CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s096

Trade Name:	KEYTRUDA
Generic or Proper Name:	(pembrolizumab)
Sponsor:	Merck Sharp & Dohme LLC.
Approval Date:	March 22, 2021
Indication:	KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated: Esophageal Cancer • for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation in combination with platinum- and fluoropyrimidine-based chemotherapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

125514Orig1s096

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 125514/S-096

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Sabrina Girty
Director, Global Regulatory Affairs
351 North Sumneytown Pike
P.O. Box 1000; UG2C-050
North Wales, PA 19454-2505

Dear Ms. Girty:

Please refer to your supplemental biologics license application (sBLA) dated and received October 13, 2020, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) injection.

This Prior Approval supplemental biologics license application provides for a new indication for pembrolizumab, for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amendable to surgical resection or definitive chemoradiation, in combination with platinum- and fluoropyrimidine-based chemotherapy. Additionally, the esophageal cancer section was updated with respect to the single agent indication for labeling consistency.

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

Patient Package Insert and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *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. For information about submitting promotional materials, see the final 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,

[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.
[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.

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]

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, contact Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704 or gina.davis@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Director (Acting)
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert or Medication Guide

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

STEVEN J LEMERY
03/22/2021 02:20:47 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s096

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) injection, for intravenous use
Initial U.S. Approval: 2014

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

Indications and Usage (1)	03/2021
Dosage and Administration (2)	03/2021
Warnings and Precautions (5)	11/2020

----------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 patients with relapsed or refractory cHL. (1.5)
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy. (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. (1.6)
- 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)
- for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. (1.7)

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - 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, 2.1)
- Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

- for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC). (1.9, 2.1)

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] (1.10, 2.1)

Esophageal Cancer

- for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test (1.11, 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] (1.12, 2.1)

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC who have been previously treated with sorafenib.[1] (1.13)

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1] (1.14)

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of patients with advanced RCC. (1.15)

Endometrial Carcinoma

- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.[1] (1.16)

Tumor Mutational Burden-High (TMB-H) Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high

(TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1] (1.17, 2.1)

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

Cutaneous Squamous Cell Carcinoma (cSCC)

- for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation. (1.18)

Triple-Negative Breast Cancer (TNBC)

- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.[2] (1.19, 2.1)

Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.[3] (1.20, 2.2)

[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.

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

[3] This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

- Melanoma: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- NSCLC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- SCLC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- HNSCC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- cHL or PMBCL: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- Urothelial Carcinoma: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- MSI-H or dMMR Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- MSI-H or dMMR CRC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Gastric Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Esophageal Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Cervical Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- HCC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- MCC: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- RCC: 200 mg every 3 weeks or 400 mg every 6 weeks with axitin b 5 mg orally twice daily. (2.2)
- Endometrial Carcinoma: 200 mg every 3 weeks or 400 mg every 6 weeks with lenvatin b 20 mg orally once daily for tumors that are not MSI-H or dMMR. (2.2)
- TMB-H Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- cSCC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- TNBC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

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

- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-dose vial (3)

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

None. (4)

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

- Immune-Mediated Adverse Reactions (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction.
- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue KEYTRUDA based on the severity of reaction. (5.2)
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- 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. (5.4)
- 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. (5.5, 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, stomatitis, headache, and weight loss. (6.1)
- KEYTRUDA in combination with axitinib: diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. (6.1)
- KEYTRUDA in combination with lenvatinib: fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, weight loss, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. (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: 03/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.

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 patients with relapsed or refractory classical Hodgkin lymphoma (cHL).

KEYTRUDA is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

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.

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.

KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

1.8 Microsatellite Instability-High or Mismatch Repair Deficient 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 (dMMR)

- 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 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

1.10 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 (14.10)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.11 Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

- in combination with platinum- and fluoropyrimidine-based chemotherapy, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.12 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 (14.12)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.13 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 (14.13)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.14 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 (14.14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.15 Renal Cell Carcinoma

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

1.16 Endometrial Carcinoma

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.16)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.17 Tumor Mutational Burden-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.17)]*. 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 TMB-H central nervous system cancers have not been established.

1.18 Cutaneous Squamous Cell Carcinoma

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.

1.19 Triple-Negative Breast Cancer

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

This indication is approved under accelerated approval based on progression-free survival *[see Clinical Studies (14.19)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.20 Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

KEYTRUDA is indicated for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications *[see Indications and Usage (1.1-1.19) and Dosage and Administration (2.2)]*. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety *[see Clinical Pharmacology (12.2) and Clinical Studies (14.20)]*. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, TMB-H Cancer, or TNBC

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 (14.10)]*. 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.
- previously treated recurrent locally advanced or metastatic esophageal cancer *[see Clinical Studies (14.11)]*.
- recurrent or metastatic cervical cancer *[see Clinical Studies (14.12)]*.

For the MSI-H/dMMR indications, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens *[see Clinical Studies (14.8, 14.9)].*

For the TMB-H indication, select patients for treatment with KEYTRUDA as a single agent based on TMB-H status in tumor specimens *[see Clinical Studies (14.17)].*

Because the effect of prior chemotherapy on test results for tumor mutation burden (TMB-H), MSI-H, or dMMR in patients with high-grade gliomas is unclear, it is recommended to test for these markers in the primary tumor specimens obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

Select patients for treatment with KEYTRUDA in combination with chemotherapy based on the presence of positive PD-L1 expression in:

- locally recurrent unresectable or metastatic TNBC *[see Clinical Studies (14.19)]*.

Information on FDA-approved tests for the detection of PD-L1 expression and TMB status is available at: http://www.fda.gov/CompanionDiagnostics. An FDA-approved test for the detection of MSI-H or dMMR is not currently available.

2.2 Recommended Dosage

Table 1: Recommended Dosage

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
Monotherapy		
Adult patients with unresectable or metastatic melanoma	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression or unacceptable toxicity
Adjuvant treatment of adult patients with melanoma	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease recurrence, unacceptable toxicity, or up to 12 months
Adult patients with NSCLC, SCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with high-risk BCG-unresponsive NMIBC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months
Pediatric patients with cHL, PMBCL, MSI-H Cancer, MCC, or TMB-H Cancer	2 mg/kg every 3 weeks (up to a maximum of 200 mg)*	Until disease progression, unacceptable toxicity, or up to 24 months
Combination Therapy†		
Adult patients with NSCLC, HNSCC, or Esophageal Cancer	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with RCC	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA in combination with axitinib 5 mg orally twice daily.‡	Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months
Adult patients with Endometrial Carcinoma	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA in combination with lenvatin b 20 mg orally once daily.	Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months
Adult patients with locally recurrent unresectable or metastatic TNBC	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months

* 30-minute intravenous infusion

† Refer to the Prescribing Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

‡ When axitinib is used in combination with KEYTRUDA, dose escalation of axitin b above the initial 5 mg dose may be considered at intervals of six weeks or longer.

2.3 Dose Modifications

No dose reduction for KEYTRUDA is recommended. In general, withhold KEYTRUDA for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue KEYTRUDA for Life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for KEYTRUDA for adverse reactions that require management different from these general guidelines are summarized in Table 2.

Table 2: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver For liver enzyme elevations in patients treated with combination therapy with axitin b, see Table 3.	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold†
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver‡	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold†
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold†
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold†
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1

Adverse Reaction	Severity*	Dosage Modification
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

* Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0

† Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

‡ If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA based on recommendations for hepatitis with no liver involvement.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

The following table represents dosage modifications that are different from those described above for KEYTRUDA or in the Full Prescribing Information for the drug administered in combination.

Table 3: Recommended Specific Dosage Modifications for Adverse Reactions for Combination

Treatment	Adverse Reaction	Severity	Dosage Modification
KEYTRUDA in combination with axitinib	Liver enzyme elevations*	ALT or AST increases to at least 3 times but less than 10 times ULN without concurrent total bilirubin at least 2 times ULN	Withhold both KEYTRUDA and axitin b until resolution to Grades 0 or 1†
		ALT or AST increases to more than 3 times ULN with concurrent total bilirubin at least 2 times ULN or ALT or AST ≥10 times ULN	Permanently discontinue both KEYTRUDA and axitinib

* Consider corticosteroid therapy

† Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. 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.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal

When administering KEYTRUDA in combination with lenvatinib for the treatment of endometrial carcinoma, interrupt one or both as appropriate. No dose reductions are recommended for KEYTRUDA. Withhold, dose reduce, or discontinue lenvatinib in accordance with the instructions in the lenvatinib prescribing information.

2.4 Preparation and Administration

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) 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.** Do not shake. 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 Diluted Solution

The product does not contain a preservative.
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 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

Discard after 6 hours at room temperature or after 96 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

- 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 Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA depending on severity *[see Dosage and Administration (2.3)]*. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) adverse reactions. Systemic corticosteroids were required in 67% (63/94) of patients with pneumonitis. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) of patients and withholding of KEYTRUDA in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA

after symptom improvement; of these, 23% had recurrence of pneumonitis. Pneumonitis resolved in 59% of the 94 patients.

In clinical studies enrolling 389 adult patients with cHL who received KEYTRUDA as a single agent, pneumonitis occurred in 31 (8%) patients, including Grades 3-4 pneumonitis in 2.3% of patients. Patients received high-dose corticosteroids for a median duration of 10 days (range: 2 days to 53 months). Pneumonitis rates were similar in patients with and without prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 21 (5.4%) patients. Of the patients who developed pneumonitis, 42% interrupted KEYTRUDA, 68% discontinued KEYTRUDA, and 77% had resolution.

Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in 69% (33/48) of patients with colitis. Additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) of patients and withholding of KEYTRUDA in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence of colitis. Colitis resolved in 85% of the 48 patients.

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA as a Single Agent

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 68% (13/19) of patients with hepatitis. Eleven percent of these patients required additional immunosuppressant therapy. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) of patients and withholding of KEYTRUDA in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence of hepatitis. Hepatitis resolved in 79% of the 19 patients.

KEYTRUDA 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 (2.3)]*.

With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. Fifty-nine 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 (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT ≥3 times ULN was observed in 1 patient receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both KEYTRUDA and axitinib. All patients with a recurrence of ALT ≥3 ULN subsequently recovered from the event.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

KEYTRUDA can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity *[see Dosage and Administration (2.3)].*

Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required

in 77% (17/22) of patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) of patients and withholding of KEYTRUDA in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Hypophysitis

KEYTRUDA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity *[see Dosage and Administration (2.3)]*.

Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in 94% (16/17) of patients with hypophysitis; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) of patients and withholding of KEYTRUDA in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Thyroid Disorders

KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity *[see Dosage and Administration (2.3)].*

Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). No patients discontinued KEYTRUDA due to thyroiditis. KEYTRUDA was withheld in <0.1% (1) of patients.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). Hyperthyroidism led to permanent discontinuation of KEYTRUDA in <0.1% (2) of patients and withholding of KEYTRUDA in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). Hypothyroidism led to permanent discontinuation of KEYTRUDA in <0.1% (1) of patients and withholding of KEYTRUDA in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. The incidence of new or worsening hypothyroidism was higher in 389 patients with cHL (17%) receiving KEYTRUDA as a single agent, including Grade 1 (6.2%) and Grade 2 (10.8%) hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity *[see Dosage and Administration (2.3)]*.

Type 1 diabetes mellitus occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. Type 1 diabetes mellitus led to permanent discontinuation in <0.1% (1) of patients and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. All patients with Type 1 diabetes mellitus required long-term insulin therapy.

Immune-Mediated Nephritis with Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 89% (8/9) of patients with nephritis. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) of patients and withholding of

KEYTRUDA in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence of nephritis. Nephritis resolved in 56% of the 9 patients.

Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity *[see Dosage and Administration (2.3)]*.

Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 40% (15/38) of patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of KEYTRUDA in 0.1% (2) of patients and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence of immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 79% of the 38 patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica

Endocrine: Hypoparathyroidism

Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

5.2 Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 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. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.3)]*.

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody.

Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 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.

5.5 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.

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.2)].*

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 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) and one randomized, open-label, active-controlled trial (KEYNOTE-204), which enrolled 389 patients with cHL; 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.

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 4 and 5 summarize selected adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-006.

Table 4: 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 5: 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 6 and 7 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-002.

Table 6: 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 7: 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 8 and 9 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-054.

Table 8: 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 9: 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 10 and 11 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-189.

Table 10: 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 11: 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 12 and 13 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-042.

Table 12: 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 13: 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 14 and 15 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-010.

Table 14: 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 15: 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 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-048.

Table 16: 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 17: 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 (5.1)]*.

Relapsed or Refractory cHL

KEYNOTE-204

The safety of KEYTRUDA was evaluated in KEYNOTE-204 *[see Clinical Studies (14.5)].* Adults with relapsed or refractory cHL received KEYTRUDA 200 mg intravenously every 3 weeks (n=148) or

brentuximab vedotin (BV) 1.8 mg/kg intravenously every 3 weeks (n=152). The trial required an ANC ≥1000/μL, platelet count ≥75,000/μL, hepatic transaminases ≤2.5 times the upper limit of normal (ULN), bilirubin ≤1.5 times ULN, and ECOG performance status of 0 or 1. The trial excluded patients with active non-infectious pneumonitis, prior pneumonitis requiring steroids, active autoimmune disease, a medical condition requiring immunosuppression, or allogeneic HSCT within the past 5 years. The median duration of exposure to KEYTRUDA was 10 months (range: 1 day to 2.2 years), with 68% receiving at least 6 months of treatment and 48% receiving at least 1 year of treatment.

Serious adverse reactions occurred in 30% of patients who received KEYTRUDA. Serious adverse reactions in ≥1% included pneumonitis, pneumonia, pyrexia, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients (2%) died from causes other than disease progression: two from complications after allogeneic HSCT and one from unknown cause.

Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 14% of patients; 7% of patients discontinued treatment due to pneumonitis. Dosage interruption of KEYTRUDA due to an adverse reaction occurred in 30% of patients. Adverse reactions which required dosage interruption in ≥3% of patients were upper respiratory tract infection, pneumonitis, transaminase increase, and pneumonia.

Thirty-eight percent of patients had an adverse reaction requiring systemic corticosteroid therapy.

Table 18 summarizes adverse reactions in KEYNOTE-204.

Table 18: Adverse Reactions (≥10%) in Patients with cHL who Received KEYTRUDA in KEYNOTE-204

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=148		Brentuximab Vedotin 1.8 mg/kg every 3 weeks N=152	
	All Grades* (%)	Grades 3- 4 (%)	All Grades* (%)	Grades 3- 4† (%)
Infections				
Upper respiratory tract infection‡	41	1.4	24	0
Urinary tract infection	11	0	3	0.7
Musculoskeletal and Connective Tissue				
Musculoskeletal pain§	32	0	29	1.3
Gastrointestinal				
Diarrhea¶	22	2.7	17	1.3
Nausea	14	0	24	0.7
Vomiting	14	1.4	20	0
Abdominal pain#	11	0.7	13	1.3
General				
Pyrexia	20	0.7	13	0.7
Fatigueᵇ	20	0	22	0.7
Skin and Subcutaneous Tissue				
Rashβ	20	0	19	0.7
Pruritus	18	0	12	0
Respiratory, Thoracic and Mediastinal				
Coughà	20	0.7	14	0.7
Pneumonitisè	11	5	3	1.3
Dyspneað	11	0.7	7	0.7
Endocrine				
Hypothyroidism	19	0	3	0
Nervous System				
Peripheral neuropathyø	11	0.7	43	7
Headacheý	11	0	11	0

* Graded per NCI CTCAE v4.0
† Adverse reactions in BV arm were Grade 3 only.
‡ Includes acute sinusitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, upper respiratory tract infection, viral upper respiratory tract infection
§ Includes arthralgia, back pain, bone pain, musculoskeletal discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity
¶ Includes diarrhea, gastroenteritis, colitis, enterocolitis
# Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
ᵇ Includes fatigue, asthenia
β Includes dermatitis acneiform, dermatitis atopic, dermatitis allergic, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, eczema, rash, rash erythematous, rash follicular, rash maculo-papular, rash papular, rash pruritic, toxic skin eruption
à Includes cough, productive cough
è Includes pneumonitis, interstitial lung disease
ð Includes dyspnea, dyspnea exertional, wheezing
ø Includes dysaesthesia, hypoaesthesia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy
ý Includes headache, migraine, tension headache

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included herpes virus infection (9%), pneumonia (8%), oropharyngeal pain (8%), hyperthyroidism (5%), hypersensitivity (4.1%), infusion reactions (3.4%), altered mental state (2.7%), and in 1.4% each, uveitis, myocarditis, thyroiditis, febrile neutropenia, sepsis, and tumor flare.

Table 19 summarizes laboratory abnormalities in KEYNOTE-204.

Table 19: Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with cHL in KEYNOTE-204

Laboratory Abnormality*	KEYTRUDA 200 mg every 3 weeks		Brentuximab Vedotin 1.8 mg/kg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Chemistry				
Hyperglycemia	46	4.1	36	2.0
Increased AST	39	5	41	3.9
Increased ALT	34	6	45	5
Hypophosphatemia	31	5	18	2.7
Increased creatinine	28	3.4	14	2.6
Hypomagnesemia	25	0	12	0
Hyponatremia	24	4.1	20	3.3
Hypocalcemia	22	2.0	16	0
Increased a kaline phosphatase	21	2.1	22	2.6
Hyperbilirubinemia	16	2.0	9	1.3
Hypoalbuminemia	16	0.7	19	0.7
Hyperkalemia	15	1.4	8	0
Hematology				
Lymphopenia	35	9	32	13
Thrombocytopenia	34	10	26	5
Neutropenia	28	8	43	17
Anemia	24	5	33	8

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 143 to 148 patients) and BV (range: 146 to 152 patients); hypomagnesemia: KEYTRUDA n=53 and BV n=50.

† Graded per NCI CTCAE v4.0

KEYNOTE-087

Among the 210 patients with cHL who received KEYTRUDA 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). Serious adverse reactions occurred in 16% of patients who received KEYTRUDA. Serious adverse reactions that occurred in ≥1% of patients included pneumonia, pneumonitis, pyrexia, dyspnea, graft versus host disease (GVHD) and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 5% of patients and dosage interruption due to an adverse reaction occurred in 26%. Fifteen percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Tables 20 and 21 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-087.

Table 20: Adverse Reactions (≥10%) in Patients with cHL who Received KEYTRUDA 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

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), and myelitis and myocarditis (0.5% each).

Table 21: Select Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with cHL who Received KEYTRUDA in KEYNOTE-087

Laboratory Abnormality*	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 who received KEYTRUDA 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). Serious adverse reactions occurred in 26% of patients. Serious adverse reactions that occurred in >2% of patients 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. Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 8% of patients and dosage interruption due to an adverse reaction occurred in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Tables 22 and 23 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-170.

Table 22: Adverse Reactions (≥10%) in Patients with PMBCL who Received KEYTRUDA 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 β	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
β Includes atrial fibrillation, sinus tachycardia, supraventricular tachycardia, tachycardia

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included hypothyroidism (8%), hyperthyroidism and pericarditis (4% each), and thyroiditis, pericardial effusion, pneumonitis, arthritis and acute kidney injury (2% each).

Table 23: Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with PMBCL who Received KEYTRUDA in KEYNOTE-170

Laboratory Abnormality*	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 24 summarizes adverse reactions in patients on KEYTRUDA in KEYNOTE-052.

Table 24: 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		
Rashᵖ	21	0.5
Pruritus	19	0.3
Edema peripheralᵝ	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
ᵖ 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
ᵝ Includes edema peripheral, peripheral swelling

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 25 and 26 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-045.

Table 25: 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‡	15	0.4	9	0
Dyspnea§	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
‡ Includes cough, productive cough
§ Includes dyspnea, dyspnea exertional, wheezing
à Includes blood urine present, hematuria, chromaturia

Table 26: 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

BCG-unresponsive High-risk NMIBC

The safety of KEYTRUDA was investigated in KEYNOTE-057, a multicenter, open-label, single-arm trial that enrolled 148 patients with high-risk non-muscle invasive bladder cancer (NMIBC), 96 of whom had BCG-unresponsive carcinoma in situ (CIS) with or without papillary tumors. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression.

The median duration of exposure to KEYTRUDA was 4.3 months (range: 1 day to 25.6 months).

KEYTRUDA was discontinued due to adverse reactions in 11% of patients. The most common adverse (>1%) reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥2%) were diarrhea (4%) and urinary tract infection (2%). Serious adverse reactions occurred in 28% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). Tables 27 and 28 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-057.

Table 27: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-057

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=148	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	29	0.7
Peripheral edema‡	11	0
Gastrointestinal		
Diarrhea§	24	2.0
Nausea	13	0
Constipation	12	0
Skin and Subcutaneous Tissue		
Rash¶	24	0.7
Pruritus	19	0.7
Musculoskeletal and Connective Tissue		
Musculoskeletal pain#	19	0
Arthralgia	14	1.4
Renal and Urinary		
Hematuria	19	1.4
Respiratory, Thoracic, and Mediastinal		
Cough Þ	19	0
Infections		
Urinary tract infection	12	2.0
Nasopharyngitis	10	0
Endocrine		
Hypothyroidism	11	0

* Graded per NCI CTCAE v4.03
† Includes asthenia, fatigue, malaise
‡ Includes edema peripheral, peripheral swelling
§ Includes diarrhea, gastroenteritis, colitis
¶ Includes rash maculo-papular, rash, rash erythematous, rash pruritic, rash pustular, erythema, eczema, eczema asteatotic, lichenoid keratosis, urticaria, dermatitis
# Includes back pain, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, neck pain
Þ Includes cough, productive cough

Table 28: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of BCG-unresponsive NMIBC Patients Receiving KEYTRUDA in KEYNOTE-057

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Chemistry		
Hyperglycemia	59	8
Increased ALT	25	3.4
Hyponatremia	24	7
Hypophosphatemia	24	6
Hypoalbuminemia	24	2.1
Hyperkalemia	23	1.4
Hypocalcemia	22	0.7
Increased AST	20	3.4
Increased creatinine	20	0.7
Hematology		
Anemia	35	1.4
Lymphopenia	29	1.6

* 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: 124 to 147 patients)
† Graded per NCI CTCAE v4.03

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

Among the 153 patients with MSI-H or dMMR CRC enrolled in KEYNOTE-177 *[see Clinical Studies (14.9)]* treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 11.1 months (range: 1 day to 30.6 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Gastric Cancer

Among the 259 patients with gastric cancer enrolled in KEYNOTE-059 *[see Clinical Studies (14.10)]*, 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

First-line Treatment of Locally Advanced Unresectable or Metastatic Esophageal Cancer/Gastroesophageal Junction

The safety of KEYTRUDA, in combination with cisplatin and FU chemotherapy was investigated in KEYNOTE-590, a multicenter, double-blind, randomized (1:1), placebo-controlled trial for the first-line treatment in patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.11)]*. A total of 740 patients received either KEYTRUDA 200 mg (n=370) or placebo (n=370) every 3 weeks for up to 35 cycles, both in combination with up to 6 cycles of cisplatin and up to 35 cycles of FU.

The median duration of exposure was 5.7 months (range: 1 day to 26 months) in the KEYTRUDA combination arm and 5.1 months (range: 3 days to 27 months) in the chemotherapy arm.

KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 67% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (19%), fatigue/asthenia (8%), decreased white blood cell count (5%), pneumonia (5%), decreased appetite (4.3%), anemia (3.2%), increased blood creatinine (3.2%), stomatitis (3.2%), malaise (3.0%), thrombocytopenia (3%), pneumonitis (2.7%), diarrhea (2.4%), dysphagia (2.2%), and nausea (2.2%).

Tables 29 and 30 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-590.

Table 29: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-590

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks Cisplatin FU n=370		Placebo Cisplatin FU n=370	
	All Grades* (%)	Grades 3-4† (%)	All Grades* (%)	Grades 3-4† (%)
Gastrointestinal				
Nausea	67	7	63	7
Constipation	40	0	40	0
Diarrhea	36	4.1	33	3
Vomiting	34	7	32	5
Stomatitis	27	6	26	3.8
General				
Fatigue‡	57	12	46	9
Metabolism and Nutrition				
Decreased appetite	44	4.1	38	5
Investigations				
Weight loss	24	3.0	24	5

* Graded per NCI CTCAE v4.03
† One fatal event of diarrhea was reported in each arm.
‡ Includes asthenia, fatigue

Table 30: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Esophageal Cancer Patients Receiving KEYTRUDA in KEYNOTE-590

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks Cisplatin FU		Chemotherapy (Cisplatin and FU)	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	83	21	86	24
Neutropenia	74	43	71	41
Leukopenia	72	21	73	17
Lymphopenia	55	22	53	18
Thrombocytopenia	43	5	46	8
Chemistry				
Hyperglycemia	56	7	55	6
Hyponatremia	53	19	54	19
Hypoalbuminemia	52	2.8	52	2.3
Increased creatinine	45	2.5	42	2.5
Hypocalcemia	44	3.9	38	2
Hypophosphatemia	37	9	31	10
Hypokalemia	30	12	34	15
Increased alkaline phosphatase	29	1.9	29	1.7
Hyperkalemia	28	3.6	27	2.6
Increased AST	25	4.4	22	2.8
Increased ALT	23	3.6	18	1.7

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/cisplatin/FU (range: 345 to 365 patients) and placebo/cisplatin/FU (range: 330 to 358 patients)
† Graded per NCI CTCAE v4.03

Previously Treated Recurrent Locally Advanced or Metastatic Esophageal Cancer

Among the 314 patients with esophageal cancer enrolled in KEYNOTE-181 *[see Clinical Studies (14.11)]* 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 (14.12)]*, 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 31 and 32 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-158.

Table 31: 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 painÞ	22	3.1
Nausea	19	0
Vomiting	19	1.0
Constipation	14	0
Metabolism and Nutrition		
Decreased appetite	21	0
Vascular		
Hemorrhageß	19	5
Infections		
UTIà	18	6
Infection (except UTI)è	16	4.1
Skin and Subcutaneous Tissue		
Rashð	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 32: 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 (14.13)]*, 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 (14.14)]*, 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 (14.15)]*. 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 33 and 34 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 33: 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 34: 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.

Endometrial Carcinoma

The safety of KEYTRUDA in combination with lenvatinib (20 mg orally once daily) was investigated in KEYNOTE-146, a single-arm, multicenter, open-label trial in 94 patients with endometrial carcinoma whose tumors had progressed following one line of systemic therapy and were not MSI-H or dMMR *[see Clinical Studies (14.16)]*. The median duration of study treatment was 7 months (range: 0.03 to 37.8 months). The median duration of exposure to KEYTRUDA was 6 months (range: 0.03 to 23.8 months). KEYTRUDA was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months.

Fatal adverse reactions occurred in 3% of patients receiving KEYTRUDA and lenvatinib, including gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS) with intraventricular hemorrhage, and intracranial hemorrhage.

Serious adverse reactions occurred in 52% of patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions in ≥3% of patients were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), hemorrhage (4%), fatigue (4%), nausea (4%), confusional state (4%), pleural effusion (4%), adrenal insufficiency (3%), colitis (3%), dyspnea (3%), and pyrexia (3%).

KEYTRUDA was discontinued for adverse reactions (Grade 1-4) in 19% of patients, regardless of action taken with lenvatinib. The most common adverse reactions (≥ 2%) leading to discontinuation of KEYTRUDA were adrenal insufficiency (2%), colitis (2%), pancreatitis (2%), and muscular weakness (2%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 49% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were: fatigue (14%), diarrhea (6%), decreased appetite (6%), rash (5%), renal impairment (4%), vomiting (4%), increased lipase (4%), weight loss (4%), nausea (3%), increased blood alkaline phosphatase (3%), skin ulcer (3%), adrenal

insufficiency (2%), increased amylase (2%), hypocalcemia (2%), hypomagnesemia (2%), hyponatremia (2%), peripheral edema (2%), musculoskeletal pain (2%), pancreatitis (2%), and syncope (2%).

Tables 35 and 36 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib.

Table 35: Adverse Reactions Occurring in ≥20% of Patients with Endometrial Carcinoma in KEYNOTE-146

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with Lenvatinib N=94	
	All Grades (%)	Grades 3-4 (%)
General		
Fatigue*	65	17
Musculoskeletal and Connective Tissue		
Musculoskeletal pain†	65	3
Vascular		
Hypertension‡	65	38
Hemorrhagic events§	28	4
Gastrointestinal		
Diarrhea¶	64	4
Nausea	48	5
Stomatitis#	43	0
Vomiting	39	0
Abdominal painÞ	33	6
Constipation	32	0
Metabolism		
Decreased appetiteß	52	0
Hypomagnesemia	27	3
Endocrine		
Hypothyroidismà	51	1
Investigations		
Weight loss	36	3
Nervous System		
Headache	33	1
Infections		
Urinary tract infectionè	31	4
Respiratory, Thoracic and Mediastinal		
Dysphonia	29	0
Dyspneaô	24	2
Cough	21	0
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia syndrome	26	3
Rashø	21	3

* Includes asthenia, fatigue, and malaise

† Includes arthralgia, arthritis, back pain, breast pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity

‡ Includes essential hypertension, hypertension, and hypertensive encephalopathy

§ Includes catheter site bruise, contusion, epistaxis, gastrointestinal hemorrhage, hematemesis, hematuria, hemorrhage intracranial, injection site hemorrhage, intraventricular hemorrhage, large intestinal hemorrhage, metrorrhagia, mouth hemorrhage, uterine hemorrhage, and vaginal hemorrhage

¶ Includes diarrhea, gastroenteritis, gastrointestinal viral infection, and viral diarrhea

Includes glossitis, mouth ulceration, oral discomfort, oral mucosal blistering, oropharyngeal pain, and stomatitis

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

ß Includes decreased appetite and early satiety

à Includes increased blood thyroid stimulating hormone and hypothyroidism

è Includes cystitis and urinary tract infection

ô Includes dyspnea and exertional dyspnea

ø Includes rash, rash generalized, rash macular, and rash maculo-papular

Table 36: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients with Endometrial Carcinoma in KEYNOTE-146

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with Lenvatinib	
	All Grades %†	Grade 3-4 %†
Chemistry		
Increased creatinine	80	7
Hypertriglyceridemia	58	4
Hyperglycemia	53	1
Hypercholesteremia	49	6
Hypoalbuminemia	48	0
Hypomagnesemia	47	2
Increased aspartate aminotransferase	43	4
Hyponatremia	42	13
Increased lipase	42	18
Increased alanine aminotransferase	35	3
Increased alkaline phosphatase	32	1
Hypokalemia	27	5
Increased amylase	19	6
Hypocalcemia	14	3
Hypermagnesemia	4	3
Hematology		
Thrombocytopenia	48	0
Leukopenia	38	2
Lymphopenia	36	7
Anemia	35	1
Increased INR	21	3
Neutropenia	12	3

* With at least 1 grade increase from baseline

† Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter (range: 71 to 92 patients).

TMB-H Cancer

The safety of KEYTRUDA was investigated in 105 patients with TMB-H cancer enrolled in KEYNOTE-158 *[see Clinical Studies (14.17)].* The median duration of exposure to KEYTRUDA was 4.9 months (range: 0.03 to 35.2 months). Adverse reactions occurring in patients with TMB-H cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

cSCC

Among the 105 patients with cSCC enrolled in KEYNOTE-629 *[see Clinical Studies (14.18)]*, the median duration of exposure to KEYTRUDA was 5.8 months (range 1 day to 16.1 months). Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. Adverse reactions occurring in patients with cSCC 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 included lymphopenia (11%).

TNBC

The safety of KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355, a multicenter, double-blind, randomized (2:1), placebo-controlled trial in patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting *[see Clinical Studies (14.19)]*. A total of 596 patients (including 34 patients from a safety run-in) received KEYTRUDA 200 mg every 3 weeks in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin.

The median duration of exposure to KEYTRUDA was 5.7 months (range: 1 day to 33.0 months).

Fatal adverse reactions occurred in 2.5% of patients receiving KEYTRUDA in combination with chemotherapy, including cardio-respiratory arrest (0.7%) and septic shock (0.3%).

Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin. Serious adverse reactions in ≥2% of patients were pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%).

KEYTRUDA was discontinued for adverse reactions in 11% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 50% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (22%), thrombocytopenia (14%), anemia (7%), increased ALT (6%), leukopenia (5%), increased AST (5%), decreased white blood cell count (3.9%), and diarrhea (2%).

Tables 37 and 38 summarize the adverse reactions and laboratory abnormalities in patients on KEYTRUDA in KEYNOTE-355.

Table 37: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Chemotherapy in KEYNOTE-355

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with chemotherapy n=596		Placebo every 3 weeks with chemotherapy n=281	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
General				
Fatigue†	48	5	49	4.3
Gastrointestinal				
Nausea	44	1.7	47	1.8
Diarrhea	28	1.8	23	1.8
Constipation	28	0.5	27	0.4
Vomiting	26	2.7	22	3.2
Skin and Subcutaneous Tissue				
Alopecia	34	0.8	35	1.1
Rash‡	26	2	16	0
Respiratory, Thoracic and Mediastinal				
Cough§	23	0	20	0.4
Metabolism and Nutrition				
Decreased appetite	21	0.8	14	0.4
Nervous System				
Headache¶	20	0.7	23	0.7

* Graded per NCI CTCAE v4.03
† Includes fatigue and asthenia
‡ Includes rash, rash maculo-papular, rash pruritic, rash pustular, rash macular, rash papular, butterfly rash, rash erythematous, eyelid rash
§ Includes cough, productive cough, upper-airway cough syndrome
¶ Includes headache, migraine, tension headache

Table 38: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA with Chemotherapy in KEYNOTE-355

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with chemotherapy		Placebo every 3 weeks with chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	90	20	85	19
Leukopenia	85	39	86	39
Neutropenia	76	49	77	52
Lymphopenia	70	26	70	19
Thrombocytopenia	54	19	53	21
Chemistry				
Increased ALT	60	11	58	8
Increased AST	57	9	55	6
Hyperglycemia	52	4.4	51	2.2
Hypoalbuminemia	37	2.2	32	2.2
Increased alkaline phosphatase	35	3.9	39	2.2
Hypocalcemia	29	3.3	27	1.8
Hyponatremia	28	5	26	6
Hypophosphatemia	21	7	18	4.8
Hypokalemia	20	4.4	18	4.0

* 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: 566 to 592 patients) and placebo + chemotherapy (range: 269 to 280 patients).

† Graded per NCI CTCAE v4.03

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 (5.5), 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 as a single agent have been established in pediatric patients with cHL, PMBCL, MCC, MSI-H cancer, and TMB-H cancer. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.5, 14.6, 14.8, 14.14, 14.17)]*.

In KEYNOTE-051, 161 pediatric patients (62 pediatric patients aged 6 months to younger than 12 years and 99 pediatric patients aged 12 to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive solid tumors received KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 24 months). Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults included pyrexia (33%), vomiting (30%), upper respiratory tract infection (29%), and headache (25%). Laboratory abnormalities that occurred at a ≥10% higher rate in pediatric patients when compared to adults were leukopenia (30%), neutropenia (26%), and Grade 3 anemia (17%).

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 3781 patients with melanoma, NSCLC, HNSCC, or urothelial carcinoma who were treated with KEYTRUDA in clinical studies, 48% were 65 years and over and 17% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Of 389 adult patients with cHL who were treated with KEYTRUDA in clinical studies, 46 (12%) were 65 years and over. Patients aged 65 years and over had a higher incidence of serious adverse reactions (50%) than patients aged younger than 65 years (24%). Clinical studies of KEYTRUDA in cHL did not include sufficient numbers of patients aged 65 years and over to determine whether effectiveness differs from that in younger patients.

Of 596 adult patients with TNBC who were treated with KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin in KEYNOTE-355, 137 (23%) were 65 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) 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 the modeling of dose/exposure efficacy and safety relationships and observed pharmacokinetic data from an interim analysis of 41 patients with melanoma treated with pembrolizumab 400 mg every 6 weeks, there are no anticipated clinically significant differences in efficacy and safety between pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks or 400 mg every 6 weeks.

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 (10 months 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.

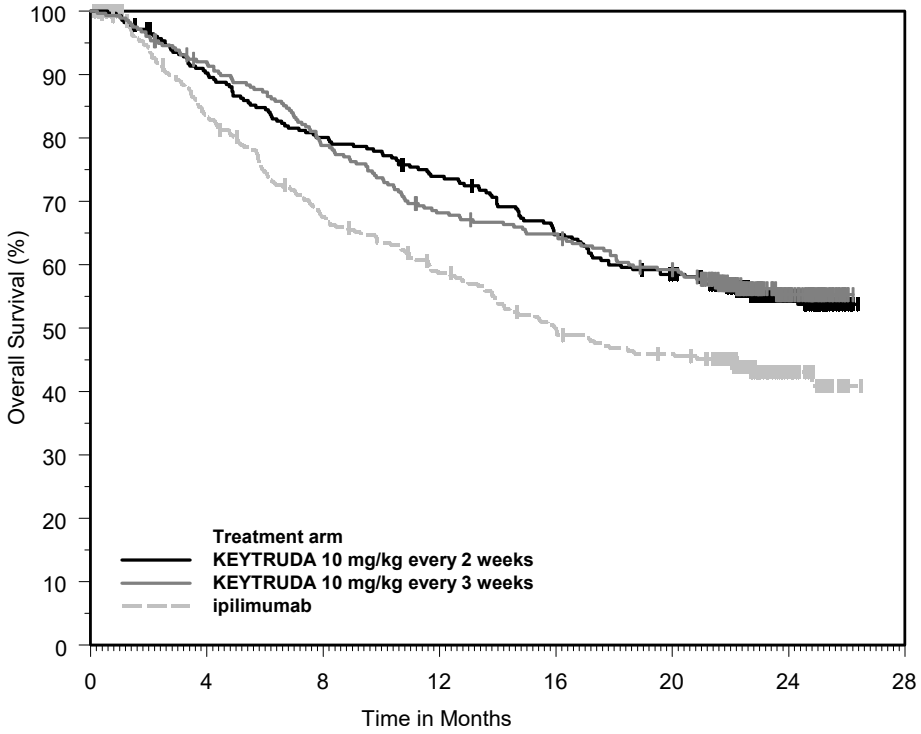
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients 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 39 and Figure 1.

Table 39: 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 40.

Table 40: Efficacy Results in KEYNOTE-002

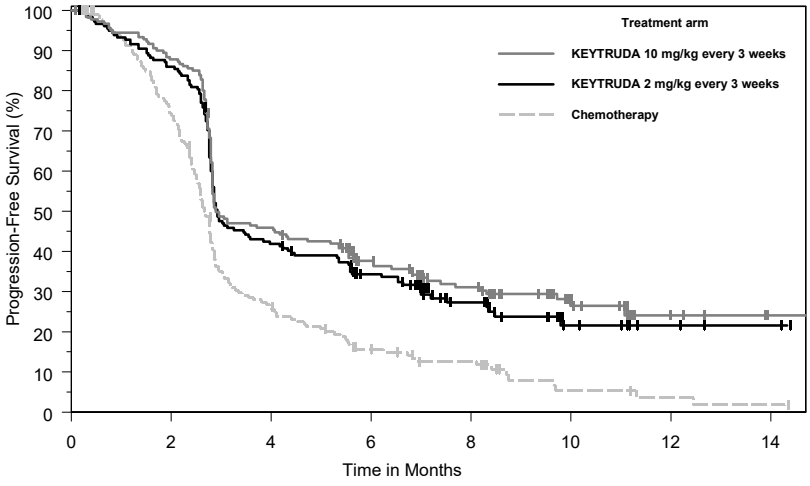
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 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 41 and Figure 3.

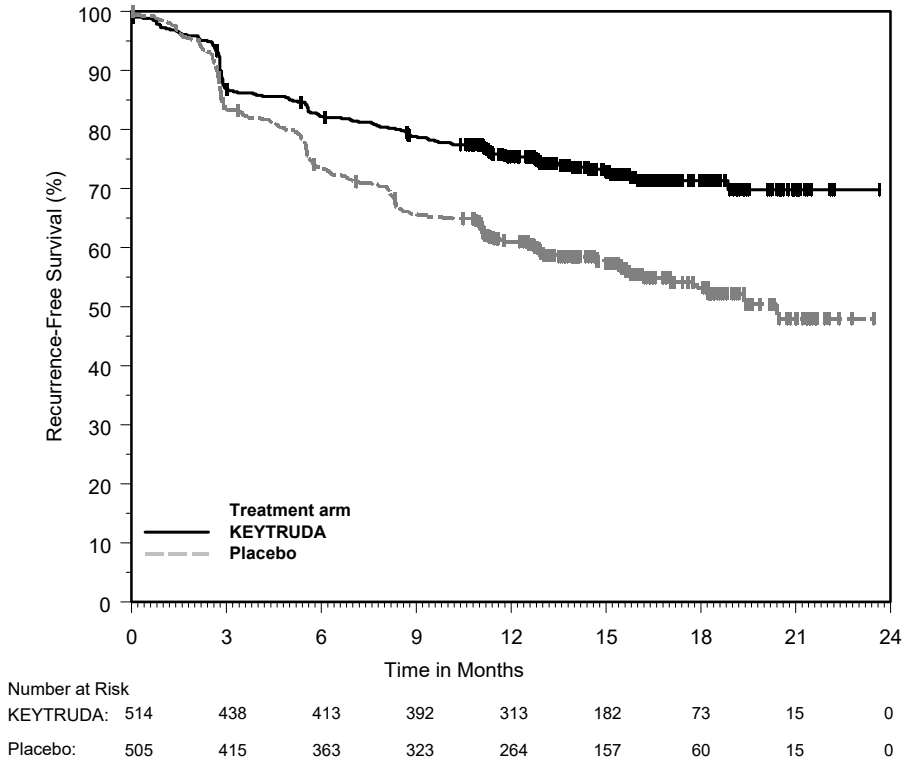
Table 41: Efficacy Results in KEYNOTE-054

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 42 and Figure 4 summarize the efficacy results for KEYNOTE-189.

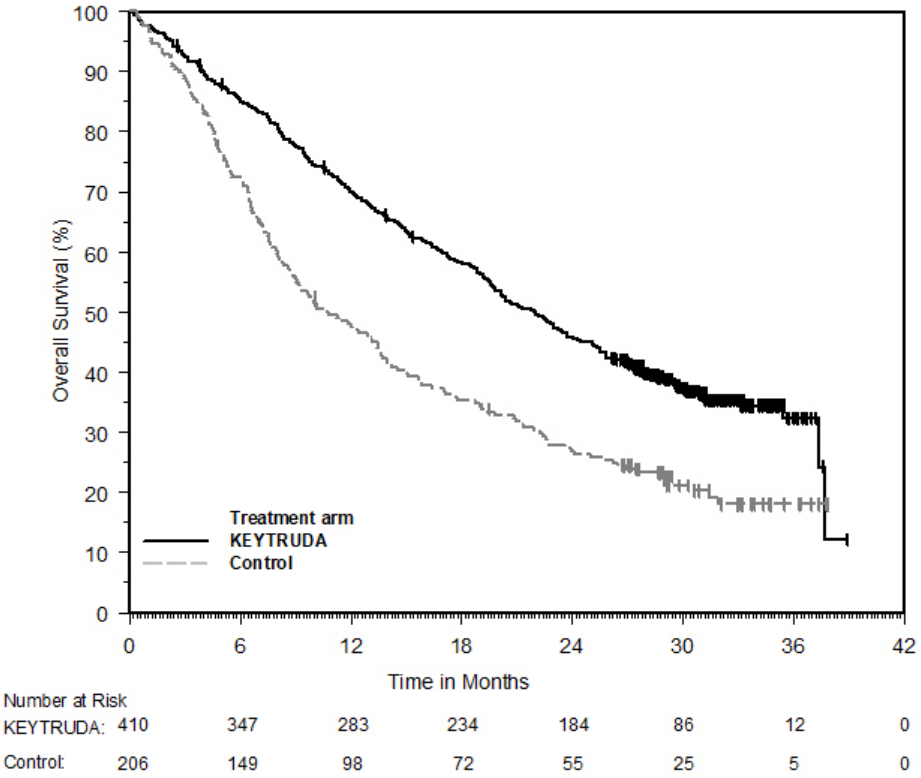
Table 42: Efficacy Results in KEYNOTE-189

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 (%)	245 (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 a 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

At the protocol-specified final OS analysis, the median in the KEYTRUDA in combination with pemetrexed and platinum chemotherapy arm was 22.0 months (95% CI: 19.5, 24.5) compared to 10.6 months (95% CI: 8.7, 13.6) in the placebo with pemetrexed and platinum chemotherapy arm, with an HR of 0.56 (95% CI: 0.46, 0.69).

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



*Based on the protocol-specified final OS analysis

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 43 and Figure 5 summarize the efficacy results for KEYNOTE-407.

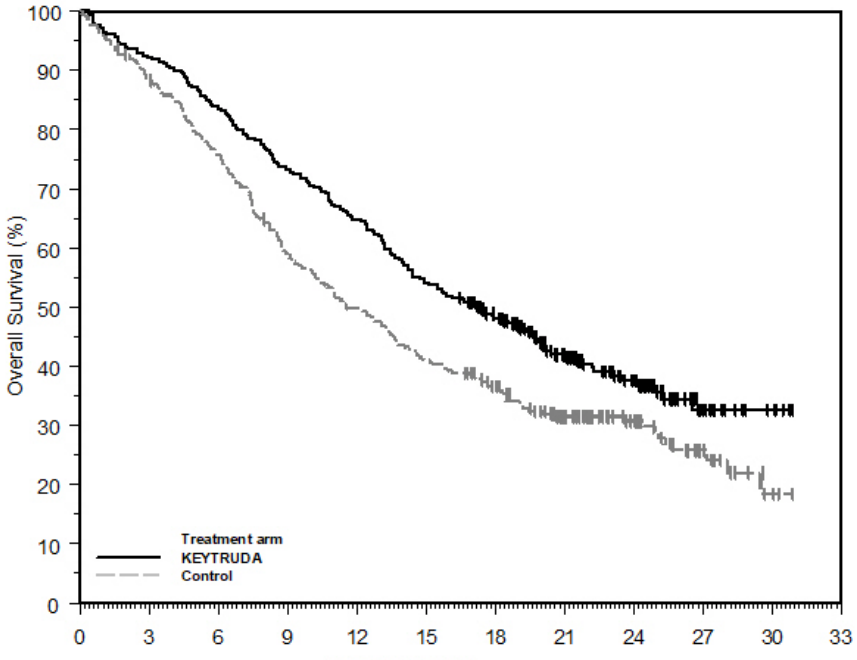
Table 43: Efficacy Results in KEYNOTE-407

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 (4.2, 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

At the protocol-specified final OS analysis, the median in the KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy arm was 17.1 months (95% CI: 14.4, 19.9) compared to 11.6 months (95% CI: 10.1, 13.7) in the placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy arm, with an HR of 0.71 (95% CI: 0.58, 0.88).

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



Number at Risk												
KEYTRUDA:	278	256	232	203	180	150	119	80	46	14	4	0
Control:	281	245	210	163	137	113	91	61	36	16	3	0

*Based on the protocol-specified final OS analysis

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 44 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%.

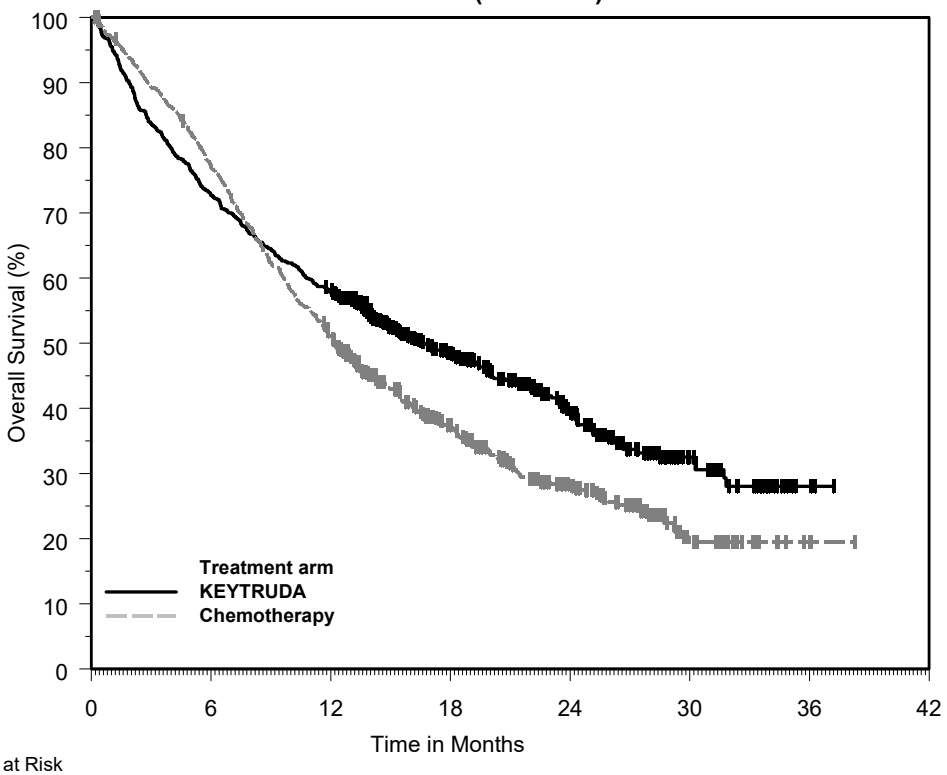
Table 44: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

	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)	6.9 (5.9, 9.0)	6.4 (6.1, 6.9)
Hazard ratio*,‡ (95% CI)	1.07 (0.94, 1.21)		0.82 (0.68, 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 45 and Figure 7 summarize the efficacy results for KEYNOTE-024.

Table 45: 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+)

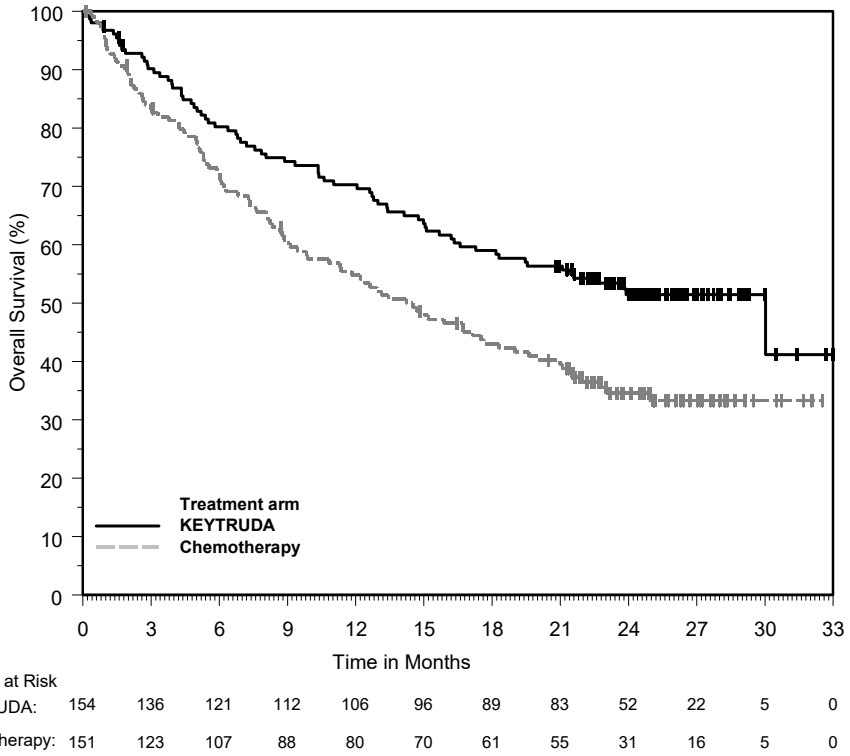
* Based on the stratified Cox proportional hazard model for the interim analysis

† 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 46 and 47 and Figure 8 summarize efficacy results in the subgroup with TPS ≥50% population and in all patients, respectively.

Table 46: 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 47: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

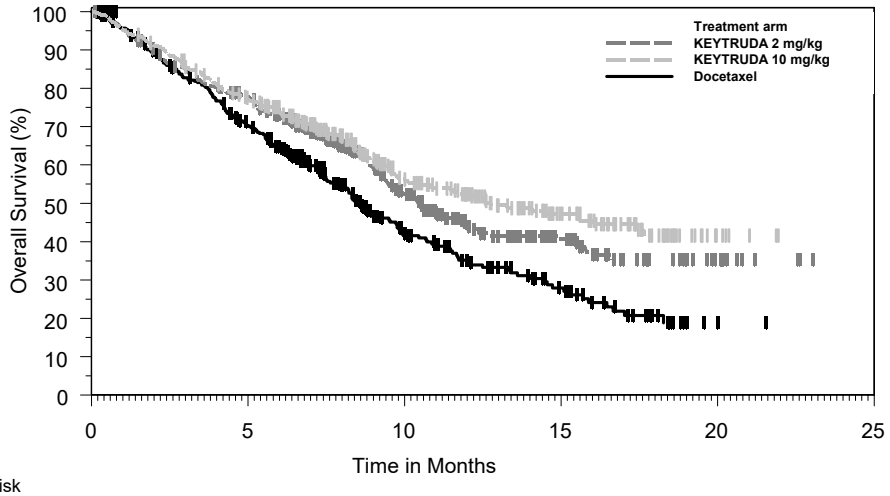
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
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 48.

Table 48: 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. Table 49 and Figure 9 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

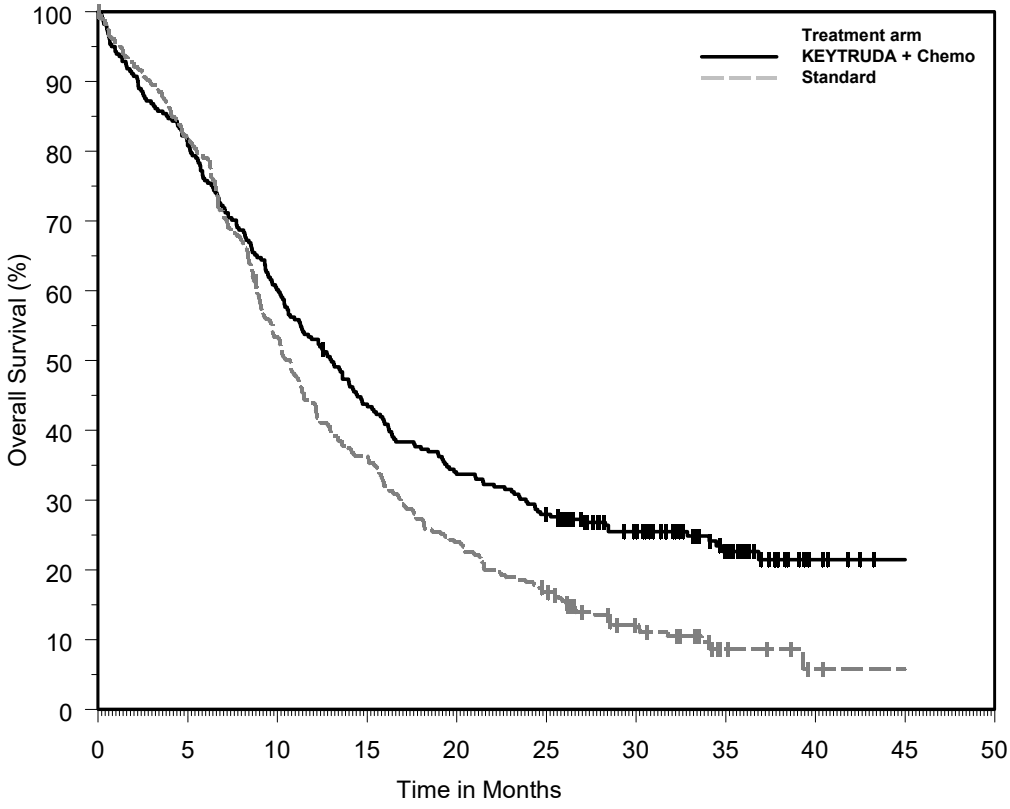
Table 49: Efficacy Results* for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048

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+)

* Results at a pre-specified interim analysis
† 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

At the pre-specified final OS analysis for the ITT population, the hazard ratio was 0.72 (95% CI: 0.60, 0.87). In addition, KEYNOTE-048 demonstrated a statistically significant improvement in OS for the subgroups of patients with PD-L1 CPS ≥1 (HR=0.65, 95% CI: 0.53, 0.80) and CPS ≥20 (HR=0.60, 95% CI: 0.45, 0.82).

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



Number at Risk											
KEYTRUDA + Chemo:	281	227	169	122	94	77	55	29	5	0	0
Standard:	278	227	147	100	66	45	23	6	1	0	0

* At the time of the protocol-specified final analysis.

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 a pre-specified interim analysis. At the time of the interim and final analyses, there was no significant difference in OS between the KEYTRUDA single agent arm and the control arm for the overall population.

Table 50 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 50: Efficacy Results* for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)

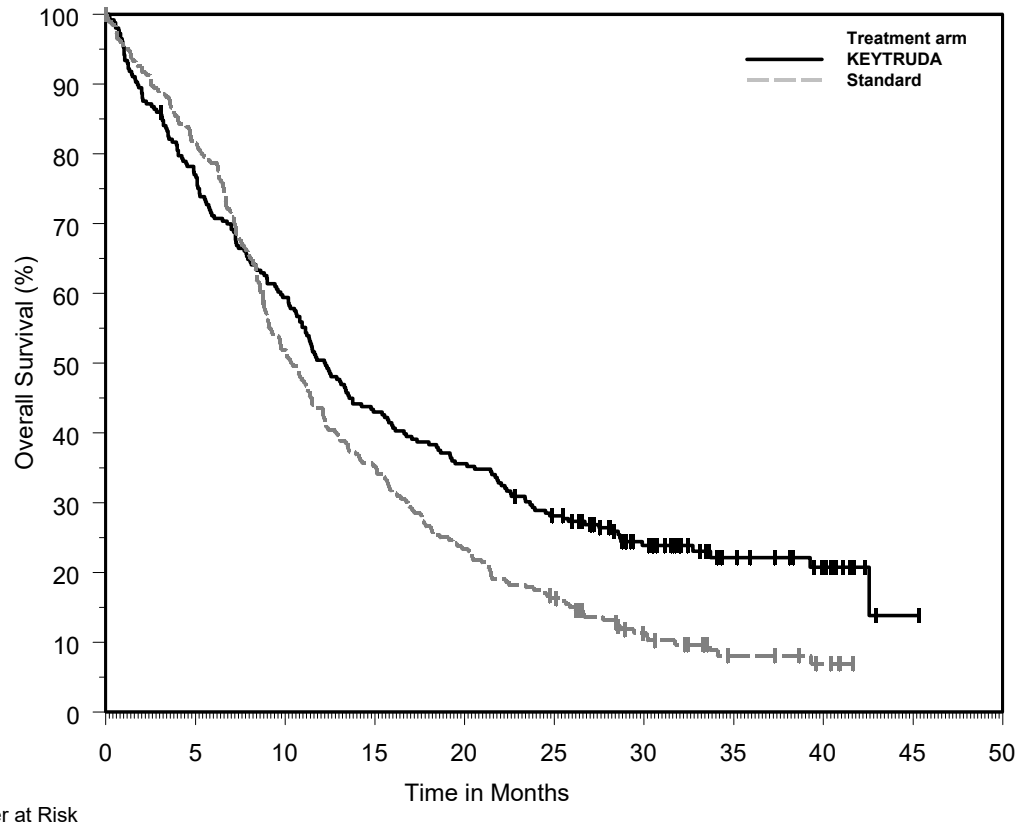
Endpoint	CPS ≥1		CPS ≥20	
	KEYTRUDA 200 mg every 3 weeks n=257	Cetuximab Platinum FU n=255	KEYTRUDA 200 mg every 3 weeks n=133	Cetuximab Platinum FU n=122
OS				
Number of events (%)	177 (69%)	206 (81%)	82 (62%)	95 (78%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0,11.5)	14.9 (11.6, 21.5)	10.7 (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)		0.97 (0.74, 1.27)	
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+)

* Results at a pre-specified interim analysis
† 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

At the pre-specified final OS analysis comparing KEYTRUDA as a single agent to cetuximab in combination with chemotherapy, the hazard ratio for the subgroup of patients with CPS ≥1 was 0.74 (95% CI: 0.61, 0.90) and the hazard ratio for the subgroup of patients with CPS ≥20 was 0.58 (95% CI: 0.44, 0.78).

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC at the time of the pre-specified final OS analysis, 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 0.86 (95% CI: 0.66, 1.12).

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



Number at Risk											
KEYTRUDA:	257	197	152	110	91	70	43	21	13	1	0
Standard:	255	207	131	89	59	40	21	9	5	0	0

* At the time of the protocol-specified final analysis.

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

KEYNOTE-204

The efficacy of KEYTRUDA was investigated in KEYNOTE-204 (NCT02684292), a randomized, open-label, active controlled trial conducted in 304 patients with relapsed or refractory cHL. The trial enrolled adults with relapsed or refractory disease after at least one multi-agent chemotherapy regimen. Patients were randomized (1:1) to receive:

- KEYTRUDA 200 mg intravenously every 3 weeks or
- Brentuximab vedotin (BV) 1.8 mg/kg intravenously every 3 weeks

Treatment was continued until unacceptable toxicity, disease progression, or a maximum of 35 cycles (up to approximately 2 years). Disease assessment was performed every 12 weeks. Randomization was stratified by prior autologous HSCT (yes vs. no) and disease status after frontline therapy (primary refractory vs. relapse <12 months after completion vs. relapse ≥12 months after completion). The main efficacy measure was PFS as assessed by BICR using 2007 revised International Working Group criteria.

The study population characteristics were: median age of 35 years (range: 18 to 84); 57% male; 77% White, 9% Asian, 3.9% Black. The median number of prior therapies was 2 (range: 1 to 10) in the KEYTRUDA arm and 3 (range: 1 to 11) in the BV arm, with 18% in both arms having 1 prior line. Forty-two percent of patients were refractory to the last prior therapy, 29% had primary refractory disease, 37% had prior autologous HSCT, 5% had received prior BV, and 39% had prior radiation therapy.

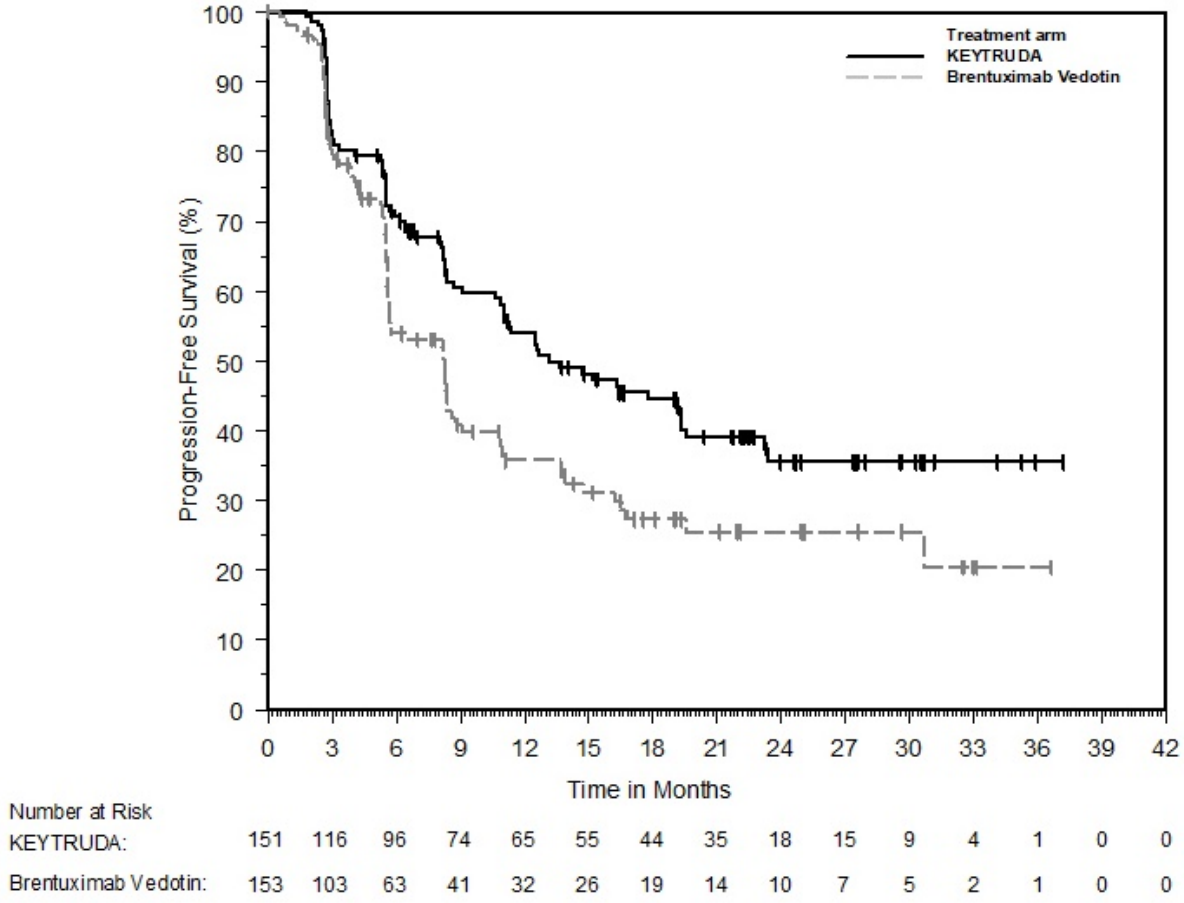
Efficacy is summarized in Table 51 and Figure 11.

Table 51: Efficacy Results in Patients with cHL in KEYNOTE-204

Endpoint	KEYTRUDA 200 mg every 3 weeks n=151	Brentuximab Vedotin 1.8 mg/kg every 3 weeks n=153
PFS		
Number of patients with event (%)	81 (54%)	88 (58%)
Median in months (95% CI)*	13.2 (10.9, 19.4)	8.3 (5.7, 8.8)
Hazard ratio† (95% CI)	0.65 (0.48, 0.88)	
p-Value‡	0.0027	
Objective Response Rate		
ORR§ (95% CI)	66% (57, 73)	54% (46, 62)
Complete response	25%	24%
Partial response	41%	30%
Duration of Response		
Median in months (range)*	20.7 (0.0+, 33.2+)	13.8 (0.0+, 33.9+)

* Based on Kaplan-Meier estimates.
† Based on the stratified Cox proportional hazard model.
‡ Based on a stratified log-rank test. One-sided p-value, with a prespecified boundary of 0.0043.
§ Difference in ORR is not statistically significant.
\+ Denotes a censored value.

Figure 11: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-204



KEYNOTE-087

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 autologous HSCT, 83% had received prior brentuximab vedotin and 36% of patients had prior radiation therapy.

Efficacy results for KEYNOTE-087 are summarized in Table 52.

Table 52: Efficacy Results in Patients with cHL 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 53.

Table 53: Efficacy Results in Patients with PMBCL 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 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 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 54.

Table 54: 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 response
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 55 and Figure 12 summarize the efficacy results for KEYNOTE-045.

Table 55: Efficacy Results in KEYNOTE-045

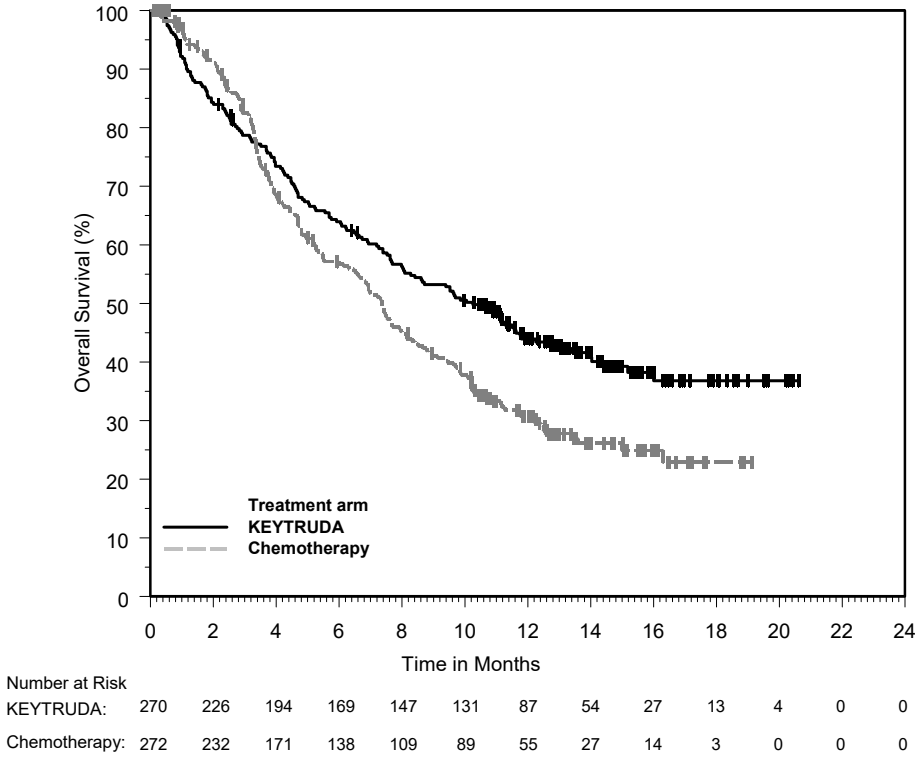
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1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

NR = not reached

Figure 12: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



BCG-unresponsive High-Risk Non-Muscle Invasive Bladder Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-057 (NCT02625961), a multicenter, open-label, single-arm trial in 96 patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. BCG-unresponsive high-risk NMIBC was

defined as persistent disease despite adequate BCG therapy, disease recurrence after an initial tumor-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Adequate BCG therapy was defined as administration of at least five of six doses of an initial induction course plus either of: at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. Prior to treatment, all patients had undergone transurethral resection of bladder tumor (TURBT) to remove all resectable disease (Ta and T1 components). Residual CIS (Tis components) not amenable to complete resection was allowed. The trial excluded patients with muscle invasive (i.e., T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma, concurrent extra-vesical (i.e., urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium, or autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC, or progressive disease. Assessment of tumor status was performed every 12 weeks for two years and then every 24 weeks for three years, and patients without disease progression could be treated for up to 24 months. The major efficacy outcome measures were complete response (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable], urine cytology, and computed tomography urography [CTU] imaging) and duration of response.

The study population characteristics were: median age of 73 years (range: 44 to 92); 44% age ≥75; 84% male; 67% White; and 73% and 27% with an ECOG performance status of 0 or 1, respectively. Tumor pattern at study entry was CIS with T1 (13%), CIS with high grade TA (25%), and CIS (63%). Baseline high-risk NMIBC disease status was 27% persistent and 73% recurrent. The median number of prior instillations of BCG was 12.

The median follow-up time was 28.0 months (range: 4.6 to 40.5 months). Efficacy results are summarized in Table 56.

Table 56: Efficacy Results in KEYNOTE-057

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=96**
Complete Response Rate (95% CI)	41% (31, 51)
Duration of Response*	
Median in months (range)	16.2 (0.0+, 30.4+)
% (n) with duration ≥12 months	46% (18)

* Based on patients (n=39) that achieved a complete response; reflects period from the time complete response was achieved

\+ Denotes ongoing response

14.8 Microsatellite Instability-High or Mismatch Repair Deficient 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 57: 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 58 and 59.

Table 58: 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 59: Response by Tumor Type

	N	Objective Response Rate n (%)	95% CI	Duration of Response 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 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks:

- mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and FU 400 mg/m^2 bolus on Day 1, then FU 2400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.
- FOLFIRI (irinotecan, leucovorin, and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and FU 400 mg/m^2 bolus on Day 1, then FU 2400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of

disease progression. The main efficacy outcome measures were 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) and OS. Additional efficacy outcome measures were ORR and DoR.

A total of 307 patients were enrolled and randomized to KEYTRUDA (n=153) or chemotherapy (n=154). The baseline characteristics of these 307 patients were: median age of 63 years (range: 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% had an ECOG PS of 0 and 48% had an ECOG PS of 1; and 27% received prior adjuvant or neoadjuvant chemotherapy. Among 154 patients randomized to receive chemotherapy,143 received chemotherapy per the protocol. Of the 143 patients, 56% received mFOLFOX6, 44% received FOLFIRI, 70% received bevacizumab plus mFOLFOX6 or FOLFIRI, and 11% received cetuximab plus mFOLFOX6 or FOLFIRI.

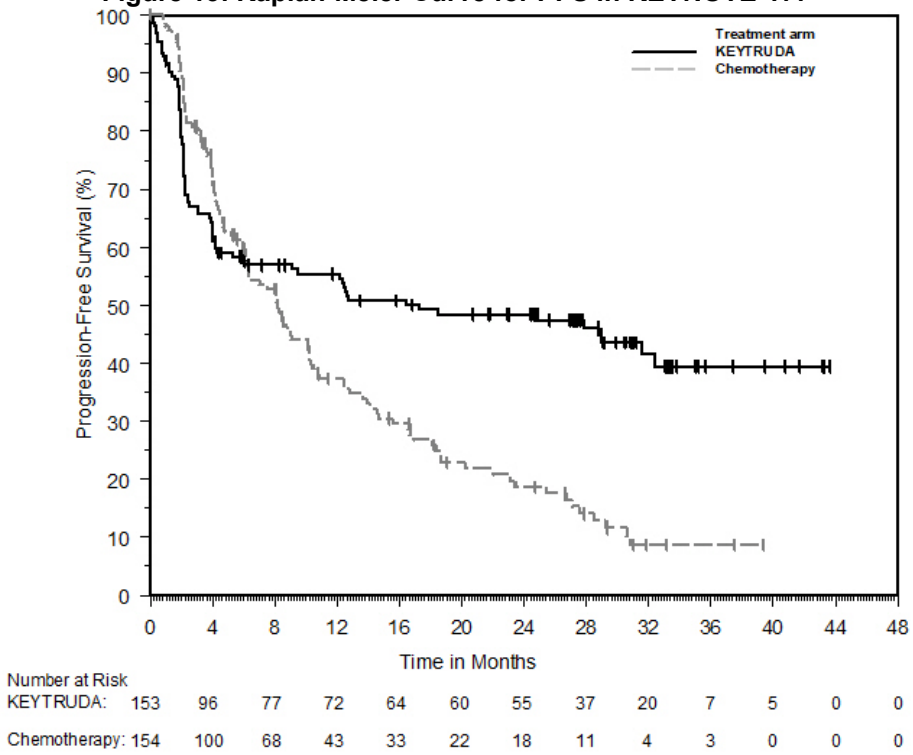
The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. At the time of the PFS analysis, the overall survival data were not mature (66% of the required number of events for the OS final analysis). The median follow-up time was 27.6 months (range: 0.2 to 48.3 months). Table 60 and Figure 13 summarize the key efficacy measures for KEYNOTE-177.

Table 60: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=153**	**Chemotherapy n=154**
PFS		
Number (%) of patients with event	82 (54%)	113 (73%)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)	
p-Value†	0.0004	
Objective Response Rate‡		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
Duration of Response‡,§		
Median in months (range)	NR (2.3+, 41.4+)	10.6 (2.8, 37.5+)
% with duration ≥12 months¶	75%	37%
% with duration ≥24 months¶	43%	18%

* Based on Cox regression model
† Two-sided p-value based on log-rank test (compared to a significance level of 0.0234)
‡ Based on confirmed response by BICR review
§ Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm
¶ Based on observed duration of response
\+ Denotes ongoing response
NR = not reached

Figure 13: Kaplan-Meier Curve for PFS in KEYNOTE-177



14.10 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.

14.11 Esophageal Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic Esophageal Cancer/Gastroesophageal Junction

KEYNOTE-590
The efficacy of KEYTRUDA was investigated in KEYNOTE-590 (NCT03189719), a multicenter, randomized, placebo-controlled trial that enrolled 749 patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation. PD-L1 status was centrally determined in tumor specimens in all patients using the PD-L1 IHC 22C3 pharmDx kit. Patients with active autoimmune disease, a medical condition that required immunosuppression, or who received prior systemic therapy in the locally advanced or metastatic setting were ineligible. Randomization was stratified by tumor histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.

Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients could be treated with KEYTRUDA for up to 24 months in the absence of disease progression. The major efficacy outcome measures were OS and PFS as assessed by the investigator 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 pre-specified analyses of OS and PFS based on squamous cell histology, CPS ≥10, and in all patients. Additional efficacy outcome measures were ORR and DoR, according to modified RECIST v1.1, as assessed by the investigator.

The study population characteristics were: median age of 63 years (range: 27 to 94), 43% age 65 or older; 83% male; 37% White, 53% Asian, and 1% Black; 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. Ninety-one percent had M1 disease and 9% had M0 disease. Seventy-three percent had a tumor histology of squamous cell carcinoma, and 27% had adenocarcinoma.

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with chemotherapy, compared to chemotherapy.

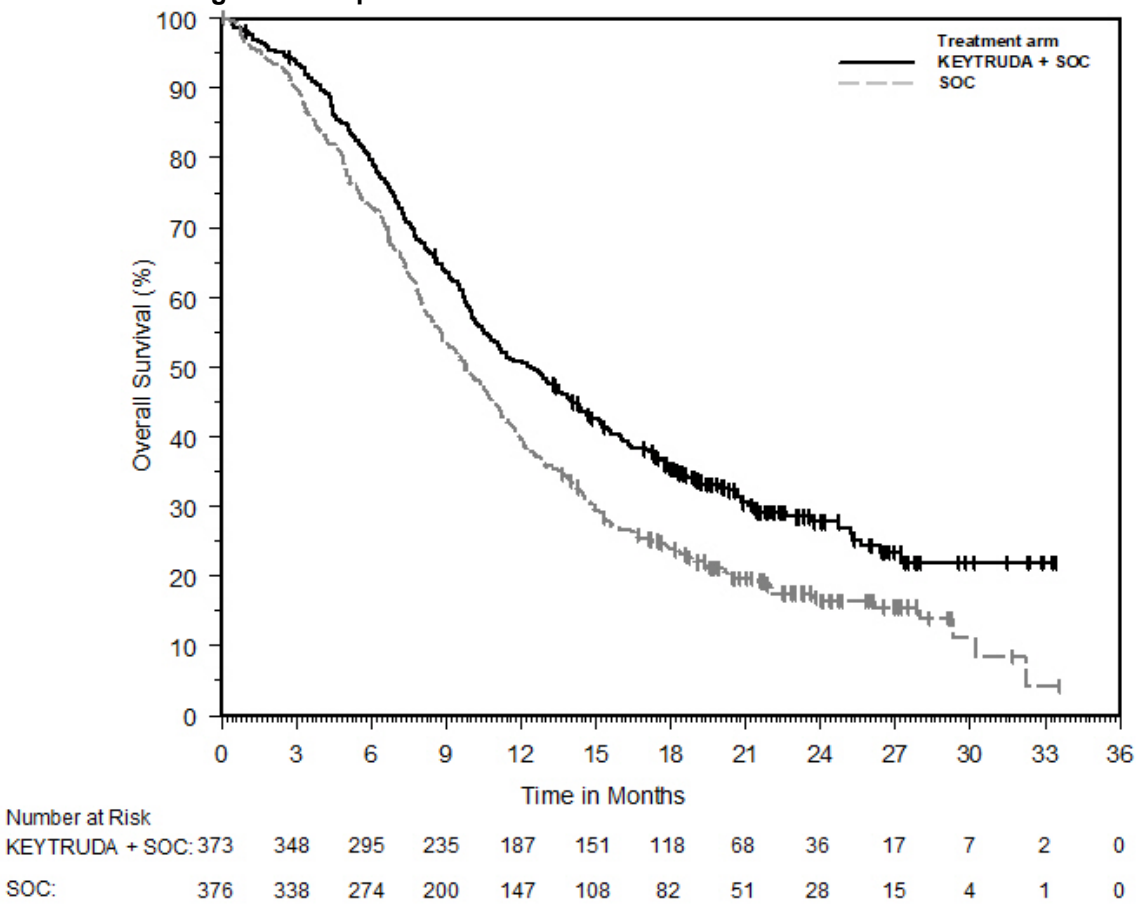
Table 61 and Figure 14 summarize the efficacy results for KEYNOTE-590 in all patients.

Table 61: Efficacy Results in Patients with Locally Advanced Unresectable or Metastatic Esophageal Cancer in KEYNOTE-590

Endpoint	KEYTRUDA 200 mg every 3 weeks Cisplatin FU n=373	Placebo Cisplatin FU n=376
OS		
Number (%) of events	262 (70)	309 (82)
Median in months (95% CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)
Hazard ratio* (95% CI)	0.73 (0.62, 0.86)	
p-Value†	<0.0001	
PFS		
Number of events (%)	297 (80)	333 (89)
Median in months (95% CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)
Hazard ratio* (95% CI)	0.65 (0.55, 0.76)	
p-Value†	<0.0001	
Objective Response Rate		
ORR, %‡ (95% CI)	45 (40, 50)	29 (25, 34)
Number (%) of complete responses	24 (6)	9 (2.4)
Number (%) of partial responses	144 (39)	101 (27)
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	8.3 (1.2+, 31.0+)	6.0 (1.5+, 25.0+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ Confirmed complete response or partial response
§ Based on the stratified Miettinen and Nurminen method

Figure 14: Kaplan-Meier Curve for Overall Survival in KEYNOTE-590



In a pre-specified formal test of OS in patients with PD-L1 CPS ≥ 10 (n=383), the median was 13.5 months (95% CI: 11.1, 15.6) for the KEYTRUDA arm and 9.4 months (95% CI: 8.0, 10.7) for the placebo arm, with a HR of 0.62 (95% CI: 0.49, 0.78; p-Value < 0.0001). In an exploratory analysis, in patients with PD-L1 CPS < 10 (n=347), the median OS was 10.5 months (95% CI: 9.7, 13.5) for the KEYTRUDA arm and 10.6 months (95% CI: 8.8, 12.0) for the placebo arm, with a HR of 0.86 (95% CI: 0.68, 1.10).

Previously Treated Recurrent Locally Advanced or Metastatic 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.

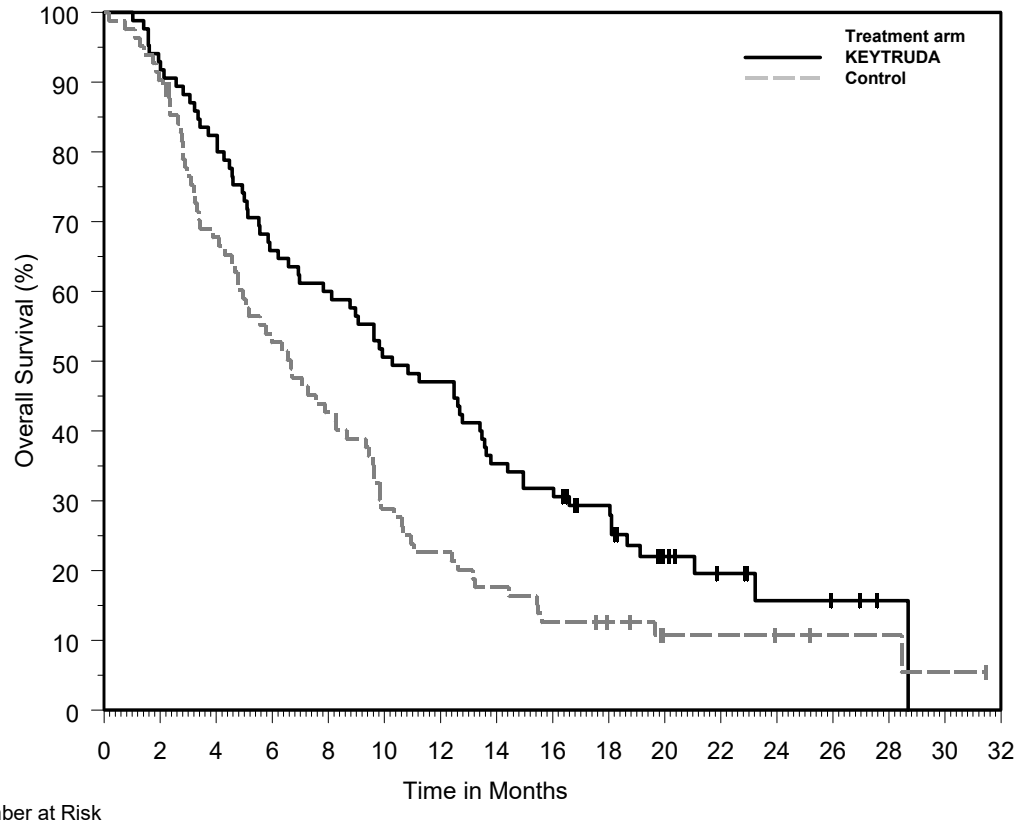
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 62 and Figure 15 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10.

Table 62: 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 15: 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.

14.12 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 63 for patients with PD-L1 expression (CPS ≥1).

Table 63: 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 response
NR = not reached

14.13 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 64.

Table 64: 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

14.14 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 65.

Table 65: 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.
\+ Denotes ongoing response

14.15 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.

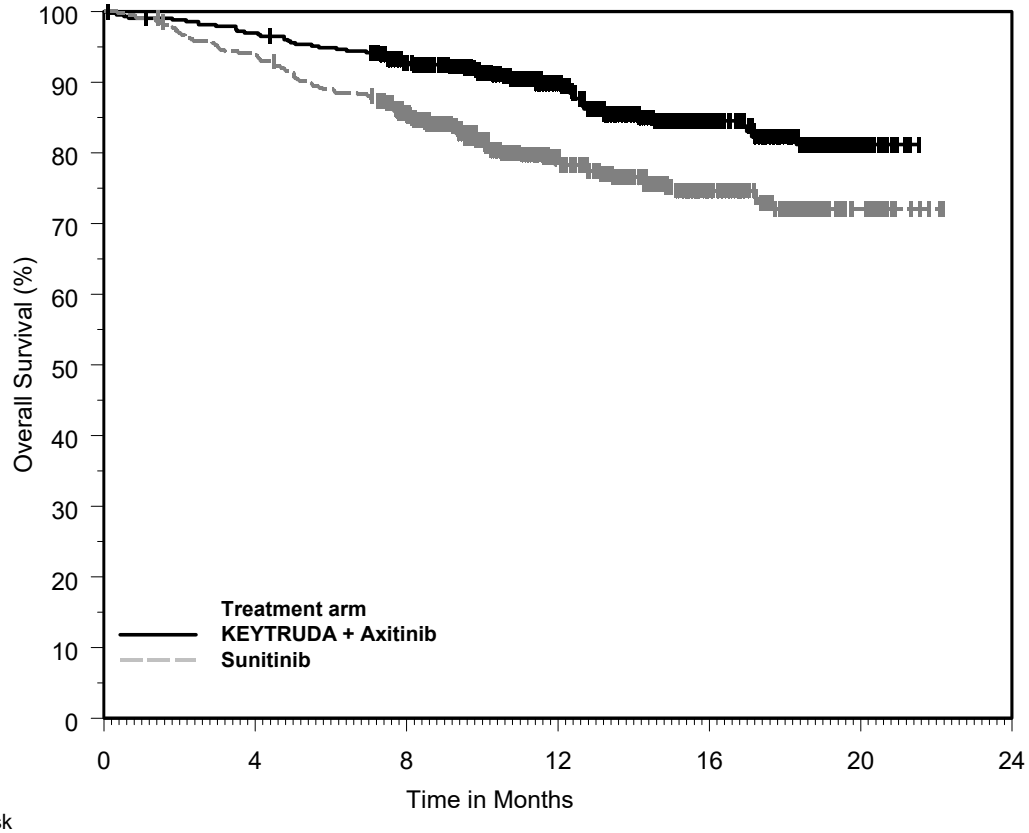
The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR, as assessed by BICR. A statistically significant improvement 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 66 and Figure 16 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 66: 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%)	213 (50%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.0 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.56, 0.84)	
p-Value†	0.0001§	
Objective Response Rate		
ORR¶ (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).
¶ Response: Best objective response as confirmed complete response or partial response
# Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region
NR = not reached

Figure 16: 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

14.16 Endometrial Carcinoma

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-146 (NCT02501096), a single-arm, multicenter, open-label, multi-cohort trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients were treated with KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily until unacceptable toxicity or disease progression as determined by the investigator. The major efficacy outcome measures were ORR and DoR as assessed by BICR using RECIST 1.1.

Administration of KEYTRUDA and lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA dosing was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 6 weeks until week 24, followed by every 9 weeks thereafter.

Among the 108 patients, 87% (n=94) had tumors that were not MSI-H or dMMR, 10% (n=11) had tumors that were MSI-H or dMMR, and in 3% (n=3) the status was not known. Tumor MSI status was determined using a polymerase chain reaction (PCR) test. Tumor MMR status was determined using an IHC test. The baseline characteristics of the 94 patients with tumors that were not MSI-H or dMMR were: median age of 66 years, 62% age 65 or older; 86% White, 6% Black, 4% Asian, and 3% other races; and ECOG PS of 0 (52%) or 1 (48%). All 94 of these patients received prior systemic therapy for endometrial carcinoma: 51% had one, 38% had two, and 11% had three or more prior systemic therapies.

Efficacy results are summarized in Table 67.

Table 67: Efficacy Results in KEYNOTE-146

Endpoint	KEYTRUDA 200 mg every 3 weeks with lenvatinib n=94*
Objective Response Rate	
ORR (95% CI)	38.3% (29, 49)
Complete response rate	10.6%
Partial response rate	27.7%
Response duration	
Median in months (range)	NR (1.2+, 33.1+)†
% with duration ≥6 months	69%

* Median follow-up time of 18.7 months
† Based on patients (n=36) with a response by independent review
\+ Denotes ongoing response
NR = not reached

14.17 Tumor Mutational Burden-High Cancer

The efficacy of KEYTRUDA was investigated in a prospectively-planned retrospective analysis of 10 cohorts (A through J) of patients with various previously treated unresectable or metastatic solid tumors with high tumor mutation burden (TMB-H) who were enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). The trial excluded patients who previously received an anti-PD-1 or other immune-modulating monoclonal antibody, or who had an 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. Assessment of tumor status was performed every 9 weeks for the first 12 months and every 12 weeks thereafter.

The statistical analysis plan pre-specified ≥10 and ≥13 mutations per megabase using the FoundationOne CDx assay as cutpoints to assess TMB. Testing of TMB was blinded with respect to clinical outcomes. The major efficacy outcome measures were ORR and DoR in patients who received at least one dose of KEYTRUDA 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 KEYNOTE-158, 1050 patients were included in the efficacy analysis population. TMB was analyzed in the subset of 790 patients with sufficient tissue for testing based on protocol-specified testing requirements. Of the 790 patients, 102 (13%) had tumors identified as TMB-H, defined as TMB ≥10 mutations per megabase. Among the 102 patients with TMB-H advanced solid tumors, the study population characteristics were: median age of 61 years (range: 27 to 80), 34% age 65 or older; 34% male; 81% White; and 41% ECOG PS of 0 and 58% ECOG PS of 1. Fifty-six percent of patients had at least two prior lines of therapy.

Efficacy results are summarized in Tables 68 and 69.

Table 68: Efficacy Results for Patients with TMB-H Cancer in KEYNOTE-158

Endpoint	KEYTRUDA 200 mg every 3 weeks	
	TMB ≥10 mut/Mb n=102*	TMB ≥13 mut/Mb n=70
Objective Response Rate		
ORR (95% CI)	29% (21, 39)	37% (26, 50)
Complete response rate	4%	3%
Partial response rate	25%	34%
Duration of Response	n=30	n=26
Median in months (range)†	NR (2.2+, 34.8+)	NR (2.2+, 34.8+)
% with duration ≥12 months	57%	58%
% with duration ≥24 months	50%	50%

* Median follow-up time of 11.1 months
† From product-limit (Kaplan-Meier) method for censored data
\+ Denotes ongoing response
NR = not reached

Table 69: Response by Tumor Type (TMB ≥10 mut/Mb)

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
Overall*	102	30 (29%)	(21%, 39%)	(2.2+, 34.8+)
Small cell lung cancer	34	10 (29%)	(15%, 47%)	(4.1, 32.5+)
Cervical cancer	16	5 (31%)	(11%, 59%)	(3.7+, 34.8+)
Endometrial cancer	15	7 (47%)	(21%, 73%)	(8.4+, 33.9+)
Anal cancer	14	1 (7%)	(0.2%, 34%)	18.8+
Vulvar cancer	12	2 (17%)	(2%, 48%)	(8.8, 11.0)
Neuroendocrine cancer	5	2 (40%)	(5%, 85%)	(2.2+, 32.6+)
Salivary cancer	3	PR, SD, PD		31.3+
Thyroid cancer	2	CR, CR		(8.2, 33.2+)
Mesothelioma cancer	1	PD		

* No TMB-H patients were identified in the cholangiocarcinoma cohort
CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

In an exploratory analysis in 32 patients enrolled in KEYNOTE-158 whose cancer had TMB ≥10 mut/Mb and <13 mut/Mb, the ORR was 13% (95% CI: 4%, 29%), including two complete responses and two partial responses.

14.18 Cutaneous Squamous Cell Carcinoma

The efficacy of KEYTRUDA was investigated in patients with recurrent or metastatic cSCC enrolled in KEYNOTE-629 (NCT03284424), a multicenter, multi-cohort, non-randomized, open-label 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 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, rapidly progressive, required urgent intervention, or occurred with a decline in performance status.

Assessment of tumor status was performed every 6 weeks during the first year, and every 9 weeks during the second year. 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.

Among the 105 patients treated, the study population characteristics were: median age of 72 years (range: 29 to 95), 71% age 65 or older; 76% male; 71% White, 25% race unknown; 34% ECOG PS of 0 and 66% ECOG PS of 1. Forty-five percent of patients had locally recurrent only cSCC, 24% had

metastatic only cSCC, and 31% had both locally recurrent and metastatic cSCC. Eighty-seven percent received one or more prior lines of therapy; 74% received prior radiation therapy.

Efficacy results are summarized in Table 70.

Table 70: Efficacy Results in KEYNOTE-629

Endpoint	KEYTRUDA n=105
Objective Response Rate	
ORR (95% CI)	34% (25, 44)
Complete response rate	4%
Partial response rate	31%
Duration of Response*	n=36
Median in months (range)	NR (2.7, 13.1+)†
% with duration ≥6 months	69%

* Median follow-up time of 9.5 months
† Based on patients (n=36) with a confirmed response by independent review
\+ Denotes ongoing response

14.19 Triple-Negative Breast Cancer

The efficacy of KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355 (NCT02819518), a multicenter, double-blind, randomized, placebo-controlled trial conducted in 847 patients with locally recurrent unresectable or metastatic TNBC, regardless of tumor PD-L1 expression, who had not been previously treated with chemotherapy in the metastatic setting. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by chemotherapy treatment (paclitaxel or paclitaxel protein-bound vs. gemcitabine and carboplatin), tumor PD-L1 expression (CPS ≥1 vs. CPS <1) according to the PD-L1 IHC 22C3 pharmDx kit, and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no).

Patients were randomized (2:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg on Day 1 every 3 weeks in combination with paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.
- Placebo on Day 1 every 3 weeks in combination with paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Assessment of tumor status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter. 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 tested in the subgroup of patients with CPS ≥10. Additional efficacy outcome measures were OS as well as ORR and DoR as assessed by BICR.

The study population characteristics for patients were: median age of 53 years (range: 22 to 85), 21% age 65 or older; 100% female; 68% White, 21% Asian, and 4% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1; and 68% were post-menopausal status. Seventy-five percent of patients had tumor PD-L1 expression CPS ≥1 and 38% had tumor PD-L1 expression CPS ≥10.

Table 71 and Figure 17 summarize the efficacy results for KEYNOTE-355.

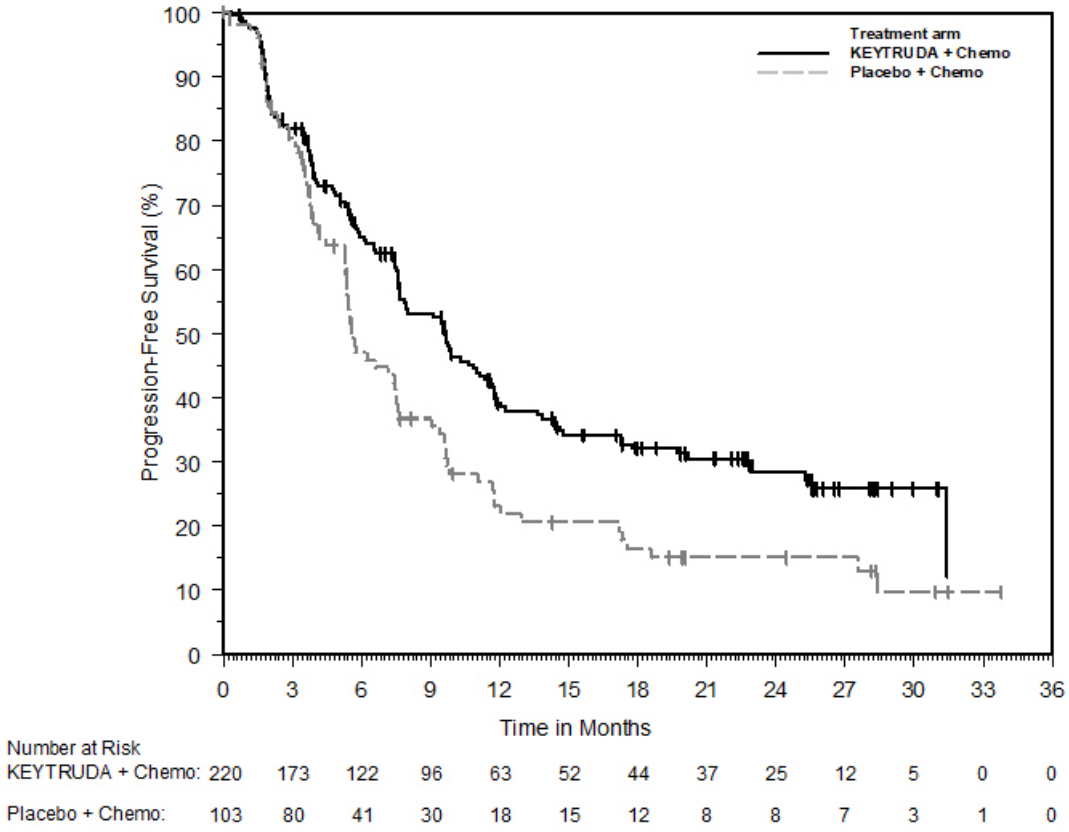
Table 71: Efficacy Results in KEYNOTE-355 (CPS ≥10)

Endpoint	KEYTRUDA 200 mg every 3 weeks with chemotherapy n=220	Placebo every 3 weeks with chemotherapy n=103
PFS		
Number of patients with event (%)	136 (62%)	79 (77%)
Median in months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
Hazard ratio* (95% CI)	0.65 (0.49, 0.86)	
p-Value†	0.0012	
ORR		
Objective confirmed response rate (95% CI)	53% (46, 60)	40% (30, 50)
Complete response rate	17%	13%
Partial response rate	36%	27%
DoR		
Median in months (95% CI)	19.3 (9.9, 29.8)	7.3 (5.3, 15.8)

* Based on stratified Cox regression model

† One-sided p-Value based on stratified log-rank test

Figure 17: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-355 (CPS ≥10)



14.20 Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

The efficacy and safety of KEYTRUDA using a dosage of 400 mg every 6 weeks for all approved adult indications was primarily based on the modeling of dose/exposure efficacy and safety relationships and observed pharmacokinetic data in patients with melanoma *[see Clinical Pharmacology (12.2)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 (5.1)]*.
  - Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
  - Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, or Type 1 diabetes mellitus *[see Warnings and Precautions (5.1)]*.
  - Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.1)]*.
  - 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 (5.1)]*.
  - 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 or worsening signs or symptoms *[see Warnings and Precautions (5.1)]*.
    - 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 (5.1)]*.

Infusion-Related Reactions

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT

- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.3)].*

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 (5.5), 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 (5.5), 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 (5.1)]*.

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uspi-mk3475-iv-2103r042

MEDICATION GUIDE
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. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any new or worsening signs or symptoms, including:

Lung problems

- cough
- shortness of breath
- chest pain

Intestinal problems

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Hormone gland problems

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Skin problems

- rash
- itching
- skin blistering or peeling
- painful sores or ulcers in your mouth or in your nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with KEYTRUDA. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:

- chest pain, irregular heartbeat, shortness of breath, swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

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

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

Rejection of a transplanted organ. Your healthcare provider 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 serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with KEYTRUDA. Your healthcare provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious.
Your healthcare provider will check you for these problems during treatment with KEYTRUDA. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider 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 when:
    - your cHL has returned **or**
    - you have tried a treatment and it did not work, **or**
  - in children when:
    - you have tried a treatment and it did not work **or**

        - your cHL has returned after you received 2 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 cancer has not spread to nearby tissue in the bladder, but is at high-risk for spreading (high-risk non-muscle-invasive bladder cancer [NMIBC]) when:
        - your tumor is a type called "carcinoma in situ" (CIS), **and**
        - you have tried treatment with Bacillus Calmette-Guerin (BCG) and it did not work, **and**
        - you are not able to or have decided not to have surgery to remove your bladder.
    - 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 cancer called colon or rectal cancer. KEYTRUDA may be used as your first treatment when your cancer:
    - has spread or cannot be removed by surgery (advanced colon or rectal cancer), **and**
    - has been shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).
- 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 esophageal or certain gastroesophageal junction (GEJ) carcinomas that cannot be cured by surgery or a combination of chemotherapy and radiation therapy.
    - KEYTRUDA may be used with platinum- and fluoropyrimidine- based chemotherapy medicines.
    - KEYTRUDA may be used alone when:
        - you have received one or more types of treatment, and it did not work or it is no longer working, **and**
        - your tumor is a type called "squamous", **and**
        - your tumor tests positive for "PD-L1".
- 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).
- a kind of uterine cancer called endometrial carcinoma. KEYTRUDA may be used with the medicine lenvatinib:
    - when your tumors are not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), **and**
    - you have received anti-cancer treatment, and it did not work or is no longer working, **and**
    - your cancer cannot be cured by surgery or radiation (advanced endometrial carcinoma).
- a kind of cancer that is shown by a test to be tumor mutational burden-high (TMB-H). KEYTRUDA may be used in adults and children to treat:
    - solid tumors that have spread or cannot be removed by surgery (advanced cancer), **and**
    - you have received anti-cancer treatment, and it did not work or is no longer working, **and**
    - you have no satisfactory treatment options.

It is not known if KEYTRUDA is safe and effective in children with TMB-H cancers of the brain or spinal cord (central nervous system cancers).

- a kind of skin cancer called cutaneous squamous cell carcinoma (cSCC). KEYTRUDA may be used when your skin cancer:
  - has returned or spread, **and**
  - cannot be cured by surgery or radiation.
- a kind of cancer called triple-negative breast cancer (TNBC). KEYTRUDA may be used with chemotherapy medicines when your breast cancer:
  - has returned and cannot be removed by surgery or has spread, **and**
  - tests positive for "PD-L1".

Before receiving KEYTRUDA, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. KEYTRUDA can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider 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 healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider 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 healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive KEYTRUDA?

- Your healthcare provider will give you KEYTRUDA into your vein through an intravenous (IV) line over 30 minutes.
- In adults, KEYTRUDA is usually given every 3 weeks or 6 weeks depending on the dose of KEYTRUDA that you are receiving.
- In children, KEYTRUDA is usually given every 3 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider 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.

Side effects of KEYTRUDA when used alone that are more common in children than in adults include: fever, vomiting, upper respiratory tract infection, headache, and low levels of white blood cells and red blood cells (anemia).

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, mouth sores, headache, and weight loss.

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.

Common side effects of KEYTRUDA when given with lenvatinib include: feeling tired, high blood pressure, joint and muscle pain, diarrhea, decreased appetite, low levels of thyroid hormone, nausea, mouth sores, vomiting, weight loss, stomach-area (abdominal) pain, headache, constipation, urinary tract infection, hoarseness, bleeding, low magnesium level, blisters or rash on the palms of your hands and soles of your feet, shortness of breath, cough, and rash.

These are not all the possible side effects of KEYTRUDA.

Call your healthcare provider 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. You can ask your pharmacist or healthcare provider for information about KEYTRUDA that is written for health professionals.

What are the ingredients in KEYTRUDA?

Active ingredient: pembrolizumab

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

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

U.S. License No. 0002

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

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usmg-mk3475-iv-2103r037

For more information, go to www.keytruda.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: March 2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s096

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-disciplinary Review and Evaluation

FDA review was conducted in conjunction with other regulatory authorities under a modified ORBIS. While the application review is completed by the FDA, the application is still under review at the other regulatory agencies (Health Canada, Therapeutic Goods Administration, and Swissmedic).

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 or the other Regulatory Authorities.

Application Type	Supplemental BLA
Application Number(s)	125514/S-096
Priority or Standard	Priority
Submit Date(s)	October 13, 2020
Received Date(s)	October 13, 2020
PDUFA Goal Date	April 13, 2021
Division/Office	Division of Oncology 3/Office of Oncologic Diseases
Review Completion Date	Refer to electronic signature stamp date
Established Name	Pembrolizumab
(Proposed) Trade Name	Keytruda
Pharmacologic Class	Programmed death 1(PD-1) receptor blocking antibody
Code name	MK-3475
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Formulation(s)	100 mg/4 mL (25 mL) solution in a single-dose vial
Dosing Regimen	200 mg every 3 weeks or 400 mg every 6 weeks
Applicant Proposed Indication(s)/Population(s	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Pembrolizumab is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation, in combination with platinum- and fluoropyrimidine-based chemotherapy.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Leah S. Her, M.S., P.M.P.
Clinical Reviewer	Leigh Marcus, M.D.
Clinical Team Leader	Sandra J. Casak, M.D.
Safety Analyst (if applicable)	Peter Schotland, Ph.D.
Statistical Reviewer	Arup Sinha, Ph.D.
Statistical Team Leader	Pallavi Mishra-Kalyani, Ph.D.
Associate Director for Labeling (ADL)	William Pierce, Pharm.D.
Cross-Disciplinary Team Leader	Sandra J. Casak, M.D.
Division Director (OB)	Shenghui Tang, Ph.D.
Division Director (OOD)	Steven Lemery, M.D., M.H.S.
Office Director (or designated signatory authority)	N/A

Additional Reviewers of Application

OPDP	Adesola Adejuwon, Pharm.D., M.B.A.
DMPP	Sharon Mills, B.S.N., R.N., C.C.R.P.

OPDP=Office of Prescription Drug Promotion; DMPP = Division of Medical Policy

Project Orbis Participants

Health Canada Review Team

(b) (6)

Therapeutic Goods Administration Review Team

(b) (6)

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Swissmedic Review Team

	(b) (6)

Glossary

5-FU	5-fluorouracil
AC	advisory committee
ADA	antidrug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEOSI	adverse event of special interest
ALT	alanine aminotransferase
ASaT	all-subjects-as-treated
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BICR	blinded independent central review
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COA	Clinical Outcome Assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPS	combined proportion score
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report

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CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
DEPI	Division of Epidemiology
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DMF	Drug Master File
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
DRISK	Division of Risk Management
EAC	esophageal adenocarcinoma
EC	esophageal cancer
ECG	electrocardiogram
ECI	event of clinical interest
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCTD	electronic common technical document
EGJ	esophagogastric junction
EOC	Executive Oversight Committee
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life in Cancer Patients Core Questionnaire
EORTC QLQ-OES18	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal Cancer Module
EQ-5D-5L	European Quality of Life 5 Dimension 5 Level
ERC	ethical review committee
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
GEJ	gastroesophageal junction
GEP	gastroenteropancreatic
GLP	good laboratory practice
GRMP	good review management practice
HA	health authority
HCC	hepatocellular carcinoma
HGRAC	Human Genetic Resources Administration of China
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRQoL	health-related quality of life

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IA	interim analysis
ICH	International Conference on Harmonization
IEC	independent ethics committee
IND	Investigational New Drug
IRB	independent review board
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
IVRS/IWRS	interactive voice response system/interactive web response system
mAb	monoclonal antibody(ies)
MARRS	Merck Adverse Event Reporting and Review System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRL QA	Merck Research Laboratories Quality Assurance
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
OCE	Oncology Center of Excellence
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death 1 ligand 1
PD-L2	programmed cell death 1 ligand 2
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMBCL	primary mediastinal B-cell lymphoma
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol

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PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PSUR	Periodic Safety Update report
QA	quality assurance
QC	quality control
Q3W	every 3 weeks
Q4W	every 4 weeks
Q9W	every 9 weeks
QoL	quality of life
QTc	corrected QT interval
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
REMS	risk evaluation and mitigation strategy
RNA	ribonucleic acid
ROW	rest of the world
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental biologics license application
SCC	squamous cell carcinoma
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TPS	tumor proportion score
US	United States
VAS	visual analogue scale

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Reference ID: 4766028

1 Executive Summary

1.1 Product Introduction

Pembrolizumab is a humanized monoclonal antibody of the IgG4/kappa (IgG4κ) isotype that binds to the programmed death 1 (PD-1) receptor and directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, releasing the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Pembrolizumab is supplied as a lyophilized powder in single-use vials for reconstitution and as a 100 mg liquid in single-use vials.

FDA first approved pembrolizumab on September 14, 2014. Prior to action on this supplement, pembrolizumab as a single agent or in combination was approved for various lines of treatment and subsets of patients with melanoma, non-small cell lung cancer, small cell lung cancer, head and neck squamous cell carcinoma, Hodgkin lymphoma, primary mediastinal B cell lymphoma, urothelial carcinoma, microsatellite instability-high (MSI-H) cancer, MSI-H colorectal cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, endometrial carcinoma, tumor mutation burden-high (TMB-H cancers), and cutaneous squamous cell carcinoma.

Pembrolizumab is administered intravenously (IV) over 30 minutes. The approved dosages for pembrolizumab are 200 mg every 3 weeks (Q3W), 400 mg every 6 weeks (Q6W), or 2 mg/kg Q3W in pediatric patients.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The study supporting this sBLA is KEYNOTE-590 (KN590), an international, open-label, randomized (1:1), double-blind, placebo-controlled trial in patients with previously untreated metastatic or locally advanced esophageal carcinoma (including tumors with epicenter 1 to 5 centimeters above the gastroesophageal junction) receiving standard of care treatment with 5-fluorouracil combined with cisplatin with pembrolizumab or placebo. Patients who were candidates for surgical resection or definitive chemoradiation; active central nervous system metastases or carcinomatous meningitis; active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. non-Asia), and ECOG performance status (0 vs. 1).

Patients were randomized in a 1:1 ratio to receive either pembrolizumab 200 mg or saline placebo intravenous (IV) every 3 weeks (Q3W), both combined with cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil (5-FU) 800 mg/m^2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4000 mg/m^2 per 3-week cycle). A total of 749 patients were randomized, 373 patients

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into the pembrolizumab arm and 376 patients into the placebo arm. The primary endpoints of the trial were progression-free survival (PFS) per RECIST v1.1 (modified to allow a maximum of 10 target lesions in total and 5 per organ) as assessed by the investigator (INV), and overall survival (OS). The study pre-specified analyses of OS and PFS based on histology, CPS ≥10, and in all patients. Additional efficacy outcome measures were overall response rate (ORR) and duration of response (DoR), according to modified RECIST v1.1, assessed by INV.

All pre-specified analyses of Study KN590 included in the statistical plan for which type I error and hierarchical testing were specified were determined to be statistically significant. In the overall population (n: 749), pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. The OS HR was 0.73 (95% CI: 0.62, 0.0.86; *p*<0.0001) with a median OS of 12.4 months (95% CI: 10.5, 14.0) in the pembrolizumab arm and 9.8 months (95% CI: 8.8, 10.8) for the placebo arm. The PFS HR was 0.65 (95% CI: 0.55, 0.76; *p*<0.0001) with a median PFS was 6.3 months (95% CI: 6.2, 6.9) in the pembrolizumab arm and 5.8 months (95% CI: 5.0, 6.0) in the placebo arm. Similarly, clinically meaningful and statistically significant improvements in OS were observed with administration of pembrolizumab in patients with esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 CPS ≥10 (n: 286) (HR 0.57; 95% CI: 0.43, 0.75; *p*<0.0001), and patients whose tumors express PD-L1 CPS ≥10 (n: 383), (HR 0.62; 95% CI: 0.49, 0.78; *p*<0.0001), patients with ESCC (n: 548), (HR 0.72; 95% CI: 0.60, 0.88; *p*=0.0006). PFS testing crossed the statistical significance boundary in these analyses too and confirmed the robustness of the study results, a finding consistent with similar results in secondary endpoints.

Of note, in exploratory subsets analyses in patients with PD-L1 CPS < 10 (n: 347), the HR was 0.86 (95% CI: 0.68, 1.10); in patients with adenocarcinoma (n: 201), the HR was 0.74 (95% CI 0.54, 1.02). To better inform prescribers, results in patients with PD-L1 CPS <10 were included in labeling.

The submitted evidence meets the statutory evidentiary standard for regular approval of pembrolizumab (b) (4)

(b) (4)

(b) (4) The observed improvement in survival the overall population with a HR of 0.73 and PFS, with an HR of 0.65, is statistically robust and clinically meaningful. This finding is supported by consistent results on secondary endpoints.

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1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Pembrolizumab is a monoclonal antibody that binds to programmed-death receptor 1 (PD-1) and blocks its interactions with both its ligands. This releases the PD-1/PD-L1-mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity. There is extensive clinical experience with pembrolizumab, which is approved by the FDA for multiple indications, either alone or in combination with other drugs including the indication 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.

The safety and effectiveness of pembrolizumab for the treatment o [redacted] (b) (4) was established by the results of a single multicenter, international, open-label, active-controlled randomized trial, Study KEYNOTE 590 (KN590). PD-L1 status was centrally determined in tumor specimens in all patients using the PD-L1 IHC 22C3 pharmDx kit. Patients with active autoimmune disease, a medical condition that required immunosuppression, or who received prior systemic therapy in the locally advanced or metastatic setting were ineligible. Randomization was stratified by tumor histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- Pembrolizumab 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.

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Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression. Patients could be treated with pembrolizumab for up to 24 months in the absence of disease progression. The major efficacy outcome measures were OS and PFS as assessed by the investigator 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 pre-specified analyses of OS and PFS based on histology (ESCC), CPS ≥10, and in all patients. Additional efficacy outcome measures were ORR and DoR, according to modified RECIST v1.1, as assessed by the investigator.

A total of 749 patients were randomized (373 and 376 patients to the pembrolizumab and placebo arms respectively); 370 patients received pembrolizumab 200 mg IV every 3 weeks and chemotherapy, while 370 patients received SOC treatment. The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 63 years (range: 27 to 94), 43% age 65 or older; 83% male; 37% White, 53% Asian, and 1% Black; 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. Ninety-one percent had M1 disease and 9% had M0 disease. Seventy-three percent had a tumor histology of squamous cell carcinoma, and 27% had adenocarcinoma.

The major efficacy outcome measures were OS and INV-PFS for patients randomized to pembrolizumab in combination with chemotherapy, compared to chemotherapy. In the overall population (n: 749), pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. The OS HR was 0.73 (95% CI: 0.62, 0.0.86; p<0.0001) with a median OS of 12.4 months (95% CI: 10.5, 14.0) in the pembrolizumab arm and 9.8 months (95% CI: 8.8, 10.8) for the placebo arm. The PFS HR was 0.65 (95% CI: 0.55, 0.76; p<0.0001) with a median PFS was 6.3 months (95% CI: 6.2, 6.9) in the pembrolizumab arm and 5.8 months (95% CI: 5.0, 6.0) in the placebo arm. Secondary endpoints, subgroup analyses, and sensitivity analyses were consistent with results of PFS and OS, and confirmed the robustness of the study results. All pre-specified analyses of Study KN590 were statistically significant.

In patients with esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 CPS ≥10 (n: 286), pembrolizumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in OS compared with chemotherapy with a HR of 0.57 (95% CI: 0.43, 0.75; p<0.0001) and a median OS of 13.9 months (95% CI: 11.1, 17.7) in the pembrolizumab arm and 8.8 months (95% CI: 7.8, 10.5) in the placebo arm. The PFS HR was 0.53 (95% CI: 0.40, 0.69), with a median PFS of 7.3 months (95% CI: 6.2, 8.2) for the pembrolizumab arm and 5.4 months (95% CI: 4.2, 6.0) for the placebo group.

In patients whose tumors express PD-L1 CPS ≥10 (n: 383, irrespective of histology), pembrolizumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. The OS HR was 0.62 (95% CI: 0.49, 0.78; p<0.0001), with

a median OS was 13.5 months (95% CI: 11.1, 15.6) in the pembrolizumab arm and 9.4 months (95% CI: 8.0, 10.7) in the placebo arm. The PFS HR was 0.51 (95% CI: 0.41, 0.65; *p*<0.0001) with a median PFS of 7.5 months (95% CI: 6.2, 8.2) for the pembrolizumab arm and 5.5 months (95% CI: 4.3, 6.0) in the placebo arm.

In patients with ESCC (n: 548), pembrolizumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. The OS HR was 0.72 (95% CI: 0.60, 0.88; *p*=0.0006) with a median OS of 12.6 months (95% CI: 10.2, 14.3) in the pembrolizumab arm and 9.8 months (95% CI: 8.6, 11.1) in the placebo arm.

In exploratory analyses, the review team evaluated the effect of the addition of pembrolizumab to standard of care chemotherapy in the subpopulation of patients with CPS <10. In patients with PD-L1 CPS < 10 (n=347), the median OS was 10.5 months (95% CI: 9.7, 13.5) for the pembrolizumab arm and 10.6 months (95% CI: 8.8, 12.0) for the placebo arm, with a HR of 0.86 (95% CI: 0.68, 1.10). While the estimation of treatment effect on OS endpoint in patients with PD-L1 CPS < 10 was numerically in the same direction and supportive of the OS results in PD-L1 CPS ≥ 10 and in the ITT population, the upper limit of the 95% CI of the estimate of OS HR in patients with PD-L1 CPS < 10 exceeded 1.0. This information was included in labeling to better support treatment decision. In an exploratory analysis of the effect of pembrolizumab in addition to chemotherapy in patients with adenocarcinoma (n=201, 72 randomized to pembrolizumab/chemotherapy and 99 to placebo/chemotherapy), the HR was 0.74 (95% CI 0.54; 1.02); the effect size in this subset appears to be similar to the ITT population, although the upper boundary of the 95% CI crosses 1.

The adverse reaction profile observed in patients receiving pembrolizumab in Study KN590 is consistent with the known pembrolizumab safety profile. Pembrolizumab was discontinued due to adverse events (AEs) in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of pembrolizumab (≥1%) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). Adverse reactions leading to interruption of pembrolizumab occurred in 67% of patients. The most common adverse reactions leading to interruption of pembrolizumab (≥2%) were neutropenia (19%), fatigue/asthenia (8%), decreased white blood cell count (5%), pneumonia (5%), decreased appetite (4.3%), anemia (3.2%), increased blood creatinine (3.2%), stomatitis (3.2%), malaise (3.0%), thrombocytopenia (3%), pneumonitis (2.7%), diarrhea (2.4%), dysphagia (2.2%), and nausea (2.2%).

The review team concluded that the overall risk:benefit assessment favored approval of pembrolizumab for the treatmen (b) (4)
(b) (4)
(b) (4) The demonstrated improvement in PFS and survival for patients

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randomized to pembrolizumab in combination with chemotherapy compared to patients randomized to placebo in combination with chemotherapy is clinically meaningful, statistically significant, and supported by subgroup analyses in Study KN590. The efficacy results in various subgroups of patients by histology and PD-L1 status were directionally consistent with the results in the ITT population, which supported the benefit risk decision for the overall population. The adverse reaction profile observed in patients receiving pembrolizumab is consistent with the adverse reaction profiles observed in prior studies and the disease setting. The most common adverse events in Study KN590 were anemia, neutropenia, nausea, fatigue/asthenia, hyperglycemia, hyponatremia, decreased appetite, thrombocytopenia, constipation, diarrhea, vomiting, stomatitis, and weight loss; however, the incidence of these events were similar between arms and the only difference of ≥ 5% was for fatigue and decreased appetite. The rate of immune-related adverse events was consistent with the known incidence for pembrolizumab. These risks are largely manageable with patient surveillance, treatment delays, and supportive care in most patients. The risks of pembrolizumab are acceptable considering the life-threatening nature of metastatic or locally advanced esophageal carcinoma. The approval of this application will likely result in the change in the standard of care for patients with treatment naïve metastatic or locally advanced esophageal carcinoma.

The application was reviewed under Project Orbis, RTOR, and the Assessment Aid.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Metastatic or locally advanced esophageal or gastroesophageal junction (GEJ) carcinoma is a serious disease with a poor prognosis. Patients with advanced disease not amenable to locoregional therapy or metastatic esophageal/GEJ cancer are treated with palliative chemotherapy. Esophageal cancer is the sixth most common cancer worldwide, with an estimated 450,000 deaths per year (Shah M, 2020); 18,440 new cases are expected in the US in 2021, and 16.170 patients are expected to die from the disease (SEER database). Median survival for patients with metastatic disease is less than a year.	Metastatic or locally advanced esophageal carcinoma is a serious, life-threatening disease with poor prognosis.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	There are 2 distinct histologic types of esophageal carcinoma: squamous cell carcinoma and adenocarcinoma. Globally, 90% patients have squamous cell histologies but the incidence of adenocarcinoma is higher in the Western world.	
Current Treatment Options	Multimodality therapy is generally offered to patients with locally advanced esophageal carcinoma (surgery, ablation, radiation, or chemoradiotherapy). For patients with locally advanced disease who are not candidates for these therapies and patients with metastatic disease, treatment options are limited to palliative chemotherapy. Combination regimens are generally used and some of the standard combinations most frequently used in the US include fluoropyrimidine and platinum agents. Selection of a regimen for a particular patient is based on the patient's general status, preferences, toxicity, institutional standards, etc. The study supporting this approval is an add-on regimen; patients will continue to receive standard of care treatment.	Although standard of care chemotherapy improves survival in patients with advanced unresectable or metastatic esophageal or GEJ carcinoma, there is a need for more effective treatment.
Benefit	The approval is supported by a single Study, KEYNOTE-590 (KN590). KN590 is an international, double-blind, placebo-controlled randomized trial in patients with metastatic or locally advanced esophageal or GEJ carcinoma who are not candidates for definitive chemoradiation and who have not received prior systemic therapy. Patients were randomized (1:1) to receive either pembrolizumab or placebo; all patients received combination therapy with fluorouracil and cisplatin. Treatment was administered until disease progression or intolerable	The submitted evidence meets the statutory evidentiary standard for approval. Results of a well-controlled randomized study showed a statistically significant and clinically meaningful improvement in survival and progression-free survival among patients who received chemotherapy in combination with pembrolizumab compared to those who

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	toxicity. A total of 749 patients were randomized, 373 to the pembrolizumab arm and 376 to placebo arm. The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The major efficacy outcome measures were investigator-assessed progression free survival (PFS) per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and overall survival (OS). The statistical plan included hierarchical testing for the intent-to-treat population, squamous cell carcinoma with PL-1 CPS ≥ 10, CPS ≥ 10 irrespective of histology, and squamous cell carcinoma irrespective of PD-L1 expression. Secondary endpoints included overall response rate (ORR) and duration of response (DOR). In the ITT population, the HR for OS was 0.73 (95% CI 0.62, 0.86; p-value < 0.0001) favoring the pembrolizumab arm. Median OS was 12.4 months. (95% CI 10.5, 14) in the pembrolizumab arm and 9.8 months (95% CI 8.8, 10.8) in the control arm. The HR for PFS was 0.65 (95% CI 0.55, 0.76; p-value < 0.0001) favoring the pembrolizumab arm. Median PFS was 6.3 months (95% CI 6.2, 6.9) in the pembrolizumab arm and 5.8 months (95% CI 5, 6) in the control arm. All prespecified analyses in the above described subpopulations were statistically significant and clinically meaningful for OS with HR of HR 0.57 (95% CI: 0.43, 0.75; p<0.0001) in patients with esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 CPS ≥10 subpopulation (n: 286), HR 0.62 (95% CI: 0.49, 0.78; p<0.0001) in patients whose tumors express PD-L1 CPS ≥10 (n: 383), and HR 0.72 (95% CI: 0.60, 0.88; p=0.0006) in patients	received placebo with chemotherapy in Study KN590. These results were consistent across predefined subgroups and secondary endpoints. Based on exploratory analyses, there is insufficient data to properly characterize the effect of pembrolizumab when added to chemotherapy for the treatment of patients with adenocarcinoma or PD-L1 CPS <10. Pembrolizumab is approved (under the accelerated approval pathway) in the refractory setting in patients with CPS ≥ 10. To inform prescribers of the observed effect in patients with PD-L1 CPS<10, data has been described in the label.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with ESCC (n: 548). PFS testing crossed the statistical significance boundary in these analyses too and confirmed the robustness of the study results, a finding consistent with similar results in secondary endpoints. In exploratory analyses, the observed benefit of the addition of pembrolizumab to chemotherapy for patients with adenocarcinoma (n=201,OS HR = 0.74,95% CI 0.54, 1.02) and patients with PD-L1 CPS < 10 (n=347 OS HR = 0.86, 95% CI: 0.68, 1.10) was smaller in magnitude but in the same direction as the treatment effect on the overall population.	
Risk and Risk Management	The observed safety profile of pembrolizumab in patients with metastatic or unresectable esophageal carcinoma patients who are not candidates for definitive chemoradiotherapy was consistent with the established safety profile of pembrolizumab in patients with other types of cancer. The addition of pembrolizumab to chemotherapy was well tolerated and the only clinically meaningful increase in toxicity was related to immune related adverse reactions. The primary risks of pembrolizumab are immune-mediated adverse reactions and infusion-related reactions; these events were observed in 27% and 12% patients in the pembrolizumab and placebo arms respectively. The most common immune-related AEs were hypothyroidism (11% vs 7% in the pembrolizumab and placebo arms respectively), hyperthyroidism (5.4% vs. 0.8% in the pembrolizumab and placebo arms respectively), and pneumonitis (6% vs. 0.5% in the	The toxicity profile of pembrolizumab is acceptable when assessed in the context of the life-threatening nature of advanced unresectable or metastatic esophageal or GEJ cancer. No new significant safety concerns were identified during review of this supplemental application that would require a new risk management plan, including a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of pembrolizumab. Significant and serious adverse reactions for pembrolizumab are predictable based on the antibody mechanism of action and well-known toxicity profiles.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pembrolizumab and placebo arms respectively). The addition of pembrolizumab to chemotherapy in the setting of treatment of patients with advanced or metastatic esophageal/GEJ cancer who are not candidates to definitive chemoradiotherapy does not appear to significantly increase the toxicity of the backbone therapy and is within the expected range of toxicity for pembrolizumab when compared with historical data.	These risks are adequately addressed in product labeling, and oncologists who treat patients with mCRC are well-trained in the monitoring and treatment of these adverse reactions. The review team determined that standard postmarketing surveillance would be sufficient for continued assessment of the safety of pembrolizumab in patients with esophageal or GEJ cancer.

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
	X	Clinical outcome assessment (COA) data, such as			Section 11.1.2.3
			X	Patient reported outcome (PRO)	Sections 11.1.2.3.1, 11.1.2.3.2, and 11.1.2.3.3
			□	Observer reported outcome (ObsRO)	

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	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Sandra Casak
Cross-Disciplinary Team Leader

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2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

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 2020, 18,440 new cases of EC will be diagnosed and 16,170 people will die of their disease. The 5-year survival rate for advanced/metastatic EC is 5% [2]. While SCC is the most common subtype of esophageal cancer globally (84% of all cases) with the highest incidence rates in Eastern Asia and Eastern Africa, adenocarcinoma is the most common subtype in high-income countries, with the highest incidence rates in Northern Europe, North America, and Oceania [3].

The FDA's Assessment:
In the U.S., based on data from the Surveillance, Epidemiology, and End Results (SEER), new cases of esophageal cancer in 2021 are expected in 18,440 people (4.3 per 100,000 people) and 16,170 deaths from the disease will be reported. At the time of diagnosis, 33% of patients will have regional spread and 39% will have metastatic disease. FDA agrees with the Applicant's position; prognosis in these patients is poor, with median survival of less than a year.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

Patients with locally advanced unresectable or metastatic carcinoma of the esophagus in the first-line treatment setting have a high unmet medical need. For decades, cytotoxic chemotherapies have remained the mainstay treatment in metastatic esophageal cancer. For previously untreated patients, combination chemotherapies are routinely used. NCCN guidelines recommend the combination of 5-FU or capecitabine with platinum agents (cisplatin, oxaliplatin, or carboplatin) [4]. The majority of patients are diagnosed with advanced/metastatic cancer, and in this setting, response to chemotherapeutic agents is poor. Various palliative chemotherapy regimens have been investigated in esophageal cancer studies and have been shown to have at least some activity in the first-line setting, with responses ranging from 20% to 52%, but with significant toxicity [5]. Additional treatment options have included adding a third treatment to 5-FU plus cisplatin, such as docetaxel or cetuximab, using capecitabine in place of 5-FU in combination with cisplatin, as well as combining paclitaxel with a platinum-based therapy. Overall, response rates are comparable across treatment regimens and overall survival remains low, emphasizing a critical need for more effective therapies in the first-line setting. Further details are provided in Module 2.5: Section 1.4.2. A summary of treatments for advanced esophageal cancer in the first-line setting are presented in [Table 1].

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Table 1: Applicant - Summary of Treatments for Advanced/Metastatic ESCC or EAC in the First-Line Treatment Setting

Product Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Recommended treatments per NCCN guidelines[a]				
Cisplatin + 5-FU	ESCC [6]	Cisplatin: 100 mg/m^2 5-FU: 1000 mg/m^2 as continuous infusion on Days 1-5	N =44 ORR: 35% TTP: 6.2 mo OS: 7.6 mo	Grade 3-4 hematological AEs: decreased WBCs and platelets (14% each); non-hematological AEs: nausea and vomiting (27% each); treatment discontinuation due to excessive toxicity (11%).
	Advanced or recurrent ESCC [7]	Cisplatin: 20 mg/m^2 5-FU: 800 mg/m^2 as continuous infusion on Days 1-5	N = 36 ORR: 33% OS:6.6 mo	Grade 3-4 hematological AEs: up to 15% (neutropenia); non-hematological AEs up to 2.5% (fever).
	Advanced ESCC (EGFR expressing) [8][8]	Cisplatin: 100 mg/m^2, Day 1 5-FU: 1000 mg/m^2 as continuous infusion on Days 1-5	N = 30 ORR: 30% PFS: 3.6 mo OS: 5.5 mo	Grade 3-4 hematological AEs: neutropenia (13%) and thrombocytopenia (7%); non-hematological AEs: fatigue(10%) and nausea (3%); treatment discontinuation due to toxicity (mainly renal) (20%)
	Stage III advanced ESCC [9][9]	Cisplatin: 6 mg/m^2 as 2-h infusion on Days 1-5 5-FU: 330 mg/m^2 as continuous infusion on Days 1-7	N = 20 ORR: 55% OS: 20.5 mo	No Grade 3-4 toxicities observed
Cisplatin + 5-FU + leucovorin [10][10]	ESCC and EAC	Cisplatin: 500 mg/m^2 30-60 min IV on Days 15, 28, 35 5-FU: 2.6 g/m^2 as continuous infusion QW preceded by Leucovorin: 500 mg/m^2 as 2-h infusion QW	N = 10 ORR: 40% OS: 10.6 mo	Grade 3-4 hematological AEs[b]: neutropenia (16%), febrile neutropenia (13%), anemia and thrombocytopenia (3% each); non-hematological AEs: vomiting and diarrhea (5% each), nausea (8%), and neuropathy (3%).
Cisplatin + 5-FU + cetuximab [8]	Advanced ESCC (EGFR expressing) previously untreated for advanced disease	Cisplatin: 100 mg/m^2, Day 1 5-FU: 1000 mg/m^2 as continuous infusion on Days 1-5 Cetuximab: 400 mg/m^2 initial dose on Day 1 followed by 250 mg/m^2 weekly thereafter	N = 32 ORR: 34% PFS: 5.9 mo OS: 9.5 mo	Grade 3-4 hematological AEs: anemia (6%) and neutropenia (22%); non-hematological AEs: diarrhea (16%), nausea (13%), sensory neuropathy (6%), acne like rash (6%), emesis (3%), fatigue (3%), and infusion-related reaction (3%); treatment discontinuation due to toxicity (mainly renal) (23%).

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Product Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Cisplatin + 5-FU + folinic acid + etoposide [11]	Inoperable or metastatic ESCC	Cisplatin: 80 mg/m^2 IV over 4 h on Day 1 Q4W 5-FU: 375 mg/m^2/day continuous IV combined with folinic acid 30 mg PO 6X/day on Days 1-4 Q4W Etoposide: 200 mg/m^2 PO on Days 3 and 5 Q4W	N = 68 ORR: 34% OS: 9.5 mo	Grade 3-4 hematological AEs: leukocytopenia (Grade 3 = 17%, Grade 4 = 16%) and thrombocytopenia (Grade 3 = 13%, Grade 4 = 7%); Grade 3 non-hematological AEs: nausea/vomiting (32%), mucositis (23%), and diarrhea (6%); treatment discontinuation due to toxicity (6%, 3 due to episode of neutropenic fever and 1 due to Grade 3 neurotoxicity).
Cisplatin + capecitabine [12] [13][12] [13]	Advanced/ recurrent/ metastatic ESCC	Cisplatin: 60 mg/m^2 IV on Day 1 Q3W Capecitabine: 1250 mg/m^2/dose PO BID on Days 1-14 Q3W OR Cisplatin: 75 mg/m^2 IV on Day 1 Q3W Capecitabine: 1000 mg/m^2/dose PO BID on Days 1-14 Q3W	N = 45 ORR: 58% TTP: 4.7 OS: 11.2 mo [12] N = 46 ORR: 57% PFS: 5.1 mo OS: 10.5 mo [13]	Grade 3-4 hematological AEs: neutropenia (17%), leucopenia (6%), anemia (1%), and thrombocytopenia (0.5%), Grade 3-4 non-hematological AEs: anorexia (9%), fatigue (5%), constipation and hand-foot syndrome (3% each), and diarrhea (2%) [12]. Grade 3-4 hematological AEs: neutropenia (16%), anemia (6%), thrombocytopenia (2%); Grade 3-4 non-hematological AEs: nausea, vomiting, and diarrhea (1% each). One death (tumor bleeding) where relationship to study treatment could not be completely ruled out [13].
Cisplatin + paclitaxel [14] [15][14] [15]	Inoperable, recurrent or metastatic ESCC or EAC or EGJ	Paclitaxel: 90 mg/m^2 IV over 3 h followed by Cisplatin: 50 mg/m^2 IV over 1 h on Day 1 Q2W OR Paclitaxel: 100 up to 200 mg/m^2 IV over 3 h followed by Cisplatin: 60 mg/m^2 IV over 1 h on Day 1 Q2W	N = 20 ORR: 40% PFS: 8 mo[c] OS: 11 mo[c] [14] N = 59 ORR: 52% PFS: n/a OS: n/a [15]	Grade 3 hematologic AEs: anemia (10%) and leucopenia (10%) [14]; Grade 3 hematologic AEs: anemia (3%) [15], Grade 3 non-hematological AEs: vomiting (14%), nausea (5%), ototoxicity (5%), nephrotoxicity (3%), and fatigue (2%); Grade 4 non-hematological AE: motor neurotoxicity (5%) [14] [15].
Oxaliplatin + 5-FU + leucovorin (FOLFOX) [16]	Metastatic ESCC or EGJ	Oxaliplatin: 100 mg/m^2 IV over 2 h on Day 1.	N = 56 ORR: 23% PFS: 4.4 mo OS: 7.7 mo	Grade 3-4 hematologic AEs: neutropenia (36%), leucopenia (29%), anemia and thrombocytopenia (11 % each).

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Product Name	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
		Leucovorin: 400 mg/m^2 IV over 2 h followed by 5-FU 400 mg/m^2 IV bolus then followed by 5-FU 2400 mg/m^2 as 46 h continuous IV infusion on Days 1 and 2. Treatment was repeated Q2W.		There were no Grade 3-4 non-hematological AEs.
Paclitaxel + carboplatin [17]	Advanced ESCC, EAC or EGJ	Paclitaxel: 200 mg/m^2 IV over 3h Carboplatin: IV at an AUC of 5 mg/h/mL	N = 35 ORR: 43% OS: 9 mo	Grade 3/4 hematological AEs of neutropenia (52%), anemia (18)%, thrombocytopenia - Grade 3 only (6%); Grade 3 non-hematological AEs of myalgia (15%), fatigue (12%), neuropathy (9%), and nausea (6%).

Abbreviations: 5-FU = 5-fluorouracil; AE = adverse event; AUC = area under the concentration-time curve; BID = twice daily; EAC = esophageal adenocarcinoma; EGJ = esophagogastric junction; ESCC = esophageal squamous cell carcinoma; IV = intravenous; mo = months; n/a = not available; NCCN = National Comprehensive Cancer Network; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PO = oral; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; QW = weekly; TTP = time to progression.

[a] Source: NCCN Guidelines [4].

[b] N = 38 (includes10 patients with esophageal cancer, 20 with stomach cancer, 21 with pancreatic cancer, 4 with biliary cancer, and 4 unknown.

[c] Median PFS and OS were based on responding patients.

The FDA's Assessment:

FDA generally agrees with the applicant's position and notes that the public will not be able to access the Module the applicant refers to regarding a submission to the NDA, "Further details are provided in Module 2.5."

The backbone chemotherapy regimen selected for Study KN590 (5-fluorouracil combined with cisplatin) is adequate, and it is a widely used for the first-line treatment of metastatic esophageal cancer in the U.S. As stated above in the summary of current treatment options, based on literature and professional medical association guidelines, any of the platinum- and fluoropyrimidine-based regimens listed are appropriate treatments. As the efficacy of these combinations is similar and decisions for each particular patient are based on institutional- and patient-preference, toxicity profile, comorbidities, etc. and it is not expected that any of these specific agents would have a different outcome when combined with pembrolizumab, the indication reflects current standard of treatment in the US. Therefore, the final indication stated (b) (4)

(b) (4)

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(b) (4)

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

As of 29-SEP-2020, KEYTRUDA® has received traditional or accelerated approval in the US for many indications, as summarized in [Table 2].

For this application, the proposed indication is fo (b) (4)

(b) (4)

Table 2: Applicant - Summary of FDA Approved Pembrolizumab Indications

Indication	Traditional Approval	Accelerated Approval
Treatment of unresectable or metastatic melanoma	X	
Adjuvant treatment of melanoma with involvement of lymph node(s) following complete resection	X	
In combination with pemetrexed and platinum chemotherapy for 1L treatment of metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.	X	
In combination with carboplatin and either paclitaxel or paclitaxel protein-bound 1L treatment of metastatic squamous NSCLC.	X	
1L treatment Stage III NSCLC, not suitable for surgical resection or definitive chemoradiation, or metastatic NSCLC, and with tumors express PD-L1 (TPS ≥1%), with no EGFR or ALK genomic tumor aberrations.	X	
Treatment of metastatic NSCLC with tumors express PD-L1 (TPS ≥1%), with disease progression on or after platinum-containing chemotherapy.	X	
In combination with platinum and FU for the 1L treatment of metastatic or with unresectable, recurrent HNSCC.	X	
1L treatment of metastatic or with unresectable, recurrent HNSCC with tumors express PD-L1 (CPS ≥1).	X	
Treatment of recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.	X	
Treatment of locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	X	
Treatment of BCG-unresponsive, high-risk, NMIBC with CIS with or without papillary tumors not eligible for or have elected not to undergo cystectomy.	X	

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Indication	Traditional Approval	Accelerated Approval
Treatment of recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus with tumors express PD-L1 (CPS ≥10), with disease progression after one or more prior lines of systemic therapy.	X	
In combination with axitinib for the 1L treatment of advanced RCC.	X	
1L treatment of unresectable or metastatic MSI-H or dMMR CRC	X	
Treatment of recurrent or metastatic cSCC that is not curable by surgery or radiation.	X	
Treatment of metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least 1 other prior line of therapy.*		X
Treatment of cHL, or who have relapsed after 3 or more prior lines of therapy (adult and pediatrics).*		X
Treatment of refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy (adults and pediatrics).*		X
Treatment of locally advanced or metastatic urothelial carcinoma not eligible for cisplatin-containing chemotherapy with tumors express PD-L1 (CPS ≥10), or not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.*		X
Treatment of unresectable or metastatic MSI-H or dMMR (adult and pediatrics). - solid tumors that have progressed following prior treatment and with no satisfactory alternative treatment options,* or - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan*.		X
Treatment of recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with tumors express PD-L1 (CPS ≥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.*		X
Treatment of recurrent or metastatic cervical cancer with disease progression on or after chemotherapy with tumors express PD-L1 (CPS ≥1).*		X
Treatment of HCC who have been previously treated with sorafenib.*		X
Treatment of recurrent locally advanced or metastatic MCC (adult and pediatrics).*		X
In combination with lenvatinib in advanced endometrial carcinoma that is not MSI-H or dMMR, with disease progression following prior systemic therapy and not suitable for curative surgery or radiation. *		X
Treatment of adult and pediatric patients with unresectable or metastatic TMB-H [≥10 mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. *		X
For use at an additional recommended dosage of 400 mg Q6W for all approved adult indications.#		X
Abbreviations: 1L=first-line; ALK=anaplastic lymphoma kinase; BCG=Bacillus Calmette-Guerin; cHL=classic Hodgkin's Lymphoma; CIS=carcinoma in situ; CPS=combined positive score; CRC=colorectal cancer; cSCC=cutaneous squamous cell carcinoma; dMMR=deficient mismatch repair; EGFR=endothelial growth factor receptor; FU-fluorouracil; HER2=human epidermal growth factor receptor 2; HNSCC=head and neck squamous cell carcinoma; MCC=Merkel cell carcinoma; MSI-H=microsatellite instability high; NMIBC=non-muscle invasive bladder cancer; NSCLC=non-small cell lung cancer; PD-L1=programmed cell death Ligand 1; PMBCL=Primary mediastinal large B-cell lymphoma; Q6W=every 6 weeks; RCC=renal cell carcinoma; SCLC=small cell lung cancer; TMB-H=tumor mutational burden-high; TPS=tumor positive score.		

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Indication	Traditional Approval	Accelerated Approval
*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. #This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.		

The FDA's Assessment:
FDA agrees with Merck's description of the currently approved indications of pembrolizumab.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
[Table 3] summarizes major regulatory milestone for KEYNOTE-590.

Table 3: Applicant - Key Regulatory Interactions Related to KEYNOTE-590 Submitted to IND-123482

Date	Comments
27-FEB-2017	FDA preliminary comments received for the Type C Pre-Phase 3 meeting to discuss clinical and statistical aspects of KEYNOTE-590.
15-JUN-2017	FDA granted Orphan Drug Designation to pembrolizumab for treatment of esophageal carcinoma
16-FEB-2018	FDA advice received regarding MSI-H testing in KEYNOTE-590.
11-OCT-2019	FDA advice received regarding inclusion of participants enrolled into the China extension into the global study population and additional statisical updates to the protocol.
26-FEB-2020	FDA advice received containing statistical comments.
24-MAR-2020	Merck correspondence to the FDA which included resolution of previous FDA statistical comments received 26-FEB-2020.
18-APR-2020	FDA advice received regarding changes to the PFS primary endpoint and interim analysis timing received. FDA also commented on Merck's revised alpha spending proposal.
31-JUL-2020	FDA statistical comment received on protocol amendment regarding the alpha boundaries for interim and final analyses.
27AUG-2020	Informal teleconference between Merck and FDA to discuss use of the Real Time Oncology Review and Assessment Aid pilots for the KEYNOTE-590 sBLA.
30-SEP-2020	FDA preliminary comments for KEYNOTE-590 Type B pre-sBLA meeting received.

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Date	Comments
02-OCT-2020	Type B pre-sBLA teleconference cancelled; FDA issued preliminary comments as meeting minutes.
Abbreviations: FDA = Food and Drug Administration; MSI-H = microsatellite instability-high; PFS = progression-free survival; sBLA = supplemental biologics license application.	

The FDA's Assessment:
FDA agrees with Merck's description of the regulatory interactions related to KEYNOTE-590.

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

4.1 Office of Scientific Investigations (OSI)

In conjunction with OSI, the FDA clinical and statistical review teams determined that inspections were not needed to confirm the integrity of the data submitted with this application. This decision was based upon the extensive clinical experience with pembrolizumab, the review teams' audit of datasets, lack of notable patterns in patient enrollment, protocol deviations, or efficacy and safety data across sites that would raise potential concerns regarding data integrity, and historical experience indicating lack of data integrity issues from previous inspections conducted by FDA for prior pembrolizumab applications.

4.2 Clinical Microbiology

4.1 No new microbiology information was submitted. Product Quality

4.2 No new quality information was submitted. Devices and Companion Diagnostic Issues

There is no companion diagnostic for this indication. Enrollment into Study KN590 was based on tumor location; specified subpopulation analyses based on PD-L1 status, data was provided by centrally determined assessments in all patients using the PD-L1 IHC 22C3 pharmDx kit, an FDA-approved assay for the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) esophageal cancer tumor tissue.

5 Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

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6 Clinical Pharmacology

No new information is provided in the current submission.

7 Sources of Clinical Data

7.1 Table of Clinical Studies

The Applicant's Position:
[Table 4] presents KEYNOTE-590 as a stand-alone study that supports efficacy and safety in the proposed indication.

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Table 4: Applicant - List of Clinical Trials Relevant to this NDA/BLA

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-590	NCT03189719	Phase 3, multisite, double-blind, randomized study of pembrolizumab plus cisplatin/5-FU vs placebo plus cisplatin/5-FU	Pembrolizumab: 200 mg IV Q3W Placebo: Normal saline IV Q3W Cisplatin 80 mg/m^2 IV Q3W 5-FU 800 mg/m^2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4000 mg/m^2 per 3-week cycle)	Primary endpoints: OS and PFS per RECIST 1.1 based on investigator assessment. Secondary endpoints: ORR per RECIST 1.1 based on investigator assessment, DOR, HRQoL, and safety and tolerability of pembrolizumab.	Pembrolizumab: up to 35 administrations or approximately 2 years Cisplatin: capped at 6 doses 5-FU: maximum of 35 cycles Or until a protocol discontinuation condition was met. Followed up for OS until death, withdrawal of consent, or the end of the study, whichever came first.	749	Participants with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/ metastatic Siewert Type 1 adenocarcinoma of the esophagogastric junction	168 centers in 26 countries

Abbreviations: 5-FU=5-fluorouracil, BLA=Biologics License Application, DOR=Duration of response, HRQoL=health-related quality of life, IV=intravenous, NCT=National Clinical Trial; NDA=New Drug Application, ORR=overall response rate, OS=overall survival, PFS=progression-free survival, Q3W=every 3 weeks, RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

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The FDA's Assessment:
FDA generally agrees with the Applicant's description of the trial design of Study KEYNOTE-590, which provided the primary efficacy data for this assessment. FDA notes that the trial was initially designed to randomize 700 patients globally, which the Applicant has referred as the "Global Cohort." Approximately 106 patients from China were planned to be randomized in the trial including patients from China randomized in the "Global Cohort" during the global enrollment period and additional Chinese patients enrolled in the "China Extension Study" enrollment period. The protocol was amended to merge "Global Cohort" and "China Extension Study", referred to as the "Global Study" population. A total of 749 patients were randomized in the "Global Study" and the primary analyses are based on this population. The review is based on data submitted on October 13, 2020.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. KEYNOTE-590

Trial Design

The Applicant's Description:

KEYNOTE-590 is an ongoing, randomized (1:1), double-blind, multisite, Phase 3 trial of pembrolizumab in combination with cisplatin and 5-FU versus placebo in combination with cisplatin and 5-FU as first-line treatment in participants with locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ. Participants were stratified by geographic region (Asia vs ROW), histology (adenocarcinoma vs squamous cell carcinoma), and ECOG PS (0 vs 1).

The enrollment period was divided into 2 periods: Global Cohort and China extension enrollment periods. The Global Cohort (n=711) and China Extension Study (n=38) were merged for the primary analyses and henceforth referred to as the Global Study population (N=749). A summary of the study design is provided in [Figure 1].

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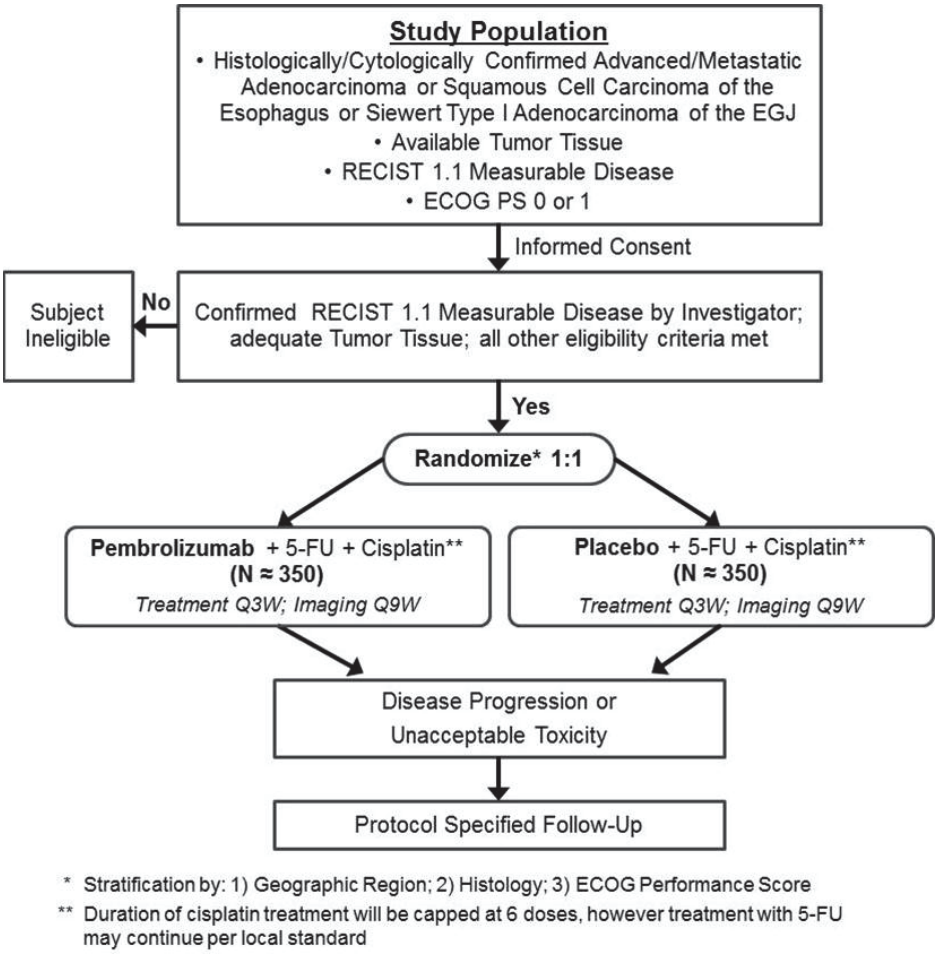
Figure 1: Applicant - KEYNOTE-590 Study Design Schematic



Abbreviations: 5-FU = 5-fluorouracil; EGJ = esophagogastric junction; ECOG PS = Eastern Cooperative Oncology Group; performance status; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; Q3W = every 3 weeks, Q9W = every 9 weeks

The FDA's Assessment:
FDA agrees with the Applicant's description of the trial design of KEYNOTE-590 as presented in this section. The number of patients randomized to each arm was well balanced.

Trial Location: KEYNOTE-590 is a global study conducted at 168 sites in Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Denmark, France, Germany, Guatemala, Hong Kong, Japan, Malaysia, Peru, Romania, Russia, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, and US.

The FDA's Assessment:
FDA acknowledges the trial sites listed above. Although some disease etiology characteristics

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and management of earlier stages of esophageal/GEJ cancer may vary between countries, the selected treatment backbone regimen (see below) for the first line treatment for these patients with esophageal and GEJ cancer is commonly used in the U.S. and results of this international study are generally applicable to the U.S. population.

Rationale for Control Group: At the time of the KEYNOTE-590 design, the combination of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin), either alone or in combination with a third drug such as epirubicin or a taxane, was, and is currently, the most effective first-line treatment option. 5-FU with cisplatin is the most common regimen for treating patients with locally advanced unresectable or metastatic carcinoma of the esophagus [7] [8][7] [8].

In the NCCN clinical practice guideline, a combination of 5-FU (750 to 1000 mg/m^2/day continuous infusion, Days 1 to 4) and cisplatin (75 to 100 mg/m^2 IV, Day 1) is listed as a recommended regimen for the first-line setting [4]. While cisplatin doses of 100 mg/m^2 Q4W may be the preferred dose in Non-Asian clinical trials, doses of 60 to 80 mg/m^2 are more common for Asian patients.

The FDA Assessment:

FDA agrees with the selection of 5FU/cisplatin as the backbone chemotherapy regimen for Study KN590.

Summary of Key Entrance Criteria*:* Participants were required to have histologically or cytologically confirmed locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ. Measurable disease based on RECIST 1.1, as determined by local site investigator/radiology assessment, ECOG PS of 0 or 1, tissue sample for PD-L1 testing by immunohistochemistry analysis, and adequate organ function were also required (as defined in the protocol). Participants were excluded if they had locally advanced resectable or potentially curable esophageal carcinoma, had received prior therapy (neoadjuvant or adjuvant therapy were allowed under certain circumstances) for advanced/metastatic EAC or ESCC or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ, had active autoimmune disease requiring systemic treatment within the past 2 years before the first dose of study treatment, had a diagnosis of immunodeficiency or known history of HIV, with known active central nervous system metastases and/or carcinomatous meningitis, or had hepatitis B or C. Other entrance criteria are described in the protocol.

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Dose Selection: The planned dose of pembrolizumab for this trial was 200 mg Q3W. The proposed doses of 80 mg/m^2 cisplatin and 800 mg/m^2 (Days 1-5) 5-FU in combination with pembrolizumab Q3W have been evaluated in a cohort of first-line participants with gastric cancer (KEYNOTE-059), in which the combination was shown to have a manageable safety profile with no treatment-related discontinuations or deaths.

Treatment Allocation: Treatment randomization occurred centrally using an IVRS/IWRS. There were 2 treatment arms, with participants assigned randomly in a 1:1 ratio to pembrolizumab + cisplatin + 5-FU or placebo + cisplatin + 5-FU.

Blinding: A double-blinding technique was used. Pembrolizumab and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The participant and the investigator who was involved in the treatment or clinical evaluation of the participants were unaware of the group assignments.

Pembrolizumab or placebo treatment was blinded to the participant, study site personnel, and Sponsor personnel.

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. All treatments that the investigator considered necessary for a participant's welfare could be administered at the discretion of the investigator in keeping with the community standards of medical care.

Treatment Compliance: The instructions for preparing and administering pembrolizumab were provided in the Pharmacy Manual. Normal saline placebo solution was prepared by the local pharmacist and administered by blinded qualified site personnel in the same manner as pembrolizumab. Preparation and administration of cisplatin and 5-FU followed the local product label and local standard procedures.

Dose Modification/Dose Discontinuation: Treatment with pembrolizumab/placebo and chemotherapy was withheld or discontinued for treatment-related toxicities or life-threatening AEs. Dose modification and toxicity management guidelines were consistent with the approved labels for pembrolizumab and chemotherapy. Dosing interruptions were permitted in the case of medical/surgical events or logistical reasons not related to study treatment. Instructions for the discontinuation of a component or entire regimen were provided in the protocol.

Administrative Structure: This study used a group sequential design based on pre-specified criteria, using an independent, external DMC to monitor safety and efficacy. The external DMC was used to monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. The DMC made recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. The DMC also reviewed interim trial results, considered the overall risk and benefit to study participants and made recommendations to the EOC if the study should continue in accordance with the protocol.

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Study Procedures: [Table 5], the Trial Flow Chart, summarizes the trial procedures to be performed at each visit.

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Table 5: Applicant - KEYNOTE-590 Trial Flow Chart

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 Last Dose	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 Anti-cancer Therapy Status												X	X
Survival Status[a]		<----------										---------->	X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[c]	
Full Physical Examination[d]	X									X			
Directed Physical Examination[d]		X	X	X	X	X	X	X	X				
Height[e], Weight, and Vital Signs (T,P,RR,BP)	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram (Local)	X												

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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 Last Dose	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**
ECOG Performance Status	X[f]	X	X	X	X	X	X	X	X	X			
PROs (HRQoL Measures)[g]		X	X	X	X	X	X	X	X[g]	X	X		
Trial Treatment Administration													
Pembrolizumab/Placebo Administration[h,i]		X	X	X	X	X	X	X	X				
Cisplatin Administration[h,j]		X	X	X	X	X	X						
5-FU Administration[h]		X	X	X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis Performed by LOCAL Laboratory													
Pregnancy Test[k]	X												
PT/INR and aPTT	X[f]												
CBC with Differential[l]	X[f]		X	X	X	X	X	X	X	X	X		
Chemistry Panel[l]	X[f]		X	X	X	X	X	X	X	X	X		
Urinalysis[l]	X[f]		X		X		X		X	X			
T3, FT4, and TSH[l]	X		X		X		X		X	X	X		
Laboratory Procedures/Assessments: Analysis Performed by CENTRAL Laboratory (not applicable for China)													
Pembrolizumab Pharmacokinetics[m]		X	X		X								

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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 Last Dose	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**
Pembrolizumab Anti-Drug Antibodies[m]		X	X		X								
Blood for Genetic Analysis[n]		X											
Blood for RNA Analyses[o]		X	X			X				X			
Blood for Plasma Biomarker Analyses[o]		X	X			X				X			
Blood for Serum Biomarker Analyses[o]		X	X			X				X			
Tumor Tissue Collection													
Newly Obtained or Archival Tumor Tissue	X[p]												
Efficacy Measurements													
Tumor Imaging	X[q]	<---------- X (every 9 weeks)[r] ---------->								X[s]		X	

Abbreviations: 5-FU=5-fluorouracil, aPTT=activated partial thromboplastin time, BP=blood pressure, CBC=complete blood count, DNA=deoxyribonucleic acid, ECI=event of clinical interest, ECOG=Eastern Cooperative Oncology Group, FBR=Future Biomedical Research, FT4=free thyroxine, HRQoL=health-related quality of life, IEC=Independent Ethics Committee, INR=international normalized ratio, IRB=Institutional Review Board, irRECIST=immune-related Response Evaluation Criteria in Solid Tumors, IV=intravenous, P=pulse, PD=progressive disease, PD-L1=programmed cell death-ligand 1, PK=pharmacokinetics, PRO=patient-reported outcome, PT=prothrombin time, Q3W=every 3 weeks, Q9W=every 9 weeks, RNA=ribonucleic acid, RR=respiratory rate, SAE=serious adverse event, T=temperature, T3=triiodothyronine, TSH=thyroid-stimulating hormone.

a. In subjects that experience site-assessed PD or start a new anticancer therapy, contact should be made (eg, by telephone) approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).
b. Cycle 1 treatment must be given within 3 days of allocation. The window for each visit is ± 3 days unless otherwise noted.
c. SAEs will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

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d. Refer to local regulations or local standard of practice for patient management regarding 5-FU and cisplatin treatment (eg, requirements for baseline and periodic audiograms for cisplatin).
e. Height will be measured at Visit 1 only.
f. ECOG performance status and laboratory tests for screening are to be performed within 14 days prior to the first dose of trial treatment.
g. See Section 7.1.2.6.2 – Electronic Patient-reported Outcomes for details regarding administration of PROs. All PROs are to be performed at Cycles 1 to 9. After Cycle 9 (Week 24), PROs are to be performed every 3 cycles (eg, Week 33, Week 42, Week 51). PROs are to be performed for up to 1 year or End of Treatment, whichever comes first, at time of discontinuation, and at the 30-day post-treatment discontinuation follow-up visit. A visit window of ± 7 days will apply to PRO visit assessments.
h. Pembrolizumab or placebo infusion is administered first, followed by the cisplatin and 5-FU infusions. Treatment with cisplatin and/or 5-FU may follow 1 to 2 days after pembrolizumab/placebo (eg, Day 2 or Day 3) as needed per local standard of care.
i. Pembrolizumab/placebo should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed. Pembrolizumab 200-mg fixed dose or placebo should be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site; however, a window of -5 minutes and +10 minutes is permitted (ie, infusion time between 25 and 40 minutes). Pembrolizumab/placebo treatment is discontinued after completion of 35 administrations (approximately 2 years).
j. Cisplatin will be capped at total of 6 doses; cisplatin dosing may occur after cycle 6 if cisplatin was withheld for one or more cycles during cycles 2 to 6.
k. For women of reproductive potential, a urine or serum pregnancy test must be performed within 72 hours prior to randomization. If first dose of study treatment occurs > 72 hours after randomization, pregnancy test must be repeated to be within 72 hours of first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable. Subjects must be excluded/discontinued in the event of a positive test result.
l. Urinalysis and thyroid function tests to be performed every other cycle. CBC (hematology) and chemistry to be performed every cycle. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.
m. Both PK and anti-pembrolizumab antibody samples: pre-dose (trough) PK and anti-pembrolizumab antibody samples will be collected within 24 hours before infusion at Cycles 1, 2 and 4 for the first approximately 100 randomized subjects. No samples should be collected for any subject randomized after 31-Jan-2018, including all subjects from China.
n. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the Future Biomedical Research (FBR) consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR. Note that this sample is not applicable for China.
o. Whole blood samples should be collected pre-dose on Day 1 of Cycle 1, Cycle 2, and Cycle 5, and again at treatment discontinuation. Leftover samples will be stored for FBR if the subject signs the FBR consent. Note that these samples are not applicable for China.
p. At screening, either a newly obtained tumor tissue specimen (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained and time of study enrollment; preferred option) or an archival tumor specimen is required prior to randomization. If submitting a newly obtained specimen, an archival tumor sample is also requested (where available) to assess the clinical utility of PD-L1 analysis in newly obtained versus archived tissue samples. Formalin-fixed, paraffin-embedded block specimens are preferred to slides.

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q. Screening tumor imaging will be performed within 21 days prior to randomization. At sites where the local regulatory body and/or IRB/ERC will not permit a second tumor imaging within a 21-day period, an already available imaging scan obtained within 28 days prior to first dose may be used with the approval of the Sponsor Clinical Director. For all subjects, already available imaging scans performed as part of routine clinical management are acceptable if they are of diagnostic quality and performed within the acceptable timeframe.

r. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of allocation and will continue to be performed Q9W (63 days ± 7 days), or earlier if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts.

s. 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.

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Participant completion, discontinuation, or withdrawal: Participants could discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator if any untoward effect occurred. In addition, a participant could be discontinued from treatment by the investigator or the Sponsor if treatment was inappropriate, the trial plan was violated, or for administrative and/or other safety reasons. A participant must have been discontinued from treatment for any of the following reasons: withdrawal of consent, confirmed radiographic PD, unacceptable AE, progression or recurrence of any malignancy or any occurrence of another malignancy or intercurrent illness that required active treatment, recurrent Grade 2 pneumonitis, confirmed positive serum pregnancy test, completion of 35 treatments with pembrolizumab/placebo, confirmed CR and had been treated for at least 8 cycles and had received at least 2 cycles of study treatment beyond the date when the initial CR was declared. Discontinuation from treatment was permanent and once a participant was discontinued, treatment was not be allowed to be restarted. Participants who discontinued trial treatment for a reason other than PD or withdrawal of consent were to be moved into the Follow-up Phase and were to be assessed by radiologic evaluation every 9 weeks to monitor disease status, until the start of new anticancer therapy, PD, death, or end of trial.

The FDA's Assessment:
The defined terms regarding treatment completion, discontinuation, and withdrawal were adequate. There was one discontinuation due to a protocol violation which occurred on the placebo arm. For reasons for discontinuation, "physician's decision" was described for 9 patients on the pembrolizumab arm versus 10 on the placebo arm, and "withdrawal of consent" for 30 patients on the pembrolizumab arm versus 23 patients on the placebo arm. Regardless of the underlying reason for discontinuation, the arms were balanced in terms of reasons for discontinuation other than adverse events. See discussion of discontinuation, violation, and withdrawal below in this section, and discontinuation, violation, and withdrawal of patients due to AE in Section 8.2.4.

Study Endpoints

The Applicant's Description:

Primary Efficacy Endpoints:

The primary endpoints were:

- OS was defined as the time from randomization to death due to any cause.
- PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment or death due to any cause, whichever occurred first.

Secondary Efficacy Endpoints:

The key secondary efficacy endpoints were:

- ORR was defined as the proportion of participants who have a CR or PR per RECIST 1.1 based on investigator assessment
- DOR for participants who demonstrate CR or PR was defined as the time from first documented evidence of CR or PR until PD per RECIST 1.1 based on investigator assessment or death due to any cause, whichever occurred first.

Secondary and Other Relevant Endpoints:

- Safety measurements including but not limited to the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. Adverse events were assessed as defined by CTCAE v4.03.
- HRQoL using the EORTC QLQ-C30 and 3 pre-specified disease-related symptom scores (dysphagia, reflux, and pain) from EORTC QLQ-OES18.
- Exploratory efficacy endpoints included HRQoL using the EQ-5D-5L questionnaire; and PFS per irRECIST based on investigator assessment.

The FDA's Assessment:

FDA agrees with the Applicant's description of the primary and secondary endpoints of KEYNOTE-590. Endpoints other than PFS per RECIST 1.1, OS, and ORR were not included in the formal hypothesis testing plan controlling for the overall study-wise Type I error rate, and so the corresponding analyses are considered exploratory.

PFS was defined as time from randomization to the first documented PD or death due to any cause. For the primary analysis of PFS, patients who started a new anti-cancer treatment prior to experiencing a PD were censored at the time of last disease assessment prior to initiation of new anti-cancer treatment. Patients who experienced a PD or died after two consecutive missed disease assessments were censored at the time of last disease assessment prior to missing visits.

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Statistical Analysis Plan and Amendments

The Applicant's Description:

Key elements of the statistical analysis plan that are summarized in [Table 6] are applicable to the Global Study population (all enrolled subjects N=749). The original supplemental SAP was finalized on 10-MAY-2017; 3 amendments followed, with the latest being finalized 17-JUL-2020.

Table 6: Applicant - KEYNOTE-590 Key Elements of Statistical Analysis Plan

Study Design Overview	A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/Metastatic Esophageal Carcinoma (KEYNOTE-590)
Treatment Assignment	Randomized in a 1:1 ratio to receive pembrolizumab with 5-fluorouracil (5-FU) and cisplatin combination therapy or placebo with 5-FU and cisplatin.
Analysis Populations	Global Study Population N=749 Efficacy: Intention to Treat Safety: All Participants as Treated
Primary Endpoints/Hypotheses	1. OS in participants with ESCC whose tumors are PD-L1 CPS ≥10. 2. OS in participants with ESCC. 3. OS in participants whose tumors are PD-L1 CPS ≥10. 4. OS in all participants. 5. PFS based on RECIST 1.1 as assessed by investigator in participants with ESCC. 6. PFS based on RECIST 1.1 as assessed by investigator in participants whose tumors are PD-L1 CPS ≥10. 7. PFS based on RECIST 1.1 as assessed by investigator in all participants.
Key Secondary Endpoints/Hypotheses	1. ORR based on RECIST 1.1 as assessed by investigator in all participants.
Statistical Methods for Key Efficacy Analyses	The primary hypotheses were evaluated by comparing the pembrolizumab + chemotherapy arm to the placebo + chemotherapy arm on PFS and OS using a stratified log-rank test. Estimation of the HR was done using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results followed a tiered approach. The tiers differ with respect to the analyses that were performed. There are no Tier I events in this study. Tier 2 parameters were assessed via point estimates with 95% CI provided for between-group comparisons; only point estimates by treatment group were provided for Tier 3 safety parameters. The between-treatment difference was analyzed using the Miettinen and Nurminen method.
Interim Analyses	One efficacy interim analysis was performed in this study.
	Interim Analysis: • Timing: (1) Enrollment is complete with a minimum follow-up of 13 months and (2) ~460 investigator-assessed PFS events have been observed in ESCC and (3) ~391 deaths have occurred in ESCC • Primary purpose: Final PFS analysis and Interim OS analysis

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Multiplicity	The overall Type I error is strongly controlled at 2.5% (1-sided), with 1.2% initially allocated to OS in ESCC with PD-L1 CPS ≥10, 1.1% to OS in ESCC, 0 to OS in PD-L1 CPS ≥10, 0 to OS in all participants, 0.2% to PFS in ESCC, 0 to PFS in PD-L1 CPS ≥10, and 0 to PFS in all participants.
Sample Size and Power	The sample size is 749 participants. As per preliminary baseline characteristics, the prevalence of ESCC with PD-L1 CPS ≥10 is 38%, PD-L1 CPS ≥10 is 51%, and ESCC is 73%. With ~233 deaths expected in ESCC with PD-L1 CPS ≥10 at the OS final analysis, the study has ~85% power for detecting an HR of 0.65 at an initially assigned 0.012 (1-sided) significance level. With ~455 deaths expected in ESCC at the OS final analysis, the study has ~88% power for detecting an HR of 0.72 at an initially assigned 0.011 (1-sided) significance level. With ~ 460 investigator-assessed PFS events expected in ESCC at the interim analysis, the study has ~82.8% power for detecting a HR of 0.7 at an initially assigned 0.002 (1-sided) significance level.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of statistical analysis plan for efficacy of KEYNOTE-590 in Table 6. A division of the overall alpha of 0.025 (1-sided) between co-primary endpoints as well as a graphical approach was used to control overall study-wise Type I error rate for

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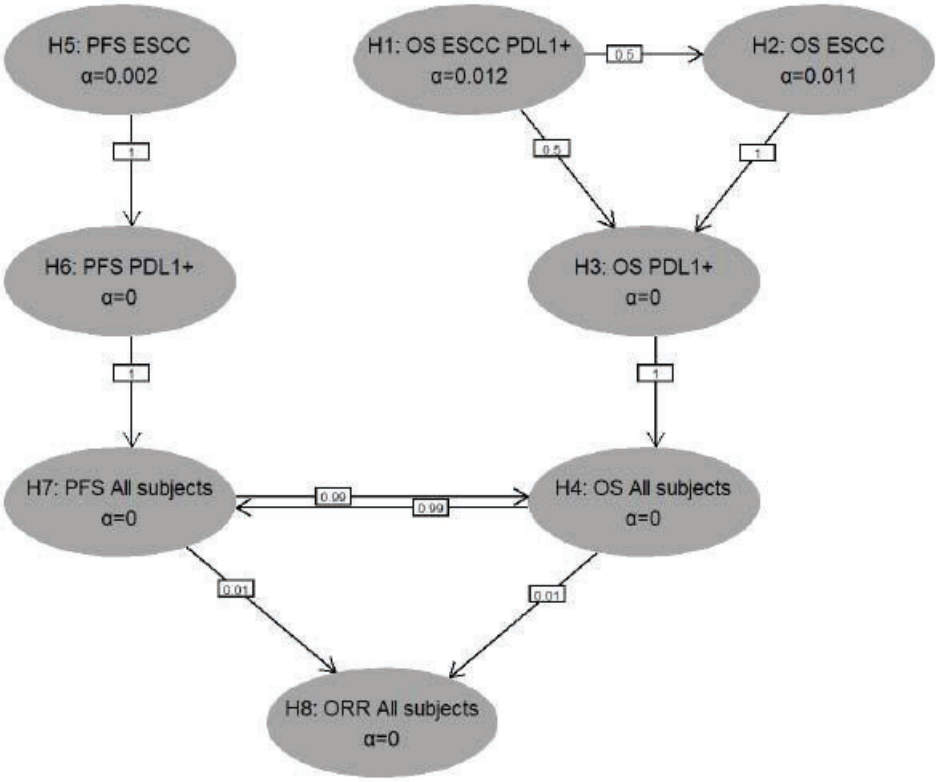
testing of multiple primary endpoints. The multiple testing schema in KEYNOTE-590 is as follows (abstracted from KEYNOTE-590 protocol amendment 09):



Abbreviations: ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

According to the final protocol of KEYNOTE-590, there was no planned interim analysis for PFS. One interim analysis for efficacy and a final analysis of OS was planned. The O'Brien and Fleming alpha spending method was used for the calculation of alpha boundaries for the interim and final efficacy analyses. This application is based on data from the time of the pre-specified final analysis of PFS and corresponding interim analysis of OS.

With respect to the statistical methods for key safety analyses, FDA agrees that data submitted for the reference population for 2799+ patients previously exposed to pembrolizumab, and

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comparison between treatment arms was sufficient. For the discussion of the results of the safety analysis, including direct comparison of treatment arms in KEYNOTE-590, see Section 8.2.

Efficacy Analysis

The ITT population, which included all randomized participants, served as the population for efficacy analysis. Participants were included in the treatment group to which they were randomized. The ITT population for the primary analyses was the Global Study population (N=749) which included all participants randomized in the Global Study.

The analysis strategy for the primary and secondary endpoints are described in [Table 7].

Table 7: Applicant - Analysis Strategy for KEYNOTE-590 Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
PFS per RECIST 1.1 by investigator	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in KEYNOTE-590-09 protocol, Table 11
OS	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at date participant last known alive
Key Secondary Analyses			
ORR per RECIST 1.1 by investigator	Testing and estimation: stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered nonresponders.
Abbreviations: ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.			

The FDA's Assessment:

FDA agrees with the Applicant's presentation of statistical analyses plans for efficacy endpoints in Table 7.

Safety Analysis

The ASaT population was used for the analysis of safety data in this study. The ASaT population consisted of all randomized participants who received at least 1 dose of study treatment. At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study treatment was required for inclusion in the analysis of each parameter. To assess change from baseline, a

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baseline measurement was also required. Safety and tolerability were assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

The FDA's Assessment:
FDA agrees with the definition for the safety (ASaT) population which consisted of all randomized patients who received at least 1 dose of study treatment. This is consistent with FDA's standard review practice.

Protocol Amendments

The Applicant's Description:

The original protocol (3475-590-00) was finalized on 14-MAR-2017 and amended 9 times. [Table 8] summarizes the key changes in the amendments.

Table 8: Applicant - Summary of Key Changes to the KEYNOTE-590 Protocol

Amendment	Key Changes
Amendment 01/France-specific (20-OCT-2017)	French Health Authority-recommended changes.
Amendment 02/Global (19-DEC-2017)	Changed primary biomarker from GEP to PD-L1; provided additional information regarding PD-L1 as a biomarker; clarified 5-FU dosing requirements; added an additional IA and updated analysis timings to allow for more mature data and adequate follow-up time; updated estimated duration of trial from 40 months to 46 months; reduced PK/ADA sampling.
Amendment 03/France-specific (02-FEB-2018)	Applied changes from Global Amendment 02 to France-specific Amendment 01.
Amendment 04/China-specific (26-SEP-2018)	Removed all sampling, analysis and objectives for exploratory biomarkers, including blood for RNA, DNA, serum and plasma and remaining tissue after PD-L1 analysis; removed all references to Future Biomedical Research for participants in China as these were not approved by HGRAC.
Amendment 05/Global (12-DEC-2018)	Extended the enrollment period beyond the Global Cohort to achieve the required sample size of the China Cohort to investigate efficacy and safety in Chinese subjects.
Amendment 06/France-specific (28-JAN-2019)	Applied changes from Global Amendment 05 to France-specific Amendment 03.

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Amendment	Key Changes
Amendment 07/Global (Not activated)	Not applicable
Amendment 08/Global (03-JAN-2020)	1. Based on results from the KEYNOTE-181 study, 3 primary objectives and corresponding hypotheses were added: OS in ESCC population; OS in ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10) population; and PFS in ESCC population. 2. Secondary objectives updated accordingly with respect to ORR and DOR endpoints in the ESCC and ESCC PD-L1 CPS ≥10 populations. Exploratory objectives were updated for PFS per irRECIST in the ESCC and ESCC PD-L1 CPS ≥10 populations. 3. Due to the short interval (~5 months) between the last participant enrolled in the Global Cohort (n=711) and in the China Extension Study (n=38), these 2 participant groups were merged into 1 "Global Study" for the primary analyses (N=749). 4. To include assessment of DOR and QoL (EORTC QLQ-C30 and EORTC QLQ-OES18) in all pre-specified populations. The statistical analyses plan was updated accordingly.
Amendment 09/Global (17-JUN-2020)	Due to higher than expected discordance rate in assessment of PD between BICR and investigator and following input from the US regulatory agency on the 2 IAs, the protocol was amended as follows: Changed the primary endpoint of PFS, and the secondary endpoints of ORR and DOR from BICR assessment to investigator assessment; deleted 1 of the 2 planned efficacy IAs and updated timing and criteria for triggering the IA; adjusted power and the number of PFS events based on updated timing of IA; added that sensitivity analyses would be conducted for PFS, ORR, and DOR endpoints based on BICR; revised the alpha spending strategy to use the minimum of planned and actual events at the IA.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of the key changes to the statistical analysis plan in the protocol amendments of KEYNOTE-590 presented in Table 8. However, FDA has the following comments:

1. In KEYNOTE-590, the initial primary endpoint PFS as assessed by BICR was changed to PFS as assessed by investigator. While FDA did not object to the Applicant's plan to revise the primary endpoint in Amendment 9, FDA, in an Advice/Information Request letter issued on April 18, 2020, recommended that the Applicant perform a sensitivity analysis for PFS according to BICR assessment and that FDA will evaluate the totality of the data with respect to robustness of PFS results. If a substantive discordance between BICR-assessed progressive disease and investigator-assessed-progressive disease is observed, FDA may consider PFS according to BICR as the primary endpoint.

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2. FDA did not agree with the Applicant's proposal for calculation of the efficacy boundary at the interim analysis using the minimum of the information fraction as determined by the planned and actual number of events in Amendment 9. In an Advice/Information Request letter issued on April 18, 2020, FDA stated that the observed number of events at the time of the interim analysis will be used for the calculation of efficacy boundary values for the review of the data as part of a marketing application.

8.1.2. KEYNOTE-590 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

The KEYNOTE-590 study was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding IEC review, informed consent and the protection of human participants in biomedical research. The protocol and any amendments, information provided to participants and any recruitment materials were reviewed and approved by the IECs (also called an IRB, ERC, or any other ethics committee). Informed consent was obtained from all participants prior to performing any study-related procedures or assessments.

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

Financial Disclosure

The Applicant's Position:

A financial disclosure review of the investigators who conducted the KEYNOTE-590 study was conducted and submitted to the sBLA.

The FDA's Assessment:
FDA agrees with the Applicant's position. Additional details are provided in Section 18.1.

Patient Disposition

The Applicant's Position:

In KEYNOTE-590, a total of 1020 participants were screened and 749 were randomized to the pembrolizumab plus chemotherapy group (373 participants) or the placebo plus chemotherapy

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group (376 participants) [Table 9]. In the pembrolizumab plus chemotherapy group, 370 participants received at least 1 dose of study intervention, 27 (7.3%) were still receiving ongoing pembrolizumab plus chemotherapy, and 108 (29.0%) were still in follow-up as of the data cutoff. In the placebo plus chemotherapy group, 370 participants received at least 1 dose of study intervention, 10 (2.7%) were still receiving ongoing treatment, and 65 (17.3%) were still in follow-up as of the data cutoff. Among the 88.6% and 97.0% of participants who discontinued treatment in the pembrolizumab plus chemotherapy group and placebo plus chemotherapy group, respectively, the most frequent reason for treatment discontinuation was progressive disease (55.1% for the pembrolizumab plus chemotherapy group and 64.6% for the placebo plus chemotherapy group).

Table 9: Applicant - Disposition of Subjects (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		376		749	
Status for Trial						
Discontinued	265	(71.0)	311	(82.7)	576	(76.9)
Death	260	(69.7)	308	(81.9)	568	(75.8)
Associated With Covid-19	1	(0.3)	0	(0.0)	1	(0.1)
Withdrawal By Subject	5	(1.3)	3	(0.8)	8	(1.1)
Not Associated With Covid-19, No Further Information	3	(0.8)	2	(0.5)	5	(0.7)
Not Associated With Covid-19, Subsequently Died	2	(0.5)	1	(0.3)	3	(0.4)
On-Going	108	(29.0)	65	(17.3)	173	(23.1)
Status for Study Medication						
Started	370		370		740	
Completed	15	(4.1)	1	(0.3)	16	(2.2)
Discontinued	328	(88.6)	359	(97.0)	687	(92.8)
Adverse Event	49	(13.2)	44	(11.9)	93	(12.6)
Clinical Progression	36	(9.7)	41	(11.1)	77	(10.4)
Complete Response	0	(0.0)	1	(0.3)	1	(0.1)
Physician Decision	9	(2.4)	10	(2.7)	19	(2.6)
Progressive Disease	204	(55.1)	239	(64.6)	443	(59.9)
Protocol Violation	0	(0.0)	1	(0.3)	1	(0.1)
Withdrawal By Subject	30	(8.1)	23	(6.2)	53	(7.2)
On-Going	27	(7.3)	10	(2.7)	37	(5.0)

If the overall count of subjects is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, subjects in population is used as

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the denominator for the percentage calculation.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl]

The FDA's Assessment:
FDA agrees with Merck's presentation of patient disposition. At the time of the primary analysis, 71% and 83% patients in the pembrolizumab and placebo arms, respectively have discontinued treatment. The main reason for treatment discontinuation was disease progression (55% disease progression as per RECIST and 10% clinical progression in the pembrolizumab arm and 65% disease progression as per RECIST and 11% clinical progression in the placebo arm).

Protocol Violations/Deviations

The Applicant's Position:

Protocol deviations were classified as per the ICH E3 classification of protocol deviations 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. Important protocol deviations were further classified as either clinically important (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) or not clinically important.

Important protocol deviations were reported for 60 participants. None of the important protocol deviations were considered to be clinically important. No participant's data were excluded from analyses due to an important protocol deviation, including those associated with the COVID-19 pandemic.

The FDA's Assessment:
FDA reviewed the protocol violations/deviations for KEYNOTE-059 and agrees with the Applicant's description of important deviations, according to ICH E2 classification of 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. No patient data were excluded from analyses due to a protocol deviation, and the reported protocol deviations/violations are unlikely to have had an important effect on the overall study results supporting this application.

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Table 10: Summary of Protocol Deviations considered "important" by Merck

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		376		749	
With one or more important protocol deviations	29	(7.8)	31	(8.2)	60	(8.0)
With no important protocol deviations	344	(92.2)	345	(91.8)	689	(92.0)
Prohibited Medications	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.1)**
Participant received radiation therapy for tumor control (with curative intent) while on treatment.	1	(0.3)	0	(0.0)	1	(0.1)
Safety Reporting	**25**	**(6.7)**	**28**	**(7.4)**	**53**	**(7.1)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	25	(6.7)	28	(7.4)	53	(7.1)
Study Intervention	**3**	**(0.8)**	**3**	**(0.8)**	**6**	**(0.8)**
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	3	(0.8)	3	(0.8)	6	(0.8)
Every subject is counted a single time for each applicable row and column. Database Cutoff Date: 02JUL2020						

Source: [P590V01MK3475: adam-adsl] [P590V01MK3475: sdtm-dv; suppdv]

Source: copied from submission on 3 Sept 2020, of CSR and SDTM-DV.

The majority of patients with important protocol deviations had a reportable safety event and/or follow up safety event information that was not reported per the timelines outlined in the protocol (n=53, 7%) or were administered improperly stored study intervention that was deemed unacceptable for use (n=6, 0.8%); one patient had prohibited medications, and had received radiation therapy for tumor control (with curative intent) while on treatment.

Patients with locally advanced esophageal carcinoma that is resectable or potentially curable with radiation therapy (as determined by local investigator), or had radiotherapy within 14 days of randomization were not eligible for enrollment in KN590. One patient randomized to the pembrolizumab arm received definitive chemoradiation for locally advanced disease more than a year before enrollment in the study and palliative radiation to a bone metastasis within 14 days of randomization; this case was reported by Merck as an important protocol deviation. It is unlikely that inclusion of this patient (who experienced disease progression after 5 months of pembrolizumab treatment) introduced bias to the study's results.

Although major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment was an exclusion criterion, 4 patients had surgeries/procedures considered to be major within 28 days of randomization: one patient had an incomplete lung wedge resection, one patient had an appendectomy, and 2 patients had abdominal laparotomies for staging with no resection. Inclusion of these patients may have increased their risk of study participation but did not appear to bias study results.

Patients who received prior neoadjuvant or adjuvant therapy with curative intent (including neoadjuvant/adjuvant treatment) with disease progression occurring during such treatment or within 6 months of cessation of treatment were not eligible. There was one patient on the SOC

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arm who had cisplatin prior to enrollment, which is unlikely to have influenced the efficacy results.

The reported protocol deviations/violations do not appear to be a significant cause of bias influencing the study results.

Table of Demographic Characteristics

The Applicant's Position:

Most participants were male (83.4%) and had a histology of squamous cell carcinoma (73.2%) [Table 11]. The rate of participants with adenocarcinoma was 26.8%.

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Table 11: Applicant - Participant Characteristics (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		376		749	
Gender						
Male	306	(82.0)	319	(84.8)	625	(83.4)
Female	67	(18.0)	57	(15.2)	124	(16.6)
Age (Years)						
< 65	201	(53.9)	226	(60.1)	427	(57.0)
>= 65	172	(46.1)	150	(39.9)	322	(43.0)
Mean	62.8		62.0		62.4	
SD	9.8		9.2		9.5	
Median	64.0		62.0		63.0	
Range	28 to 94		27 to 89		27 to 94	
Race						
American Indian Or Alaska Native	9	(2.4)	12	(3.2)	21	(2.8)
Asian	201	(53.9)	199	(52.9)	400	(53.4)
Black Or African American	5	(1.3)	2	(0.5)	7	(0.9)
Multiple	5	(1.3)	9	(2.4)	14	(1.9)
American Indian Or Alaska Native, White	3	(0.8)	6	(1.6)	9	(1.2)
Black Or African American, White	2	(0.5)	3	(0.8)	5	(0.7)
White	139	(37.3)	139	(37.0)	278	(37.1)
Missing	14	(3.8)	15	(4.0)	29	(3.9)
Ethnicity						
Hispanic Or Latino	42	(11.3)	57	(15.2)	99	(13.2)
Not Hispanic Or Latino	315	(84.5)	296	(78.7)	611	(81.6)
Not Reported	2	(0.5)	1	(0.3)	3	(0.4)
Unknown	12	(3.2)	20	(5.3)	32	(4.3)
Missing	2	(0.5)	2	(0.5)	4	(0.5)
Region						
Asia	196	(52.5)	197	(52.4)	393	(52.5)
Rest of World	177	(47.5)	179	(47.6)	356	(47.5)
Primary Diagnosis						

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Subject Characteristics (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Squamous Cell Carcinoma of the Esophagus	274	(73.5)	274	(72.9)	548	(73.2)
Adenocarcinoma of the Esophagus	58	(15.5)	52	(13.8)	110	(14.7)
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	41	(11.0)	50	(13.3)	91	(12.1)
Metastatic Staging						
M0	29	(7.8)	37	(9.8)	66	(8.8)
M1	344	(92.2)	339	(90.2)	683	(91.2)
Brain Metastasis						
Yes	1	(0.3)	2	(0.5)	3	(0.4)
No	372	(99.7)	374	(99.5)	746	(99.6)
Current Disease Stage						
IB	0	(0.0)	1	(0.3)	1	(0.1)
IIB	1	(0.3)	0	(0.0)	1	(0.1)
III	4	(1.1)	6	(1.6)	10	(1.3)
IIIA	4	(1.1)	5	(1.3)	9	(1.2)
IIIB	8	(2.1)	12	(3.2)	20	(2.7)
IIIC	12	(3.2)	13	(3.5)	25	(3.3)
IV	268	(71.8)	289	(76.9)	557	(74.4)
IVA	9	(2.4)	7	(1.9)	16	(2.1)
IVB	65	(17.4)	41	(10.9)	106	(14.2)
IVC	1	(0.3)	1	(0.3)	2	(0.3)
IVE	1	(0.3)	1	(0.3)	2	(0.3)
ECOG Performance Scale						
0	149	(39.9)	150	(39.9)	299	(39.9)
1	223	(59.8)	225	(59.8)	448	(59.8)
2	1	(0.3)	1	(0.3)	2	(0.3)
Histology						
Adenocarcinoma	99	(26.5)	102	(27.1)	201	(26.8)
Squamous Cell Carcinoma	274	(73.5)	274	(72.9)	548	(73.2)
Disease Status						
Metastatic	344	(92.2)	339	(90.2)	683	(91.2)

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Subject Characteristics (ITT Population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Unresectable - Locally Advanced	29	(7.8)	37	(9.8)	66	(8.8)
PD-L1 Status						
CPS >= 10	186	(49.9)	197	(52.4)	383	(51.1)
CPS < 10	175	(46.9)	172	(45.7)	347	(46.3)
Not evaluable	6	(1.6)	6	(1.6)	12	(1.6)
Missing	6	(1.6)	1	(0.3)	7	(0.9)
MSI Status						
Normal	69	(18.5)	43	(11.4)	112	(15.0)
Unknown[a]	7	(1.9)	3	(0.8)	10	(1.3)
Missing[b]	297	(79.6)	330	(87.8)	627	(83.7)

[a] Results not available due to tissue inadequacy or assay-issue.
[b] Not evaluated as tissue was not available.
Database Cutoff Date: 02JUL2020

Source: [P590V01MK3475: adam-adsl]

The FDA's Assessment:
FDA agrees with the Applicant's presentation of patient characteristics in KEYNOTE-590. See FDA assessment below for details of both demographics and baseline characteristics.

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

The Applicant's Position:

Among participants who either achieved an on-study CR or PR or were continuing in the study without PD as assessed by investigator per RECIST 1.1, 112 participants were evaluable for MSI status; none were MSI-H.

The FDA's Assessment:
FDA agrees with the Applicant's description of baseline characteristics. FDA notes that there were more men (84%) enrolled on KEYNOTE-590 than women, which reflects the male predominance with respect to the diagnosis of esophageal carcinoma. The incidence of esophageal adenocarcinoma in men is 6–10 times higher than in women, and the incidence of squamous esophageal cell carcinoma is 2–3 times higher in men than women (Mathieu et al, 2014).

Squamous cell cancer (ESCC) continues to be the major type of esophageal cancer in Asia, while the incidence of esophageal adenocarcinoma (EAC) is increasing in the Western world. When stratified by histology, in the U.S., the overall incidence is greater for EAC (2.59 95% CI 2.57-

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2.61) than for ESCC (1.29 95% CI 1.28-1.30) (Patel and Benipal, 2018) and predominately affects Whites (Zhang et al, 2012). In Study KEYNOTE-590, 53% of patients were enrolled in Asia and 48% enrolled from the rest of the world (region was a prespecified randomization factor); 37% of patients were of White descent; 27% of patients had adenocarcinoma and 73% had ESCC. Baseline demographic and disease characteristics were balanced between arms. Less than 1% of patients were Black, underscoring that Black patients were underrepresented in the trial.

Half of the patients enrolled had a CPS≥ 10 tumor status (51%), and 46% had CPS <10; 2.5% patients were not evaluable for CPS. CPS tumor status was balanced between arms and due to the large sample size overall, the missing data is not likely to influence the efficacy outcomes.

In contrast, data on microsatellite instability (MSI) were missing in 84% (n=627) of patients. MSI is a known prognostic factor in many cancers. Based on a meta-analysis by Lorenzi et al, for stages 3-4 esophageal cancers, the prevalence of MSI-H/dMMR was 18% (95%CI: 4%, 39%; 2 studies; 62 patients) (Lorenzi et al, 2020). According to van Laarhovene, between 6 to 24% of resected GEJ adenocarcinomas are reported to be MSI-H (van Laarhovene et al, 2020). These data, however, may not represent the incidence of microsatellite instability in the metastatic setting where the incidence is frequently lower than in resectable disease (Le et al, 2017); in this paper assessing microsatellite instability across various tumors, the incidence in esophageal and GEJ tumors was less than 2%.

In a previous meeting with FDA “Advice/Information Request” on sent on 16 Feb 2018, it was agreed upon that as an alternative to testing tumor specimens for all patients, it would be acceptable to determine MSI-H/dMMR tumor status only in those patients with esophageal cancer enrolled in clinical studies across Merck’s clinical development for esophageal cancer who achieve a complete or partial response per RECIST v1.1. Among patients who either achieved an on-study CR or PR or were continuing in the study without PD per RECIST 1.1, 112 patients were evaluable for MSI status; none were MSI-H.

Based on the demographic and baseline characteristic described, there are no imbalances in the demographic and disease baseline characteristics and this reviewer finds no potential for bias in the safety population or confounders for efficacy outcomes.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant’s Position:

- Treatment Compliance: Study intervention was administered in the clinic by qualified site personnel, ensuring compliance .

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- Concomitant Medications: The most frequently reported prior and concomitant medications were dexamethasone and aprepitant.

- Rescue Medication: Rescue medications and supportive care were allowed in KEYNOTE-590 study as deemed necessary by the treating investigator as per protocol.

The FDA's Assessment:
FDA agrees with the Applicant's position and description. Thyroid therapy was more frequently administered in patients in the pembrolizumab arm (15% vs 12% in the pembrolizumab and placebo arms, respectively), and corticosteroids for systemic use was higher in the pembrolizumab arm compared to the placebo arm (92%, 89% respectively). The difference between incidence of thyroid and corticosteroid use between arms does not appear to be clinically meaningful, and one might expect the incidence on the pembrolizumab arm to be higher, considering the incidence of immune-related adverse reactions observed in the study, which is consistent with the known safety profile of pembrolizumab. Patients in the pembrolizumab arm received more antithrombotic agents (31%) than in the placebo arm (26%); however, as duration of treatment was longer in the pembrolizumab arm and patients with cancer have increased incidence of VTE (Rickles and Falanga, 2001), this small imbalance between arms cannot be conclusively attributed to immune checkpoint inhibition. Furthermore, in the assessment of safety of Study KN590, there was no excess of thrombosis in the pembrolizumab arm nor was the incidence out of proportion when compared to prior supplements for pembrolizumab (See 8.2).

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

The results presented are from the IA for KEYNOTE-590, with a data cutoff date of 02-JUL-2020, which was after a minimum of 13 months of follow-up. In all participants, pembrolizumab plus chemotherapy, compared to placebo plus chemotherapy, demonstrated a statistically significant improvement in OS. The HR was 0.73 (95% CI: 0.62, 0.86; $p<0.0001$, which is less than the p-value crossing boundary of 0.01421 for statistical significance), representing a 27% reduction in the risk of death compared to chemotherapy plus placebo [Table 12].

In all participants, pembrolizumab plus chemotherapy compared to placebo plus chemotherapy also demonstrated a statistically significant improvement in PFS as assessed by the investigator. The HR was 0.65 (95% CI: 0.55, 0.76; $p<0.0001$, which is less than the p-value crossing boundary of 0.02477 for statistical significance), representing a 35% reduction in the risk of disease progression or death compared to placebo plus chemotherapy. PFS rates at 12 months were 24.9% (95% CI: 20.4, 29.6) and 11.9% (95% CI: 8.7, 15.7) in the pembrolizumab plus

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chemotherapy and the placebo plus chemotherapy groups, respectively [Table 12]. PFS results based on BICR assessment per RECIST 1.1 were consistent with the investigator assessment.

OS and PFS results for all participants in the Global Cohort (n=711) were consistent with the primary analysis in the Global Study population (n=749).

Table 12: Applicant - Primary Efficacy Outcomes – KEYNOTE-590

	All Participants	
Efficacy Endpoint	**Pembrolizumab plus Chemotherapy (N=373)**	**Placebo plus Chemotherapy (N=376)**
Primary Outcome: OS		
Number of events (%)	262 (70.2)	309 (82.2)
Median OS, months[†](95% CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)
HR (95% CI)[‡]	0.73 (0.62, 0.86)	
P-value (superiority statistic)[‡‡]	<0.0001	
OS rate, % (95% CI) at 12 Months[†]	50.6 (45.4, 55.6)	39.4 (34.4, 44.3)
OS rate, % (95% CI) at 18 Months[†]	35.3 (30.4, 40.2)	24.0 (19.8, 28.5)
OS rate, % (95% CI) at 24 Months[†]	27.7 (22.7, 32.8)	16.3 (12.4, 20.6)
Primary Outcome: PFS (Investigator Assessed per RECIST 1.1)		
Number of events (%)	297 (79.6)	333 (88.6)
Median PFS (95% CI), months[†]	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)
HR (95% CI)[‡]	0.65 (0.55, 0.76)	
P-value (superiority statistic)[‡‡]	<0.0001	
PFS rate, % (95% CI) at 12 Months[†]	24.9 (20.4, 29.6)	11.9 (8.7, 15.7)
PFS rate, % (95% CI) at 18 Months[†]	15.8 (12.0, 20.0)	5.5 (3.3, 8.5)

Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

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

[‡] Based on Cox regression model with treatment as a covariate stratified by geographic region (Asia vs Rest of the world) and tumor histology (Squamous cell carcinoma vs adenocarcinoma) and ECOG performance status (0 versus 1).

[‡‡] One-sided p-value based on stratified log-rank test.

Database Cutoff Date: 02-JUL-2020

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the investigator-assessed PFS and OS results in the ITT population (referred to as the all-comers Global Study population above,

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n=749). FDA has the following additional comments:

1. The formal testing plan for KEYNOTE-590 included several co-primary endpoints that were formally tested and found to be statistically significant prior to the tests of OS and PFS in the ITT population in the Mauer and Bretz graphical testing approach. The results of these endpoints are included in Table 13 below.

Table 13. Analysis of progression-free survival and overall survival of the pre-specified primary endpoints other than the ITT population

	Progression-free Survival (investigator)		Overall Survival	
	Pembrolizumab+ chemotherapy N=373	Placebo+ chemotherapy N=376	Pembrolizumab+ chemotherapy N=373	Placebo+ chemotherapy N=376
ESCC PD-L1 ≥10, N	143	143	143	143
Events (%)	109 (76)	127 (89)	94 (66)	121 (85)
Median, months (95% CI)[1]	7.3 (6.2, 8.2)	5.4 (4.2, 6.0)	13.9 (11.1, 17.7)	8.8 (7.8, 10.5)
Hazard Ratio (95% CI)[2]	0.53 (0.40, 0.69)		0.57 (0.43, 0.75)	
p-value[3]	Not tested		<0.0001	
ESCC, N	274	274	274	274
Events (%)	219 (80)	244 (89)	190 (69)	222 (81)
Median, months (95% CI)[1]	6.3 (6.2, 6.9)	5.8 (5.0, 6.1)	12.6 (10.2, 14.3)	9.8 (8.6, 11.1)
Hazard Ratio (95% CI)[2]	0.65 (0.54, 0.78)		0.72 (0.60, 0.88)	
p-value[3]	<0.0001		0.0006	
PD-L1 ≥10, N	186	197	186	197
Events (%)	140 (75)	174 (88)	124 (67)	165 (84)
Median, months (95% CI)[1]	7.5 (6.2, 8.2)	5.5 (4.3, 6.0)	13.5 (11.1, 15.6)	9.4 (8.0, 10.7)
Hazard Ratio (95% CI)[2]	0.51 (0.41, 0.65)		0.62 (0.49, 0.78)	
p-value[3]	<0.0001		<0.0001	

[1] Kaplan-Meier method; [2]Stratified Cox proportional hazard model; [3]Stratified log-rank test

2. FDA does not agree with the Applicant's calculation of the alpha boundary for statistical significance for OS at the interim analysis. FDA calculates the alpha boundary for interim analyses based on observed information fraction rather than the minimum of planned and actual events (the Applicant's proposal). The alpha boundary as calculated by FDA is 0.017 using a 91% observed information fraction, and the OS interim analysis was statistically significant using this efficacy boundary.

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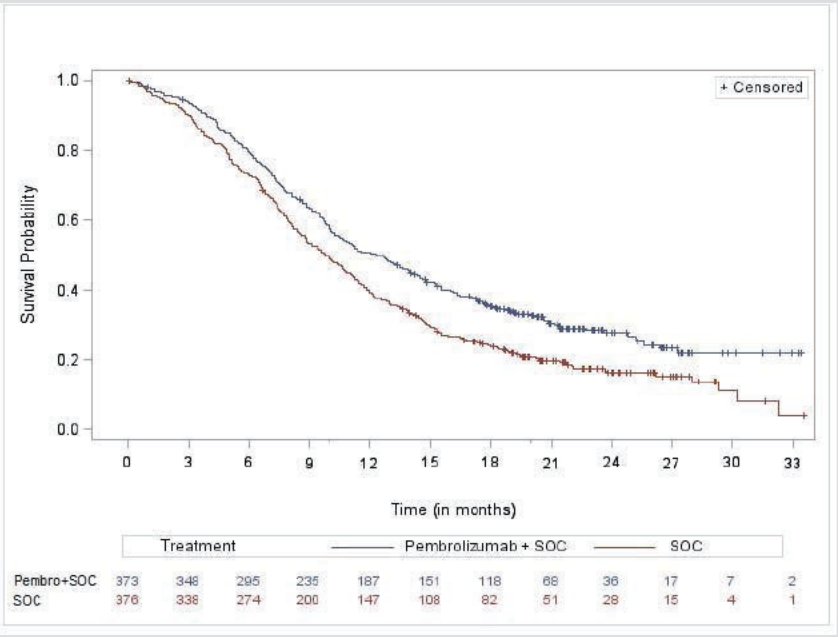
The Kaplan-Meier (K-M) plot for OS in the ITT population is presented in Figure 2 below. Upon visual inspection of K-M plot as well as the log-negative log plot of survivor functions for each arm, the proportional hazards assumption holds for OS in this population.

Figure 2. Kaplan-Meier plot of Overall Survival in KEYNOTE-590 (ITT population)



Estimation of treatment effect of BICR-assessed PFS in the ITT population was supportive of the observed effect for investigator-assessed PFS. The median PFS per BICR was 6.5 months (95% CI: 6.2, 8.0) in the pembrolizumab plus chemotherapy arm and 6.0 months (95% CI: 5.7, 6.2) in the placebo arm, with a corresponding hazard ratio of 0.67 (95% CI: 0.56, 0.79). In the ITT population, a total of 522 investigator-assessed PD events were observed, 246 in pembrolizumab plus chemotherapy arm and 276 in the placebo plus chemotherapy arm. The overall discordance rate for BICR overall assessment of progressive disease for each patient with observed investigator assessed PD was 28% (148 out of 522); 27% (66 out of 246) in the pembrolizumab plus chemotherapy arm and 30% (82 out of 276) in placebo plus chemotherapy arm. There were a total of 163 investigator-assessed non-PD events. The overall discordance rate for BICR overall assessment of non-PD for each patient with observed investigator assessed non-PD was 18% (29 out of 163); 13% (12 out of 96) in the pembrolizumab plus chemotherapy and 25% (17 out of 67) in the placebo plus chemotherapy arm. These discordance rates are considered acceptable and the results of both PFS analyses are consistent. Given the effect on OS and double-blind design, the protocol-specified analysis of investigator-assessed PFS was acceptable.

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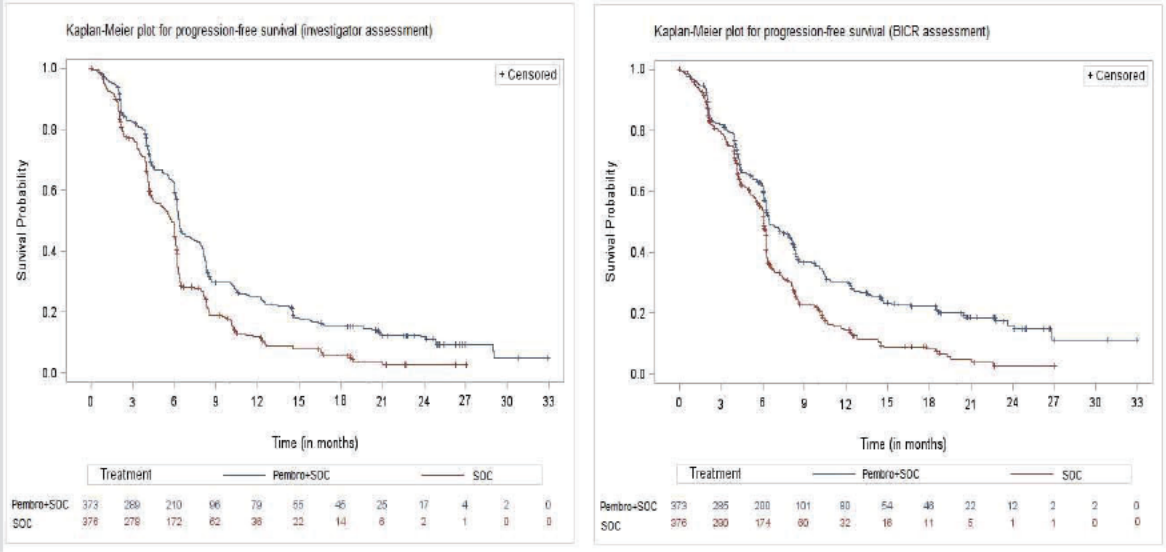
The Kaplan-Meier plots for PFS by investigator and BICR assessment are presented in Figure 3 below. Upon visual inspection of the K-M plots as well as the log-negative log plot of survivor functions of each treatment arm, there may be concerns for non-proportionality in the first 6 months of follow-up for PFS in this population. However, after 6 months there is a separation of the survival curves for the two arms, and the exploratory analyses of landmark rates provide some description of the difference in PFS rate over time to complement the estimates of median PFS and hazard ratio.

Figure 3. Kaplan-Meier plots for Progression-Free Survival in KEYNOTE-590 (ITT population)



3. FDA considers the landmark rates of time-to-event endpoints, such as PFS or OS rates at 12 months, presented by the Applicant to be exploratory only.

Data Quality and Integrity

The Applicant's Position:

Quality and integrity of study data were assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures.

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

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Part of this study was conducted during the COVID-19 pandemic. Contingency measures were implemented to manage study conduct during the pandemic. There were no changes in the planned conduct of the study or planned analyses due to the COVID-19 pandemic and no data integrity concerns were reported.

The FDA's Assessment:
FDA acknowledges the Applicant's position; the review did not uncover any data integrity issues. FDA agrees that the sBLA submission was complete and of adequate quality.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

In all participants, the confirmed ORR based on investigator assessment was 45.0% and 29.3% in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups, respectively, reflecting a statistically significant 15.8% improvement ($p<0.0001$, which is less than the p-value boundary of 0.025 for statistical significance) compared to placebo plus chemotherapy [Table 14].

ORR results for all participants in the Global Cohort (n=711) were consistent with the primary analysis in the Global Study population (n=749).

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Table 14: Applicant - Secondary Efficacy Outcomes - KEYNOTE-590

	All Participants	
Efficacy Endpoint	**Pembrolizumab plus Chemotherapy (N=373)**	**Placebo plus Chemotherapy (N=376)**
Secondary Efficacy Outcomes: ORR and DOR (Investigator Assessed per RECIST 1.1)		
ORR		
ORR, % (95% CI)	45.0 (39.9, 50.2)	29.3 (24.7, 34.1)
P-value‡‡‡	<0.0001	
DOR (Confirmed CR or PR)		
Number of responders	168	110
Median DOR, months†† (range)	8.3 (1.2+ - 31.0+)	6.0 (1.5+ - 25.0+)

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; ORR = objective response rate or Overall response rate; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

Response was assessed based on investigator assessment per RECIST 1.1; only confirmed responses are included. The 95% CIs for response rates were calculated based on the binomial exact method.

‡‡‡ One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

†† From product-limit (Kaplan-Meier) method for censored data.

"+" indicates there was no progressive disease by the time of last disease assessment.

Database Cutoff Date: 02-JUL-2020

The FDA's Assessment:
FDA agrees with the Applicant's description of the results for investigator-assessed ORR and DOR.

Dose/Dose Response

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Pembrolizumab has previously been approved in esophageal cancer at a dose of 200 mg every 3 weeks or 400 mg every 6 weeks (U.S. package insert, Keytruda, accessed on 4 March 2021). The patients on KEYNOTE-590 were exposed predominantly to the 200 mg every 3 weeks dose but pharmacokinetic and dose response studies, as reflected in the Keytruda label, support the use of the 400 mg every 6 weeks dosage.

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Durability of Response

The Applicant's Position:

In all participants, the median duration of response was 8.3 months in the pembrolizumab plus chemotherapy group and 6.0 months in the placebo plus chemotherapy group [Table 14]. By KM estimation, 18.1% of participants in the pembrolizumab plus chemotherapy group and 6.1% of participants in the placebo plus chemotherapy group had extended responses for ≥24 months.

The FDA's Assessment:
FDA agrees with the Applicant's description of the results of investigator-assessed DOR.

Persistence of Effect

The Applicant's Position:

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

The FDA's Assessment:
Persistence of effect is a term better suited for continuous variables (hypertension, biomarker monitoring, etc.) than to characterize or compare the effect of treatment on the selected endpoints. Treatment effect and study outcomes are described elsewhere in this section.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
The Applicant's Position:

PROS were evaluated using the EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D. Results from PROs analyses showed EORTC QLQ-C30 global health status/QoL mean score change from baseline to the prespecified Week 18 timepoint in both intervention groups with an LS mean difference of -0.10 points (95% CI: -3.40, 3.20). The LS mean difference from baseline in physical functioning score at Week 18 was 0.85 (95% CI: -2.56, 4.27). Median time to deterioration for global health status/QoL and for physical functioning was not reached for both intervention groups.

For EORTC QLQ-OES18, the LS mean difference from baseline to Week 18 for pain between the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group was -2.94 (95% CI: -5.86, -0.02). For dysphagia, the LS mean changes from baseline to Week 18 were 0.78 (95% CI: -3.25, 4.81) and 3.13 (95% CI: -1.02, 7.28) for the pembrolizumab plus chemotherapy group and placebo plus chemotherapy group, respectively. For reflux, the LS mean changes

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from baseline to Week 18 were -0.43 (95% CI: -2.91, 2.06) and 0.76 (95% CI: -1.08, 3.33), respectively.

The LS mean change from baseline to Week 18 in EQ-5D VAS was -2.29 (95% CI: -4.35, -0.24) and -3.49 (95%CI: -5.61, -1.37) for the pembrolizumab plus chemotherapy group and placebo plus chemotherapy group, respectively.

The FDA's Assessment:

While FDA does not object to the presentation of the data for the EORTC QLQ-C30 and EORTC QLQ-OES18 instruments, PRO endpoints were not included in the formal testing plan for KEYNOTE-590. Given the lack of control for the Type I error rate for these analyses, and that the protocol did not pre-specify clinically meaningful changes for the proposed PRO endpoints (or for changes in sub-domains), FDA considers these results to be exploratory. The results of the EQ-5D VAS instrument were not independently verified.

FDA performed independent analyses and confirmation of the completion rates for the EORTC QLQ-C30 and EORTC QLQ-OES18 instruments. The distributions of completion rates for both instrument in each treatment arm over time were comparable, and are presented below in Table 15 and Table 16 respectively.

Table 15. Completion rate of EORTC QLQ-C30 in KEYNOTE-590 (PRO Full Analysis Set population)

Analysis visit (# completed/# eligible) (%)	Pembrolizumab + chemotherapy N=366	Placebo + chemotherapy N=364
Baseline	356/366 (97)	355/364 (97)
Week 3	318/328 (97)	293/315 (93)
Week 6	291/306 (95)	282/297 (95)
Week 9	265/280 (95)	282/307 (92)
Week 12	256/275 (93)	241/268 (90)
Week 15	237/258 (92)	227/246 (92)
Week 18	225/250 (90)	206/223 (92)
Week 21	206/220 (94)	191/200 (96)
Week 24	208/222 (94)	190/204 (93)
Week 33	155/183 (85)	128/145 (88)
Week 42	109/127 (86)	74/90 (82)

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Week 51	80/90 (89)	42/56 (75)
Week 60	31/78 (40)	27/42 (64)

Note. PRO Full Analysis Set is defined as all randomized patients who have at least one PRO assessment available for the specific endpoint and have received at least one dose of study intervention.

Table 16. Completion rate of EORTC QLQ-OES18 in KEYNOTE-590 (PRO Full Analysis Set population)

Analysis visit, (# completed/# eligible) (%)	Pembrolizumab + chemotherapy N=366	Placebo + chemotherapy N=360
Baseline[1]	355/366 (97)	350/360 (97)
Week 3	313/327 (96)	285/311 (92)
Week 6	288/306 (94)	273/292 (94)
Week 9	264/280 (94)	278/303 (92)
Week 12	256/274 (93)	237/265 (89)
Week 15	236/258 (92)	224/244 (92)
Week 18	224/249 (90)	204/220 (93)
Week 21	205/220 (93)	189/197 (96)
Week 24	207/221 (94)	188/201 (94)
Week 33	154/183 (84)	125/143 (87)
Week 42	109/127 (86)	74/88 (84)
Week 51	80/90 (89)	42/55 (76)
Week 60	31/78 (40)	26/41 (63)

Note. PRO Full Analysis Set is defined as all randomized patients who have at least one PRO assessment available for the specific endpoint and have received at least one dose of study intervention.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

The FDA's Assessment:

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FDA has conducted additional analysis of overall survival based on selected patient characteristics in the ITT population, as presented in Table 17 below. While these subgroup analyses are considered exploratory, there were no obvious outliers.

Table 17. Overall survival by selected patient characteristics (ITT population)

	Pembrolizumab plus Chemotherapy (N=373)	Placebo plus Chemotherapy (N=376)	
	# of deaths/n	# of deaths/n	HR (95% CI)
Age, in years			
< 65 (n=427)	147/201	185/226	0.76 (0.61, 0.95)
≥ 65 (n=322)	115/172	124/150	0.69 (0.53, 0.89)
Sex			
Male (n=625)	216/306	266/319	0.70 (0.58, 0.84)
Female (n=124)	46/67	43/57	0.89 (0.59, 1.35)
Geographic region			
Asia (n=393)	128/196	160/197	0.64 (0.51, 0.81)
Ex-Asia (n=356)	134/177	149/179	0.83 (0.66, 1.05)
Race[1]			
Asian (n=400)	132/201	161/199	0.66 (0.52, 0.83)
White (n=278)	106/139	117/139	0.80 (0.62, 1.05)
Black or African American (n=7)	4/5	1/2	---
American Indian/Alaska Native (n=21)	8/9	11/12	---
Multiple (n=14)	4/5	8/9	---
Histology			
Adenocarcinoma (n=201)	72/99	87/102	0.74 (0.54, 1.02)
Squamous cell carcinoma (n=548)	190/274	222/274	0.72 (0.60, 0.88)
ECOG[2]			
0 (n=299)	95/149	112/150	0.72 (0.55, 0.94)
1 (n=448)	166/223	196/225	0.73 (0.59, 0.90)
PD-L1 CPS[3]			
< 10 (n=347)	132/175	139/172	0.86 (0.68, 1.10)
≥ 10 (n=383)	124/186	165/197	0.62 (0.49, 0.78)

[1]29 patients had a missing race, 14 in the pembrolizumab arm and 15 in the placebo arm. [2] 2 patients had a ECOG score of 2, 1 in each arm. [3] 19 patients had a PD-L1 CPS missing or not evaluable, 12 in the pembrolizumab arm and 7 in the placebo arm.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

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

FDA's independent analyses of the efficacy results for KEYNOTE-590 , in general, concurs with the Applicant's position and presentation on the efficacy results of the primary endpoints of investigator-assessed PFS and OS, as well as the secondary endpoints of ORR and DOR. KEYNOTE-590 met its primary endpoints and key secondary endpoints (PFS, OS and ORR) in the intent-to-treat population of patients with locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ, with results that were statistically significant and clinically meaningful. Pembrolizumab in combination with cisplatin and 5-FU yields a net favorable benefit-risk profile compared to placebo in combination with cisplatin and 5-FU as a first-line treatment in the intended patient population. PFS results by BICR were consistent with investigator-assessed PFS in KEYNOTE-590.

(b) (4)

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:

Only results from the single KEYNOTE-590 study are presented, as this is a stand-alone study that supports efficacy and safety in the proposed indication.

The FDA's Assessment:
FDA agrees.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

Only results from the single KEYNOTE-590 study are presented, as this is a stand-alone study that supports efficacy and safety in the proposed indication.

The FDA's Assessment:
FDA agrees.

8.2 Review of Safety

The Applicant's Position:

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

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The safety results from KEYNOTE-590 demonstrate that pembrolizumab plus cisplatin and 5-FU had a tolerable safety profile that generally reflects the known safety profiles of the components. Generally, AEs were effectively managed by standard clinical practice as applicable for pembrolizumab monotherapy and the chemotherapy administered. No new safety concerns were identified.

The FDA's Assessment:
FDA agrees with the Applicant's position. While there were some differences between the as treated safety population and the population represented in the pembrolizumab RSD, FDA did not consider these differences to be clinically important as this is expected given the heterogenous patient populations represented in both groups. Overall, a review of the safety profile of the KEYNOTE-590 safety dataset did not reveal unexpected safety events for the pembrolizumab arm versus placebo arm and the underlying disease.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety review focuses on the comparison of safety data from the participants in KEYNOTE-590 who received pembrolizumab plus chemotherapy with the safety data from participants who received placebo plus chemotherapy [Table 18].

Table 18: Applicant - Safety Datasets

KEYNOTE-590 pembrolizumab + chemotherapy N=370	KEYNOTE-590 placebo + chemotherapy N=370
Safety data from participants with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction adenocarcinoma (Siewert type 1) who received pembrolizumab in combination with chemotherapy in KEYNOTE-590	Safety data from participants with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction adenocarcinoma (Siewert type 1) who received placebo in combination with chemotherapy in KEYNOTE-590

The FDA's Assessment:
As stated in the pre sBLA meeting, FDA agreed with Merck's approach to the safety review and requested submission of data from Study KEYNOTE-590 and the Reference Safety Dataset (RDS) for pembrolizumab (N=2799).

8.2.2. Review of the Safety Database

Overall Exposure

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The Applicant's Position:

The number of participants exposed to pembrolizumab in KEYNOTE-590 is presented in [Table 19]. The median duration of exposure was 5.7 months in the pembrolizumab plus chemotherapy group and 5.1 months in the placebo plus chemotherapy group. Mean exposure was 7.7 months in the pembrolizumab plus chemotherapy group and 5.8 months in the placebo plus chemotherapy group. The percentage of participants with duration of exposure ≥6 months was 45.1% in the pembrolizumab plus chemotherapy group and 35.4% in the placebo plus chemotherapy group.

Table 19: Applicant - Summary of Drug Exposure (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy‡‡ (N=370)	KN590 Data for Placebo + Chemotherapy¶¶ (N=370)
Duration On Therapy (month)		
Mean	7.7	5.8
Median	5.68	5.11
SD	6.84	4.76
Range	0.03 to 26.02	0.10 to 26.58
Number of cycle		
Mean	11.0	8.5
Median	8.00	7.00
SD	9.35	6.43
Range	1.00 to 35.00	1.00 to 35.00

Each subject is counted once on each applicable duration category row.
Duration of Exposure is calculated as (last dose date - first dose date +1)/30.4367 (months).
‡‡ Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.
¶¶ Includes all subjects who received at least one dose of chemotherapy in KN590.

Source: [ISS: adam-adsl; adexsum]

The FDA's Assessment:

FDA agrees with the Applicant's position. FDA replicated the applicant's analysis (under the RTOR program, datasets were submitted prior to submission of the full application, on September 3, 2020). As patients were treated until disease progression, the median exposure to pembrolizumab was slightly longer in KEYNOTE-590 for patients on the pembrolizumab arm compared with the placebo arm (5.7 months vs 5.1 months, respectively), reflecting the treatment effect on PFS of pembrolizumab in the treated population (See Efficacy endpoints in 8.1.2).

Relevant characteristics of the safety population:

The Applicant's Position:

The demographic and other baseline characteristics of the KEYNOTE-590 population were representative of participants with metastatic esophageal cancer [Table 20].

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

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Table 20: Applicant - Subject Characteristics (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]	
	n	(%)	n	(%)
Subjects in population	370		370	
Gender				
Male	305	(82.4)	314	(84.9)
Female	65	(17.6)	56	(15.1)
Age (Years)				
<65	201	(54.3)	221	(59.7)
>=65	169	(45.7)	149	(40.3)
Mean	62.8		62.0	
SD	9.8		9.2	
Median	64.0		62.0	
Range	28 to 94		27 to 89	
Race				
American Indian Or Alaska Native	9	(2.4)	12	(3.2)
Asian	201	(54.3)	197	(53.2)
Black Or African American	5	(1.4)	2	(0.5)
Multiracial	5	(1.4)	9	(2.4)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)
White	136	(36.8)	135	(36.5)
Missing	14	(3.8)	15	(4.1)
Ethnicity				
Hispanic Or Latino	41	(11.1)	55	(14.9)
Not Hispanic Or Latino	313	(84.6)	293	(79.2)
Not Reported	2	(0.5)	1	(0.3)
Unknown	12	(3.2)	19	(5.1)
Missing	2	(0.5)	2	(0.5)
Age category (year)				
<65	201	(54.3)	221	(59.7)
65-74	132	(35.7)	117	(31.6)
75-84	36	(9.7)	30	(8.1)
>=85	1	(0.3)	2	(0.5)
ECOG performance scale				
[0] Normal Activity	148	(40.0)	146	(39.5)
[1] Symptoms, but ambulatory	221	(59.7)	223	(60.3)
Other/Missing	1	(0.3)	1	(0.3)
Geographic Region				
US	17	(4.6)	22	(5.9)
Ex-US	353	(95.4)	348	(94.1)

[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.
[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

Source: [ISS: adam-adsl]

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The FDA's Assessment:
FDA agrees with the applicant's position. As only 9 patients enrolled in the study did not receive treatment, there are no demographic and baseline disease characteristics differences between the safety and ITT populations. Additional discussions regarding applicability to the U.S. population can be found in Section 8.1.1.

Adequacy of the safety database:
The Applicant's Position:

The clinical safety data supporting this sBLA are derived from KEYNOTE-590. The number of participants with esophageal cancer included in this study represents an adequate size, considering exposure to appropriate dose, duration of treatment, participant demographics, and disease characteristics for this study population.

The FDA's Assessment:
FDA agrees with the applicant's position. FDA considers the size of the dataset adequate to characterize the safety of pembrolizumab and 5FU/cisplatin for the first line treatment of patients with esophageal carcinoma.

8.2.3. 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. Sponsor QA carried out periodic, independent audits to ensure the accuracy and integrity of the clinical study data. There were no issues with data integrity or analysis that precluded the inclusion of data in the safety analysis. The sBLA submission contains all required components of the eCTD. The overall quality and integrity of the application is sufficient for substantive review to be completed.

The FDA's Assessment:
FDA acknowledges the Applicant's position; the review did not uncover any data integrity issues. FDA agrees that the sBLA submission was complete.

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Categorization of Adverse Event

The Applicant's Position:

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence, severity, causality, and outcome of AEs/ SAEs; and changes in vital signs and laboratory values.

For the time period beginning at treatment allocation/randomization through 30 days (AEs) and 90 days (SAEs) following cessation of trial treatment (or 30 days following cessation of trial treatment if the participant initiated new anticancer therapy), AEs and SAEs whether or not assessed as related to the Sponsor or Comparator's product, were recorded.

AEs were graded by the investigator using NCI CTCAE version 4.03 and coded using MedDRA version 23.0.

AEOSI are immune-mediated events and immune-related reactions associated with pembrolizumab. The frequency and maximum severity of AEOSI analyses are based on a predefined list of preferred AE terms deemed clinically consistent with the identified risks of pembrolizumab (AEOSIs) and potentially associated with an immune etiology. This list was developed by the Sponsor and includes AEOSI terms identified to allow consistent assessment of AEOSIs across pembrolizumab studies.

The FDA's Assessment:
FDA conducted an audit of the coding of the terms in the safety dataset. Verbatim terms for safety events were accurately coded using the MedDRA dictionary. FDA analyses, conducted under the auspices of RTOR, were conducted using different cutoffs than the Applicant's and although the numbers may be slightly different, the review team agrees with the Applicant's conclusions about differences between arms. In the dataset, the number of deaths is seemingly higher because disease progression was included, refer to "Deaths" in 8.2.4.

Routine Clinical Tests

The Applicant's Position:

The schedule of assessments in the KEYNOTE-590 study, as outlined in the protocol, is shown in [Table 5]. It presents the frequency of laboratory testing, vital signs, physical exam, and AE monitoring.

The FDA's Assessment:
In both arms, patients were tested for routine monitoring on Day 1 of each cycle. Thyroid monitoring was scheduled every 2 cycles. Monitoring for safety was adequate and consistent with the standard of care.

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8.2.4. Safety Results

A summary of AEs is provided in [Table 21].

Table 21: Applicant - Adverse Event Summary (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more adverse events	370	(100.0)	368	(99.5)
with no adverse event	0	(0.0)	2	(0.5)
with drug-related[†] adverse events	364	(98.4)	360	(97.3)
with toxicity grade 3-5 adverse events	318	(85.9)	308	(83.2)
with toxicity grade 3-5 drug-related adverse events	266	(71.9)	250	(67.6)
with serious adverse events	205	(55.4)	204	(55.1)
with serious drug-related adverse events	117	(31.6)	97	(26.2)
who died	28	(7.6)	38	(10.3)
who died due to a drug-related adverse event	9	(2.4)	5	(1.4)
discontinued any drug due to an adverse event	90	(24.3)	74	(20.0)
discontinued Pembrolizumab or placebo	54	(14.6)	45	(12.2)
discontinued any chemotherapy	75	(20.3)	69	(18.6)
discontinued all drugs	23	(6.2)	28	(7.6)
discontinued any drug due to a drug-related adverse event	72	(19.5)	43	(11.6)
discontinued Pembrolizumab or placebo	35	(9.5)	15	(4.1)
discontinued any chemotherapy	58	(15.7)	42	(11.4)
discontinued all drugs	16	(4.3)	10	(2.7)
discontinued any drug due to a serious adverse event	58	(15.7)	47	(12.7)
discontinued Pembrolizumab or placebo	47	(12.7)	43	(11.6)
discontinued any chemotherapy	43	(11.6)	41	(11.1)
discontinued all drugs	21	(5.7)	27	(7.3)
discontinued any drug due to a serious drug-related adverse event	38	(10.3)	17	(4.6)
discontinued Pembrolizumab or placebo	29	(7.8)	14	(3.8)
discontinued any chemotherapy	25	(6.8)	16	(4.3)
discontinued all drugs	14	(3.8)	10	(2.7)

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

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

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

[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.

[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

Source: [ISS: adam-adsl; adae]

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Deaths

The Applicant's Position:

The overall incidence of AEs resulting in death was 7.6% in the pembrolizumab plus chemotherapy group and 10.3% in the placebo plus chemotherapy group [Table 22]. One death from the pembrolizumab plus chemotherapy group was due to COVID-19. The majority of AEs resulting in death were not considered drug-related by investigator assessment. Most fatal outcomes were likely due to underlying disease and/or intercurrent illness. Of the 9 deaths in the pembrolizumab plus chemotherapy group considered drug-related by investigator assessment[Table 21], 1 (pneumonitis) was considered to be related to pembrolizumab; 4 (interstitial lung disease, pulmonary embolism, diarrhea, and hepatic failure) were considered to be related to both pembrolizumab and chemotherapy; and 4 (multiorgan function disorder, febrile neutropenia, pneumonia, and acute kidney injury) were considered to be related to chemotherapy only. There were 5 deaths in the placebo plus chemotherapy group that were considered drug-related by the investigator (sepsis, interstitial lung disease, death, febrile neutropenia, and multiorgan failure). The most frequently reported AEs leading to death were related to respiratory infections (pneumonia, pneumonia aspiration, and pulmonary sepsis).

The PT "death" was reported in situations where limited information on the cause of death was available, or where the investigator could not assign a specific AE term in a participant with comorbidities and confounding factors that led to death.

Table 22: Applicant - Subjects With Adverse Events Resulting in Death Up to 90 Days of Last (Incidence > 0% in Either Treatment Group) Dose By Decreasing Frequency of Preferred Term (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more adverse events	28	(7.6)	38	(10.3)
with no adverse events	342	(92.4)	332	(89.7)
Pneumonia	6	(1.6)	10	(2.7)
Pneumonia aspiration	3	(0.8)	2	(0.5)
Pulmonary sepsis	3	(0.8)	0	(0.0)
Death	2	(0.5)	7	(1.9)
Acute kidney injury	1	(0.3)	0	(0.0)
Acute myocardial infarction	1	(0.3)	0	(0.0)
Acute respiratory failure	1	(0.3)	1	(0.3)
COVID-19	1	(0.3)	0	(0.0)
Cardio-respiratory arrest	1	(0.3)	0	(0.0)
Clostridium difficile colitis	1	(0.3)	0	(0.0)
Diarrhoea	1	(0.3)	1	(0.3)
Febrile neutropenia	1	(0.3)	1	(0.3)
Hepatic failure	1	(0.3)	0	(0.0)

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

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	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]	
	n	(%)	n	(%)
Interstitial lung disease	1	(0.3)	1	(0.3)
Multiple organ dysfunction syndrome	1	(0.3)	1	(0.3)
Oesophageal fistula	1	(0.3)	0	(0.0)
Oesophagobronchial fistula	1	(0.3)	0	(0.0)
Pneumonitis	1	(0.3)	0	(0.0)
Pulmonary embolism	1	(0.3)	0	(0.0)
Sudden cardiac death	1	(0.3)	0	(0.0)
Upper gastrointestinal haemorrhage	1	(0.3)	2	(0.5)
Aspiration	0	(0.0)	1	(0.3)
Cardiac arrest	0	(0.0)	2	(0.5)
Cerebral haemorrhage	0	(0.0)	1	(0.3)
Cerebrovascular accident	0	(0.0)	1	(0.3)
Gastrointestinal haemorrhage	0	(0.0)	1	(0.3)
Haematemesis	0	(0.0)	1	(0.3)
Respiratory failure	0	(0.0)	1	(0.3)
Sepsis	0	(0.0)	3	(0.8)
Tracheal haemorrhage	0	(0.0)	1	(0.3)

Every subject is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.
[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

Source: [ISS: adam-adsl; adae]

The FDA's Assessment:

FDA agrees with the Applicant's statement that the proportion of patients with AEs resulting in death was similar in both arms. The overall incidence of AEs resulting in death based on the ADAE dataset was 13% in the pembrolizumab plus chemotherapy group and 19% in the placebo plus chemotherapy group; however, after censoring for cause of death in which the preferred term was associated with disease progression, 7.5% patients in the pembrolizumab arm and 10.2% patients in the placebo arm died within 90 days of the last treatment administration due to possible treatment-related toxicities. In both arms, preferred terms that could be grouped as pneumonia (pneumonia, pneumonia aspiration, and pulmonary sepsis) were the most common cause of death (3% in each arm).

Of note, the causes of death in each arm could be related to the underlying esophageal cancer or disease progression, i.e. GI hemorrhages, fistulas, pulmonary embolism, hematemesis, etc., and it is not possible to make a determination as to whether treatment contributed to the patients' deaths. The proportion of patients in the KEYNOTE-590 pembrolizumab group who experienced an AE leading to death was consistent with the RSD and no common toxicity cause of death could be identified.

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Serious Adverse Events

The Applicant's Position:

The overall incidence of SAEs was 55.4% in the pembrolizumab plus chemotherapy group and 55.1% in the placebo plus chemotherapy group [Table 23]. The most frequently reported SAE (≥5%) in both the pembrolizumab plus chemotherapy group (10.3%) and the placebo plus chemotherapy group (8.6%) was pneumonia. The largest difference was noted for pneumonitis, which was 3.2% in the pembrolizumab plus chemotherapy group and 0.0% in the placebo plus chemotherapy group. Pneumonitis is a known AEOSI for pembrolizumab; for details refer to Significant Adverse Events sub-section below.

Table 23: Applicant - Subjects With Serious Adverse Events Up to 90 Days of Last Dose (Incidence ≥ 5% in Either Treatment Group) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more adverse events	205	(55.4)	204	(55.1)
with no adverse events	165	(44.6)	166	(44.9)
Pneumonia	38	(10.3)	32	(8.6)

Every subject is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.
[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

Source: [ISS: adam-adsl; adae]

The overall incidence of drug-related SAEs was 31.6% in the pembrolizumab plus chemotherapy group and 26.2% in the placebo plus chemotherapy group. The most frequently reported drug-related SAEs (≥2% incidence in either treatment group) in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups were: pneumonia (3.5% vs 0.8%), pneumonitis (3.2% vs 0.0%), febrile neutropenia (2.4% vs 3.2%), acute kidney injury (2.2% vs 1.4%), vomiting (2.2% vs 1.6%), and platelet count decreased (1.4% vs 2.2%). Pneumonitis is a known AEOSI for pembrolizumab (refer to Significant Adverse Events sub-section below).

The FDA's Assessment:

FDA replicated Merck's analysis of non-fatal SAEs that assessed 196 patients per arm (53%) hospitalized for treatment of an event; some SAEs were clearly unrelated to treatment (benign prostatic hyperplasia, alcohol overdose, overdose, etc.). The most frequently reported SAE (≥5%) in both the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group was pneumonia (grouped terms pneumonia, pneumonia aspiration, pulmonary sepsis, and pneumonia influenza), 14% and 10%, respectively. The incidence of SAEs did not differ appreciably between the treatment groups aside from pneumonitis (grouped

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terms pneumonitis and interstitial lung disease), occurring in 3.2%, and 0.3%, respectively. Pneumonitis is an expected immune-related adverse reaction to pembrolizumab and is included in labelling (U.S. package insert, Keytruda, accessed on 4 March 2021). The incidence of SAEs were consistent with the RSD.

Regarding immune-related SAE, these events included adrenal insufficiency, autoimmune colitis, autoimmune hepatitis, Basedow's disease, colitis, enterocolitis, hepatitis, hyperthyroidism, hypophysitis, hypopituitarism, interstitial lung disease, myasthenia gravis, pneumonitis, rash.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

The types and incidences of AEs leading to discontinuations are as follows:

- For discontinuation of any study intervention, the most common AEs leading to treatment discontinuation of chemotherapy in the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group were pneumonia (2.7% and 2.4%) and blood creatinine increased (2.2% and 3.0%).

- For discontinuation of all study intervention, incidences of AEs were <1.0% in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups, with the exception of pneumonia, which was reported in the chemotherapy group in 1.6% of participants.

- For discontinuation of pembrolizumab, the most common AE leading to treatment discontinuation of pembrolizumab in the pembrolizumab plus chemotherapy group was pneumonitis (1.6%). In the placebo plus chemotherapy group, pneumonitis was reported as an AE leading to discontinuation of placebo in 0.0% of participants. Pneumonitis is a known AEOSI for pembrolizumab; for details refer to refer to Significant Adverse Events sub-section below.

The FDA's Assessment:
FDA agrees with the Applicant's description and replicated the analysis. Pembrolizumab was discontinued for adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of pembrolizumab (≥1%) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). Pneumonitis is a known adverse reaction for pembrolizumab (U.S. package insert, Keytruda, accessed on 4 March 2021). The most common AEs leading to treatment discontinuation of chemotherapy in both treatment groups were pneumonia (pembrolizumab plus chemotherapy: 2.4%; chemotherapy: 2.2%) and blood creatinine increased (pembrolizumab plus chemotherapy: 1.9%; chemotherapy: 3.0%).

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The treatment discontinuations observed in KEYNOTE-590 are consistent with the known safety profile of pembrolizumab and chemotherapy.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

The incidence of AEs leading to treatment interruption for all study interventions was 50.3% in the pembrolizumab plus chemotherapy group and 48.6% in the placebo plus chemotherapy group. The incidence of AEs leading to treatment interruption of pembrolizumab/placebo was 66.8% in the pembrolizumab plus chemotherapy group and 63.2% in the placebo plus chemotherapy group. The incidence of AEs leading to treatment interruption of any study intervention was 70.8% in the pembrolizumab plus chemotherapy group and 65.4% in the placebo plus chemotherapy group.

The FDA's Assessment:
Adverse reactions leading to interruption of pembrolizumab occurred in 67% of patients. The most common adverse reactions leading to interruption of pembrolizumab (≥2%) were neutropenia (19%), fatigue/asthenia (8%), decreased white blood cell count (5%), pneumonia (5%), decreased appetite (4.3%), anemia (3.2%), increased blood creatinine (3.2%), stomatitis (3.2%), malaise (3.0%), thrombocytopenia (3.0%), malaise (3.0%), pneumonitis (2.7%), diarrhea (2.4%), dysphagia (2.2%), and nausea (2.2%).

The incidence of AEs leading to interruption of pembrolizumab/placebo was comparable between the 2 treatment groups (pembrolizumab plus chemotherapy: 67%; chemotherapy: 63%). The incidence of AEs leading to interruption of any chemotherapy was higher in the pembrolizumab plus chemotherapy group (65%) compared with the chemotherapy group (59%). The most common AEs leading to treatment interruption of pembrolizumab/placebo or chemotherapy in both treatment groups were neutrophil count decreased and neutropenia.

The treatment interruption, delays, and dose modifications observed in KEYNOTE-590 are consistent with the known safety profile of pembrolizumab and chemotherapy.

Significant Adverse Events

The Applicant's Position:

AEOSI are immune-mediated events and infusion-related reactions known to be associated with pembrolizumab. The incidence of AEOSI was 25.7% in the pembrolizumab plus chemotherapy group and 11.6% in the placebo plus chemotherapy group [Table 24]. The most common AEOSI categories (≥5%) in the pembrolizumab plus chemotherapy group were hypothyroidism (10.8%), pneumonitis (6.2%), and hyperthyroidism (5.7%) [Table 25]. The most common AEOSI category (≥5%) in the placebo plus chemotherapy group was hypothyroidism (6.5%).

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AEOSI observed in the pembrolizumab plus chemotherapy group were mostly low grade and manageable, as more than half of the AEOSI were reported as either resolving (12.6%) or resolved (40.0%) at the time of data cutoff [Table 26]. The majority of AEOSI reported in the pembrolizumab plus chemotherapy group were mild to moderate (Grade 1 or 2) in severity [Table 27]. Grade 3 to 5 AEOSI occurred in 7.0% of participants, including 0.5% with fatal AEOSI [Table 27].

There were 3 reported deaths due to an AEOSI in KEYNOTE-590; all were due to pneumonitis. Two participants died in the pembrolizumab plus chemotherapy group (one was reported as pneumonitis and the other as interstitial lung disease) and 1 participant died in the placebo plus chemotherapy group (reported as interstitial lung disease).

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Table 24: Applicant - Adverse Event Summary for AEOSI (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more adverse events	95	(25.7)	43	(11.6)
with no adverse event	275	(74.3)	327	(88.4)
with drug-related[†] adverse events	91	(24.6)	35	(9.5)
with toxicity grade 3-5 adverse events	26	(7.0)	8	(2.2)
with toxicity grade 3-5 drug-related adverse events	25	(6.8)	6	(1.6)
with serious adverse events	30	(8.1)	7	(1.9)
with serious drug-related adverse events	28	(7.6)	5	(1.4)
who died	2	(0.5)	1	(0.3)
who died due to a drug-related adverse event	2	(0.5)	1	(0.3)
discontinued any drug due to an adverse event	16	(4.3)	2	(0.5)
discontinued Pembrolizumab or placebo	14	(3.8)	2	(0.5)
discontinued any chemotherapy	6	(1.6)	1	(0.3)
discontinued all drugs	3	(0.8)	0	(0.0)
discontinued any drug due to a drug-related adverse event	16	(4.3)	2	(0.5)
discontinued Pembrolizumab or placebo	14	(3.8)	2	(0.5)
discontinued any chemotherapy	6	(1.6)	1	(0.3)
discontinued all drugs	3	(0.8)	0	(0.0)
discontinued any drug due to a serious adverse event	12	(3.2)	2	(0.5)
discontinued Pembrolizumab or placebo	11	(3.0)	2	(0.5)
discontinued any chemotherapy	4	(1.1)	1	(0.3)
discontinued all drugs	2	(0.5)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	12	(3.2)	2	(0.5)
discontinued Pembrolizumab or placebo	11	(3.0)	2	(0.5)
discontinued any chemotherapy	4	(1.1)	1	(0.3)
discontinued all drugs	2	(0.5)	0	(0.0)

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

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 Pembrolizumab or chemotherapy in KN590.

[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

Source: [ISS: adam-adsl; adae]

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Table 25: Applicant - Subjects With Adverse Events of Special Interest (AEOSI) (Incidence > 0% in Either Treatment Group) By AEOSI Category (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more adverse events	95	(25.7)	43	(11.6)
with no adverse events	275	(74.3)	327	(88.4)
Adrenal Insufficiency	4	(1.1)	2	(0.5)
Colitis	8	(2.2)	6	(1.6)
Encephalitis	0	(0.0)	0	(0.0)
Hepatitis	5	(1.4)	0	(0.0)
Hyperthyroidism	21	(5.7)	3	(0.8)
Hypophysitis	3	(0.8)	0	(0.0)
Hypothyroidism	40	(10.8)	24	(6.5)
Infusion Reactions	6	(1.6)	4	(1.1)
Myositis	1	(0.3)	0	(0.0)
Nephritis	1	(0.3)	2	(0.5)
Pancreatitis	2	(0.5)	1	(0.3)
Pneumonitis	23	(6.2)	2	(0.5)
Severe Skin Reactions	4	(1.1)	2	(0.5)
Thyroiditis	1	(0.3)	0	(0.0)
Type 1 Diabetes Mellitus	1	(0.3)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

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

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

†† Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.

¶ Includes all subjects who received at least one dose of chemotherapy in KN590.

Source: [ISS: adam-adsl; adae]

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Table 26: Applicant - Summary of Outcome for Subjects With AEOSI (Incidence > 0% in Either Treatment Group) (ASaT Population)

		KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]	
	Outcome	n	(%)	n	(%)
Subjects in population		370		370	
With one or more AEOSI	**Overall**	**95**	**(25.7)**	**43**	**(11.6)**
	Fatal	2	(2.1)	1	(2.3)
	Not Resolved	41	(43.2)	15	(34.9)
	Resolving	12	(12.6)	7	(16.3)
	Unknown	0	(0.0)	0	(0.0)
	Sequelae	2	(2.1)	0	(0.0)
	Resolved	38	(40.0)	20	(46.5)

Every subject is counted once for each specific AEOSI according to the worst outcome; the ordering of the outcomes is as follows: Fatal>Not Resolved>Resolving>Unknown>Sequelae>Resolved.

"Subjects in population" is used for percentage calculation for the Overall row in each section. Within each section, the overall total is used for percentage calculation for each outcome.

Outcome: Resolved = RECOVERED/RESOLVED, Resolving = RECOVERING/RESOLVING, Sequelae = RECOVERED/RESOLVED WITH SEQUELAE, Not resolved = NOT RECOVERED/NOT RESOLVED.

[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.

[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

Source: [ISS: adam-adsl; adae]

Table 27: Applicant - Subjects With Adverse Events of Special Interest (AEOSI) by Maximum Toxicity Grade (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more adverse events	95	(25.7)	43	(11.6)
Grade 1	26	(7.0)	16	(4.3)
Grade 2	43	(11.6)	19	(5.1)
Grade 3	24	(6.5)	7	(1.9)
Grade 4	0	(0.0)	0	(0.0)
Grade 5	2	(0.5)	1	(0.3)
with no adverse events	275	(74.3)	327	(88.4)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.

Only the highest reported grade of a given adverse event is counted for the individual subject.

Grades are based on NCI CTCAE version 4.0.

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

[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.

[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

Source: [ISS: adam-adsl; adae]

The FDA's Assessment:

As expected, the incidence of AEOSI was higher in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group. FDA agrees with the Applicant's

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description of the more frequently reported events for each arm; in FDA's analysis grouping terms categorized as autoimmune, 27% of patients in the pembrolizumab arm and 12% of the placebo arm experienced one of these events. The most common AEOSI categories in the pembrolizumab arm were hypothyroidism (11% vs. 7% in the placebo arm), hyperthyroidism (5.4% vs. 0.8% in the placebo arm), and pneumonitis (6% vs. 0.5% in the placebo arm). Pneumonitis has been discussed in Section 8.2.4 of this review. Section 5 of the Keytruda USPI includes thyroid disorders information; in a pooled analysis of >2799 patients who have received pembrolizumab the incidence of hyperthyroidism was 3.4% and 8% of patients were diagnosed with hypothyroidism (U.S. package insert, Keytruda, accessed on 4 March 2021). Most events were Grade 1-2 in severity. Although it is expected that there would be an increase of thyroid disorders with the use of pembrolizumab, there was a high background rate in the control arm and the excess number of events observed with pembrolizumab is within the expected range. The remainder of the events (in alphabetical order) included: adrenal insufficiency, autoimmune colitis, autoimmune hepatitis, Basedow's disease, colitis, enterocolitis, hepatitis, hypersensitivity, hypophysitis, hypopituitarism, interstitial lung disease, myasthenia gravis, myopathy, pancreatitis, pruritus, rash, tubulointerstitial nephritis, type 1 diabetes mellitus. Corticosteroids were administered to treat AEOSI in 47% of patients in the pembrolizumab arm and 26% in the chemotherapy group arm.

The incidence and type of AEOSI observed in KEYNOTE-590 are consistent with the known safety profile of pembrolizumab based on its mechanism of action of the drug.

Treatment-Emergent Adverse Events and Adverse Reactions

The frequency, type, and severity of AEs and drug-related AEs observed in the pembrolizumab plus chemotherapy group were as expected based on the established individual safety profiles of pembrolizumab monotherapy and of the chemotherapy administered. The overall incidence of AEs was 100% in the pembrolizumab plus chemotherapy group and 99.5% in the placebo

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plus chemotherapy group [Table 28]. A rainfall plot comparing commonly reported AEs (≥10% incidence) is depicted in [

Figure 4]. These events were predominantly not serious, Grade 1 to 3 [Table 29], and were managed with standard medical care. Severe skin reactions and hypothyroidism are known AEOSI for pembrolizumab; for details refer to the Significant Adverse Events subsection herein.

Table 28: Applicant - Subjects With Adverse Events (Incidence ≥ 10% in Either Treatment Group) By Decreasing Frequency of Preferred Term (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy[††]		KN590 Data for Placebo + Chemotherapy[¶¶]	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more adverse events	370	(100.0)	368	(99.5)
with no adverse events	0	(0.0)	2	(0.5)
Nausea	249	(67.3)	232	(62.7)
Anaemia	187	(50.5)	208	(56.2)
Decreased appetite	164	(44.3)	141	(38.1)
Fatigue	149	(40.3)	126	(34.1)
Constipation	148	(40.0)	149	(40.3)
Neutrophil count decreased	139	(37.6)	111	(30.0)
Diarrhoea	135	(36.5)	123	(33.2)
Vomiting	126	(34.1)	117	(31.6)
Stomatitis	100	(27.0)	95	(25.7)
Neutropenia	97	(26.2)	90	(24.3)
White blood cell count decreased	97	(26.2)	69	(18.6)
Weight decreased	87	(23.5)	90	(24.3)
Blood creatinine increased	79	(21.4)	78	(21.1)
Hyponatraemia	68	(18.4)	77	(20.8)
Hypokalaemia	67	(18.1)	71	(19.2)
Platelet count decreased	62	(16.8)	62	(16.8)
Asthenia	60	(16.2)	45	(12.2)
Dysphagia	60	(16.2)	63	(17.0)
Cough	59	(15.9)	56	(15.1)
Mucosal inflammation	59	(15.9)	68	(18.4)
Hiccups	56	(15.1)	53	(14.3)
Alopecia	55	(14.9)	39	(10.5)
Pyrexia	55	(14.9)	44	(11.9)
Pneumonia	54	(14.6)	52	(14.1)
Insomnia	49	(13.2)	44	(11.9)
Malaise	48	(13.0)	43	(11.6)
Rash	44	(11.9)	26	(7.0)
Hypothyroidism	40	(10.8)	24	(6.5)
Dysgeusia	38	(10.3)	32	(8.6)
Neuropathy peripheral	37	(10.0)	37	(10.0)
Hypoalbuminaemia	35	(9.5)	49	(13.2)
Thrombocytopenia	28	(7.6)	37	(10.0)

Every subject is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.
[††] Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.
[¶¶] Includes all subjects who received at least one dose of chemotherapy in KN590.

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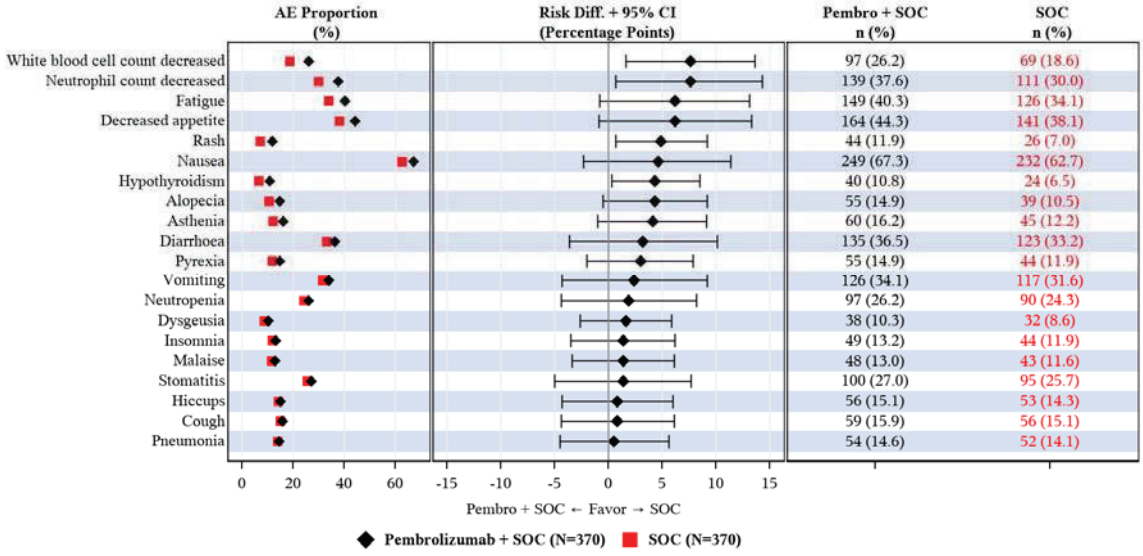
Source: [ISS: adam-adsl; adae]

Figure 4: Applicant - Between-treatment Comparisons in Adverse Events
Selected Adverse Events (>=10% Incidence) and Sorted by Risk Difference
(ASaT Population)



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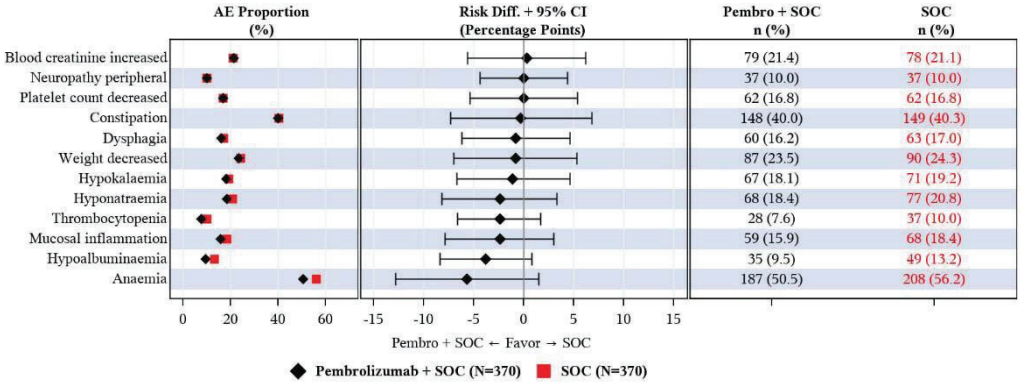
Between-treatment Comparisons in Adverse Events
Selected Adverse Events (>=10% Incidence) and Sorted by Risk Difference
(ASaT Population) (Continued)



Abbreviations: AE = adverse event; ASaT = All Subjects as Treated; CI = confidence interval; Pembro = pembrolizumab; SOC = standard of care, which represents the placebo plus chemotherapy group and the pembrolizumab plus chemotherapy group.
Database Cutoff Date: 02JUL2020
Source: [P590V01MK3475: adam-adsl; adae]

Table 29: Applicant - Subjects With Adverse Events by Maximum Toxicity Grade (ASaT Population)

	KN590 Data for Pembrolizumab + Chemotherapy††		KN590 Data for Placebo + Chemotherapy¶¶	
	n	(%)	n	(%)
Subjects in population	370		370	
with one or more adverse events	370	(100.0)	368	(99.5)
Grade 1	7	(1.9)	3	(0.8)
Grade 2	45	(12.2)	57	(15.4)
Grade 3	219	(59.2)	210	(56.8)
Grade 4	71	(19.2)	60	(16.2)
Grade 5	28	(7.6)	38	(10.3)
with no adverse events	0	(0.0)	2	(0.5)

Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted a single time for that system organ class.
Only the highest reported grade of a given adverse event is counted for the individual subject.
Grades are based on NCI CTCAE version 4.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
†† Includes all subjects who received at least one dose of Pembrolizumab or chemotherapy in KN590.
¶¶ Includes all subjects who received at least one dose of chemotherapy in KN590.
Source: [ISS: adam-adsl; adae]

The FDA's Assessment:

FDA replicated the Applicant's analysis and Table 30. A revised table (grouping terms, deletion of laboratory terms, and rounding of numbers) will be included in labeling.

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Table 30: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE 590

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks Cisplatin FU n=370		Placebo Cisplatin FU n=370	
	All Grades* (%)	Grades 3-4† (%)	All Grades* (%)	Grades 3-4† (%)
Gastrointestinal				
Nausea	67	7	63	7
Constipation	40	0	40	0
Diarrhea	36	4.1	33	3
Vomiting	34	7	32	5
Stomatitis	27	6	26	3.8
General				
Fatigue‡	57	12	46	9
Metabolism and Nutrition				
Decreased appetite	44	4.1	38	5
Investigations				
Weight loss	24	3.0	24	5

* Graded per NCI CTCAE v4.03
† One fatal event of diarrhea was reported in each arm.
‡ Includes asthenia, fatigue

The incidence of events was similar between arms except for immune-related AEs (see separate discussion on AEOSI in "Significant Adverse Events"). The review team agrees that the addition of pembrolizumab, has not appeared to meaningfully increase the toxicity of the backbone chemotherapy, particularly when considering the different lengths of exposure to treatment. Some patients, however, can experience severe/serious toxicity following exposure to pembrolizumab, generally due to immune related adverse events (See "Serious adverse events" above).

Laboratory Findings

The Applicant's Position:

No new safety concerns based on laboratory abnormalities were reported in the pembrolizumab plus chemotherapy group. The following safety observations were noted:

- The majority of laboratory abnormalities in both treatment groups were CTCAE Grade 1 to 2 toxicity.
- The largest between-treatment difference (>5% difference) in laboratory abnormalities (all grades) between the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups were: ALT increased (23.2% and 17.7%), calcium decreased (43.8% and 37.6%), calcium increased (7.5% and 12.6%), and phosphate decreased (36.9% vs 30.5%).
- There was 1 participant each in the pembrolizumab plus chemotherapy group and in the placebo plus chemotherapy group who met the specified threshold of abnormal hepatic

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tests (i.e., AST or ALT ≥3x the upper limit of normal and total bilirubin ≥2× the upper limit of normal and alkaline phosphatase <2x the upper limit of normal). Evaluation of these events suggested these were not drug-induced hepatic disorders.

The differences in Grade 3 to 4 laboratory abnormalities in the pembrolizumab plus chemotherapy group were consistent with the established safety profiles of the chemotherapies administered.

The FDA's Assessment:

FDA agrees with the applicant's analysis and Table 31 will be included in labeling. As with AEs, the incidence of lab abnormalities was similar between arms for most analytes but there were some that had a higher incidence of the abnormality on the placebo arm, for example thrombocytopenia and hypokalemia. The differences were small and are routinely addressed by the treating oncologist. Only one patient experienced increased (Grade 1) amylase in the pembrolizumab arm. Thyroid function analytes (thyroxine, thyroxine free, and tri-iodothyronine) reporting (Table 14.3-23 of the CSR) was inconsistent with the reported AEs of hypothyroidism or hyperthyroidism, which appear to have better captured the incidence of thyroid toxicity.

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Table 31: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Esophageal Cancer Patients in KEYNOTE 590

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks Cisplatin FU		Chemotherapy (Cisplatin and FU)	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	83	21	86	24
Neutropenia	74	43	71	41
Leukopenia	72	21	73	17
Lymphopenia	55	22	53	18
Thrombocytopenia	43	5	46	8
Chemistry				
Hyperglycemia	56	7	55	6
Hyponatremia	53	19	54	19
Hypoalbuminemia	52	2.8	52	2.3
Increased creatinine	45	2.5	42	2.5
Hypocalcemia	44	3.9	38	2
Hypophosphatemia	37	9	31	10
Hypokalemia	30	12	34	15
Increased alkaline phosphatase	29	1.9	29	1.7
Hyperkalemia	28	3.6	27	2.6
Increased AST	25	4.4	22	2.8
Increased ALT	23	3.6	18	1.7

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/cisplatin/FU (range: 345 to 365 patients) and placebo/cisplatin/FU (range: 330 to 358 patients)

† Graded per NCI CTCAE v4.03

Vital Signs

The Applicant's Position:

There were no clinically significant changes noted in vital sign measurements, physical examination assessments, or other observations related to safety in this study.

The FDA's Assessment:
FDA agrees.

Electrocardiograms (ECGs)

The Applicant's Position:

ECG testing was performed once during screening using local standard procedures [Table 5]. Clinically significant abnormal findings were not identified.

The FDA's Assessment:
FDA agrees.

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QT

The Applicant's Position:

No clinically meaningful effects on QTc interval were identified in the analyses included in previous submissions, which included participants with melanoma and participants with NSCLC.

The FDA's Assessment:
FDA agrees.

Immunogenicity

The Applicant's Position:

No new information concerning immunogenicity is provided in the current submission

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

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

The results from KEYNOTE-590 were generally consistent with the established pembrolizumab safety profile and the components of chemotherapy, and no new safety issues were identified.

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

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

The Applicant's Position:

Results from the patient-reported outcomes analyses are in Section 8.1.2.

The FDA's Assessment:
FDA notes the above.

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8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

In KEYNOTE-590, there were no trends identified in the incidence of AEs by age, sex, ECOG status, or region between the 2 treatment groups.

The FDA's Assessment:
FDA agrees with the Applicant's analysis.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:
FDA agrees.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:

No new information concerning human carcinogenicity or tumor development is provided in this supplement.

The FDA's Assessment:
FDA agrees.

Human Reproduction and Pregnancy
The Applicant's Position:

No new information concerning human reproduction and pregnancy is provided in this supplement.

The FDA's Assessment:
FDA agrees.

The US FDA granted pembrolizumab an orphan designation for the treatment of esophageal carcinoma on 15-JUN-2017 (17-5787). Since pembrolizumab has an orphan drug designation for esophageal carcinoma, it is exempt from the PREA requirements and no pediatric studies have been conducted in esophageal carcinoma.

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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-590. Any administration of a participant with ≥20% of cisplatin or 5-FU and ≥1000 mg (5 times the protocol-defines dose) of pembrolizumab is considered as an overdose.

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 this drug, and their occurrence in clinical studies with administration of pembrolizumab is unknown.

The FDA's Assessment:
FDA agrees.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Position:

The safety profile of pembrolizumab postmarketing approval was summarized in the PSUR covering the period 04-SEP-2018 through 03-SEP-2019. There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

The FDA's Assessment:
FDA agrees.

Expectations on Safety in the Postmarket Setting
The Applicant's Position:

Postmarket data from the safety reporting database (ie, 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-590. There are no specific safety concerns not already included in pembrolizumab labeling expected from off-label use.

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The FDA's Assessment:
FDA agrees.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:
The incidence, type, and severity of AEs in the KEYNOTE-590 pembrolizumab plus chemotherapy group were similar to, and consistent with, the results previously reported for pembrolizumab. No immune-mediated AEs were identified in the KEYNOTE-590 pembrolizumab plus chemotherapy group that were considered to represent a new identified risk. The safety profile of pembrolizumab remains unchanged with the addition of data from participants with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction.

The FDA's Assessment:
The adverse reaction profile observed in patients receiving pembrolizumab in KEYNOTE-590 is consistent with the known pembrolizumab safety profile. Incidences of AEs, Grade 3 to 5 AEs, SAEs, discontinuation due to AEs, and discontinuation due to SAEs were similar between treatment groups.

Incidence rates of discontinuation of any drug within the treatment regimen due to drug-related AEs and drug-related SAEs were slightly higher in the pembrolizumab plus chemotherapy group (24%) than in the chemotherapy group (20%). As expected, the incidence of AEOSI was higher in the pembrolizumab plus chemotherapy group (26%) compared with the chemotherapy group (12%). The most common AEOSI categories in the pembrolizumab plus chemotherapy group were hypothyroidism (11%), pneumonitis (6%), and hyperthyroidism (6%). The incidence of the most frequently reported laboratory abnormalities was similar between the treatment groups and the majority of the events were Grade 1 to 2.

FDA agrees with the Applicant's position that pembrolizumab has an acceptable safety profile in patients with advanced unresectable or metastatic esophageal or GEJ cancer with no prior therapy for advanced disease (given the improvement in OS). The safety of patients on KEYNOTE-590 were consistent with the RSD of 2799+ subjects with melanoma or non-small cell lung cancer [NSCLC] who have received pembrolizumab.

SUMMARY AND CONCLUSIONS

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8.3 Statistical Issues

The FDA's Assessment:

The statistical assessment of efficacy was based on the submitted data and results of the primary endpoints of investigator-assessed PFS per RECIST 1.1 and OS for the comparison of pembrolizumab in combination with cisplatin and 5-FU versus placebo in combination with cisplatin and 5-FU as first-line treatment in participants with locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ in KEYNOTE-590. The primary endpoints were evaluated in multiple primary analysis populations using pre-specified decision rules. O'Brien-Fleming alpha-spending method and graphical approach by Maurer and Bretz were used to control overall study-wise Type I error rate at one-sided alpha of 0.025. The study met statistical significance on all pre-specified primary endpoints and the key secondary endpoint ORR under the formal testing plan.

There are no major statistical issues during the review process; however, FDA has the following review comments:

1. KEYNOTE-590 protocol was amended (Amendment 09) to change the primary endpoint from BICR-assessed PFS to investigator-assessed PFS. According to the Applicant, the rationale for this change was that there were higher than expected discordance rate (~27%) between BICR-assessed PD and investigator-assessed PD. The estimation of treatment effect of BICR-assessed PFS in the ITT population (HR=0.67, 95% CI: 0.56, 0.79) was supportive of the treatment effect of investigator-assessed PFS.

2. OS results in both the pre-specified analyses population PD-L1 CPS ≥ 10 and in the next analyses population in the hierarchy, ITT population, are statistically significant. While the estimation of treatment effect on OS endpoint in patients with PD-L1 CPS < 10 (n=347, HR: 0.86, 95% CI: 0.68, 1.10) was numerically in the same direction and supportive of the OS results in the PD-L1 CPS ≥ 10 and in the ITT populations, the upper limit of the 95% CI of the estimate of OS HR in patients with PD-L1 CPS < 10 exceeded 1.0. The Kaplan-Meier curves for OS in patients with PD-L1 CPS ≥ 10 and PD-L1 CPS < 10 are provided in Figure 5. In an exploratory analysis, in patients with adenocarcinoma (n=201) the treatment effect on OS (HR=0.74, 95% CI: 0.54, 1.02) was in the same direction and supportive of the effect observed in the ITT population.

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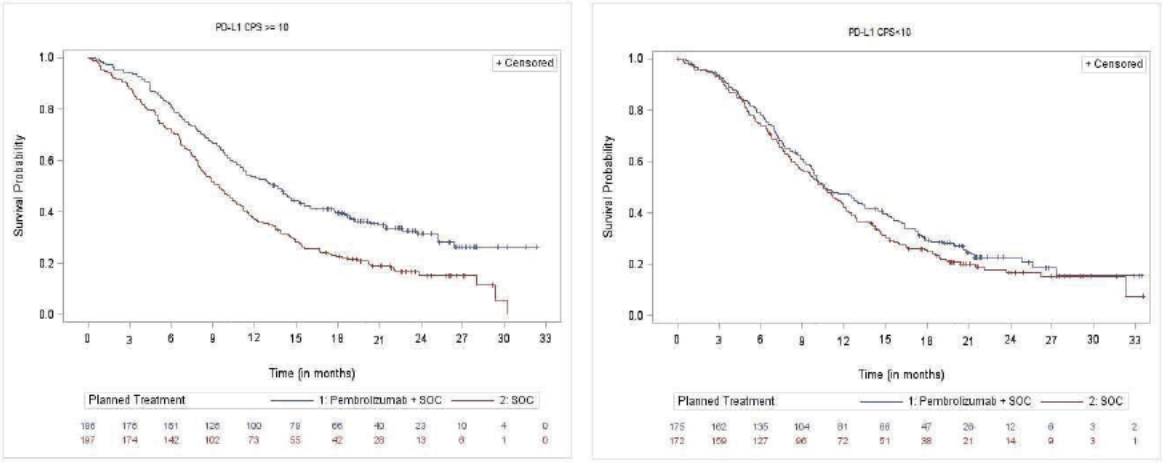
Figure 5. Kaplan-Meier curves of overall survival by PD-L1 expression (ITT population)



8.4 Conclusions and Recommendations

The FDA's Assessment:

The clinical and statistical review teams determined that the evidence submitted provides substantial evidence of the effectiveness of pembrolizuma (b) (4)

(b) (4)

The primary support for the effectiveness of pembrolizumab for this indication was derived from the results of a multicenter, randomized, open-label, active-controlled randomized trial, Study KEYNOTE 590 (NCT03189719). The major efficacy outcome measures were OS and INV-PFS for patients randomized to pembrolizumab or placebo in combination with chemotherapy. Treatment continued until unacceptable toxicity or disease progression. Patients could be treated with pembrolizumab for up to 24 months in the absence of disease progression. No crossover from placebo arm to pembrolizumab arm was allowed.

The HR for OS was 0.73 (95% CI 0.62, 0.86; p-value < 0.0001) favoring the pembrolizumab arm. Median OS was 12.4 months. (95% CI 10.5, 14) in the pembrolizumab arm and 9.8 months (95% CI 8.8, 10.8) in the SOC arm. The HR for PFS was 0.65 (95% CI 0.55, 0.76; p-value < 0.0001) favoring the pembrolizumab arm. Median PFS was 6.3 months. (95% CI 6.2, 6.9) in the pembrolizumab arm and 5.8 months (95% CI 5, 6) in the SOC arm. KEYNOTE-590 demonstrated a clinically meaningful, statistically significant improvement in INV-assessed PFS and OS. Secondary endpoints, subgroup analyses, and sensitivity analyses were consistent with results of PFS and OS, and confirmed the robustness of the study results. All pre-specified analyses of KEYNOTE- 590 were statistically significant.

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In patients with esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 CPS ≥10 (n: 286), pembrolizumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in OS compared with chemotherapy with a HR of 0.57 (95% CI: 0.43, 0.75; p<0.0001) and a median OS of 13.9 months (95% CI: 11.1, 17.7) in the pembrolizumab arm and 8.8 months (95% CI: 7.8, 10.5) in the placebo arm. The PFS HR was 0.53 (95% CI: 0.40, 0.69), with a median PFS of 7.3 months (95% CI: 6.2, 8.2) for the pembrolizumab arm and 5.4 months (95% CI: 4.2, 6.0) for the placebo group.

In patients whose tumors express PD-L1 CPS ≥10 irrespective of histology (n: 383), pembrolizumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. The OS HR was 0.62 (95% CI: 0.49, 0.78; p<0.0001), with a median OS was 13.5 months (95% CI: 11.1, 15.6) in the pembrolizumab arm and 9.4 months (95% CI: 8.0, 10.7) in the placebo arm. The PFS HR was 0.51 (95% CI: 0.41, 0.65; p<0.0001) with a median PFS of 7.5 months (95% CI: 6.2, 8.2) for the pembrolizumab arm and 5.5 months (95% CI: 4.3, 6.0) in the placebo arm.

In patients with ESCC (n: 548), pembrolizumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. The OS HR was 0.72 (95% CI: 0.60, 0.88; p=0.0006) with a median OS of 12.6 months (95% CI: 10.2, 14.3) in the pembrolizumab arm and 9.8 months (95% CI: 8.6, 11.1) in the placebo arm.

The adverse reaction profile observed in patients receiving pembrolizumab in KEYNOTE-590 is consistent with the known pembrolizumab safety profile, and manageable through dose delays and supportive care in most patients. For the most common adverse events in KEYNOTE-590, only fatigue and decreased appetite had an increased incidence of ≥ 5% in the pembrolizumab arm when compared to the placebo arm. Lab abnormalities observed with an increased incidence (≥ 5%) in the pembrolizumab arm were hypophosphatemia, hypocalcemia, and increased ALT. The rate of immune-related adverse events was consistent with the known incidence for pembrolizumab. Pembrolizumab was discontinued due to adverse events in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of pembrolizumab (≥1%) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). No new safety signals were evident from review of the safety data included in this application.

The review team concluded that the overall risk:benefit assessment favored approval of pembrolizuma (b) (4)
(b) (4)
(b) (4). The demonstrated improvement in PFS and survival for patients randomized to pembrolizumab in combination with chemotherapy compared to patients randomized to placebo in combination

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with chemotherapy SOC is clinically meaningful, statistically significant, and supported by subgroup analyses in KEYNOTE-590. The adverse reaction profile observed in patients receiving pembrolizumab is consistent with the adverse reaction profiles observed in prior studies and the disease setting. The risks of pembrolizumab are acceptable considering the life-threatening nature of metastatic or locally advanced esophageal and GEJ carcinoma. The approval of this application will likely result in the change in the standard of care for patients with treatment naïve metastatic or locally advanced esophageal carcinoma.

X X

Arup Sinha
Primary Statistical Reviewer

Pallavi Mishra-Kalyani
Statistical Team Leader

X X

Leigh Marcus
Primary Clinical Reviewer

Sandra Casak
Clinical Team Leader

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9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
This supplemental application was not referred to an Advisory Committee meeting or external consultants. The clinical effect on OS and PFS and risk-benefit profile of the addition of pembrolizumab to SOC chemotherapy is considered to be favorable.

10 Pediatrics

The Applicant's Position:
The combination of pembrolizumab plus chemotherapy was not studied in pediatric patients. The Sponsor has submitted a PREA waiver.

The FDA's Assessment:
An orphan drug designation was granted to pembrolizumab for the treatment of esophageal carcinoma (15 June 2017). A full waiver was requested for all pediatric age groups; clinical studies are impossible or highly impractical because the number of pediatric patients with esophageal carcinoma is so small.

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11 Labeling Recommendations

The Applicant's Position:
The Sponsor has provided proposed labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
INDICATIONS AND USAGE	Added indication fo (b) (4) (b) (4)	Amended the esophageal cancer section and indication as follows: **Esophageal Cancer** KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either: - in combination with platinum- and fluoropyrimidine-based chemotherapy, or - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test The slight change in the single agent indication (b) (4) (b) (4) was to

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		make the labeling consistent wit (b) (4) (b) (4) (b) (4) the expected similar biology of squamous tumors.
DOSAGE AND ADMINISTRATION	Added esophageal cancer to the recommended dosing for combination therapy.	FDA agrees and accepted the changes.
ADVERSE REACTIONS	Updated section 6 to include a summary of safety for esophageal cancer in combination with chemotherapy.	FDA made minor editorial changes to Merck's proposal label changes.
CLINICAL STUDIES	Added study description and efficacy results for KEYNOTE-590.	FDA made minor editorial changes to Merck's proposal label changes.

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12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
No REMS have been requested. Pembrolizumab has been used extensively in patients with cancer.

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13 Postmarketing Requirements and Commitment

The FDA's Assessment:

No post market requirements or commitments were required.

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ON ORIGINAL

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14 Division Director (DHOT) (NME ONLY)

X

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15 Division Director (OCP)

X

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16 Division Director (OB)

KEYNOTE-590 implemented a graphical approach to testing multiple primary endpoints while controlling the overall study-wise Type I error rate. The testing hierarchy of overall survival in this study was a gate-keeping approach that stepped in selection of subpopulations with specific criteria, where the first population tested was the subgroups selected by squamous cell histology and PD-L1 status (CPS ≥ 10), followed by testing in the subgroup of patients with squamous cell histology, then in the subgroup with patients with PD-L1 CPS ≥ 10, and finally in the overall population (all randomized). The results for OS were statistically significant in each subgroup, so the expansion to larger subpopulations provided consistent results of a OS benefit in the overall population.

Furthermore, exploratory analyses of overall survival in the complementary subgroups of those tested in the formal testing hierarchy, were consisted in direction of effect. Specifically, the hazard ratio for OS in patients with PD-L1 CPS < 10 (n=347) was 0.86 with a 95% CI of (0.68, 1.10), and the hazard ratio for OS in patients with adenocarcinoma (n=201) was 0.74 with a 95% CI of (0.54, 1.02). These results reinforced the OS benefit demonstrated in the formally tested subgroups, and the totality of the efficacy evidence supported substantial evidence of treatment effect in the overall population of KEYNOTE-590.

X _____

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17 Division Director (Clinical)

I agree with the review teams' conclusions with respect to the approvability of this application and will not restate the overall results demonstrating an improvement in overall survival in the ITT population. One issue that I will discuss in greater detail is regarding the data in the PD-L1 low subgroup(s). Although the confidence interval for the hazard ratio of the PD-L1 (CPS) less than 10 subgroup crossed 1, this was a non-stratified subgroup, the point estimate was 0.86 (directionally favoring pembrolizumab), and the study was not designed to be adequately powered to assess for a treatment effect for pembrolizumab in this subgroup. Additionally, the data were not always consistent when further subgrouped by histology; for example, among patients with PD-L1 CPS less than 10, the HR for OS was 0.99 (0.74, 1.32) for squamous histology whereas it was 0.66 (0.42, 1.04) for adenocarcinoma histology (which occurs more frequently in the US). From a statistical perspective, care should be taken not to over-interpret subgroup analyses; nevertheless, the study cannot rule out differential effects based on PD-L1 expression at various cut-points.

As such, it may be considered as arbitrary if the indication was limited to PD-L1-high patients when the ITT analysis was positive (and the study did not limit the enrollment of PD-L1-low patients). The effect in the PD-L1-low subgroup was smaller in magnitude but in the same direction as the treatment effect on the overall population. FDA assesses subgroup analyses to investigate robustness of results or bona fide interactions, and does not expect the confidence intervals to exclude 1 for each subgroup as subgroups are generally not powered to demonstrate a (nominally) statistically significant effect.

Based on the data from KEYNOTE 590, it may be appropriate to forgo PD-L1 testing and the expected treatment effect would be that based on the ITT population. Alternatively, although caution is generally recommended with respect to the interpretation of estimates based on non-prespecified subgroups, it may be reasonable for a clinician to discuss the results by PD-L1 status with their patients to come to a treatment decision (with a plausible biological rationale for a differential effect). Such an approach was taken with respect to HER2 expression in the approval of trastuzumab for HER2-positive gastric cancer. Furthermore, (future) data external to KEYNOTE 590 may further inform treatment decisions if they either strengthen or weaken the association between PD-L1 status and treatment effect.

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18 Appendices

18.1 References

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[To the Applicant: Insert text here.]

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Reference ID: 4766028

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18.2 Financial Disclosure

The Applicant's Position:

Disclosure of financial interests of the investigators who conducted the KEYNOTE-590 study are described in the current submission, including statements of due diligence (FDA forms 3454) in cases where the Sponsor was unable to obtain a signed form from the investigator.

The FDA's Assessment:

The FDA agreed with the Applicant's position and has completed the table below with the provided data.

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

Covered Clinical Study (Name and/or Number):* KEYNOTE-590

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1554		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 (bu (b) (6).		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 1 Sponsor of covered study: 0		
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) _____		
Is an attachment provided with the reason:	N/A☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

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

Reference ID: 4766028

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Leigh Marcus	CDER/OOD/DO3	Sections: 2-13	**Select one:** ☒ Authored ☐ Approved
	Signature: Leigh J. Marcus -S Digitally signed by Leigh J. Marcus -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013338033, cn=Leigh J. Marcus -S Date: 2021.03.19 09:14:12 -04'00'			
Clinical Team Leader	Sandra Casak	CDER/OOD/DO3	Sections: 1 (authored) Sections 2 – 13 (approved)	**Select one:** ☒ Authored ☒ Approved
	Signature: Refer to electronic signature on the final page of this review			
Statistical Reviewer	Arup Sinha	CDER/OTS/DBV	Sections: 8	**Select one:** ☒ Authored ☐ Approved
	Signature: Arup K. Sinha -S Digitally signed by Arup K. Sinha -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Arup K. Sinha -S, 0.9.2342.19200300.100.1.1=2002660630 Date: 2021.03.19 09:57:49 -04'00'			
Statistical Team Leader	Pallavi Mishra-Kalyani	CDER/OTS/DBV	Sections: 8	**Select one:** ☒ Authored ☒ Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001675542, cn=Pallavi S. Mishra-kalyani -S Date: 2021.03.18 20:28:15 -04'00'			
Deputy Division Director (OB)	Yuan-Li Shen	CDER/OTS/DBV	Sections: 8	**Select one:** ☐ Authored ☒ Approved
	Signature: Yuan-li Shen -S Digitally signed by Yuan-li Shen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuan-li Shen -S, 0.9.2342.19200300.100.1.1=1300142755 Date: 2021.03.22 08:49:35 -04'00'			
Associate Director for Labeling (ADL)	Bill Pierce	CDER/OOD/IO	Sections: 11 and prescribing information, patient information	**Select one:** ☒ Authored ☒ Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2021.03.19 07:49:50 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Cross-Disciplinary Team Leader (CDTL)	Sandra Casak	CDER/OOD/DO3	Sections: 1 (authored) Sections 2 – 13 (approved)	**Select one:** ☒ Authored ☒ Approved
	Signature: Refer to electronic signature on the final page of this review			
Division Director (Clinical)	Steven Lemery	CDER/OOD/DO3	Sections: All	**Select one:** ☐ Authored ☒ Approved
	Signature: Refer to electronic signature on the final page of this review			

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/s/

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SANDRA J CASAK
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STEVEN J LEMERY
03/22/2021 02:11:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s096

OTHER REVIEW(S)

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

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

Memorandum

Date: March 1, 2021

To: Steven Lemery, M.D., Director
Division of Oncology 3 (DO3)

Leah Her, MS, PMP Regulatory Project Manager, DO3

From: Kevin Wright, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for Keytruda (pembrolizumab) injection, for intravenous use

BLA: 125514/Supplement 096

In response to DO3's consult request dated November 6, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for Keytruda (pembrolizumab) injection, for intravenous use (Keytruda). This supplement (S-096) proposes a new indication: (b) (4)

(b) (4)

OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO3 (Leah Her) on February 18, 2021, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on February 26, 2021.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

101 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

KEVIN WRIGHT
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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:	February 26, 2021
To:	Leah Her, MS PMP Regulatory Project Manager **Division of Oncology 3 (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kevin Wright, Pharm D **Team Leader** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	KEYTRUDA (pembrolizumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 125514
Supplement Number:	S-096
Applicant:	Merck Sharp & Dohme, Corp.

1 INTRODUCTION

On October 13, 2020, Merck Sharp & Dohme Corp. submitted for the Agency's review a Prior Approval Supplement- Efficacy to their approved Biologics License Application (BLA) for KEYTRUDA (pembrolizumab) injection. With his supplement, the Applicant proposes a new indication for KEYTRUDA, (b) (4)

(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 3 (DO3) on November 6, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for KEYTRUDA (pembrolizumab) injection.

2 MATERIAL REVIEWED

- Draft KEYTRUDA (pembrolizumab) MG received on October 13, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on February 18, 2021.
- Draft KEYTRUDA (pembrolizumab) injection Prescribing Information (PI) received on October 13, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on February 18, 2021.
- Approved KEYTRUDA (pembrolizumab) injection labeling dated November 13, 2020.

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 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/

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LASHAWN M GRIFFITHS
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