-4).

The percentage of participants with PD-L1 CPS ≥10 was well balanced between the pembrolizumab and SOC arms (34.1% and 36.6%) for overall population (KEYNOTE-181 CSR, Table 10-4), as expected in a randomized study.

MSI status was tested for all participants achieving confirmed CR, or unconfirmed CR or PR as determined by BICR per RECIST 1.1. Of the 102 participants who had adequate samples to enable testing, 95 had successful testing (KEYNOTE-181 CSR, 16.2.4.3). Only one participant was determined to be MSI-H and was not a confirmed responder. At the final analysis, there were 62 confirmed responses, 41 in the pembrolizumab arm and 21 in the SOC arm. MSI status was determined for 33 of the 41 responders in the pembrolizumab arm: six responders lacked adequate tissue and/or blood to enable testing, and testing failed for two responders. In the SOC arm, MSI status was determined for 16 of the 21 responders: three responders lacked adequate tissue and/or blood to enable testing, and testing failed for two responders (KEYNOTE-181 CSR, Sec. 16.2.4.3).

This very low prevalence of MSI-H status in esophageal cancer patients in KEYNOTE181 is consistent with the experience in KEYNOTE180, and published literature; and it is unlikely that MSI-H would make meaningful difference in the interpretation of KEYNOTE181 data.

Table 12
Subject Characteristics
(ITT Population, Subjects with PD-L1 CPS ≥10)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	107		115		222	
Gender						
Male	92	(86.0)	99	(86.1)	191	(86.0)
Female	15	(14.0)	16	(13.9)	31	(14.0)
Age (Years)						
< 65	56	(52.3)	59	(51.3)	115	(51.8)
>= 65	51	(47.7)	56	(48.7)	107	(48.2)
Subjects with data	107		115		222	
Mean	63.3		63.1		63.2	
SD	9.4		9.9		9.6	
Median	64.0		64.0		64.0	
Range	42 to 81		33 to 81		33 to 81	
Race						
Asian	61	(57.0)	55	(47.8)	116	(52.3)
Multiple	0	(0.0)	1	(0.9)	1	(0.5)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.9)	1	(0.5)
White	45	(42.1)	55	(47.8)	100	(45.0)
Missing	1	(0.9)	3	(2.6)	4	(1.8)
Ethnicity						
Hispanic or Latino	3	(2.8)	6	(5.2)	9	(4.1)
Not Hispanic or Latino	103	(96.3)	106	(92.2)	209	(94.1)
Not Reported	1	(0.9)	1	(0.9)	2	(0.9)
Unknown	0	(0.0)	2	(1.7)	2	(0.9)
ECOG Performance Scale						
0	45	(42.1)	36	(31.3)	81	(36.5)
1	62	(57.9)	79	(68.7)	141	(63.5)
Geographic Region of Enrolling Site						
Asia	60	(56.1)	55	(47.8)	115	(51.8)
ex-Asia	47	(43.9)	60	(52.2)	107	(48.2)
Current Disease Presentation						

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Locally Advanced	9	(8.4)	10	(8.7)	19	(8.6)
Metastatic	98	(91.6)	105	(91.3)	203	(91.4)
Brain Metastasis						
Y	1	(0.9)	1	(0.9)	2	(0.9)
N	106	(99.1)	114	(99.1)	220	(99.1)
Metastatic Staging						
M0	9	(8.4)	10	(8.7)	19	(8.6)
M1	98	(91.6)	105	(91.3)	203	(91.4)
Histological subtype						
Squamous cell carcinoma	85	(79.4)	82	(71.3)	167	(75.2)
Adenocarcinoma of esophagus and EGJ Siewert type I	22	(20.6)	33	(28.7)	55	(24.8)
PD-L1 Status						
PD-L1 CPS >= 10	107	(100.0)	115	(100.0)	222	(100.0)
Prior Adjuvant or Neoadjuvant Therapy						
Yes	6	(5.6)	16	(13.9)	22	(9.9)
No	101	(94.4)	99	(86.1)	200	(90.1)
Number of Prior Therapy						
1	103	(96.3)	114	(99.1)	217	(97.7)
2	4	(3.7)	1	(0.9)	5	(2.3)
Prior Anthracycline Therapy						
Yes	6	(5.6)	6	(5.2)	12	(5.4)
No	101	(94.4)	109	(94.8)	210	(94.6)
Prior Monoclonal Antibody Therapy						
Yes	3	(2.8)	6	(5.2)	9	(4.1)
No	104	(97.2)	109	(94.8)	213	(95.9)
Prior Irinotecan Therapy						
Yes	1	(0.9)	2	(1.7)	3	(1.4)
No	106	(99.1)	113	(98.3)	219	(98.6)

	Pembrolizumab 200 mg		SOC		Total	
	n	(%)	n	(%)	n	(%)
Prior Platinum Therapy						
Yes	106	(99.1)	113	(98.3)	219	(98.6)
No	1	(0.9)	2	(1.7)	3	(1.4)
Prior Fluoropyrimidine Therapy						
Yes	93	(86.9)	97	(84.3)	190	(85.6)
No	14	(13.1)	18	(15.7)	32	(14.4)
Prior Taxane Therapy						
Yes	27	(25.2)	42	(36.5)	69	(31.1)
No	80	(74.8)	73	(63.5)	153	(68.9)
Database Cutoff Date: 15OCT2018.						

Source: [P181V01MK3475: adam-adsl]
* [Argentina, Australia, Brazil, Canada, China, Colombia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hongkong, Ireland, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, Norway, Peru, Portugal, Russia, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, UK, USA]

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The FDA's Assessment:

FDA agrees with the results presented in this section for the demographics and baseline characteristics in patients with PD-L1 CPS ≥10 in the ITT population.

A summary of the demographic and baseline disease characteristics of the subpopulation of patients with ESCC whose tumors expressed PD-L1 CPS ≥10 is also provided in Table 13. Overall, the pembrolizumab and control arms were well-balanced with respect to key demographic and baseline disease characteristics, with a few exceptions. In particular, patients in the pembrolizumab arm were more likely to have an ECOG performance scale score of 0 and more patients received prior adjuvant or neoadjuvant therapy in the SOC arm. The most common first line chemotherapy that patients received was 5-FU or platinum chemotherapy or a combination of both.

Table 13
Baseline Demographic and Disease Characteristics (ESCC, PD-L1 CPS ≥10; FDA's Assessment)

	Pembrolizumab 200 mg N=85	SOC N=82	Total N=167
Age, years			
Mean (SD)	64.6 (8.6)	62.7 (10.6)	63.7 (9.6)
Median (Min, Max)	65 (45, 80)	64 (33, 79)	65 (33, 80)
≥65, n (%)	46 (54)	39 (48)	85 (51)
<65, n (%)	39 (46)	43 (52)	82 (49)
Sex, n (%)			
Male	74 (87)	67 (82)	141 (84)
Female	11 (13)	15 (18)	26 (16)
Race, n (%)			
White	26 (31)	27 (33)	53 (32)
Asian	59 (69)	54 (66)	113 (68)
Native Hawaiian Or Other Pacific Islander	0 (0)	1 (1)	1 (0.6)
Ethnicity			
Not Hispanic or Latino	83 (98)	78 (95)	161 (96)
Hispanic or Latino	2 (2)	4 (5)	6 (4)
Geographic Region of Enrolling Site, n (%)			
Asia	58 (68)	54 (66)	112 (67)
Ex-Asia	27 (32)	28 (34)	55 (33)
ECOG, n (%)			
0	36 (42)	28 (34)	64 (38)
1	49 (58)	54 (66)	103 (62)
Current Disease Presentation, n (%)			
Metastatic	76 (89)	74 (90)	150 (90)
Locally Advanced	9 (11)	8 (10)	17 (10)
Brain Metastasis, n (%)			
No	85 (100)	82 (100)	167 (100)

	Pembrolizumab 200 mg N=85	SOC N=82	Total N=167
Metastatic Staging, n (%)			
M0	9 (11)	8 (10)	17 (10)
M1	76 (89)	74 (90)	150 (90)
Prior Adjuvant or Neoadjuvant Therapy, n (%)			
Yes	5 (6)	10 (12)	15 (9)
No	80 (94)	72 (88)	152 (91)
Number of Prior Therapy, n (%)			
1	82 (97)	81 (99)	163 (98)
2	3 (3)	1 (1)	4 (2)
Prior Anthracycline Therapy, n (%)			
Yes	2 (2)	1 (1)	3 (2)
No	83 (98)	81 (99)	164 (98)
Prior Monoclonal Antibody Therapy, n (%)			
Yes	0 (0)	1 (1)	1 (1)
No	85 (100)	81 (99)	166 (99)
Prior Irinotecan Therapy, n (%)			
Yes	0 (0)	1 (1)	1 (1)
No	85 (100)	81 (99)	166 (99)
Prior Platinum Therapy, n (%)			
Yes	85 (100)	81 (99)	166 (99)
No	0 (0)	1 (1)	1 (1)
Prior Fluoropyrimidine Therapy, n (%)			
Yes	73 (86)	68 (83)	141 (84)
No	12 (14)	14 (17)	26 (16)
Prior Taxane Therapy, n (%)			
Yes	23 (27)	32 (39)	55 (33)
No	62 (73)	50 (61)	112 (67)

Source: FDA reviewer's analyses.

The Applicant's Position:

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

There were no additional demographic characteristics aside from those presented above.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:
Treatment Compliance: Study intervention was administered in the clinic by qualified site personnel, ensuring compliance (KEYNOTE-181 CSR, Sec. 10.4).

Concomitant Medications: Overall, the concomitant treatments administered were representative of those commonly prescribed for patients of the target population and were not considered to have impacted the study results. The most common were drugs for acid-related disorders, mostly omeprazole (KEYNOTE-181 CSR, Table 14.1-11).

Rescue Medication: Rescue medications and supportive care were allowed in KEYNOTE-181 study as deemed necessary by the treating investigator as per protocol (KEYNOTE-181 CSR, Sec. 16.1.1).

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses, OS)

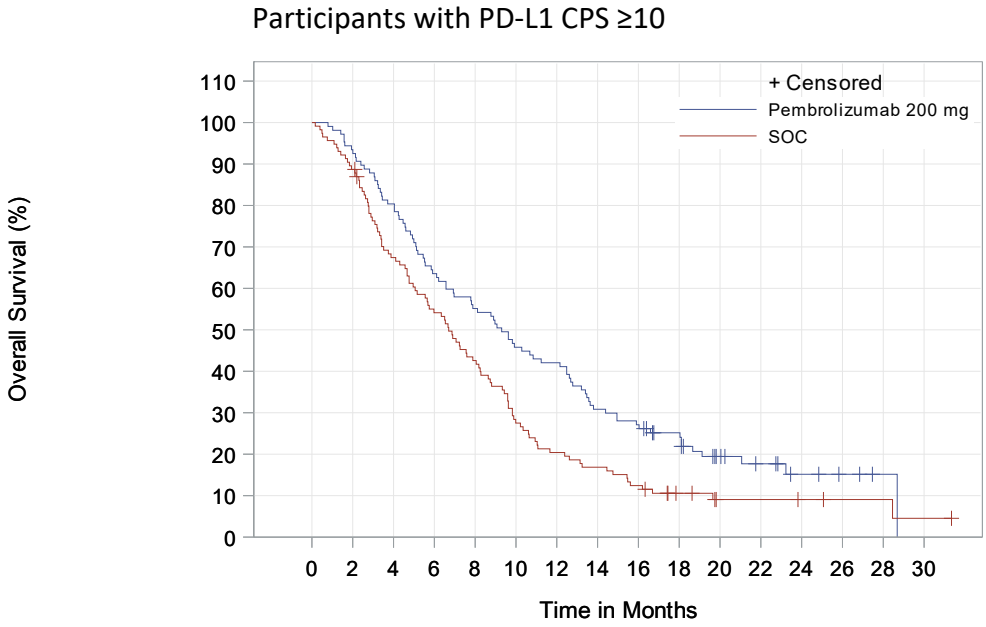
The Applicant's Position:
For participants with tumors expressing PD-L1 CPS ≥10, pembrolizumab demonstrated a clinically meaningful improvement in OS compared with SOC (HR 0.70 [95% CI: 0.52, 0.94]; p=0.00855). Median OS was 9.3 months for pembrolizumab vs. 6.7 months for SOC, and the OS rate was 63.6% vs. 54.1% at 6 months [Table 14]. A 30% reduction in the risk of death was observed in the pembrolizumab arm and median OS was 2.6 months longer for pembrolizumab than SOC. The KM curves separated early, and the durable survival benefit of pembrolizumab was illustrated by the continued separation over time [Figure 3], with more than 2-fold higher OS rates for pembrolizumab versus SOC at 12 months (42.1% vs. 20.4%) and 18 months (25.2% vs. 10.6%) [Table 14].

In participants with ESCC, pembrolizumab provided a clinical improvement in OS compared with SOC although it was not statistically significant (KEYNOTE-181 CSR, Sec. 11.1.2) (HR 0.77 [95% CI: 0.63, 0.96]; p=0.00894) [Table 14]. The durable survival benefit from pembrolizumab is demonstrated by a separation in the KM curve at about Month 6 that remained separated over time [Figure 3], with higher observed OS rates for pembrolizumab versus SOC at 12 months (38.9% vs. 24.9%) and 18 months (23.1% vs. 11.3%) [Table 14].

In all participants (KEYNOTE-181 CSR, Sec. 11.1.3), while directionally favorable, the improvement in OS with pembrolizumab was not statistically significant compared with SOC (HR 0.89 [95% CI: 0.75, 1.05]; p=0.08431) [Table 14]. The median OS was identical for pembrolizumab and SOC, and the KM curves did not separate until Month 8 [Figure 3]. After Month 8, a favorable survival benefit was observed with pembrolizumab than SOC, with higher OS rates for pembrolizumab at 12 and 18 months [Table 14].

The OS results in participants with ESCC and all participants are supportive of the clinically meaningful treatment effect of pembrolizumab compared to SOC in participants with PD-L1 CPS ≥10.

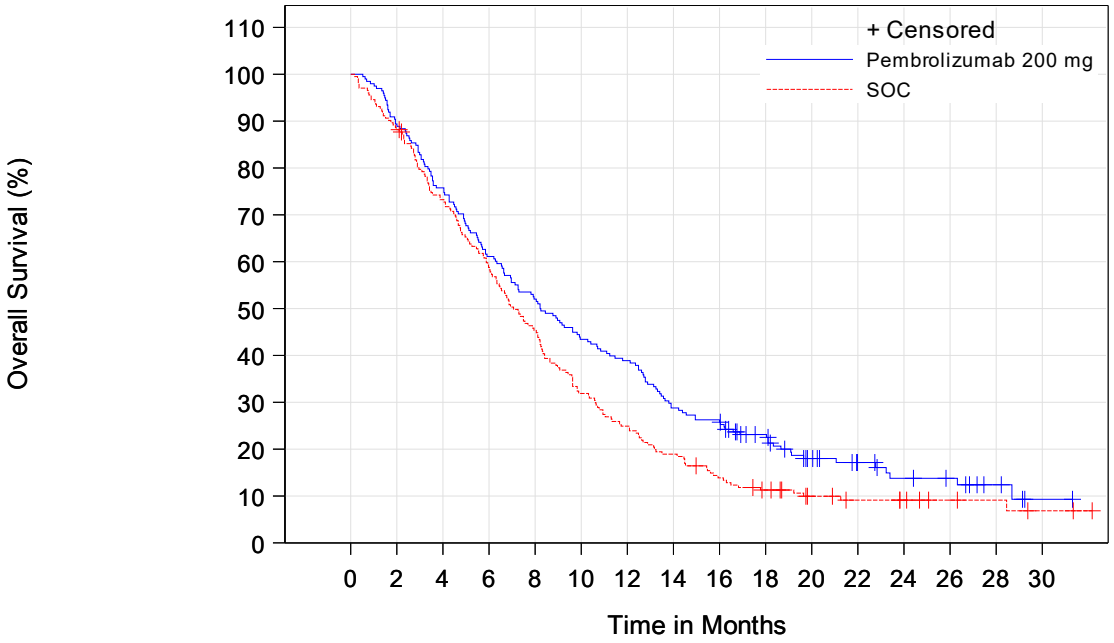
Figure 3
KEYNOTE-181 Kaplan-Meier Estimates of Overall Survival (ITT Population)



Number of subjects at risk

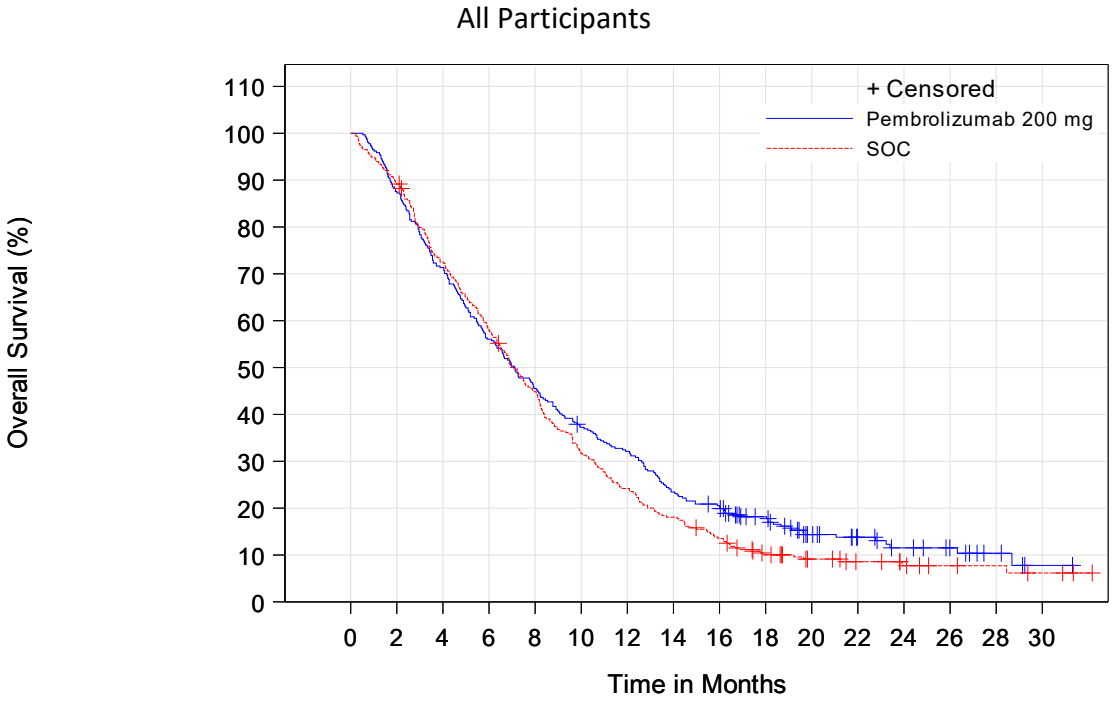
Pembrolizumab 200 mg	107	100	86	68	59	49	45	33	29	23	13	9	5	3	1	0
SOC	115	102	76	61	48	31	23	19	14	8	4	4	3	2	2	1

Participants with Squamous cell Carcinoma



Number of subjects at risk

Pembrolizumab 200 mg	198	177	150	121	103	86	77	57	52	38	24	17	12	10	5	1
SOC	203	179	147	118	91	64	50	38	27	20	13	10	8	5	4	2



Database Cutoff Date: 15OCT2018.
Data from KEYNOTE-181 CSR, Figure 11-1, Figure 11-3, and Figure 11-5.

Table 14
KEYNOTE-181 Summary of Efficacy Outcomes
(ITT Population, Participants with PD-L1 CPS ≥10, ESCC, and All Participants)

	PD-L1 CPS ≥10		ESCC		All Participants	
	Pembrolizumab (N=107)	**SOC (N=115)**	**Pembrolizumab (N=198)**	**SOC (N=203)**	**Pembrolizumab (N=314)**	**SOC (N=314)**
Primary Outcome: OS						
Number of events (%)	88 (82.2)	103 (89.6)	166 (83.8)	182 (89.7)	271 (86.3)	284 (90.4)
Median OS (95% CI), months[†]	9.3 (6.6, 12.5)	6.7 (5.1, 8.2)	8.2 (6.7, 10.3)	7.1 (6.1, 8.2)	7.1 (6.2, 8.1)	7.1 (6.3, 8.0)
HR (95% CI)[‡]	0.70 (0.52, 0.94)		0.77 (0.63, 0.96)		0.89 (0.75, 1.05)	
P-value [‡‡]	0.00855		0.00894		0.08431	
OS rate, % (95% CI) at 6 Months[†]	63.6 (53.7, 71.9)	54.1 (44.5, 62.8)	61.1 (53.9, 67.5)	58.8 (51.7, 65.2)	56.1 (50.4, 61.3)	58.1 (52.4, 63.3)

	PD-L1 CPS ≥10		ESCC		All Participants	
	Pembrolizumab (N=107)	**SOC (N=115)**	**Pembrolizumab (N=198)**	**SOC (N=203)**	**Pembrolizumab (N=314)**	**SOC (N=314)**
OS rate, % (95% CI) at 12 Months†	42.1 (32.6, 51.2)	20.4 (13.5, 28.3)	38.9 (32.1, 45.6)	24.9 (19.2, 31.1)	32.1 (27.0, 37.3)	24.2 (19.6, 29.1)
OS rate, % (95% CI) at 18 Months†	25.2 (17.4, 33.7)	10.6 (5.8, 17.1)	23.1 (17.5, 29.2)	11.3 (7.4, 16.1)	18.2 (14.1, 22.7)	10.0 (7.0, 13.8)
Secondary Efficacy Outcomes: PFS, ORR, DOR						
PFS (BICR per RECIST 1.1)						
Number of events (%)	96 (89.7)	107 (93.0)	185 (93.4)	191 (94.1)	295 (93.9)	297 (94.6)
Median PFS (95% CI) , months†	2.6 (2.1, 4.1)	3.0 (2.1, 3.7)	2.2 (2.1, 3.2)	3.1 (2.2, 3.9)	2.1 (2.1, 2.2)	3.4 (2.8, 3.9)
HR (95% CI) ‡	0.73 (0.54, 0.97)		0.92 (0.75, 1.13)		1.11 (0.94, 1.31)	
P-value‡‡	0.015		0.216		0.886	
PFS rate, % (95% CI) at 6 Months†	33.6 (24.9, 42.6)	28.5 (20.4, 37.1)	27.3 (21.3, 33.6)	26.8 (20.8, 33.1)	23.5 (19.0, 28.4)	30.3 (25.2, 35.5)
PFS rate, % (95% CI) at 9 Months†	24.9 (17.1, 33.5)	16.2 (9.9, 23.7)	18.0 (13.0, 23.7)	16.3 (11.5, 21.8)	14.7 (11.0, 18.9)	17.3 (13.3, 21.8)
PFS rate, % (95% CI) at 12 Months†	20.8 (13.6, 29.1)	6.7 (2.9, 12.5)	15.3 (10.6, 20.7)	9.4 (5.8, 14.1)	12.0 (8.6, 15.9)	9.9 (6.8, 13.6)
ORR (BICR per RECIST 1.1)						
ORR (95% CI), in %	21.5 (14.1, 30.5)	6.1 (2.5, 12.1)	16.7 (11.8, 22.6)	7.4 (4.2, 11.9)	13.1 (9.5, 17.3)	6.7 (4.2, 10.0)
Difference in % Pembrolizumab vs. SOC:						
Estimate (95% CI)	15.1 (6.2, 24.7)		9.2 (3.0, 15.8)		6.4 (1.7, 11.2)	
P-value‡‡‡	0.0006		0.0022		0.0037	
DOR (Confirmed CR or PR, BICR per RECIST 1.1)						
Number of responders	23	7	33	15	41	21
Median DOR (range), months††	9.3 (2.1+-22.6+)	7.7 (4.3-16.8+)	8.5 (2.1+-25.8+)	10.7 (2.1+-16.8+)	8.5 (2.1+ - 25.8+)	10.7 (1.8+ - 16.8+)

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs ex-Asia) and tumor histology (Squamous cell carcinoma vs adenocarcinoma/Siewert type 1 adenocarcinoma of the EGJ).
‡‡ One-sided p-value based on stratified log-rank test.
‡‡‡ One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.
†† From product-limit (Kaplan-Meier) method for censored data.

	PD-L1 CPS ≥10		ESCC		All Participants	
	Pembrolizumab (N=107)	SOC (N=115)	Pembrolizumab (N=198)	SOC (N=203)	Pembrolizumab (N=314)	SOC (N=314)

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.
Response was assessed based on Central Radiology Assessment (BICR = Blinded Independent Central Radiology Review) per RECIST 1.1; only confirmed responses are included. The 95% CIs for response rates were calculated based on the binomial exact method.
"+" indicates there was no progressive disease by the time of last disease assessment.
CR=complete response; DOR=duration of response; ESCC=esophageal squamous cell carcinoma; HR=hazard ratio; ITT=intent-to-treat; PD-L1 CPS=programmed cell death ligand-1 combined positive score; ORR=Objective response rate or Overall response rate; Pembro=pembrolizumab; PFS=progression-free survival; PR=partial response; SD=stable disease; SOC=standard of care.
Database Cutoff Date: 15-OCT-2018
Data derived from KEYNOTE-181 CSR, Table 11-1, Table 11-2, Table 11-3, Table 11-4, Table 11-6, Table 11-7, Table 11-8, Table 11-9, Table 11-11, Table 11-12, Table 11-13, Table 11-14, Table 11-15, Table 14.2-14, Table 14.2-21, Table 14.2-26, Table 14.2-31, and Table 14.2-34.

Data Quality and Integrity

Quality and integrity of study data were assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures, as detailed in the KEYNOTE-181 protocol, Sec. 10.

The clinical study program was carried out in accordance with GCP guidelines. MRL QA independently assessed quality through a comprehensive, risk-based audit program to ensure adherence with applicable GCP, Good Pharmacovigilance Practices regulations and applicable company policies and procedures. Audit information and serious GCP compliance issues (including significant quality issues, unblinding events that have impacted data integrity and compliance issues reported to health authorities) are provided in the KEYNOTE-181 CSR, Sec 16.1.8 and 16.1.8.2.

Efficacy Results – Secondary and other relevant endpoints (PFS, ORR, and DOR)

Per the study protocol, the secondary hypotheses of PFS and ORR in all participants were not formally tested because pembrolizumab was not superior to SOC for OS in all participants. In the results discussed below, nominal p-values, which were not adjusted for multiplicity, are provided for descriptive purposes. No formal testing was planned for the other secondary efficacy endpoints, and nominal p-values are also provided for descriptive purposes.

Progression-free Survival (*KEYNOTE-181 CSR, Sec. 11.2.1*)
In participants with PD-L1 CPS ≥10, the PFS HR of 0.73 (95% CI: 0.54, 0.97) favored pembrolizumab and the median PFS was similar between the pembrolizumab and SOC arms [Table 14]. The durable benefit of pembrolizumab is demonstrated by a separation in the KM curve at Month 7 that continued to separate over time [Figure 4], with higher PFS rates for

pembrolizumab than SOC at 9 and 12 months [Table 14]. These PFS results, together with OS results, show consistent, robust benefits of pembrolizumab versus SOC in the PD-L1 CPS ≥10 population.

Results of PFS sensitivity analyses and investigator-based PFS evaluation were consistent with those from the primary PFS analysis based on BICR (KEYNOTE-181 CSR, Table 14.2-29, Table 14.2-30, Table 14.2-69, 14.2-70, Figure 14.2-40, Figure 14.2-41, and Figure 14.2-42).

PFS results in participants with ESCC and all participants are shown in [Figure 4] and summarized in [Table 14].

***Overall Response Rate* (KEYNOTE-181 CSR, Sec. 11.2.2)**
Pembrolizumab improved ORR (CR + PR) in participants with PD-L1 CPS ≥10 threefold compared with SOC (21.5% vs. 6.1%) [Table 14]. The treatment difference in ORR was 15.1% (95% CI: 6.2%, 24.7%) (nominal p-value unadjusted for multiplicity, p=0.0006) [Table 14]. A confirmed CR occurred for 4 (3.7%) participants in the pembrolizumab arm and 1 (0.9%) participant in the SOC arm, and a confirmed PR occurred for 19 (17.8%) participants in the pembrolizumab arm and 6 (5.2%) participants in the SOC arm (KEYNOTE-181 CSR, Table 14.2-33). These results demonstrate a broader response to pembrolizumab than SOC in participants with PD-L1 CPS ≥10. The observed treatment difference in ORR, together with PFS and OS results, show consistent, robust benefits of pembrolizumab versus SOC in the PD-L1 CPS ≥10 population.

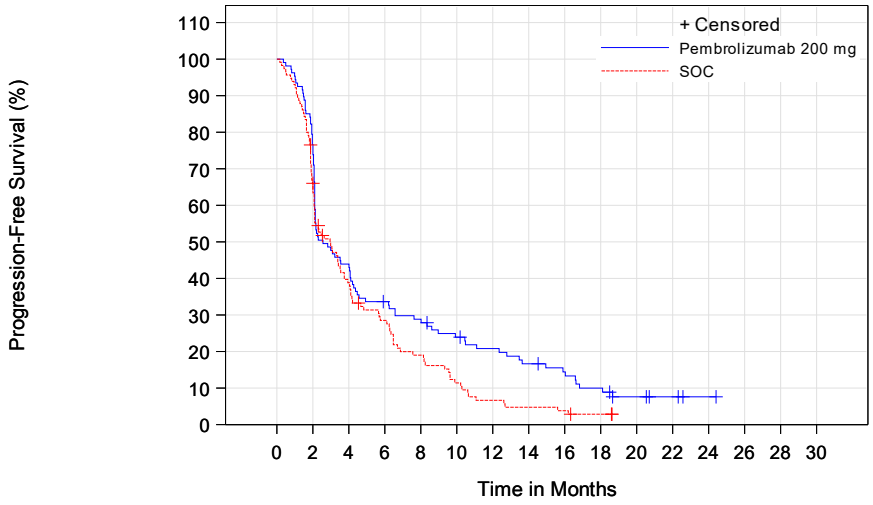
ORR results in participants with ESCC and in all participants are summarized in [Table 14].

Duration of Response (*KEYNOTE-181 CSR, Sec. 11.2.3*)
The median DOR in participants with PD-L1 CPS ≥10 was 1.6 months longer for pembrolizumab relative to SOC [Table 14]. The small number of participants in the SOC arm with a response makes interpretation difficult, but the KM estimates indicate durable responses in the pembrolizumab arm; DOR of ≥6 and ≥9 months were higher for pembrolizumab than SOC (KEYNOTE-181 CSR, Table 14.2-17). At the data cutoff date, responses were ongoing for four (17.4%) participants in the pembrolizumab arm and one (14.3%) participant in the SOC arm (KEYNOTE-181 CSR, Table 14.2-35). Median times to response were similar between intervention arms, and the mean time to response was 1.4 months shorter in the pembrolizumab arm compared with the SOC arm, indicating no delay in the response to pembrolizumab relative to SOC (KEYNOTE-181 CSR, Table 14.2-34).

DOR results in participants with ESCC and in all participants are summarized in [Table 14].

Figure 4
KEYNOTE-181 Kaplan-Meier Estimates of Progression-Free Survival (ITT Population)

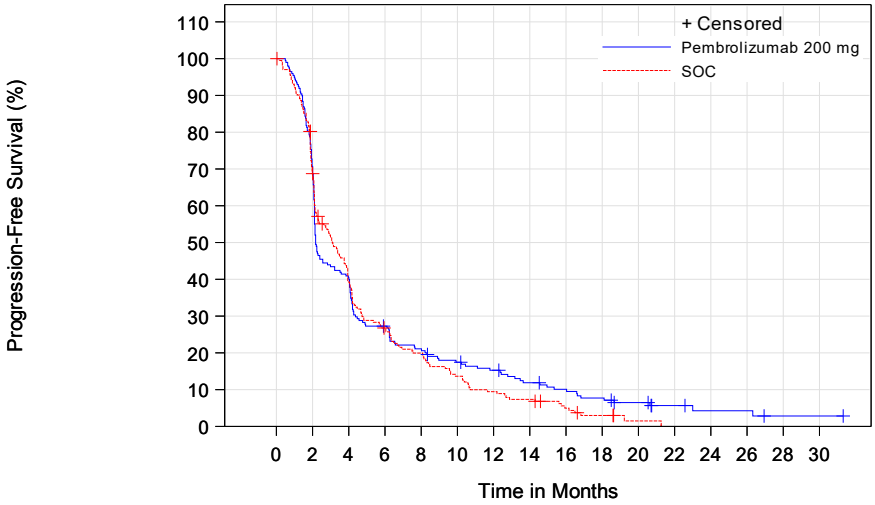
Participants with PD-L1 CPS >=10 (Primary Censoring Rule)



Number of subjects at risk

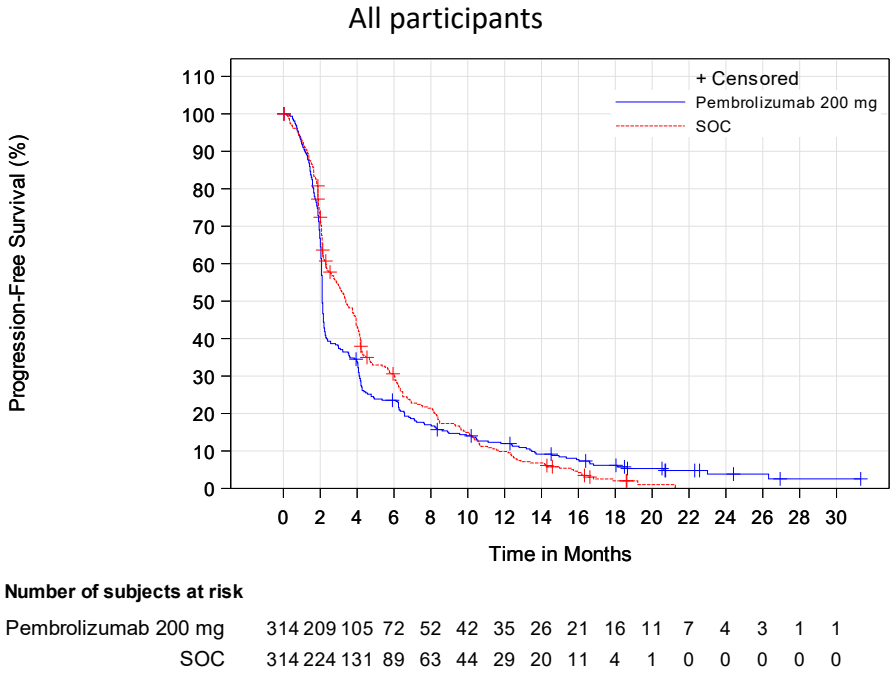
Pembrolizumab 200 mg	107	82	47	35	30	24	20	16	13	9	5	3	1	0	0	0
SOC	115	75	42	30	20	12	7	5	4	2	0	0	0	0	0	0

Participants with Squamous cell Carcinoma (Primary Censoring Rule)



Number of subjects at risk

Pembrolizumab 200 mg	198	140	80	53	41	33	28	21	17	13	9	5	3	3	1	1
SOC	203	137	77	51	38	26	18	14	8	4	1	0	0	0	0	0



Database Cutoff Date: 15OCT2018.
Data from KEYNOTE-181 CSR, Figure 11-7, Figure 11-8, and Figure 11-9.

Dose/Dose Response

Not applicable.

Durability of Response

Durability of response is discussed in the previous section for Efficacy Results – Secondary and other relevant endpoints (DOR).

Persistence of Effect

Persistence of effect is discussed in the previous OS and DOR results sections [Efficacy Results – Primary Endpoint (Including Sensitivity Analyses, OS) and Efficacy Results Secondary and other relevant endpoints (PFS, ORR, and DOR)].

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Completion rates were high for all participants and for participants with PD-L1 CPS ≥10 and with ESCC, in both the pembrolizumab and SOC arms for the EORTC QLQ C30, EORTC QLQ-OES18, and EQ-5D questionnaires, and decreased at each time point as more participants discontinued from the study due to disease progression (KEYNOTE-181 CSR, Sec. 11.4.1). Outcomes were similar and stable over time for participants receiving pembrolizumab and SOC for EORTC QLQ-C30 (KEYNOTE-181 CSR, Sec. 11.4.2), for EORTC OES-18 (KEYNOTE-181 CSR, Sec. 11.4.3), or for

EQ-5D VAS (KEYNOTE-181 CSR, Sec. 11.4.4). Participants treated with pembrolizumab showed some improvement in VAS scores at Week 9 compared to baseline, while the participants treated with SOC showed worsening in VAS scores at Week 9 compared to baseline. (KEYNOTE-181 CSR, Sec. 11.4.4).

Additional Analyses Conducted on the Individual Trial

Not applicable.

Review of Effectiveness

The FDA's Assessment:

FDA agrees with the majority of the results of the primary and secondary efficacy analyses, as summarized by Merck above. However, FDA does not agree with Merck's interpretation of these results. The KEYNOTE-181 trial failed to meet the pre-specified thresholds (as outlined in Table 15) to demonstrate a statistically significant improvement in OS in any of the three pre-specified primary patient populations, with observed hazard ratios of 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. Because a statistically significant improvement in OS was not demonstrated in any of the three pre-specified OS analyses, there was no alpha left for formal testing of the key secondary efficacy endpoints, i.e. PFS or ORR. Therefore, no PFS or ORR efficacy claims can be made based on these results.

In addition, FDA disagrees with the following aspects of the efficacy analyses:

1. The information level of a log-rank test obtained at an interim analysis should be based on the information fraction, defined as the percentage of the number of events observed at an interim analysis compared to the number of events planned for the final analysis, instead of the calendar-time fraction at the interim analysis. Therefore, FDA does not agree with Merck's calendar-time-based method to calculate the alpha boundaries for the interim and final analyses of OS; instead, FDA used O'Brien-Fleming boundaries determined by the Lan-DeMets approach based on the information fraction. Table 15 provides the alpha boundaries used by Merck and the FDA. Irrespective of whether the boundaries calculated by Merck or the boundaries calculated by FDA are used, the study failed to meet the pre-specified thresholds to demonstrate a statistically significant improvement in OS in any of the three pre-specified primary patient populations at the interim analysis and at the final analysis.
2. FDA does not agree with the final analysis of OS for the ITT population. The number of OS events planned for the final analysis in the ITT population was reached at the time of the interim analysis. Therefore, FDA considers the OS analysis in the ITT population performed at the interim analysis to be the final analysis of OS in the ITT population, and the alpha boundary for this analysis was 0.008 (see Table 15). OS in the ITT population could be tested again if there was alpha left to this hypothesis testing at the final analysis; however, the hypothesis tests of OS in the ESCC and CPS ≥10 populations were

not rejected, and so there was no alpha left to this hypothesis at the final analysis. Therefore, Merck's final OS analysis in the ITT population is considered exploratory.

3. The p-values for the analyses of the secondary endpoints PFS and ORR are considered nominal because there is no alpha left for conducting formal testing on PFS and ORR.
4. The estimated PFS and OS rates at 6, 9, 12 months are exploratory. Point estimate of event rates at a fixed time point for time-to-event endpoints can be misleading because it does not represent the entire effect size of the treatment and the chosen landmark time is arbitrary.
5. Since there is no pre-specified statistical testing procedure to control the type I error for PRO endpoints, all of the PRO analyses are considered exploratory. No claims can be made based on these analyses.

Table 15
Alpha Boundaries for Testing OS in ESCC, PD-L1 CPS ≥10, and ITT at Interim and Final Analyses by Merck vs. by FDA, KEYNOTE-181 (FDA Analysis)

	ESCC	PD-L1 CPS ≥10	ITT
# Events planned (interim, final)	251, 310	172, 213	385, 473
# Events observed (interim, final)	299, 348	161, 191	486, 555
Actual time of interim			
Merck (calendar fraction)	76%	76%	76%
FDA (information fraction)	96.5% (299/310)	75.6% (161/213)	100%
Alpha allocation (interim, final)			
Merck	0.0023, 0.0077	0.0027, 0.0085	0.0023, 0.0162
FDA	0.0069, 0.0063	0.0027, 0.0082	0.0080, None[2]
One-sided p-value (interim[1], final)	0.021, 0.0089	0.003, 0.0086	0.177, NA[3]

Source: FDA reviewer's assessment.

[1] These were provided in Merck's response to FDA's information request dated 3/11/2019.

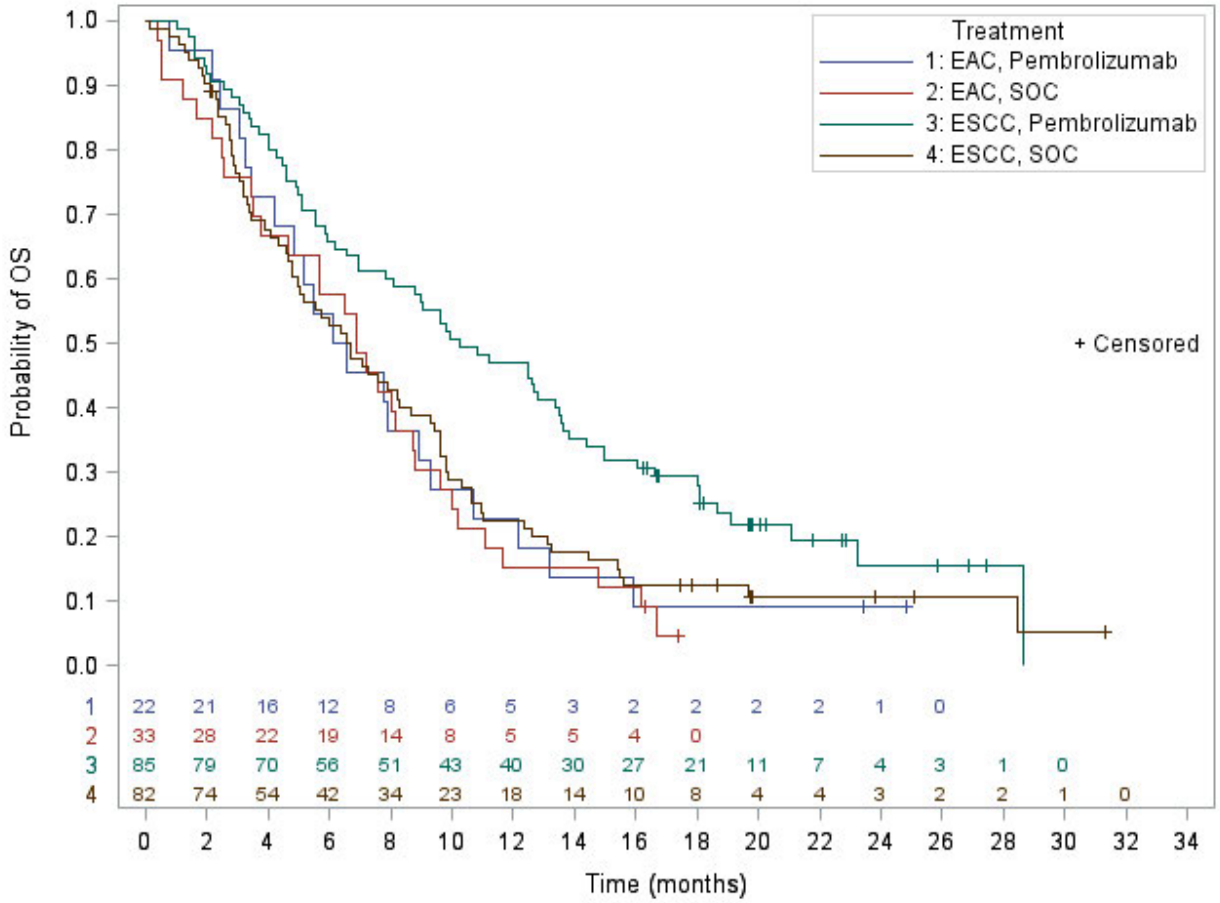
[2, 3] FDA considers the OS analysis in the ITT population done at the interim analysis as the final analysis of OS in the ITT population with alpha=0.008; there was no alpha left for this hypothesis testing at the final analysis. NA=Not Applicable.

Discussion of the clinical benefit in patients whose tumors expressed PD-L1 (CPS ≥10)

The original submission was filed by FDA based on data provided by Merck demonstrating a statistically significant improvement (p-value=0.0074) in OS favoring pembrolizumab in patients whose tumors expressed PD-L1 (CPS ≥10), with a 2.6 month improvement (9.3 vs. 6.7 months) in median OS and a HR of 0.69 (95% CI: 0.52, 0.93). Following identification and correction of a data error after the submission (see the Data Quality and Integrity session below), the improvement in median OS remained 2.6 months and the HR was 0.70 (95% CI: 0.52, 0.94); however, the results were no longer statistically significant as the p-value increased to 0.0086, compared to the alpha boundary 0.0082.

Despite the failure of the primary hypothesis tests, based on the totality of evidence, a subpopulation that may provide support of the treatment benefits from pembrolizumab was identified (see the FDA's Assessment in the Summary and Conclusion section). A clinically meaningful prolongation of OS was observed in the subgroup of patients with squamous cell histology who have tumors that express PD-L1 (CPS ≥10). The results in this subpopulation (Page 63 of Merck's CSR dated 6/4/2019) were further reviewed in comparison with the complementary subgroups, indicating that the treatment benefit may be both dependent on tumor PD-L1 expression and histologic subtype. Figure 5 shows the Kaplan-Meier curves by histologic subtype in patients whose tumors expressed PD-L1 (CPS ≥10). The survival curve for patients with ESCC who received pembrolizumab separates from the other three curves, indicating that improvement in OS conferred by pembrolizumab was observed primarily in this subgroup of patients. However, it is noteworthy that there were only 55 patients with adenocarcinoma in the CPS≥10 population overall and the Kaplan-Meier estimates with this small number of patients may not be reliable. Additionally, the study was not designed prospectively analyze subgroups by histology and tumor PD-L1 expression status.

Figure 5
Kaplan-Meier Curves of OS by Histology in Patients Whose Tumors Expressed PD-L1 (CPS ≥10), KEYNOTE-181 (FDA Analysis)



Source: FDA reviewer's assessment.

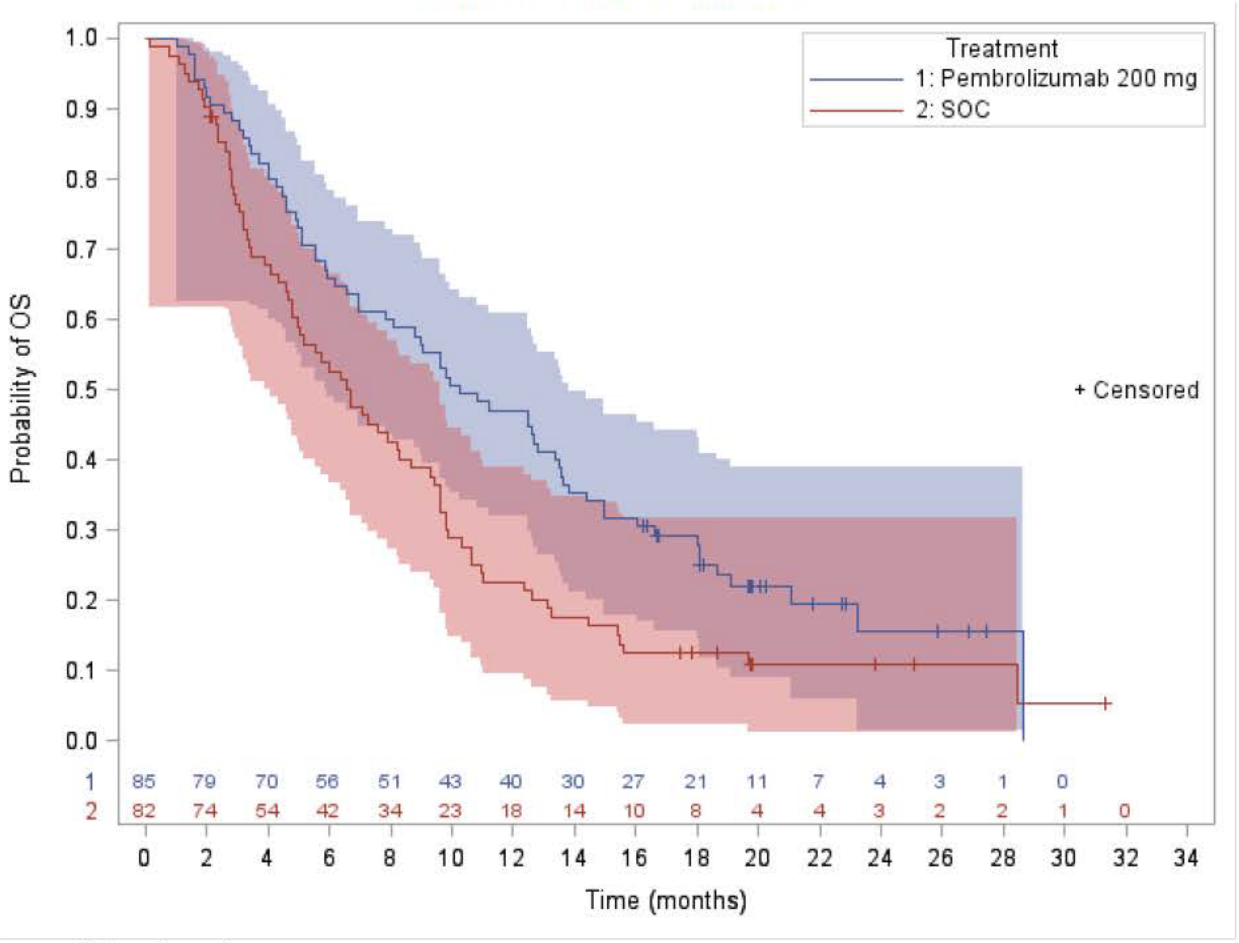
Results for patients with ESCC whose tumors expressed PD-L1 (CPS ≥10) are provided in Table 16. The Kaplan-Meier curves, with Hall-Wellner confidence bands displaying the pointwise confidence intervals at each timepoint, for OS and PFS in this subpopulation are shown in Figure 6 and Figure 7. The results in the subpopulation of patients with ESCC tumors expressing PD-L1 (CPS ≥10) indicate a larger estimated treatment benefit compared to the three primary populations where the study failed to demonstrate a significant improvement in OS in the pembrolizumab arm compared to the SOC arm.

Table 16
Efficacy Results in Patients with ESCC Whose Tumors Expressed PD-L1 (CPS ≥10), KEYNOTE-181 (FDA Analysis)

	Pembrolizumab (N=85)	SOC (N=82)
Primary Endpoint: OS		
Number of events, n (%)	68 (80)	72 (88)
Median (95% CI), months	10.3 (7.0, 13.5)	6.7 (4.8, 8.6)
Median follow-up (95% CI), months	20.2 (19.6, 25.8)	19.8 (17.8, 31.3)
Hazard Ratio [1] (95% CI)	0.64 (0.46, 0.90)	
Secondary Endpoint: PFS (BICR per RECIST 1.1)		
Number of events, n (%)	76 (89)	76 (93)
Median (95% CI), months	3.2 (2.1, 4.4)	2.3 (2.1, 3.4)
Median follow-up (95% CI), months	20.5 (18.5, 22.6)	18.6 (18.6, 18.6)
Hazard Ratio [1] (95% CI)	0.66 (0.48, 0.92)	
Secondary Endpoints: ORR and DOR (BICR per RECIST 1.1)		
Response, n (%)		
CR	4 (5)	1 (1)
PR	15 (18)	5 (6)
SD	22 (26)	30 (37)
PD	33 (39)	32 (39)
ORR, n (%)	19 (22)	6 (7)
95% CI for ORR, %	(14, 33)	(3, 15)
Median DOR in responders (range), months[2]	9.3 (2.1+, 18.8+)	7.7 (4.3, 16.8+)

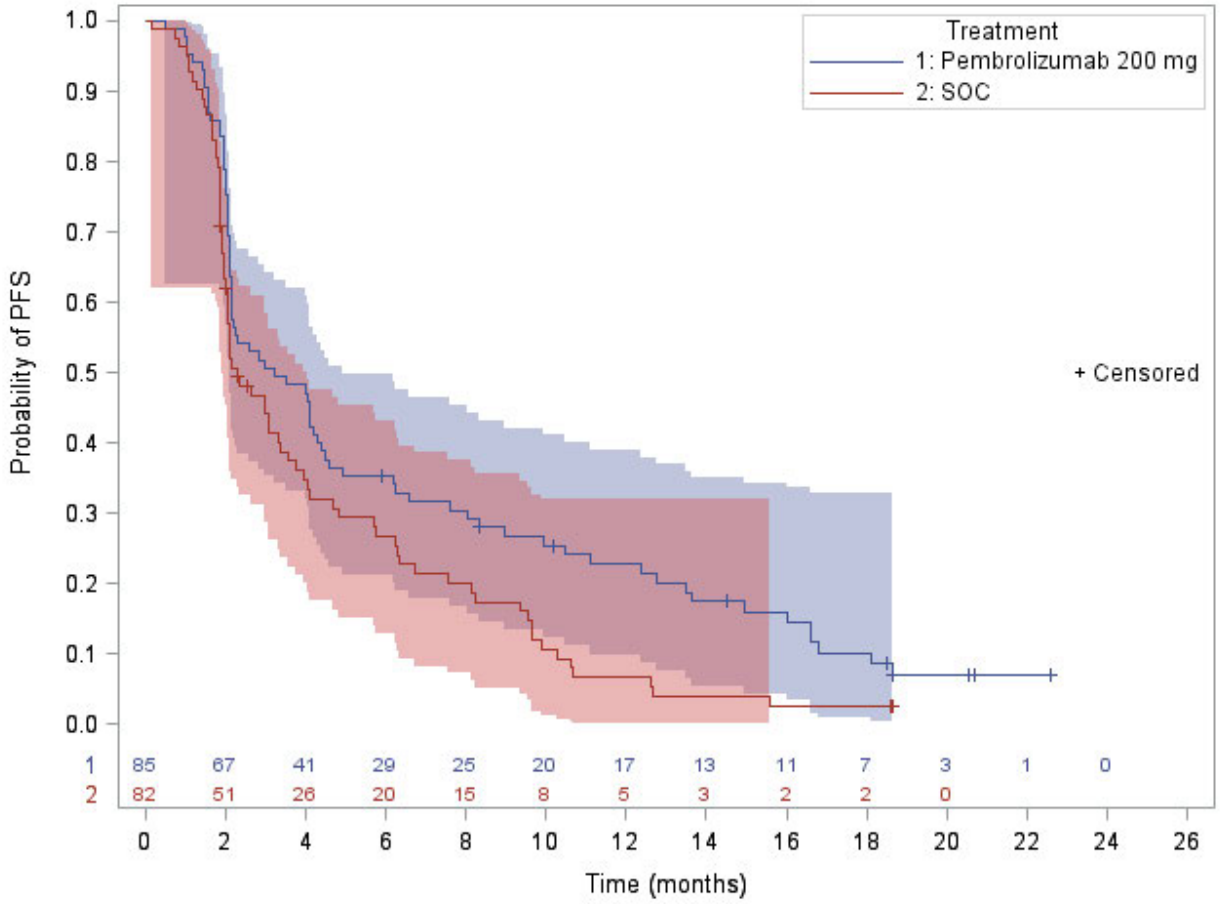
Source: FDA reviewer's assessment.
[1] Stratified Cox proportional hazards model by geographic region (Asia vs ex-Asia).
[2] + means duration of response was censored at the time point and not observed.

Figure 6
Kaplan-Meier Curves for OS in Patients with ESCC Whose Tumors Expressed PD-L1 CPS ≥10, KEYNOTE-181 (FDA Analysis)



Source: FDA reviewer's assessment.

Figure 7
Kaplan-Meier Curves for PFS in Patients with ESCC Whose Tumors Expressed PD-L1 CPS ≥10, KEYNOTE-181 (FDA Analysis)



Source: FDA reviewer's assessment.

Reviewer Comments: The *confidence bands indicate that though there is separation of curves for both OS and PFS, the confidence intervals for the estimated survival probability at each time overlap the curve of the other treatment arm. Though the wide confidence intervals are likely due to small sample size of the subgroups, the interpretation of the Kaplan-Meier curves for each endpoint should be exercised with caution.*

Subgroup Analysis

Table 17 displays subgroup analyses performed by FDA for OS in patients with ESCC whose tumors had PD-L1 expression with a CPS ≥10. The subgroup results below appear to be consistent with the OS results in all patients with ESCC and those whose tumors expressed PD-L1 CPS ≥10.

The median survival in the pembrolizumab arm was longer than that in the SOC arm in all of the analyzed subgroups except for the subgroup of patients who are White (median OS was the

same in the two arms for this subgroup). The hazard ratio estimate was less than 1, favoring pembrolizumab, for all of the analyzed subgroups.

Table 17
Subgroup Results in Patients with ESCC Whose Tumors Expressed PD-L1 CPS ≥10, KEYNOTE-181 (FDA's Assessment)

Subgroup	Total	Event/Total		Median, month		Hazard Ratio (95% CI) [1]
		Pembro	SOC	Pembro	SOC	
Age Category						
≥65 years	85	37/46	31/39	10.4	9.4	0.81 (0.50, 1.31)
<65 years	82	31/39	41/43	10.3	5.7	0.47 (0.29, 0.76)
Sex						
Male	141	58/74	58/67	10.6	7.1	0.64 (0.44, 0.92)
Female	26	10/11	14/15	9.9	5.2	0.64 (0.28, 1.48)
Race						
White	53	23/26	25/27	6.7	6.7	0.75 (0.42, 1.33)
Asian	113	45/59	46/54	12.6	6.5	0.60 (0.39, 0.90)
Region						
Asia	112	44/58	46/54	12.7	6.5	0.59 (0.39, 0.90)
Ex-Asia	55	24/27	26/28	7.8	6.7	0.74 (0.42, 1.30)
ECOG						
0	64	28/36	25/28	12.6	9.5	0.55 (0.32, 0.95)
1	103	40/49	47/54	6.2	5.7	0.72 (0.47, 1.10)
Current Disease Presentation						
Metastatic	150	61/76	65/74	11.0	6.3	0.62 (0.44, 0.88)
Locally Advanced	17	7/9	7/8	9.8	10.3	0.84 (0.29, 2.43)
Prior Adjuvant or Neoadjuvant Therapy						
Yes	15	4/5	10/10	5.9	4.0	0.69 (0.21, 2.25)
No	152	64/80	62/72	11.0	6.7	0.64 (0.45, 0.91)

Source: FDA reviewer's analyses.
[1] Unstratified Cox proportional hazards model.
Pembro=pembrolizumab 200 mg

Statistical Reviewer Comment: *These subgroup results should be interpreted with caution because the sample size in each subgroup was not planned to power such analyses for detecting the same magnitude of the treatment effect. Therefore, the subgroup analyses are considered exploratory. Nevertheless, OS results consistently favor pembrolizumab across the subgroups analyzed.*

Data Quality and Integrity
The FDA reviewer was able to reproduce the efficacy results based on the submitted ADaM dataset for Study KEYNOTE-181. However, following submission and during review of this efficacy supplement, both FDA and Merck identified data errors that affect the results of the

efficacy analyses, and Merck requested a meeting to discuss this new information. The meeting package and corrected efficacy datasets were submitted to FDA on April 11, 2019. In the meeting package, Merck stated that further investigation revealed that 2 patients (shown below) had died prior to database lock dates (IA and FA) and had disposition listed as death but did not have their death dates entered in the appropriate field; for these 2 patients the death dates were not recorded in the variable used for OS analysis and therefore were censored to alive status at the IA and FA (Table 18).

Table 18
Summary of Identified Overall Survival Data Errors in KEYNOTE-181

Patient	Treatment	CPS	Histology	Country	Original OS	Actual OS
(b) (6)	Pembro	≥10	ESCC	(b) (6)	Censored at DCO	Died 11 months
	SOC	<10	ESCC		Censored at DCO	Died 12 months

Statistical Reviewer Comment: *The efficacy assessments by FDA in this document were based on the dataset submitted on April 11, 2019 with the corrected survival data.*

7.1.3. Assessment of Efficacy Across Trials

The Applicant's Position:

Because KEYNOTE-180 and KEYNOTE-028 were single arm studies with participants with substantially more advanced stages of disease (different lines of therapy), a formal comparative analysis or pooled analyses of pivotal data (KEYNOTE-181) and supporting data (KEYNOTE-028 and KEYNOTE-180) were not conducted. However, while KEYNOTE-180 and KEYNOTE-028 were not controlled studies, they do demonstrate the efficacy of pembrolizumab across multiple lines of therapy. Efficacy results for these two studies are summarized in (KEYNOTE-180 CSR, Sec. 11; KEYNOTE-028 CSR, Sec. 11).

Data from KEYNOTE 181 confirms durable benefit seen in KEYNOTE-180, and further highlights the benefit of pembrolizumab monotherapy in comparison to an active comparator. In KEYNOTE-181, in all participants, 13.1% (N=41) experienced objective responses and there was evidence of durability [Table 14]. Further, the ORR was nearly two-fold higher than SOC (ORR=6.7%). Data from KEYNOTE-180 also corroborates the enhanced efficacy of pembrolizumab in participants with PD-L1 CPS ≥10 and participants with ESCC observed in KEYNOTE-181.

Thus, efficacy data from KEYNOTE-181 provide further confidence in the importance of clinical benefit seen from KEYNOTE-180 and both KEYNOTE-181 and KEYNOTE-180 demonstrated clinically meaningful benefit of pembrolizumab in participants with advanced/metastatic esophageal cancer.

The FDA's Assessment:
Although a formal pooled analysis of efficacy was not performed, the results of KEYNOTE-180 (submitted to sBLA 125514/S-55) provide additional information supporting the approval of pembrolizumab in the subpopulation of patients with ESCC whose tumors express PD-L1 with CPS≥10. In KEYNOTE-180, the ORR in the overall population was 10% (95% CI: 5, 17) but the exploratory analysis of ORR in the subset of patients (N=35) with ESCC and CPS ≥ 10 showed a response rate of 20% (95% CI: 8,37). The median follow-up time for DOR in the 7 patients with a tumor response was 16.5 months. The median DOR was not reached and the range of DOR was from 4.2 months to 25.1+ months. Thus, the totality of the data also strongly suggests that the population deriving benefit is the ESCC patients with CPS≥10. Please see the review of sBLA 125514/S-55 for additional details regarding FDA's review of this trial.

Primary Endpoints

Not applicable as only one pivotal trial.

Secondary and Other Endpoints

Not applicable as only one pivotal trial.

Subpopulations

The Applicant's Position:
Not applicable as only one pivotal trial.

Additional Efficacy Considerations

None.

7.1.4. Integrated Assessment of Effectiveness

The Applicant's Position:
KEYNOTE-181 is the first Phase 3 study to show a survival benefit in patients with esophageal cancer in the 2L setting.

In participants with PD-L1 CPS ≥10, data from KEYNOTE-181 demonstrated a clinically meaningful improvement in OS for pembrolizumab compared to SOC. Efficacy data from the SOC arm of KEYNOTE-181 are consistent with historical data (see 2.5, Table 2.5-esophageal2: 1). Improvement of OS in the pembrolizumab arm versus SOC is supported by favorable PFS and ORR relative to SOC, and longer duration of responses versus SOC. The improved durability of clinical benefit is highlighted by favorable 12- and 18-month OS rates. Consequently, the efficacy of pembrolizumab shown in KEYNOTE-181 marks an important advancement in the treatment of esophageal cancer with 2L therapy and can address the unmet need of these patients with poor prognosis.

The OS results in participants with ESCC and all participants are supportive of the clinically meaningful effect of pembrolizumab compared with SOC in participants with PD-L1 CPS ≥10. ORR and DOR results in participants with ESCC and all participants are also supportive of the beneficial effects of pembrolizumab therapy versus SOC in the PD-L1 CPS ≥10 population.

Results of KEYNOTE-180 provide further confidence in the importance of the clinical benefit seen from KEYNOTE-181, with general consistency in efficacy between the studies that demonstrated clinically meaningful benefit of pembrolizumab in participants with advanced/metastatic esophageal cancer.

The FDA's Assessment:

A clinically meaningful improvement in OS was observed in Study KEYNOTE-181 in patients with ESCC with PD-L1 CPS ≥10. In the FDA exploratory analysis conducted in patients with ESCC whose tumors expressed PD-L1 CPS ≥10 (the patient population for whom FDA is recommending approval), the median OS was 10.3 months for the pembrolizumab arm vs. 6.7 months for the SOC arm. The HR (pembrolizumab/SOC) is 0.64 with the 95% CI (0.46, 0.90). The OS results observed in this subgroup are internally consistent with the PFS and ORR results in this subpopulation, which also favored the pembrolizumab arm (Table 16).

The efficacy of pembrolizumab in patients with ESCC with PD-L1 CPS ≥10 is further supported by the results of KEYNOTE-180, which showed clinically meaningful and durable responses in this population of patients who had received 2 or more prior lines of systemic chemotherapy. Among the 35 patients enrolled in this trial with PD-L1 positive ESCC, the ORR was 20% (95% CI: 8,37) compared to 10% (95% CI: 5,17) in the overall population. The median follow-up time for DOR in the 7 patients with a tumor response was 16.5 months. The median DOR was not reached and the range of DOR was from 4.2 months to 25.1+ months (please see FDA's review of sBLA 125514/S-55 for additional details).

Although the results of KEYNOTE-181 failed to meet the pre-specified alpha level to declare statistical significance in any of the 3 primary analysis populations, the review team determined that the totality of evidence, comprising the results of the exploratory subgroup analysis of OS in patients with PDL1+ (CPS ≥10) ESCC in KEYNOTE-181, supported by data from KEYNTOTE-180 and information supporting the approval of pembrolizumab for other PD-L1 positive cancers (such as NSCLC and gastric cancer), constitute substantial evidence of effectiveness. There remains residual uncertainty with regards to whether pembrolizumab confers a clinical benefit to patients with adenocarcinoma of the esophagus that has progressed after one or more prior lines of therapy and the benefit in patients with different levels of PDL-1 expression. Hence the review team recommends regular approval of pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic squamous esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

7.2 Review of Safety

The Applicant's Position:
The results of KEYNOTE-181 demonstrate that pembrolizumab, when administered as monotherapy, has an improved safety profile when compared with SOC (investigator's choice paclitaxel, docetaxel, or irinotecan) and is well tolerated in participants with recurrent locally advanced or metastatic esophageal cancer with disease progression on or after one line of prior systemic therapy. The safety profile of participants treated with pembrolizumab in KEYNOTE-181 was consistent with the RSD with no new risks observed correlating to treatment with pembrolizumab (2.5, Sec. 5).

The FDA's Assessment:
The safety analysis of the data from KEYNOTE-181 reveals that the safety profile for patients treated with pembrolizumab from KEYNOTE-181 is generally consistent with the previously established safety profile of pembrolizumab monotherapy. No new safety risks were observed in KEYNOTE-181 and no new immune-mediated adverse reactions were identified from review of the results of this trial. The frequency of drug-related AEs leading to death was low and similar in both arms (1.6% in the pembrolizumab arm and 1.7% in the chemotherapy arm). Overall, SAEs observed in the pembrolizumab and chemotherapy arms in KEYNOTE-181 were generally consistent with known risks associated with pembrolizumab and chemotherapy treatment.

7.2.1. Safety Review Approach

The Applicant's Position:
The safety review is indication-specific and primarily focuses on the comparison of safety data from participants in the KEYNOTE-181 study who received pembrolizumab to safety data from participants who received SOC (investigator's choice of paclitaxel, docetaxel, or irinotecan). In addition, this document provides comparisons of safety data from KEYNOTE-181 (pembrolizumab arm) to the established safety profile for pembrolizumab monotherapy from the RSD. Pooled safety data for pembrolizumab in the indication population (including data from KEYNOTE-181 [pembrolizumab arm], and two additional studies that enrolled previously treated patients with esophageal cancer: a single-arm Phase 2 study KEYNOTE-180 and a cohort from the proof-of-concept Phase 1b study KEYNOTE-028 [Cohort A4, esophageal cancer participants]) are also included for context. Safety results are presented for the following four datasets:

1. *KEYNOTE-181 Dataset for Pembrolizumab* (N=314): Participants with advanced/metastatic esophageal cancer who have progressed on or after one previous line of standard therapy (2L) and who received at least one dose of pembrolizumab constitute the Indication Safety Dataset (hereafter, KEYNOTE-181 [pembrolizumab arm]).

2. *Esophageal Safety Dataset for Pembrolizumab* (N=458): All participants with advanced/metastatic esophageal cancer from KEYNOTE-181 (2L), KEYNOTE-180 (2 or more previous lines of therapy), and KEYNOTE-028 Cohort A4 (any line of therapy) who received at least one dose of pembrolizumab constitute the Esophageal Safety Dataset. This dataset is the most comprehensive safety pool for pembrolizumab in esophageal cancer.

3. *Reference Safety Dataset for Pembrolizumab* (N=2799): The 2799 participants from the RSD consist of 1567 participants with advanced melanoma from studies KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006, and 1232 participants with NSCLC from studies KEYNOTE-001 and KEYNOTE-010 who received at least 1 dose of pembrolizumab. This safety dataset is considered the established safety profile for pembrolizumab.

4. *Cumulative Running Safety Dataset for Pembrolizumab* (N=6784): Participants from KEYNOTE-181 (pembrolizumab arm), the RSD, KEYNOTE-180 and KEYNOTE-028 Cohort A4 (esophageal cancer), and participants treated with pembrolizumab in KEYNOTE-012 Cohort B and Cohort B2 (HNSCC), Cohort C (urothelial tract cancer), and Cohort D (gastric cancer), KEYNOTE-013 Cohort 3 (HL) and Cohort 4A (PMBCL), KEYNOTE-017 (Merkel cell cancer), KEYNOTE-024 (NSCLC), KEYNOTE-028 Cohort B4 (cervical cancer), KEYNOTE-040 (HNSCC), KEYNOTE-042 (NSCLC), KEYNOTE-045 and KEYNOTE-052 (urothelial tract cancer), KEYNOTE-054 (melanoma), KEYNOTE-055 (HNSCC), KEYNOTE-059 Cohort 1 (gastric cancer), 087 (HL), KEYNOTE-158 Cohort E (cervical cancer), KEYNOTE-164 Cohort A (colorectal cancer), and KEYNOTE-170 (PMBCL), and KEYNOTE-224 (hepatocellular cancer) constitute the Cumulative Running Safety Dataset (2.7.4, Sec 1.1).

The FDA's Assessment:

FDA provided concurrence with the pooling strategy for the four different ISS safety datasets at the January 25, 2019, pre-sBLA meeting. FDA's assessment of safety for the proposed indication relied mainly on the 314 patients who received pembrolizumab in KEYNOTE-181. The Esophageal Safety dataset of 458 patients with esophageal cancer who received pembrolizumab and the Reference Safety Dataset for Pembrolizumab (N=2799) were used for comparison purposes.

7.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

The number of participants exposed to pembrolizumab in KEYNOTE-181, the esophageal safety dataset, and the RSD is shown in [Table 19].

Safety analyses in KEYNOTE-181 were conducted using the ASaT Population (participants who received at least 1 dose of study intervention).

Table 19
Number of Participants in Esophageal and Pooled Safety Datasets

Study/pooled dataset	Study Title	Number of participants included in safety dataset
Indication Safety Dataset (N=314)		
KEYNOTE-181	A Phase III Randomized Open-Label Study of Single Agent Pembrolizumab vs. Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects with Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus that have Progressed after First-Line Standard Therapy (KEYNOTE-181)	Esophageal: 314
Esophageal Safety Dataset (N=458)		
KEYNOTE-181	A Phase III Randomized Open-Label Study of Single Agent Pembrolizumab vs. Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects with Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus that have Progressed after First-Line Standard Therapy (KN-181)	Esophageal: 314
KEYNOTE-180	A Phase 2 Study of Pembrolizumab Monotherapy in Third Line, Previously Treated Subjects with Advanced/Metastatic Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus or Advanced/Metastatic Siewert Type I Adenocarcinoma of the Esophagogastric Junction (KEYNOTE-180)	Esophageal: 121
KEYNOTE-028 (Cohort A4)	Phase IB Study of Pembrolizumab (MK-3475) in Subjects with Select Advanced Solid Tumors	Esophageal: 23
Reference Safety Dataset (N=2799)		
KEYNOTE-001	Phase 1 Study of Single Agent Pembrolizumab (MK-3475) in Patients With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma	Melanoma: 655 NSCLC: 550
KEYNOTE-002	Randomized, Phase 2 Study of Pembrolizumab (MK-3475) versus Chemotherapy in Patients with Advanced Melanoma (KEYNOTE-002)	Melanoma: 357
KEYNOTE-006	A Multicenter, Randomized, Controlled, Three-Arm, Phase 3 Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Patients with Advanced Melanoma	Melanoma: 555
KEYNOTE-010	A Phase 2/3 Randomized Trial of Two Doses of MK-3475 (SCH900475) Versus Docetaxel in Previously Treated Subjects With Non-Small Cell Lung Cancer	NSCLC: 682

In KEYNOTE-181, participants were enrolled from 08-DEC-2015 to 16-JUN-2017; and the LPLV (data cutoff for this analysis) was 15-OCT-2018. Duration of exposure was measured from the date of the first dose to the date of the last dose of study intervention received (2.7.4, Sec. 1.2).

At the data cutoff, 314 participants received at least one dose of pembrolizumab; a total of 296 participants received SOC. Five participants in the pembrolizumab arm completed the full 35 cycles of treatment (2.7.4, Sec. 1.2.1).

The mean duration of exposure was longer in the pembrolizumab arm compared with the SOC arm (4.0 months vs. 3.1 months); however, the median duration of exposure was similar (2.1 months vs. 2.0 months). By the end of the study, more participants had remained on pembrolizumab for longer than 12 months (6.7% for ≥12 months) compared with SOC (2.4% for ≥12 months), as shown in Table 20.

Table 20
Exposure by Duration in KEYNOTE-181 (ASaT Population)

	Pembrolizumab 200 mg (N=314)		SOC (N=296)	
	n	(%)	n	(%)
Duration of Exposure				
>0 m	314	(100.0)	296	(100.0)
≥ 1 m	243	(77.4)	230	(77.7)
≥ 3 m	122	(38.9)	118	(39.9)
≥ 6 m	57	(18.2)	41	(13.9)
≥ 12 m	21	(6.7)	7	(2.4)
Each subject is counted once on each applicable duration category row. Duration of exposure is the time from the first dose date to the last dose date. Database Cutoff Date: 15OCT2018.				

Source: (2.7.4, Table 3)

The mean exposure to pembrolizumab was shorter for participants in KEYNOTE-181 (pembrolizumab arm) compared with those within the RSD (4.0 months vs. 6.5 months); the median duration of exposure in the KEYNOTE-181 (pembrolizumab arm) was also shorter compared with the RSD (2.0 months vs. 4.0 months). The proportions of participants who remained on pembrolizumab for ≥6 months and ≥12 months in KEYNOTE-181 were lower than that in the RSD (≥6 months: 18.2% vs. 41.2%; ≥12 months: 6.7% vs. 21.4%). The observed differences in exposure to pembrolizumab are likely associated with the poorer prognosis of participants with previously treated esophageal cancer in KEYNOTE-181 compared with participants in the RSD, which is supported by a higher proportion of participants with ECOG PS 1 in KEYNOTE-181 when compared with the RSD (2.7.4, Sec. 1.2.2, and 1.3.2).

In the Esophageal Safety Dataset, a total of 458 participants received at least one dose of pembrolizumab. The mean exposure for these participants was 4.1 months and was consistent with that in KEYNOTE-181 (pembrolizumab arm) (2.7.4, Sec. 1.2.2).

The FDA's Assessment:
FDA agrees with Merck's exposure analysis for patients enrolled in Study KEYNOTE-181 as shown in Table 19. FDA agrees with Merck's assessment that the shorter duration of exposure of patients in KEYNOTE-181 compared to the RSD for pembrolizumab may be due to the shorter survival in patients undergoing second line treatment for advanced esophageal cancer.

Relevant characteristics of the safety population:

The Applicant's Position:
In KEYNOTE-181, the demographics and baseline characteristics of the ITT population were similar between treatment arms and were representative of participants with advanced/metastatic esophageal cancer who receive previous chemotherapy, as shown in [Table 12].

Compared with the RSD, KEYNOTE-181 (pembrolizumab arm) had a higher proportion of male participants (86.9% in KEYNOTE-181 vs. 59.3% in the RSD), a higher proportion of participants with ECOG PS 1 (59.6% vs. 48.1%), a higher proportion of Asian participants (40.1% vs. 8.3%), and a lower proportion of White/Caucasian participants (57.0% vs. 88.4%). These findings are consistent with the known epidemiology of esophageal cancer (2.7.4. Sec 1.3).

The FDA's Assessment:
FDA agrees with Merck's analysis of demographics of the safety population in Study KEYNOTE-181 as shown in Table 12. As can be seen from the table, in general, there were no major imbalances that are unexplained regarding exposure to pembrolizumab in Study KEYNOTE-181 and the demographics of study KEYNOTE-181 is representative of the advanced esophageal cancer population.

Adequacy of the safety database:

The Applicant's Position:
The clinical safety data supporting this sBLA is primarily derived from KEYNOTE-181. Safety data from other esophageal cancer studies and the entire clinical program are also referenced where appropriate. The safety database is of an adequate size, considering exposure to appropriate dose, duration treatment, patient demographics, and disease characteristics with reference to a US target population.

The FDA's Assessment:
The safety profile of pembrolizumab is well established, with a total exposure of more than 6784 patients in clinical trials and more patients in the postmarketing setting. The size of the safety database for KEYNOTE-181 supported by supplemental data from KEYNOTE-180 and KEYNOTE-028 is adequate to support the benefit-risk assessment for the proposed indication in

advanced esophageal cancer.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
Data quality assurance included QA and QC oversight activities implemented at the investigation site and centrally by the Sponsor in accordance with ICH GCP 5.1 (KEYNOTE-181 CSR, Sec. 9.6). Sponsor QA carried out periodic, independent audits to ensure the accuracy and integrity of the clinical study data (KEYNOTE-181 CSR, Sec. 16.1.8). There were no issues with data integrity or analysis that precluded the inclusion of data in the safety analysis.

The sBLA submission contains all required components of the eCTD. The overall quality and integrity of the application is sufficient for substantive review to be completed.

The FDA's Assessment:
Overall, FDA agrees that there were no significant data quality or reporting issues identified during the review of this supplemental BLA (aside from the data error relating to censoring of two patients who had died prior to the data cutoff date that affected the efficacy analysis for OS, as described in the Data Quality and Integrity subsection of Section 7.1.2 of this review). However, FDA issued several information requests during the review cycle to obtain clarification and additional information regarding safety data included in the sBLA.

Categorization of Adverse Event

The Applicant's Position:
Non-serious adverse events up to 30 days after the last dose treatment intervention and serious adverse events within the 90-day follow-up in KEYNOTE-181 are shown in [Table 21].

Pembrolizumab's markedly improved safety profile relative to SOC is demonstrated by substantially less frequent drug-related Grade 3 to 5 AEs and by lower frequencies of most other categories of AEs in the pembrolizumab arm compared with the SOC arm. Drug-related AEs, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, and drug-related SAEs were reported less frequently in the pembrolizumab arm compared with the SOC arm, indicating that pembrolizumab was associated with a lower incidence of serious and life-threatening toxicity compared with SOC.

Table 21
Adverse Event Summary (ASaT Population) for KEYNOTE-181

	Pembrolizumab 200 mg		SOC	
	n	(%)	n	(%)
Subjects in population	314		296	
with one or more adverse events	300	(95.5)	288	(97.3)
with no adverse event	14	(4.5)	8	(2.7)
with drug-related[†] adverse events	202	(64.3)	255	(86.1)
with toxicity grade 3-5 adverse events	170	(54.1)	183	(61.8)
with toxicity grade 3-5 drug-related adverse events	57	(18.2)	121	(40.9)
with serious adverse events	124	(39.5)	121	(40.9)
with serious drug-related adverse events	40	(12.7)	57	(19.3)
who died	30	(9.6)	32	(10.8)
who died due to a drug-related adverse event	5	(1.6)	5	(1.7)
discontinued drug due to an adverse event	40	(12.7)	42	(14.2)
discontinued drug due to a drug-related adverse event	19	(6.1)	19	(6.4)
discontinued drug due to a serious adverse event	35	(11.1)	30	(10.1)
discontinued drug due to a serious drug-related adverse event	15	(4.8)	10	(3.4)

[†] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
Database Cutoff Date: 15OCT2018.

Source: (2.7.4, Table 8)

The FDA's Assessment:

FDA agrees with Merck's analysis of adverse events as shown in Table 21, but notes that the trial was not designed to prospectively compare the safety of pembrolizumab with the safety of the control arm therapies. MedDRA version 21.0 was used for coding of adverse events. The definitions of AEs and SAEs provided in the protocol were appropriate. Review of verbatim terms in the adverse event dataset to determine whether MedDRA preferred terms were appropriately coded revealed no apparent instances of grossly inaccurate coding. Based on the known safety profile of pembrolizumab, Merck also designated certain adverse events as Adverse Events of Special Interest (AEOSI) and developed a pre-specified list of PTs to characterize the nature and frequency of each AEOSI across the clinical program, regardless of causality as reported by investigators. This list was also submitted by Merck and the list is acceptable and similar to those used in prior pembrolizumab supplements.

Routine Clinical Tests

The Applicant's Position:
The schedule of assessment in the KEYNOTE-181 study, as outlined in the protocol, is shown above in [Table 5]. It presents the frequency of laboratory testing, vital signs, physical exam, and AE monitoring.

The FDA's Assessment:
AEs were monitored throughout the study and graded in severity according to National Cancer Institute CTCAE version 4.0. After the end of study intervention, each participant was followed for 30 days for AE monitoring. SAEs were collected for 90 days after the end of study intervention or 30 days after the end of study intervention if the participant initiated new anticancer therapy, whichever was earlier. FDA agrees that the schedule of assessments in KEYNOTE-181 was adequate to monitor and assess the safety of pembrolizumab in patients with esophageal cancer.

7.2.4. Safety Results

Deaths

The Applicant's Position:
The overall incidence of AEs leading to death was similar between the pembrolizumab arm and SOC arm (9.6% vs 10.8%). The frequency of drug-related AEs leading to death was low and also similar in both arms (1.6% in the pembrolizumab arm and 1.7% in the SOC arm). The fatal AEs reported were consistent with the known safety profiles of pembrolizumab and chemotherapy (2.7.4, Sec. 2.1.1.3). Five fatal AEs in KEYNOTE-181 (pembrolizumab arm) were considered drug-related by the investigator: pneumonitis (two participants), death, myocarditis, and esophageal hemorrhage (one participant each). The PT "death" was reported in situations where limited information on the cause of death was available, or where the investigator could not assign a specific AE term in a participant with comorbidities and confounding factors that led to death. Apart from death, for the remaining cases, these were either known AEOSIs associated with pembrolizumab or their causality to pembrolizumab was confounded by the underlying disease (2.7.4, Sec. 2.1.2.3).

The proportion of participants who experienced an AE leading to death in KEYNOTE-181 (pembrolizumab arm, 9.6%) was higher than that observed in the RSD (3.9%). However, the incidence of drug-related deaths in the KEYNOTE-181 (pembrolizumab arm) was low and consistent with that in the RSD (1.6% vs 0.4%). No new safety signals were identified upon review of these events. The observed higher incidence of participants with AEs leading to death is likely associated with differences in prognosis of participants with previously treated esophageal cancer compared with the participants in the RSD (evidenced by a higher proportion of participants with ECOG PS 1 in KEYNOTE-181 and the esophageal dataset versus the RSD) and does not represent a new safety signal (2.5, Sec. 5.4) (2.7.4, Sec. 2.1.2.3)

The FDA's Assessment:

FDA reviewed all available death narratives of the patients in KEYNOTE-181 as of the data cutoff date of 15 October 2018. FDA agrees with Merck's assessment of patient deaths, as described above and summarized in Table 21. The number of patients reported to have an AE leading to death was similar in both arms of study KEYNOTE-181 (9.6% vs 10.8% in the pembrolizumab and control arms, respectively). The most common PT's for fatal AE related to pembrolizumab include death from unknown cause (1.6%), esophageal hemorrhage (1.3%), aspiration pneumonia (1.3%), pneumonia (1%), completed suicide (0.6%), gastrointestinal hemorrhage (0.6%), and pneumonitis (0.6%). In general, fatal AEs were rare and a few events such as pneumonitis and pneumonia were likely to be related to pembrolizumab, although underlying disease may also be implicated for some events. This reviewer also reviewed the narratives for patients whose cause of death was unknown and agrees with the investigator assessment that cause of death could not be ascertained. The difference between the incidence of fatal AEs on the pembrolizumab arm on Study KEYNOTE-181 and the RSD may be due to the poor prognosis and complicated disease course that is typically associated with multiple co-morbidities in patients with esophageal cancer who have previously received one prior line of systemic chemotherapy.

Serious Adverse Events

The Applicant's Position:

The overall incidence of SAEs was similar in the two treatment arms (39.5% in the pembrolizumab arm and 40.9% in the SOC arm). Of the commonly reported SAEs (≥1% incidence in either arm), febrile neutropenia and pneumonia were reported with a ≥2% lower frequency in the pembrolizumab arm relative to the SOC arm. When the frequency of SAEs of pneumonia were combined with that of aspiration pneumonia (8.0% vs 8.4%), no clinically meaningful differences were noted between treatment arms. Febrile neutropenia is a known AE associated with SOC chemotherapy (2.7.4, Sec. 2.1.1.4.1).

Dysphagia (3.5% vs 0.3%) and pneumonitis (2.2% vs. 0.0%) were reported with a ≥2% higher frequency in pembrolizumab arm relative to SOC arm. Most dysphagia events were low grade, and the incidence of Grade 3 to 5 events was similar between treatment arms. Furthermore, most participants (10 of 11) with dysphagia SAEs in the pembrolizumab arm experienced events that were not drug-related. Pneumonitis is a known AEOSI associated with pembrolizumab (2.7.4, Sec. 2.1.1.4.1).

The overall incidence of drug-related SAEs was lower in the pembrolizumab arm than in the SOC arm (12.7% vs. 19.3%). Of the commonly reported drug-related SAEs (≥1% incidence in either arm), febrile neutropenia (0.0% in the pembrolizumab arm vs. 7.1% in the SOC arm) was reported with a ≥2% lower frequency in the pembrolizumab arm relative to the SOC arm, whereas pneumonitis (2.2% vs. 0.0%) was reported with a ≥2% higher frequency in the pembrolizumab arm relative to the SOC arm. These are expected findings; febrile neutropenia and pneumonitis are known AEs associated with SOC and pembrolizumab, respectively (2.7.4,

Sec. 2.1.1.4.2). The lower incidence of drug-related SAEs indicates a notably improved safety profile for pembrolizumab versus SOC.

The proportion of participants in KEYNOTE-181 (pembrolizumab arm) who experienced at least one SAE was consistent with that observed in the RSD. Of the most frequently reported (≥1% incidence in any dataset) SAEs in the KEYNOTE-181 (pembrolizumab arm), dysphagia and pneumonia aspiration were reported with a ≥2% higher incidence in KEYNOTE-181 (pembrolizumab arm) compared with the RSD. Based on medical review, these events are likely related to the underlying disease. Patients with esophageal cancer often experience swallowing disorders related to esophageal obstruction and dysfunction. Swallowing disorders are a major predisposing condition for aspiration that can result in pneumonia. (2.7.4, Sec. 2.1.2.4.1).

The proportion of participants in KEYNOTE-181 (pembrolizumab arm) who experienced at least one drug-related SAE was also consistent with that of the RSD; there were no new safety signals for pembrolizumab. The most common drug-related SAE (≥1% incidence in any dataset) in KEYNOTE-181 (pembrolizumab arm) was pneumonitis, which occurred at a similar frequency to the RSD (2.7.4, Sec. 2.1.2.4.2).

The FDA's Assessment:

FDA agrees with Merck's analysis of SAEs. The most frequently reported SAEs (≥2% incidence) in patients receiving pembrolizumab included pneumonia (4.5%), dysphagia (3.5%), pneumonia aspiration (3.5%), and pneumonitis (2.2%). The SAEs reported in the chemotherapy arm were consistent with those expected of the chemotherapy agent received, such as febrile neutropenia, pneumonia, pyrexia, diarrhea, vomiting, anemia and nausea. The most frequently reported drug-related (as determined by the investigator) SAEs (≥1% incidence) reported for patients receiving pembrolizumab included pneumonitis (2.2%), autoimmune hepatitis (1%), colitis (1%). No new drug related SAEs were observed on the pembrolizumab arm.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

In KEYNOTE-181, similar proportions of participants discontinued treatment because of an AE in the pembrolizumab and SOC arms. The incidence of drug-related AEs leading to treatment discontinuation were also similar between treatment arms (6.1% in the pembrolizumab arm and 6.4% in the SOC arm). The frequencies of all commonly reported AEs and drug-related AEs leading to treatment discontinuation were similar in both arms (2.7.4, Sec. 2.1.1.5.1).

The proportion of participants who experienced AEs leading to treatment discontinuation in KEYNOTE-181 (pembrolizumab arm) was consistent with that observed in the RSD; there were no new safety signals for pembrolizumab. The incidence of drug-related AEs leading to treatment discontinuation was low and similar to the RSD. (2.7.4, Sec. 2.1.2.5.1).

The FDA's Assessment:
FDA agrees with Merck's analysis of AEs that led to study drug discontinuation. The most common AEs that led to treatment discontinuation were autoimmune hepatitis (1.6%) followed by esophageal hemorrhage (1.3%), pneumonia (1%) and pneumonitis (1%).

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:
In KEYNOTE-181, the overall incidence of AEs leading to treatment interruption in the pembrolizumab arm (26.8%) was lower than that in the SOC arm (37.5%). Of the commonly reported AEs in this category (≥2% incidence in either arm), neutrophil count decreased, WBC count decreased, neutropenia, febrile neutropenia, anemia, and fatigue were reported with a ≥2% lower frequency in the pembrolizumab arm relative to the SOC arm, whereas AST increased was reported with a ≥2% higher frequency in the pembrolizumab arm relative to the SOC arm. The higher incidence of AST increase is not considered clinically meaningful, considering most events (9 of 10 events) were low-grade AEs (Grade 2). Only one Grade 2 event was associated with AEs of increased ALT and immune-mediated hepatitis; however, these AEs resolved by the time of the data cutoff. The incidence of drug-related AEs leading to treatment interruption in the pembrolizumab arm (12.1%) was also lower than that in the SOC arm (25.3%). In regard to commonly reported drug-related AEs, the findings were similar to those in AEs leading to treatment interruption, in which most AEs in the pembrolizumab arm were not considered clinically meaningful (low grade and resolved by the time of data cutoff) (2.7.4, Sec. 2.1.1.5.2).

The proportion of participants who experienced AEs and drug-related AEs leading to treatment interruption in KEYNOTE-181 (pembrolizumab arm) was consistent with that in the RSD; there were no new safety signals for pembrolizumab. The most common AE leading to treatment interruption (≥2% incidence in any dataset) in KEYNOTE-181 (pembrolizumab arm) was increased AST. Of the most frequently reported (≥2% incidence in any dataset) drug-related AEs leading to treatment interruption in KEYNOTE-181 (pembrolizumab arm), none of the events were reported with a ≥2% higher incidence compared with the RSD (2.7.4, Sec. 2.1.2.5.2).

The FDA's Assessment:
In general, the number of patients who had treatment interrupted due to an AE was low in both arms and lower on the pembrolizumab arm compared to the chemotherapy arm. The flat dose of pembrolizumab appears to be reasonably well tolerated in the esophageal cancer population in KEYNOTE-181.

Significant Adverse Events

The Applicant's Position:
Adverse events of special interest are immune-mediated events and infusion-related reactions

known to be associated with pembrolizumab. In KEYNOTE-181, the overall incidence of AEOSIs was higher in the pembrolizumab arm (23.2%) compared with the SOC arm (7.4%). Most participants with AEOSIs in the pembrolizumab arm reported low-grade events. Serious AEOSIs were relatively infrequent. Incidences of hypothyroidism, thyroiditis, and hyperthyroidism events were higher in the pembrolizumab arm versus the SOC arm, which is consistent with the known safety profile of pembrolizumab (2.7.4, Sec. 2.1.1.5.3).

The proportion of participants who experienced at least one AEOSI in KEYNOTE-181 (pembrolizumab arm) was consistent with that in the RSD. The incidence of the most commonly reported AEOSIs by category (≥2% incidence in either arm) in KEYNOTE-181 (pembrolizumab arm) was generally similar to that observed in the RSD; none occurred at a ≥5% higher incidence compared with the RSD. Of note, AEOSIs of immune-mediated hepatitis were more frequently reported in KEYNOTE-181 (pembrolizumab arm) compared with the RSD (2.2% vs. 0.7%). Seven immune-mediated hepatitis events occurred in seven participants treated with pembrolizumab, none occurred in the SOC arm. Three of the seven events were considered serious and drug-related. Medical review of the seven events identified three events that resolved 21, 25, and 127 days after the initiation of steroids; these events were consistent with immune-mediated hepatitis. The remaining four events were confounded by disease progression resulting in death (2.7.4, Sec. 2.1.2.5.3).

The FDA's Assessment:

In general, FDA agrees with Merck's analysis of AEOSI. The most common AEOSI categories in the pembrolizumab arm were hypothyroidism (11.8%), hyperthyroidism (4.1%), pneumonitis (4.8%), and hepatitis (2.2%) (Table 22). No new AEOSI were identified based upon review of data from KEYNOTE-181.

Table 22
Incidence of AEOSI in KEYNOTE-181

AEOSI/Preferred Term	*Pembrolizumab*		*Chemotherapy*	
	N	*%*	*N*	*%*
Colitis	3	1	2	0.7
Colitis	3	1	1	0.3
Enterocolitis	0	0	1	0.3
Guillain-Barre Syndrome	1	0.3	0	0
Guillain-Barre Syndrome	1	0.3	0	0
Hepatitis	7	2.2	0	0
Autoimmune hepatitis	6	1.9	0	0
Immune-mediated hepatitis	1	0.3	0	0
Hyperthyroidism	13	4.1	2	0.7
Hyperthyroidism	13	4.1	2	0.7
Hypophysitis	1	0.3	0	0
Hypophysitis	1	0.3	0	0
Hypothyroidism	37	11.8	7	2.4

Hypothyroidism	36	11.5	7	2.4
Myxedema	1	0.3	0	0
Infusion Reactions	3	1.0	8	2.7
Hypersensitivity	0	0	4	1.4
Infusion Related reaction	3	1.0	4	1.4
Myocarditis	1	0.3	0	0
Myocarditis	1	0.3	0	0
Myositis	2	0.6	0	0
Myositis	1	0.3	0	0
Polymyositis	1	0.3	0	0
Nephritis	2	0.6	0	0
Nephritis	1	0.3	0	0
Nephrotic syndrome	1	0.3	0	0
Pneumonitis	15	4.8	2	0.7
Interstitial lung disease	2	0.6	1	0.3
Pneumonitis	13	4.1	1	0.3
Severe skin reactions	2	0.6	1	0.3
Dermatitis bullous	0	0	1	0.3
Erythema multiforme	1	0.3	0	0
Rash	1	0.3	0	0
Thyroiditis	1	0.3	0	0
Thyroiditis	1	0.3	0	0
Type 1 Diabetes mellitus	1	0.3	0	0
Type 1 Diabetes mellitus	1	0.3	0	0

Source: FDA reviewer's analysis, Datasets: ADAE, MAED

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Pembrolizumab's markedly improved safety profile relative to SOC is demonstrated by substantially less frequent drug-related Grade 3 to 5 AEs and by lower frequencies of most other categories of AEs in the pembrolizumab arm compared with the SOC arm. Drug-related AEs, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, and drug-related SAEs were reported less frequently in the pembrolizumab arm compared with the SOC arm, indicating that pembrolizumab was associated with a lower incidence of serious and life-threatening toxicity compared with SOC. The safety profile showed no new safety signals for pembrolizumab and is generally consistent with the established safety profile of pembrolizumab (RSD)Table 22.

A comparison of the most frequently reported AEs (sorted by decreasing incidence in the pembrolizumab arm) showed that participants treated with pembrolizumab experienced fewer AEs (≥5% lower incidence) of alopecia, decreased WBC count, decreased neutrophil count, neutropenia, anemia, peripheral sensory neuropathy, diarrhea, nausea, fatigue, vomiting, and

pyrexia compared with those treated with SOC. These events are known to be associated with cytotoxic chemotherapies used as SOC (2.7.4, Sec. 2.1.1.2.1).

AEs reported with a ≥5% higher incidence in the pembrolizumab arm compared with the SOC arm were hypothyroidism and dysphagia. Hypothyroidism is a known AEOSI associated with pembrolizumab. Dysphagia is likely related to the underlying disease, and the higher observed incidence of dysphagia in the pembrolizumab arm is not considered clinically meaningful as most participants experienced events that were low-grade (Grade 1-2) and not drug-related (2.7.4, Sec. 2.1.1.2.1).

The FDA's Assessment:

FDA notes that the comparison of the incidences of adverse events between the pembrolizumab and chemotherapy control arm is exploratory, as such comparisons were not pre-specified and the trial was not powered to show a statistically significant difference in AEs between the treatment arms. In general, the most common adverse events reported in the pembrolizumab and chemotherapy arms were consistent with the known safety profile of the individual drugs. The most frequently reported (≥5% incidence) pembrolizumab-related AEs (as determined by the investigator) were fatigue, hypothyroidism, decreased appetite, asthenia, nausea, and diarrhea. The most common adverse events related to chemotherapy were alopecia, anemia, nausea, fatigue, diarrhea, neutrophil count decreased, white blood cell count decreased, decreased appetite, peripheral sensory neuropathy, asthenia, vomiting, and neutropenia. More Grade 3-5 treatment-emergent adverse events occurred in the chemotherapy arm than the pembrolizumab arm (62% vs. 54%). The most frequently reported Grade 3 to 5 AEs related to pembrolizumab in the opinion of the investigator were autoimmune hepatitis (1.6%), asthenia (1.3%), and anemia (1.3%). The most frequently reported Grade 3 to 5 drug-related AEs (as determined by the investigator) in the chemotherapy arm were white blood cell count decreased (10.1%) and neutrophil count decreased (9.8%).

Table 23
Treatment-Emergent Adverse Events (TEAE) Occurring in ≥ 5% of the Safety Population In Any Arm, KEYNOTE-181

TEAE	3475-181 MK-3475 200 mg Q3W Grade 1-5 N = 314		3475-181 SOC Grade 1-5 N = 296		Esophageal Safety Set Grade 1-5 N = 458		Reference Safety Dataset Grade 1-5 N = 2799	
	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4
Any TEAE	303 (96)	122 (39)	290 (98)	131 (44)	441 (96)	180 (39)	2727 (97)	1163 (42)
Blood and Lymphatic System Disorders	59 (19)	23 (7)	123 (42)	72 (24)	87 (19)	37 (8)	487 (17)	122 (4)
Anemia	53 (17)	19 (6)	85 (29)	31 (10)	77 (17)	31 (7)	347 (12)	89 (3)
Febrile neutropenia	1 (0.3)	1 (0.3)	26 (8.8)	26 (8.8)	1 (0.2)	1 (0.2)	2 (0.1)	2 (0.1)
Neutropenia	0 (0)	0 (0)	39 (13)	26 (9)	0 (0)	0 (0)	17 (0.6)	5 (0.2)
Endocrine Disorders	48 (15)	3 (1)	10 (3)	0 (0)	69 (15)	7 (1)	335 (12)	26 (0.9)
Hypothyroidism	36 (11)	0 (0)	7 (2)	0 (0)	49 (11)	0 (0)	236 (8)	3 (0.1)
Gastrointestinal Disorders	210 (66.9)	50 (15.9)	206 (69.6)	48 (16.2)	293 (64)	69 (15.1)	1704 (60.9)	227 (8.1)
Nausea	60 (19)	3 (1)	84 (28)	9 (3)	87 (19)	5 (1.1)	685 (24)	33 (1)
Constipation	57 (18)	3 (1)	56 (19)	1 (0.3)	85 (19)	4 (0.9)	497 (18)	12 (0.4)
Dysphagia	49 (16)	15 (5)	28 (9)	8 (3)	60 (13)	20 (4)	59 (2)	7 (0.3)
Diarrhea	39 (12)	3 (1)	83 (28)	9 (3)	61 (13)	4 (0.9)	625 (22)	36 (1)
Vomiting	39 (12)	5 (2)	55 (19)	9 (3)	61 (13)	6 (1)	387 (14)	32 (1)
Abdominal pain	37 (12)	6 (2)	29 (10)	4 (1)	48 (10)	7 (1)	274 (10)	27 (1)
Abdominal pain upper	14 (4)	3 (1)	17 (6)	1 (0.3)	22 (5)	3 (0.7)	115 (4)	4 (0.1)
Dry mouth	9 (3)	0 (0)	7 (2)	0 (0)	17 (4)	0 (0)	142 (5)	1 (0)

TEAE	3475-181 MK-3475 200 mg Q3W Grade 1-5 N = 314		3475-181 SOC Grade 1-5 N = 296		Esophageal Safety Set Grade 1-5 N = 458		Reference Safety Dataset Grade 1-5 N = 2799	
	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4
Stomatitis	9 (3)	0 (0)	28 (9)	0 (0)	10 (2)	0 (0)	59 (2)	1 (0)
General Disorders and Administration Site Conditions	167 (53)	17 (5)	198 (67)	15 (5)	239 (52)	30 (7)	1856 (66)	192 (7)
Fatigue	70 (22)	5 (2)	89 (30)	6 (2)	110 (24)	9 (2)	1044 (37)	69 (2)
Asthenia	45 (14)	8 (2)	43 (14)	6 (2)	55 (12)	10 (2)	362 (13)	34 (1)
Pyrexia	33 (10)	1 (0.3)	50 (17)	0 (0)	45 (10)	2 (0.4)	357 (13)	13 (0.5)
Edema peripheral	19 (6)	1 (0.3)	19 (6)	0 (0)	31 (7)	1 (0.2)	286 (10)	11 (0.4)
Malaise	15 (5)	0 (0)	19 (6)	0 (0)	22 (5)	2 (0.4)	47 (2)	4 (0.1)
Chest pain	10 (3)	2 (0.6)	13 (4)	1 (0.3)	15 (3)	3 (0.7)	166 (6)	13 (0.5)
Chills	1 (0.3)	0 (0)	5 (2)	0 (0)	3 (0.7)	0 (0)	153 (5)	0 (0)
Infections and Infestations	107 (34)	33 (10)	118 (40)	43 (14)	158 (34)	50 (11)	1182 (42)	207 (7)
Pneumonia	22 (7)	11 (3)	26 (9)	14 (5)	40 (9)	23 (5)	140 (5)	65 (2)
Upper respiratory tract infection	12 (4)	0 (0)	14 (5)	1 (0.3)	19 (4)	0 (0)	182 (6)	3 (0.1)
Urinary tract infection	8 (2)	3 (1)	6 (2)	1 (0.3)	11 (2)	4 (0.9)	162 (6)	14 (0.5)
Nasopharyngitis	8 (2)	0 (0)	9 (3)	0 (0)	15 (3)	0 (0)	182 (6)	0 (0)
Lung infection	4 (1)	1 (0.3)	7 (2)	3 (1)	10 (2)	4 (0.9)	45 (2)	8 (0.3)
Investigations	114 (36)	30 (10)	134 (45)	50 (17)	163 (36)	45 (10)	865 (31)	129 (5)
Weight decreased	40 (13)	6 (2)	34 (11)	0 (0)	49 (11)	6 (1)	219 (8)	8 (0.3)
Aspartate aminotransferase increased	26 (8)	5 (2)	14 (5)	1 (0.3)	39 (8)	8 (2)	168 (6)	24 (0.9)

TEAE	3475-181 MK-3475 200 mg Q3W Grade 1-5 N = 314		3475-181 SOC Grade 1-5 N = 296		Esophageal Safety Set Grade 1-5 N = 458		Reference Safety Dataset Grade 1-5 N = 2799	
	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4
Alanine aminotransferase increased	22 (7)	3 (1)	9 (3)	0 (0)	34 (7)	8 (1.7)	172 (6)	25 (0.9)
Blood alkaline phosphatase increased	14 (4)	5 (2)	14 (5)	1 (0.3)	25 (5)	7 (1)	112 (4)	16 (0.6)
Blood bilirubin increased	7 (2)	2 (0.6)	3 (1)	1 (0.3)	16 (3)	6 (1)	51 (2)	14 (0.5)
Neutrophil count decreased	3 (1)	2 (0.6)	52 (18)	29 (10)	4 (0.9)	2 (0.4)	21 (0.8)	3 (0.1)
White blood cell count decreased	2 (0.6)	1 (0.3)	53 (18)	30 (10)	4 (0.9)	1 (0.2)	28 (1)	2 (0.1)
Metabolism and Nutrition Disorders	142 (45)	35 (11)	131 (44)	36 (12.2)	203 (44)	58 (13)	1109 (40)	232 (8)
Decreased appetite	78 (25)	9 (3)	76 (26)	7 (2)	109 (24)	15 (3)	630 (22)	26 (0.9)
Hyponatremia	19 (6)	8 (2)	19 (6)	9 (3)	26 (6)	11 (2)	146 (5)	62 (2)
Hyperglycemia	18 (6)	3 (1)	15 (5)	4 (1)	22 (5)	5 (1)	130 (5)	29 (1)
Hypoalbuminemia	17 (5)	0 (0)	15 (5)	5 (2)	20 (4)	0 (0)	89 (3)	15 (0.5)
Dehydration	17 (5)	4 (1)	14 (5)	1 (0.3)	26 (6)	7 (1)	106 (4)	28 (1)
Hypokalemia	16 (5)	1 (0.3)	28 (9)	9 (3)	25 (5)	4 (0.9)	124 (4)	25 (0.9)
Musculoskeletal and Connective Tissue Disorders	85 (27)	11 (3)	85 (29)	7 (2)	125 (27)	18 (4)	1411 (50)	126 (4)
Back pain	37 (12)	5 (2)	24 (8)	1 (0.3)	50 (11)	9 (2)	349 (12)	38 (1)
Arthralgia	19 (6)	2 (0.6)	16 (5)	1 (0.3)	24 (5)	3 (0.7)	504 (18)	17 (0.6)
Musculoskeletal pain	9 (3)	1 (0.3)	6 (2)	0 (0)	17 (4)	1 (0.2)	226 (8)	16 (0.6)
Pain in extremity	8 (2)	0 (0)	8 (3)	0 (0)	13 (3)	1 (0.2)	237 (8)	12 (0.4)

TEAE	3475-181 MK-3475 200 mg Q3W Grade 1-5 N = 314		3475-181 SOC Grade 1-5 N = 296		Esophageal Safety Set Grade 1-5 N = 458		Reference Safety Dataset Grade 1-5 N = 2799	
	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4
Myalgia	8 (2)	0 (0)	25 (8)	1 (0.3)	18 (4)	1 (0.2)	253 (9)	8 (0.3)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	75 (24)	13 (4)	39 (13)	2 (0.7)	108 (24)	22 (5)	256 (9)	75 (3)
Malignant neoplasm progression	56 (18)	9 (3)	31 (10)	1 (0.3)	80 (17)	17 (4)	1 (0)	1 (0)
Nervous System Disorders	63 (20)	13 (4)	125 (42)	15 (5)	97 (21)	17 (4)	1037 (37)	103 (4)
Headache	15 (5)	2 (0.6)	11 (4)	1 (0.3)	23 (5)	2 (0.4)	400 (14)	13 (0.5)
Dizziness	7 (2)	0 (0)	9 (3)	1 (0.3)	11 (2)	0 (0)	244 (9)	7 (0.3)
Neuropathy peripheral	6 (2)	0 (0)	26 (9)	4 (1)	13 (3)	1 (0.2)	76 (3)	2 (0.1)
Dysgeusia	6 (2)	0 (0)	17 (6)	0 (0)	11 (2)	0 (0)	69 (2)	0 (0)
Peripheral sensory neuropathy	3 (1)	0 (0)	52 (18)	1 (0.3)	3 (0.7)	0 (0)	29 (1)	0 (0)
Pneumonitis (GT)	15 (5)	1 (0.3)	2 (0.7)	1 (0.3)	24 (5)	3 (0.7)	94 (3)	32 (1)
Pneumonitis	13 (4)	1 (0.3)	1 (0.3)	0 (0)	21 (5)	3 (0.7)	87 (3)	31 (1)
Interstitial lung disease	2 (0.6)	0 (0)	1 (0.3)	1 (0.3)	3 (0.7)	0 (0)	7 (0.3)	1 (0)
Psychiatric Disorders	40 (13)	2 (0.6)	39 (13)	2 (0.7)	68 (15)	6 (1)	523 (19)	24 (0.9)
Insomnia	25 (8)	0 (0)	16 (5)	0 (0)	36 (8)	0 (0)	218 (8)	2 (0.1)
Anxiety	12 (4)	0 (0)	7 (2)	0 (0)	21 (5)	1 (0.2)	141 (5)	5 (0.2)
Delirium	2 (0.6)	1 (0.3)	0 (0)	0 (0)	9 (2)	4 (0.9)	11 (0.4)	1 (0)
Renal and Urinary Disorders	19 (6)	2 (0.6)	15 (5)	3 (1)	34 (7)	7 (1)	272 (10)	36 (1)
Acute kidney injury	4 (1.3)	2 (0.6)	3 (1)	2 (0.7)	12 (2.6)	6 (1.3)	40 (1.4)	15 (0.5)

TEAE	3475-181 MK-3475 200 mg Q3W Grade 1-5 N = 314		3475-181 SOC Grade 1-5 N = 296		Esophageal Safety Set Grade 1-5 N = 458		Reference Safety Dataset Grade 1-5 N = 2799	
	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4	Grades 1-5	Grades 3-4
Respiratory, Thoracic and Mediastinal Disorders	117 (37)	26 (8)	95 (32)	16 (5)	181 (40)	37 (8)	1392 (50)	224 (8)
Cough	40 (13)	1 (0.3)	30 (10)	0 (0)	65 (14)	1 (0.2)	615 (22)	6 (0.2)
Dyspnea	31 (10)	4 (1)	17 (6)	1 (0.3)	48 (10)	5 (1)	534 (19)	76 (3)
Pneumonitis	13 (4)	1 (0.3)	1 (0.3)	0 (0)	21 (5)	3 (0.7)	87 (3)	31 (1)
Pneumonia aspiration	12 (4)	6 (2)	8 (3)	5 (2)	18 (4)	10 (2)	6 (0.2)	2 (0.1)
Productive cough	11 (3)	0 (0)	14 (5)	2 (0.7)	17 (4)	0 (0)	142 (5)	2 (0.1)
Oropharyngeal pain	7 (2)	0 (0)	5 (2)	0 (0)	13 (3)	0 (0)	91 (3)	0 (0)
Skin and Subcutaneous Tissue Disorders	70 (22)	3 (1)	135 (46)	3 (1)	106 (23)	4 (0.9)	1361 (49)	40 (1)
Pruritus	23 (7)	0 (0)	8 (3)	0 (0)	38 (8)	0 (0)	562 (20)	4 (0.1)
Rash	20 (6)	1 (0.3)	25 (8)	0 (0)	32 (7)	1 (0.2)	500 (18)	9 (0.3)
Dry skin	9 (3)	0 (0)	4 (1)	0 (0)	15 (3)	0 (0)	165 (6)	0 (0)
Alopecia	4 (1)	0 (0)	88 (30)	1 (0.3)	4 (0.9)	0 (0)	52 (2)	0 (0)
Vitiligo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	171 (61)	0 (0)

Source: FDA reviewer's analysis, adae.xpt. Variables used: USUBJID, STUDYID, AEDECOD, AEBODSYS, AETOXGR.

Laboratory Findings

The Applicant's Position:

There were no new safety concerns identified for pembrolizumab monotherapy based on the laboratory results reported in KEYNOTE-181.

Compared with those treated with SOC, participants treated with pembrolizumab experienced fewer (>10% lower incidence) laboratory abnormalities with clinically meaningful (Grade 3 to 4 events) worsening from baseline according to the CTCAE for protocol-specified laboratory tests (based on the highest postbaseline toxicity grade per laboratory test) of leukocytes decreased (0.7% in the pembrolizumab arm vs 24.3% in the SOC arm) and neutrophils decreased (1.1% vs. 22.2%). The events of leukopenia and neutropenia are known to be associated with cytotoxic chemotherapies used as SOC (2.7.4, Sec. 3).

Specifically, liver function laboratory values were evaluated for DILI. In KEYNOTE-181. No participant in either arm had liver function laboratory values that satisfied the predetermined criteria for DILI (2.7.4, Sec. 3).

The incidence of the most frequently reported laboratory abnormalities with a clinically meaningful worsening of a laboratory value from baseline in KEYNOTE-181 (pembrolizumab arm) was generally consistent with that of the RSD. Discontinuations from treatment with pembrolizumab due to abnormal laboratory evaluations were infrequent in KEYNOTE-181 (pembrolizumab arm) and were consistent with that observed within the RSD (2.7.4, Sec. 3).

Discontinuations from treatment with pembrolizumab due to abnormal laboratory evaluations were infrequent in KEYNOTE-181 (pembrolizumab arm) and were consistent with that observed within the RSD (2.7.4, Sec. 3).

The FDA's Assessment:
FDA agrees with Merck's analysis of laboratory data and no new laboratory-based safety signals emerged in KEYNOTE-181.

Vital Signs

The Applicant's Position:
There were no clinically significant changes noted in vital signs or physical examination safety parameters in the pembrolizumab or SOC arm in KEYNOTE-181 (KEYNOTE-181 CSR, Sec. 12.4).

The FDA's Assessment:
FDA concurs with Merck's analysis.

Electrocardiograms (ECGs)

The Applicant's Position:
ECG testing was performed once during screening using local standard procedures [Table 5 5]. Clinically significant abnormal findings were not identified.

The FDA's Assessment:
FDA agrees with Merck's analysis.

QT

The Applicant's Position:
No clinically meaningful effects on QTc interval were identified in the analyses included in previous submissions, which included participants with melanoma and participants with NSCLC in KEYNOTE-001 (2.5, Sec. 3.4).

The FDA's Assessment:
FDA agrees with Merck's analysis.

Immunogenicity

The Applicant's Position:
The ADA rate in esophageal cancer (3.9% in KEYNOTE-181), independent of histology, is consistent with the established ADA profile for pembrolizumab monotherapy (2.5, Sec. 3.6).

The FDA's Assessment:
FDA agrees with Merck's analysis.

7.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:
The results from KEYNOTE-181 demonstrated that the safety profile of pembrolizumab was similar to the RSD, and no new safety issues were identified.

The FDA's Assessment:
FDA agrees that there were no new safety signals that emerged from KEYNOTE-181 compared to the RSD and approved product labeling for Keytruda. FDA further analyzed the AEOSI of immune-mediated pneumonitis in the advanced esophageal cancer population as discussed below.

AEOSI of Immune-Mediated Pneumonitis

In the esophageal cancer dataset (N=458), 24 patients (5.2%) experienced an AEOSI of pneumonitis. Three patients had Grade 1 pneumonitis (0.7%), 15 had Grade 2 pneumonitis (3.3%), two had Grade 3 pneumonitis (0.4%), one had Grade 4 pneumonitis (0.2%), and three had Grade 5 pneumonitis (0.7%). The median time to onset in the esophageal cancer dataset was 84.0 days (range: 3 days to 565 days). This reviewer analyzed the patients with reported AE preferred terms under the AEOSI of pneumonitis and reviewed narratives to evaluate for possible risk factors for pneumonitis. An information request was also sent to Merck on June 11, 2019 regarding possible risk factors for pneumonitis, including prior radiation therapy to the thoracic region; Merck's analysis in response to this information request is shown in Table 24 below. Merck concluded that a definitive association between prior thoracic radiation and pneumonitis was not evident in patients treated with pembrolizumab in KEYNOTE-180. Nonetheless, based on the reference safety dataset of 2799 patients, the Keytruda label contains a warning for the serious event of immune mediated pneumonitis and describes prior thoracic radiation as a risk factor for this immune-mediated adverse reaction.

Table 24
Merck Analysis of Patients with Immune-Mediated Pneumonitis Using the Esophageal Safety Dataset (N=458)

	With Treatment-Emergent Pneumonitis Events		Without Treatment-Emergent Pneumonitis Events	
	n	(%)	n	(%)
Subjects in population	24		434	
Age (Years)				
<65	10	(41.7)	232	(53.5)
>=65	14	(58.3)	202	(46.5)
Subjects with data	24		434	
Mean	66.2		62.6	
SD	9.6		9.8	
Median	68.5		64.0	
Range	47 to 81		23 to 87	
Gender				
Male	20	(83.3)	372	(85.7)
Female	4	(16.7)	62	(14.3)
With prior radiation				
Yes	13	(54.2)	269	(62.0)
No	11	(45.8)	165	(38.0)
With prior thoracic radiation				
Yes	12	(50.0)	219	(50.5)
No	12	(50.0)	215	(49.5)
Includes all subjects who received at least one dose of Pembrolizumab in KN181, KN180 and KN028 Cohort A4. Database Cutoff Date for KN028-Cohort A4: 31JAN2018, KN180: 30JUL2018, KN181: 15OCT2018				

Source: Sponsor Analysis, FDA Information request June 11, 2019

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

The Applicant's Position:

A similar number of participants in each intervention arm completed the EORTC QLQ-C30 questionnaire. The compliance rates for the EORTC QLQ-30 were similar and high in the pembrolizumab and SOC arms at baseline (94.5% and 95.8%) and Week 9 (88.9% and 83.9%). Compliance rates were similar for the EORTC QLQ-OES18 and EQ-5D (KEYNOTE-181 CSR, Sec. 11.4).

For all participants and for participants with ESCC, there were no clinically meaningful differences between intervention arms for the EORTC QLQ-C30, EORTC OES-18, or EQ-5D VAS (KEYNOTE-181 CSR, Sec. 11.4).

Participants treated with pembrolizumab showed some improvement in VAS scores at Week 9 compared to baseline, while the participants treated with SOC showed worsening in VAS scores at Week 9 compared to baseline (KEYNOTE-181 CSR, Sec. 11.4.4).

The FDA's Assessment:
Please refer to the discussion of COA endpoints in Section 7.1.2.

7.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:
In KEYNOTE-181, there were no trends identified in the incidence of AEs by age, sex, ECOG status, race, and region (US, EU, and Asia) between the two treatment arms (KEYNOTE-181 CSR, Sec. 12.1.3.3).

There were no trends identified in the incidence of AEs by age, sex, ECOG status, or region between KEYNOTE-181 (pembrolizumab arm) and the RSD (2.7.4, Sec. 4.1 and Sec. 4.2).

The FDA's Assessment:
FDA agrees with Merck's analysis.

7.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Not applicable

The FDA's Assessment:
Not applicable

7.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:
No new information concerning human carcinogenicity or tumor development is provided in this supplement.

The FDA's Assessment:
FDA agrees with Merck's position.

Human Reproduction and Pregnancy

The Applicant's Position:
No new information concerning human reproduction and pregnancy is provided in this supplement.

The FDA's Assessment:
FDA agrees with Merck's position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:
The FDA granted pembrolizumab orphan designation for the treatment of esophageal carcinoma in June 2017 (17-5787). Because pembrolizumab has orphan drug designation for esophageal carcinoma, it is exempt from the PREA requirements and no pediatric studies have been conducted in esophageal carcinoma.

The FDA's Assessment:
FDA agrees that this application is exempt from the PREA requirement to conduct pediatric studies of pembrolizumab due to the orphan designation of pembrolizumab for the treatment of esophageal carcinoma.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
There were no reports of overdose in KEYNOTE-181. Any administration of a participant with ≥1000 mg (5 times the protocol-defines dose) of pembrolizumab is considered as an overdose (2.7.4, Sec. 4.6).

Potential for drug abuse or dependence is not expected for an anti-PD-1 mAb, and no reports of drug abuse with pembrolizumab have occurred (2.7.4, Sec. 4.7). No withdrawal or rebound effects are expected with this drug, and their occurrence in clinical studies with administration of pembrolizumab is unknown (2.7.4, Sec. 4.8).

The FDA's Assessment:
FDA agrees with Merck's position.

7.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:
The safety profile of pembrolizumab postmarketing approval was summarized in the PSUR covering the period 04-MAR-2018 through 03-SEP-2018 (2.7.4, Sec. 5). There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country (2.7.4, Sec. 5). interval 04-MAR-2018 to 03-SEP-2018.

The FDA's Assessment:
The PSUR covering the time period from 04-MAR-2018 to 03-SEP-2018 indicates that approximately 29,253 subjects have been treated with pembrolizumab in the clinical trial program, of which approximately 22,527 subjects participated in Merck-sponsored clinical trials (approximately 14,392 subjects received pembrolizumab monotherapy and approximately 8,135 subjects received pembrolizumab in combination with one or more other chemotherapy or biologic agents), and 6,726 subjects received pembrolizumab monotherapy in either the Expanded Access Program (approximately 5,806 subjects in KEYNOTE-030) or in the Temporary Authorization for Use in France (approximately 920 subjects in KEYNOTE-049) as of 03-SEP-2018. There were no changes to the overall risk benefit profile of pembrolizumab recommended based on the information described in this PSUR. Pembrolizumab has not been withdrawn from investigational use for reasons related to safety or efficacy in any country.

Expectations on Safety in the Postmarket Setting The Applicant's Position:
Postmarket data from the safety reporting database (i.e., MARRS) is routinely reviewed for pembrolizumab. The MARRS database contains all data from postmarket sources, including health care providers, consumers, and scientific literature as well as competent authorities worldwide. The Sponsor continues to monitor postmarket data associated with pembrolizumab.

There are no specific safety concerns associated with subpopulations not adequately represented in the safety database. No difference in pembrolizumab administration in the postmarket setting is expected relative to KEYNOTE-181. There are no specific safety concerns not already included in pembrolizumab labeling expected from off-label use.

The FDA's Assessment:
Pembrolizumab has been marketed in the U.S. since 2014 and the safety profile of pembrolizumab is well-established. Since the initial approval, pembrolizumab labeling has been revised to include additional immune-mediated adverse events identified in ongoing clinical trials with pembrolizumab. These include potential risks of hypophysitis, nephritis, uveitis, type 1 diabetes mellitus, severe skin reactions, myositis, pancreatitis, Guillain-Barré Syndrome, fatal pneumonitis, myocarditis, Stevens Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), encephalitis, and sarcoidosis. FDA will continue to monitor pembrolizumab safety in the post marketing setting.

7.2.11. Integrated Assessment of Safety

The Applicant's Position:
The results of KEYNOTE-181 demonstrated that pembrolizumab when administered as monotherapy is well tolerated in participants with recurrent locally advanced or metastatic esophageal cancer with disease progression on or after one line of previous systemic therapy and has a more favorable safety profile when compared with SOC (investigator's choice paclitaxel, docetaxel, or irinotecan).

The safety profile for participants treated with pembrolizumab from KEYNOTE-181 is generally consistent with the previously established safety profile of pembrolizumab monotherapy (RSD). No new safety risks associated with pembrolizumab exposure were observed in KEYNOTE-181.

The key exposure, safety, and tolerability findings from KEYNOTE-181 were:

- The mean duration of exposure was longer in the pembrolizumab arm compared with the SOC arm (4.0 months vs. 3.1 months). Median duration of exposure was similar between the 2 intervention arms.
- The mean exposure to pembrolizumab was shorter for participants in KEYNOTE-181 compared with those within the RSD (4.0 months vs. 6.5 months). The observed differences in exposure to pembrolizumab are likely associated with the poorer prognosis of participants with previously treated esophageal cancer in KEYNOTE-181 compared with participants in the RSD.
- Compared with those who received SOC, participants who received pembrolizumab showed a generally lower frequency of most categories of AEs. The incidence of drug-related AEs (64.3% vs. 86.1%) and Grade 3 to 5 drug-related AEs (18.2% vs. 40.9%) was notably lower among participants treated with pembrolizumab compared with participants treated with SOC.
- The reported AEs with a ≥5% higher incidence in the pembrolizumab arm compared with the SOC arm were hypothyroidism and dysphagia. Hypothyroidism is a known AEOSI associated with pembrolizumab. Most dysphagia events were low-grade, not drug-related, and likely related to the underlying disease. Fewer pembrolizumab-treated participants experienced AEs (all grades and Grade 3 to 5) commonly seen with cytotoxic chemotherapies given as SOC, such as hematologic toxicities, fatigue, nausea, vomiting, peripheral sensory neuropathy, and alopecia.
- The safety profile of pembrolizumab in KEYNOTE-181 in participants with advanced/metastatic esophageal cancer is also consistent with the established safety profile of pembrolizumab observed in the RSD and showed no new safety signals for pembrolizumab. While a higher incidence of dysphagia was observed in KEYNOTE-181 (pembrolizumab arm) compared with the RSD (15.6% vs. 2.1%), this finding is consistent with what is expected for this population of patients.

The FDA's Assessment:
The ISS safety datasets for this application were pooled into four different safety datasets as

described in Section 7.2.1 above. FDA's analysis of ISS focused on the comparison of the esophageal safety dataset (N=458) to the reference safety dataset (2799) already described in Keytruda product labeling. The median duration of exposure in the esophageal safety dataset was shorter compared with the RSD (2.0 months vs. 4.0 months, respectively). Adverse events were reported by 95% of patients in the esophageal safety dataset and 97% of patients in the RSD. Common adverse event rates were comparable between the esophageal safety dataset and the RSD except for a higher incidence of dysphagia in the esophageal safety dataset (13%) compared with the RSD (2.1%). The higher observed incidence of dysphagia in the esophageal safety dataset is likely to be related to the underlying cancer and does not represent a new safety signal as the incidence of dysphagia in the chemotherapy arm of KEYNOTE-181 (9.5%) was also higher than the RSD. SAEs of pneumonia (5.9% vs. 3%) dysphagia (2.4% vs. 0.2%) and aspiration pneumonia (3.5% vs. 0.1%) were seen at a higher rate in the esophageal safety dataset compared to the RSD, which can be anticipated due to known complications of esophageal cancer. The AEOSI incidence rates were generally similar between the esophageal safety dataset and the RSD except for immune-mediated hepatitis, which was higher in the esophageal safety dataset than the RSD (1.5% vs. 0.7%); however, given the small number of patients who experienced immune-mediated hepatitis and the temporal relationship between disease progression and hepatitis for four of these events, definitive conclusions cannot be made regarding this potential slight increase in the risk of immune-mediated hepatitis in this patient population.

SUMMARY AND CONCLUSIONS

7.3 Statistical Issues

The FDA's Assessment:

There were several important statistical concerns to address in this submitted supplemental BLA, including the failure of the three primary hypotheses of KEYNOTE-181, the calculation of boundaries for the interim and final analyses, the proposed max-combo log-rank test, and the post-hoc analysis of a clinically relevant subgroup.

First, FDA does not agree with Merck's calendar-time-based method to calculate the alpha boundaries for the interim and final analyses of OS. The information level of a log-rank test obtained at an interim analysis should be based on the information fraction, defined as the percentage of number of events observed at an interim analysis compared to the max number of events planned for the final analysis, instead of calendar-time fraction at the interim analysis. Therefore, FDA used O'Brien-Fleming boundaries determined by the Lan-DeMets approach based on the event-time information fraction. However, irrespective of the method of boundary calculation (Merck's or FDA's), the study failed to meet the pre-specified thresholds to demonstrate a statistically significant improvement in OS in any of the three pre-specified

primary patient populations at the interim analysis and at the final analysis.

In addition, FDA does not agree with using the stratified maximum weighted log-rank (max-combo) test as the primary testing approach to test OS (as well as PFS) in all subjects. This is because there is limited prior knowledge in literature on the true OS distribution in this disease setting and the pre-specified parameters required for a weighted log-rank test are prone to misspecification. FDA's assessment for OS in the ITT population was primarily based on the results of the log-rank test, which is more robust for analyses of random data patterns. The results of the stratified maximum weighted log-rank test were considered as supportive evidence.

Finally, in light of the failure of KEYNOTE-181 to meet its primary objective for establishing treatment effect of pembrolizumab, there was insufficient evidence to conclude a treatment benefit of pembrolizumab in any of the planned analysis populations. However, due to the observed results in the combined subgroups of patients with ESCC tumors expressing PD-L1 (CPS ≥ 10) and the biologic plausibility of a larger effect size in this group supported by clinical experience with pembrolizumab in patients with PD-L1 positive ESCC in KEYNOTE-180 and other PD-L1 cancers, and emerging data indicating there are differences in genomic patterns in ESCC and EAC that may influence response to immunotherapy [25], post-hoc analyses were conducted in this population. A clinically meaningful effect on the primary endpoints of OS and secondary endpoints of PFS and ORR were observed, although there was no formal statistical comparison conducted in this exploratory analysis.

7.4 Conclusions and Recommendations

The FDA's Assessment:

Results from KEYNOTE-181 demonstrate that pembrolizumab provided a clinically meaningful benefit in OS in participants with ESCC and CPS ≥10 despite missing the pre-specified alpha level to declare statistical significance in all 3 primary analysis populations. FDA's determination that the OS results in the population of patients with ESCC tumors expressing PD-L1 (CPS ≥ 10) constitute substantial evidence of effectiveness was made in the context of the totality of clinical experience with pembrolizumab in a variety of PD-L1 positive cancers (such as gastric cancer and non-small cell lung cancer), the supportive data showing an improvement in PFS and ORR in this subpopulation, the narrow margin for failure to demonstrate an improvement in OS in the pre-specified PD-L1 positive and ESCC populations, data from KEYNOTE-181 showing durable responses in a third- and later-line setting in patients with ESCC whose tumors express PD-L1 (CPS≥10), and an understanding that a prolongation of overall survival of the magnitude shown in this patient population constitutes a meaningful clinical benefit.

The safety profile of pembrolizumab in KEYNOTE-181 is consistent with the established safety profile of pembrolizumab and no new safety risks were identified.

The clinical and statistical review teams therefore recommend regular approval of

pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic squamous esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

X	X
Mengdie Yuan, Ph.D. Primary Statistical Reviewer	Pallavi Mishra-Kalyani, Ph.D. Statistical Team Leader

X X

Abhilasha Nair, M.D.
Primary Clinical Reviewer

Martha Donoghue, M.D.
Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The Division did not refer this efficacy supplement to an advisory committee because the application did not raise significant public health questions regarding the role of pembrolizumab for the proposed indication. Pembrolizumab is a marketed biologic approved for the treatment of several solid tumor and hematologic malignancies. The safety profile of pembrolizumab is well established in patients with advanced malignancies. The demonstrated benefit-risk profile for pembrolizumab is favorable in patients with recurrent locally advanced or metastatic squamous esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression on or after one or more prior lines of systemic therapy.

9 Pediatrics

The Applicant's Position:
The FDA granted pembrolizumab orphan designation for the treatment of esophageal carcinoma in June 2017 (17-5787). Because pembrolizumab has orphan drug designation for esophageal carcinoma, it is exempt from the PREA requirements and no pediatric studies have been conducted in esophageal carcinoma.

The FDA's Assessment:
FDA agrees with Merck's position. Pursuant to section 505B(k)(1), applications for approved drugs or biological products for which orphan designation has been granted are exempt from the PREA section 505B(a)(a)(A) requirement to conduct a pediatric assessment. Additionally, the requirements under FDARA for the conduct of pediatric investigations for drugs with a mechanism of action that is substantially relevant to one or more pediatric cancers are not applicable to supplemental applications.

10 Labeling Recommendations

10.1 Prescription Drug Labeling

The Applicant's Position:
The Sponsor has provided the proposed labeling in the submission in module 1.14.1.3.

The FDA's Assessment:
Labeling negotiations on Merck's proposed Prescribing Information for BLA 125514/S-55/56 are ongoing at the time of this review. A high-level summary of significant proposed labeling changes is presented in Table 25 below.

Table 25
Summary of Significant Proposed Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Merck's Proposed Labeling**	**FDA's proposed Labeling**
Indication and Usage	(b) (4)	Revised indications to "for the treatment of patients with recurrent locally advanced or metastatic squamous

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Merck's Proposed Labeling**	**FDA's proposed Labeling**
	[redacted]	esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy. (1 [redacted] 2.1)" [redacted]
Dosage and Administration	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.	No changes
Adverse Reactions	Added a paragraph on the safety experience in KEYNOTE-181	Minor editorial changes
Clinical Studies	Added a subsection for esophageal cancer	Edited for brevity [redacted]

11 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:
The safety profile or pembrolizumab is well characterized in the product labeling, and a REMS is not necessary for this indication.

The FDA's Assessment:
The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of pembrolizumab for the indicated population given the well-established safety profile of pembrolizumab and the experience of the medical oncology community in managing immune-mediated adverse reactions, based on use of pembrolizumab and other marketed products of the same class. Product labeling for pembrolizumab, which includes recommendations for monitoring and dosage modification for immune-mediated adverse events are sufficient to ensure the safe and effective use of pembrolizumab in patients with PD-L1 positive (CPS ≥10) ESCC.

12 Postmarketing Requirements and Commitment

The FDA's Assessment:

No postmarketing requirements or commitments are recommended for this indication.

13 Associate Division Director (OB)

I concur with the team's assessments on the effect of pembrolizumab in the subpopulation of patients with ESCC whose tumors express PD-L1 with CPS≥10.

The observed hazard ratios in OS are 0.77 (95% CI: 0.63, 0.96; p=0.00894) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94; p=0.00855) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05; p=0.00843) in all randomized patients.

Even though the primary efficacy analyses of OS failed to pass the FDA calculated significance level per the interim analysis plan in any of the three pre-specified primary patient populations (0.0069, 0.0027 and 0.0080 for patients with ESCC, PD-L1 CPS≥10 and ITT population, respectively; see Table 15), the benefit of pembrolizumab was further observed based on the post-hoc analyses of OS in the patients with ESCC whose tumors express PD-L1 CPS ≥10 (HR=0.64, 95% CI=0.46, 0.90). Such treatment effect was supported by the results of PFS (HR= 0.66, 95% CI=0.48, 0.92) and ORR (22 %, 95% CI: 14%, 33% vs 7%, 95% CI: 3%, 15% for pembrolizumab and chemotherapy arm, respectively) in the same subpopulation. In addition, subgroup analyses based on the subpopulation further demonstrate consistent results in favor of pembrolizumab treated arm. Though treatment benefit of pembrolizumab in the subpopulation was observed, there was no formal statistical comparison conducted in the exploratory analyses.

Based on the post-hoc analyses, the biological plausibility and clinical experience described in the review, a clinically meaningful effect of pembrolizumab was observed. However, the benefit/risk ratio of pembrolizumab used in the subpopulation will be deferred to the clinical review team.

X _____

Yuan-Li Shen, Dr. P.H.

14 Division Director (Clinical)

I concur with the recommendations of the review team that pembrolizumab should be approved as a single agent for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy. My recommendation is based on the totality of the data from KEYNOTE-180 and KEYNOTE-181, which demonstrated highly durable responses in refractory patients with disease progression on two or more lines of systemic therapy and improved survival, progression-free survival and durable responses among patients with disease progression on one or more lines of systemic therapy as compared to an active control arm. Additionally, I considered the data observed in prior clinical studies of pembrolizumab in epithelial malignancies in which PD-L1 tumor expression is an apparent predictive marker for larger treatment effects.

While KEYNOTE-181 failed to demonstrate treatment effects of pembrolizumab on survival in any of the populations at the boundaries for control of Type I error rate at the final analysis, which the FDA statistical reviewer determined to be a one-sided alpha of 0.0063, 0.0082, and no alpha left in patients with ESCC/patients with PD-L1 CPS ≥10/all patients, respectively, the results in the ESCC and PD-L1 CPS ≥10 subgroups were close to the prespecified boundary and likely failed due to inaccurate assumptions regarding the magnitude of the treatment effect.

	PD-L1 CPS ≥10		**ESCC**		**All Participants**	
	Pembrolizumab (N=107)	**SOC (N=115)**	**Pembrolizumab (N=198)**	**SOC (N=203)**	**Pembrolizumab (N=314)**	**SOC (N=314)**
Primary Outcome: OS						
Number of events (%)	88 (82.2)	103 (89.6)	166 (83.8)	182 (89.7)	271 (86.3)	284 (90.4)
Median OS (95% CI), months[†]	9.3 (6.6, 12.5)	6.7 (5.1, 8.2)	8.2 (6.7, 10.3)	7.1 (6.1, 8.2)	7.1 (6.2, 8.1)	7.1 (6.3, 8.0)
HR (95% CI)[‡]	0.70 (0.52, 0.94)		0.77 (0.63, 0.96)		0.89 (0.75, 1.05)	
P-value [‡‡]	0.00855		0.00894		0.08431	

As noted in the review, there is biologic plausibility for the role of PD-L1 tumor expression predicting a larger treatment effect with pembrolizumab than in tumors that are PD-L1-negative. Prior clinical studies of pembrolizumab in different primary cancers of epithelial origin suggest a differential (and larger) treatment effect in patients with PD-L1-expressing tumors. These studies are KEYNOTE 048 conducted in patients with squamous cell cancer of the head and neck; KEYNOTE-052 and KEYNOTE-361 conducted in patients with urothelial cancers; and KEYNOTE-158 conducted in patients with cervical cancers. Additionally, differential (larger) treatment effects correlating increasing intensity of PD-L1 tumor expression were observed in

KEYNOTE-042, KEYNOTE-024, and KEYNOTE-010 conducted in patients with lung cancer. There is also biologic plausibility for differential treatment effects with anti-PD-L1 antibodies based on histologic subtype in esophageal cancer, as these are biologically different cancers with different etiologic risk factors. This is supported by the very compelling survival curves presented in Figure 5 of this review. Finally, the results of exploratory analyses in the subgroup of patients with PD-L1 CPS ≥ 10 squamous cell esophageal cancer showing a larger treatment effect than in either the ESCC subgroup or the PD-L1 CPS ≥ 10 subgroup are consistent between trials (KEYNOTE-181 and KEYNOTE-180) and efficacy endpoints (OS, PFS, ORR) providing additional confidence in the validity of the results on survival observed in the exploratory subgroup.

I further agree that the risk:benefit profile is favorable in this population in whom a 5-year survival rate is less than 5% and that REMS are not required to ensure safe use of this product, which has nearly 5 years of marketing experience in the U.S.

X

Patricia Keegan, M.D.

15 Appendices

15.1 References

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The FDA's Reference:

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15.2 Financial Disclosure

The Applicant's Position:

Disclosure of financial interests of the investigators who conducted the KEYNOTE-181 study are described in the current submission, including statements of due diligence (FDA forms 3454) in cases where the Sponsor was unable to obtain a signed form from the investigator (Module 1.3.4).

The FDA's Assessment:

3475-181: A Phase III Randomized Open-label Study of Single Agent Pembrolizumab vs Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects with Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus that have Progressed after First-Line Standard Therapy (KEYNOTE-181)

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

Total number of investigators identified: Study KEYNOTE-181 had a total of 1666 investigators and sub-investigators.		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
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: None Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Study 3475-181 or KEYNOTE-181 had a total of 1666 investigators and sub investigators of which 1662 reported that they did not enter into any financial arrangements whereby the value of compensation to the investigator would be expected to affect the outcome of the studies as defined in 21 CFR 54.2(a). After multiple attempts financial information was not able to obtained from 2 sub-investigators: (b) (6) and (b) (6) at site (b) (6). For these two sub-investigators, Merck performed due diligence and an internal search performed for proprietary or financial interests and significant payments of other sorts. No financial interests or arrangements were identified by Merck.

Merck also submitted Form 3455, which contained a list of 2 investigators who had disclosable arrangements to report which were in excess of $25,000.

Investigators with Disclosable Financial Arrangements

Product/Protocol/Site	Investigator/ Sub-Investigator	Role	Financial Interests and/or Arrangements
3475-181 (b) (6)	(b) (6)	Sub-Investigator	Internal search for financial interest revealed: Significant Payments of Other Sorts: Amount: $58,307.79 Received payments for Speaker Fees.
3475-181-(b) (6)	(b) (6)	Sub-Investigator	Internal search for financial interest revealed: Significant Payments of Other Sorts: Amount: $80,443.61 Received payments for Speaker Fees.

The FDA's Assessment:

FDA agrees that it is unlikely that the financial arrangements disclosed by Merck influenced the overall results of KEYNOTE-181. Due to the large size of the study, which enrolled patients in 32 countries globally with consistent effects on then primary endpoint of overall survival, it is unlikely that any potential bias on the part of the two sub-investigators at sites (b) (6) and (b) (6) (which enrolled a total of (b) (6) patients) due to financial conflicts of interest had an impact on the overall study results.

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/s/

SHARON K SICKAFUSE
07/30/2019 06:11:15 PM

YUAN L SHEN on behalf of MENGDIE YUAN
07/30/2019 07:54:39 PM

YUAN L SHEN on behalf of PALLAVI S MISHRA-KALYANI
07/30/2019 07:57:44 PM

YUAN L SHEN
07/30/2019 07:59:07 PM

MARTHA B DONOGHUE on behalf of ABHILASHA NAIR
07/30/2019 08:43:05 PM

MARTHA B DONOGHUE
07/30/2019 08:43:55 PM

PATRICIA KEEGAN
07/30/2019 08:48:25 PM

Application Type	sBLA
Application Number	125514/S-56
Priority or Standard	Priority
Submit Date	1-30-2019
Received Date	1-30-2019
PDUFA Goal Date	7-30-2019
Division/Office	DOP2/OHOP
Review Completion Date	7-3-2019
Established Name	Pembrolizumab
Trade Name	Keytruda
Pharmacologic Class	Programmed Death-Receptor-1 (PD-1) Blocking Antibody
Applicant	Merck Sharp & Dohme Corp.
Formulations	50 mg lyophilized powder; 100 mg/4 mL (25 mg/mL) solution For Injection: 50 mg lyophilized powder in single-dose vial Injection: 100 mg/4 mL (25 mg/mL) solution in single-dose vial
Dosing Regimen	200 mg IV every 3 weeks
Applicant Proposed Indication	(b) (4) [redacted]
Regulatory project manager	Sharon Sickafuse, MS
Clinical reviewer	Abhilasha Nair,MD
Cross Discipline Team Leader	Martha Donoghue, MD

The primary clinical review of safety and efficacy for this sBLA is complete and has been added to the sBLA Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized.

Based on the review of the safety and efficacy data from studies KN-180 and KN-181, the clinical review team recommends approval of pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic squamous esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior line of systemic therapy (b) (4) [redacted] pending resolution of the product labelling issues. Please refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

ABHILASHA NAIR
07/05/2019 11:28:59 AM

MARTHA B DONOGHUE
07/05/2019 11:35:31 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s056

PRODUCT QUALITY REVIEW(S)

Memorandum of Review:

Submission Tracking Number (STN):	BLA 125514/SUPPL-56 (Seq. 0674)
Subject:	Efficacy supplement
Stamp Date:	01/30/2019
Review Date:	07/22/2019
Primary Reviewer:	Shadia Zaman, Ph.D., DBRR1/OBP/OPQ/CDER
Secondary Reviewer:	Brian Janelsins, Ph.D., TL, DBRR1/OBP/OPQ/CDER
RBPM:	Andrew Shiber
Consults:	None
Applicant:	Merck Sharp & Dohme Corp
Product:	Pembrolizumab
Proposed Indication:	(b) (4) [redacted]
Goal Date:	7/30/19

1. Summary Basis of Recommendation:

a. Recommendation: I recommend approval of this supplement from a CMC perspective.

b. Justification: This memo is for efficacy supplement 56 in support of a new indication (see above). No CMC changes were proposed. A categorical exclusion from environmental assessment per 21 CFR 25.31(c) was claimed and was determined to be acceptable. The binding anti-drug antibody (ADA) assay that was used to generate immunogenicity data in support of the new indication is the same assay that has been validated and reviewed during the original BLA submission. While issues with the drug tolerance of the assay have been documented, this has not been a concern from the clinical and clinical pharmacology perspectives. Based on product knowledge, the new indication, detection of similar ADA incidences across the new and historical indications, and no updates proposed to the label regarding immunogenicity data, there will not be a recommendation for Merck to improve the drug tolerance of their binding ADA assay to support the new indication.

2. Review:

Note: *Reviewer comments are in italicized text.*

1.12.14 Environmental Analysis

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

***Reviewer comment**: This is acceptable.*

Immunogenicity Assessment

Reviewer comment: Sections 2.7.2, 5.3.1.4, and 5.3.5.1 were reviewed for this assessment.

An immunogenicity assessment was performed in the clinical study KEYNOTE-181 (KN181), a phase III study of single agent pembrolizumab vs physicians' choice of single agent paclitaxel or docetaxel in subjects with advanced/metastatic squamous cancer and adenocarcinoma of esophagus that have progressed after first-line standard therapy. The overall treatment emergent positive ADA incidence for patients receiving pembrolizumab was 3.9% based on 11 out of 283 evaluable subjects with no neutralizing antibodies in any of the positive subjects. Immunogenicity assessment was also performed separately on subjects with squamous cell carcinoma (N = 182) and adenocarcinoma (N = 101). The ADA incidence was 4.4% and 3.0%, respectively, for squamous cell carcinoma and adenocarcinoma patients receiving pembrolizumab. The ADA incidence in esophageal cancer is consistent with the established ADA profile for pembrolizumab monotherapy in patients with melanoma, NSCLC, HNSCC, and UC.

During the clinical study KN181, samples were collected at pre-dose Cycle 1, 2, 4, 6, 8, and at every four cycles thereafter and 30 days after discontinuation of study drug. At these testing time points, the pharmacokinetic data from KN181 (Figure 2.7.2 in Section 2.7.2) show that the concentration of pembrolizumab at pre-dose Cycle 2 is approximately 5 – 50 µg/mL and at steady state (e.g., Cycle 8) is approximately 25 – 100 µg/mL.

***Reviewer comment:** The binding ADA assay is tolerant in detecting ADAs as low as 250 ng/mL in the presence of up to 25 µg/mL of pembrolizumab (validation report 03TVDB, Section 5.3.1.4; Seq. 0004). Based on the current information in the approved label, Merck uses a subset analysis approach to determine ADA incidences, where they only analyze samples whose drug concentrations are within the drug tolerance range of the assay. This method of sample selection would lead to the omission of a significant portion of the KN181 clinical samples for immunogenicity analysis. Therefore, the reported ADA incidence may not be accurate. Considering the ADA profile is similar between the new and historical indications, the label will not be updated regarding immunogenicity data, and there are no current safety and efficacy issues that are suspected to be due to the development of ADAs, a recommendation for Merck to*

optimize the drug tolerance of their assay in support of the new indication will not be requested. This approach has been recommended by the clinical and clinical pharmacology teams in the review of previous pembrolizumab indications that included immunogenicity data in the submissions.

3. Future Inspection Items:

None

APPEARS THIS WAY
ON ORIGINAL

Brian Janelsins

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Date: 7/23/2019 10:15:09AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s056

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - MEMO

BLA #:	125514
Supplement #:	55, 56
Drug Name:	KEYTRUDA® (Pembrolizumab)
Indication(s):	treatment of patients with recurrent locally advanced or metastatic squamous esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test [see Dosage and Administration (2.1)], with disease progression on or after one or more prior lines of systemic therapy (b) (4)
Applicant:	Merck Sharp & Dohme Corp.
Date(s):	Receipt Date: 1/30/2019 Filing Date: 3/29/2019 PDUFA Date: 7/30/2019
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Mengdie Yuan
Concurring Reviewers:	Pallavi Mishra-Kalyani, Statistical Team Leader Yuan-Li Shen, Statistical Associate Director
Medical Division:	Office of Hematology and Oncology Products, Division of Oncology Products 2
Clinical Team:	Abhilasha Nair, Clinical Reviewer Martha Donoghue, Clinical Team Leader Patricia Keegan, Division Director
Project Manager:	Sharon Sickafuse

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

MENGDIE YUAN
07/03/2019 02:57:53 PM

PALLAVI S MISHRA-KALYANI
07/05/2019 07:16:52 AM

YUAN L SHEN
07/05/2019 08:12:05 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s056

OTHER REVIEW(S)

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

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

Memorandum

Date: 7/2/19

To: Sharon Sickafuse, Senior Regulatory Health Project Manager, DOP2

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, Team Leader, OPDP

Subject: OPDP Labeling Comments for KEYTRUDA (pembrolizumab) for injection, for intravenous use; KEYTRUDA (pembrolizumab) injection, for intravenous use

BLA: 125514/Supplements 55 & 56

In response to DOP2's consult request dated February 4, 2019, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for BLA 125514 KEYTRUDA (pembrolizumab) for injection, for intravenous use; KEYTRUDA (pembrolizumab) injection, for intravenous use (Keytruda) S-55 & S-56. These supplements add an indication for the treatment of patients with recurrent locally advanced or metastatic squamous esophageal cancer.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide emailed to OPDP on June 17, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed and comments on the proposed MG were sent under separate cover.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

PI

Section	Statement from Draft (if applicable)	OPDP Comment
14. (b) (4) Esophageal Cancer	"(b) (4) in patients whose ESCC tumors expressed PD L1 (CPS≥ 10) an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy."	We note that the PI includes the information that (b) (4) [redacted] (b) (4) [redacted]

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/s/

RACHAEL E CONKLIN
07/02/2019 03:21:48 PM

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 28, 2019
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form, and Route:	KEYTRUDA (pembrolizumab) for injection, for intravenous use KEYTRUDA (pembrolizumab) for injection, for intravenous use
Application Type/Number:	BLA 125514
Supplement Number:	S-055 and S-056
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On January 18, 2019 Merck Sharp & Dohme Corp. submitted for the Agency's review Prior Approval Supplements (PAS) – Efficacy to their approved Biologics License Application (BLA) 125514/S-055 and S-056 for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection. With this supplement, the Applicant proposes to add the following (b) (4) new indications for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection:

- S-55 proposes: (b) (4)
- S-56 proposes: (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on February 4, 2019 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 January 18, 2019, and received by DMPP and OPDP on June 17, 2019.
- Draft KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection Prescribing Information (PI) received on January 18, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 17, 2019.

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/

MORGAN A WALKER
06/28/2019 12:33:04 PM

RACHAEL E CONKLIN
06/28/2019 12:35:04 PM

BARBARA A FULLER
06/28/2019 12:50:08 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s056

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123482

MEETING MINUTES

Merck Sharp & Dohme Corp.
Attention: Robert Kester
Director, Global Regulatory Affairs
Oncology & In-vitro Diagnostics Group
126 E. Lincoln Ave.
P.O. Box 2000
RY 34-B295
Rahway, NJ 07065

Dear Mr. Kester:

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

We also refer to the meeting between representatives of your firm and the FDA on January 25, 2019. The purpose of the meeting was to discuss the content and format of a proposed sBLA for the treatment of (b) (4) , based on the results of study KEYNOTE-181, "A Phase III Randomized Open-Label Study of Single Agent Pembrolizumab vs. Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects with Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus that have Progressed after First-Line Standard Therapy.".

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

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

APPEARS THIS WAY ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: pre-sBLA

Meeting Date: January 25, 2019

Application Number: IND 123482
Product Name: Pembrolizumab
Indication: (b) (4) [redacted]

Sponsor/Applicant Name: Merck Sharp & Dohme Corp.

Meeting Chair: Martha Donoghue
Meeting Recorder: Sharon Sickafuse

FDA ATTENDEES

Office of Hematology and Oncology Products
Gideon Blumenthal, M.D.
Meredith Chuk, M.D.
Peter Schotland, M.D.

Division of Oncology Products 2
Martha Donoghue, M.D.
Abhilasha Nair, M.D.
Patricia Keegan, M.D.
Sharon Sickafuse, M.S.

Office of Biostatistics
Division V
Pallavi Mishra-Kalyani, Ph.D.
Mengdie, Yuan, Ph.D.

CDRH
Office of In Vitro Diagnostics and Radiological Health
Division of Molecular Genetics and Pathology
Janaki Veeraraghavan, Ph.D.

SPONSOR ATTENDEES
Shailaja Suryawanshi
Michael Miller
Robert Kester
Soonmo (Peter) Kang
Gregory Lubiniecki
Jonathan Cheng
John Coumbis
Christine Gause
Julie Anne Zawisa
Stacie Noreika
Pooja Bhagia
Scott Korn

BACKGROUND
On November 7, 2018, Merck submitted a meeting request (SDN 595) to discuss the content and format of a proposed sBLA seeking regular approval of pembrolizumab for (b) (4) based on the results of study KEYNOTE-181, "A Phase III Randomized Open-Label Study of Single Agent Pembrolizumab vs. Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects with Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus that have Progressed after First-Line Standard Therapy." The meeting package was submitted on December 20, 2018 as SDN 605. A Study Data Standardization Plan was submitted as an amendment to the meeting package on January 3, 2019, as SDN 607.

Regulatory
Pembrolizumab is approved in the U.S. for multiple oncologic indications in adult and pediatric populations.

On June 15, 2017, FDA granted Orphan Drug Designation to pembrolizumab for the treatment of esophageal cancer.

The design of KEYNOTE-181 (KN-181) was discussed during an EOP2/PP3 meeting held on August 17, 2015. During that meeting, FDA recommended a primary endpoint of overall survival (OS) rather than progression-free survival (PFS) in second-line esophageal cancer based on the short life-expectancy of patients with this disease and the lack of effectiveness of subsequent therapies. FDA stated that demonstration of an effect on PFS that is large in magnitude (for example, an increase in median PFS of > 4 months or longer), clinically important, statistically robust such that a second trial would not be considered feasible or ethical, and with a favorable risk/benefit profile may also be sufficient to support filing of an sBLA for the proposed indication. The protocol was submitted on September 30, 2015.

(b) (4)

FDA expressed willingness to consider reviewing data for the two supplements under the Real Time Oncology Review (RTOR) pilot program. A teleconference was held to discuss these submissions and their format on January 16, 2019, and RTOR submissions for both pending supplements were submitted on January 18, 2019.

Clinical and Statistical

Table 1 shows the ongoing trials of pembrolizumab in advanced esophageal cancer.

Trial ID/Status	Trial Type/Design	Trial Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KEYNOTE-028 Ongoing/Enrollment completed	Phase 1 Multicenter, non-randomized, open-label, multicohort	PD-L1 positive patients Cohort of 23 advanced esophageal cancer patients (2L+)	Pembrolizumab monotherapy (10 mg/kg Q2W)	ORR
KEYNOTE-180 Ongoing/Enrollment completed	Phase 2 Global multicenter, non-randomized, open-label, single arm, multicohort	Advanced esophageal cancer patients who progressed on at least 2 prior chemotherapy regimens(3L+), N=121	Pembrolizumab monotherapy (200 mg Q3W)	ORR
KEYNOTE-181 Ongoing/Enrollment completed	Phase 3 Global multicenter, randomized, controlled, open-label trial	Advanced/metastatic esophageal cancer who progressed on or after 1 line of prior systemic therapy, 2L, N=628	Pembrolizumab monotherapy (200 mg Q3W) or investigators choice (paclitaxel, docetaxel, or irinotecan)	OS
KEYNOTE-590 Ongoing/Enrolling	Phase 3 Global multicenter, randomized, double-blind, placebo-controlled	Previously untreated locally advanced unresectable or metastatic esophageal cancer, 1L, target N= ~700	Pembrolizumab (200 mg Q3W) or placebo in combination with chemotherapy	PFS, OS

Abbreviations: 1L=first line, 2L=second line; 2L+=second line and above, N=number of patients; OS=overall survival; ORR=objective response ratio or rate; PD-L1=programmed cell death-1 ligand-1; PFS=progression-free survival; Q2W=once every 2 weeks; Q3W=once every 3 weeks

KEYNOTE-181 is a randomized, multi-center, international, open-label trial of pembrolizumab versus the investigator's choice of paclitaxel, docetaxel, or irinotecan (SOC arm) in 628 patients with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, or advanced/metastatic Siewert type I adenocarcinoma of the esophagogastric junction (EGJ). Patients were randomized in a 1:1 ratio to receive pembrolizumab 200 mg IV every 3 weeks or investigator's choice of the one of the following agents: paclitaxel, docetaxel, or irinotecan

(determined prior to randomization). Randomization was stratified by tumor histology [squamous cell esophageal cancer (ESCC) vs. esophageal adenocarcinoma (EAC)] and by geographic region (Asia vs. ex-Asia). Enrollment into the study was performed in two periods, global enrollment and China extension enrollment, of which only the participants enrolled in the global enrollment period at 219 sites in 33 countries are included in the proposed sBLA submission. Approximately 120 subjects from China would be enrolled in the China Cohort (including 11 subjects enrolled in China during the global enrollment period).

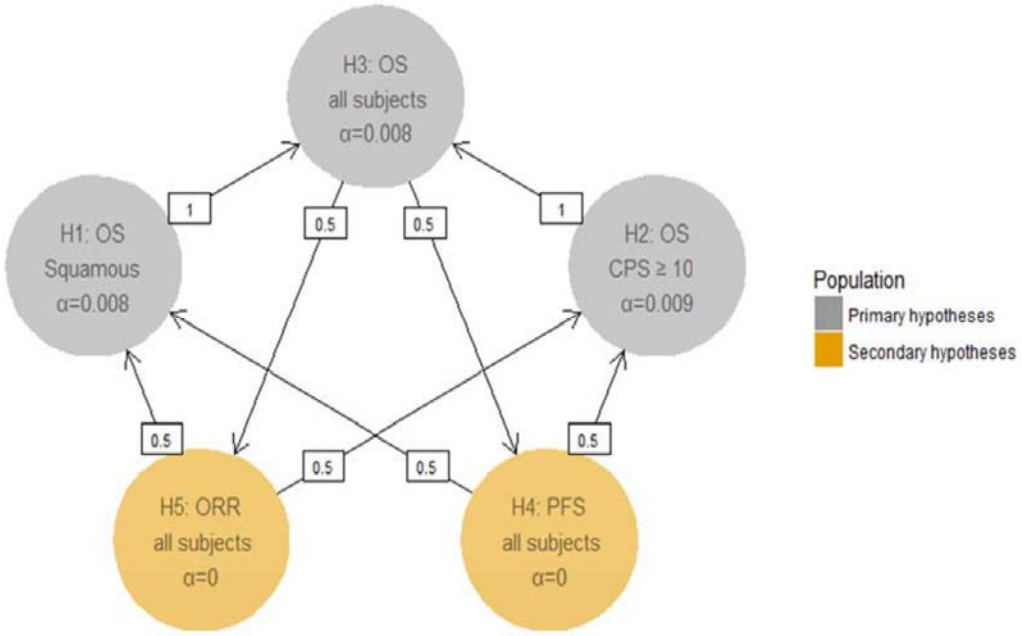
Patients with documented radiographic or clinical disease progression on one previous line of standard therapy with histologically or cytologically-confirmed diagnosis of adenocarcinoma (Siewert type 1 adenocarcinoma of the EGJ with HER -2/neu negative tumors or Her 2 positive tumors with progression on a prior line of therapy containing trastuzumab) or squamous cell carcinoma of the esophagus were enrolled regardless of PDL1 status. Patients with metastatic disease or locally advanced, unresectable disease, measurable disease per RECIST 1.1, ECOG PS 0 or 1 and adequate organ function were eligible. Patients with known central nervous system (CNS) metastases and/or carcinomatous meningitis (includes past history or current metastasis), active autoimmune disease, who have received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 antibody, or previous participation in pembrolizumab clinical trials were ineligible. The primary efficacy endpoint was overall survival (OS) evaluated in three populations (all participants, PD-L1 CPS ≥10, and ESCC). Key secondary efficacy endpoints included progression-free survival (PFS) and overall response rate (ORR) as determined by independent radiology review and RECIST 1.1 in all participants. The hypotheses of treatment difference for OS and PFS curves in participants with ESCC and in participants with PD-L1 CPS ≥10 was tested using the stratified log rank test. The hypotheses of treatment difference for OS and PFS curves in all participants was tested using the stratified maximum weighted log rank test (primary analysis) and stratified log rank test (sensitivity analysis). The stratified Miettinen and Nurminen's method was used for comparison of the ORRs between treatment arms.
One interim analysis of OS was planned to be performed after (1) enrollment is completed, (2) approximately 251 OS events and 385 OS events have been observed among subjects with ESCC and all subjects, respectively, and (3) 8 months after the last subject randomized. In addition, if there are fewer than 172 OS events among subjects with PD-L1 CPS ≥10 at the time, the interim efficacy analysis may be delayed for up to 2 months or when the target number of OS events in subjects with PD-L1 CPS ≥10 is reached, whichever occurs first. The O-Brien Fleming boundary method was utilized for alpha allocation.

The multiplicity strategy below was proposed to control the overall Type-I error rate at 2.5% (one-sided) for the three primary hypotheses:

- superiority for OS in the pembrolizumab arm among patients with ESCC;
- superiority for OS in the pembrolizumab arm among patients with PD-L1 CPS ≥10; or
- superiority for OS in the pembrolizumab arm among the intent-to-treat population (ITT) (all randomized patients); and,

for the two secondary hypotheses:

- superiority for PFS in the pembrolizumab arm in the ITT population
- superiority for ORR in the pembrolizumab in the ITT population.



Source: Figure 4 in KEYNOTE 181-05.

As of the data cutoff date of October 15, 2018, 628 participants (314 in each arm) were included in the ITT population. Treatment was ongoing in 9 (2.9%) participants in the pembrolizumab arm; no participants were ongoing in the SOC arm; 225 (71.7%) and 192 (64.9%) participants in the pembrolizumab and SOC arms, respectively, had discontinued due to disease progression. The median duration of follow-up for the final analysis was 7.1 months for the pembrolizumab arm and 6.9 months for the SOC arm. Of the 628 participants in the ITT population, the majority were male (86.6%), <65 years of age (56.7%), and white (56.1%). Sixty one percent of patients were enrolled outside Asia. A total of 401 (63.9%) participants had ESCC, 227 (36.1%) participants had EAC and EGJ Siewert type I and 222 (35.4%) participants had tumors with a PD-L1 CPS ≥10 status. 97.6% had received prior standard of care in the first line (2L participants).

Efficacy results

The trial met only one of the three co-primary endpoints (improvement in OS in the subgroup of patients with esophageal cancers having CPS ≥10), corresponding to a 2.6 month improvement in median OS. There was no alpha left for testing of secondary or other endpoints.

	Pembrolizumab	Physician's Single Agent of Choice[1]
Co-Primary Endpoints		
Overall Survival in ESCC		
Number of patients	198	203
Number of events	165	181
Median OS (months)	8.2	7.1
Hazard Ratio (95% CI)	0.78 (0.63, 0.96)	

	Pembrolizumab	Physician's Single Agent of Choice[1]
p-value (one-sided)	NS[2,3]	
Overall Survival in CPS ≥10		
Number of patients	107	115
Number of events	87	103
Median OS (months)	9.3	6.7
Hazard Ratio (95% CI)	0.69 (0.52, 0.93)	
p-value	0.0074[4]	
Overall Survival in ITT		
Number of patients	314	314
Number of events	270	283
Median OS (months)	7.1	7.1
Hazard Ratio	0.89 (0.75, 1.05)	
p-value	NS[2,5]	

[1] docetaxel, paclitaxel, or irinotecan

[2] NS=non-significant

[3] p=0.0095 (one-sided) as compared to p=0.0077 (one-sided)

[4] p=0.0074 (one-sided) as compared to p=0.0085 (one-sided)

[5] p=0.0874 (one-sided) as compared to p=0.0162 (one-sided)

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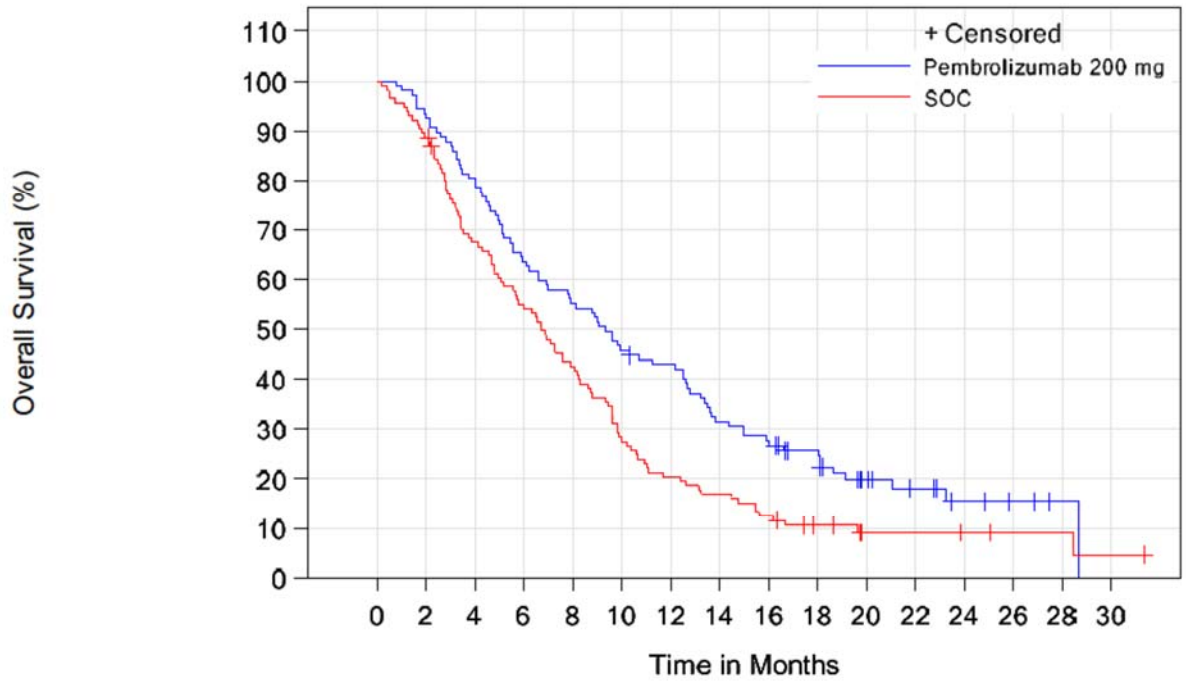
Figure 2 **Kaplan-Meier Estimates of Overall Survival (ITT Population, Subjects with PD-L1 CPS ≥10)**



Number of subjects at risk

Pembrolizumab 200 mg	107	100	86	68	59	49	45	33	29	23	13	9	5	3	1	0
SOC	115	102	76	61	48	31	23	19	14	8	4	4	3	2	2	1

The secondary endpoints of comparing PFS and ORR in the ITT population cannot be tested formally, as there is no alpha remaining for these comparisons. Therefore, all analyses of secondary endpoints are considered exploratory.

In exploratory analyses of PFS and ORR in the subgroup of patients with esophageal cancers with CPS ≥10, there was no indication of a detrimental effect on PFS or ORR with pembrolizumab as compared to chemotherapy.

Merck attempted to evaluate MSI tumor status for patients enrolled in KN-181 who achieved a confirmed or unconfirmed response per RECIST v1.1 and was able to obtain tissue from 102 of the 628 patients enrolled. Of these 102 patients, a result for MSI-H status was obtained in 93% (n=95) of the 102 patients. One (1%) of these 95 patients had an MSI-H tumor and the remaining 99% had either MSS or MSI-L status.

Safety
Merck states that adverse reactions reported in those who received pembrolizumab were "generally consistent" with the established safety profile for pembrolizumab.

FDA preliminary comments were emailed to Merck on January 23, 2019.

SPONSOR QUESTIONS AND FDA RESPONSES

1. *KEYNOTE-181 is a randomized, multi-center, open-label Phase 3 trial of pembrolizumab versus the investigator's choice of paclitaxel, docetaxel, or irinotecan in participants with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, or advanced/metastatic Siewert type I adenocarcinoma of the EGJ. Does the Agency agree that the results from KEYNOTE-181 could support consideration for regular approval for the treatment of patients with* (b) (4) [redacted] ,,

   FDA Response:
   Yes, FDA agrees that demonstration of a statistically significant improvement in OS in the subgroup of patients with (b) (4) [redacted] enrolled in Study KN-181 would support the filing of an application seeking traditional approval of pembrolizumab for this indication. However, a final determination regarding approval, including the risk:benefit assessment, will be made after the sBLA is submitted.

   For a single randomized trial to support a sBLA, the trial should be well designed, well conducted, and internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. A determination that the results of KN-181as a single trial constitute substantial evidence of clinical benefit will be based upon the magnitude and statistical robustness of the effect on OS and the risk:benefit assessment as determined during the sBLA review. Please refer to the FDA Guidance for Industry, entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf.

   Discussion:
   Merck did not have any questions or comments.

2. *Given the clinically meaningful and favorable treatment effect of pembrolizumab monotherapy in patients with squamous cell esophageal cancer in KEYNOTE-181 and the high unmet medical need in this patient population, would the FDA consider an indication for the treatment of* (b) (4) [redacted]

   FDA Response:
   (b) (4) [redacted]

[redacted] (b) (4)

Discussion:
Merck did not have any questions or comments.

3. *The Sponsor is targeting submission of this sBLA in late January 2019 and the initial data cutoff for the KEYNOTE-181 final analysis is 15-OCT- 2018. Does the Agency agree with the Sponsor's plan to not provide a SUR?*

FDA Response:
Yes, FDA agrees that given the established safety profile of pembrolizumab as a single agent in more than 3000 patients, a safety update is not needed to characterize the safety of the proposed dose and schedule of pembrolizumab for the proposed population.

Discussion:
Merck did not have any questions or comments.

4. *Merck is planning to submit a dossier consisting of the KEYNOTE-181 CSR as the pivotal study and reference the previously submitted KEYNOTE-180 and KEYNOTE-028 Cohort A4 CSRs (submitted as a supplement to BLA 125514, in seq. 629 on 01-NOV-2018) as supportive data from pembrolizumab monotherapy in previously treated patients with esophageal cancer. In addition, Merck is planning to provide Modules 2.5, 2.7.2, 2.7.3, 2.7.4 and an ISS. Does the Agency agree that a dossier with these components would be acceptable to support review of the sBLA?*

FDA Response:
Yes, FDA agrees to the proposed components of the dossier but insufficient information regarding its contents was provided for FDA to agree on the detailed contents of the ISE, ISS and SCS.

Discussion:
See Merck's slides #7, #10, and #11.

FDA acknowledged the information presented in the slides and advised that it appears acceptable.

FDA asked whether the Summary of Clinical Efficacy for the sBLA based on the results of KN-181would contain an integrated assessment of efficacy placing the results from KN-180 in the context of the results from KN-181. Merck stated that the sBLA will contain a tabular presentation of efficacy results by trial, but will not contain a discussion addressing this question. Merck stated that they will provide an analysis of the efficacy of pembrolizumab [redacted] (b) (4) for esophageal cancer in the context of the results of KN-181 either in the original sBLA or as an amendment.

FDA clarified that the efficacy data did not need to be pooled given the differences in the patient populations studied.

5. *The safety analysis proposed for inclusion in Module 2.7.4 and the ISS for this sBLA will consist of a 4 column table with the following format to facilitate review of the safety data of pembrolizumab monotherapy in previously treated patients with esophageal cancer: KEYNOTE-181 pembrolizumab monotherapy dataset, esophageal pooled pembrolizumab monotherapy dataset (KEYNOTE-181/KEYNOTE-180/KEYNOTE-028-Cohort A4), Reference Safety Dataset for pembrolizumab monotherapy (KEYNOTE-001/KEYNOTE 002/KEYNOTE 006/KEYNOTE 010), and cumulative pembrolizumab monotherapy safety dataset. Does the Agency agree with this approach to presenting the safety data in Module 2.7.4 and the ISS?*

FDA Response:
Yes, in general FDA agrees with the skeleton summary of the safety analysis plan described in the meeting package. However, the meeting package contains insufficient details regarding the proposed format and content of the safety analyses for FDA to provide concurrence with the contents of the SCS and ISS. The meeting package is also missing details on the presentation of safety information including the approach to the analysis of key adverse reactions of interest and approach to combining related preferred terms. FDA recommends that the analysis of adverse reactions employ the same approach for aggregating related preferred terms that is currently used to describe adverse reactions in the approved prescribing information for Keytruda. For any planned deviations in the list of preferred terms that will be used for a composite adverse reaction term, please provide justification for the change. Also include an analysis of safety in key subgroups such as age, gender, and other key baseline characteristics.

Discussion:
See Merck's slides #8-11.

FDA acknowledged the information presented in the slides and advised that it appeared acceptable.

6. *A Study Data Standardization Plan (SDSP) in support of the development program and registration of pembrolizumab for patients with previously treated esophageal cancer as described in Question 1 was submitted on January 3, 2019, as an amendment to the meeting package. Is the Agency in agreement with the SDSP, prepared in accordance with the Study Data Technical Conformance Guide v4.1 dated 30-MAR-2018?*

FDA Response:
Merck has indicated that the sBLA will be fully compliant with current C-DISC standards and MedDRA version 21, therefore the proposed Study Data Standardization Plan appears acceptable.

Discussion:
Merck did not have any questions or comments.

FDA ADDITIONAL COMMENTS

7. Confirm that the proposed sBLA will contain a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of independent review committee determined PFS (or investigator assessed PFS) event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity Analysis of the SAP should be included as well.

   Discussion:
   Merck did not have any questions or comments.

8. Include the following in the sBLAs:

   a. SAS programs that produced all efficacy results;

      Discussion:
      Merck did not have any questions or comments.

   b. All raw as well as derived variables in .xpt format;

      Discussion:
      Merck did not have any questions or comments.

   c. SAS programs by which the derived variables were produced from the raw variables;

      Discussion:
      Merck did not have any questions or comments.

   d. Results of any interim analysis, if performed; and,

      Discussion:
      See Merck's slide #14.

      FDA asked Merck to provide the number of events that occurred at the time of the interim analysis for each patient population. Merck agreed to do so.

   e. PRO data if Merck has done any analyses.

      Discussion:
      Merck did not have any questions or comments.

9. Pending resolution of the lapse in appropriations, FDA is unable to accept sPMAs. FDA recommends that DAKO submit the sPMA data in a presubmission for agency review.

Discussion:
Merck did not have any questions or comments.

ADDITIONAL DISCUSSION ITEM

10. Merck stated that they would like to align with the FDA clinical review division on the communication plan (e.g., scheduled teleconferences) for the RTOR process for the proposed supplements based on KEYNOTE-180 and KEYNOTE-181 as indicated in the FDA SOP on the RTOR Pilot. Merck proposed regularly scheduled teleconferences with the FDA clinical review division as part of the RTOR Pilot. Merck stated that this is based on the suggestion in the FDA SOP and would provide a regular forum if needed for discussing any questions the review division might have. If there is not a topic for discussion for the week, then the meeting could be canceled.

    FDA stated that they need to discuss internally and would get back to Merck.

    Post-Meeting Addendum:
    FDA proposed a teleconference approximately two weeks after receipt of the sBLA submissions, around the time of filing each submission, and then as needed. Merck agreed to this plan.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review

resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products;
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential;
- Regulations and related guidance documents. A sample tool illustrating the format for Highlights and Contents; and,
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in

submission in the format described, the Applicant can describe location or provide a link to the requested information.

ATTACHMENT
Merck's presentation

16 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SHARON K SICKAFUSE
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