CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s055

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

125514Orig1s055

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s055

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:

125514Orig1s055

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.

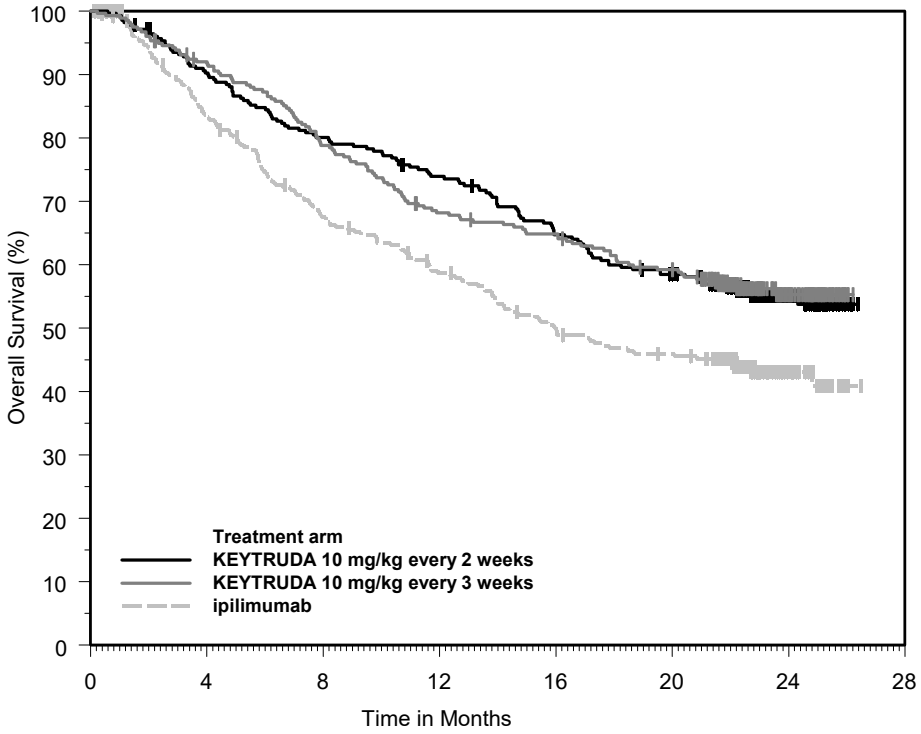
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients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

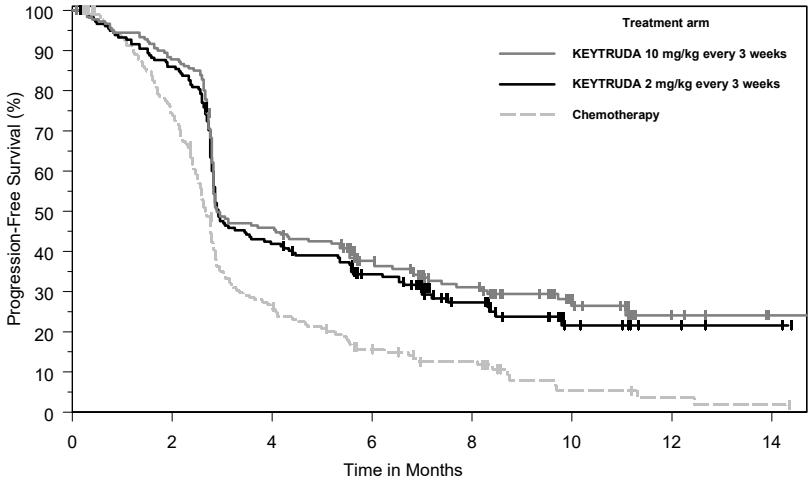
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8,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

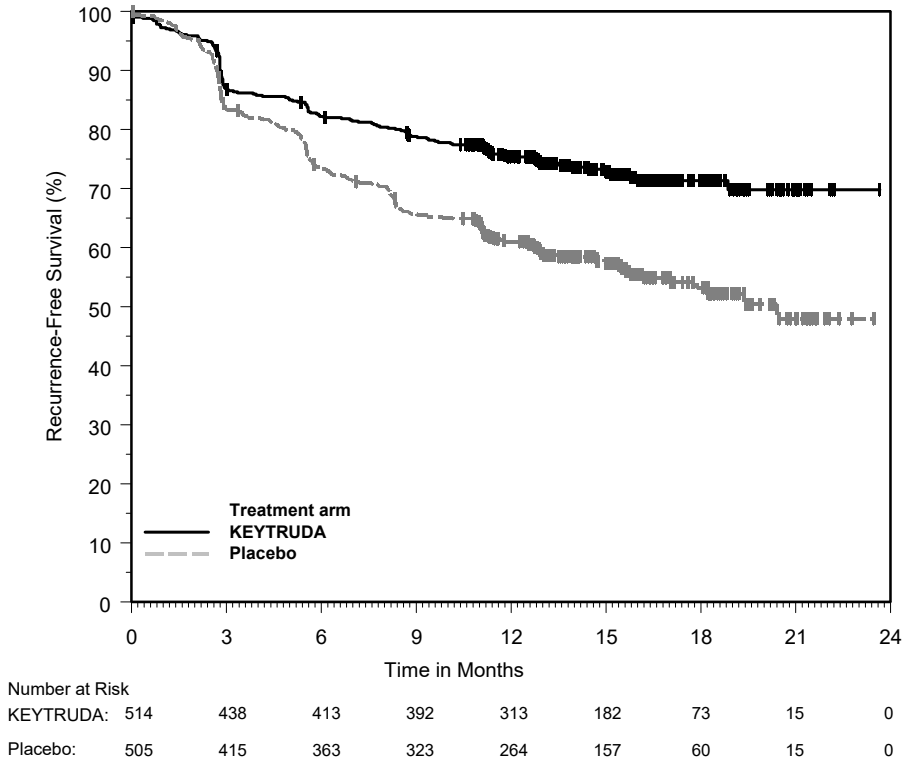
† Stratified by American Joint Committee on Cancer 7th edition (AJCC) stage

± 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.

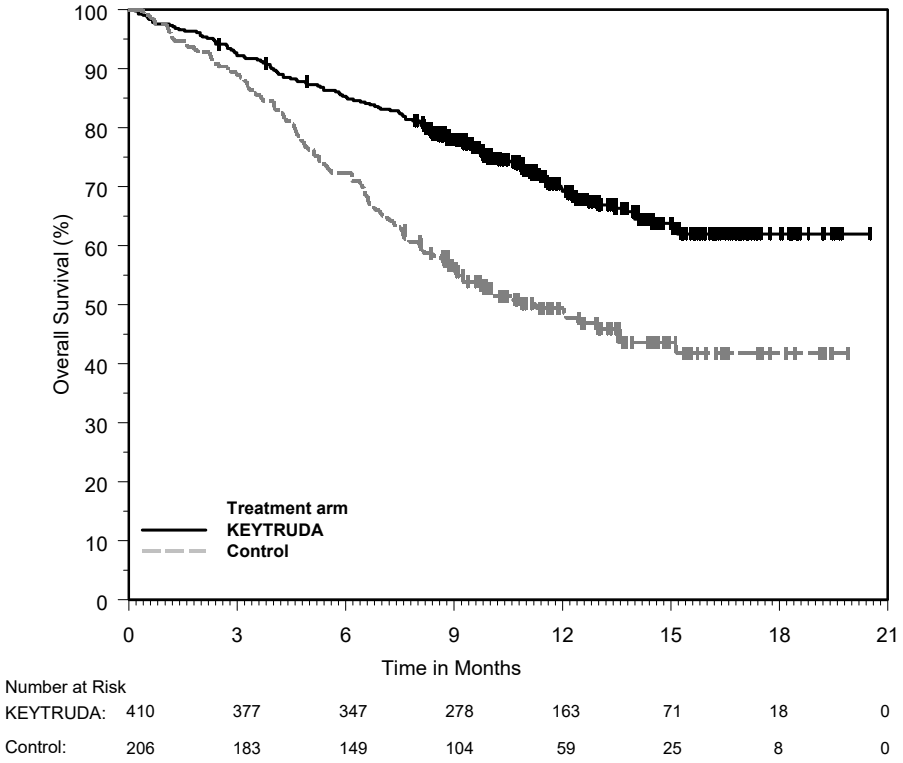
The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 30 and Figure 4 summarize the efficacy results for KEYNOTE-189.

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.

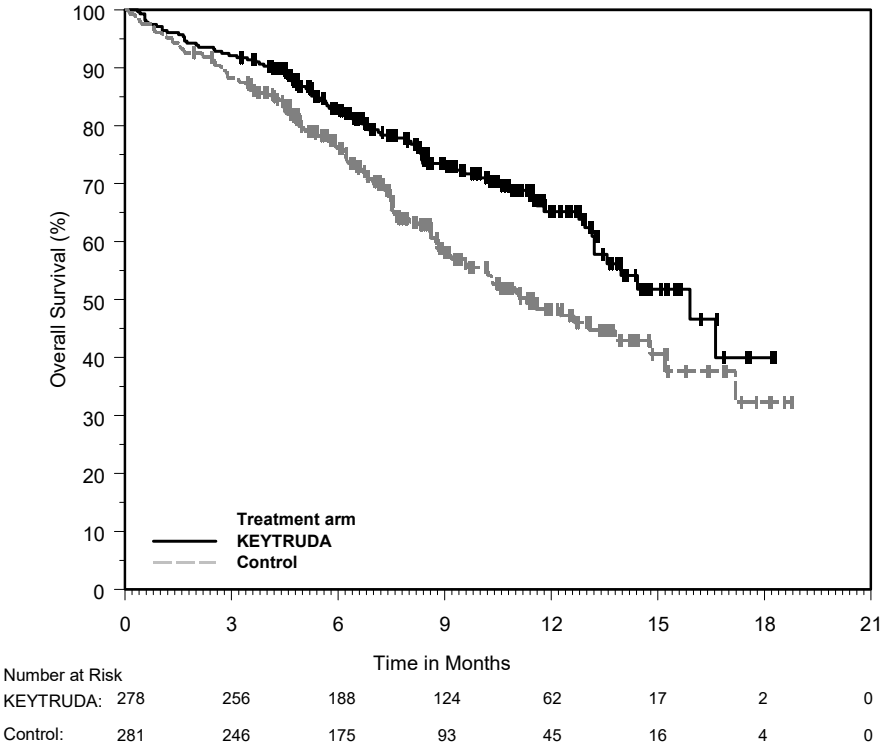
The trial demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy compared with patients randomized to placebo with carboplatin and either paclitaxel or paclitaxel 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%.

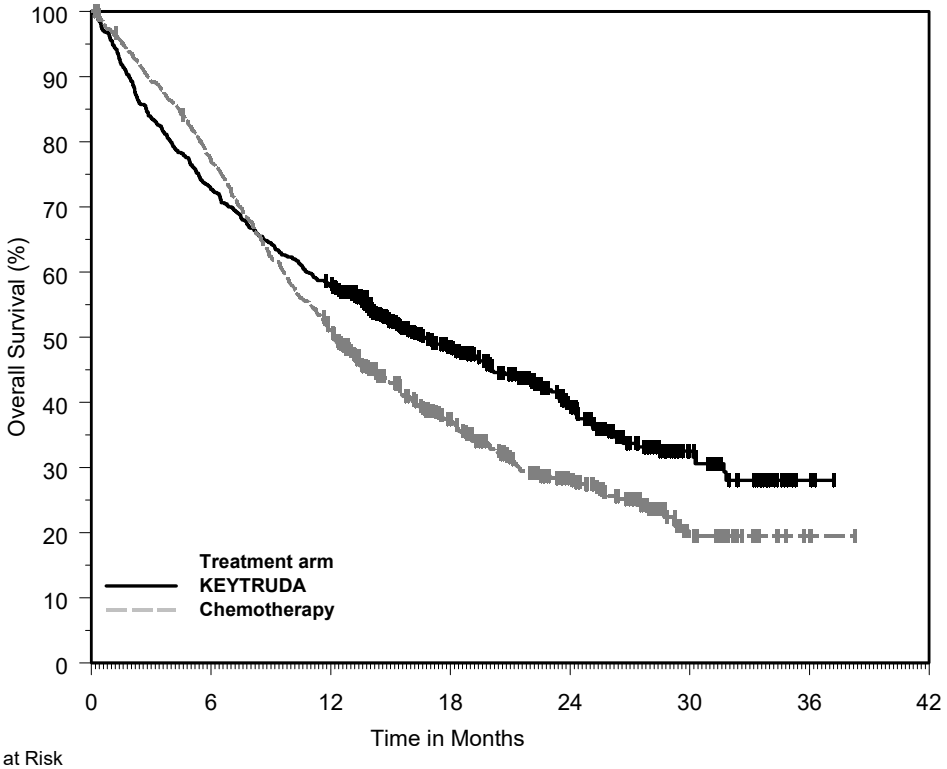
Table 32: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

	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+)

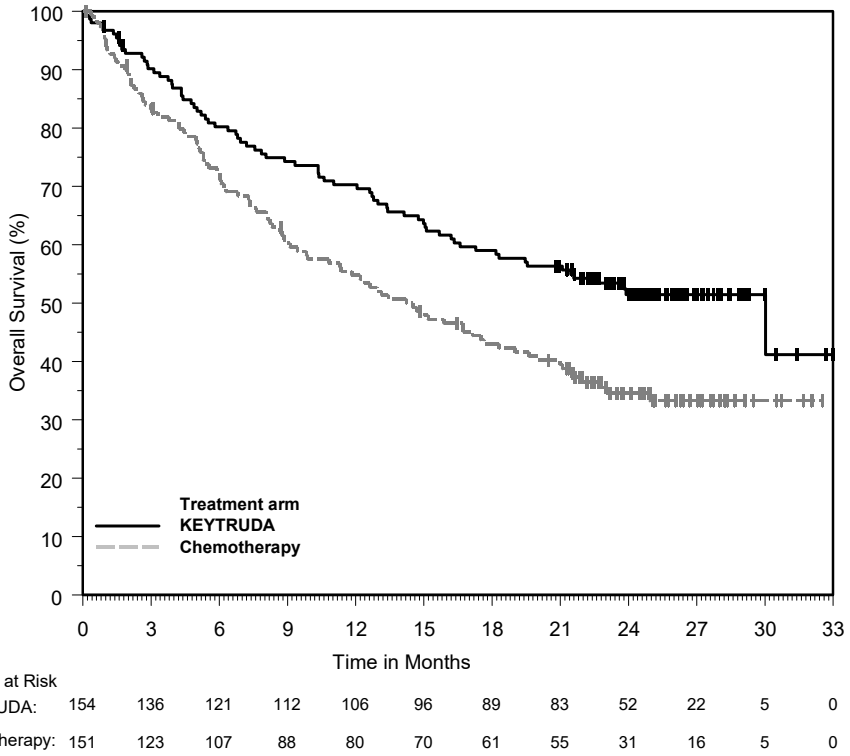
* Based on the stratified Cox proportional hazard model for the interim analysis

† 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

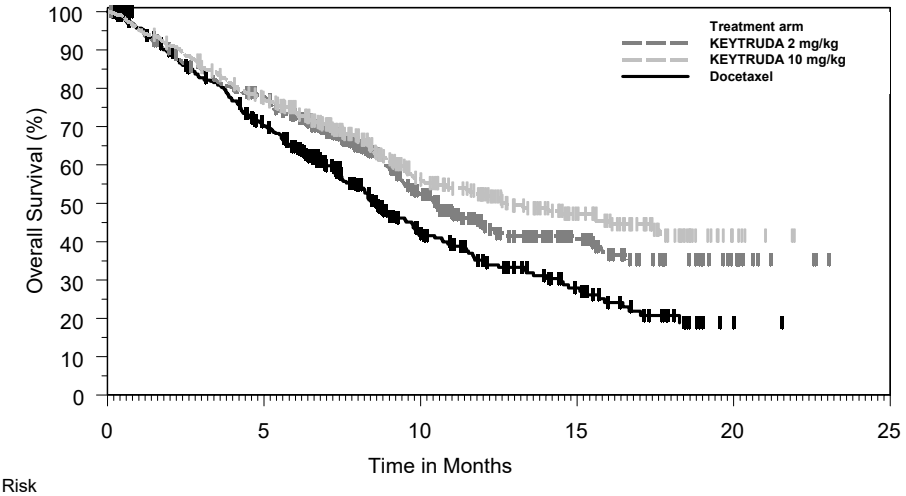
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)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

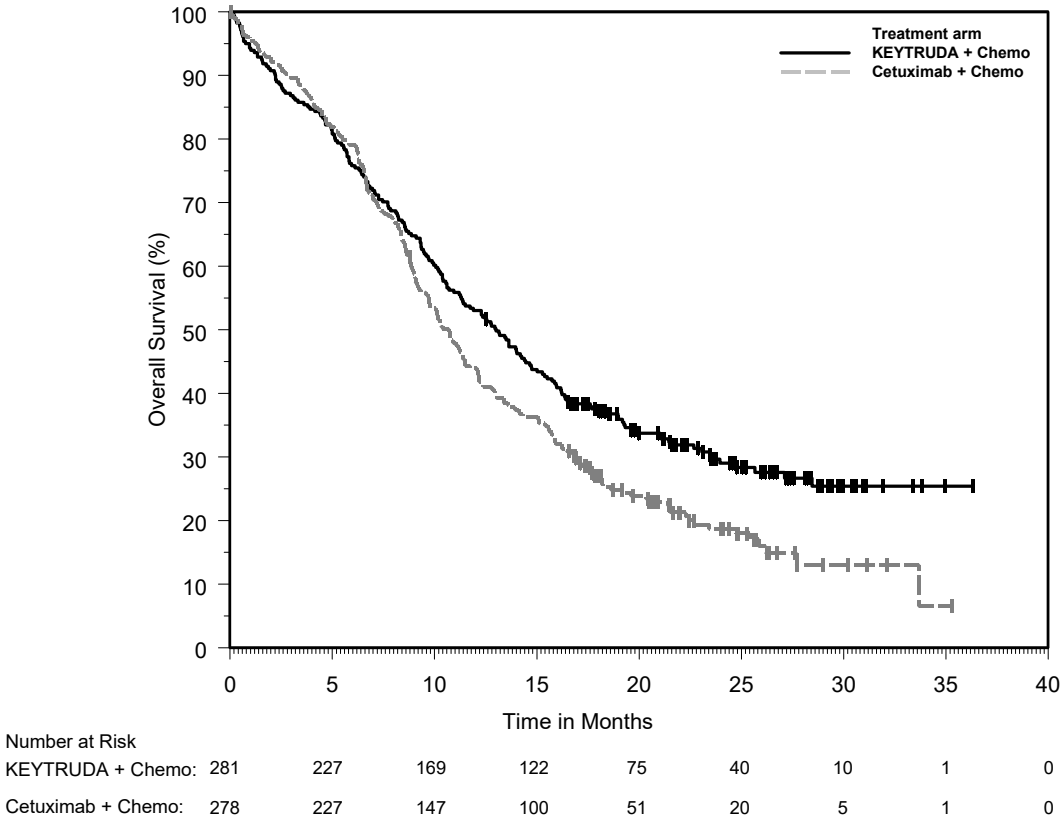


Table 38 summarizes efficacy results for KEYTRUDA as a single agent in the subgroups of patients with CPS ≥1 HNSCC and CPS ≥20 HNSCC. Figure 10 summarizes the OS results in the subgroup of patients with CPS ≥1 HNSCC.

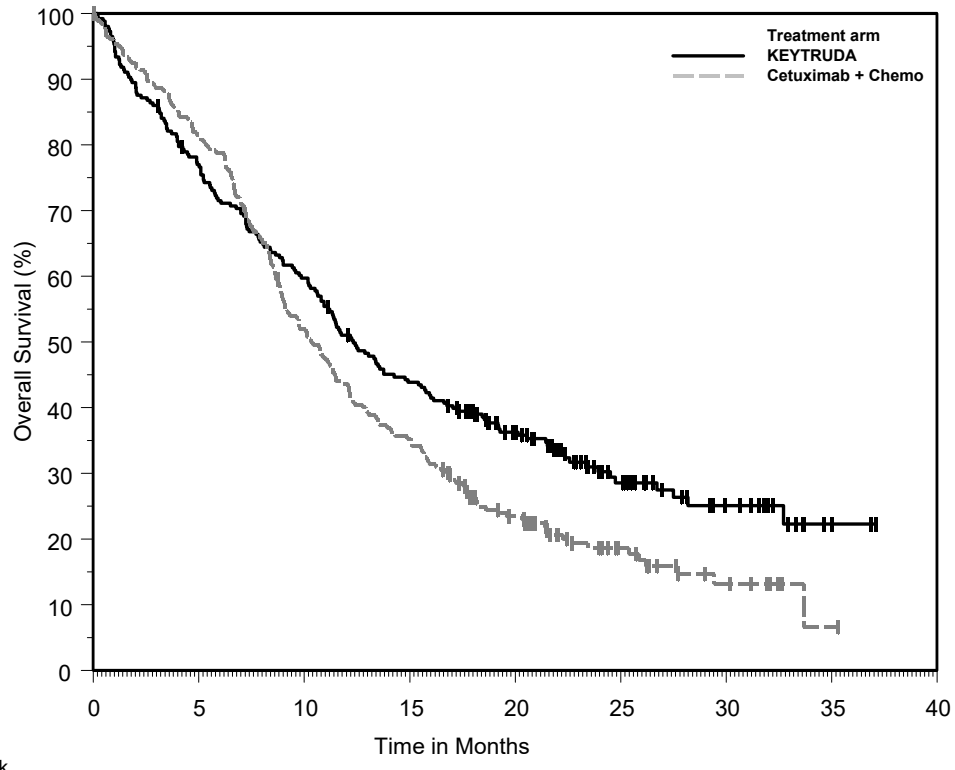
Table 38: Efficacy Results for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)

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

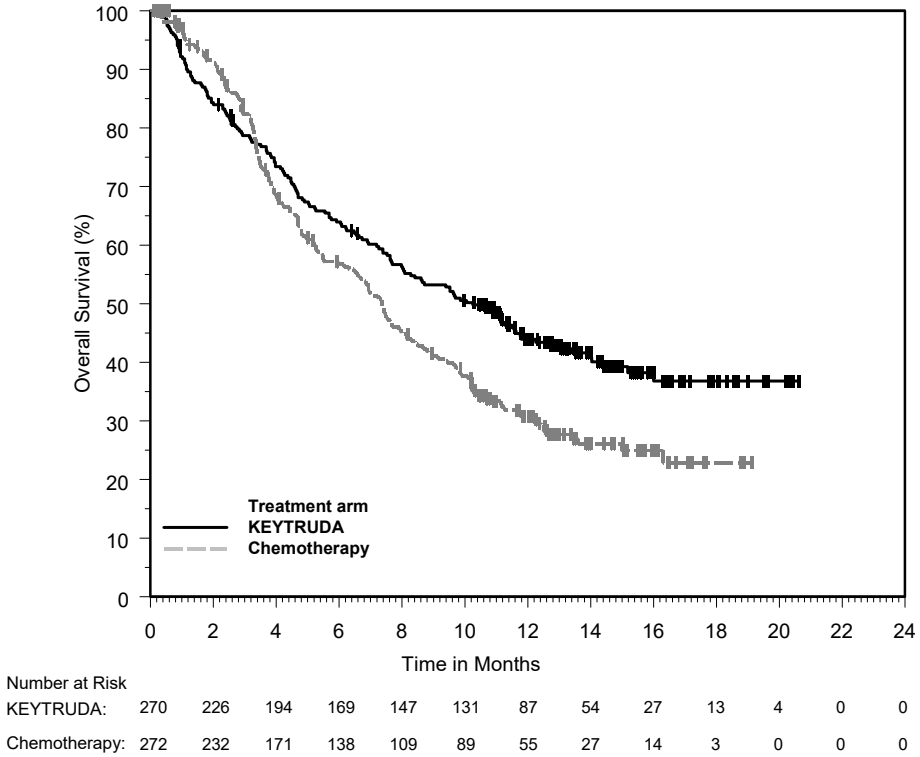
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1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

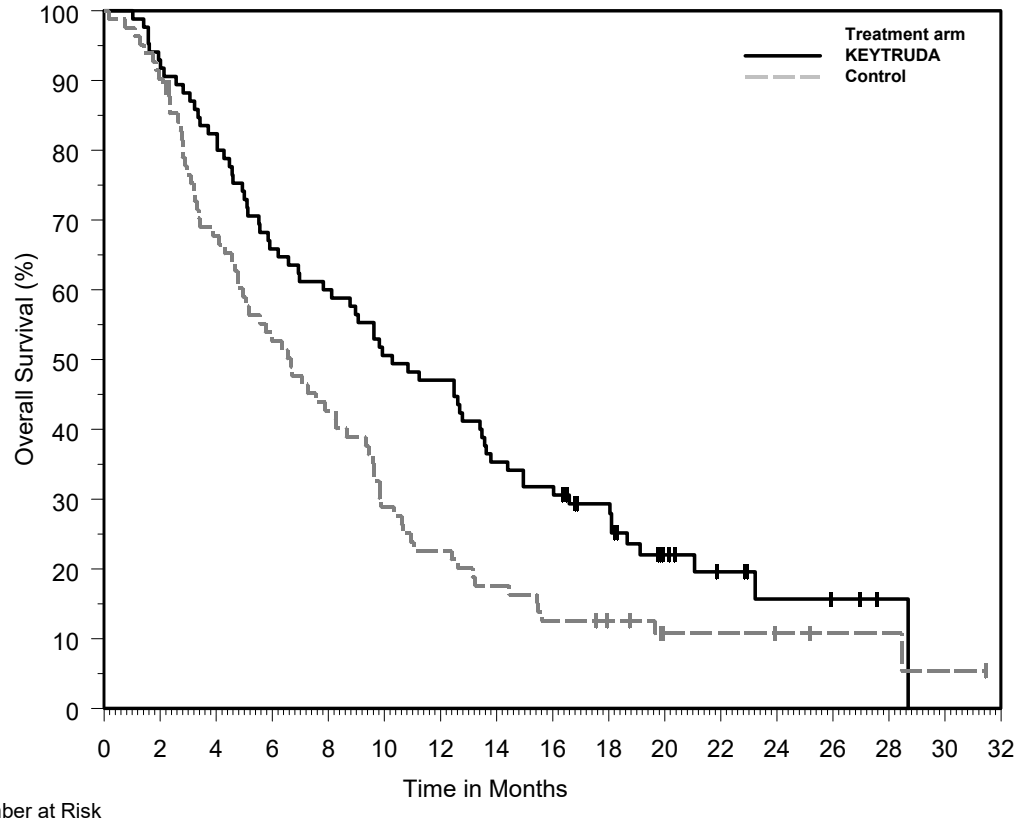
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement 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

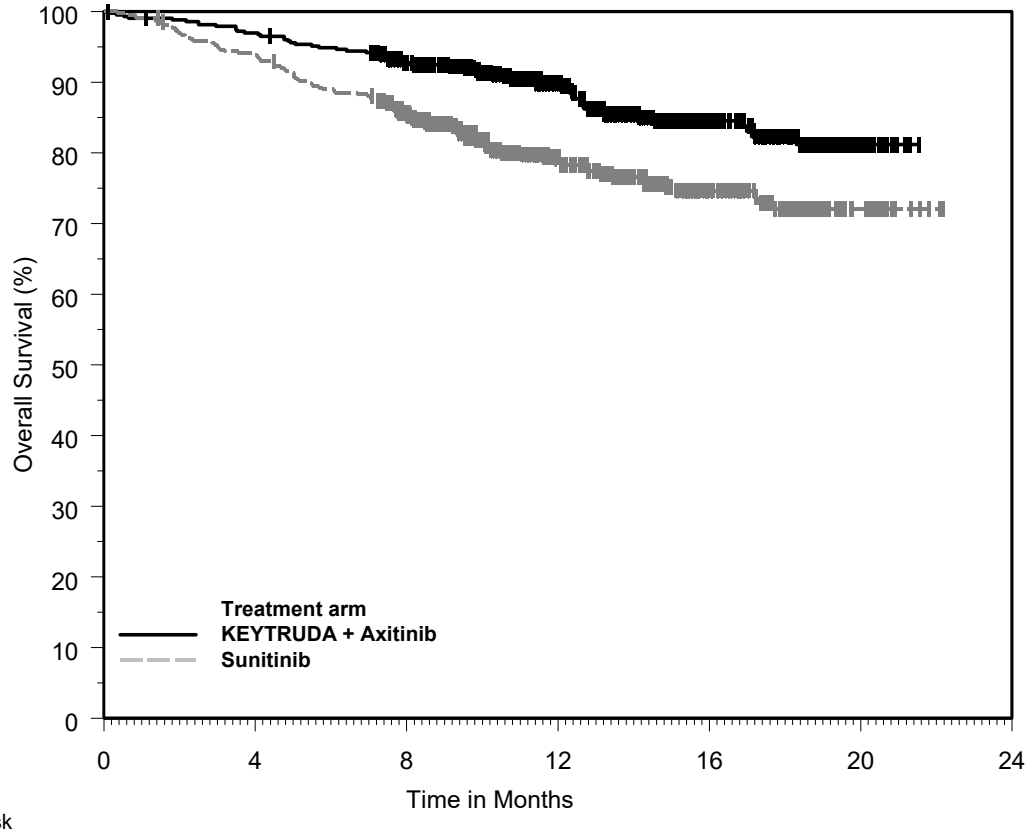
‡ p-Value (one-sided) is compared with the allocated alpha of 0.0001 for this interim analysis (with 39% of the planned number of events for final analysis).

§ 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:

125514Orig1s055

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	125514/S-55
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	7-30-2019
Established Name	Pembrolizumab
Trade Name	Keytruda
Pharmacologic Class	Programmed Death-Receptor-1 (PD-1) Blocking Antibody
Applicant	Merck Sharp & Dohme Corp.
Formulations	For Injection: 50 mg lyophilized powder 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)
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.

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OPDP=Office of Prescription Drug Promotion

Glossary

1L	first-line
2L	second-line
2L+	second-line or later therapies (participants who have received 1 or more prior therapies)
3L	third-line
3L+	third-line or later therapies (participants who have received 2 or more prior therapies)
4L+	fourth-line or later therapies (participants who have received 3 or more prior therapies)
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEOSI	adverse event of special interest
ALP	alkaline phosphatase
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	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
CF	cisplatin and fluorouracil
CFR	Code of Federal Regulations
cHL	classical Hodgkin Lymphoma
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
COG	Gefitinib for Oesophageal Cancer Progressing after Chemotherapy Study
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
CTD	Common Technical Document
DCR	disease control rate
DMC	data monitoring committee
dMMR	mismatch repair deficient
DOR	duration of response
EAC	esophageal adenocarcinoma
ECG	electrocardiogram
ECI	event of clinical interest
ECOG PS	Eastern Cooperative Oncology Group performance status
eCTD	electronic common technical document
GEJ	gastroesophageal junction adenocarcinoma
ESCC	esophageal squamous cell carcinoma
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GE	gastroesophageal
GEJ	gastroesophageal junction
GEP	intratumoral immune-related gene expression profile
GRMP	good review management practice
HCC	hepatocellular carcinoma
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
ICH	International Conference on Harmonization
IHC	immunohistochemistry
IND	Investigational New Drug
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
mAb	monoclonal antibody
MARRS	Merck Adverse event Reporting and Review System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRL	Merck Research Laboratories

MSI-H	microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSCLC	non-small cell lung cancer
Q3W	every 3 weeks
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiologically based pharmacokinetic modeling
PBRER	Periodic Benefit-Risk Evaluation Report
PD	progressive disease
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
PFS	progression free survival
PI	prescribing information
PK	pharmacokinetic(s)
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
PSUR	Periodic Safety Update report
PT	preferred terms
QA	quality assurance
QC	quality control
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RSD	reference safety dataset
RTOR	real time oncology review
sBLA	supplemental biologics license application
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGE	special government employee
SOC	standard of care
SLR	systematic literature review

TCF	taxotere in combination with cisplatin and fluorouracil
TEAE	treatment emergent adverse event
TPS	tumor proportion score
TTP	time to progression
UC	urothelial carcinoma
USPI	United States Prescribing Information
VEGFR	vascular endothelial growth factor receptor

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). Prior to this approval, pembrolizumab was not approved for the treatment of patients with esophageal cancer other than microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) esophageal cancers. 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 the observation of highly durable response rate in this subpopulation of patients receiving third and later line treatment in a single arm trial, KEYNOTE-180 (submitted to this sBLA), supported by the evidence of effectiveness observed in an additional single, adequate and well-controlled, randomized trial, KEYNOTE-181 (data submitted under sBLA 125514/S-56). In KEYNOTE-181, a clinically meaningful improvement in overall survival (OS) was observed in patients with PD-L1+ (CPS ≥10) ESCC who had received one prior line of systemic chemotherapy and were randomized to pembrolizumab compared to those randomized to a single agent systemic treatment of the treating physician's choice (TPC).

KEYNOTE-180 (NCT02559687) is a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer with disease progression 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 dosage regimen for pembrolizumab was identical. The major efficacy outcome measures were 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.

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. Patients with responses were confirmed not to have MSI-H tumors.

A key review issue during review of this sBLA was identification of the patient population that derived clinical benefit from pembrolizumab. In KEYNOTE-180, the ORR (according to independent central review per RECIST 1.1) was 9.9% (95% CI: 5.2,16.7) for the overall population (n=121). The majority (9/12) of responding patients had ESCC and/or PD-L1+ tumors (8/12). Although interpretation of differences in efficacy across subsets is difficult due to the small sample size of KEYNOTE-180, the review team determined that pembrolizumab was effective for the second-and later-line treatment of patients with recurrent advanced or metastatic ESCC whose tumors express PD-L1 (CPS ≥10) based upon observed differences in response rate observed in KEYNOTE-180, together with the following additional information:

- Results of KEYNOTE-181, which demonstrated a clinically meaningful improvement in OS in patients with recurrent locally advanced or metastatic ESCC whose tumors express PD-L1 (CPS ≥10) following receipt of one prior systemic chemotherapy who were randomized to placebo compared to a control arm consisting of a single-agent chemotherapy chosen by the investigator prior to randomization (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.
- The totality of data with pembrolizumab in other cancers, such as non-small cell lung cancer and gastric cancer, where increased efficacy was demonstrated in a subpopulation with PD-L1 positive tumors.
- Emerging clinical knowledge regarding the biological differences between ESCC and EAC suggesting that underlying differences in tumor molecular characteristics 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 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.

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, approximately 17,650 new cases of EC will be diagnosed and 16,080 people will die of their disease in 2019 [24]. Nearly 50% of patients diagnosed with esophageal cancer present with metastatic disease [2]. The 5-year survival rate of advanced unresectable or metastatic EC is 3.4% [3]. 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 [4], EAC predominates in the US, accounting for 63.5% of all EC cases [5]. 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, NCCN treatment guidelines [10] 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 anti-tumor activity of pembrolizumab for the treatment of with patients with PD-L1 positive (CPS ≥10) ESCC who had received at least two prior lines of systemic treatment was established by the results of a single trial, KEYNOTE-180 (NCT02559687). KEYNOTE-180 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. The major efficacy outcome measures were 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 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 clinical benefit of pembrolizumab was verified by the results of an adequate and well-controlled trial, KEYNOTE-181, submitted to sBLA 125514/S-56. 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 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 Keytruda 200 mg intravenously (IV) every 3 weeks or a treatment of physician's choice (TPC) consisting of single-agent treatment with any one of the following drugs, all given intravenously: paclitaxel 80-100 mg/m^2 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. 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 Keytruda or chemotherapy continued until unacceptable toxicity, disease progression, or a maximum of 24 months. 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. 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), 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 pembrolizumab (n=314) 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 KEYTRUDA 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 (ITT population); however, in an exploratory analysis conducted in patients whose ESCC tumors expressed PD-L1 (CPS ≥10) based on the observations in KEYNOTE-180, a larger treatment effect on 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.

The review of safety for this new indication was based primarily upon data from KEYNOTE-180 and KEYNOTE-181. The adverse event profile observed in the more refractory patient population treated with pembrolizumab in KEYNOTE-180 (n=121) was consistent with the known safety profile of pembrolizumab and the safety results of KEYNOTE-181. The most frequently reported (incidence ≥20% of patients) AE in KEYNOTE-180 was fatigue (28.1%). The most frequently reported (incidence ≥2% of patients) SAE in KEYNOTE-180 were pneumonia (10.7%), aspiration pneumonia (4.1%), acute kidney injury (3.3%), lung infection (2.5%), and pneumonitis (2.5%). The proportion of patients who experienced AEs leading to treatment discontinuation in KEYNOTE-180 was 10.7%. The most frequently reported (incidence ≥2% of participants) AE leading to treatment discontinuation was pneumonitis (3.3%). The most frequently reported (incidence ≥2% of participants) AEs leading to treatment interruption were pneumonia (5.0%), malaise (3.3%), diarrhea, AST increased, and blood bilirubin increased (2.5% each. Immune-mediated adverse events reported in ≥1% of patients included hypothyroidism (9.1%), pneumonitis (7.4%), hyperthyroidism (3.3%), colitis (2.5%), hypophysitis (1.7%), and type 1 diabetes mellitus (1.7%). Of the 9 patients with pneumonitis, one had a fatal event. The incidence of pneumonitis in KEYNOTE-180 (7.4%) was higher than the incidence of pneumonitis in the reference safety dataset for pembrolizumab (3.4%). It is likely that this observed difference is related to receipt of radiation therapy to the chest wall area in many of the patients enrolled in KEYNOTE-180, and reflects the increased risk for pneumonitis in this population. Drug-related deaths were infrequent with an incidence of 0.8% (1 event of pneumonitis).

In 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. The ORR and DOR observed in KEYNOTE-180 are clinically meaningful in this highly refractory patient population enrolled in this trial. Importantly, the clinical benefit of pembrolizumab in patients with PD-L1+ (CPS ≥10) recurrent or metastatic ESCC was verified through the observed improvement in OS in patients randomized to pembrolizumab compared to TPC in the second-line setting in KEYNOTE-181. 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 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 , and the risk:benefit assessment favors treatment with pembrolizumab in the patient population recommended for approval.

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.	EC is a serious and life threatening disease, with a 5-year survival rate of 3.4%.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The 5-year survival rate of advanced/metastatic EC is approximately 3.4% [3]. • 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 [4], EAC predominates in the US, accounting for 63.5% of all EC cases [5].	
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. • 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, NCCN treatment guidelines [10] 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), which show marginal benefit.	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.
Benefit	• In KEYNOTE-180, among the 121 patients with locally advanced or metastatic EC who progressed on or after at least 2 prior systemic treatments for advanced disease, 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	KEYNOTE-180 demonstrated a clinically meaningful ORR and DOR in patients with recurrent locally advanced or metastatic ESCC whose tumors express PD-L1 (CPS ≥10) with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 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.	disease progression after two or more prior lines of systemic therapy. The clinical benefit of pembrolizumab in patients with recurrent locally advanced or metastatic ESCC whose tumors express PD-L1 (CPS ≥10) was verified in KEYNOTE-181, through demonstration of 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. (See FDA's review of sBLA 125514/S-56 for details).
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-180 and KEYNOTE-181 is consistent with the known safety profile of pembrolizumab. Additionally, KEYNOTE-181 showed an OS benefit for patients with PD-L1+ (CPS ≥10) ESCC, which further supports the safety of pembrolizumab in this patient	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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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. • The primary risks of pembrolizumab are immune-mediated adverse reactions and infusion-related reactions. • The most frequently reported (incidence ≥2% of patients) SAE in KEYNOTE-180 were pneumonia (10.7%), aspiration pneumonia (4.1%), acute kidney injury (3.3%), lung infection (2.5%), and pneumonitis (2.5%). The proportion of patients who experienced AEs leading to treatment discontinuation in KEYNOTE-180 was 10.7%. The most frequently reported (incidence ≥2% of participants) AE leading to treatment discontinuation was pneumonitis (3.3%). The most frequently reported (incidence ≥2% of participants) AEs leading to treatment interruption were pneumonia (5.0%), malaise (3.3%), diarrhea, AST increased, and blood bilirubin increased (2.5% each). • Immune-mediated adverse events reported in ≥1% of patients in KEYNOTE-180 included hypothyroidism (9.1%), pneumonitis (7.4%), hyperthyroidism (3.3%), colitis (2.5%), hypophysitis (1.7%), and type 1 diabetes mellitus (1.7%). Of the 9 patients with pneumonitis, one had a fatal event. The incidence of pneumonitis in KEYNOTE-180 (7.4%) was higher than the incidence of pneumonitis in the reference safety dataset for pembrolizumab (3.4%). It is likely that this observed difference is related to receipt of radiation therapy to the chest wall	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
	area in many of the patients enrolled in KEYNOTE-180, and reflects the increased risk for pneumonitis in this population. Drug-related deaths were infrequent with an incidence of 0.8% (1 event of pneumonitis)	

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)	
			☐	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.		

This application did not include patient experience data.

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, esophageal cancer is considered an orphan disease. The American Cancer Society estimates that in the US in 2019, 17,650 new cases of esophageal cancers will be diagnosed and 16,080 people will die of their disease (https://www.cancer.org/cancer/esophagus-cancer/about/key-statistics.html). Nearly 50% of patients diagnosed with esophageal cancer present with metastatic disease [2], and the 5-year survival rate of advanced/metastatic esophageal cancer remains at 3.4% [3]. The poor prognosis of advanced esophageal cancer underscores the need for new therapies to improve long-term outcomes.

The incidence and histological type of esophageal cancer varies with geographic location. While the rate of ESCC exceeds EAC in more than 90% of all countries [4], in the US, EAC predominates, accounting for 63.5% of all esophageal carcinoma cases [5].

The FDA's Assessment:
FDA agrees with Merck's assessment of the prevalence and serious nature of unresectable or metastatic esophageal cancer.

2.2 Analysis of Current Treatment Options

The Applicant's Position:
There is no established standard of care and no FDA-approved treatment for (b) (4) [redacted]. Once patients experience disease progression (b) (4) [redacted], best supportive care or study participation have been the options available.

An estimated ≤15% of this population who have started a 1L regimen are candidates for further systemic therapy [6], and even fewer maintain adequate performance status to be eligible for clinical studies. As a result, there are little data in this clinical setting to support further therapy with any therapeutics. Furthermore, treatment guidelines have been extrapolated from gastric and gastroesophageal junction cancer studies, despite the differences in biology between gastric and esophageal cancers [7].

Cytotoxic chemotherapies have remained the mainstay treatment in metastatic esophageal cancer for decades, although they are not approved by FDA for 3L therapy or beyond. No consistent benefit has been seen from any specific chemotherapy regimen, and no survival benefit has been seen compared to best supportive care [8]. Taxanes (docetaxel or paclitaxel) or irinotecan are routinely used for 2L esophageal cancer if patients are fit for further therapy [9] [10] [11]. In the 2L setting, taxanes or irinotecan monotherapy have a marginal benefit with a wide range of ORR (0% to 28%), a median OS ranging from 4 months to about 8 months, and a brief duration of response, typically ranging from 4 to 6 months [12] [13] [14] [15] [16] [17] [18] [19] [2] [10]. Overall, evidence to support treatment with chemotherapy in the 2L setting (and beyond) is weak, given the lack of durable responses, high rate of life-threatening toxicity, and a dearth of studies with adequate sample sizes.

The most appropriate data to use as benchmark in the 3L+ setting came from the only large randomized Phase 3 study conducted in a 2L+ esophageal cancer population (N=450), which was the "Gefitinib for Oesophageal Cancer progressing after Chemotherapy" (COG study): this trial compared gefitinib monotherapy versus placebo [20] [21]. The COG study, conducted in 48 United Kingdom centers, was negative: gefitinib failed to improve OS (HR 0.90, 95% CI: 0.74-1.09). The median OS was 3.73 months with gefitinib and 3.67 months with placebo. Gefitinib and placebo resulted in ORRs of 3% and 0%, respectively. Approximately 39% of the participants were patients with 3L+ esophageal cancer, but a subgroup efficacy analysis was not reported for them. Survival data reported in the placebo group provide evidence to gauge the expected survival for patients with 3L+ metastatic esophageal cancer. However, the trial likely overestimates the survival expected from 3L+ patients, as the data analyzed also included the 2L population [20].

The FDA's Assessment:

FDA agrees with Merck's assessment regarding current treatment options for (b) (4)

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 US 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 2-OCT-2015, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy 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 17-MAY-2017 (melanoma) and 24-OCT-2016 (NSCLC).

As of 22-JAN-2019, KEYTRUDA® has received regular or accelerated approval in the US for a number of indications, as summarized in [Table 1].

Table 1
Summary of FDA Approvals of Pembrolizumab as of 22-January-2019

	Regular Approval	Accelerated Approval
Unresectable or metastatic melanoma	X	
Metastatic NSCLC as monotherapy based on PD-L1 TPS level and in combination with chemotherapy regardless of PD-L1 expression	X	
Locally advanced or metastatic UC with disease progression during or following platinum-containing chemotherapy	X	
Recurrent/metastatic HNSCC with disease progression on or after platinum-containing chemotherapy		X
Refractory cHL, or who have relapsed after 3 or more prior lines of therapy		X
Refractory primary mediastinal large B-cell lymphoma, or who have relapsed after 2 or more prior lines of therapy		X

	Regular Approval	Accelerated Approval
Locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and who 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 mismatch repair deficient solid tumors that have progressed following prior treatment or CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan		X
Gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 CPS≥1 with disease progression on or after two or more prior 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 Merck's regulatory history of the approvals of pembrolizumab (BLA 125514). 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 2] summarizes major regulatory milestones for KEYNOTE-180.

Table 2
Major Regulatory Milestones for Pembrolizumab Esophageal Cancer Study KEYNOTE-180

Date	Milestone
IND 110080	
17-Jan-2014	New protocol submitted: MK-3475 PN 028: "Phase IB Study of MK-3475 in Subjects with Select Advanced Solid Tumors" (included esophageal cohort A4)
IND 123482	

Date	Milestone
21-Nov-2014	Original IND 123482 submitted for gastric cancer. IND opened with protocol KEYNOTE-059
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.
21-Sep-2015	New protocol submitted: KEYNOTE-180 for third-line esophageal cancer treatment
21-Mar-2016	Agreed initial Pediatric Study Plan for esophageal cancer submitted
15-Jun-2017	Orphan Drug Designation granted to pembrolizumab for treatment of "esophageal carcinoma" (Designation number #17-5787)
25-Oct-2017	White Paper submitted describing PD-L1 CPS≥10 biomarker selection for esophageal carcinoma in place of Gene Expression Profiling
01-Dec-2017	Preliminary Comments on KEYNOTE-180 pre-sBLA Background Package: FDA recommended that Merck request a pre-sBLA meeting after a minimum follow-up of 12 months for all responding patients following onset of observed confirmed response. FDA also requested MSI-H status for KEYNOTE-180 participants.
18-Sep-2018	Pre-sBLA meeting for KEYNOTE-180: Merck and FDA agreed that the KEYNOTE-180 sBLA could be submitted provided that top-line results from KEYNOTE-181 are provided to FDA within 30 days of KEYNOTE-180 sBLA submission. Minutes received from FDA on 19-SEP-2018.
(b) (4)	(b) (4)
30-Nov-2018	Top line results of KEYNOTE-181 submitted
(b) (4)	(b) (4)
16-Jan-2019	Teleconference: FDA agreed that the planned KEYNOTE-180 sBLA would be reviewed under the Real Time Oncology Review (RTOR) pilot
18-Jan-2019	RTOR pre-submission package for KEYNOTE-180 submitted

The FDA's Assessment:

FDA agrees with the regulatory history described by Merck above. In addition:

- At the December 2017 pre-sBLA meeting, FDA stated that FDA considers the currently available data from KEYNOTE-180 immature given the limited duration of follow-up of responding patients. FDA advised Merck that because the ORR is relatively low [9.9% (95% CI: 5.2, 16.7) per RECIST 1.1 as assessed by BICR], durability of responses will be a key component of the overall risk: benefit assessment for pembrolizumab for the proposed indication of (b) (4). FDA concurred that KEYNOTE-181 or KEYNOTE-590 could serve as a confirmatory trial for an accelerated approval of pembrolizumab in (b) (4) based on the results of KEYNOTE-180. FDA also stated that the sBLA should contain an evaluation of subsets defined by histology (squamous vs. adenocarcinoma), by PD-L1 status, and by MSI-H status (b) (4)
- (b) (4).
- (b) (4)

(b) (4)

- (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.

APPEARS THIS WAY
ON ORIGINAL

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

4.1 Office of Scientific Investigations (OSI)

The results of studies KEYNOTE-180 and KEYNOTE-181 did not appear to be driven by any single site and because the primary endpoint of the KEYNOTE-181 trial was overall survival (OS), which is a hard endpoint that is not prone to bias, no OSI inspections were scheduled for this sBLA.

4.2 Product Quality

No new chemistry, manufacturing, and controls changes for pembrolizumab were proposed in this sBLA and no new immunogenicity data were provided. 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.
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 Issue

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.

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:
Comprehensive review of the key clinical pharmacology findings for pembrolizumab as monotherapy from melanoma, NSCLC, HNSCC, HL, UC, MSI-H cancer, GEJ adenocarcinoma and HCC indications, which have been approved in one or more countries including the US, the EU and Japan, have been discussed extensively in previous submissions. The key clinical pharmacology characteristics are summarized in the current pembrolizumab USPI [22]. The Sponsor has sought feedback on 13-JAN-2017 from the US FDA on streamlining the strategy for PK and immunogenicity assessment of pembrolizumab monotherapy studies [23]. Thus, no new information concerning pharmacology and clinical pharmacokinetics is provided in the current submission.

The FDA's Assessment:
No clinical pharmacology data were submitted in the S-55 application which is acceptable for the rationale Merck stated above.

5.2.2. General Dosing and Therapeutic Individualization

5.2.2.1. General Dosing

The Applicant's Position:
The final recommended dosing for this submission is pembrolizumab 200 mg IV Q3W. This dose is approved for multiple other solid tumor indications and is supported by modeling and simulation.

The FDA's Assessment:
Merck's statement above is factually correct. No clinical pharmacology data were submitted in the S-55 application.

5.2.2.2. Therapeutic Individualization

The Applicant's Position:
There are no dose modification recommendations based on intrinsic or extrinsic factors in this patient population.

The FDA's Assessment:
Merck's statement above is factually correct.

5.2.2.3. Outstanding Issues

The Applicant's Position:
Not applicable.

5.3 Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
No new information concerning pharmacology and clinical pharmacokinetics is provided in the current submission. Please see [Sec. 5.2.2.1] for rationale.

5.3.2. Clinical Pharmacology Questions

5.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:
No new information concerning pharmacology and clinical pharmacokinetics is provided in the current submission.

5.3.2.2. 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.

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

The Applicant's Position:
An alternative dosing regimen or management strategy is not required for subpopulations based on intrinsic patient factors.

The FDA's Assessment:
Merck's statement above is factually correct.

5.3.2.4. 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:
Merck's statement above is factually correct.

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6 Sources of Clinical Data

6.1 Table of Clinical Studies

The Applicant's Position:

[Table 3] presents KEYNOTE-180 as a stand-alone study that supports efficacy and safety in the proposed indication. The current submission also provides data from KEYNOTE-028, the first KEYNOTE study with an esophageal cancer cohort that was designed to establish proof of concept. KEYNOTE-028 was a multi-cohort trial of pembrolizumab in participants with PD-L1 positive advanced solid tumors; participants with ESCC or EAC (including GEJ) were enrolled in Cohort A4. More information about KEYNOTE-028 is in the KEYNOTE-028 CSR, and in the 2.7.3, Sec. 2.2.

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Table 3
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
Study to Support Efficacy and Safety								
KEYNOTE-180	NCT02559687	A single-arm, open-label, multisite study of pembrolizumab administered to participants with previously treated advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert Type 1 adenocarcinoma of the esophagogastric junction	200 mg IV Q3W	Primary endpoint: Incidence of CR or PR based upon central imaging vendor assessments per RECIST 1.1. Secondary endpoints: Safety and tolerability of pembrolizumab, DOR, OS, and PFS, and an assessment of PD-L1 immunohistochemistry in esophageal cancer for its utility to predict pembrolizumab efficacy.	Up to 2 years of treatment. Participants continued pembrolizumab until 1 or more of the discontinuation conditions in the protocol were met. All participants were followed up for OS until death, withdrawal of consent, or the end of the study, whichever came first.	121 patients were enrolled as of the data cutoff date	Patients with previously treated, advanced/metastatic ESCC including advanced/metastatic Siewert type I adenocarcinoma of the GEJ, or EAC	43 centers in 10 countries

The FDA's Assessment:

FDA agrees with the design of KEYNOTE-180 as discussed above. Although the Merck proposed to rely on the results of study KEYNOTE-180 as the sole trial to support the efficacy of pembrolizumab for the proposed indication in patients with (b) (4), FDA also relied on the results of Study KEYNOTE-181 to support approval of pembrolizumab for the treatment of patients with ESCC whose tumors express PD-L1 (CPS ≥10) with disease progression after one or more prior lines of systemic chemotherapy (refer to FDA's review of sBLA 125514/S-56 for additional details).

The design of Study KEYNOTE-181 and KEYNOTE-28 (which provide supportive safety and efficacy data) is outlined in Table 4 below:

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Table 4
Clinical Trials Relevant to BLA 125514/S-55

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. 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 -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	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	9 centers in 6 countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. enrolled	Study Population	No. of Centers and Countries
				assessment and confirmed per RECIST 1.1); safety. Secondary endpoints: DOR, PFS, OS			therapy is not considered appropriate	

Source: Unireview BLA 125514/S-56 Table 3

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7 Statistical and Clinical Evaluation

7.1 Review of Relevant Individual Trials Used to Support Efficacy

KEYNOTE-180

The Applicant's Position:

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). The patients enrolled in this study were previously treated with 2 or more lines of therapy.

The trial design is summarized in [Figure 1]. See KEYNOTE-180-04 protocol, Sec. 2 for more information.

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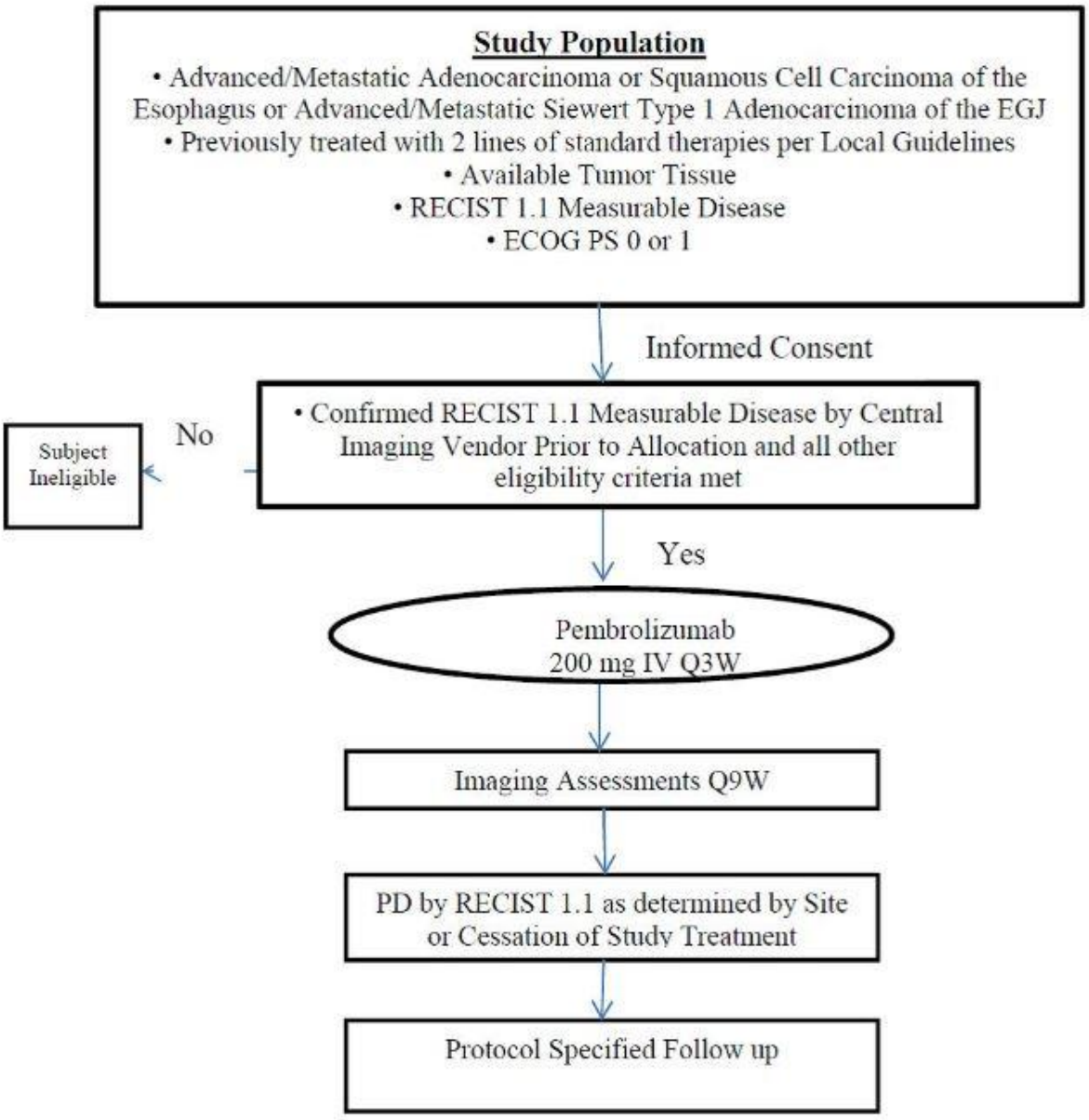
Figure 1
KEYNOTE-180 Trial Diagram



Summary of Key Entrance Criteria: Participants were required to have histologically proven 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 2 previous lines of standard therapy. Participants must also have had measurable disease based on RECIST 1.1, as determined by central imaging vendor assessment, and demonstrated adequate organ function as defined in the KEYNOTE-180-04 protocol, Sec. 5.1.2. Patients with active autoimmune disease requiring

systemic treatment within the 2 years prior to 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 KEYNOTE-180-04 protocol, Sec. 5.1.

Treatment Allocation: Treatment allocation occurred centrally using an interactive voice response system/integrated web response system. All enrolled subjects were allocated to receive pembrolizumab 200 mg IV Q3W as monotherapy in an unblinded fashion. No stratification of any sort was used in this trial (KEYNOTE-180-04 protocol, Sec. 5.3).

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-180-04 protocol, Sec. 5.5).

Treatment Compliance: The total volume of pembrolizumab infused was compared to the total volume prepared to determine compliance with each dose of pembrolizumab administered. The instructions for preparing and administering pembrolizumab were provided in the Pharmacy Manual (KEYNOTE-180-04 protocol, Sec. 7.1.1.9.1).

Dose Modification: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab are provided in the KEYNOTE-180-04 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 one 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 Discontinuation: Participants continued pembrolizumab until one or more of the discontinuation conditions in the KEYNOTE-180-04 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. All participants were followed up for OS until death, withdrawal of consent, or the end of the study, whichever came first.

Discontinuation of treatment was considered for subjects who attained a centrally confirmed CR, and who had received at least 8 cycles (approx. 6 months) of pembrolizumab, and who received at least 2 cycles of pembrolizumab beyond the date when initial CR was declared. Subjects who discontinued pembrolizumab therapy due to CR and then experienced radiographic disease progression were eligible for up to 17 additional cycles (approx. 1 year) of pembrolizumab in a Second Course Phase, at the discretion of the investigator if:

- No cancer treatment was administered since the last dose of pembrolizumab

- The subject met the parameters listed in the Inclusion/Exclusion criteria
- The trial was still ongoing

Subjects resumed pembrolizumab therapy at the same dose level and on the same schedule as those at the time of initial discontinuation (KEYNOTE-180-04 protocol, Sec. 5.8.2).

Study Procedures: [Table 5], the Trial Flow Chart, summarizes the trial procedures to be performed at each visit. A Trial Flow Chart for retreatment with pembrolizumab in the Second Course Phase is in the KEYNOTE-180-04 protocol, Sec. 6.2.

Target tumors were monitored using RECIST 1.1 (modified by the Sponsor to follow 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. RECIST 1.1 was used by the site for study intervention decisions until the first radiologic evidence of PD. Following the first radiologic evidence of PD, study intervention decisions were made by the adaption of RECIST 1.1 (described in the KEYNOTE-180-04 protocol, Sec. 2.1) and termed irRECIST. This adaption accounts for the tumor response pattern observed with pembrolizumab (e.g., tumor flare). 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 (KEYNOTE-180-04 protocol, Sec. 7.1.2.1).

Table 5
KEYNOTE-180 Trial Flow Chart
Initial Treatment Phase with Pembrolizumab

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 12 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
Survival Status		<----------										---------->	X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[q]	
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)[c]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X[r]	X	X	X	X	X	X	X	X	X			
Pembrolizumab Administration		X[b]	X	X	X	X	X	X	X				
LOCAL Laboratory Assessments													
Pregnancy Test[d]	X[d]		X	X	X	X	X	X	X		X		
PT/INR and aPTT	X[e]												
CBC with Differential[f]	X[e]		X	X	X	X	X		X[f]	X	X		
Chemistry Panel[f]	X[e]		X	X	X	X	X		X[f]	X	X		
Urinalysis[g]	X[e]		X		X		X		X	X			
T3, FT4, and TSH[g]	X[e]		X		X		X		X	X	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 12 Weeks
CENTRAL Laboratory Assessments													
Pembrolizumab Pharmacokinetics[h, i]		X[i]	X		X		X		X[h,i]				
Pembrolizumab Anti-Drug Antibodies (ADA)[h]		X	X		X		X		X[h]				
Blood for Genetics[j]		X											
Whole Blood for Biomarker Studies (serum and plasma)[k]		X											
Whole Blood for Correlative Studies (RNA and DNA)[k]		X	X	X						X			
Tumor Tissue Collection													
Newly Obtained Tumor Tissue[m]	X												
Archival Tumor Tissue[n]	X												
Efficacy Measurements													
Tumor Imaging[o]	X[l]	← X[o] →								X[p]		X	

a. After subjects who experience confirmed site-assessed PD or who start a new anti-cancer therapy, each subject will be contacted by telephone for survival approximately every 12 weeks until the subject withdraws consent, is lost to follow-up, death, or the trial ends. In addition, upon Sponsor request, subjects may be contacted for survival status at any time during the course of the trial.

b. Cycle 1 treatment must be given within 3 days of allocation. The window for each visit is ± 3 days unless otherwise noted.

c. Height will be measured at Visit 1 only.

d. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to 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 a positive test results. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

e. Laboratory tests for screening and determining eligibility are to be performed within10 days prior to the first dose of trial treatment.

f. CBC (Hematology) with diff and Chemistry to be performed every cycle.

g. UA and thyroid function tests will be performed every other cycle. T3 is preferred; if not available free T3 may be tested.

h. Both PK and Anti-pembrolizumab 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.

i. PK Samples: additional post-dose (peak) PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8. An additional single PK sample should be drawn at; 24 hours (Day 2), between 72 and 168 hours (Day 4-8) and 336 hours (Day 15) after Cycle 1 dosing.

j. Details for collection can be found in Section 7.1.3 Laboratory Procedure/Assessments

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 12 Weeks

k. Whole blood samples for correlative studies (DNA and RNA) should be collected pre-dose on Day 1 of Cycle 1, Cycle 2, and Cycle 3, and at treatment discontinuation if subject discontinues prior to Cycle 3. Whole blood for Biomarker Samples (plasma and serum) to be collected pre-dose on Day 1 of Cycle 1 only.

l. Screening tumor imaging will be performed within 28 days prior to allocation. Confirmation of baseline measurable disease per RECIST 1.1 by the central imaging vendor is required prior to subject allocation. . Confirmation of baseline measurable disease per RECIST 1.1 by the central imaging vendor is required prior to subject allocation.

m. Newly-obtained tissue is preferred; FFPE block specimens are preferred to slides. Newly obtained tissue is defined as no intervening treatment (local or systemic) involving the site of tissue biopsy once tissue biopsy is obtained and time of study enrollment.

n. Archival tumor tissue will also be requested (where available) to assess the clinical utility of immune-related PD-L1 and GEP assessment in newly obtained vs. archived tissue samples.

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.

p. In order to follow irRECIST criteria, if a subject is discontinued from study therapy prior to 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 prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.

q. 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

KEYNOTE-180 Study Endpoints

Efficacy Endpoints

Primary Efficacy Endpoints

The primary efficacy endpoint/objective of the study was to evaluate ORR of pembrolizumab in all subjects and in subjects whose tumors were classified as GEP intermediate or high and in subjects whose tumors were classified as GEP high. The rationale for evaluating GEP in this study is discussed in the KEYNOTE-180 protocol, Sec. 4.2.2. However, the Sponsor decided not to focus on GEP in this submission based on emerging data from an interim analysis of KEYNOTE-180 conducted in AUG-2017. The Sponsor concluded that the GEP provided no improvement over the PD-L1 IHC CPS assay in terms of clinical utility, and decided to prioritize the PD-L1 IHC CPS assay over the GEP in the entire esophageal program (KEYNOTE-180 CSR, Sec. 9.8.2). ORR was evaluated per RECIST 1.1 assessed by the central imaging vendor (KEYNOTE-180-04 protocol, Sec. 8.4.1.1).

Secondary Efficacy Endpoints

The secondary efficacy endpoints/objectives of this study were to evaluate DOR, and PFS per RECIST 1.1 assessed by the central imaging vendor and OS. PD-L1 immunohistochemistry in esophageal cancer was also to be evaluated for its utility to predict pembrolizumab efficacy (KEYNOTE-180-04 protocol, Sec. 8.4.1.2).

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints/objectives of this study were to evaluate ORR, DOR, and PFS per irRECIST assessed by the central imaging vendor (KEYNOTE-180-04 protocol, Sec. 3.3).

Safety Endpoints

The safety endpoint/objective of this trial was to characterize the safety and tolerability of pembrolizumab in the patient population being studied (KEYNOTE-180-04 protocol, Sec. 3.2 and Sec. 4.2.4.3). Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs (KEYNOTE-180-04 protocol, Sec. 8.6.2). The primary safety analysis was based on subjects who experienced toxicities as defined by CTCAE, v4.0 (KEYNOTE-180-04 protocol, Sec. 4.2.4.3). The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered were recorded. AEs were analyzed including for all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events were collected and designated as ECIs, defined as:

1. an overdose of pembrolizumab, defined as any dose higher than ≥1000 mg (5 times the protocol-defined dose),
2. an elevated AST or ALT lab value greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing (KEYNOTE-180-04 protocol, Sec. 4.2.4.3 and 7.2.3.2).

KEYNOTE-180 Statistical Analysis Plan and Amendments

The statistical analysis of the data obtained from KEYNOTE-180 was analyzed by the Clinical Biostatistics department of the Sponsor. This trial was conducted as an open-label study, i.e., subjects, investigators, and Sponsor personnel were aware of subject treatment.

Efficacy Analysis

The ASaT population consists of all allocated subjects who received at least one dose of study treatment and was used for the analysis of efficacy in KEYNOTE-180. The analysis population for DOR consisted of responders.

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

Table 6
KEYNOTE-180: Analysis Strategy for Efficacy Variables

Endpoint/Variable‡ (Description, Time Point)	**Statistical Method**	**Analysis Population**	**Missing Data Approach**
Primary Endpoint			
ORR: proportion of subjects in the analysis population who have a complete response (CR) or partial response (PR) based upon blinded central imaging vendor assessments per RECIST 1.1.	Exact method (Clopper & Pearson) based on binomial distribution	ASaT	Subjects with missing data are considered non-responders
Secondary Endpoints			
DOR: for subjects who demonstrated CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of disease progression or death based on the subject's best overall response using central imaging vendor assessments per RECIST 1.1, Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, and have not been determined to be lost to follow-up are considered ongoing responders at the time of analysis.	Kaplan-Meier (KM) curves and median estimates from the KM curves.	All responders	Non-responders are excluded from analysis

Endpoint/Variable‡ (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
PFS: the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first, based on central imaging vendor assessments per RECIST 1.1,	Kaplan-Meier (KM) curves and median estimates from the KM curves.	ASaT	Censored at last assessment
OS: the time from first day of study treatment to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.	Kaplan-Meier (KM) curves and median estimates from the KM curves.	ASaT	Censored at last known alive date

Furthermore, censoring rules for DOR and PFS are provided in Table 1 and Table 2, in the Supplemental Statistical Analysis Plan, in the KEYNOTE-180 CSR, Sec. 16.1.9.1.1.

Safety Analysis

The ASaT population was also used for the analysis of safety data in this study. At least one laboratory or vital sign measurement obtained after at least one dose of study treatment was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required.

Safety and tolerability were assessed by a clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Counts and percentages of AEs were provided in the KEYNOTE-180 CSR.

Protocol Amendments

The original protocol (KEYNOTE-180-00) was finalized on 24-AUG-2015, and amended 5 times. Two of the amendments (KEYNOTE-180-03 and KEYNOTE-180-05) were country specific (Germany). [Table 7] summarizes the key changes in the amendments.

Table 7
Summary of Key Changes to the KEYNOTE-180 Protocol

Protocol or Amendment (Date Finalized at Sponsor)	Key Changes
Protocol (24-AUG-2015)	Original Protocol
Amendment 01 (21-JUL-2016)	Clarified that curative chemoradiotherapy counts as a line of therapy if recurrence occurs during treatment or within 6 months of cessation of treatment, added a new entrance criterion to limit enrollment to only third line subjects, allowed for use of radiotherapy to a solitary lesion for symptom relief, and revised the

	timing of baseline scans relative to first dose from 28 days to 14 days.
Amendment 02 (5-DEC-2016)	Indicated that the protocol will use pre-specified gene expression profile cut-offs, instead of deriving the cut-offs from the KEYNOTE-180 data, clarified that curative chemoradiotherapy counts as a line of therapy if recurrence occurs during treatment or within 6 months of cessation of treatment, clarified that additional malignancies that progressed or required active treatment within the last 5 years are excluded, emphasized that treatment should be discontinued for recurrent Grade 2 pneumonitis, and added a new table to the Sample Size section of the protocol entitled "Two-sided 95% Confidence Interval of ORR with 100 Subjects".
Amendment 03 (12-JAN-2017)	Country-specific amendment for Germany only: Same key changes as for Amendment 02.
Amendment 04 (29-NOV-2017)	Dose modification table modified to add myocarditis
Amendment 05 (30-NOV-2017)	Country-specific amendment for Germany only: Same key changes as for Amendment 04.

The FDA's Assessment:
FDA agrees with Merck's above descriptions of the general study design, study procedures, statistical analysis plan, and protocol amendments.

7.1.1. KEYNOTE-180 Study Results

The Applicant's Position:

Compliance with Good Clinical Practices

The KEYNOTE-180 study was conducted in compliance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding IRB/IEC review, informed consent and the protection of human participants in biomedical research.

The study was also approved by an independent IRB/IECs in association with each study center and was performed in accordance with ethical principles from the Declaration of Helsinki. The IRB/IECs consulted for this study met the definition as outlined in US CFR Title 21, Part 56 or equivalent country-specific regulations.

Informed consent was obtained and documented in accordance with the principles and provisions in Section 4.8 of the ICH E6 Guideline for Good Clinical Practice, US CFR Title 21 Part 50, Protection of Human Subjects, and/or local country/cultural consent practices and/or requirements where applicable. Informed consent was obtained from all patients prior to the

performance of any study procedures.

Financial Disclosure

Disclosure of financial interests of the investigators who conducted the KEYNOTE-180 study are described in the current submission (Module 1.3.4).

The FDA's Assessment:
Please see financial disclosure review at the end of this review; this financial disclosure review has also been uploaded to DARRTS.

Patient Disposition

A total of 185 participants were screened, and 121 were enrolled across 43 global study sites in 10 countries. Sixty-four of the nonrandomized participants were screen failures. The primary reason for screen failure was not meeting Inclusion Criterion #7 (in 15 patients who did not have measurable disease based on RECIST 1.1 as determined by central imaging vendor assessment).

All 121 participants received at least 1 dose of study medication, and 2 participants completed the study intervention regimen per protocol. Fourteen (11.6%) participants were alive and continuing in the study at the time of data cut off (30-JUL-2018). The median duration of participant follow-up at data cut off for this submission was 5.8 months (range: 0.2 to 27.8 months) from first dose to date of death or data cutoff (KEYNOTE-180 CSR, Table 14.2-1). Two (1.7%) participants were still receiving study intervention at the time of data cutoff. The primary reason for discontinuation of study intervention was progressive disease (63.6%). One hundred seven (88.4%) participants discontinued from the study (including from study post-treatment follow-up), the most frequent reason for discontinuation being death (85.1%). No participant was excluded from the study analyses (KEYNOTE-180 CSR, Sec. 10.1).

The FDA's Assessment:
FDA agrees with the Merck's analysis of disposition of patients in KEYNOTE-180 as described above.

Protocol Violations/Deviations

In the KEYNOTE-180 study, protocol deviations were classified as important (those that may significantly impact the quality or integrity of key trial data or that may significantly affect a participant's rights, safety, or well-being) or not important. A total of 20 important deviations were reported in 15 participants across the following categories (KEYNOTE-180 CSR, Sec. 10.2):

- Five participants did not receive an amended consent form at their next scheduled visit following an update to the risk language. Three of these participants signed the amended consent form at a subsequent visit, and two died and did not sign the amended consent form.

- Three participants signed the incorrect version of the Future Biomedical Research consent at the time of consenting for participation in the study. Two of them signed the correct version of the Future Biomedical Research consent at a later date, and one discontinued the study before signing the correct form.
- Two participants did not meet the inclusion/exclusion criteria upon enrolling in the study. One participant had a hemoglobin value that did not meet the inclusion criteria, and one participant had a platelet value that did not meet the inclusion criteria.
- Four participants experienced SAEs that were not reported by the site within 24 hours of learning of the event (but were included in the analysis of safety).
- Two participants did not have the post discontinuation safety follow-up visit performed as required by the protocol within 30 days of discontinuation. Both died due to progressive disease within 6 weeks of discontinuation.
- One participant's local laboratory data were reviewed by site personnel not trained on the study. This person was eventually trained on the requirements of the study, and added to FDA 1572 and Site Signature and Delegation of Responsibility Log. Throughout the duration of the study, the principal investigator reviewed and maintained oversight of all labs at the site.

Some participants had multiple deviations under the same category. No important protocol deviations were classified as GCP compliance issues, and none were considered clinically important.

No participant data were excluded from analyses due to an important protocol deviations, and therefore, the important protocol deviations reported in the KEYNOTE-180 study did not influence the overall efficacy conclusions. The study conclusions are robust and representative of the overall study data.

The FDA's Assessment:
Upon review of the reported protocol deviations and available narratives, the protocol deviations were few in number and are unlikely to have impacted the results of KEYNOTE-180.

Table of Demographic Characteristics

Overall, for all baseline characteristics, participants in the KEYNOTE-180 study were representative of patients with advanced/metastatic esophageal cancer [Table 8] (KEYNOTE-180 CSR, Sec. 10.4). Demographic and baseline characteristics are summarized by histology in [KEYNOTE-180 CSR, Table 14.1-8], and by baseline PD-L1 status in [KEYNOTE-180 CSR, Table 14.1-9].

Table 8
KEYNOTE-180 Subject Characteristics
(ASaT Population)

	Pembrolizumab 200 mg	
	n	(%)
Subjects in population	121	
Gender		
Male	100	(82.6)
Female	21	(17.4)
Age (Years)		
<65	57	(47.1)
≥65	64	(52.9)
Mean	63.5	
SD	10.6	
Median	65.0	
Range	33 to 87	
Race		
Asian	42	(34.7)
Black Or African American	2	(1.7)
White	71	(58.7)
Missing	6	(5.0)
Ethnicity		
Hispanic Or Latino	2	(1.7)
Not Hispanic Or Latino	108	(89.3)
Not Reported	10	(8.3)
Unknown	1	(0.8)
ECOG Performance Scale		
0	44	(36.4)
1	77	(63.6)
Geographic Region of Enrolling Site		
Asia	39	(32.2)
Non-Asia	82	(67.8)
Current Disease Presentation		
Locally Advanced	1	(0.8)
Metastatic	120	(99.2)

KEYNOTE-180 Subject Characteristics
(ASaT Population)

	Pembrolizumab 200 mg	
	n	(%)
Brain Metastasis		
Y	5	(4.1)
N	116	(95.9)
Metastatic Staging		
M0	1	(0.8)
M1	120	(99.2)
GEP Status		
High (GEP Score ≥ -0.945)	24	(19.8)
Intermediate (-1.540 ≤ GEP Score < -0.945)	27	(22.3)
Low (GEP Score < -1.540)	67	(55.4)
Missing	3	(2.5)
PD-L1 Status		
CPS>=10	58	(47.9)
CPS<10	63	(52.1)
Histological Subtype		
Squamous Cell Carcinoma	63	(52.1)
Adenocarcinoma†	58	(47.9)
HER2 Status‡		
Positive	13	(10.7)
Negative	48	(39.7)
Unknown	47	(38.8)
Missing	13	(10.7)
Last Prior Line of Therapy		
Second Line	106	(87.6)
Third Line	13	(10.7)
Fourth Line	2	(1.7)
Prior Anthracycline Therapy		
Yes	14	(11.6)
No	107	(88.4)
Prior Monoclonal Antibody Therapy		

KEYNOTE-180 Subject Characteristics
(ASaT Population)

	Pembrolizumab 200 mg	
	n	(%)
Yes	31	(25.6)
No	90	(74.4)
Prior Irinotecan Therapy		
Yes	24	(19.8)
No	97	(80.2)
Prior Platinum Therapy		
Yes	121	(100.0)
Prior Fluoropyrimidine Therapy		
Yes	121	(100.0)
Prior Taxane Therapy		
Yes	104	(86.0)
No	17	(14.0)
MSI Status[§]		
MSI-H	1	(0.8)
Normal	97	(80.2)
Unknown	6	(5.0)
Missing	17	(14.0)

[†]18 of the 58 (31 %) adenocarcinoma subjects had Siewert type 1 adenocarcinoma of the EGJ.
[‡]HER2 Status was not required for subjects with ESCC; 3 subjects with ESCC reported a negative HER2 Status.
[§] MSI Status of normal is defined as Non-MSI-H
Database Cutoff Date: 30JUL2018

Source: [P180V01MK3475: adam-adsl]

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

Per protocol, all randomized participants were previously treated with at least 2 lines of standard treatment. The majority of participants received 2 prior lines of standard treatment (87.6%), 13 participants (10.7%) received 3 prior lines of standard treatment, and two participants (1.7%) received 4 prior lines of standard treatment. All participants were treated with fluoropyrimidine and platinum therapies, and 86% with taxane therapy. The prior treatments were representative of heavily treated (3L+) advanced esophageal cancer patients [Table 8] (KEYNOTE-180 CSR, Sec. 10.4).

The FDA's Assessment:
FDA agrees with the results presented in Table 8 for the demographics and baseline characteristics in the ASaT population. In addition, a summary of the demographics and baseline characteristics of in the indicated population (patients with ESCC whose tumors expressed PD-L1 CPS ≥10) is also provided in Table 9.

Table 9
Baseline Demographic and Characteristics (ESCC, PD-L1 CPS≥10; FDA's Assessment)

KEYNOTE-180	Pembrolizumab 200 mg N=35
Age, years	
Mean (SD)	64.1 (9.2)
Median (Min, Max)	65 (47, 81)
≥65, n (%)	18 (51)
<65, n (%)	17 (49)
Sex, n (%)	
Male	25 (71)
Female	10 (29)
Race, n (%)	
Asian	24 (69)
White	9 (26)
Black or African American	2 (6)
Ethnicity	
Not Hispanic or Latino	34 (97)
Hispanic or Latino	1 (3)
Geographic Region of Enrolling Site, n (%)	
Asia	23 (66)
Ex-Asia	12 (34)
ECOG, n (%)	
0	14 (40)
1	21 (60)
Current Disease Presentation, n (%)	
Metastatic	35 (100)
Brain Metastasis, n (%)	
No	34 (97)
Yes	1 (3)
Metastatic Staging, n (%)	
M1	35 (100)
MSI Status, n (%)	
Normal	30 (86)
Unknown	1 (3)
Missing	4 (11)
Number of Prior Therapies, n (%)	
2	30 (86)
3	4 (11)
4	1 (3)
GEP Status	
High (≥ -0.945)	8 (23)
Intermediate (≥-1.540, <-0.945)	9 (26)
Low (<-1.540)	18 (51)

Source: FDA reviewer's analyses.

The FDA's Assessment:
As presented in Table 9, the majority of the 35 patients who had squamous cell carcinoma of the esophagus and CPS ≥10 had progressed following receipt of at least two lines of prior therapy. The majority of these patients were male, Asian, and with an ECOG PS of 1.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

- Treatment Compliance*:* Pembrolizumab was administered in the clinic by qualified site personnel, ensuring compliance.
- Concomitant medications were reviewed as part of study monitoring and were found to not impact study data.
- Rescue Medication*:* No rescue medication (intended to immediately relieve symptoms associated with an adverse event) or supportive medications were specified to be used in this trial (KEYNOTE-180-04 protocol, Sec. 5.6).

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

APPEARS THIS WAY ON ORIGINAL

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

(ORR) (2.7.3, Sec. 2.1.2.1.1)
The ASaT population (all participants who received at least one dose of study treatment) served as the primary population for the analysis of efficacy data in KEYNOTE-180 and was comprised of 121 participants with 3L+ metastatic esophageal cancer (2.7.3, Sec. 1.3).

The primary results from KEYNOTE-180 demonstrate that treatment with pembrolizumab achieved a clinically meaningful benefit in a heavily pretreated (3L+) population of participants with esophageal cancer [10] (KEYNOTE-180 CSR, Figure 11-1). The ORR (central review per RECIST 1.1) was 9.9% for the overall population [10]. Of 106 participants with at least 1 post-baseline central review tumor assessment (the other 15 participants died before having a post-baseline central review tumor assessment), 43 participants experienced a reduction of measurable target lesion size (tumor burden). These included 23 participants who achieved a target lesion reduction of >30% from baseline (KEYNOTE-180 CSR, Figure 11-1).

Responses were observed regardless of histology or PD-L1 expression. The ORR in participants with ESCC was 14.3%, in participants with EAC was 5.2%, in participants with PD-L1 CPS ≥10 was 13.8%, and in participants with PD-L1 CPS <10 was 6.3% [10], (KEYNOTE-180 CSR, Sec. 11.2.1), (KEYNOTE-180 CSR, Table 11-7).

Durable responses were observed regardless of histology or PD-L1 expression. In the ESCC population, median DOR was not reached (4.2 - 25.1+); in the EAC population, median DOR was not reached (2.1 - 15.6+); in the CPS ≥10 population, median DOR was not reached (4.2 - 25.1+); and in the CPS <10 population, median DOR was also not reached (2.1 – 17.3+) (KEYNOTE-180 CSR, Table 14.2-23 and Table 14.2-38). Overall, seven of the twelve responders had a DOR of ≥6 months. Five of the twelve responders had a DOR of ≥12 months; four of these with a response of ≥15 months and one additional responder had a DOR of ≥11.9 months (KEYNOTE-180 CSR, Sec. 11.1.2). The duration of CR for two participants was 17.3+ months and 18.7+ months. As of the data cutoff date, four of the twelve responders had ongoing responses (2.7.3, Table 7). These observed durable responses are clinically meaningful for patients who have progressed after two or more lines of therapy and who have no therapeutic options available.

Table 10
KEYNOTE-180 Summary of Efficacy Outcomes
(ASaT Population)

	Overall	ESCC	PD-L1 CPS ≥10
Number of Subjects	121	63	58
ORR Analysis (Central Radiology Assessment per RECIST 1.1, Confirmed Responses)			
ORR % (95% CI[†])	9.9 (5.2, 16.7)	14.3 (6.7, 25.4)	13.8 (6.1, 25.4)
Objective response, n (%)			
Complete Response (CR)	2 (1.7)	2 (3.2)	1 (1.7)
Partial Response (PR)	10 (8.3)	7 (11.1)	7 (12.1)
Stable Disease (SD)	25 (20.7)	16 (25.4)	13 (22.4)
Progressive Disease (PD)	71 (58.7)	34 (54.0)	33 (56.9)
Non-Evaluable (NE)	0 (0.0)	0 (0.0)	0 (0.0)
No Assessment (NA)	13 (10.7)	4 (6.3)	4 (6.9)
Response Duration (Central Radiology Assessment per RECIST 1.1, Confirmed Responses)			
Subjects with a Response (n)	12	9	8
Time to Response (months)			
Median (range)	4.1 (2.0 - 5.2)	4.1 (2.0 - 4.4)	4.1 (2.0 - 4.4)
Response Duration[‡] (months)			
Median(range[§])	Not Reached (2.1 - 25.1+)	Not Reached (4.2 - 25.1+)	Not Reached (4.2 - 25.1+)
PFS (Central Radiology Assessment per RECIST 1.1, Confirmed Responses)			
Median in months (95% CI)[‡]	2.0 (1.9, 2.1)	2.1 (2.0, 2.4)	2.0 (1.9, 2.2)
PFS Rate(95% CI) at 3 Months % [‡]	28.1 (20.4, 36.3)	36.5 (24.9, 48.2)	32.8 (21.2, 44.8)
PFS Rate(95% CI) at 6 Months % [‡]	14.9 (9.2, 21.8)	15.9 (8.2, 25.9)	20.7 (11.4, 31.8)
PFS Rate(95% CI) at 9 Months % [‡]	9.1 (4.8, 15.0)	11.1 (4.9, 20.2)	13.8 (6.4, 23.9)
OS			
Median in months (95% CI)[‡]	5.8 (4.5, 7.2)	6.8 (5.4, 9.3)	6.3 (4.4, 10.2)
OS Rate(95% CI) at 3 Months % [‡]	73.6 (64.7, 80.5)	81.0 (68.9, 88.7)	74.1 (60.8, 83.5)
OS Rate(95% CI) at 6 Months % [‡]	48.8 (39.6, 57.3)	57.1 (44.0, 68.3)	51.7 (38.2, 63.6)
OS Rate(95% CI) at 9 Months % [‡]	33.9 (25.6, 42.3)	39.7 (27.7, 51.4)	39.7 (27.2, 51.9)
OS Rate(95% CI) at 12 Months % [‡]	27.3 (19.7, 35.4)	31.7 (20.7, 43.3)	34.5 (22.6, 46.6)

[†]Based on binomial exact confidence interval method.

[‡]From product-limit (Kaplan-Meier) method for censored data.

[§]"+" indicates there is no progressive disease by the time of last disease assessment.

'No Assessment (NA)' counts subjects who had a baseline assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.

ORR=overall response rate; DCR=disease control rate; OS=overall survival; PFS= progression-free survival.

Database Cutoff Date: 30JUL2018

Source: [P180V01MK3475: adam-adsl; adintdt; adrs; adtte]

Data Quality and Integrity

Quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures, as detailed in the KEYNOTE-180-04 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 is provided in the KEYNOTE-180 CSR, Sec.16.1.8.

Efficacy Results - Secondary and other relevant endpoints

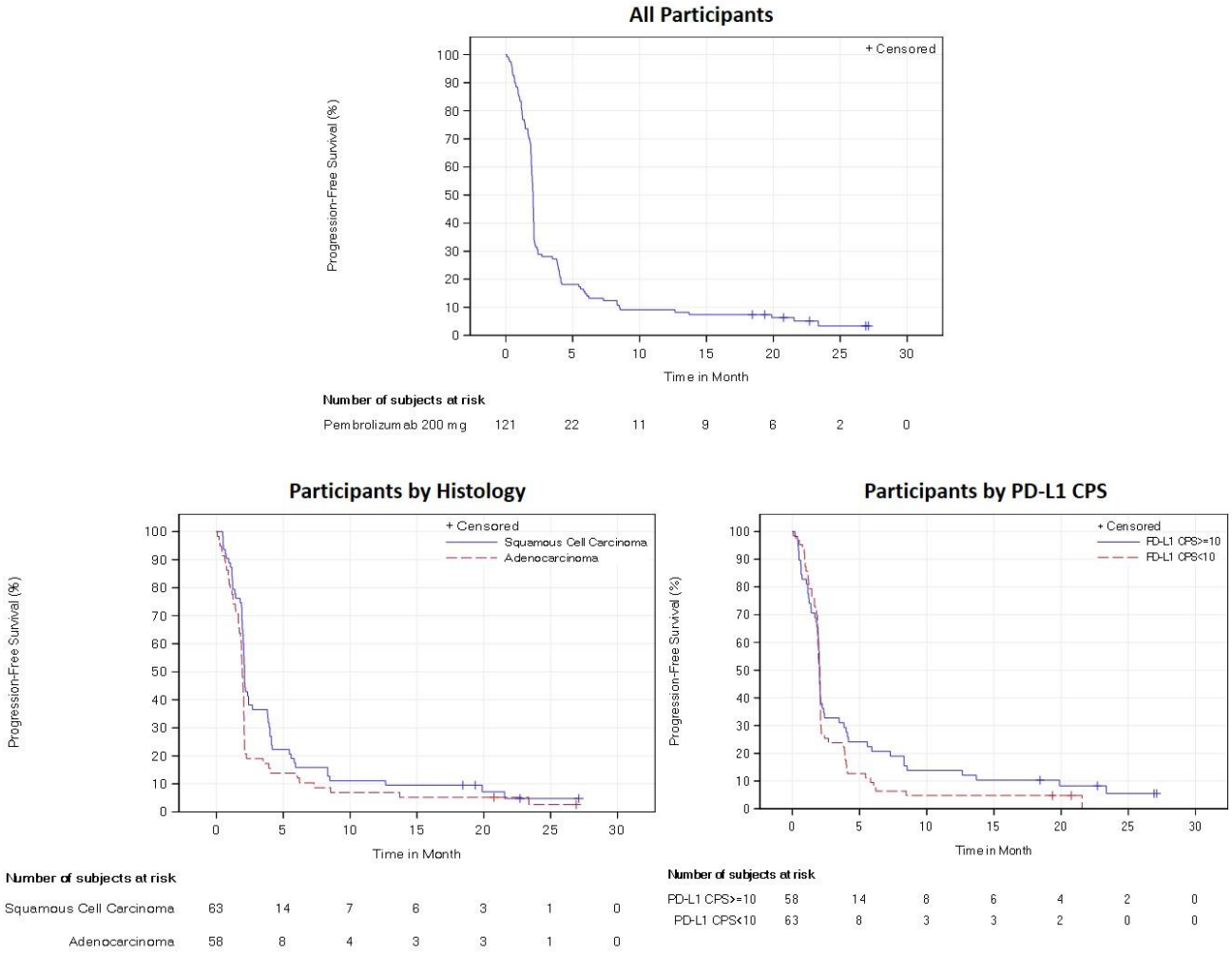
DOR (2.7.3, Sec. 2.1.2.1.2)
Among the twelve responders, responses to pembrolizumab were durable in this heavily pretreated population (3L+). As of the data cutoff date, all responding participants (central review per RECIST 1.1) had been followed for a minimum of twelve months after onset of observed confirmed response, and the median DOR per central review was not reached (range: 2.1 to 25.1+)[Table 10] (KEYNOTE-180 CSR, Sec. 16.2.6.3).

Of the twelve responders in overall population, seven, five, and four participants had a DOR of ≥6, ≥12, and ≥15 months, respectively. At the time of data cutoff, two responders were continuing pembrolizumab and four responders had ongoing responses (KEYNOTE-180 CSR, Sec. 11.1.2, Sec. 16.2.6.3 and Figure 14.2-3). The majority of responders continued to experience a reduction of tumor burden after achieving objective response (KEYNOTE-180 CSR, Figure 11-2).

Similar to the observations in the overall population, durable responses were seen in both ESCC and EAC participants (KEYNOTE-180 CSR, Sec. 11.2.2), in participants with PD-L1 CPS ≥10, and in participants with CPS <10 [Table 10](KEYNOTE-180 CSR, Sec. 11.3.2).

The overall population achieved a median PFS (central review per RECIST 1.1) of 2.0 months with a 6-month PFS rate of 14.9% by Kaplan-Meier estimation [10] [Figure 2]. Similar PFS results as seen with the overall population were observed for participants with ESCC, and for participants with PD-L1 CPS ≥10 [10] [Figure 2].

Figure 2
KEYNOTE-180 Kaplan-Meier Estimates of Progression-Free Survival Based on Central Radiology Assessment per RECIST 1.1 (ASaT Population)



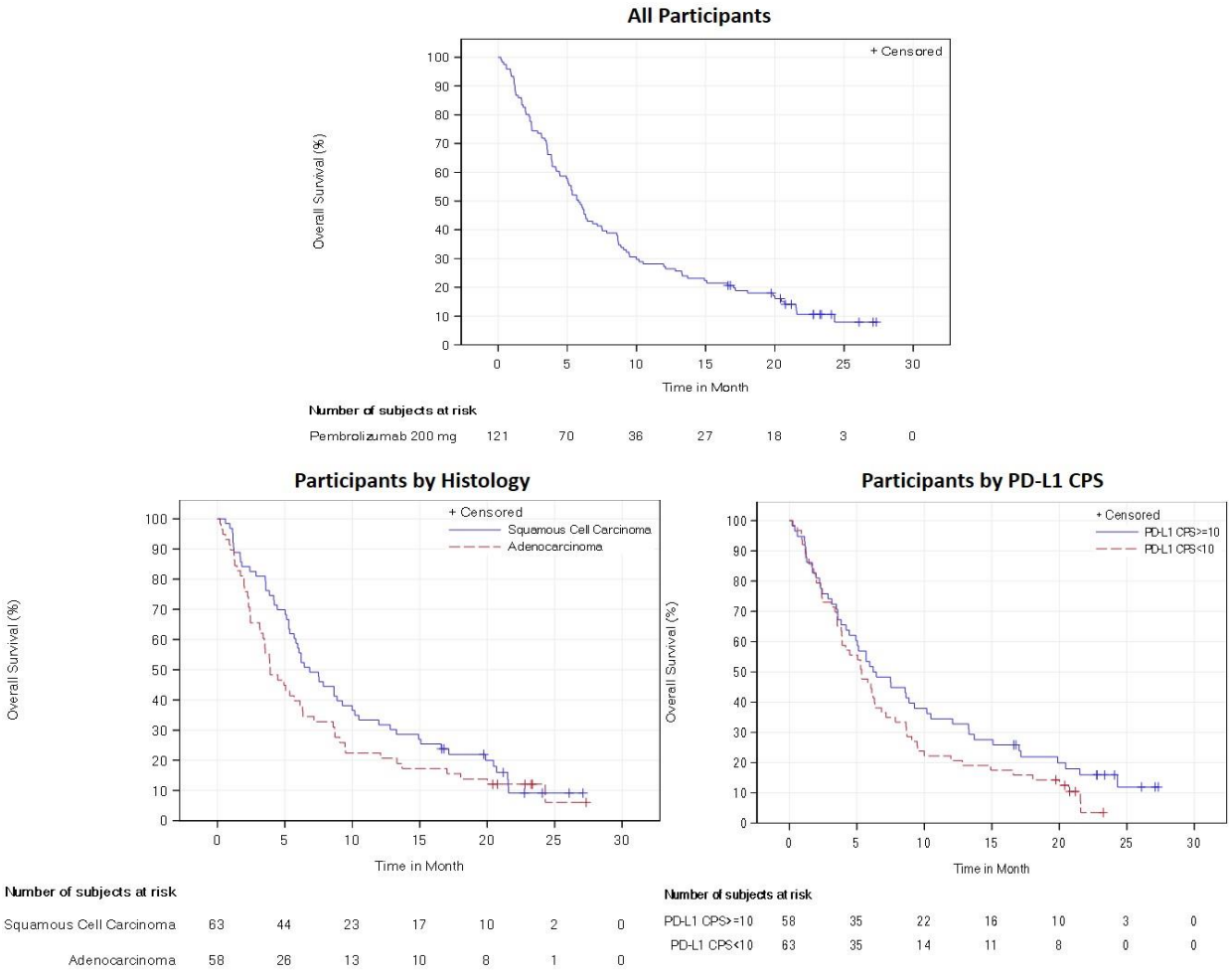
Database Cutoff Date: 30JUL2018
Data derived from KEYNOTE-180 CSR, Figure 11-4, Figure 14.2-16 and Figure 14.2-30

OS (2.7.3, Sec. 2.1.2.1.3)

The OS data provide additional evidence for durable clinical benefit with pembrolizumab treatment. The overall population achieved a median OS of 5.8 months with a 6-, 9-, and 12-month OS rate of 48.8%, 33.9%, and 27.3% by Kaplan-Meier estimation, respectively [Table 10] []. Similar OS results were observed for participants with ESCC [Table 10] [Figure 3], and for participants with PD-L1 CPS ≥10 [Table 10] [Figure 3].

The tail of the Kaplan-Meier curves suggests durable clinical benefit for the overall population and for the population by histologies and PD-L1 expression levels, an important finding in a population of heavily-pretreated patients [Figure 3].

Figure 3
Kaplan-Meier Estimates of Overall Survival (ASaT Population)



Database Cutoff Date: 30JUL2018
Data derived from KEYNOTE-180 CSR, Figure 11-3, Figure 11-5 and Figure 11-6

Subgroup Analyses of Tumor Response

Responses were observed in all the subgroups assessed, and were generally consistent across multiple subgroups defined by demographic factors, histology, and biomarker status, indicating the robustness of the clinical benefit observed. However, the results should be interpreted with caution due to the small number of participants in certain subgroups (2.7.3, Figure 5).

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

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
Not applicable as PRO data were not collected in this study.

Additional Analyses Conducted on the Individual Trial

Efficacy Results by Baseline GEP Status

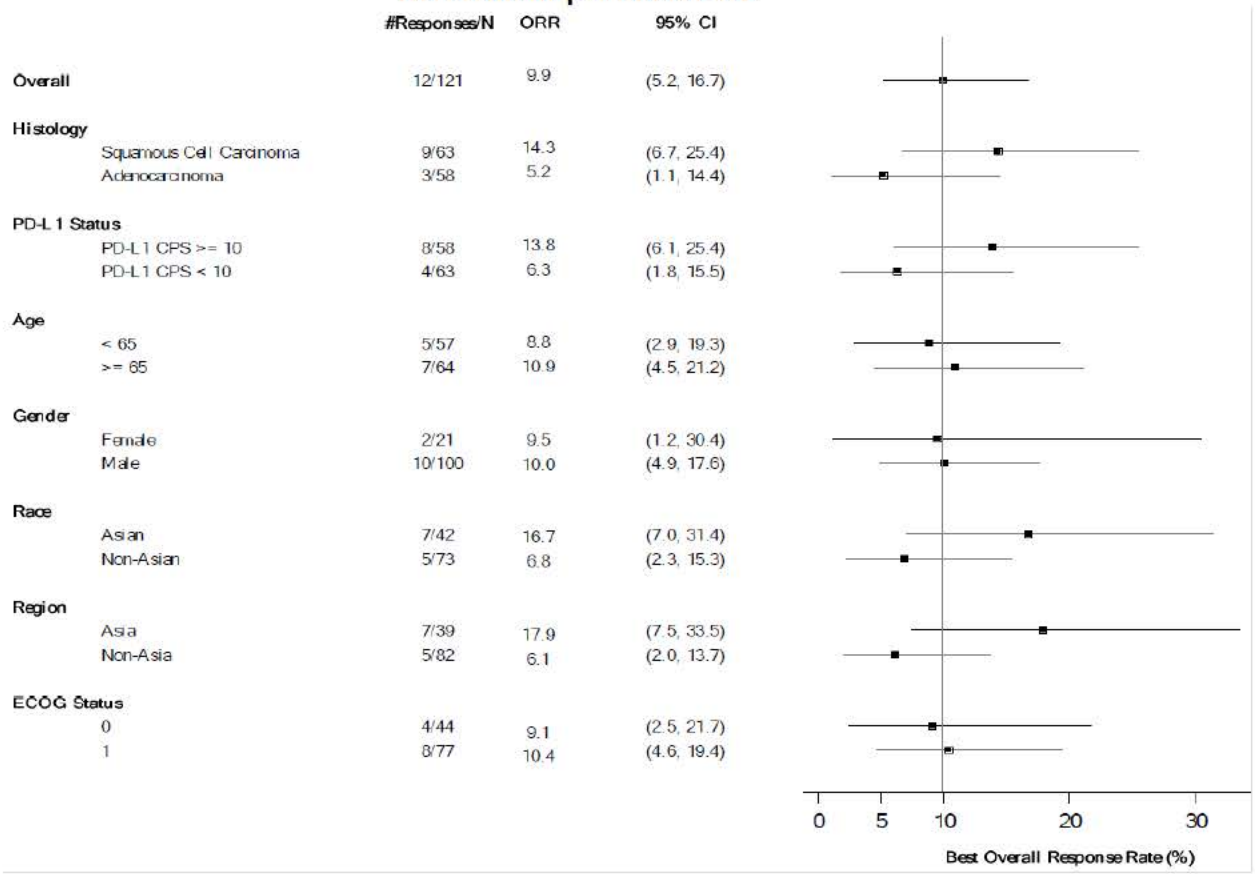
As discussed in the KEYNOTE-180 Study Endpoints subsection of this review (Sec. 0), the Sponsor decided to prioritize the PD-L1 IHC CPS assay over the GEP (KEYNOTE-180 CSR, Sec. 9.8.2). Efficacy summaries by histology and GEP status are provided in the KEYNOTE-180 CSR, Sec. 11.4.3.

Integrated Review of Effectiveness

The FDA's Assessment:
FDA generally agrees with the summary of the efficacy results by Merck; however, FDA disagrees with the following aspects of the interpretation of the analysis results:

- Analyses of time to event endpoints are not interpretable in a single arm study. FDA considers the analyses of OS and PFS including the presentation of the KM plots to be descriptive.
- The forest plot for subgroup analyses of the primary endpoint of ORR (confirmed by central review per RECIST 1.1) in the ASaT population by Merck is displayed in Figure 4. Inconsistent results were observed for the tumor responses for PD-L1 status, histology, race and region.

Figure 4
Subgroup Results for Objective Response Rate (Confirmed) Based on Central Radiology Assessment per RECIST 1.1



Source: Figure 14.2-52 on Page 315 of Merck's CSR.

Table 11 provides the ORR results by PD-L1 status and histology. Although the 95% confidence intervals are wide due to the small sample sizes of the subgroups, the point estimate for ORR in patients with squamous cell carcinoma whose tumors expressed PD-L1 with a CPS ≥10 markedly higher than the point estimate for ORR in patients with ESCC and CPS <10, and for patients with EAC irrespective of level of PD-L1 expression. These findings are consistent with the results of pembrolizumab in the second-line setting (Study KEYNOTE-181). However, it is noteworthy that the KEYNOTE-180 trial was not prospectively designed for these analyses.

Table 11
Responses by PDL1 Status and Histology, KEYNOTE-180 (FDA Analysis)

	CPS≥10	CPS<10
ESCC	N=35	N=28
ORR, % (95% CI)	20% (8, 37)	7% (1, 24)
CR, n (%)	1 (3)	1 (3)
PR, n (%)	6 (17)	1 (3)

	CPS≥10	CPS<10
Adenocarcinoma	**N=23**	**N=35**
ORR, % (95% CI)	4% (0, 22)	5% (1, 14)
CR, n (%)	0	0
PR, n (%)	1 (4)	2 (6)

Source: FDA reviewer's assessment.

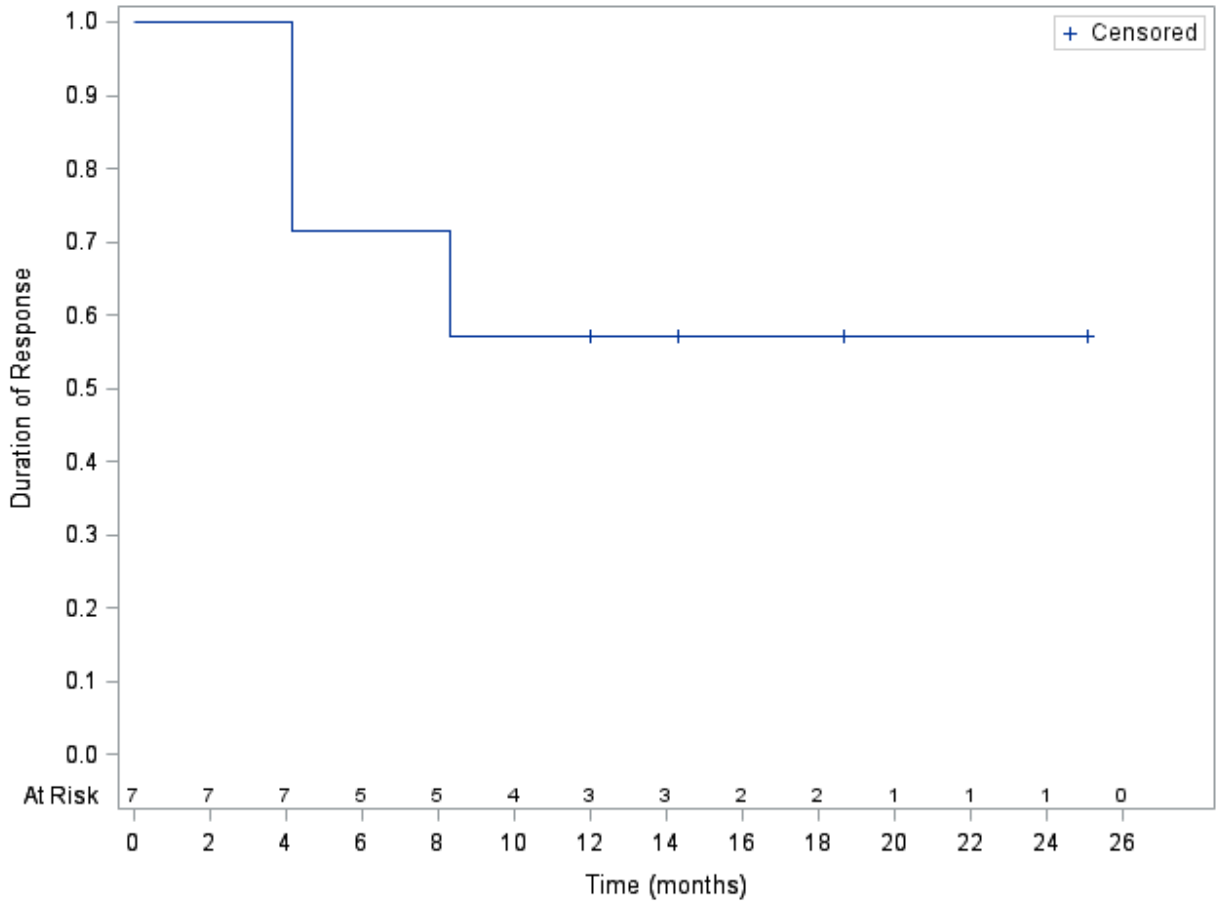
Further exploration of efficacy in patients with ESCC whose tumors expressed PD-L1 CPS ≥10 (the indicated patient population) are summarized in Table 12. The median follow-up time for DOR in the 7 patients with a tumor response was 16.5 months. The median DOR was not reached and the range of DOR was from 4.2 months to 25.1+ months (see Figure 5).

Table 12
Summary of Responses in Patients with ESCC Whose Tumors Expressed PD-L1 CPS≥10, KEYNOTE-180 (FDA's Assessment)

	Pembrolizumab (N=35)
Response, n (%)	
CR	*1 (3)*
PR	*6 (17)*
SD	*7 (20)*
PD	*21 (60)*
ORR (CR+PR), n (%)	7 (20)
95% CI for ORR, %	(8, 37)

Source: FDA reviewer's assessment.

Figure 5
Duration of Response Among Responders in Patients with ESCC Whose Tumors Expressed PD-L1 CPS≥10, KEYNOTE-180 (FDA's Assessment)



Source: FDA reviewer's assessment

7.1.2. Assessment of Efficacy Across Trials

The Applicant's Position:
A formal comparative analysis or pooled analyses of pivotal data (KEYNOTE-180) and supporting data (KEYNOTE-028) were not conducted due to differences in key study characteristics (eligibility criteria with respect to PD-L1 status and testing method used, required prior lines of therapy). Nevertheless, both studies independently show that treatment with pembrolizumab achieved a clinically meaningful and durable clinical benefit in heavily pretreated participants with metastatic esophageal cancer who lack effective therapy options.

Primary Endpoints

Not applicable as only one pivotal study is included.

Secondary and Other Endpoints

Not applicable as only one pivotal study is included.

Subpopulations

Not applicable as only one pivotal study is included.

Additional Efficacy Considerations

None.

The FDA's Assessment:

Although a formal pooled analysis of the results of KEYNOTE-180 and KEYNOTE-181 was not performed, the FDA review relied on the results of the randomized trial KEYNOTE-181 to identify the subset of patients with esophageal cancer that derived the most benefit from treatment with pembrolizumab following receipt of two or more lines of systemic chemotherapy. The OS, PFS and ORR results in patients enrolled in KEYNOTE-181 with squamous cell carcinoma of the esophagus and CPS ≥10 are summarized in Table 13 below.

Table 13
Efficacy Results in Patients with ESCC and CPS ≥10 in KEYNOTE-181

	Pembrolizumab (N=85)	SOC (N=82)
Primary Endpoint: OS		
Number of events, n (%)	68 (80)	72 (88)
Median (95% CI), month	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), month	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)

	Pembrolizumab (N=85)	SOC (N=82)
ORR, n (%)	19 (22)	6 (7)
95% CI for ORR, %	(10, 17)	(4, 10)
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.

7.1.3. Integrated Assessment of Effectiveness

The Applicant's Position:

The results of KEYNOTE-180 demonstrate clinically meaningful antitumor activity of pembrolizumab in heavily pretreated participants (3L+, including 12.4% who were 4L+ during the study) with metastatic esophageal cancer. In this population, where no effective therapeutics are available, pembrolizumab treatment resulted in a clinically meaningful tumor response (ORR 9.9%). Importantly, 23 of 106 participants with at least one post-baseline central review tumor assessment experienced reductions in tumor size of >30% from baseline. Durability of responses has been a critical attribute in assessing the clinical value of pembrolizumab, and durable responses were noted in these heavily pretreated esophageal cancer participants. As of the data cutoff date, all confirmed responding participants had been followed for a minimum of 12 months after onset of response, and the median DOR per central review was not reached (range: 2.1 to 25.1+). Seven responders had a DOR of ≥6 months. Five responders (57.0%) had a DOR of ≥12 months. In addition, four of the twelve responders had ongoing responses at data cutoff. For a population with 3L+ metastatic esophageal cancer having no effective treatment options, DOR of ≥6 months is a notable result. The KEYNOTE-180 OS data further support the durability of the clinical benefit. The median OS was 5.8 months and the OS rates at 6 and 12 months by Kaplan-Meier estimation were 48.8% and 27.3%.

Efficacy data in the ESCC and CPS ≥10 populations further demonstrate the consistency and robustness of pembrolizumab therapy in patients with advanced/metastatic esophageal cancer.

There is no study that provides historical ORR or OS exclusively in the 3L+ setting. As discussed in [Sec. 2.2], the only Phase 3 study that included 3L patients (along with 2L) revealed ORRs of 0% and 3% with placebo and gefitinib, respectively [20], indicating that the ORR observed in KEYNOTE-180 is higher than the expected ORR in the 3L+ setting. Taking the DOR into consideration, clinical efficacy in KEYNOTE-180 is clinically important considering that the current recommendation for 3L+ esophageal cancer patients is best supportive care of clinical trial participation.

A clinically meaningful and durable benefit was noted in participants with tumors of both histologies (ESCC and EAC) and for the biomarker subgroups. In addition, for the demographic and biomarker subgroups assessed (age, gender, ECOG score, Asian vs non-Asian), ORRs were consistent, indicating the robustness of the clinical benefit observed.

The efficacy results observed in the KEYNOTE-028 (Cohort A4) esophageal cancer participants support the findings of KEYNOTE-180, with durable responses in a heavily-pretreated population (KEYNOTE-028 CSR), generally consistent with the results of KEYNOTE-180.

Data from KEYNOTE-181, the randomized, open-label, confirmatory trial of pembrolizumab versus physician's choice of single agent chemotherapy in subjects with advanced/metastatic adenocarcinoma and squamous cell carcinoma of the esophagus that have progressed after first-line standard therapy, are consistent with the durable benefit seen in KEYNOTE-180, and further highlight pembrolizumab monotherapy's benefit in comparison to an active comparator in a randomized phase 3 trial. In the all participant population in KEYNOTE-181 (N=628), 13% (N= 41) of participants experienced objective responses, nearly two-fold higher than the ORR seen with SOC (6.7%), and there was evidence of durability. Similar results were seen with the ESCC population and with the PD-L1 CPS ≥1 population where ORR was two-fold and three-fold higher with pembrolizumab than with SOC, respectively. It is important to note that in the all participants population the ORR (9.9% [95% CI: 5.2, 16.7]) seen with pembrolizumab monotherapy in KEYNOTE-180 is favorable compared with the ORR in the all participants population seen with the chemotherapies used in KEYNOTE-181 (6.7% [95% CI: 4.2, 10.0]), despite participants in KEYNOTE-180 being in a substantially more advanced setting. Thus, efficacy data from KEYNOTE-181 (with a much larger sample size [N=628], than in KEYNOTE-180 study [N=121], and with 62 participants with objective responses in the overall population) provide further confidence in the importance of the clinical benefit seen with pembrolizumab monotherapy in KEYNOTE-180 (KEYNOTE-180 CSR, Sec. 11) (KEYNOTE-181 CSR, Sec. 11).

Considering the high unmet medical need in this population, the durable clinical benefit demonstrated in KEYNOTE-180 supports pembrolizumab as an important treatment option for [redacted] (b) (4) .

The FDA's Assessment:

As can be seen from the results of the single arm open label trial, KEYNOTE-180, and the randomized open label trial, KEYNOTE-181, consistent clinical benefit is observed in patients with ESCC whose tumors have high levels of PD-L1 expression (CPS ≥ 10).

7.2 Review of Safety

The Applicant's Position:
Safety results from KEYNOTE-180 establish the tolerability of pembrolizumab among participants with 3L+ metastatic esophageal cancer. Results also indicate that no new safety signals were observed in KEYNOTE-180. The types and frequencies of AEs were generally consistent with the RSD, which represents the established safety profile of pembrolizumab in approved indications. Relevant differences observed between KEYNOTE-180 participants and the RSD were considered due to underlying metastatic esophageal cancer in a heavily pretreated population.

The FDA's Assessment:
FDA agrees with Merck's conclusions regarding the safety of pembrolizumab in patients with 3L+ metastatic esophageal cancer; however, because of the small sample size and single arm design of KEYNOTE-180, FDA's assessment of safety of pembrolizumab in patients with esophageal cancer is based on analysis of safety data from KEYNOTE-181 and pooled data from trials included in the integrated summary of safety, in addition to the results of KEYNOTE-180 as described below.

7.2.1. Safety Review Approach

The Applicant's Position:

Overall Approach
The review of safety focuses on the safety profile of pembrolizumab in the context of its intended use for the treatment of (b) (4) . Results of analyses conducted to evaluate the safety of pembrolizumab in the indication population from the pivotal, single-arm Phase 2 study, KEYNOTE-180, and the results observed in other studies in other indications in which pembrolizumab monotherapy was administered, are included. Safety results for pembrolizumab are presented for the following two datasets:

1. KEYNOTE-180 Safety Dataset (N=121): Heavily pretreated participants with advanced/metastatic esophageal cancer (who have received at least two prior lines of standard therapy [3L+]) from the KEYNOTE-180 study are the primary focus of this Assessment Aid and this filing and comprise the Indication/Esophageal Safety Dataset. Participants in the KEYNOTE-180 Safety Dataset received at least one dose of pembrolizumab up to the data cutoff date of 30-JUL-2018.
2. RSD (N=2799): The 2799 pembrolizumab-treated 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. This dataset represents the established safety profile for pembrolizumab

monotherapy.

The comparison of KEYNOTE-180 safety data to the RSD is the focus of the safety summary. The RSD is a dataset with pooled data from monotherapy clinical studies in melanoma and NSCLC [Table 14], as part of the Sponsor's product development of pembrolizumab.

Safety Issues Identified in Pembrolizumab Clinical Development Program

The mechanism of action of pembrolizumab involves the interruption of the binding of PD 1 to its ligands, thereby interrupting the down modulation of T cell immune response. It is therefore anticipated that adverse reactions associated with pembrolizumab would include immune mediated AEs. Based upon the mechanism of action, the Sponsor developed a broad list of immune mediated AEOSIs to evaluate and monitor. Infusion-related reactions are also included in the AEOSI list, though they are not immune mediated. Based on ongoing monitoring, the Sponsor has identified those AEOSIs that have been observed and assessed as related to pembrolizumab (Investigator's Brochure, Edition 16, 29-JUN-2018, Sec. 5.4). AEOSIs in KEYNOTE-180 and the RSD are compared in [Sec. 7.2.4].

The FDA's Assessment:
FDA agrees with the pooling of safety datasets as described above for the analysis of the safety of pembrolizumab in this disease. In addition, the clinical reviewer also reviewed the esophageal safety dataset (N=458) as described below for certain safety analyses.

Esophageal Safety Dataset for Pembrolizumab (N=458): All participants with advanced/metastatic esophageal cancer from KEYNOTE-181 (2L), KEYNOTE-180 (two 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.

7.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:
The number of participants exposed to pembrolizumab in KEYNOTE-180 and the RSD is shown in [Table 14] (2.7.4, Sec. 1.1).

Table 14
Number of Participants in Esophageal and Pooled Safety Datasets

Study ID	Study Title	Number of participants included in safety dataset
Indication/Esophageal Safety Dataset (N=121)		
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
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

Safety analyses in KEYNOTE-180 were conducted using the ASaT population which includes all participants who received at least one dose of study treatment. Duration of exposure was measured from the date of the first dose to the date of the last dose of pembrolizumab received. As of the 30-JUL-2018 data cutoff date, a total of 121 participants received at least one dose of pembrolizumab (ASaT population) and two participants were still receiving treatment.

In KEYNOTE-180, participants were exposed to pembrolizumab for a median of two months (range: 0 [1 day] to 24 months), resulting in a median of 4 administrations (range: 1 to 35 administrations) (KEYNOTE-180 CSR, Table 10-3). As would be expected in this heavily pre-treated population with a short life expectancy, the median exposure to pembrolizumab was shorter compared with the RSD (2 versus 4 months, respectively), and a smaller percentage of participants remained on therapy at specific examined timepoints compared with the RSD [Table 15] (2.7.4, Sec. 1.2).

Table 15
Summary of Duration of Exposure

	KEYNOTE-180 data for MK-3475‖‖ (N=121)	Reference Safety Dataset for MK-3475†† (N=2799)
Study Days On-Therapy (Months)		
Mean	3.9	6.5
Median	2	4
SD	5.09	5.93
Range	0 to 24	0 to 30
Study Days On-Therapy	N (%)	N (%)
>0 months	121 (100.0)	2,799 (100.0)
>=1 month	86 (71.1)	2,394 (85.5)
>=3 months	50 (41.3)	1,656 (59.2)
>=6 months	19 (15.7)	1,153 (41.2)
>=12 months	12 (9.9)	600 (21.4)

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as last dose date - first dose date + 1.
‖‖ Includes all subjects who received at least one dose of MK-3475 in KEYNOTE-180.
†† Includes all subjects who received at least one dose of MK-3475 in KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3; KEYNOTE-002 (original phase), KEYNOTE-006, and KEYNOTE-010.
MK-3475 Database Cutoff Date for Melanoma (KEYNOTE-001-Melanoma: 18APR2014, KEYNOTE-002: 28FEB2015, KEYNOTE-006: 03MAR2015)
MK-3475 Database Cutoff Date for Lung (KEYNOTE-001-NSCLC: 23JAN2015, KEYNOTE-010: 30SEP2015)
MK-3475 Database Cutoff Date for Esophageal (KEYNOTE-180: 30JUL2018)

Source: [ISS: adam-adsl; adexsum]

The FDA's Assessment:
FDA agrees with Merck's analysis of exposure to pembrolizumab.

Relevant characteristics of the safety population:

The Applicant's Position:
The KEYNOTE-180 efficacy and safety populations were identical (ASaT) [Table 8]. Overall, for all baseline characteristics, participants in the KEYNOTE-180 study were representative of patients with advanced/metastatic esophageal cancer (KEYNOTE-180 CSR, Sec. 10.4.1).

The KEYNOTE-180 Safety Dataset represents a heavily pretreated (3L+) esophageal cancer patient population. There was a higher percentage of male participants, an older population (≥65 years), a higher proportion of Asian participants, and a higher proportion of participants with ECOG PS 1 in the KEYNOTE-180 Safety Dataset compared with the RSD (2.7.4, Sec. 1.3).

The FDA's Assessment:
FDA agrees with Merck's analysis.

Adequacy of the safety database:

The Applicant's Position:
The clinical safety data supporting this sBLA are derived from KEYNOTE-180 and comparisons are made to the RSD. The study population in KEYNOTE-180 adequately represents the target population for the indication. Exposure, demographic, disease, and other baseline characteristics were representative of the intended patient population with the proposed indication.

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 additional patients in the postmarketing setting. The size of the safety database for KEYNOTE-180 supported by supplemental data from KEYNOTE-181 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-180 CSR, Sec. 9.6). Sponsor QA carried out periodic, independent audits to ensure the accuracy and integrity of the clinical study data (KEYNOTE-180 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 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 sBLA. However, FDA issued several information requests during the review cycle to obtain additional information and clarification regarding some aspects of the data and analyses included in the sBLA.

Categorization of Adverse Event

The Applicant's Position:
Non-serious adverse events up to 30 days after the last dose of pembrolizumab and serious adverse events up to 90 days after the last dose are displayed by category in [Table 16]. The safety profile of pembrolizumab in the KEYNOTE-180 Safety Dataset, summarized in the following sections, showed no new safety signals for pembrolizumab and is generally consistent with the established safety profile of pembrolizumab (RSD).

Table 16
Adverse Event Summary for KEYNOTE-180 and RSD

	KEYNOTE-180 data for MK-3475‖‖		Reference Safety Dataset for MK-3475††	
	n	(%)	n	(%)
Subjects in population	121		2,799	
with one or more adverse events	116	(95.9)	2,727	(97.4)
with no adverse event	5	(4.1)	72	(2.6)
with drug-related† adverse events	70	(57.9)	2,062	(73.7)
with toxicity grade 3-5 adverse events	65	(53.7)	1,273	(45.5)
with toxicity grade 3-5 drug-related adverse events	19	(15.7)	386	(13.8)
with non-serious adverse events	116	(95.9)	2,671	(95.4)
with serious adverse events	47	(38.8)	1,042	(37.2)
with serious drug-related adverse events	13	(10.7)	282	(10.1)
with dose modification‡ due to an adverse event	47	(38.8)	884	(31.6)
who died	7	(5.8)	110	(3.9)
who died due to a drug-related adverse event	1	(0.8)	10	(0.4)
discontinued drug due to an adverse event	13	(10.7)	334	(11.9)
discontinued drug due to a drug-related adverse event	7	(5.8)	146	(5.2)
discontinued drug due to a serious adverse event	7	(5.8)	253	(9.0)
discontinued drug due to a serious drug-related adverse event	2	(1.7)	101	(3.6)

† Determined by the investigator to be related to the drug.

‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

‖‖ Includes all subjects who received at least one dose of MK-3475 in KEYNOTE-180.

†† Includes all subjects who received at least one dose of MK-3475 in KEYNOTE-001 Part B1, B2, B3, D, C, F1, F2, F3; KEYNOTE-002 (original phase), KEYNOTE-006, and KEYNOTE-010.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

MK-3475 Database Cutoff Date for Melanoma (KEYNOTE-001-Melanoma: 18APR2014, KEYNOTE-002: 28FEB2015, KEYNOTE-006: 03MAR2015)

MK-3475 Database Cutoff Date for Lung (KEYNOTE-001-NSCLC: 23JAN2015, KEYNOTE-010: 30SEP2015)

MK-3475 Database Cutoff Date for Esophageal (KEYNOTE-180: 30JUL2018)

Source: [ISS: adam-adsl; adae]

The FDA's Assessment:

FDA agrees with Merck's analysis of adverse events as shown in the table above. MedDRA version 21.0 was used for the 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.

Routine Clinical Tests

The Applicant's Position:
The protocol (KEYNOTE-180-04 Sec. 6.0 and Sec. 7.0) and Trial Flow Chart shown in [Table 5] outline the frequency of laboratory testing, vital signs, physical exam, and AE monitoring for KEYNOTE-180.

The FDA's Assessment:
FDA agrees with Merck's analysis

7.2.4. Safety Results

Deaths

The Applicant's Position:
The proportion of participants in the KEYNOTE-180 safety dataset who experienced an AE leading to death was similar with the RSD (5.8% vs 3.9%). The seven AEs that led to death in the KEYNOTE-180 Safety Dataset were pneumonia aspiration (two participants), pneumonia, pneumonitis, tumor necrosis, cerebrovascular accident, and chronic obstructive pulmonary disease (one participant each) (2.7.4, Sec. 2.1.2).

One of the AEs leading to death (pneumonitis) was considered to be drug related by the investigator. This participant received five cycles of treatment. Six days after the last dose of pembrolizumab, the participant developed a drug-related serious AEOSI of pneumonitis (Grade 3 at onset) as determined by the investigator, and for which the participant received methylprednisolone IV for two days. The participant was discontinued from study treatment and subsequently died due to Grade 5 pneumonitis three days after onset of the event (2.7.4, Sec. 2.1.2, KEYNOTE-180 CSR, Sec. 12.2.1.1, and Sec. 16.2.7.1.4).

Complete narratives for all seven cases of AEs leading to death are in (KEYNOTE-180 CSR, Sec. 16.2.7.2).

The FDA's Assessment:
FDA reviewed all available death narratives of the patients in KEYNOTE-180 as of the data cutoff of July 30, 2018. FDA agrees with Merck's assessment of death as stated above. Except for the fatal event of pneumonitis, all other events appear to be unrelated to pembrolizumab and related to the underlying esophageal cancer.

Serious Adverse Events

The Applicant's Position:
The proportion of participants in the KEYNOTE-180 Safety Dataset who experienced at least one SAE was consistent with the RSD. The most frequently reported (incidence ≥2% of participants) SAEs in the KEYNOTE-180 Safety Dataset were pneumonia (10.7%), pneumonia aspiration (4.1%), acute kidney injury (3.3%), lung infection (2.5%), and pneumonitis (2.5%). The SAE with a ≥5 percentage-point higher incidence in the KEYNOTE-180 Safety Dataset versus the RSD was pneumonia (10.7% vs. 3.0%). Of these events, only one event of pneumonia was considered drug related. Medical review of these events suggests that it is likely they are associated with the underlying metastatic esophageal cancer and that these events do not represent a new safety signal (2.7.4, Sec. 2.1.3.1).

The proportion of participants in the KEYNOTE-180 Safety Dataset who experienced at least one drug related SAE was also consistent with the RSD. Drug-related SAEs experienced by more than one participant (incidence ≥1% of participants) in the KEYNOTE 180 Safety Dataset were pneumonitis (2.5%), hypopituitarism, and diabetic ketoacidosis (1.7% each) (2.7.4, Sec. 2.1.3.2).

The FDA's Assessment:
FDA agrees with Merck's analysis of SAEs. The SAEs that were reported appear to be related to the underlying disease except for the event of immune-mediated pneumonitis. The most frequently reported drug-related SAEs reported in Study KN-180 were pneumonitis (2.5%), hypopituitarism (1.7%), and diabetic ketoacidosis (1.7%).

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:
The proportion of participants who experienced AEs leading to treatment discontinuation in the KEYNOTE-180 Safety Dataset (10.7%) was consistent with the RSD (11.9%), demonstrating the tolerability of pembrolizumab in heavily pretreated metastatic esophageal cancer participants (ISS, Table 20). In the KEYNOTE-180 Safety Dataset, the most frequently reported (incidence ≥2% of participants) AE leading to treatment discontinuation was pneumonitis (3.3%) (2.7.4, Sec. 2.1.4.1).

The proportion of participants who experienced drug-related AEs leading to treatment discontinuation in the KEYNOTE-180 Safety Dataset was consistent with the RSD (ISS, Table 21). Seven (5.8%) participants in KEYNOTE-180 experienced drug-related AEs leading to treatment discontinuation. The most frequently reported (incidence ≥1%) drug-related AE leading to discontinuation of pembrolizumab in the KEYNOTE-180 Safety Dataset was pneumonitis (3.3%) (2.7.4, Sec. 2.1.4.1)

The FDA's Assessment:
FDA agrees with Merck's analysis; pembrolizumab at the dose administered appears to be well

tolerated by the refractory esophageal cancer population.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:
Considering the difference in sample size, the proportion of participants who experienced AEs leading to treatment interruption in the KEYNOTE-180 Safety Dataset (32.2%) was generally similar to that in the RSD (22.2%) (ISS, Table 22). In the KEYNOTE-180 Safety Dataset, the most frequently reported (incidence ≥2% of participants) AEs leading to treatment interruption were pneumonia (5.0%), malaise (3.3%), diarrhea, AST increased, and blood bilirubin increased (2.5% each) (2.7.4, Sec. 2.1.4.2).

The proportion of participants who experienced drug-related AEs leading to treatment interruption reported in the KEYNOTE-180 Safety Dataset (14.9%) was consistent with the RSD (12.5%) (ISS, Table 23). The most frequently reported (incidence ≥1% of participants) drug related AEs leading to treatment interruption in the KEYNOTE-180 Safety Dataset were diarrhea (2.5%), pneumonitis, hypopituitarism, diabetic ketoacidosis, and blood ALP increased (1.7% each). Based upon the small number of subjects affected and comparison with the RSD, the events of diarrhea and blood ALP increased were considered not clinically meaningful (2.7.4, Sec. 2.1.4.2).

The FDA's Assessment:
In general, the number of patients who had treatment interrupted due to an AE was few in KEYNOTE-180 and comparable to that observed in the RSD.

Significant Adverse Events

The Applicant's Position:
A pre-specified list of PTs was developed by the Sponsor to consistently characterize the nature and frequency of each AEOSI across the clinical program, regardless of causality as reported by investigators. These PTs are considered to be medically equivalent to immune-mediated events and infusion-related reactions. The list of PTs is continually updated based on emerging pembrolizumab safety data. Version 14.0 was used at the time of the data cutoff date of 30-JUL-2018.

No new indication-specific, immune-mediated AE causally associated with pembrolizumab was identified in KEYNOTE-180 (2.7.4, Sec. 2.1.4.3).

A total of 26 participants (21.5%) in the KEYNOTE-180 Safety Dataset experienced one or more AEOSI, including PTs that are known, identified, and potential risks of pembrolizumab treatment (ISS, Table 25). The majority of AEOSI reported were mild to moderate (Grade 1 or 2). Seven (5.8%) participants experienced Grade 3-5 AEOSI: 4 participants experienced Grade 3 AEOSI, two participants experienced Grade 4 AEOSI (pneumonitis and diabetic ketoacidosis), and one participant experienced a fatal (Grade 5) AEOSI (pneumonitis) (ISS, Table 68). In the

KEYNOTE-180 Safety Dataset, the most frequently reported (incidence ≥1% of participants) AEOSI were hypothyroidism (9.1%), pneumonitis (7.4%), hyperthyroidism (3.3%), colitis (2.5%), hypophysitis (1.7%), and Type 1 diabetes (1.7%) (2.7.4, Table 10).

The AEOSI category with a higher incidence in the KEYNOTE-180 Safety Dataset versus the RSD was pneumonitis (7.4% vs. 3.4%). Nine pneumonitis events occurred in nine participants; of these, three events were Grade 3, 4, and 5 AEs (one event each) and all were considered serious (ISS, Table 67 and KEYNOTE-180 CSR Sec. 12.2.4). It is likely that the observed difference is related to the preponderance of participants in the KEYNOTE-180 Safety Dataset who received radiation to the chest area, and reflects the increased risk for pneumonitis in this population. Six out of the nine participants who experienced pneumonitis (including interstitial lung disease) received prior radiation to the chest area (KEYNOTE-180 CSR, Sec. 12.2.4).

The FDA's Assessment:
As summarized in Table 17, AEOSIs reported in ≥1% of participants included hypothyroidism (9.1%), pneumonitis (7.4%), hyperthyroidism (3.3%), colitis (2.5%), hypophysitis (1.7%), and type 1 diabetes mellitus (1.7%). Of the nine patients with pneumonitis, one had a fatal event. One patient had a Grade 3 event and one a Grade 4 event. No new AEOSI emerged from review of the safety data from KEYNOTE-180.

Table 17
Incidence of AEOSI in KEYNOTE-180

AEOSI/Preferred Term	Pembrolizumab	
	N	%
Colitis	3	2.5
Colitis	2	1.7
Enterocolitis	1	0.8
Hyperthyroidism	4	3.3
Hyperthyroidism	4	3.3
Hypophysitis	2	1.7
Hypophysitis	2	1.7
Hypothyroidism	11	9.1
Hypothyroidism	11	9.1
Infusion Reactions	1	0.8
Infusion Related reaction	1	0.8
Nephritis	1	0.8
Nephritis	1	0.8
Pancreatitis	1	0.8
Pneumonitis	9	7.4
Interstitial lung disease	1	0.8
Pneumonitis	8	6.6
Thyroiditis	1	0.8
Thyroiditis	1	0.8

Type 1 Diabetes mellitus	2	1.7
Diabetic ketoacidosis	2	1.7
Type 1 Diabetes mellitus	1	0.8
Uveitis	1	0.8
iritis	1	0.8

Source: FDA reviewer Analysis

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:
The most frequently reported (incidence ≥20% of participants) AE in the KEYNOTE-180 Safety Dataset was fatigue (28.1%) and the incidence of this AE was consistent with that seen in the RSD (2.7.4, Sec. 2.1.1.1 and Table 5).

The AE with a ≥5 percentage-point higher incidence in the KEYNOTE-180 Safety Dataset versus the RSD was pneumonia (14.0% vs. 5.0%). All other frequently reported AEs in KEYNOTE-180 had an incidence that was consistent with that observed in the RSD. Medical review of the available data revealed that the higher observed incidence of pneumonia in the KEYNOTE-180 Safety Dataset is consistent with the underlying disease and does not represent a new safety signal. 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. 2.1.1.1).

The FDA's Assessment:
FDA agrees with Merck's analysis of common adverse events. The higher incidence of pneumonia seen in KEYNOTE-180 is likely related to the underlying disease and multiple prior lines of chemotherapy.

Laboratory Findings

The Applicant's Position:
No changes occurred in the safety profile of pembrolizumab with the addition of new laboratory data from participants with advanced/metastatic esophageal cancer (2.7.4, Sec. 3).

In the KEYNOTE-180 Safety Dataset, the most frequently reported (incidence >10%) laboratory abnormalities with a clinically meaningful (Grade 3-4) worsening in CTCAE grades for protocol-specified laboratory tests were decreased lymphocytes (18.2%) and decreased hemoglobin (10.7%) (ISS, Table 111).

The proportion of participants who experienced clinically meaningful worsening from baseline in laboratory test toxicity grade (based on the highest postbaseline toxicity grade per laboratory test) in the KEYNOTE-180 Safety Dataset were generally consistent with the RSD, except for the following AEs which showed a ≥5 percentage-point increase in KEYNOTE-180 compared with the RSD: decreased lymphocytes (18.2% vs. 7.9%), increased AST (9.8% vs. 2.1%), and decreased hemoglobin (10.7% vs. 4.5%) (ISS, Table 111). The higher proportion of participants with increases in these parameters in the KEYNOTE-180 Safety Dataset was expected, considering that participants in KEYNOTE-180 had generally worse ECOG PS and their disease was more advanced compared with participants in the RSD.

Two participants (1.7%) in the KEYNOTE-180 Safety Dataset were discontinued from pembrolizumab because of AEs based on laboratory investigations, one participant because of increased ALT (which was considered drug related) and one participant because of increased blood bilirubin; this is similar to the proportion of participants with these parameters leading to discontinuation from pembrolizumab in the RSD (ISS, Table 20 and Table 21).

None of the participants had laboratory values that satisfied the protocol-specified criteria for potential drug-induced liver injury.

The FDA's Assessment:
No new laboratory-based safety signals emerged in KEYNOTE-180.

Vital Signs

The Applicant's Position:
There were no clinically meaningful findings in vital sign measurements or other observations related to safety in KEYNOTE-180 (KEYNOTE-180 CSR, Sec 12.4).

The FDA's Assessment:
FDA agrees with Merck's analysis.

Electrocardiograms (ECGs)

The Applicant's Position:
ECG testing was performed once during screening using local standard procedures and additional time points were collected as clinically necessary [Table 5]. Clinically significant

abnormal findings were not identified.

The FDA's Assessment:
FDA agrees with Merck's analysis.

QT

The Applicant's Position:
No new information is provided in the current supplement. No clinically meaningful effects of pembrolizumab on cardiac QTc interval were identified in the analyses included in previous applications, which included participants with melanoma and participants with NSCLC (Investigator's Brochure, Edition 16, 29-JUN-2018, Sec. 5.2.1.4).

The FDA's Assessment:
FDA agrees with Merck's analysis.

Immunogenicity

The Applicant's Position:
No new immunogenicity data are available (2.5, Sec. 5.5). Since a robust characterization of the immunogenicity of pembrolizumab has been provided in previous submissions in other monotherapy indications in the non-adjuvant setting, the Summary of Clinical Pharmacology (Module 2.7.2) is not included in the submission consistent with the agreement obtained with the FDA (2.5, Sec 3).

The FDA's Assessment:
Merck's position is factually correct.

7.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:
Safety results are described in [Sec. 7.2.4].

The proportion of participants with drug interruptions and discontinuations due to AEs in KEYNOTE-180 was low in this heavily pretreated population compared with the RSD. AEOSI were relatively infrequent (overall incidence of 21.5%). The frequency, severity, and nature of AEOSI among participants with metastatic esophageal cancer were consistent with the RSD, with no identification of new indication-specific, immune-mediated AEs causally related to pembrolizumab. The incidence of pneumonitis in KEYNOTE-180 (7.4%) was higher than in the RSD (3.4%). It is likely that this observed difference is related to the preponderance of participants in KEYNOTE-180 who received radiation to the chest area, and reflects the increased risk for pneumonitis in this population. Drug-related deaths were infrequent with an

incidence of 0.8% (1 event of pneumonitis). As a result, the safety profile of pembrolizumab remains unchanged with the addition of data from participants with metastatic esophageal cancer.

The FDA's Assessment:
FDA agrees that there were no new safety signals that emerged from KEYNOTE-180; in general, the adverse reaction profile of pembrolizumab observed in KEYNOTE-180 is consistent with approved product labeling for KEYTRUDA.

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

The Applicant's Position:
Not applicable; no COA data were collected in KEYNOTE-180.

7.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:
Adverse events were assessed in subgroups of participants for the intrinsic factors of age, sex, and ECOG PS. No important differences were seen between KEYNOTE-180 and the RSD in the incidence of AEs based on age (<65 versus ≥65 years of age), gender, or ECOG PS (2.7.4, Sec. 4.1). With respect to sex, in KEYNOTE-180 there were some differences in the incidences of types of AEs and discontinuations; however, these differences do not follow a pattern suggestive of an impact of sex on the overall AE profile. The differences observed in KEYNOTE-180 based on sex were also likely related to the small sample size of the female population and should be evaluated with caution.

The FDA's Assessment:
Because KEYNOTE-180 was a small single arm trial, interpretation of analyses of adverse events by demographic subgroup are difficult to interpret.

7.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
No studies were conducted to evaluate a specific safety concern associated with pembrolizumab.

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 submission.

The FDA's Assessment:
FDA agrees.

Human Reproduction and Pregnancy

The Applicant's Position:
There were no reports of pregnancy in the KEYNOTE-180 Safety Dataset up to the data cutoff. No new information concerning human reproduction and pregnancy is provided in this submission.

The FDA's Assessment:
FDA agrees.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:
No new information concerning pediatrics and assessment of effects on growth is provided in this submission.

The FDA's Assessment:
FDA agrees.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
There were no reports of overdose in KEYNOTE-180 up to the data cutoff. An overdose was defined as any participant infused with a dose of ≥ 1000 mg (≥5 × the indicated dose) (KEYNOTE-180-04 Protocol, Sec. 7.2.1).

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.

No withdrawal or rebound effects are expected with an anti-PD-1 mAb and none have been observed in pembrolizumab clinical studies to date.

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 was summarized in the Periodic Safety Update Report covering the period 29-DEC-2017 through 28-JUN-2018. There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country (2.7.4, Sec. 5).

The FDA's Assessment:
Based on the review of the PSUR dated 04-MAR-2018 to 03-SEP-2018, 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 through 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. 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-180. There are no specific safety concerns not already included in pembrolizumab labeling expected from off-label use.

The FDA's Assessment:
FDA agrees with Merck's assessment.

7.2.11. Integrated Assessment of Safety

The Applicant's Position:
The results from the KEYNOTE-180 Safety Dataset consistently demonstrated a favorable

tolerability of pembrolizumab in participants with metastatic esophageal cancer (3L+) that was similar to the tolerability previously identified in the RSD, as evidenced by the following:

- AEs associated with pembrolizumab treatment were typically Grade 1 to 2 and reversible (ISS, Table 10).
- The increased frequency of pneumonia (14.0% of participants) in this study was likely related to the underlying condition and not due to pembrolizumab therapy (2.7.4, Sec. 2.1.1.1).
- Considering the difference in sample size, the proportion of participants with drug interruptions (32.2%) and discontinuations (10.7%) due to AEs in this heavily pretreated population was generally similar compared with the RSD (22.2% and 11.9%) which supports that pembrolizumab was reasonably well tolerated by patients with metastatic esophageal cancer in this study (ISS, Table 22 and Table 20).
- AEOSI were relatively infrequent and their overall frequency, severity, and nature were consistent with the RSD. No new indication-specific immune-mediated AEs causally related to pembrolizumab were identified.
- The incidence of pneumonitis in KEYNOTE-180 (7.4%) appeared to be higher than in the RSD (3.4%), which may be related to prior history of radiation to the chest area, which increases the risk of pneumonitis in this population.
- Drug-related deaths were infrequent with an incidence of 0.8% (1 event of pneumonitis).

No new safety risks were identified for pembrolizumab with the inclusion of safety data from participants with metastatic esophageal cancer in KEYNOTE-180, and therefore no changes to the current Warnings and Precautions section of the PI specific to this indication are warranted.

Safety is an important consideration for previously treated esophageal cancer patients, especially in the 3L+ setting where disease is more advanced and performance status is worse. Similar to efficacy, there was consistency between KEYNOTE-180 and KEYNOTE-181 with respect to general safety profile, and KEYNOTE-181 demonstrated an improved safety profile relative to SOC. Considering the high morbidity that patients with 3L+ esophageal cancer often have to manage, the favorable and consistent safety profile of pembrolizumab monotherapy observed in two separate trials is a critical consideration (KEYNOTE-180 CSR, Sec. 12) (KEYNOTE-181 CSR, Sec. 12).

The FDA's Assessment:

FDA agrees with Merck's analysis above. Results from the single arm trial KEYNOTE-180 demonstrate that the adverse reaction profile of pembrolizumab in patients with esophageal cancer treated in third line and beyond is acceptable. Serious adverse events were observed in 39% of patients and Grade 3-5 adverse events were observed in 54% of patients with most related to the underlying refractory disease in the opinion of the investigator. The AEOSI observed in KEYNOTE-180 were consistent with those observed in the RSD. No new immune-mediated AEs related to pembrolizumab were identified. Similarly, when the adverse events observed in KEYNOTE -180 are compared to those observed in the RSD or the esophageal safety

dataset the incidences are in general similar.

Table 18
Treatment-Emergent Adverse Events (TEAE) Occurring in ≥5% of the Safety Population (any safety dataset) in KEYNOTE-180

TEAE	Analysis Set					
	3475-180 Grade 1-5 N = 121		EC 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
Any TEAE	116 (96)	58 (48)	437 (95)	206 (45)	2727 (97)	1163 (42)
Blood and Lymphatic System Disorders	21 (17)	9 (7)	87 (19)	37 (8)	487 (17)	122 (4)
Anemia	18 (15)	8 (7)	77 (17)	31 (7)	347 (12)	89 (3)
Febrile neutropenia	0 (0)	0 (0)	1 (0.2)	1 (0.2)	2 (0.1)	2 (0.1)
Neutropenia	0 (0)	0 (0)	0 (0)	0 (0)	17 (0.6)	5 (0.2)
Endocrine Disorders	16 (13)	3 (2)	69 (15)	7 (1)	335 (12)	26 (0.9)
Hypothyroidism	11 (9)	0 (0)	49 (11)	0 (0)	236 (8)	3 (0.1)
Gastrointestinal Disorders	69 (57)	15 (12)	293 (64)	69 (15)	1704 (61)	227 (8)
Constipation	23 (19)	1 (0.8)	85 (19)	4 (0.9)	497 (18)	12 (0.4)
Nausea	23 (19)	1 (0.8)	87 (19)	5 (1)	685 (24)	33 (1)
Vomiting	20 (16)	1 (0.8)	61 (13)	6 (1)	387 (14)	32 (1)
Diarrhea	19 (16)	1 (0.8)	61 (13)	4 (0.9)	625 (22)	36 (1)
Abdominal pain	9 (7)	0 (0)	48 (10)	7 (1.5)	274 (10)	27 (1)
Dysphagia	8 (7)	3 (2)	60 (13)	20 (4)	59 (2)	7 (0.3)
Dry mouth	7 (6)	0 (0)	17 (4)	0 (0)	142 (5)	1 (0)
Abdominal pain upper	6 (5)	0 (0)	22 (5)	3 (0.7)	115 (4)	4 (0.1)
Stomatitis	0 (0)	0 (0)	10 (2)	0 (0)	59 (2)	1 (0)
General Disorders and Administration Site Conditions	61 (50)	12 (10)	239 (52)	30 (7)	1856 (66)	192 (7)
Fatigue	34 (28)	4 (3)	110 (24)	9 (2)	1044 (37)	69 (2)
Edema peripheral	10 (8)	0 (0)	31 (7)	1 (0.2)	286 (10)	11 (0.4)
Pyrexia	9 (7)	1 (0.8)	45 (10)	2 (0.4)	357 (13)	13 (0.5)
Asthenia	9 (7)	2 (2)	55 (12)	10 (2)	362 (13)	34 (12)

TEAE	Analysis Set					
	3475-180 Grade 1-5 N = 121		EC 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
Malaise	6 (5)	2 (1.7)	22 (4.8)	2 (0.4)	47 (2)	4 (0.1)
Chest pain	4 (3)	0 (0)	15 (3)	3 (0.7)	166 (6)	13 (0.5)
Chills	2 (2)	0 (0)	3 (0.7)	0 (0)	153 (6)	0 (0)
Infections and Infestations	42 (35)	16 (13)	158 (34)	50 (10.9)	1182 (42)	207 (7)
Pneumonia	17 (14)	12 (10)	40 (9)	23 (5)	140 (5)	65 (2)
Upper respiratory tract infection	6 (5)	0 (0)	19 (4)	0 (0)	182 (6)	3 (0.1)
Lung infection	6 (5)	3 (2)	10 (2)	4 (0.9)	45 (2)	8 (0.3)
Nasopharyngitis	4 (3)	0 (0)	15 (3)	0 (0)	182 (6)	0 (0)
Urinary tract infection	1 (0.8)	0 (0)	11 (2)	4 (0.9)	162 (5.8)	14 (0.5)
Investigations	43 (35.5)	13 (11)	163 (36)	45 (10)	865 (31)	129 (5)
Aspartate aminotransferase increased	13 (11)	3 (2)	39 (8)	8 (2)	168 (6)	24 (0.9)
Alanine aminotransferase increased	12 (10)	5 (4)	34 (7)	8 (2)	172 (6)	25 (0.9)
Blood alkaline phosphatase increased	10 (8)	2 (2)	25 (5)	7 (1)	112 (4)	16 (0.6)
Blood bilirubin increased	9 (7)	4 (3)	16 (3)	6 (1)	51 (2)	14 (0.5)
Weight decreased	7 (6)	0 (0)	49 (11)	6 (1)	219 (8)	8 (0.3)
Neutrophil count decreased	1 (0.8)	0 (0)	4 (0.9)	2 (0.4)	21 (0.8)	3 (0.1)
White blood cell count decreased	1 (0.8)	0 (0)	4 (0.9)	1 (0.2)	28 (1)	2 (0.1)
Metabolism and Nutrition Disorders	49 (40)	18 (15)	203 (44)	58 (13)	1109 (40)	232 (8)
Decreased appetite	24 (20)	4 (3)	109 (24)	15 (3)	630 (22)	26 (0.9)
Hyponatremia	7 (6)	3 (2)	26 (6)	11 (2)	146 (5)	62 (2)
Hypokalemia	7 (6)	2 (2)	25 (5)	4 (0.9)	124 (4)	25 (0.9)
Dehydration	6 (5)	3 (2)	26 (6)	7 (1)	106 (4)	28 (1)

TEAE	Analysis Set					
	3475-180 Grade 1-5 N = 121		EC 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
Hyperglycemia	4 (3)	2 (2)	22 (5)	5 (1.1)	130 (5)	29 (1)
Hypoalbuminemia	3 (2)	0 (0)	20 (4)	0 (0)	89 (3)	15 (0.5)
Musculoskeletal and Connective Tissue Disorders	36 (30)	7 (6)	125 (27)	18 (4)	1411 (50)	126 (4)
Back pain	12 (10)	4 (3)	50 (11)	9 (2)	349 (12)	38 (1)
Myalgia	8 (7)	1 (0.8)	18 (3.9)	1 (0.2)	253 (9)	8 (0.3)
Musculoskeletal pain	6 (5)	0 (0)	17 (4)	1 (0.2)	226 (8)	16 (0.6)
Pain in extremity	5 (4)	1 (0.8)	13 (3)	1 (0.2)	237 (8)	12 (0.4)
Arthralgia	5 (4)	1 (0.8)	24 (5)	3 (0.7)	504 (18)	17 (0.6)
Nervous System Disorders	32 (26)	3 (2)	97 (21)	17 (4)	1037 (37)	103 (4)
Neuropathy peripheral	7 (6)	1 (0.8)	13 (3)	1 (0.2)	76 (3)	2 (0.1)
Headache	6 (5)	0 (0)	23 (5)	2 (0.4)	400 (14)	13 (0.5)
Dysgeusia	5 (4)	0 (0)	11 (2)	0 (0)	69 (2)	0 (0)
Dizziness	4 (3)	0 (0)	11 (2)	0 (0)	244 (9)	7 (0.3)
Peripheral sensory neuropathy	0 (0)	0 (0)	3 (0.7)	0 (0)	29 (1)	0 (0)
Pneumonitis (GT)	9 (7)	2 (2)	24 (5)	3 (0.7)	94 (3)	32 (1)
Pneumonitis	8 (7)	2 (2)	21 (5)	3 (0.7)	87 (3)	31 (1)
Interstitial lung disease	1 (0.8)	0 (0)	3 (0.7)	0 (0)	7 (0.3)	1 (0)
Psychiatric Disorders	23 (19)	4 (3)	68 (15)	6 (1)	523 (19)	24 (0.9)
Insomnia	10 (8.3)	0 (0)	36 (8)	0 (0)	218 (8)	2 (0.1)
Anxiety	6 (5)	1 (0.8)	21 (5)	1 (0.2)	141 (5)	5 (0.2)
Delirium	6 (5)	3 (2)	9 (2)	4 (0.9)	11 (0.4)	1 (0)
Renal and Urinary Disorders	13 (11)	4 (3)	34 (7)	7 (1)	272 (10)	36 (1)
Acute kidney injury	6 (5)	3 (2)	12 (3)	6 (1)	40 (1)	15 (0.5)
Respiratory, Thoracic and Mediastinal Disorders	59 (49)	10 (8)	181 (39)	37 (8)	1392 (50)	224 (8)
Cough	24 (20)	0 (0)	65 (14)	1 (0.2)	615 (22)	6 (0.2)

TEAE	Analysis Set					
	3475-180 Grade 1-5 N = 121		EC 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
Dyspnea	16 (13)	1 (0.8)	48 (10)	5 (1)	534 (19)	76 (3)
Pneumonitis	8 (7)	2 (2)	21 (5)	3 (0.7)	87 (3)	31 (1)
Oropharyngeal pain	6 (5)	0 (0)	13 (3)	0 (0)	91 (3)	0 (0)
Pneumonia aspiration	6 (5)	4 (3)	18 (4)	10 (2)	6 (0.2)	2 (0.1)
Productive cough	5 (4)	0 (0)	17 (4)	0 (0)	142 (5)	2 (0.1)
Skin and Subcutaneous Tissue Disorders	31 (26)	0 (0)	106 (23)	4 (0.9)	1361 (49)	40 (1)
Pruritus	13 (11)	0 (0)	38 (8)	0 (0)	562 (20)	4 (0.1)
Rash	10 (8)	0 (0)	32 (7)	1 (0.2)	500 (18)	9 (0.3)
Dry skin	3 (2)	0 (0)	15 (3)	0 (0)	165 (6)	0 (0)
Alopecia	0 (0)	0 (0)	4 (0.9)	0 (0)	52 (2)	0 (0)
Vitiligo	0 (0)	0 (0)	0 (0)	0 (0)	171 (6)	0 (0)

Source: adae. xpt, reviewer analysis

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.

SUMMARY AND CONCLUSIONS

7.3 Statistical Issues

The FDA's Assessment:

There were no statistical concerns with the conduct or analysis of KEYNOTE-180. However, the small sample size of the study limits the interpretation of the results, particularly when

considering results in subgroups. The post-hoc analysis of the indicated population, patients with ESCC and CPS ≥10, included only 35 patients from the KEYNOTE-180 population. The response rate in this population (20%, 95% CI: 8, 37) should be interpreted in the context of biologic plausibility, what constitutes a clinically meaningful benefit for this population, as well as the supportive clinical evidence from other studies, such as KEYNOTE-181.

7.4 Conclusions and Recommendations

The FDA's Assessment:

The totality of evidence based on the results from KEYNOTE-180 and KEYNOTE-181 demonstrate that pembrolizumab provided a clinically meaningful benefit as evidenced by an improved ORR and prolonged durability of response in patients with ESCC and CPS ≥10 in KEYNOTE-180 who had received at least two prior lines of systemic chemotherapy and an improvement in OS against an active TPC comparator in patients with ESCC and CPS ≥10 who had received one prior line of systemic chemotherapy in KEYNOTE-181. The safety profile of pembrolizumab in KEYNOTE-180 and KEYNOTE-181 is consistent with the established safety profile of pembrolizumab and no new safety risks were identified. The review team therefore 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.

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Statistical Team Leader

X X

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Martha Donoghue, Ph.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 that would benefit from advice from an external committee of experts. 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.

APPEARS THIS WAY ON ORIGINAL

9 Pediatrics

The Applicant's Position:
Not applicable. KEYNOTE-180 enrolled patients ≥18 years of age.

The FDA's Assessment:
FDA granted pembrolizumab orphan designation for the treatment of esophageal carcinoma in June 2017 (17-5787). 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 modules 1.14.1.2 and 1.14.1.3.

The FDA's Assessment:
Labeling negotiations on Merck's proposed Prescribing Information for BLA 125514/S-55 and S-56 are ongoing at the time of this review.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant'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 esophageal cancer whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
		or more prior lines of systemic therapy. (1.9, 2.1)" (b) (4)
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 change
Clinical Studies	Added subsection for esophageal cancer	Edited for brevity and added results for the squamous esophageal cancer expressing PD-L1 (indicated population).

11 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:
The safety profile of pembrolizumab is well characterized in the product labeling, and a REMS is not necessary for this indication.

The FDA's Assessment:
A risk evaluation and mitigation strategy (REMS) is 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. Recommendations for safe and effective use of pembrolizumab, including monitoring for immune-mediated adverse events, included in Keytruda product labeling and a patient medication guide are sufficient to mitigate patient risk and support the safe use of pembrolizumab in patients with metastatic or locally advanced ESCC whose tumors express PD-L1 (CPS ≥10).

APPEARS THIS WAY ON ORIGINAL

12 Postmarketing Requirements and Commitment

The FDA's Assessment:

No postmarketing requirements or commitments are recommended for this indication.

APPEARS THIS WAY ON ORIGINAL

13 Associate Division Director (OB)

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Yuan-Li Shen, Dr. P.H.

14 Division Director (Clinical)

I concur with the recommendations of the review team with approval of pembrolizumab, 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, based on the totality of the data from both KEYNOTE-180 and KEYNOTE-181, which demonstrate 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. The results of each study, in which assessment in subgroups based on histologic subtype and PD-L1 tumor expression, demonstrate an effect which is greatest in the intersection of the overlapping subgroups i.e., those with both squamous cell histology and PD-L1 tumor expression. The consistency of these effects within the overlapping subgroups provides confidence in the results, which were not pre-specified. 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 a REMS is 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

The Applicant's References:

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The FDA's References:

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15.2 Financial Disclosure

The Applicant's Position:

Disclosure of financial interests of the investigators who conducted the KEYNOTE-180 study are described in the current submission (Module 1.3.4).

The FDA's Assessment:

Covered Clinical Study (Name and/or Number):

3475-180: (KEYNOTE-180) A Phase II 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 1 Adenocarcinoma of the Esophagogastric Junction

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: Study KEYNOTE-180 had a total of 460 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): 1		
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**:** None Proprietary interest in the product tested held by investigator**:** None Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3):0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant) N/A

Study 3475-180 or KEYNOTE-180 had a total of 460 investigators and sub investigators of which 459 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). Merck also submitted Form 3455 which contained an investigator who had disclosable arrangements to report:

Product/Protocol/Site	Investigator/ Sub-Investigator	Role	Financial Interests and/or Arrangements
3475-180-(b) (6)	(b) (6).	Sub-Investigator	Equity Interest: Amount: $200,000.00 Merck Stock valued at $200,000.00 as reported by investigator on 11-03-2016.

The FDA's Assessment:

FDA agrees that it is unlikely that the financial arrangements disclosed by Merck played a part in influencing the overall results of KEYNOTE-180. The (b) (6) enrolled by the investigator at site (b) (6) and as the primary endpoint of Study KEYNOTE-180 was ORR by central imaging review, it is unlikely that any potential bias on the part of the single sub-investigator at this site 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 06:32:09 PM

YUAN L SHEN on behalf of MENGDIE YUAN
07/30/2019 07:55:08 PM

YUAN L SHEN on behalf of PALLAVI S MISHRA-KALYANI
07/30/2019 07:58:27 PM

YUAN L SHEN
07/30/2019 07:59:45 PM

MARTHA B DONOGHUE on behalf of ABHILASHA NAIR
07/30/2019 08:41:43 PM

MARTHA B DONOGHUE
07/30/2019 08:44:41 PM

PATRICIA KEEGAN
07/30/2019 08:47:47 PM

Application Type	sBLA
Application Number	125514/S-55
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 11:26:50 AM

MARTHA B DONOGHUE
07/05/2019 11:33:31 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s055

PRODUCT QUALITY REVIEW(S)

Memorandum of Review:

Submission Tracking Number (STN):	BLA 125514/SUPPL-55
Subject:	Efficacy supplement
Primary Reviewer:	Shadia Zaman, Ph.D., DBRR1/OBP/OPQ/CDER
Secondary Reviewer:	Jennifer Swisher, Ph.D., TL, DBRR1/OBP/OPQ/CDER
RBPM:	Andrew Shiber
Consults:	None
Applicant:	Merck Sharp & Dohme Corp
Product:	Pembrolizumab
Indication:	(b) (4)
Goal Date:	7/30/19

- **Recommendation: I recommend approval of this supplement from a CMC perspective.**

- **Future Inspection Items: None**

- **Executive Summary:** This memo is for efficacy supplement 55 for the treatment of (b) (4) A categorical exclusion from environmental assessment per 21 CFR 25.31(c) was claimed and is acceptable. No new immunogenicity data were provided in this submission.

- **Review:**

Reviewer comments are in italicized text.

1.12.14 Environmental Analysis

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

Reviewer comment: *This is acceptable.*

Shadia Zaman

Digitally signed by Shadia Zaman
Date: 7/02/2019 08:18:56AM
GUID: 583dce940076eea0edb730e401622d6d

Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 7/02/2019 08:22:00AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s055

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/

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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:

125514Orig1s055

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:

125514Orig1s055

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: Michael D. Miller, Ph.D.
Executive Director, Global Regulatory Affairs
351 N. Sumneytown Pike
UG2C-050
North Wales, PA 19454

Dear Dr. Miller:

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 September 18, 2018. The purpose of the meeting was to discuss the content and format of a proposed sBLA, to be submitted under the provisions of 21 CFR 610.41, intended to support a new indication for pembrolizumab for the treatment of patients with (b) (4) , based on the results from 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." .

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 or email sharon.sickafuse@fda.hhs.gov.

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

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: pre-sBLA
Meeting Date: September 18, 2018

Application Number: IND 123482
Product Name: Pembrolizumab
Indication: [redacted] (b) (4)

Sponsor/Applicant Name: Merck Sharp & Dohme Corp. (Merck)

Meeting Chair: Martha Donoghue
Meeting Recorder: Sharon Sickafuse

FDA ATTENDEES
Office of Hematology and Oncology Products
Division of Oncology Products 2
Martha Donoghue, M.D.
Patricia Keegan, M.D.
Abhilasha Nair, M.D.
Sharon Sickafuse, M.S.

Office of Biostatistics
Division V
Weishi (Vivian) Yuan, Ph.D.

SPONSOR ATTENDEES
Michael D. Miller, Ph.D., Executive Director, Regulatory Affairs
Stacie Noreika, Pharm.D., Post-Doctoral Fellow, Regulatory Affairs
Gregory M. Lubiniecki, M.D., Associate Vice President, Clinical Research
Jonathan Cheng, M.D., Vice President, Clinical Research
S. Peter Kang, M.D., Executive Director, Clinical Research
Pooja Bhagia, M.D., Director, Clinical Research
Christine Gause, Ph.D., Executive Director, Biostatistics
Shailaja Suryawanshi, Ph.D., Director, Biostatistics
Scott Korn, M.D., Vice President, Regulatory Affairs

Manish A. Shah, M.D., FASCO, Chief, Solid Tumor Oncology Service, Director, Gastrointestinal Oncology Program, Co-Director, Center for Advanced Digestive Care, Bartlett Family Associate Professor of Gastrointestinal Oncology, Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine

BACKGROUND

On June 19, 2018, Merck submitted a meeting request (SDN 552) to discuss the content and format of a proposed sBLA, to be submitted under the provisions of 21 CFR 610.41, intended to support a new indication for pembrolizumab for the treatment of (b) (4) based on the results from KEYNOTE-180 (KN-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." The meeting package was submitted on August 17, 2018 as SDN 574.

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 study KN-180 was discussed during a EOP2/PP3 meeting held on August 17, 2015. During this meeting, FDA stated that if the if the trial demonstrates an overall response rate (ORR) that is large in magnitude, durable and consistent across relevant subgroups (for example, adenocarcinoma and squamous cell carcinoma histologies) such that it is reasonably likely to predict clinical benefit, the results from KN-180 may support a request for accelerated approval (b) (4); however, FDA did not agree that a response rate that excludes a 10% lower bound of the 95% CI alone will be sufficient to support approval.

FDA also recommended that Merck enroll a sufficient number of patients with squamous cell carcinoma (SCC) of the esophagus from the U.S. (or in countries with a similar demographic profile and standards of care) in order to ensure that the activity of the drug in the U.S. is similar to that in Asia where higher response rates to chemotherapy have been reported in SCC. FDA stated that they will evaluate the results and numbers of patients in each subgroup in order to determine whether pembrolizumab should be approved for (b) (4).

On September 28, 2017, Merck submitted a meeting request (SDN 453) to discuss a proposed sBLA, to be submitted under the provisions of 21 CFR 610.41, intended to support a new indication for pembrolizumab for (b) (4), based on data from study

KN-180. The meeting was scheduled for December 5, 2017, and the meeting package was submitted on November 15, 2017, as SDN 481.

The meeting package submitted on December 5, 2017, stated that that data from KEYNOTE-028 would provide additional supportive evidence and Merck also proposed that the results of KEYNOTE-181 (KN-181) or KEYNOTE-590 (KN-590) would serve as a confirmatory trial to support regular approval. In the preliminary responses issued on December 1, 2017, FDA recommended a longer duration of follow-up for responders (at least 12 months of follow-up from the onset of response in all responding patients). FDA also stated that because the ORR is relatively low [9.9% (95% CI: 5.2, 16.7) per RECIST 1.1 as assessed by an independent review committee], durability of responses will be a key component of the overall risk: benefit assessment for pembrolizumab for the proposed indication. FDA also stated that an evaluation of subsets defined by histology, PD-L1 status, and MSI-H status is expected in the sBLA. FDA also requested Merck to confirm that an assessment of MSI-H status is being conducted in all patients enrolled in KN-181 and KN-590; in their December 5, 2017 response (SDN 492) to FDA's preliminary responses, Merck stated that every effort will be made to collect and analyze samples for MSI-H status in these trials.

Clinical

The current pre-sBLA meeting package contains updated data from KN-180 (database cutoff: June 13, 2018) and the esophageal cancer cohort in study KEYNOTE-028, entitled "Phase IB Study of Pembrolizumab (MK-3475) in Subjects with Select Advanced Solid Tumors" (database cutoff: January 31, 2018). Merck states that the proposed sBLA will include the Reference Safety Data comprising patients with melanoma and non-small cell lung cancer (NSCLC) treated with pembrolizumab in studies KN-001, KN-002, KN-006, and KN-010 to allow a comparison of the safety of pembrolizumab in patients with metastatic esophageal carcinoma to the established safety profile of pembrolizumab. Merck proposed that either KN-181 or KN-590 serve as a confirmatory trial to support regular approval of pembrolizumab for the proposed indication.

In response to FDA's request, Merck submitted results of a systematic literature search of trials investigating third line treatment of patients with advanced or metastatic esophageal cancer. Because no studies were identified for this third line population, Merck expanded the search to the second line setting (2L) and beyond (3L+). and included 12 studies in the 2L population. Merck states that these studies either enrolled esophageal squamous cell carcinoma (ESCC) patients only, or studied combination therapies typically used in the first- or second-line setting, thus making the information from these trials irrelevant in the context of 3L+ clinical setting. Additional searches identified one randomized Phase 3 trial comparing gefitinib monotherapy with placebo in previously treated advanced esophageal cancer (Dutton SJ et al, 2014). Gefitinib failed to improve the overall survival (OS): HR 0.90, 95% CI 0.74–1.09. The median OS was 3.73 months (95% CI 3.23–4.50) with gefitinib and 3.67 months (2.97–4.37) with placebo. Gefitinib and placebo demonstrated an ORR of 3% and 0%, respectively.

Table 1 shows the trials ongoing and or completed of pembrolizumab in advanced esophageal cancer.

Table 1: Summary of Merck-Sponsored Pembrolizumab Clinical Trials in Subjects with Esophageal Cancer

Trial ID / Status	Trial Type/Design	Trial Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KEYNOTE-028 (KN028) 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 (KN180) Ongoing/Enrollment completed	Phase 2 Global muticenter, non-randomized, open-label, single arm, multicohort	Advanced esophageal cancer patients (N=121) who progressed on at least 2 prior chemotherapy regimens (3L+)	Pembrolizumab monotherapy (200 mg Q3W)	ORR
KEYNOTE-181 (KN181) Ongoing/ Enrollment completed	Phase 3 Global multicenter, randomized, controlled, open-label trial	Advanced/metastatic esophageal cancer, 2L, N=628	Pembrolizumab monotherapy (200 mg Q3W) or Investigators choice (paclitaxel, docetaxel, or irinotecan)	OS
KEYNOTE-590 (KN590) Ongoing/Enrolling	Phase 3 Global multicenter, randomized, double-blind, placebo-controlled	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, 3L=third line; 5-FU=5-fluorouracil; GEJ=gastro-esophageal junction; 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; vs=versus.

Source: August 2018 meeting package

KEYNOTE-180

KEYNOTE-180 (KN-180), entitled "A Phase 2 Study of Pembrolizumab Monotherapy in Third Line, Previously Treated Subjects with Advanced/Metastatic Siewert Type I Adenocarcinoma of the Esophagogastric Junction" is an ongoing, single-arm, open-label, multicenter trial of pembrolizumab 200 mg IV every three weeks (Q3W) in 121 adult patients with previously treated advanced or metastatic esophageal cancer (regardless of histology or PDL-1 status) who received at least 2 previous lines of standard therapy (3L+ population). Treatment will continue until confirmed progressive disease by irRECIST, unacceptable adverse events, intercurrent illness that prevents further treatment, investigator's decision to withdraw, withdrawal of consent, pregnancy, noncompliance, administrative reasons, or receipt of 35 treatments (approximately 2 years). The primary endpoint is ORR per RECIST 1.1 assessed by a central imaging vendor in all patients. Secondary endpoints include duration of response (DoR), progression-free survival (PFS), and OS. Pembrolizumab efficacy was also evaluated using the PD-L1 Combined Positive Score (CPS) cutpoint of ≥10. Subjects with a CPS of ≥10 were considered PD-L1 positive. The sample size was calculated based upon an assumption that if the

true ORR is 22%, a sample size of 100 would provide 91% power to rule out a 10% lower bound of the 95% CI, calculated by the exact method.

Safety Results:
According to Merck, the adverse events experienced in this population are consistent with the established pembrolizumab safety profile.

Efficacy Results
Merck states that the updated KN-180 ORR and DoR data in this meeting package are based on a data cut-off date of June 13, 2018, and proposes that the complete dataset intended for filing the sBLA will have a last patient last visit date of July 30, 2018. The meeting package included updated ORR and DoR after a minimum follow-up of 12 months for all responding patients following onset of observed confirmed response as well as MSI-H data from KN-180.

A total of 121 patients were enrolled, including 63 (52.1%) patients with esophageal squamous cell carcinoma (ESCC) and 58 (49.9%) patients with esophageal adenocarcinoma (EAC). Forty-eight percent of the patients had PD-L1 positive tumors, defined as a CPS ≥10. The majority of patients were male (82.6%), enrolled in non-Asian countries (67.8%), and had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (63.6%) at baseline.

Of the 121 patients enrolled, MSI data were available for 98 patients. Only one patients was identified as MSI-H and this patient was a non-responder. Approximately 85% of patients had received 2 prior therapies and 15% patients had received 3 or more prior lines of therapy. All patients had been previously treated with fluoropyrimidine (5FU, capecitabine or S1) and platinum agents. Additional prior therapies included taxanes (86.0%), irinotecan (19.8%), monoclonal antibody therapy (25.6%) (20 patients received ramucirumab), and anthracyclines (11.6%). All EGJ Siewert Type I adenocarcinoma patients with HER2 positive tumors had received an anti-HER2/neu antibody.

The ORR remains unchanged (9.9% (95% CI: 5.2, 16.7)) for the overall population and for subgroups based on histology (adenocarcinoma versus squamous) and level of PDL-1 expression [CPS ≥10 vs. CPS <10]. Merck states that with additional follow-up of 9 months (resulting in a minimum of 12 months follow-up for all 12 responding subjects), the median DoR has not been reached (range: 2.1 - 22.8+ months). Six of the 12 (57.0%) responders had a DoR of at least 12 months; 3 responders had a DoR of at least 15 months (Table 2 and Table 3). Of the 12 responders, two patients had an unknown MSI status and the remaining were microsatellite stable (MSS) patients.

Table 2: Summary of updated DoR (highlighted rows have updated follow-ups) in KEYNOTE-180

Country	Subject Number	PD-L1 Status (CPS≥10)	DOR (in months) (LPLV 18Sep2017)	DOR (in months) (Data Extract 13Jun2018)	Current Status	Histology
(b) (6)		NEGATIVE	5.3	13.8	Response ongoing	Adenocarcinoma of the GEJ
		POSITIVE	5.4	5.4	PD	Adenocarcinoma of the GEJ
		NEGATIVE	4.1	15.2	Response ongoing	Squamous
		NEGATIVE	4.4	4.4	PD	Squamous
		POSITIVE	1.9	8.3	PD	Squamous
		POSITIVE	4.2	4.2	PD	Squamous
		POSITIVE	12.0	12.0	PD	Squamous
		POSITIVE	12.2	14.3	PD	Squamous
		NEGATIVE	2.1	2.1	PD	Adenocarcinoma of the GEJ
		POSITIVE	4.2	4.2	PD	Squamous
		POSITIVE	14.4	22.8	Response ongoing	Squamous
		POSITIVE	8.3	16.6	Response ongoing	Squamous

Source: August 2018 meeting package

Table 3: Updated efficacy results from KEYNOTE-028 and KEYNOTE-180

Independent Central Radiology Review (RECIST 1.1 Confirmed Responses)	Objective Response Rate (CR+PR) % (95% CI)	Response Duration (Months) Median (range)
KN-180: all subject (N=121)	9.9 (5.2, 16.7)	Not Reached (2.1, 228.+)
KN180 by Histology:		
Squamous Cell Carcinoma (N=63)	14.3 (6.7, 25.4)	Not Reached (4.2, 22.8+)
Adenocarcinoma (N=58)	5.2 (1.1, 14.4)	Not Reached (2.1,, 13.8+)
KN180 by PD-L1 Status:		
PD-L1 positive (CPS ≥10) (N=58)	13.8 (6.1, 25.4)	Not Reached (4.2, 22.8+)
PD-L1 negative (CPS <10) (N=63)	6.3 (1.8, 15.5)	Not Reached (2.1, 15.2+)
KN028 Cohort A4 (esophageal cancer, pembrolizumab monotherapy, PD-L1 positive*) (N=23)	18.2 (5.2, 40.3)	21.4 (12.0, 38.4+)
Only confirmed responses are included. *PD-L1 positive status was defined as PD-L1 expression in ≥1% of cells using a prototype assay Database extraction date for KN180: 13JUN2018 Database cutoff date for KN028: 31JAN2018		

Source: August 2018 meeting package

KEYNOTE-028 (Cohort A4)

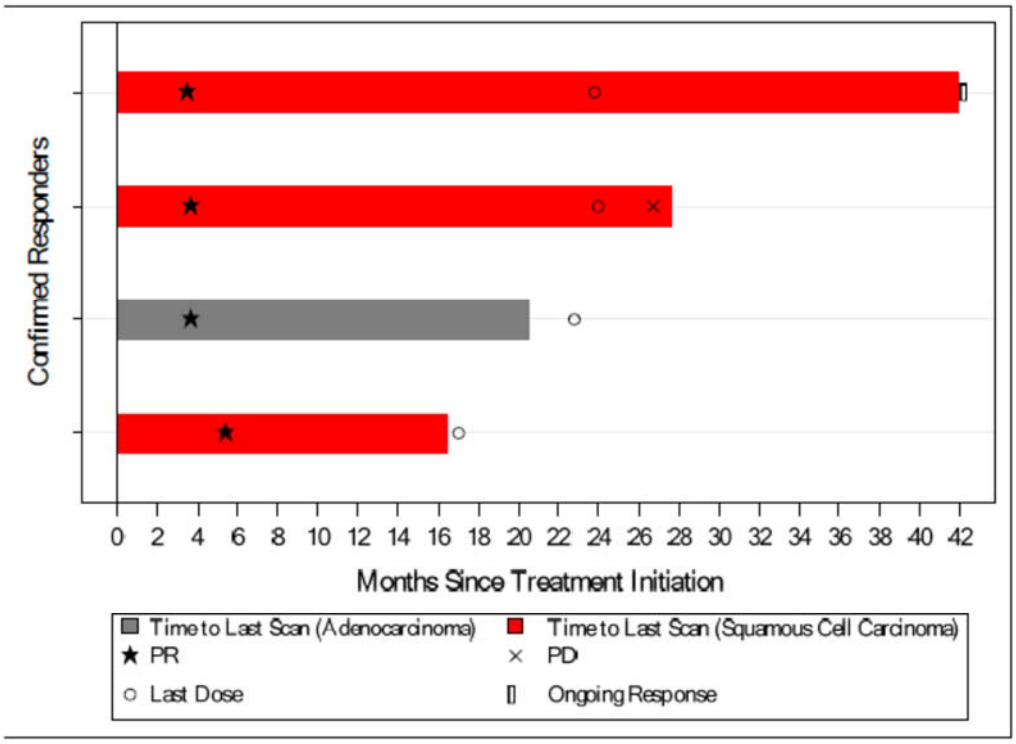
KEYNOTE-028 was a nonrandomized, multicohort, multicenter trial of pembrolizumab in patients with PD-L1 positive advanced and/or metastatic solid tumors. The primary endpoint was ORR per RECIST 1.1) as determined by the investigator. Secondary efficacy endpoints included DoR, PFS, and OS. Study treatment consisted of 10 mg/kg pembrolizumab on Day 1 of each 2-week cycle (Q2W). Treatment was planned to continue until disease progression or unacceptable toxicity, for a maximum of 24 months. Cohort A4 of this trial included 23 subjects with PD-L1 positive, advanced and/or metastatic ESCC or EAC, including Siewert Type 1 EAC of the esophagogastric junction (EGJ). PD-L1 positive status was defined as PD-L1 expression in ≥1% of cells in tumor nests or PD-L1 positive stromal bands determined centrally using a prototype assay (Qualtek, Goleta, CA). Eligible subjects must have met one of the following criteria: (a) have failed prior standard therapy; (b) be one for whom no standard therapy exists; or (c) be one for whom standard therapy is not considered appropriate by the patient and treating physician; (d) ECOG performance status 0 to 1, and (e) no autoimmune disease.

Efficacy Results (Tables 3 and Figure 1)'

Of the 90 patients with esophageal cancer who were screened, 37 (44.6%) had PD-L1- positive tumors. Of the 23 patients treated, 83% were men, and the median age was 65 years. Approximately 9% of patients had received 1 prior therapy, 39% of patients had received 2 prior therapies and 44% patients had received 3 prior lines of therapy. More than half the patients had squamous cell carcinoma (78.3%).

Merck states for the 23 patients, the ORR according to RECIST 1.1 per BIRC assessment was 18.2% (95% CI: 5.2%, 40.3%). For the 4 responders (partial response), the median time to response was 3.7 months (range 3.5 to 5.4 months) and median DoR was 21.4 months (range 12.0 to 38.4+ months), where "+" indicates there is no progressive disease by the time of last disease assessment.

Figure 1: Swimmers plot for KEYNOTE-028



The initial response is marked by the star sign. 'Time to Last Scan' shows the time from treatment initiation until last scan.
Database Cutoff Date: 31JAN2018
Source: [P028V02MK3475: adam-adsl; adrs; adtte; adintdt]

Source: August 2018 meeting package

In response to an information request, Merck stated that of the 23 enrolled patients on KN-028, 17 patients had MSI information available and MSI status was unknown in the remaining six patients. Merck stated that one of the four responders was MSI-H and the rest were MSS. The rest of the 13 patients with known MSI information were MSS and all were non-responders. Merck also stated that two of the four responders received fourth line treatment, one received first line treatment, and one received third line treatment.

KEYNOTE-181

KEYNOTE-181 is a randomized, multi-center, open-label trial of pembrolizumab 200 mg IV every 3 weeks versus investigator's choice of paclitaxel, docetaxel, or irinotecan in patients with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, or advanced/metastatic Siewert type I adenocarcinoma of the EGJ. The primary efficacy endpoint is OS with three primary analysis populations (all patients, ESCC and PD-L1 CPS ≥10). PFS and ORR are secondary efficacy endpoints. MSI information for all responders will also be collected. Patients were enrolled without regard to biomarker status.

Global enrollment was completed on June 16, 2017, with 628 patients enrolled, including 11 patients from China. Enrollment into a China-specific extension cohort will continue until an additional 112 patients are enrolled.

Merck expects results from the final analysis to be available in November 2018.

KEYNOTE-590
KEYNOTE-590 is a randomized, double-blind, placebo-controlled multicenter trial evaluating pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU) versus placebo in combination with cisplatin and 5-FU as first-line treatment in 700 patients with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ. The primary efficacy endpoints are OS and PFS in 2 primary analysis populations (all patients and in patients with tumors with a PD-L1 CPS ≥10). ORR is a secondary endpoint. Study treatment consists of pembrolizumab 200 mg IV every 3 -weeks plus cisplatin and 5-FU, or placebo IV every 3-weeks plus cisplatin and 5-FU.

FDA preliminary comments were emailed to Merck on September 14, 2018.

SPONSOR QUESTIONS AND FDA RESPONSES

1. *KEYNOTE-180 (KN180; N = 121) is a single arm Phase II study of pembrolizumab monotherapy in subjects who had progressed on or after two or more prior lines of therapy (3L+) for advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert Type I adenocarcinoma of the esophagogastric junction (EGJ). Does the Agency concur that given the absence of treatment options for the population, results from KN180 could support consideration for accelerated approval for* (b) (6) *under 21 CFR 601 subpart E?*

   FDA Response:
   While there appears to be activity in a limited number of patients, FDA does not agree that the available data from KN-180 are sufficient to support filing of an application seeking accelerated approval of pembrolizumab for (b) (6) In addition to the low response rate, the population likely to derive clinical benefit has not been adequately characterized. Specifically, it is unclear to what extent the likelihood of response is driven by histology, PD-L1 status, or MSI-H status. FDA recommends that Merck submit a request for a meeting to discuss the results of KN-181 when available (approximately November 2018).

   Discussion:
   See Merck's presentation which provided updated information on duration of response. FDA noted that the majority of responders had squamous histology and that evidence of activity was stronger in this subgroup. FDA stated that even with the updated data, this would be a challenging application to file, absent the topline results of Study KN-181.

FDA requested that the topline results of Study KN-181 be provided to the FDA approximately 30 days after submission of the proposed sBLA. As the database lock is approximately November 8th, FDA requested that the sBLA be filed no sooner than the beginning of November to allow adequate time to review the data from Study KN-181 prior to the filing decision on the planned sBLA. Merck agreed to provide the topline results of Study KN-181 as outlined above.

2. *Does the Agency agree that the updated duration of response data based on the July 2018 database lock are sufficient to support consideration for accelerated approval for* (b) (6) *?*

FDA Response:
Please see FDA's response to Question 1.

Discussion:
See discussion for Question 1.

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.

Please refer to 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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf.

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Submission of topline Study KN-181 results	Merck	Early December

ATTACHMENT
Merck's presentation

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

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

/s/

SHARON K SICKAFUSE
09/19/2018