CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s097

Trade Name:	KEYTRUDA
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp & Dohme Corp.
Approval Date:	May 5, 2021
Indication:	KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated: Melanoma • for the treatment of patients with unresectable or metastatic melanoma. • for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. Non-Small Cell Lung Cancer (NSCLC) • in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC. • as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations and is: ○ stage III where patients are not candidates for surgical

resection or definitive chemoradiation, or
    - metastatic.
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease profression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

Head and Neck Squamous Cell Cancer (HNSCC)

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

Classical Hodgkins Lymphoma (cHL)

- for the treatment of adult patients with relapsed or refractory cHL.
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more prior lines of therapy.[1]

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

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

Urothelial Carcinoma

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

for any platinum-containing chemotherapy regardless of PD-L1 status.[1]

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during of following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- for the treatment of patient 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.

Microsatellite Instability-High Cancer

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

Micorsatellite Instability-High or Mismatched Repair Deficient Colorectal Cancer (CRC)

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

Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.[1]
- as a single agent for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 [Combined Positive Score

(CPS)≥1] as determined by an FDA-aproved test with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotheraoy and if appropriate, HER2/neu-targeted therapy.[1]

Esophageal Cancer

- for the treatment of patients with 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-fluoropyrimidine-based chemotherapy, or
    - as a single agent after one of more prior line of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by as FDA-approved test.

Cervical Cancer

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

Hepatocellular Carcinoma (HCC)

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

Merkel Cell Cancer MCC

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

Renal Cell Carcinoma (RCC)

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

Endometrial Carcinoma

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

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]
- Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system 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.

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]

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

[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 or 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

125514Orig1s097

CONTENTS

Reviews / Information Included in this BLA Review.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s097

APPROVAL LETTER

BLA 125514/S-097

ACCELERATED APPROVAL

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Christopher Cox, Ph.D.
Director, Global Regulatory Affairs
351 North Sumneytown Pike
UG2D-044
North Wales, PA 19454

Dear Dr. Cox:

Please refer to your supplemental biologics license application (sBLA), dated November 6, 2021, 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:

> *Keytruda, in combination with trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma.*

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

WAIVER OF 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, and the 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).

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated February 23, 2021. This requirement, along with required completion dates, is listed below.

This postmarketing clinical trial is subject to the reporting requirements of 21 CFR 601.70:

4033-1 Submit the final progression-free survival and final overall survival analyses and datasets for the ongoing clinical trial KEYNOTE-811, "A Phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants With HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma" to verify and describe the clinical benefit of pembrolizumab with trastuzumab plus chemotherapy for patients with HER2-positive advanced or metastatic gastric or gastroesophageal adenocarcinoma.

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

Final Protocol Submission: 06/2018 (completed)
Trial Completion: 03/2024
Final Report Submission: 09/2024

Submit clinical protocols to your IND 123482 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

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

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

PROMOTIONAL MATERIALS

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

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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]

REPORTING REQUIREMENTS

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

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

- Content of Labeling

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

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
05/05/2021 10:00:21 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s097

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, Small Cell Lung Cancer – Accelerated Approval Indication Removed (1)	03/2021
Indications and Usage (1)	05/2021
Dosage and Administration (2)	05/2021
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)

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. (1.3)
- 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. (1.3, 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. (1.3)

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult patients with relapsed or refractory cHL. (1.4)
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy. (1.4)

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

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

Urothelial Carcinoma

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

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] (1.7, 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). (1.8, 2.1)

Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.[1] (1.9)
- as a single agent for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1] (1.9, 2.1)

Esophageal Cancer

- for the treatment of patients with 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. (1.10, 2.1)

Cervical Cancer

- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.[1] (1.11, 2.1)

Hepatocellular Carcinoma (HCC)

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

Merkel Cell Carcinoma (MCC)

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

Renal Cell Carcinoma (RCC)

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

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] (1.15)

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] (1.16, 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. (1.17)

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] (1.18, 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] (1.19, 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)
- 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 axitinib 5 mg orally twice daily. (2.2)
- Endometrial Carcinoma: 200 mg every 3 weeks or 400 mg every 6 weeks with lenvatinib 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 antibody 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: 05/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Melanoma
1.2 Non-Small Cell Lung Cancer
1.3 Head and Neck Squamous Cell Cancer
1.4 Classical Hodgkin Lymphoma
1.5 Primary Mediastinal Large B-Cell Lymphoma

1.6 Urothelial Carcinoma
1.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer
1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer
1.9 Gastric Cancer
1.10 Esophageal Cancer
1.11 Cervical Cancer
1.12 Hepatocellular Carcinoma
1.13 Merkel Cell Carcinoma
1.14 Renal Cell Carcinoma
1.15 Endometrial Carcinoma
1.16 Tumor Mutational Burden-High Cancer
1.17 Cutaneous Squamous Cell Carcinoma
1.18 Triple-Negative Breast Cancer
1.19 Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

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
2.2 Recommended Dosage
2.3 Dose Modifications
2.4 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
5.1 Severe and Fatal Immune-Mediated Adverse Reactions
5.2 Infusion-Related Reactions
5.3 Complications of Allogeneic HSCT
5.4 Increased Mortality in Patients with Multiple Myeloma when KEYTRUDA is Added to a Thalidomide Analogue and Dexamethasone
5.5 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
14.1 Melanoma
14.2 Non-Small Cell Lung Cancer
14.3 Head and Neck Squamous Cell Cancer
14.4 Classical Hodgkin Lymphoma
14.5 Primary Mediastinal Large B-Cell Lymphoma
14.6 Urothelial Carcinoma
14.7 Microsatellite Instability-High or Mismatch Repair Deficient Cancer
14.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer
14.9 Gastric Cancer
14.10 Esophageal Cancer
14.11 Cervical Cancer
14.12 Hepatocellular Carcinoma
14.13 Merkel Cell Carcinoma
14.14 Renal Cell Carcinoma
14.15 Endometrial Carcinoma
14.16 Tumor Mutational Burden-High Cancer
14.17 Cutaneous Squamous Cell Carcinoma
14.18 Triple-Negative Breast Cancer
14.19 Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

KEYTRUDA® 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 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.

1.4 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.

1.5 Primary Mediastinal Large B-Cell Lymphoma

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

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

1.6 Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (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 (14.6)]*. 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.

1.7 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 (14.7)]*. 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.

1.8 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).

1.9 Gastric Cancer

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ 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.

These indications are approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.9)]*. Continued approval of these indications may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.10 Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with 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)]*.

1.11 Cervical Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

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

1.12 Hepatocellular Carcinoma

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

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

1.13 Merkel Cell Carcinoma

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

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

1.14 Renal Cell Carcinoma

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

1.15 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 (14.15)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.16 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 (14.16)]*. 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.

1.17 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.

1.18 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 (14.18)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.19 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 (1.1-1.18) 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 (14.19)]*. 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 (14.3)]*.
- metastatic urothelial carcinoma *[see Clinical Studies (14.6)]*.
- metastatic gastric cancer *[see Clinical Studies (14.9)]*. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.
- previously treated recurrent locally advanced or metastatic esophageal cancer *[see Clinical Studies (14.10)]*.
- recurrent or metastatic cervical cancer *[see Clinical Studies (14.11)]*.

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 (14.7, 14.8)].*

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 (14.16)].*

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 (14.18)]*.

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, 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 Gastric Cancer	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to trastuzumab and 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 lenvatinib 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.

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment

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

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 axitinib, 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†

Adverse Reaction	Severity*	Dosage Modification
	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
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 axitinib 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).

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 (14.3)]*. 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 (14.3)]*, 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 (14.4)].* 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
Þ 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 alkaline 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 (14.4)]*, 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 (14.5)],* 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 (14.6)]*. 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		
Rash[Þ]	21	0.5
Pruritus	19	0.3
Edema peripheral[ß]	14	1.1
Infections		
Urinary tract infection	19	9
Blood and Lymphatic System		
Anemia	17	7
Respiratory, Thoracic, and Mediastinal		
Cough	14	0
Dyspnea	11	0.5
Renal and Urinary		
Increased blood creatinine	11	1.1
Hematuria	13	3.0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
§ Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements
¶ Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper
# Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, increased transaminases, hyperbilirubinemia, increased blood bilirubin, increased alanine aminotransferase, increased aspartate aminotransferase, increased hepatic enzymes, increased liver function tests
Þ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneiform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized
ß 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 (14.6)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible.

The median duration of exposure was 3.5 months (range: 1 day to 20 months) in patients who received KEYTRUDA and 1.5 months (range: 1 day to 14 months) in patients who received chemotherapy.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). 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 Þ	15	0.4	9	0
Dyspnea ß	14	1.9	12	1.2
Renal and Urinary				
Hematuria à	12	2.3	8	1.6

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

Table 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 (14.8)]* 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

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric Cancer with Trastuzumab and Chemotherapy

The safety analysis of Study KEYNOTE-811 included 217 patients with HER2-positive gastric cancer who received KEYTRUDA 200 mg, trastuzumab, and CAPOX (n=189) or FP (n=28) every 3 weeks, compared to 216 patients who received placebo, trastuzumab, and CAPOX (n=187) or FP (n=29) every 3 weeks *[see Clinical Studies (14.9)]*.

The median duration of exposure to KEYTRUDA was 5.8 months (range: 1 day to 17.7 months).

The study population characteristics were: median age of 63 years (range: 19 to 84), 43% age 65 or older; 81% male; 58% White, 35% Asian, and 0.9% Black; 44% ECOG PS of 0 and 56% ECOG PS of 1.

KEYTRUDA and placebo were discontinued due to adverse reactions in 6% of patients in each arm. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 58% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (18%), thrombocytopenia (12%), diarrhea (6%), anemia (3.7%), hypokalemia (3.7%), fatigue/asthenia (3.2%), decreased appetite (3.2%), increased AST (2.8%), increased blood bilirubin (2.8%), pneumonia (2.8%), increased ALT (2.3%), and vomiting (2.3%).

In the KEYTRUDA arm versus placebo, there was a difference of ≥5% incidence between patients treated with KEYTRUDA versus standard of care for diarrhea (53% vs 44%), and nausea (49% vs 44%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

There was a difference of ≥5% incidence between patients treated with KEYTRUDA versus standard of care for increased ALT (34% vs 29%), and increased creatinine (20% vs 10%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

Previously Treated Gastric Cancer

Among the 259 patients with gastric cancer enrolled in KEYNOTE-059 *[see Clinical Studies (14.9)]*, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 21.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression or with clinical evidence of ascites by physical exam were ineligible. Adverse reactions occurring in patients with gastric cancer were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Esophageal Cancer

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

Cervical Cancer

Among the 98 patients with cervical cancer enrolled in Cohort E of KEYNOTE-158 *[see Clinical Studies (14.11)]*, the median duration of exposure to KEYTRUDA was 2.9 months (range: 1 day to 22.1 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%). Tables 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 pain[Þ]	22	3.1
Nausea	19	0
Vomiting	19	1.0
Constipation	14	0
Metabolism and Nutrition		
Decreased appetite	21	0
Vascular		
Hemorrhage[ß]	19	5
Infections		
UTI[à]	18	6
Infection (except UTI)[è]	16	4.1
Skin and Subcutaneous Tissue		
Rash[ð]	17	2.0
Endocrine		
Hypothyroidism	11	0
Nervous System		
Headache	11	2.0
Respiratory, Thoracic and Mediastinal		
Dyspnea	10	1.0

* Graded per NCI CTCAE v4.0

† Includes asthenia, fatigue, lethargy, malaise

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

§ Includes edema peripheral, peripheral swelling

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

Includes colitis, diarrhea, gastroenteritis

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

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

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

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

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

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

MCC

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

RCC

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

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

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

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

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

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

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

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

Tables 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 erythrodysesthesia 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 sunitinib (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 (14.15)]*. 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
Dyspneað	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

ð 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 (14.16)].* 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 (14.17)]*, 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 (14.18)]*. 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 (14.4, 14.5, 14.7, 14.13, 14.16)]*.

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.

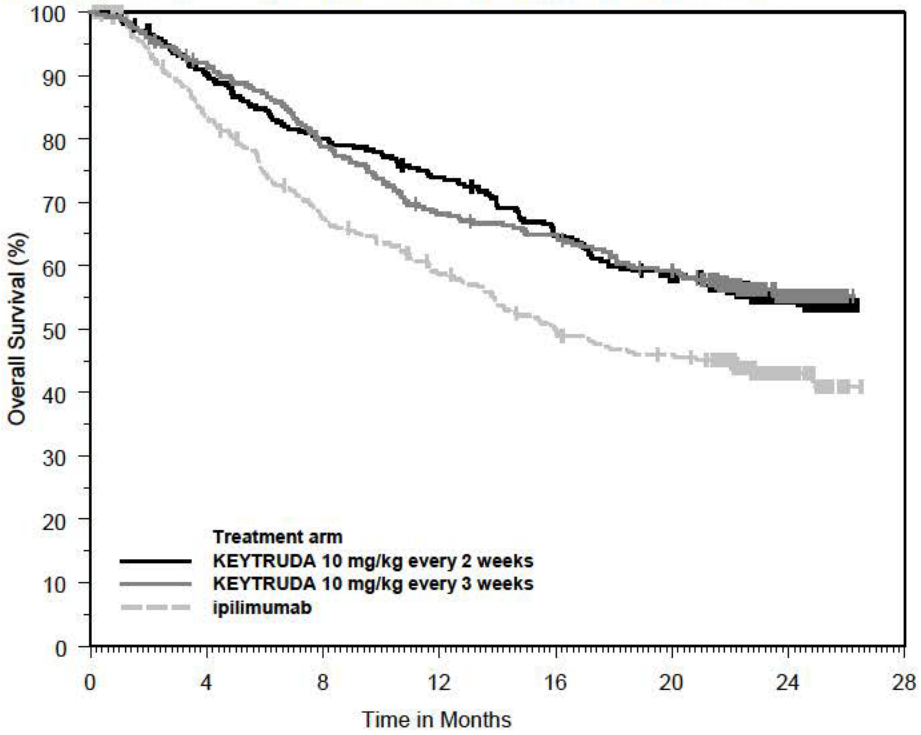
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients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

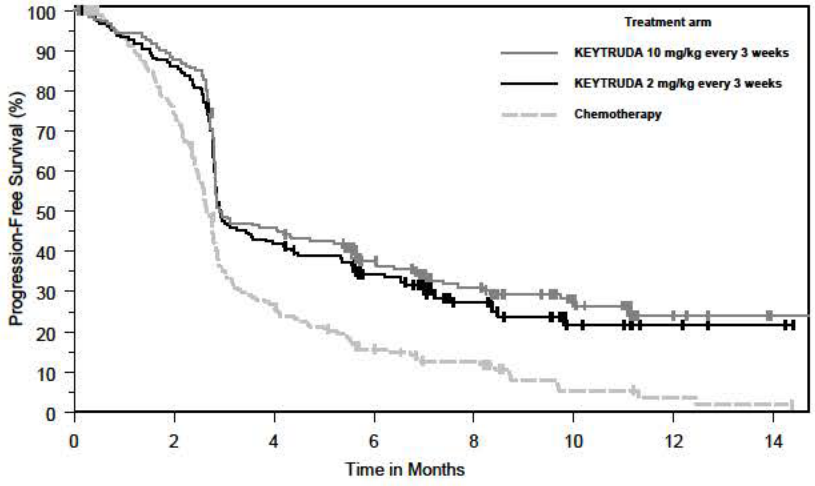
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8,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

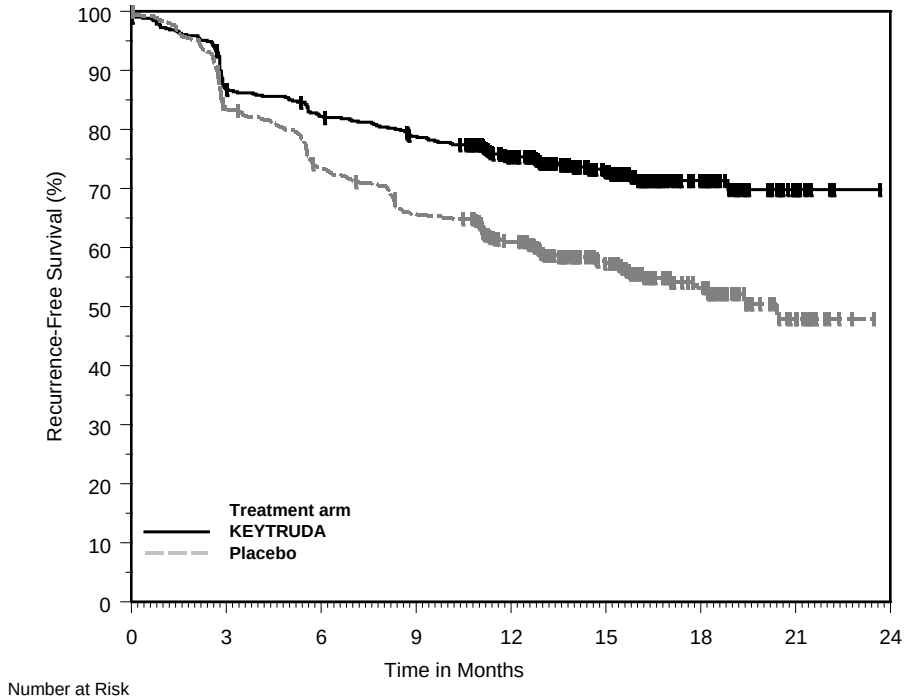
† Stratified by American Joint Committee on Cancer 7th edition (AJCC) stage

± 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



Number at Risk

KEYTRUDA:	514	438	413	392	313	182	73	15	0
Placebo:	505	415	363	323	264	157	60	15	0

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.

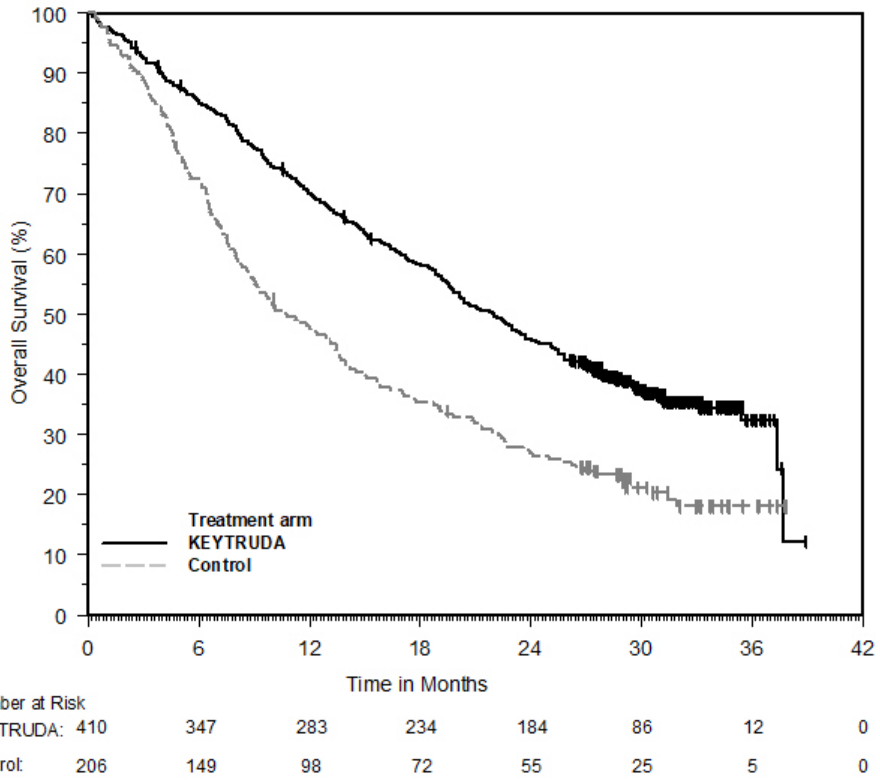
Table 42: Efficacy Results in KEYNOTE-189

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.

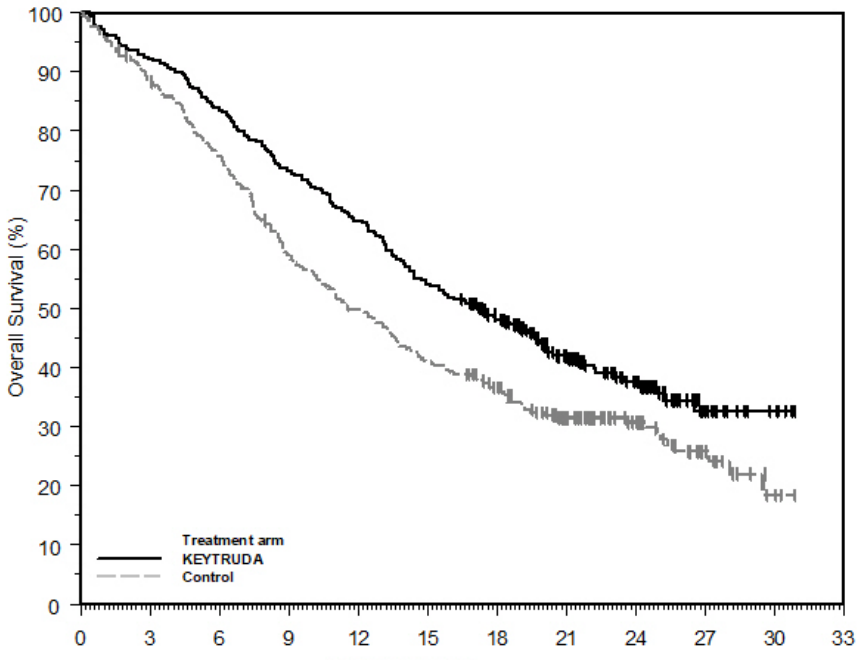
Table 43: Efficacy Results in KEYNOTE-407

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%.

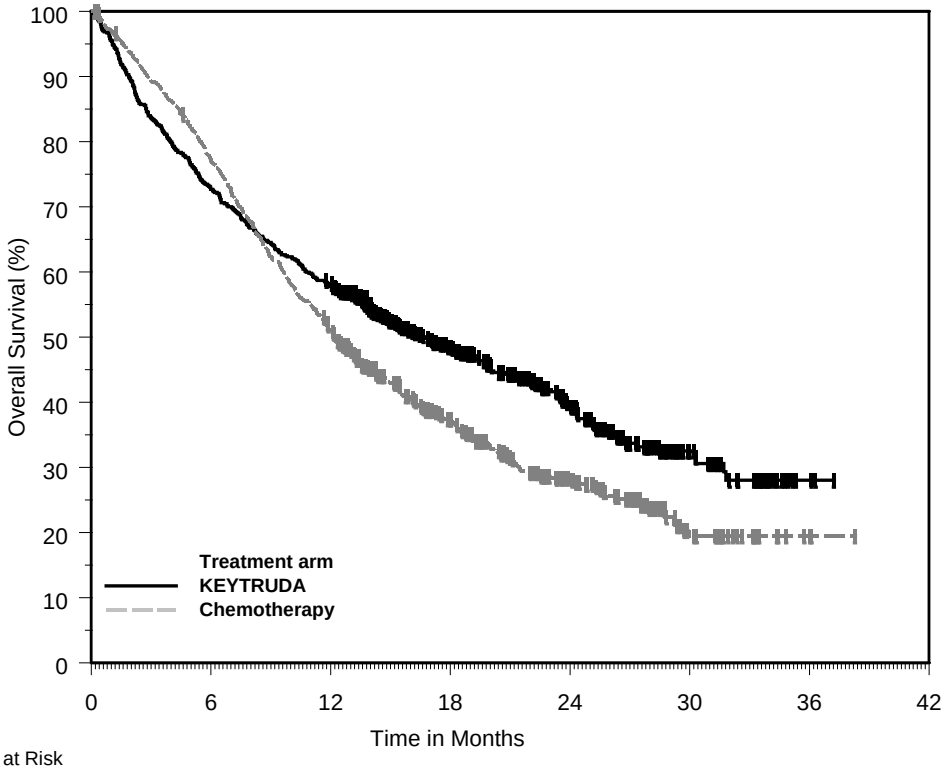
Table 44: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

	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+)

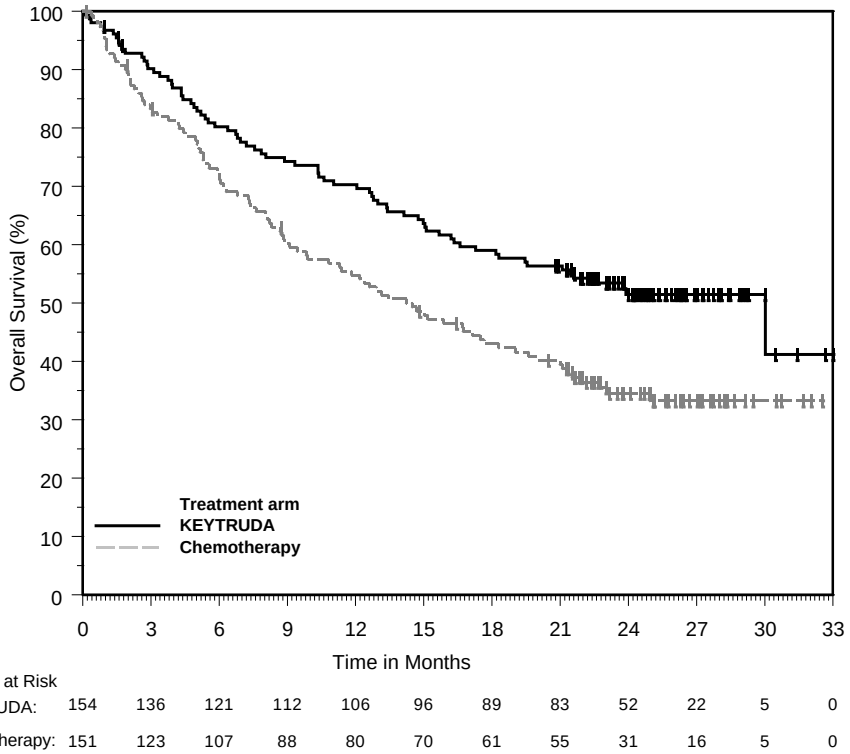
* Based on the stratified Cox proportional hazard model for the interim analysis

† 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*



Number at Risk												
KEYTRUDA:	154	136	121	112	106	96	89	83	52	22	5	0
Chemotherapy:	151	123	107	88	80	70	61	55	31	16	5	0

*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

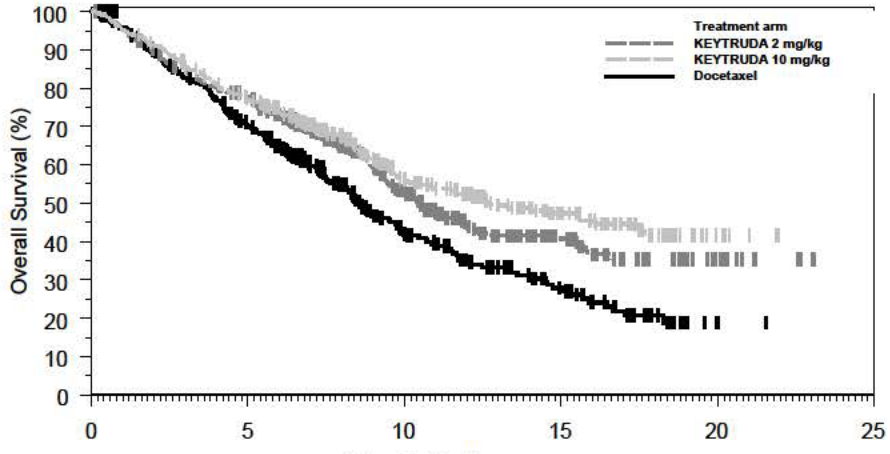
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
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 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 48 and Figure 9 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

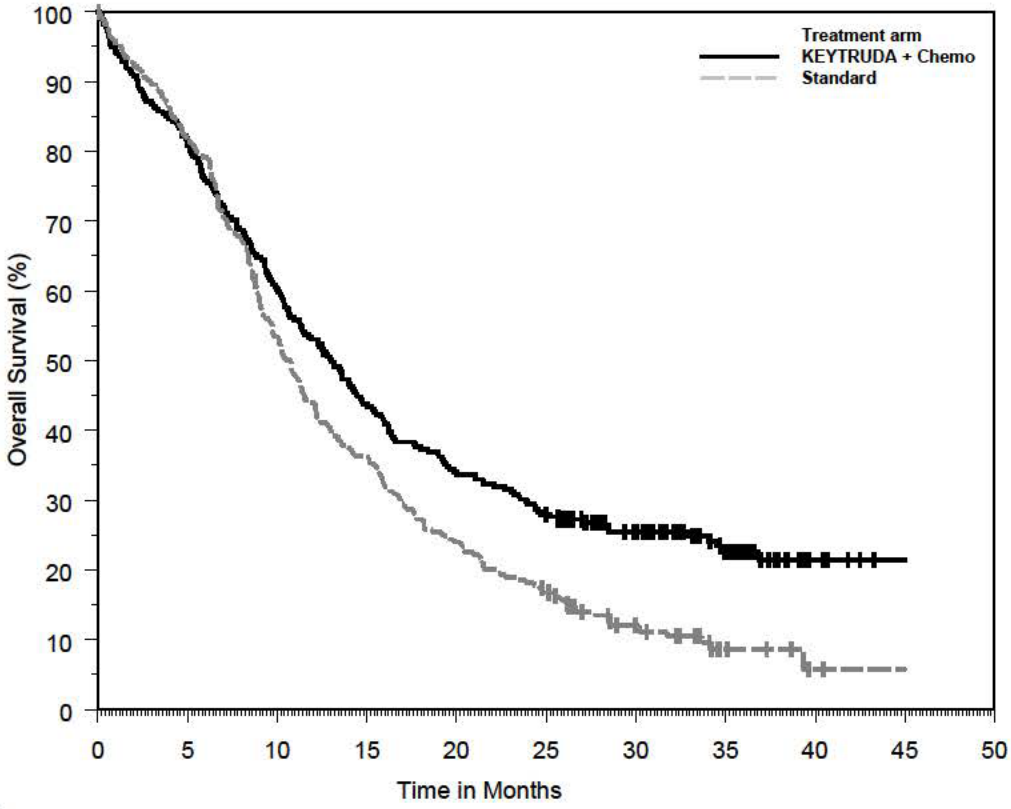
Table 48: Efficacy Results* for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048

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 49 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 49: Efficacy Results* for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)

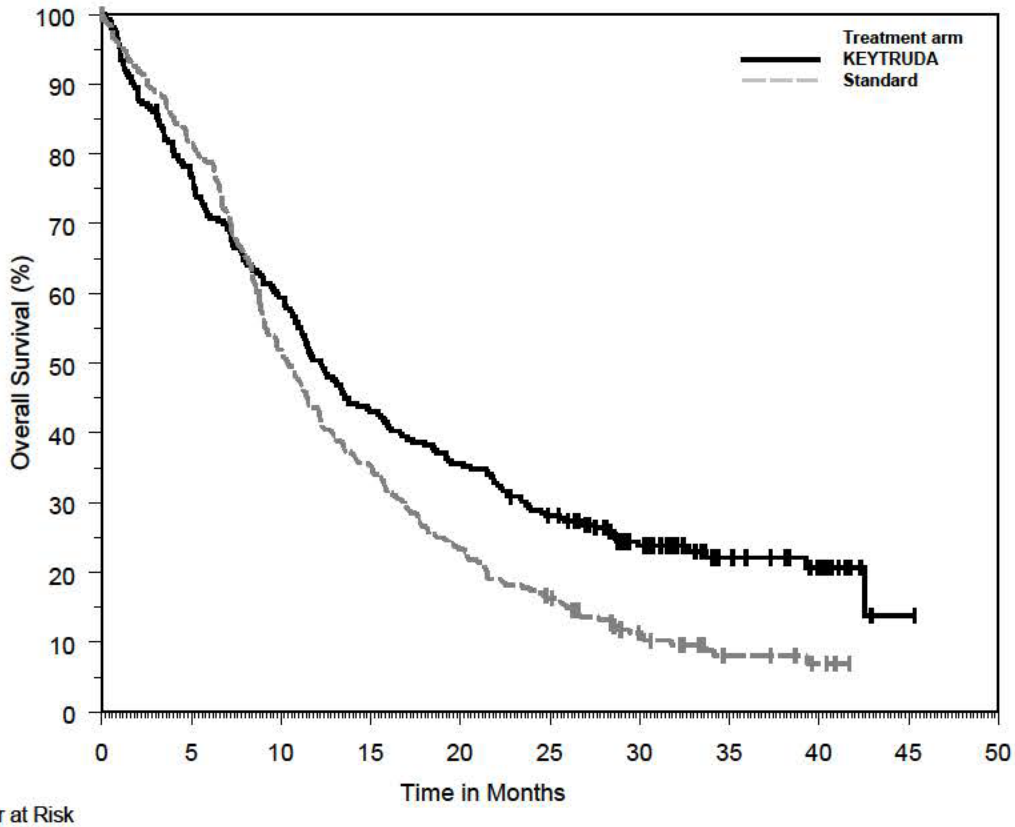
Endpoint	CPS ≥1		CPS ≥20	
	KEYTRUDA 200 mg every 3 weeks n=257	Cetuximab Platinum FU n=255	KEYTRUDA 200 mg every 3 weeks n=133	Cetuximab Platinum FU n=122
OS				
Number of events (%)	177 (69%)	206 (81%)	82 (62%)	95 (78%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0,11.5)	14.9 (11.6, 21.5)	10.7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

14.4 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.

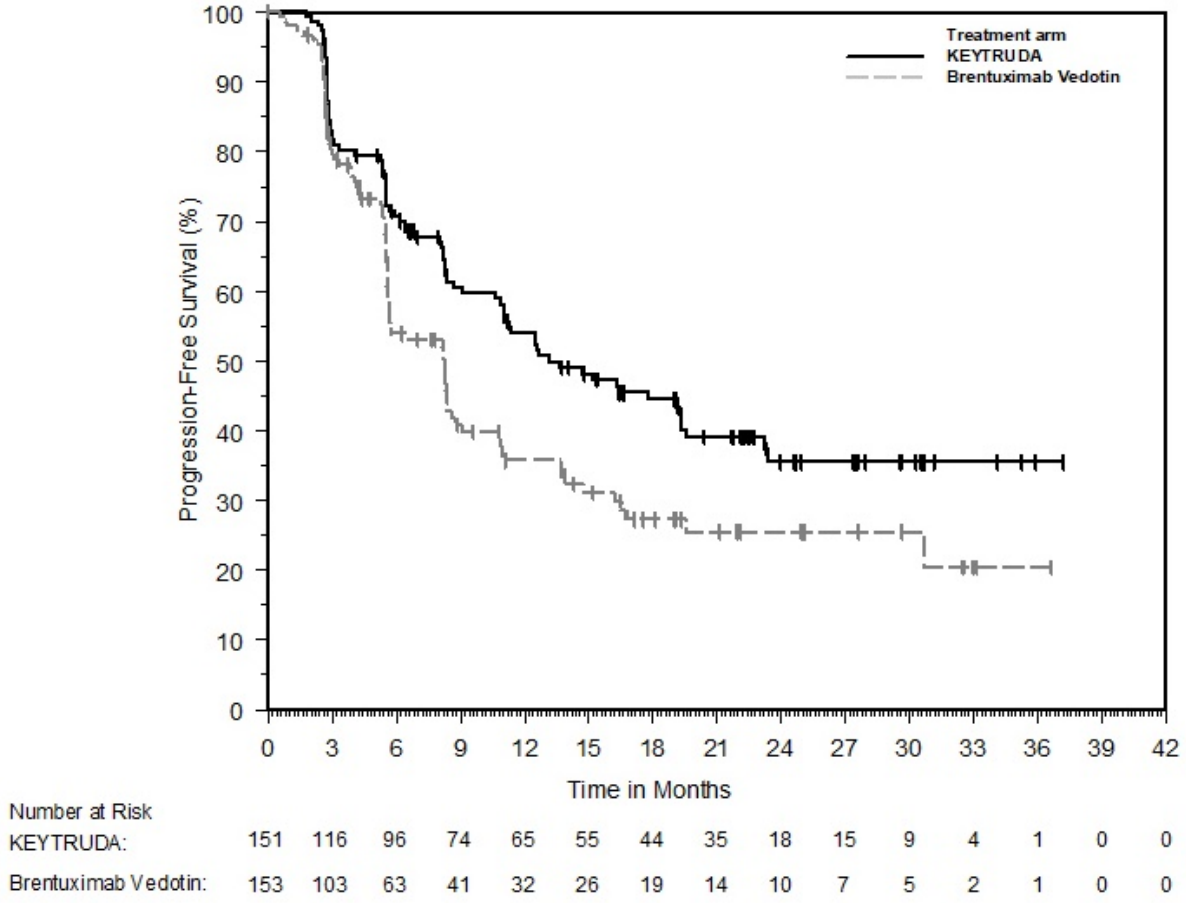
Efficacy is summarized in Table 50 and Figure 11.

Table 50: 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 51.

Table 51: 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

14.5 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 52.

Table 52: 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

14.6 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 53.

Table 53: 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 54 and Figure 12 summarize the efficacy results for KEYNOTE-045.

Table 54: Efficacy Results in KEYNOTE-045

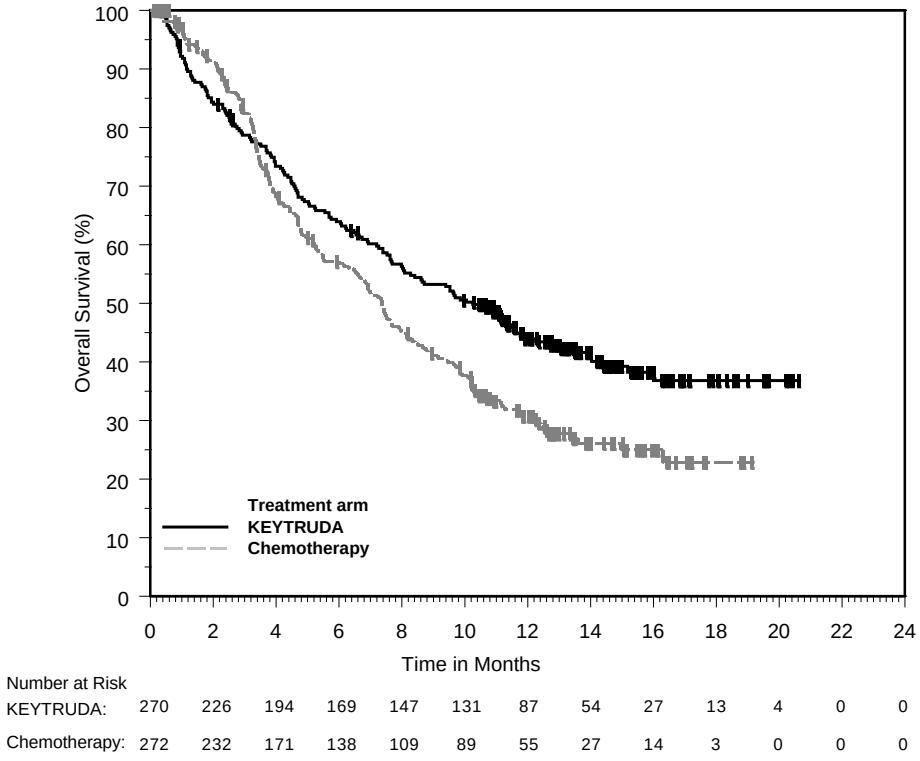
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (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 55.

Table 55: 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

14.7 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 56: 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 57 and 58.

Table 57: 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 58: 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

14.8 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.

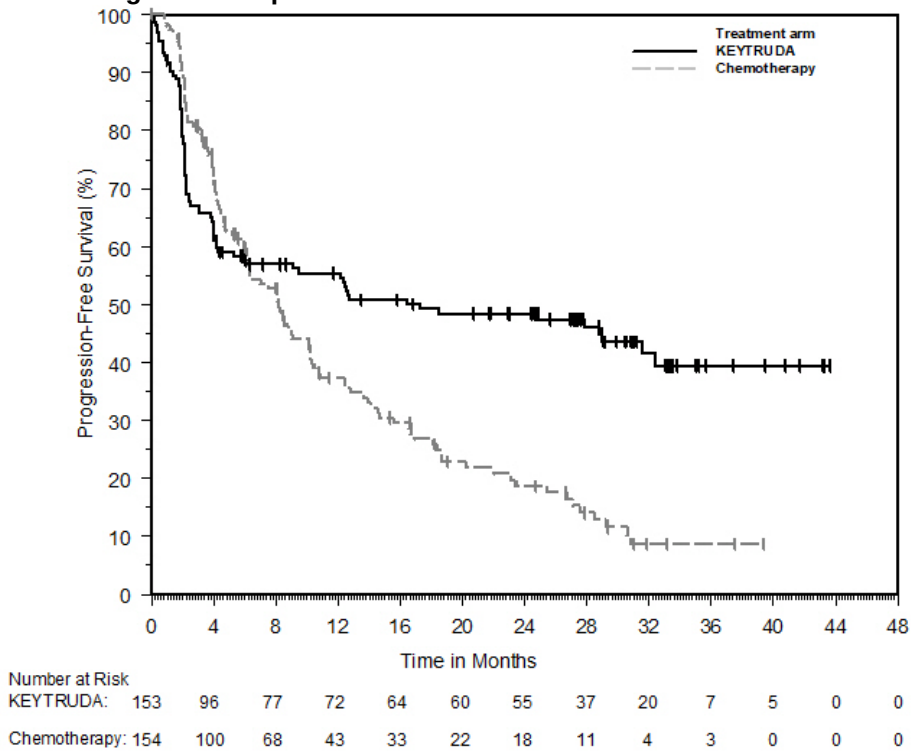
The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. At the time of the PFS analysis, the overall survival data were not mature (66% of the required number of events for the OS final analysis). The median follow-up time was 27.6 months (range: 0.2 to 48.3 months). Table 59 and Figure 13 summarize the key efficacy measures for KEYNOTE-177.

Table 59: 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



14.9 Gastric Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

The efficacy of KEYTRUDA in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811 (NCT03615326), a multicenter, randomized, double-blind, placebo-controlled trial that was designed to enroll 692 patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS $\geq$1 or CPS <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms.

- KEYTRUDA 200 mg, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX). KEYTRUDA was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.
- Placebo, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).

All study medications, except oral capecitabine, were administered as an intravenous infusion for every 3 week cycle. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. In an interim efficacy analysis, major outcome measures assessed were ORR and DoR by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

At the time of the interim analysis, ORR and DoR were assessed in the first 264 patients randomized. Among the 264 patients, the population characteristics were: median age of 62 years (range: 19 to 84), 41% age 65 or older; 82% male; 63% White, 31% Asian, and 0.8% Black; 47% ECOG PS of 0 and 53% ECOG PS of 1. Ninety-seven percent of patients had metastatic disease (stage IV) and 3% had locally advanced unresectable disease. Eighty-seven percent had tumors that expressed PD-L1 with a CPS ≥1. Ninety-one percent (n=240) had tumors that were not MSI-H, 1% (n=2) had tumors that were MSI-H, and in 8% (n=22) the status was not known. Eighty-seven percent of patients received CAPOX.

A statistically significant improvement in ORR was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy. Efficacy results are summarized in Table 60.

Table 60: Efficacy Results for KEYNOTE-811

Endpoint	**KEYTRUDA 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=133**	**Placebo Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=131**
Objective Response Rate		
ORR* (95% CI)	74% (66, 82)	52% (43, 61)
Complete response rate	11%	3.1%
Partial response rate	63%	49%
p-Value†	<0.0001	
Duration of Response	n=99	n=68
Median in months (range)	10.6 (1.1+, 16.5+)	9.5 (1.4+, 15.4+)
% with duration ≥6 months	65%	53%

* Response: Best objective response as confirmed complete response or partial response

† p-Value based on stratified Miettinen and Nurminen method (compared to an alpha boundary of 0.002)

Previously Treated Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

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

Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a CPS ≥1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. The baseline characteristics of these 143 patients were: median age of 64 years, 47% age 65 or older; 77% male; 82% White and 11% Asian; and 43% ECOG PS of 0 and 57% ECOG PS of 1. Eighty-five percent had M1 disease and 7% had M0 disease. Fifty-one percent had two and 49% had three or more prior lines of therapy in the recurrent or metastatic setting.

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

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

14.10 Esophageal Cancer

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

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.

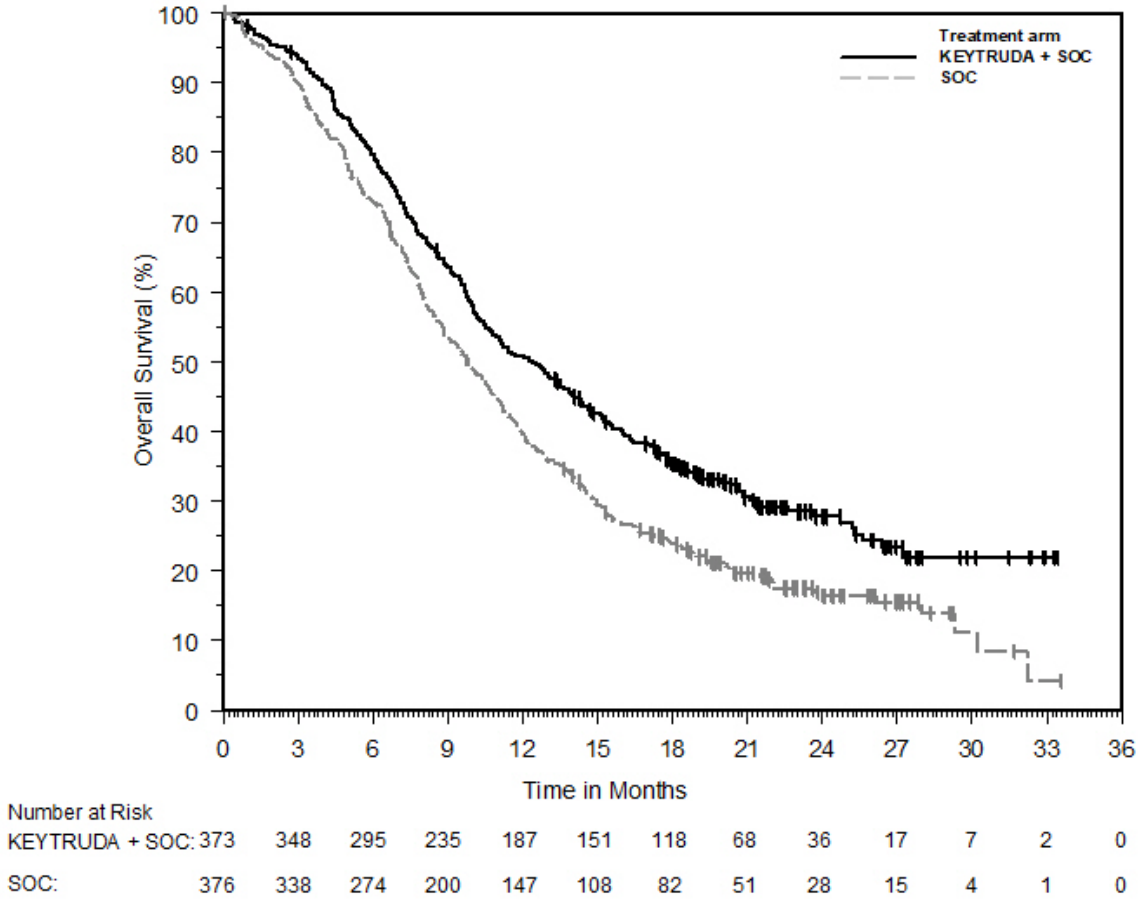
Table 61 and Figure 14 summarize the efficacy results for KEYNOTE-590 in all patients.

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.

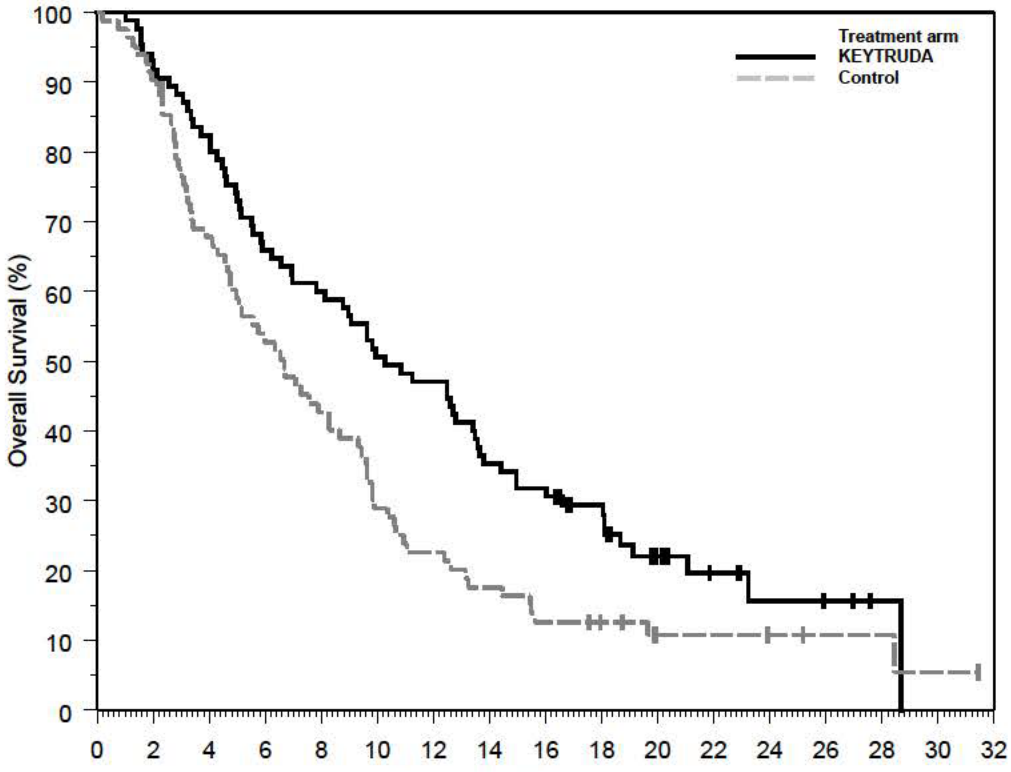
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement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

14.11 Cervical Cancer

The efficacy of KEYTRUDA was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort (Cohort E) in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg intravenously every 3 weeks

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

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

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

14.12 Hepatocellular Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-224 (NCT02702414), a single-arm, multicenter trial in 104 patients with HCC who had disease progression on or after sorafenib or were intolerant to sorafenib; had measurable disease; and Child-Pugh class A liver impairment. Patients with active autoimmune disease, greater than one etiology of hepatitis, a medical condition that required immunosuppression, or clinical evidence of ascites by physical exam were ineligible for the trial. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity, investigator-assessed confirmed disease progression (based on repeat scan at least 4 weeks from the initial scan showing progression), or completion of 24 months of KEYTRUDA. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR and DoR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

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

Efficacy results are summarized in Table 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

14.13 Merkel Cell Carcinoma

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

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

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

Efficacy results are summarized in Table 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

14.14 Renal Cell Carcinoma

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

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

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

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

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

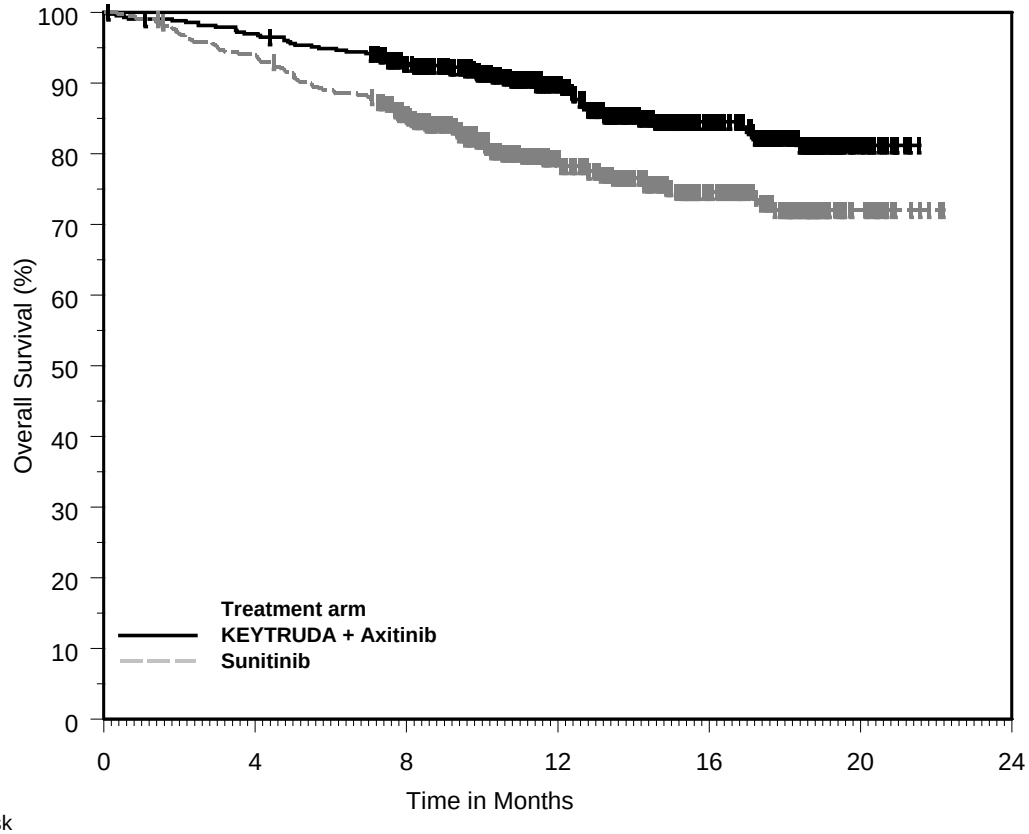
The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR, as assessed by BICR. A statistically significant improvement in OS was demonstrated at the pre-specified interim analysis in patients randomized to KEYTRUDA in combination with axitinib compared with sunitinib. The trial also demonstrated statistically significant improvements in PFS and ORR. Table 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 + Axitinib:	432	417	378	256	136	18	0
Sunitinib:	429	401	341	211	110	20	0

14.15 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

14.16 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.

14.17 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

14.18 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.

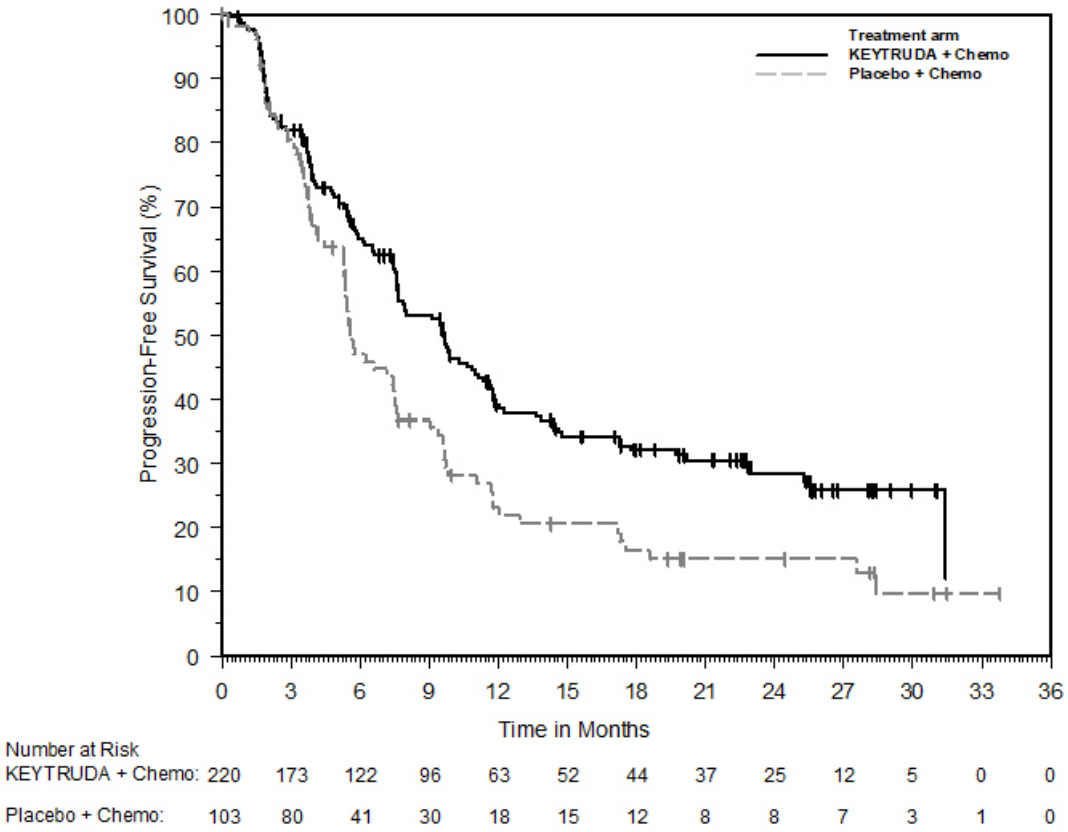
Table 71: Efficacy Results in KEYNOTE-355 (CPS ≥10)

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)



14.19 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)]*.

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

uspi-mk3475-iv-2105r044

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 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.
  - KEYTRUDA may be used with the medicine trastuzumab with fluoropyrimidine and platinum chemotherapy as your first treatment when your stomach cancer:
    - is HER2-positive, **and**
    - has spread or cannot be removed by surgery (advanced gastric cancer).
  - KEYTRUDA may be used alone when your stomach cancer:
    - tests positive for "PD L1", **and**
    - 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 is HER2-positive, you also received a HER2-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

usmg-mk3475-iv-2105r039

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s097

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-Disciplinary Review and Evaluation

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

Application Type	Supplemental BLA
Application Number(s)	125514/S-097
Priority or Standard	Priority
Submit Date(s)	November 6, 2020
Received Date(s)	November 6, 2020
PDUFA Goal Date	May 6, 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)	in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation 8

Additional Reviewers of Application 8

Glossary 9

1 Executive Summary 12
1.1 Product Introduction 12
1.2 Conclusions on the Substantial Evidence of Effectiveness 12
1.3 Benefit-Risk Assessment (BRA) 14
1.4 Patient Experience Data 19

2 Therapeutic Context 21
2.1 Analysis of Condition 21
2.2 Analysis of Current Treatment Options 23

3 Regulatory Background 25
3.1 U.S. Regulatory Actions and Marketing History 25
3.2 Summary of Presubmission/Submission Regulatory Activity 28

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 30
4.1 Office of Scientific Investigations (OSI) 30
4.2 Product Quality 30
4.3 Clinical Microbiology 30
4.4 Devices and Companion Diagnostic Issues 30

5 Nonclinical Pharmacology/Toxicology 31

6 Clinical Pharmacology 32
6.1 Executive Summary 32
6.2 Summary of Clinical Pharmacology Assessment 32
6.2.1. Pharmacology and Clinical Pharmacokinetics 32
6.2.2. General Dosing and Therapeutic Individualization 33
6.2.2.1. General Dosing 33

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.

6.2.2.2. Therapeutic Individualization 33
6.2.2.3. Outstanding Issues 34
6.3 Comprehensive Clinical Pharmacology Review 34
6.3.1. General Pharmacology and Pharmacokinetic Characteristics 34
6.3.2. Clinical Pharmacology Questions 34

7 Sources of Clinical Data 37
7.1 Table of Clinical Studies 37

8 Statistical and Clinical Evaluation 39
8.1 Review of Relevant Individual Trials Used to Support Efficacy 39
8.1.1. KEYNOTE-811 39
8.1.2. Study Results 48
8.1.3. Integrated Review of Effectiveness 60
8.1.4. Assessment of Efficacy Across Trials 60
8.1.5. Integrated Assessment of Effectiveness 61
8.2 Review of Safety 61
8.2.1. Safety Review Approach 61
8.2.2. Review of the Safety Database 62
8.2.3. Adequacy of Applicant's Clinical Safety Assessments 63
8.2.4. Safety Results 64
8.2.5. Analysis of Submission-Specific Safety Issues 79
8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability 80
8.2.7. Safety Analyses by Demographic Subgroups 80
8.2.8. Specific Safety Studies/Clinical Trials 80
8.2.9. Additional Safety Explorations 80
8.2.10. Safety in the Postmarket Setting 81
8.2.11. Integrated Assessment of Safety 82

SUMMARY AND CONCLUSIONS 83
8.3 Statistical Issues 83
8.4 Conclusions and Recommendations 83

9 Advisory Committee Meeting and Other External Consultations 86

10 Pediatrics 87

11 Labeling Recommendations 88

12 Risk Evaluation and Mitigation Strategies (REMS) 90

13 Postmarketing Requirements and Commitment 91

14 Division Director (DHOT) (NME ONLY) 92

15 Division Director (OCP) 93

16 Division Director (OB) 94

17 Division Director (Clinical) 95

18 Office Director (or designated signatory authority) 96

19 Appendices 97

19.1 References 97

19.2 Financial Disclosure 100

19.3 Nonclinical Pharmacology/Toxicology 101

19.4 OCP Appendices (Technical documents supporting OCP recommendations) 101

19.5 Additional Safety Analyses Conducted by FDA 101

Applicant's Table of Tables

Applicant Table 1 Summary of FDA-approved First-line Therapies for Advanced and Metastatic HER2-positive Gastric Cancer..... 24
Applicant Table 2 Summary of FDA-approved Pembrolizumab Indications 25
Applicant Table 3 Key Regulatory Interactions Related to KEYNOTE-811..... 29
Applicant Table 4 Listing of Clinical Trials Relevant to this NDA/BLA..... 38
Applicant Table 5 Summary of Key Changes to the KEYNOTE-811 Protocol..... 47
Applicant Table 6 Disposition of Participants (ITT Population and First 264 Patients Randomized in the ITT Population) 50
Applicant Table 7 Summary of Follow-up Duration 50
Applicant Table 8 Subject Characteristics (ITT Population and First 264 Patients Randomized in the ITT Population) 52
Applicant Table 9 Efficacy Endpoint Results Pembrolizumab + SOC versus SOC (First 264 Participants Randomized in the ITT Population) KEYNOTE-811 IA1..... 57
Applicant Table 10 Summary of Drug Exposure (Global Cohort) (ASaT Population)..... 62
Applicant Table 11 Adverse Event Summary (Global Cohort) (ASaT Population) 65
Applicant Table 12 Subjects With Adverse Events Resulting in Death by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups) (Global Cohort) (ASaT Population)..... 67
Applicant Table 13 Adverse Event Summary AEOSI (Global Cohort) (ASaT Population)..... 71
Applicant Table 14 Subjects With Adverse Events of Special Interest (AEOSI) by AEOSI category (Incidence > 0% in One or More Treatment Groups) (Global Cohort) (ASaT Population)..... 72
Applicant Table 15 Subjects With Adverse Events by Decreasing Incidence (Incidence ≥ 10% in One or More Treatment Groups) (Global Cohort) (ASaT Population)..... 74

Applicant's Table of Figures

Applicant Figure 1 Study Design for KEYNOTE-811 – Global Cohort 40
Applicant Figure 2 Between-treatment Comparisons in Adverse Events Selected Adverse Events (>=10% Incidence) and Sorted by Risk Difference (Global Cohort) (ASaT Population) 75

FDA's Table of Tables

Table 1 Lab abnormalities worsened from baseline in 20% patients in Study KN811 78

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Gina Davis
Office of Clinical Pharmacology Reviewer(s)	Blaire Osborn, Pharm D.
Office of Clinical Pharmacology Team Leader(s)	Hong Zhao, Pharm D.
Clinical Reviewer	Leigh Marcus, MD
Clinical Team Leader	Sandra J. Casak, MD
Safety Analyst (if applicable)	Jonathan Herz
Statistical Reviewer	Somak Chatterjee, PhD
Statistical Team Leader	Pallavi Mishra-Kalyani, PhD
Associate Director for Labeling (ADL)	William F. Pierce, Pharm D
Cross-Disciplinary Team Leader	Sandra J. Casak, MD
Division Director (OB)	Shenghui Tang, PhD
Division Director (OOD)	Steven Lemery, MD, MHSc.
Office Director (or designated signatory authority)	N/A

Additional Reviewers of Application

OPDP	Adesola Adejuwon/Kevin Wright
DMPP	Sharon Mills

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

Glossary

AE	adverse event
ADA	anti-drug antibodies
AEOSI	adverse event of special interest
ASaT	all subjects as treated
AST	aspartate aminotransferase
BICR	blinded independent central review
BLA	Biologics License Application
CAPOX	capecitabine plus oxaliplatin
CFR	Code of Federal Regulations
cHL	classical Hodgkin Lymphoma
CI	confidence interval
COVID	coronavirus
CR	complete response
DEPI	Division of Epidemiology
DMC	Data Monitoring Committee
DMEPA	Division of Medication Error Prevention and Analysis
DRISK	Division of Risk Management
DOR	duration of response
ECG	electrocardiogram
ECOG PS	European Cooperative Oncology Group Performance Score
eCTD	electronic common technical document
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FP	cisplatin plus 5-FU
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
HCC	hepatocellular carcinoma
HER2	human endothelial growth factor receptor 2
HR	hazard ratio
HNSCC	head and neck squamous cell carcinoma
IA1	interim analysis 1
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

IND	Investigational New Drug
IRB	Institutional Review Board
iRECIST	immune Response Evaluation Criteria in Solid Tumors for immune-based therapeutics
IRT	interactive response technology
ITT	intention to treat
IV	intravenous
KM	Kaplan Meier
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRL	Merck Research Laboratories
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI-H	microsatellite instability high
N/n	number
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
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QA	Quality Assurance
QC	Quality Control
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
ROW	Rest of World

SAE	serious adverse event
sBLA	supplemental Biologics License Application
SOC	standard of care
SOX	S-1 + oxaliplatin
ToGA	Trastuzumab for Gastric Cancer study
TTP	time to progression
TTR	time to recurrence
UC	urothelial cancer
US	United States
USPI	Unites States Prescribing Information
vs	versus

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 primary trial supporting this sBLA is Study KEYNOTE-811 (Study KN811), an ongoing, international, double-blinded, randomized (1:1) trial in patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma receiving standard of care first-line treatment with trastuzumab and chemotherapy (fluoropyrimidine/cisplatin [FP] or capecitabine/oxaliplatin [CAPOX]) combined with pembrolizumab or placebo. HER2 positive was defined as a tumor with immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH]-positive as per central review assessment. Patients with previous therapy for locally advanced unresectable or metastatic gastric/GEJ cancer; 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 PD-L1 status (CPS ≥1 vs. < 1), geographic region (Europe/Israel/North America/Australia vs. Asia vs. rest of the world), and selected chemotherapy backbone (FP vs. CAPOX).

Patients were randomized in a 1:1 ratio to receive either pembrolizumab 200 mg or saline placebo intravenously (IV) every 3 weeks (Q3W). All patients received trastuzumab (8 mg/kg loading dose and then 6 mg/kg maintenance Q3W thereafter) combined with FP (cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil 800 mg/m^2/day continuous IV infusion on each of Days 1 to 5 Q3W) or CAPOX (oxaliplatin 130 mg/m^2 IV on Day 1 and capecitabine 1000 mg/m^2 on Days 1-14 of each 21-day cycle). The primary endpoints of the trial are progression-free survival (PFS) per RECIST v1.1 (modified to allow a maximum of 10 target lesions in total and 5 per organ) and overall survival (OS); although overall response rate (ORR) is a secondary endpoint, the data supporting this submission represented the analysis conducted at the first interim analysis (IA1), which was timed to be performed when the first ~260 patients randomized had been followed up for at least 8.5 months. Alpha was allocated for this analysis of ORR as part of the study's overall approach to controlling the two sided Type 1 error at 5% or less.

As of the data cutoff date (June 17, 2020) for IA1, 434 patients of the planned total 692 were randomized. Two-hundred sixty-four patients are included in this analysis, 133 and 131 in the pembrolizumab and placebo arms, respectively. IA1 of KN811 demonstrated a clinically meaningful, statistically significant improvement in a blinded, independent central review (BIRC) of ORR. In the ITT population, the ORR was 74.4% (95% CI 66.2, 81.6) in the pembrolizumab arm and 51.9% (95% CI 43.0, 60.7) in the placebo arm (one-sided p-value=0.00006, one-sided p-value boundary=0.002). These responses included complete responses in 11.3% and 3.1% patients in the pembrolizumab and placebo arms, respectively. The median duration of response (DoR) estimated using the KM method was 10.6 months (95% CI 1.1; 16.5) in the pembrolizumab arm vs. 9.5 months (95% CI 1.4, 15.4) in the placebo arm; 70.3% and 61.4% patients have responses lasting ≥ 6 months.

The submitted evidence meets the statutory evidentiary standard for accelerated approval of pembrolizumab in combination with chemotherapy for the first-line treatment of patients with metastatic or locally advanced unresectable HER2 positive gastric or GEJ adenocarcinoma. The observed improvement of 22% in ORR, supported with durable responses is statistically significant and clinically meaningful and reasonably likely to predict for clinical benefit. Merck has agreed to a post marketing requirement to submit the final progression free survival and overall survival analyses of KN811 to verify and further describe the benefit of pembrolizumab with trastuzumab plus chemotherapy for patients with HER2-positive advanced or metastatic gastric or gastroesophageal adenocarcinoma.

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 accelerated approval for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) 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.

The safety and effectiveness of pembrolizumab for the treatment of patients with metastatic or unresectable, locally advanced HER2-positive gastric or GEJ adenocarcinoma was established by the interim analysis results of an ongoing, multicenter, international, double-blinded randomized trial, Study KEYNOTE-811 (KN811). HER2 status was centrally confirmed in tumor specimens in all patients using the FDA approved Dako HercepTest (IHC) and Dako HER2 IQFISH 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 PD-L1 status (CPS ≥1 vs. < 1 as assessed by a central lab using the Dako PD-L1 22C3 pharmDx kit), geographic region (Europe/Israel/North America/Australia vs. Asia vs. rest of the world), and selected chemotherapy backbone (FP vs. CAPOX).

Patients were randomized in a 1:1 ratio to receive either pembrolizumab 200 mg or saline placebo intravenously (IV) every 3 weeks (Q3W). All patients received trastuzumab (8 mg/kg loading dose and then 6 mg/kg maintenance Q3W thereafter) in combination with FP (cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil 800 mg/m^2/day continuous IV infusion on each of Days 1 to 5 Q3W) or CAPOX (oxaliplatin 130 mg/m^2 IV on Day 1 and capecitabine 1000 mg/m^2 on Days 1-14 of each 21-day cycle).

The primary endpoints of KN811 are progression-free survival (PFS) per RECIST v1.1 (modified to allow a maximum of 10 target lesions in total and 5 per organ) and overall survival (OS). Although overall response rate (ORR) is a secondary endpoint, the data supporting this submission represent the analysis conducted at the first interim analysis (IA1), which was timed to be performed when the first ~260 patients randomized had been followed up for at least 8.5 months. Alpha was allocated for this analysis of ORR as part of the study's overall approach to controlling

the two sided Type 1 error at 5% or less.

A total of 434 of the planned 692 patients were randomized at the time of data cutoff for IA1 and 264 patients are included in this analysis (133 and 131 in the pembrolizumab and placebo arms respectively). The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 60.6 years (range: 19 to 84), 41% age 65 or older; 82% male; 63% White, 31% Asian, and 1% Black; 47% had an ECOG PS of 0 and 53% had an ECOG PS of 1. Ninety-seven percent had metastatic disease. Most patients (70%) had gastric adenocarcinoma and 30% had GEJ adenocarcinoma; 81% patients had tumors with HER2 3+ and 87% had PD-L1 CPS ≥1.

IA1 of KN811 demonstrated a clinically meaningful, statistically significant improvement in BIRC-assessed ORR. In the ITT population, the ORR was 74.4% (95% CI 66.2, 81.6) in the pembrolizumab arm and 51.9% (95% CI 43.0, 60.7) in the placebo arm (one-sided p-value=0.00006, one-sided p-value boundary=0.002). These responses included complete responses in 11.3% and 3.1% patients in the pembrolizumab and placebo arms, respectively. The median duration of response (DoR) estimated using the KM method was 10.6 months (95% CI 1.1; 16.5) in the pembrolizumab arm vs. 9.5 months (95% CI 1.4, 15.4) in the placebo arm; 70.3% and 61.4% patients have responses lasting ≥ 6 months. The benefit of the addition of pembrolizumab was generally consistent across exploratory subsets analyses based on different patient demographic and baseline disease/tumor characteristics.

The adverse reaction profile observed in patients receiving pembrolizumab in Study KN811 is consistent with the known pembrolizumab safety profile. Pembrolizumab was discontinued due to adverse events (AEs) in 6% of patients. The most common adverse reaction resulting in permanent discontinuation of pembrolizumab (≥1%) was pneumonitis (1.4%). Adverse reactions leading to interruption of any of the multidrug component occurred in 71% and 66% of patients in the pembrolizumab and placebo arms, respectively. The most common interruptions of any drug appear to be related to common toxicities of chemotherapy (hematological toxicity, diarrhea, vomiting, nausea, etc.).

The review team concludes that the submitted evidence meets the statutory evidentiary standard for accelerated approval of pembrolizumab in combination with chemotherapy for the first line treatment of patients with metastatic or locally advanced unresectable HER2 positive gastric or GEJ adenocarcinoma. The observed improvement of 22% in ORR, supported with durable responses is statistically significant and clinically meaningful and reasonably likely to predict for clinical benefit. Merck has agreed to a post marketing requirement to submit the final progression free survival and overall survival analyses of KN811 to verify and further describe the benefit of pembrolizumab with trastuzumab plus chemotherapy for patients with HER2-positive advanced or metastatic gastric or gastroesophageal adenocarcinoma. At this time, the study is too immature to assess for an effect on survival.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	In the US, it is estimated that there will be 27,600 new cases of gastric cancer and 11,010 deaths from the disease in 2020 (SEER database). HER2 is overexpressed or amplified in 7% to 34% of gastric cancers; even when targeted therapy is available, locally advanced unresectable or metastatic HER2 gastric/GEJ cancer is a serious condition. The median survival of patients with metastatic disease is approximately 14 months.	Locally advanced or unresectable HER2 positive gastric/GEJ carcinoma is a serious, life-threatening condition with a poor prognosis.
Current Treatment Options	The standard of care for the first-line treatment of patients with advanced unresectable, or metastatic HER2 positive gastric/GEJ carcinoma is limited to the combination of trastuzumab, a HER2-directed monoclonal antibody, in combination with a platinum and a fluoropyrimidine agent. The approval of trastuzumab was supported by the ToGA study, a randomized, open-label study of trastuzumab in combination with chemotherapy (capecitabine plus cisplatin or fluorouracil plus cisplatin) versus chemotherapy alone in 584 patients with HER2-positive, unresectable or metastic gastric or GEJ adenocarcinoma. The median OS was 13.8 months (95% CI: 12–16) in those assigned to trastuzumab plus chemotherapy and 11.1 months (95% CI: 10, 13) in those assigned to chemotherapy alone (HR=0.74; 95% CI: 0.60–0.91; p=0.0046; ORR were 47% and 35% in the trastuzumab plus chemotherapy and chemotherapy arms, respectively (Bang YJ, 2010). The study supporting this approval, KN811, is an add-on regimen; patients will continue to receive standard of care treatment.	Although trastuzumab is an available effective treatment for patients with HER2-positive gastric and GEJ carcinoma, prognosis is dismal with an estimated survival of 14 months.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	This approval is supported by a single Study, KEYNOTE-811 (KN811). KN811 is an international, double-blind, placebo-controlled, randomized, ongoing trial in patients with metastatic or locally advanced HER2-positive gastric or GEJ adenocarcinoma who have not received prior systemic therapy. Patients were randomized (1:1) to receive either pembrolizumab or placebo; all patients received combination therapy with trastuzumab and a fluoropyrimidine and platinum agent (fluorouracil/cisplatin or capecitabine/oxaliplatin). Treatment was administered until disease progression or intolerable toxicity. The primary endpoints of KN811 are progression-free survival and overall survival; although blinded central review of overall response rate (ORR) is a secondary endpoint, the data supporting this submission represent the analysis conducted at the first interim analysis (IA1), which was timed to be performed when the first ~260 patients randomized had been followed up for at least 8.5 months. Alpha was allocated for this analysis of ORR as part of the study's overall approach to controlling the two sided Type 1 error at 5% or less. A total of 264 patients were randomized and included in this analysis, 133 to the pembrolizumab arm and 131 to placebo arm (the study enrolled 434 patients at the time of data cutoff and it is ongoing). The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. In the ITT population, the ORR was 74.4% (95% CI 66.2, 81.6) in the pembrolizumab arm and 51.9% (95% CI 43.0, 60.7) in the placebo arm (one-sided p-value=0.00006, one-sided p-value boundary=0.002). These	The submitted evidence meets the statutory evidentiary standard for accelerated approval. Results of a well-controlled randomized study showed a statistically significant and clinically meaningful improvement in response rate supported by durable responses among patients who received trastuzumab and chemotherapy in combination with pembrolizumab compared to those who received placebo with trastuzumab and chemotherapy in Study KN811. These results are reasonably likely to predict for clinical benefit in this patient population. Study KN811 is ongoing and the results of its primary endpoints, progression-free and overall survival will be submitted as a post-marketing requirement to verify and further describe the benefit of pembrolizumab with trastuzumab plus chemotherapy for patients with HER2-positive advanced or metastatic gastric or gastroesophageal junction adenocarcinoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	responses included complete responses in 11.3% and 3.1% patients in the pembrolizumab and placebo arms respectively. The median duration of response (DoR) estimated using the KM method was 10.6 months (95% CI 1.1; 16.5) in the pembrolizumab arm vs. 9.5 months (95% CI 1.4, 15.4) in the placebo arm; 70.3% and 61.4% patients have responses lasting ≥ 6 months. The benefit of the addition of pembrolizumab was generally consistent across exploratory subsets analyses based on different patient demographic and baseline disease/tumor characteristics, although as expected, the magnitude of the benefit differed in small subsets.	
Risk and Risk Management	The observed safety profile of pembrolizumab in patients with metastatic or unresectable HER2-positive gastric or GEJ adenocarcinoma was consistent with the established safety profile of pembrolizumab in patients with other types of cancer. The addition of pembrolizumab to trastuzumab and chemotherapy was well tolerated. The most common adverse reaction resulting in permanent discontinuation of pembrolizumab (≥1%) was pneumonitis (1.4%). Adverse reactions leading to interruption of any of the multidrug component occurred in 71% and 66% of patients in the pembrolizumab and placebo arms, respectively. The most common interruptions of any drug appear to be related to common toxicities of chemotherapy (hematological toxicity, diarrhea, vomiting, nausea, etc.).	The toxicity profile of pembrolizumab is acceptable when assessed in the context of the life-threatening nature of advanced unresectable or metastatic HER2 positive gastric 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. These risks are adequately addressed in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		product labeling, and oncologists who treat patients with gastric/GEJ adenocarcinoma are well-trained in the monitoring and treatment of these adverse reactions.

1.4 Patient Experience Data

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

Reviewer's note: although the comparison between arms of the change from baseline in health-related quality of life using the EORTC QLQ-C30 and the EORTC QLQ-STO22 is a tertiary/exploratory objective, these analyses were not conducted at the time of the interim analysis of efficacy results supporting this application.

				Section where discussed, if applicable
□	The patient experience data that was submitted as part of the application, include:			
	□	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		

	□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.		

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

Gastric cancer remains a major health problem worldwide. Gastric cancer is the fifth most common cancer in the world [1] and was the third-leading cause of cancer death globally in 2018 [2]. Gastric cancer incidence varies markedly by geographic region. In the US, it is estimated that there will be 27,600 new cases (16,980 in males and 10,620 in females) of gastric cancer and 11,010 deaths from the disease (6,650 in males and 4,360 in females) in 2020 [3]. More than 70% of cases occur in developing countries. Half the world total occurs in Eastern Asia, and the highest rates in the world occur in South Korea [2]. In the European Union, incidence and mortality for gastric cancer were estimated at 82,000 (51,000 in males and 31,000 in females) and 58,000 (35, 000 in males and 23,000 in females), respectively in 2012 [1]. By stage, 28% of gastric cancer cases are diagnosed as localized followed by regional (26%) and distant (36%), with 5-year relative survival rates of 69.5%, 32%, and 5.5%, respectively [4]. Median OS for advanced/metastatic disease is less than 1 year [5].

HER2 is a transmembrane tyrosine kinase receptor and is overexpressed or amplified in 7% to 34% of gastric cancer [5]. Innate and adaptive immune mechanisms are emerging as key players in modulation of the effects of HER2 targeted agents such as trastuzumab. A growing body of preclinical and clinical evidence shows that the immune system contributes substantially to the therapeutic effects of trastuzumab in solid tumors [6] [7].

The FDA's Assessment:

FDA agrees with the applicant's position. As stated above, in the U.S., based on data from the Surveillance, Epidemiology, and End Results (SEER), new cases of gastric cancer in 2021 are expected in 27,600 people (7.3 per 100,000 people) and 11,010 deaths from the disease were reported in 2020 (https://seer.cancer.gov/statfacts/html/stomach.html). In Western countries, patients are more often diagnosed at an inoperable advanced stage, when outcomes are poorer. Despite these differences, standard of care treatment for locally advanced/metastatic disease is similar across regions. Testing for HER2-positive status is standard of care in all patients considered candidates for combination therapy that includes trastuzumab. Greater heterogeneity of immunostaining for HER2 has been recognized in gastric carcinomas compared with breast carcinomas and panel guidelines were developed regarding HER2 testing for gastric cancers. In the Trastuzumab for Gastric Cancer (ToGA) trial, the results of which served as the basis for the approval of trastuzumab in gastric cancer, 53% of patients were Asian, and HER2 positivity (22.1%) was similar between European and Asian patients (23.6% and 23.9% respectively). In trials of HER2- directed agents in gastric cancer including ToGA, there have been no notable differences described in treatment response between patients

from Asia and patients from other regions. In Study KN811, HER2 positivity was confirmed by a central lab using the FDA-approved assays Dako HercepTest (IHC) and Dako HER2 IQFISH pharmDx Kit.

APPEARS THIS WAY
ON ORIGINAL

2.2 Analysis of Current Treatment Options

The Applicant's Position:

Systemic chemotherapy is the mainstay of treatment for advanced and metastatic gastric cancer. Both the NCCN and ESMO Guidelines recommend the combination of trastuzumab plus fluoropyrimidine- and platinum-based chemotherapy for first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma [8] [9]. This was based on the results from the Phase 3, open-label, randomised controlled ToGA study (n=584) of trastuzumab in combination with chemotherapy (capecitabine plus cisplatin or fluorouracil plus cisplatin) versus chemotherapy alone. With a median follow-up of 18.6 months in the combination arm, ORR was 47% (CR: 5% and PR: 42%), median DOR was 6.9 months, and TTP was 7.1 months, with the majority of patients progressing. Median OS was 13.8 months (95% CI: 12–16) in those assigned to trastuzumab plus chemotherapy (HR=0·74; 95% CI: 0·60–0·91; *p*=0·0046). The most common AEs for this combination included nausea (67%), vomiting (50%), and neutropenia (53%). Rates of overall Grade 3 or 4 AEs were 68% and cardiac AEs were 6% [5].

In addition, the Phase 2, open-label, non-randomized HERXO study (n=45) of capecitabine and oxaliplatin and trastuzumab as first-line treatment for HER2-positive advanced gastric cancer patients showed similar results to other the ToGA study. With a median follow-up of 13.7 months, ORR was 46.7% (95% CI: 31.9–62.0), median DOR 9.4 months, and median TTR was 2.3 months. The estimated median PFS and OS were 7.1 months and 13.8 months, respectively. Regarding safety, 44.4% of the participants had ≥ Grade 3 AEs; the most common (10% incidence) included diarrhea (26.6%), fatigue (15.5%), nausea (20.0%), and vomiting (13.3%). Two participants (4.4%) developed asymptomatic Grade 2 LVEF reduction and 1 participant was diagnosed with clinically relevant congestive heart failure. The study concluded the combination of capecitabine-oxaliplatin-trastuzumab was promising and effective [10].

No further advance has been made in the treatment of HER2-positive gastric cancer patients. Second-line treatments include chemotherapy combination and monotherapies where the median OS remains less than 1 year (<10 months) [11] [12] [13] [14] [15].

Further details are provided in Module 2.5. A summary of approved treatments for first-line treatment of advanced and metastatic HER2-positive gastric cancer are presented in Applicant Table 1.

Applicant Table 1
Summary of FDA-approved First-line Therapies for Advanced and Metastatic HER2-positive Gastric Cancer

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Trastuzumab in combination with fluoropyrimidine + platinum-based chemotherapy	1L HER2-overexpressing metastatic gastric or GEJ adenocarcinoma	2010*	Trastuzumab: Initial dose: 8 mg/kg as 90-minute IV infusion; Subsequent doses: 6 mg/kg a 30-minute IV infusion Q3W + fluoropyrimidine + platinum-based chemotherapy	Median OS = 13.8 months (HR=0·74; 95% CI: 0·60–0·91; p=0·0046)	The most common AEs for this combination included nausea (67%), vomiting (50%), and neutropenia (53%). Rates of overall Grade 3 or 4 AEs were 68% and cardiac AEs were 6%	Trastuzumab is used in combination with chemotherapy as 1L treatment for HER2 gastric cancer/GEJ patients

Abbreviations: 1L=first-line; AE=adverse event; CI=Confidence interval; FDA=Food and Drug Administration; GEJ=gastroesophageal junction; HER2=human epidermal growth factor 2; HR=Hazard ratio; IV=intravenous; OS=overall survival; Q3W=every 3 weeks.
Source: [5]

*Traditional approval

The FDA's Assessment:

FDA generally agrees with the applicant's position with respect to the ToGA trial; however, FDA 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." Additionally, conclusions based the results of the HERXO trial should be interpreted with caution given the trial was a small single arm trial.

Based on the results of the ToGA study, several other studies with different drugs and biologicals targeting the HER2 receptor/pathway were conducted. The LOGiC trial (Hecht et al, 2016; Press et al, 2017) compared lapatinib (a small-molecule tyrosine kinase inhibitor of epidermal growth factor receptor and HER2) in combination with capecitabine plus oxaliplatin versus capecitabine plus oxaliplatin alone in HER2-positive advanced or metastatic esophageal, gastric, or GEJ adenocarcinoma and no prior systemic therapy. The results exhibited no significant difference in median OS (12.2 vs 10.5 months, HR = 0.91; 95% CI 0.73–1.12, P = 0.3492) and median PFS (6.0 vs 5.4 months, P = 0.0381).

In the JACOB trial (Tabernero et al, 2018), 780 patients with HER2 positive metastatic gastric or

GEJ cancer were assigned to pertuzumab (a monoclonal HER2-targeted antibody that binds to a different epitope on the HER2 receptor protein than trastuzumab), trastuzumab, and chemotherapy or placebo combined with trastuzumab and chemotherapy. At a median follow-up of 24.4 months in the pertuzumab group and 25.0 months in the placebo group, no statistically significant difference was found in the primary endpoint of OS (17.5 vs 14.2months, HR = 0.84, P = 0.057), although there was a significant increase in median PFS (8.5 vs 7.0 months, HR = 0.73, 95% CI 0.62–0.86).

The comparator arm selected for Study KN811 (trastuzumab combined with 5-fluorouracil and cisplatin) is adequate, and acceptable as first line therapy in the U.S. After review of the literature above, FDA concludes that any platinum- or fluoropyrimidine- containing chemotherapy regimen is considered adequate as first-line treatment for locally advanced or metastatic gastric or GEJ adenocarcinoma in the U.S.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

As of 16-OCT-2020, KEYTRUDA® has received traditional or accelerated approval in the US for many indications as summarized in Applicant Table **2**.

Applicant Table 2
Summary of FDA-approved Pembrolizumab Indications

Tumor Type	Approval Type	Indication
Melanoma	Traditional	• For the treatment of patients with unresectable or metastatic melanoma. • For the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

Tumor Type	Approval Type	Indication
Non-Small Cell Lung Cancer	Traditional	• In combination with pemetrexed and platinum chemotherapy, as first- line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC. • As a single agent for the first-line treatment of patients with metastatic NSCLC expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is: - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or - metastatic. • As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA- approved test, with disease 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.
Small Cell Lung Cancer	Accelerated	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.
Head and Neck Squamous Cell Cancer	Traditional	• In combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC. • As a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. • As a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.
Classical Hodgkin Lymphoma	Traditional	• For the treatment of adult patients with relapsed or refractory cHL. • For the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.
Primary Mediastinal Large B-Cell Lymphoma	Traditional	For the treatment of adult and pediatric patients with refractory 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.
Urothelial Carcinoma	Accelerated	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, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

Tumor Type	Approval Type	Indication
Urothelial Carcinoma	Traditional	• 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. • For the treatment of patients with BCG-unresponsive, high-risk, NMIBC with CIS with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
Microsatellite Instability-High or Mismatch Repair Deficient Cancer	Accelerated	For the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR - Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or - Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. 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	Traditional	For the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer.
Gastric Cancer	Accelerated	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, 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.
Esophageal Cancer	Traditional	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, with disease progression after one or more prior lines of systemic therapy.
Cervical Cancer	Accelerated	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.
Hepatocellular Carcinoma	Accelerated	For the treatment of patients with HCC who have been previously treated with sorafenib.
Merkel cell Carcinoma	Accelerated	Treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.
Renal Cell Carcinoma	Traditional	In combination with axitinib, for the first-line treatment of patients with advanced RCC.

Tumor Type	Approval Type	Indication
Endometrial Carcinoma	Accelerated	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.
Tumor Mutational Burden-High Cancer	Accelerated	For the treatment of adult and pediatric patients with unresectable or metastatic 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. 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	Traditional	For the treatment of patients with recurrent or metastatic cSCC that is not curable by surgery or radiation.
Adult Indications: Additional Dosing Regimen of 400 mg Q6W	Accelerated	For use at an additional recommended dosage of 400 mg Q6W for all approved adult indications.
Abbreviations: ALK=anaplastic lymphoma kinase; BCG= *Bacillus* Calmette-Guerin; cHL=classical Hodgkin Lymphoma; CIS=carcinoma in situ; CPS=combined positive score; cSCC=cutaneous squamous cell carcinoma; dMMR=deficient mismatch repair; EGFR=endothelial growth factor receptor; FDA=Food and Drug Administration; FU=fluorouracil; HCC=hepatocellular carcinoma; HNSCC=head and neck squamous 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 proportion score.		

The FDA's Assessment:
FDA agrees.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Applicant Table 3 summarizes key regulatory interactions for KEYNOTE-811.

Applicant Table 3
Key Regulatory Interactions Related to KEYNOTE-811

Date	Comments
21-NOV-2014	Merck submission of original IND 123482 for gastric cancer. The IND was opened with protocol KEYNOTE-059.
16-JUN-2015	FDA grants Orphan Drug Designation to pembrolizumab for treatment of gastric cancer, including gastroesophageal junction adenocarcinoma.
13-JAN-2017	Type C meeting between Merck and FDA to discuss plans for clinical pharmacology and pharmacometrics in future KEYTRUDA submissions.
22-SEP-2017	FDA grants accelerated approval for KEYTRUDA in 3L+ gastric cancer.
02-MAY-2018	Type B EOP Meeting between Merck and FDA to discuss the design of KEYNOTE-811. FDA suggested several changes to the proposed study design that were implemented by Merck. FDA indicated that a compelling improvement in ORR at the first interim analysis may support accelerated approval.
06-JUN-2018	Submission of new protocol KEYNOTE-811 for previously untreated HER2-positive gastric cancer to IND 123482.
22-JUN-2020	FDA statistical comments and request for information received related to KEYNOTE-811 Amendment 05.
29-JUN-2020	Response to FDA statistical comments and request for information related to KEYNOTE-811 received on 22-JUN-2020.
27-AUG-2020	Informal teleconference between Merck and FDA to discuss use of the RTOR and Assessment Aid pilots for the KEYNOTE-811 sBLA.
14-SEP-2020	Submission of proposed KEYNOTE-811 RTOR content and timelines
02-NOV-2020	Type B pre sBLA meeting to discuss content and format of the KEYNOTE-811 IA1 sBLA submission.
Abbreviations: 3L+=third-line plus; EOP=end of phase; FDA=Food and Drug Administration; IA1=interim analysis 1; IND=Investigational New Drug; ORR=objective response rate; RTOR=real-time oncology review; sBLA=supplemental Biologics License Application.	

The FDA's Assessment:

FDA agrees with the description of the interactions for KN811. On the June 2020 communication, FDA discouraged the administrative assessment of progression-free survival (PFS) at the time of the ORR analysis and requested alpha allocation for this assessment using the O'Brien-Fleming method. FDA also requested that Merck specify a detailed analysis plan and rigorous firewall for study conduct (including persons who will be unblinded) in the protocol. Although Amendment 5included a PFS analysis at IA1 despite the immaturity of the data, the interim PFS analysis was removed in Amendment 6 (see Applicant's table 5).

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 these applications. This decision was based upon the extensive clinical experience with pembrolizumab, lack of notable patterns in patient enrollment, protocol deviations, or efficacy and safety data across sites that would raise potential concerns regarding data integrity, historical experience indicating lack of data integrity issues from inspections conducted by FDA during review of prior pembrolizumab supplements, and use of an independent radiological review committee, which mitigates the potential for bias.

4.2 Product Quality

No new quality information was submitted.

4.3 Clinical Microbiology

Not applicable

4.4 Devices and Companion Diagnostic Issues

The study supporting this sBLA selected patients with HER2+ (defined as IHC3+ or 2+ if ISH positive) gastric or GEJ adenocarcinoma. HER2 status was centrally confirmed in tumor specimens in all patients using the FDA approved Dako HercepTest (IHC) and Dako HER2 IQFISH pharmDx Kit following the ASCO/CAP guidelines.

Tumor PD-L1 expression (a randomization stratification factor) using CPS score (≥1 vs. < 1) was assessed by a central lab using the FDA approved Dako PD-L1 22C3 pharmDx kit.

5 Nonclinical Pharmacology/Toxicology

No new information concerning nonclinical pharmacology and pharmacokinetics is provided in this supplement.

The FDA's Assessment:

No new information is provided in the current submission.

X X

Primary Reviewer Supervisor

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

The pembrolizumab concentrations and the immunogenicity of pembrolizumab were assessed in KEYNOTE-811, a randomized, double-blind study comparing pembrolizumab (MK-3475) in combination with trastuzumab plus chemotherapy (referred to as SOC) to placebo in combination with SOC as first-line treatment in participants with HER2-positive advanced gastric or gastric esophageal junction adenocarcinoma.

Pembrolizumab, administered as a 200 mg dose Q3W IV infusion, has been extensively evaluated for other approved indications. No changes to clinical pharmacology-pertinent labeling are proposed in this supplement submission.

No patient developed treatment-emergent anti-drug antibodies (TE-ADA) to pembrolizumab when it was administered with trastuzumab plus chemotherapy in KEYNOTE-811.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Pembrolizumab pharmacokinetic disposition and immunogenicity rates are not affected by the co-administration with SOC (trastuzumab plus chemotherapy) in study participants with HER2-positive advanced gastric or GEJ adenocarcinoma and are consistent with the previously approved indications. Similarly, the pharmacokinetic disposition and immunogenicity rates of the SOC component trastuzumab are not affected by the co-administration of pembrolizumab in this patient population.

The FDA's Assessment:

FDA agrees with the Applicant's position. PK samples were obtained prior to dosing in Cycle 1, 2, 4, 8 and every 4th cycle thereafter. Samples were also obtained at 0.5 h after the end of infusion in Cycles 1 and 8. Mean peak and trough concentrations in the KEYNOTE-811 study fell within the range presented for the reference model developed by the Applicant based on data from 2993 patients with other cancer indications.

Immunogenicity samples (both pembrolizumab and trastuzumab) were obtained prior to dosing in Cycles 1, 2, 4, 8 and every 4th cycle of pembrolizumab administration. The sampling schedule

was adequate to evaluate the emergence and persistence of ADAs. There were no instances of treatment-emergent ADAs for pembrolizumab in KEYNOTE-811.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

The proposed indication in this application is for the use of pembrolizumab in combination with trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma.

The approved doses of pembrolizumab in the US for the treatment of all adult indications are 200 mg Q3W and 400 mg Q6W as monotherapy or in combination therapies. The clinical data from KEYNOTE-811 shows efficacy at 200 mg Q3W, which in conjunction with an integrated body of evidence in previously approved indications, supports the recommendation of 200 mg Q3W to the indication above. No clinical data are currently available in patients with previously untreated HER2-positive gastric/GEJ adenocarcinoma at 400 mg Q6W. The 400 mg Q6W regimen is considered a suitable dosing option for pembrolizumab based on the expected similarity of PK exposures, target saturation, efficacy and safety profile with those for the approved dosing regimens of 200 mg Q3W or 2 mg/kg Q3W.

The FDA's Assessment:
FDA agrees with the Applicant's position. KEYNOTE-811 used pembrolizumab administered on a 200 mg Q3W schedule in alignment with an approved dosing regimen for other indications. Mean peak and trough concentrations in the KEYNOTE-811 study fell within the range presented for the reference model developed by the Applicant based on data from 2993 patients with other cancer indications. The 400 mg Q6W regimen is also included in the labeling as an approved dosing regimen for all adult indications.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

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

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

6.2.2.3. Outstanding Issues

The Applicant's Position:

There are no outstanding issues with regard to clinical pharmacology.

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

6.3 Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

Comprehensive review of the key clinical pharmacology findings for pembrolizumab from melanoma, NSCLC, HNSCC, cHL, UC, MSI-H cancer, GEJ adenocarcinoma and HCC indications, which have been approved in one or more countries including the US, the EU and Japan, have been discussed extensively in previous submissions. The key clinical pharmacology characteristics are summarized in the current pembrolizumab USPI. Pembrolizumab pharmacokinetics are not affected by the co-administration with SOC in this patient population and are consistent with the previously approved indications.

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

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

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

- Flat dose-/exposure-response relationships across numerous tumor types, with similar efficacy and safety profiles over a 5-fold exposure range between 2 mg/kg Q3W and 10 mg /kg Q2W. Exposures of a fixed-dose of 200 mg Q3W are well within the exposure range of 2 mg/kg Q3W to 10 mg/kg Q2W

- Similarity in PK of pembrolizumab among tumor types and no effects of intrinsic and extrinsic factors on pembrolizumab PK profile were found.

No new information is provided in the current submission.

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

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

The Applicant's Position:

The proposed dosing regimen of pembrolizumab as 200 mg IV Q3W in combination with SOC is appropriate for previously untreated locally advanced or metastatic HER2-positive gastric/GEJ adenocarcinoma. An additional recommended dosage of 400 mg Q6W has been approved for all adult indications, and therefore approval is also sought for this. An assessment of the impact of ethnicity on the pharmacokinetic parameters, clearance and central volume of distribution, conducted with a reference PK dataset showed that the pharmacokinetics of pembrolizumab were consistent across ethnicity and region.

The FDA's Assessment:
FDA agrees with the Applicant's position. The proposed regimen has been previously approved. Clinical trial data support the use of the 200 mg Q3W fixed dose. The 400 mg Q6W regimen is also approved for all adult indications.

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

The Applicant's Position:

No specific dosing modifications are required or recommended based on intrinsic factors.

The FDA's Assessment:
FDA agrees with the Applicant's position. Based on earlier data, there are no dose adjustments required for age, race or sex or renal impairment. The impact of moderate to severe hepatic impairment is unknown.

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

The Applicant's Position:

There are no clinically relevant food-drug or drug-drug interactions with pembrolizumab. Pembrolizumab pharmacokinetics and immunogenicity rates are not affected by the co-administration with SOC in this patient population and are consistent with the previously approved indications.

The FDA's Assessment:

FDA agrees with the Applicant's position. No ADAs were detected after administration of pembrolizumab with SOC in study KEYNOTE-811. The likelihood of drug-drug or food-drug interactions is low due to the characteristics of pembrolizumab as a monoclonal antibody and the intravenous route of administration.

X	X
Primary Reviewer	Team Leader

7 Sources of Clinical Data

7.1 Table of Clinical Studies

The Applicant's Position:

Applicant Table 4 presents KEYNOTE-811 as a stand-alone study that supports efficacy and safety in the proposed indication. All studies are listed in the pembrolizumab IB.

APPEARS THIS WAY
ON ORIGINAL

Applicant Table 4
Listing 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
		Controlled Studies to Support Efficacy and Safety						
KEYNOTE-811	NCT03615326	A Phase 3, randomized, double-blind trial comparing trastuzumab plus chemotherapy and pembrolizumab with trastuzumab plus chemotherapy and placebo. Participants were stratified by PD-L1 status, geographic region, and selected chemotherapy backbone.	Trastuzumab and pembrolizumab plus either FP or CAPOX* OR Trastuzumab and placebo plus FP and CAPOX*	Primary: PFS and OS Secondary: ORR and DOR	Treatment will be administered until disease progression is radiographically documented and verified by BICR or after receiving 35 treatments, unacceptable toxicity, or study withdrawal.	ITT/ASaT: 434 randomized 433 treated IA1 Efficacy: 264 randomized/ treated	First-line HER2 positive advanced gastric or gastroesophageal junction adenocarcinoma	20 countries 186 sites

Abbreviations: 5-FU=5 fluorouracil; ASaT=all subjects as treated; BICR=blinded independent central review; BLA=Biologics License Application; CAPOX=oxaliplatin plus capecitabine; DOR=duration of response; FP=cisplatin plus 5-FU; HER2=human endothelial growth factor receptor 2; IA1=interim analysis 1; ITT=intention to treat; NDA=New Drug Application; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.
* Investigators choice of chemotherapy backbone.

The FDA's Assessment:
FDA agrees with the Applicant's description of the trial design of KEYNOTE-811 as presented in this section. FDA agrees with the selected patient population, treatment arms, primary and secondary endpoints of PFS, OS, ORR and DOR, and randomization stratification factors of geographic region, PD-L1 status, and chemotherapy regimen.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. KEYNOTE-811

Trial Design

The Applicant's Description:

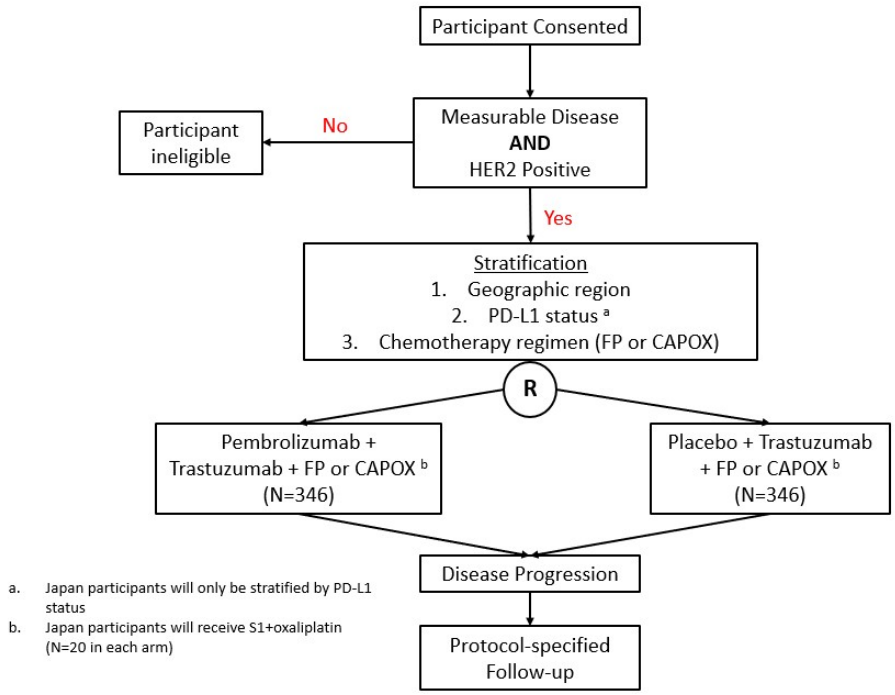
KEYNOTE-811 is an ongoing, Phase 3, randomized, double-blind study comparing pembrolizumab + SOC (trastuzumab plus chemotherapy) with placebo + SOC (trastuzumab plus chemotherapy) as first-line treatment in participants with HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma. Participants are randomized 1:1 to receive pembrolizumab (200 mg Q3W) or placebo in combination with trastuzumab plus chemotherapy (investigator's choice of FP or CAPOX). Treatment randomization for the global cohort is stratified by geographic region (Europe/Israel/North America/Australia, Asia, or ROW), PD-L1 status (positive or negative), and chemotherapy regimen (FP or CAPOX).

A Japan-specific SOX (S-1 + oxaliplatin) cohort is enrolling participants who are treated with pembrolizumab plus trastuzumab and SOX or trastuzumab and SOX. Data for this cohort is analyzed separately from the global cohort and are not presented in this document.

The total projected enrollment in the global cohort for KEYNOTE-811 is 692 randomized participants. The first participant was randomized on 07-NOV-2018; 434 participants were randomized as of 17-JUN-2020, the data cutoff for IA1.

The study design is depicted in [Applicant Figure 1].

Applicant Figure 1
Study Design for KEYNOTE-811 – Global Cohort



Abbreviations: CAPOX=capecitabine plus oxaliplatin; FP=cisplatin plus 5-fluorouracil; HER2=human epidermal growth factor receptor 2; PD-L1=programmed cell death-ligand 1

- **Trial Location:**

  The KEYNOTE-811 study has been conducted in Australia, Brazil, Chile, China, France, Germany, Guatemala, Ireland, Israel, Italy, Japan, New Zealand, Poland, Russia, South Korea, Spain, Turkey, Ukraine, United Kingdom, United States.

- **Rationale for Control Group:**

  Both the NCCN and ESMO Guidelines recommend the combination of trastuzumab plus fluoropyrimidine- and platinum-based chemotherapy for first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma [8] [9]. Therefore, the control group selected for the KEYNOTE-811 study was based on this combination of trastuzumab with chemotherapy. Investigators were given a choice for the chemotherapy backbone; FP (cisplatin plus 5-fluorouracil) or CAPOX (capecitabine plus oxaliplatin). Both these chemotherapy regimens are globally accepted as part of the recommended SOC combination with trastuzumab.

- **Summary of Key Entrance Criteria:**

  Male/female adult (≥18 years) participants with previously untreated, locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma, with

measurable disease according to RECIST 1.1, an ECOG PS of 0 or 1, and a life expectancy of >6 months. Participants were excluded if they had received prior systemic therapy for locally advanced unresectable or metastatic gastric/GEJ cancer or if they had received radiotherapy within 14 days of randomization. Prior neoadjuvant or adjuvant therapy was permitted as long as treatment was completed at least 6 months prior to randomization and there was no evidence of progression.

- **Dose Selection:**

  The dose of pembrolizumab to be used in combination for the KEYNOTE-811 study was 200 mg Q3W. The dose of SOC therapies used were according to the recommended dosage for the approved combinations:

  * Pembrolizumab IV 200 mg Q3W + trastuzumab IV (8 mg/kg [loading dose] and then 6 mg/kg [maintenance dose]) Q3W + FP or CAPOX doublet chemotherapy

  * Placebo IV Q3W + trastuzumab IV (8 mg/kg [loading dose] and then 6 mg/kg [maintenance dose]) Q3W + FP or CAPOX doublet chemotherapy

- **Treatment Allocation:**

  Treatment allocation/randomization in KEYNOTE-811 occurred centrally using IRT; participants were randomly assigned in a 1:1 ratio to pembrolizumab or placebo in combination with trastuzumab and either FP or CAPOX (Investigator's choice of chemotherapy backbone).

  Treatment allocation/randomization was stratified according to the following factors:

  1. Geographic region – (Europe/Israel/North America/Australia vs Asia vs Rest of the World (including South America))

  2. PD-L1 status (positive vs negative)

  3. Chemotherapy regimen (FP or CAPOX)

- **Blinding:**

  KEYNOTE-811 is a placebo-controlled, randomized study; therefore, the Sponsor, investigator, and participant is not aware of treatment assignment. Individuals involved in the study treatment administration or clinical evaluation of the participants (including BICR review of imaging) were unaware of the group assignments.

- **Concomitant Medications:**

  Participants were prohibited from receiving investigational treatment within 4 weeks of randomization, systemic treatment for autoimmune disease in the last 2 years, systemic/immunosuppressant treatment within 7 days of randomization, radiation therapy within 14 days of randomization, any prior immune checkpoint inhibitor, and a live vaccine within 30 day of planned dosing date. During the screening and study period, participants were prohibited from receiving antineoplastic systemic chemotherapy or immunotherapy, investigational agents, local therapy for palliation, and live vaccines.

  All treatments that the investigator considers necessary for a participant's welfare were permitted at the discretion of the investigator in keeping with the local and institutional standards of medical care.

- **Treatment Compliance:**

  Interruptions from the protocol-specified treatment plan for greater than 12 weeks between pembrolizumab doses for non-study medication-related or administrative reasons required consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management. For those medications taken at home, the site validated compliance with study medication at each site visit according to their standard operating procedure.

- **Dose Modification/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, trastuzumab and chemotherapy components (FP/CAPOX). 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:**

  An external DMC was used to monitor the interim data from the KEYNOTE-811 study, considering the overall risk and benefit to participants and recommending whether the study should continue in accordance with the protocol. The DMC made recommendations regarding participant safety and the continued ethical integrity of the study.

- **Study Procedures:**

  The study flow charts are provided in the KEYNOTE-811 Protocol.

- **Subject Completion, Discontinuation, or Withdrawal:**

  Participants treated with pembrolizumab who attained a locally confirmed CR following at least 8 treatments (approximately 6 months) were discontinued from treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR .

  Participants were permitted to withdraw consent at any time for any reason or be dropped from the study at the discretion of the investigator should any untoward effect occur, as summarized in the KEYNOTE-811 Protocol. A participant who discontinued from the study was not replaced. Participants discontinuing the study were monitored post study; safety follow-up 30 days post last dose, every 6 weeks until disease progression, and every 12 weeks for survival follow-up.

The FDA's Assessment:
FDA agrees with Merck's description of the trial design.

As stated in Section 2.1, the percentage of HER2 positive gastric/GEJ adenocarcinoma is similar across regions, and there are no known differences in the magnitude of effect of trastuzumab between geographic regions for these patients. Although standard of care therapy for first line treatment of HER2+ gastric and GEJ cancer may vary slightly between countries, the chosen backbone treatment (trastuzumab and fluoropyrimidine- and platinum- based chemotherapy) is consistent with treatment practices in the U.S. and therefore applicable to the U.S. population of patients with locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma.

FDA agrees with the relevance of the stratification factors of geographic region, PD-L1 status, and chemotherapy regimen for KEYNOTE-811. The defined terms regarding treatment completion, discontinuation, and withdrawal were sufficient. See **Error! Reference source not found.** and **Error! Reference source not found.** for further details.

Study Endpoints

The Applicant's Description:

The KEYNOTE-811 study endpoints are summarized below:

Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Secondary Endpoints:

- ORR per RECIST 1.1 by BICR
- DOR per RECIST 1.1 by BICR
- AEs and discontinuation of study treatment due to AEs

Exploratory Endpoints:

- PRO and utility scores
- PFS and ORR per iRECIST
- Genomic correlation and molecular biomarkers

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

Statistical Analysis Plan and Amendments

The Applicant's Description:

- Efficacy Analysis:

  The ITT population for the efficacy analysis consists of the first 264 randomized participants whether or not treatment was administered for IA1

  The dual primary hypotheses of PFS and OS were not evaluated at IA1. The stratified Miettinen and Nurminen method with sample size weights were used for analysis of ORR.

- Safety Analysis:

  The ASaT population was the population used for the analysis of safety data. The ASaT population consists of all randomized participants who received at least 1 dose of study medication.

  Between-treatment differences in the percentage of participants with events were analyzed using the Miettinen and Nurminen method.

The results presented in this document represent IA1 which was timed to be performed when the first ~260 participants randomized had been followed up for at least 8.5 months. The primary purpose was to test the hypothesis of ORR in the first ~260 participants randomized and to perform a safety review of the ITT population for assessment of risk/benefit.

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

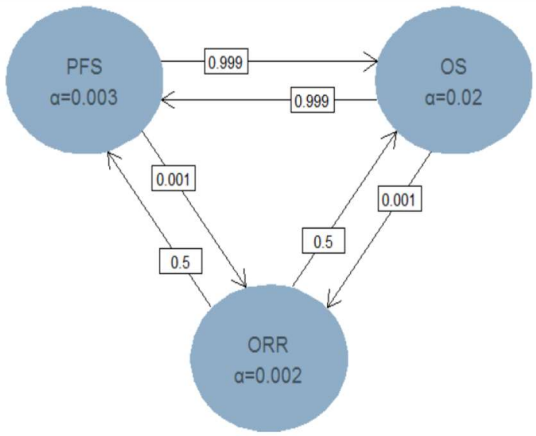
The co-primary endpoints of KEYNOTE-811 are PFS as assessed by BICR per RECIST 1.1 and OS. Assuming a median PFS of 6.7 months in the placebo arm and 9.6 months in the pembrolizumab arm, a total of 606 PFS events are needed to detect a hazard ratio of 0.70 with 95% power at an initial 1-sided alpha level of 0.003. Additionally, assuming a median OS of 13.8

months in the placebo arm and 18.4 months in the pembrolizumab arm, a total of 551 deaths are needed to detect a hazard ratio of 0.75 with 90% power at a 1-sided alpha level of 0.020. The primary analyses will be stratified log-rank tests performed on the ITT population.

The key secondary endpoint is ORR as assessed by BICR per RECIST 1.1. Assuming a response rate of 48% in the placebo arm and 78% in the pembrolizumab arm, a difference in ORR of 25% will provide 90% power at an initial 1-sided alpha level of 0.002. A stratified Miettinen-Nurminen method will be used for the analysis of ORR.

Three interim analyses were planned for this study. The first interim analysis based on the first 260 patients is considered the final analysis for ORR. Neither PFS nor OS was planned to be formally tested at the first interim analysis. The second interim analysis will be conducted after 542 (90%) PFS events, which would also correspond to 73% information fraction for OS. The third interim analysis will be the final PFS analysis to be conducted after 606 (100%) PFS events, which would also correspond to 89% information fraction for OS. The final OS analysis will occur at 551 (100%) deaths. The O'Brien-Fleming method with Lan-Demets spending function will be utilized for evaluation of efficacy boundaries.

The Meurer and Bretz graphical method, as shown in the following figure, is used for the overall control of type I error.



* ref: Protocol amendment 6 for KEYNOTE-811, page 140

Initial α allocations to PFS, OS and ORR are 0.003, 0.020 and 0.002 respectively. Weights for reallocation of the original α in the event of a statistically significant result of the other endpoints are provided in the boxes on the lines connecting the respective hypotheses.

Protocol Amendments

The Applicant's Description:

The original KEYNOTE-811 protocol was finalized on 11-APR-2018 and was amended 6 times. Applicant Table 5 summarizes the key changes in the amendments.

APPEARS THIS WAY ON ORIGINAL

Applicant Table 5
Summary of Key Changes to the KEYNOTE-811 Protocol

Protocol or Amendment	Global or Local	Key Changes
Protocol (11-APR-2018)		Original Protocol
Amendment 01 (31-MAY-2018)	Global	In response to Health Authority input, removed the stratification factor of ECOG and added stratification by PD-L1 expression, subgroup analysis based on MSI status, and requirement to re-consent participants upon disease progression.
Amendment 02 (16-AUG-2018)	Global	In response to Health Authority input, added language indicating TB, HIV, hepatitis B, and hepatitis C testing (as per UK-specific requirements), updated language and requirement regarding MSI sample collection, extended pregnancy and contraception requirement to conform with trastuzumab guideline, and clarified exclusion regarding cardiac disease history.
Amendment 03 (24-JAN-2019)	Local (France)	In response to Health Authority input, changes were made regarding safety monitoring procedures for trastuzumab and chemotherapy backbone.
Amendment 04 (27-FEB-2019)	Global	Updated Biomarker Collection Information and incorporated Amendment 3 changes to apply globally.
Amendment 05 (20-MAY-2020)	Global	Updated protocol and SAP language regarding the definition of curative surgical resection and modification of PFS primary censoring rule associated with curative surgical resection, removed the ORR futility analysis for IA1, and added a PFS analysis for IA1
Amendment 06 (07-JUL-2020)	Global	Updated SAP language to remove PFS analysis at IA1 in response to Health Authority Input.
Abbreviations: ECOG=European Cooperative Oncology Group; HIV=human immunodeficiency virus; IA1=interim analysis 1; MSI-microsatellite instability; ORR=objective response rate; PD-L1=Programmed cell death Ligand 1; PFS=Progression-free survival; SAP=statistical analysis plan; TB=tuberculosis; UK=United Kingdom.		

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

APPEARS THIS WAY ON ORIGINAL

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

The KEYNOTE-811 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, as stated in the MSD Code of Conduct for Interventional Clinical Trials in the study protocol. The Code of Conduct includes a description of how the study was monitored to ensure compliance with GCP.

The protocol and any amendments, information provided to participants and any recruitment material(s) were reviewed and approved by the IEC(s) (also called an IRB, ERC, or any other ethics committee). The IEC(s) consulted for this study met the definition of an "IEC" as outlined in US CFR Title 21, Part 56 or equivalent country specific regulations.

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

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-811 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 19.2.

Patient Disposition

The Applicant's Position:

The efficacy data presented in this document represents results from the first 264 randomized participants included in IA1.

As of the data cutoff date of 17-JUN-2020 for IA1, 434 participants were randomized, and 433 were treated (217 in the pembrolizumab + SOC group and 216 in the SOC group). The median duration of follow-up in the ITT population was 8.4 months (range, 0.1 to 19.0) in the pembrolizumab + SOC group and 7.7 months (range, 0.5 to 17.9) in the SOC group (see Applicant Table 7). A total of 58.5% participants in the pembrolizumab + SOC group and 48.1% in the SOC group remain on treatment. A total of 41.5% participants in the pembrolizumab + SOC group and 51.9% in the SOC group discontinued study treatment; the most frequently cited reason for treatment discontinuation in both treatment groups was disease progression. Overall, 22.1% of participants in the pembrolizumab + SOC group and 28.1% in the SOC group died on study (Applicant Table 6).

The median duration of follow-up in the first 264 randomized participants included in IA1 was 11.1 months (range, 2.2 to 19.0) in the pembrolizumab + SOC group and 10.4 months (range, 0.5 to 17.9) in the SOC group (see Applicant Table 7). Of the first 264 randomized participants (133 participants in the pembrolizumab + SOC group and 131 participants in the SOC group), a total of 40.6% participants in the pembrolizumab + SOC group and 28.5% in the SOC group remain on treatment. A total of 59.4% participants discontinued pembrolizumab + SOC treatment and 71.5% of participants discontinued SOC treatment; the primary reason being progressive disease in both treatment groups. Overall, 32.3% of participants in the pembrolizumab + SOC group and 40.5% in the SOC group died on study (Applicant Table 6).

APPEARS THIS WAY
ON ORIGINAL

Applicant Table 6
Disposition of Participants
(ITT Population and First 264 Patients Randomized in the ITT Population)

	ITT Population		First 264 Patients Randomized in the ITT Population	
	Pembrolizumab + SOC	SOC	Pembrolizumab + SOC	SOC
	n (%)	n (%)	n (%)	n (%)
Participants in population	217	217	133	131
Status for Study Medication of Treatment Phase				
Started	217	216	133	130
Discontinued	90 (41.5)	112 (51.9)	79 (59.4)	93 (71.5)
Adverse Event	10 (4.6)	14 (6.5)	7 (5.3)	10 (7.7)
Clinical Progression	6 (2.8)	12 (5.6)	4 (3.0)	9 (6.9)
Non-Study Anti-Cancer Therapy	2 (0.9)	3 (1.4)	2 (1.5)	3 (2.3)
Physician Decision	1 (0.5)	2 (0.9)	1 (0.8)	2 (1.5)
Progressive Disease	65 (30.0)	76 (35.2)	59 (44.4)	64 (49.2)
Withdrawal By Subject	6 (2.8)	5 (2.3)	6 (4.5)	5 (3.8)
Associated With Covid-19	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.8)
Participants Ongoing	127 (58.5)	104 (48.1)	54 (40.6)	37 (28.5)
Status for Trial				
Discontinued	48 (22.1)	62 (28.6)	43(32.3)	54 (41.2)
Death	48 (22.1)	61 (28.1)	43 (32.3)	53 (40.5)
Withdrawal By Subject	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.8)
Not Associated With Covid-19, No Further Information	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.8)
Participants Ongoing	169 (77.9)	155 (71.4)	90 (67.7)	77 (58.8)

Abbreviations: ITT=intention to treat; n=number; SOC=standard of care.
Database Cutoff Date: 17JUN2020.

Applicant Table 7
Summary of Follow-up Duration

	ITT Population		First 264 Patients Randomized in the ITT Population	
	Pembrolizumab + SOC	SOC	Pembrolizumab + SOC	SOC
	n (%)	n (%)	n (%)	n (%)
Subjects in population	217	216	133	131
Follow-up duration (months)				
Median (Range)	8.4 (0.1, 19.0)	7.7 (0.5, 17.9)	11.1 (2.2, 19.0)	10.4 (0.5, 17.9)
Mean (SD)	8.6 (4.6)	8.1 (4.4)	11.1 (3.7)	10.3 (4.1)

Abbreviations: ITT=intention to treat; n=number; SD=standard deviation; SOC=standard of care.
Database Cutoff Date: 17JUN2020.

The FDA's Assessment:
FDA agrees with the Merck's presentation of patient disposition. In the IA1 analysis population, more patients discontinued treatment in the placebo arm than in the pembrolizumab arm (59% and 72%, in the pembrolizumab and placebo arms, respectively), and more patients in the placebo arm discontinued treatment due to AEs (5% vs 8% in the pembrolizumab and placebo arms respectively), clinical progression (3% vs 7% in the pembrolizumab and placebo arms respectively), progressive disease (44% vs. 49% in the pembrolizumab and placebo arms respectively), or death (32% vs. 41% in the pembrolizumab and placebo arms respectively) than compared with the pembrolizumab arm, a finding consistent with the observed ORR and duration of response.

Protocol Violations/Deviations

The Applicant's Position:

In KEYNOTE-811, 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 study 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 13 participants in each intervention group in this cohort. Of these, 1 participant in the pembrolizumab + SOC group had an important protocol deviation that was considered to be clinically important. This participant took capecitabine continuously beyond 2 weeks for multiple cycles and experienced Grade 1 to 3 AEs that were considered to be related to capecitabine. The participant was included in the efficacy and safety analyses.

Important protocol deviations included 3 participants who did not meet inclusion/exclusion criteria. These participants were not HER2-positive per central vendor; however, local test results for all 3 participants were HER2-positive.

No participant's data in the study were excluded from analyses due to an important protocol deviation, and no important protocol deviation in the study was classified as a serious GCP noncompliance issue.

Part of this study was conducted during the COVID-19 pandemic. No protocol deviation associated with the COVID-19 pandemic was considered an important protocol deviation.

Important protocol deviations reported in the KEYNOTE-811 study did not influence the overall efficacy conclusions. The study conclusions are representative of the overall study data.

The FDA's Assessment:
FDA agrees with the Applicant's description of protocol deviations/violations for KEYNOTE-811.

Of the described protocol violations, none is likely to bias the study towards a positive result in the pembrolizumab arm. Increased capecitabine dosing would result in increased toxicity and risk to the patient but unlikely better activity (as toxicity results in dose interruptions and reductions). Regarding the 3 patients that were HER2-positive per local test but negative for the central vendor, given the small number of patients, it is unlikely that inclusion of these patients has an impact on study results. As described in Section 2.1, intratumor HER2 overexpression/amplification in gastric cancer is heterogeneous and therefore it is expected that some degree of discordance between local and central review occurs. It is unlikely that any of the protocol violations resulted in potential bias or confounders for the outcomes for KEYNOTE-811.

Table of Demographic Characteristics

The Applicant's Position:

All enrolled participants (n=434, ITT population) in KEYNOTE-811, as per the data cutoff , had a diagnosis of locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma. Participants were primarily male and <65 years of age, were PD-L1 positive, and had not received prior gastrectomy/esophagectomy (Applicant Table 8).

The characteristics of the first 264 randomized participants (the efficacy population) were similar to the ITT population (n=434) (Applicant Table 8).

The baseline characteristics of the KEYNOTE-811 population were generally well-balanced between both treatment groups (Applicant Table 8).

Applicant Table 8
Subject Characteristics
(ITT Population and First 264 Patients Randomized in the ITT Population)

	ITT Population		First 264 Patients Randomized in the ITT Population	
	Pembrolizumab + SOC	SOC	Pembrolizumab + SOC	SOC
	n (%)	n (%)	n (%)	n (%)
Subjects in population	217	216	133	131
Gender				
Male	179 (82.5)	173 (80.1)	112 (84.2)	104 (79.4)
Female	38 (17.5)	43 (19.9)	21 (15.8)	27 (20.6)
Age (Years)				
<65	128 (59.0)	118 (54.6)	78 (58.6)	78 (59.5)
>=65	89 (41.0)	98 (45.4)	55 (41.4)	53 (40.5)
Mean	60.1	61.7	60.3	60.9
SD	12.2	10.6	12.3	10.9

	ITT Population		First 264 Patients Randomized in the ITT Population	
	Pembrolizumab + SOC	SOC	Pembrolizumab + SOC	SOC
	n (%)	n (%)	n (%)	n (%)
Median	62.0	63.5	62.0	61.0
Range	19 to 84	32 to 83	19 to 84	32 to 83
Race				
American Indian Or Alaska Native	3 (1.4)	4 (1.9)	3 (2.3)	2 (1.5)
Asian	76 (35.0)	77 (35.6)	40 (30.1)	41 (31.3)
Black Or African American	2 (0.9)	2 (0.9)	2 (1.5)	0 (0.0)
Multiracial	3 (1.4)	4 (1.9)	1 (0.8)	3 (2.3)
White	129 (59.4)	122 (56.5)	86 (64.7)	81 (61.8)
Missing	4 (1.8)	7 (3.2)	1 (0.8)	4 (3.1)
Ethnicity				
Hispanic Or Latino	25 (11.5)	29 (13.4)	19 (14.3)	16 (12.2)
Not Hispanic Or Latino	186 (85.7)	179 (82.9)	112 (84.2)	112 (85.5)
Not Reported	3 (1.4)	7 (3.2)	2 (1.5)	2 (1.5)
Unknown	3 (1.4)	1 (0.5)	0 (0.0)	1 (0.8)
Geographic Region				
US	12 (5.5)	12 (5.6)	8 (6.0)	10 (7.6)
Ex-US	205 (94.5)	204 (94.4)	125 (94.0)	121 (92.4)
ECOG Performance Scale				
[0] Normal Activity	101 (46.5)	88 (40.7)	65 (48.9)	59 (45.0)
[1] Symptoms, but ambulatory	116 (53.5)	128 (59.3)	68 (51.1)	72 (55.0)
Primary Location at Diagnosis				
Adenocarcinoma of the gastroesophageal junction	62 (28.6)	75 (34.6)	37 (27.8)	42 (32.1)
Adenocarcinoma of the stomach	155 (71.4)	142 (65.4)	96 (72.2)	89 (67.9)
Disease Status				
Locally advanced	7 (3.2)	5 (2.3)	5 (3.8)	3 (2.3)
Metastatic	210 (96.8)	212 (97.7)	128 (96.2)	128 (97.7)
Prior Gastrectomy/Esophagectomy				
Yes	34 (15.7)	44 (20.3)	22 (16.5)	25 (19.1)
No	183 (84.3)	173 (79.7)	111 (83.5)	106 (80.9)
PD-L1 Status (CPS>=1)				
Positive	184 (84.8)	181 (83.4)	117 (88.0)	112 (85.5)
Negative	33 (15.2)	36 (16.6)	16 (12.0)	19 (14.5)
Tumor Burden				

	ITT Population		First 264 Patients Randomized in the ITT Population	
	Pembrolizumab + SOC	SOC	Pembrolizumab + SOC	SOC
	n (%)	n (%)	n (%)	n (%)
< Median	98 (45.2)	107 (49.3)	62 (46.6)	65 (49.6)
>= Median	107 (49.3)	101 (46.5)	62 (46.6)	61 (46.6)
Missing	12 (5.5)	9 (4.1)	9 (6.8)	5 (3.8)
HER2 Status				
IHC 1+	1 (0.5)	1 (0.5)	NA	NA
IHC 2+ ISH Equivocal	0 (0.0)	1 (0.5)	NA	NA
IHC 2+ ISH Positive	36 (16.6)	45 (20.7)	24 (18.0)	27 (20.6)
IHC 3+	180 (82.9)	170 (78.3)	109 (82.0)	104 (79.4)
MSI Status				
MSI High	2 (0.9)	1 (0.5)	1 (0.8)	1 (0.8)
non-MSI-High	171 (78.8)	174 (80.2)	120 (90.2)	120 (91.6)
Unknown	44 (20.3)	42 (19.4)	12 (9.0)	10 (7.6)
Chemotherapy Regimen				
CAPOX	189 (87.1)	187 (86.2)	115 (86.5)	115 (87.8)
FP	28 (12.9)	30 (13.8)	18 (13.5)	16 (12.2)

Abbreviations: CAPOX=capecitabine plus oxaliplatin; CPS=combined positive score; FP= cisplatin plus 5-FU; HER2=human endothelial growth factor receptor 2; IHC=immunohistochemistry; ISH=in-situ hybridization ITT=intention to treat; MSI=microsatellite instability; n=number; PD-L1=programmed cell death Ligand 1; SD=standard deviation; SOC=standard of care; US=United States, .
Database Cutoff Date: 17JUN2020.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of patient characteristics in KEYNOTE-811. FDA's analysis in this section will focus on the 264 patients included in the IA1 (the safety analysis includes all 433 patients). As expected, the majority (82%) of patients are men. The lifetime risk of developing gastric cancer is higher in men (about 1 in 96) than in women (about 1 in 152); the ToGA trial for patients with HER2+ gastric and GEJ cancer enrolled 76% of men and 24% women (Bang et al, 2010). The median age of patients enrolled in KN811 is 62 years old; the average age of people diagnosed with gastric cancer in the U.S. is 68 years old (https://www.cancer.org/cancer/stomach-cancer/about/key-statistics.html accessed on 9 March 2021).

In Study KEYNOTE-811, the majority of patients were White (63%) and men (82%). Black and African American patients were underrepresented in the trial.

The majority of patients (93%) were enrolled ex-U.S. However, as described in Section 2.1,

there are no differences in the incidence of HER2 positive gastric/GEJ cancer, the standard of care is similar across regions, and the selected backbone therapy (trastuzumab in combination with a fluoropyrimidine- and platinum- containing chemotherapy) is the standard of care in the U.S.; therefore, the review team considers that the disease and treatment characteristics reflects the characteristics of the U.S. clinical studies population.

As expected, 60% of tumors were of gastric origin. A slightly higher proportion of patients with GEJ adenocarcinoma were enrolled in the placebo arm (28% vs. 32% in the pembrolizumab and placebo arms, respectively).

PD-L1 status has been studied as a biomarker in many cancers including GI cancer (Yamashita et al, 2020). Involvement of PD-L1 status in HER2 positive patients or potential interactions are not clearly known (Beer et al, 2020). PD-L1 status and HER2+ were studied retrospectively from tumor specimens in patients enrolled on the ToGA trial (Bang et al, 2010), and matched with HER negative samples, with the aim of the study to test the expression and distribution level of PD-L1 in HER2 positive gastroesophageal cancers and compare these values against the matched HER2 negative samples. In KEYNOTE-811, 88% of patients had tumors with CPS ≥1 while 14% had CPS <1.

Data from The Cancer Genome Atlas (TCGA) project in 295-treatment naive, primary gastric adenocarcinomas found microsatellite instability (MSI)-high in 22% patients; however, this may overestimate the incidence of microsatellite instability in the metastatic setting and in the group of patients defined by HER-2 positivity. A Memorial Sloan Kettering Cancer Center next generation sequencing (NGS) study exploring a panel with 410 cancer-associated genes found MSI-H in <3% of gastric cancer patients (Kelly and Janjigiang, 2016). Although the correlation between HER2 and MSI-H is yet to be known, it appears that most patients would not have both HER2 amplification and MSI-H. Only 2 patients with known MSI-H were enrolled in KN811. In the IA1 population.

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

The Applicant's Position:

No additional demographic characteristics aside from those presented above were reported.

The FDA's Assessment:
FDA agrees.

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 for all treatments administered under the KEYNOTE-811

protocol, with the exception of capecitabine which was administered orally. Compliance was checked by counting the number of tablets returned.

Concomitant Medications: Overall, the concomitant treatments administered were representative of those frequently prescribed for patients of the target population and were not considered to have impacted the study results. The most common concomitant medication was steroids in both KEYNOTE-811 treatment groups.

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

In the IA1 population, a total of 76% and 77% of patients in the pembrolizumab arm and the placebo arm, respectively, received systemic corticosteroids. Thyroid therapy was administered to 16% of patients in the pembrolizumab arm (20 patients received levothyroxine, and one patient each received propranolol and potassium iodide) and 12% of patients in the placebo arm. In the safety population (N=434), antineoplastic drugs were administered in 8% of patients in the pembrolizumab arm vs 5% in the placebo arm. Overall, 18% and 25% of patients in the pembrolizumab arm and placebo arm, respectively, received new oncological medications post-treatment.

The difference between incidence of thyroid and corticosteroid use between arms does not appear to be clinically meaningful.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

The primary efficacy endpoints of PFS and OS were not analyzed at IA1 and will be analyzed at future analyses according to the prespecified analysis plan.

The FDA's Assessment:
This application is based on the results from the first interim analysis with a data cut-off of June 17, 2020, where only ORR was tested in the first 264 patients enrolled in KEYNOTE-811. The applicant remained blinded to PFS and OS outcome data at the time of the data cut-off date.

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, as detailed in the KEYNOTE-811 Protocol.

The clinical study program was performed 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.

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:

Please note pembrolizumab + SOC refers to pembrolizumab in combination with trastuzumab plus chemotherapy, and SOC refers to placebo in combination with trastuzumab plus chemotherapy.

The data presented in this document represent efficacy data from the first 264 participants randomized in the ITT population.

Pembrolizumab + SOC provided a statistically significant improvement in ORR based on BICR assessment per RECIST 1.1 in participants with previously untreated locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma.

The ORR was 74.4% (95% CI: 66.2, 81.6) in the pembrolizumab + SOC group and 51.9% (95% CI: 43.0, 60.7) in the SOC group, representing a 22.7% difference in ORR (95% CI: 11.2, 33.7, one-sided *p*-value=0.00006, one-sided *p*-value boundary=0.002).

Participants in the pembrolizumab + SOC and SOC groups achieved a CR or PR as follows:

- CR: 11.3% in the pembrolizumab + SOC group and 3.1% in the SOC group
- PR: 63.2% in the pembrolizumab + SOC group and 48.9% in the SOC group

Analysis of ORR by prespecified subgroups was consistent with the primary findings.

Applicant Table 9 summarizes the KEYNOTE-811 efficacy results.

Applicant Table 9
Efficacy Endpoint Results
Pembrolizumab + SOC versus SOC
(First 264 Participants Randomized in the ITT Population)
KEYNOTE-811
IA1

	Pembrolizumab + SOC (N=133)	SOC (N=131)
ORR % (95% CI)	74.4 (66.2, 81.6)	51.9 (43.0, 60.7)
ORR difference (%) pembrolizumab + SOC vs SOC (95% CI)	22.7 (11.2, 33.7), *p* = 0.00006	

Complete Response % (95% CI)	11.3 (6.5, 17.9)	3.1 (0.8, 7.6)
Partial Response % (95% CI)	63.2 (54.4, 71.4)	48.9 (40.0, 57.7)
Median time to response (months (range)	1.4 (1.2 – 5.6)	1.5 (1.0 – 5.5)
Median DOR (months (range))	10.6 (1.1+ - 16.5+)	9.5 (1.4+ - 15.4+)
Participants with Extended Responses (KM Est): ≥ months 6 (%) ≥ months 9 (%)	 70.3 58.4	 61.4 51.1
Abbreviations: BICR=blinded independent central review; CI=confidence interval; DOR=duration of response; Est=estimation; KM=Kaplan-Meier; N=number; ORR=objective response rate; RECIST=response evaluation criteria in solid tumors; SOC=standard of care Responses are based on BICR assessment per RECIST 1.1. Database Cutoff Date: 17JUN2020.		

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the results of IA1. ORR assessed by investigator (77% in the pembrolizumab arm vs 56% in the SOC arm) was consistent with BICR assessment (74% in the pembrolizumab arm vs 52% in the SOC arm). Exploratory subgroup analyses of ORR in important clinical and demographic subgroups are provided in Table 1. There are no obvious outliers in these exploratory subgroup analyses. The number of patients with CPS PD-L1 <1% was too low to make efficacy conclusions.

Table 1 FDA's analysis of ORR by subgroups

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	Responders/n	ORR (95% CI)	Responders/n	ORR (95% CI)
Gender				
Female	14/21	67 (43, 85)	13/27	48 (29, 68)
Male	85/112	76 (67, 83)	55/104	53 (43, 63)
Age (years)				
<65	54/78	69 (58, 79)	39/78	50 (38, 62)
≥65	45/55	82 (69, 91)	29/53	55 (40, 68)
Race				
White	62/86	72 (61, 81)	34/81	42 (31, 53)
Black/African American	1/2	50 (1, 99)	0/0	-
Asian	31/40	78 (62, 89)	28/41	68 (52, 82)
Other	5/5	100 (48, 100)	6/9	67 (30, 93)
PD-L1 Status				
CPS ≥ 1	89/117	76 (67, 83)	57/112	51 (41, 60)
CPS < 1	10/16	62 (35, 85)	11/19	58 (33, 80)
PD-L1 Status				
CPS ≥ 10	41/52	79 (65, 89)	23/39	59 (42, 74)

CPS < 10	58/81	72 (60, 81)	45/92	49 (38, 60)

Source: FDA reviewer-generated analysis of Applicant provided data

Dose/Dose Response

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Pembrolizumab has previously been approved in gastric an esophageal cancer at a dose of 200 mg every 3 weeks or 400 mg every 6 weeks (U.S. package insert, Keytruda, accessed on 10 March 2021). Patients on KEYNOTE-811 were treated with pembrolizumab 200mg 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.

Durability of Response

The Applicant's Position:

Applicant Table 9 summarizes the duration of responses observed in the KEYNOTE-811 study.

The median DOR for the pembrolizumab + SOC group was 10.6 months (range: 1.1+ to 16.5+) and 9.5 months (range: 1.4+ to 15.4+) in the SOC group.

Participants with extended response duration by KM estimation ≥6 months were 70.3% and 61.4%, and ≥9 months were 58.4% and 51.1%, in the pembrolizumab + SOC and SOC groups, respectively.

Median time to treatment response was 1.4 and 1.5 months in the pembrolizumab + SOC and SOC groups, respectively.

The FDA's Assessment:
In general, FDA agrees with the Applicant's description. The 95% confidence interval for the Kaplan-Meier estimated median DOR is (8.3, NE) in the pembrolizumab arm and (5.5, NE) in the SOC arm, where NE implies "not evaluable". The observed (not Kaplan-Meier estimated) 6-month landmark rates of DoR were 65% in the pembrolizumab arm, as compared to 53% in the placebo arm.

Persistence of Effect

The Applicant's Position:

Persistence of effect is summarized in Applicant Table 9.

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. Duration of response is described above. Treatment effect and study outcomes are described elsewhere in this section.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Although PROs will be assessed in KN811 as a tertiary, exploratory endpoint, results will be available upon final analyses of the study. No analysis of PROs were conducted for IA1.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
FDA's independent analyses of the efficacy results for KN811, in general, concurs with the Applicant's position and presentation on the efficacy results of the primary endpoint for IA1 of BIRC-assessed ORR, as well as the secondary endpoint of DOR. The difference in the observed response rates (77% in the pembrolizumab arm and 56% in the SOC arm) in the first 264 patients enrolled in the study, is statistically significant and clinically meaningful for patients with locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma. Pembrolizumab in combination with trastuzumab and chemotherapy yields a net favorable benefit-risk profile compared to placebo in combination with trastuzumab and chemotherapy as a first-line treatment in the intended patient population. ORR results by investigators' assessment were consistent with BIRC-assessed ORR in KN811. As this supplement will be approved under the accelerated approval pathway, FDA and Merck agreed that the final PFS and OS analyses on the ITT of Study KN811 will serve to verify and describe the clinical benefit of the addition of pembrolizumab to standard of care therapy in the indicated population.

8.1.4. Assessment of Efficacy Across Trials

Only results from the single KEYNOTE-811 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

Only results from the single KEYNOTE-811 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:

The results from KEYNOTE-811 demonstrate that pembrolizumab in combination with trastuzumab and chemotherapy has a tolerable and manageable safety profile that generally reflects the known safety profiles of the components. Overall, no new safety concerns were identified for the use of pembrolizumab in combination with trastuzumab and chemotherapy in patients with advanced gastric or GEJ adenocarcinoma.

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-811 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-811 who received pembrolizumab plus trastuzumab plus chemotherapy with the safety data from participants who received placebo plus trastuzumab plus chemotherapy.

The FDA's Assessment:
FDA agreed with Merck's approach to the safety review, as discussed in the pre-sBLA meeting held on November 2, 2020. Merck submitted ISS data for:

- Study KN811
- Gastric cancer safety dataset for pembrolizumab monotherapy pooled from KN012 (cohort D), KN059 (Cohorts 1 and 3), KN061, and KN062 (monotherapy arm) studies

- Reference safety dataset for monotherapy pembrolizumab pooled from KN001 (lung and melanoma), KN002 (melanoma), KN006 (melanoma), and KN010 (lung) studies.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

KEYNOTE-811 is a stand-alone study that supports the safety of pembrolizumab in the proposed indication.

In KEYNOTE-811, as of the data cutoff of 17-JUN-2020, 433 participants (pembrolizumab + SOC: 217; SOC: 216) had received at least 1 dose of study treatment.

The median exposure to study medication in KEYNOTE-811 was similar for participants in the pembrolizumab + SOC group and the SOC group (202.7 days and 179.1 days, respectively) (Applicant Table 10).

Applicant Table 10
Summary of Drug Exposure
(Global Cohort)
(ASaT Population)

	Pembrolizumab + SOC (N=217)	SOC (N=216)
Number of Days on Therapy (days)		
Mean	202.7	179.1
Median	188.0	161.5
SD	127.5	118.9
Range	2.0 to 540.0	1.0 to 542.0
Number of Cycles		
Mean	9.3	8.4
Median	8.0	7.0
SD	5.7	5.3
Range	1.0 to 25.0	1.0 to 25.0
Database Cutoff Date: 17JUN2020.		

Source: [P811V01MK3475: 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 6 Nov 2020).

Relevant characteristics of the safety population:

The Applicant's Position:

The demographics and baseline characteristics of the KEYNOTE-811 population were representative of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma, as summarized in Applicant Table 8.

The FDA's Assessment:
FDA generally agrees with the applicant's position. Demographic and other baseline characteristics were generally similar between the arms regarding the safety dataset. As for applicability to the U.S. population, gender, location of the primary tumor, CPS score, and MSI-H enrolled on KEYNOTE-811, were discussed under "Table of Demographic Characteristics" in Section 8.1.2).

Adequacy of the safety database:

The Applicant's Position:

The clinical safety data supporting this sBLA are derived from KEYNOTE-811. The number of participants with HER2-positive gastric/GEJ adenocarcinoma 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 in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma.

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 are 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.

Categorization of Adverse Event

The Applicant's Position:

Safety data presented in this document includes the KEYNOTE-811 pembrolizumab + SOC and SOC treatment groups.

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

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

All AEs were captured from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator. All AEs meeting serious criteria were captured from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever occurred first.

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.

Routine Clinical Tests

The Applicant's Position:

The schedule of assessment is provided in the KEYNOTE-811 Protocol. It presents the frequency of laboratory testing, vital signs, physical examinations, 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.

8.2.4. Safety Results

The AE profile observed in the KEYNOTE-811 for the pembrolizumab + SOC group was generally consistent with the established safety profiles of either SOC regimen alone or pembrolizumab monotherapy. All AE categories occurred at similar rates in the pembrolizumab + SOC group and the SOC group (Applicant Table 11), even when adjusted for exposure.

Applicant Table 11
Adverse Event Summary
(Global Cohort)
(ASaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Subjects in population	217		216	
with one or more adverse events	211	(97.2)	212	(98.1)
with no adverse event	6	(2.8)	4	(1.9)
with drug-related[†] adverse events	208	(95.9)	205	(94.9)
with toxicity grade 3-5 adverse events	124	(57.1)	124	(57.4)
with toxicity grade 3-5 drug-related adverse events	103	(47.5)	97	(44.9)
with serious adverse events	68	(31.3)	83	(38.4)
with serious drug-related adverse events	42	(19.4)	37	(17.1)
who died	7	(3.2)	10	(4.6)
who died due to a drug-related adverse event	2	(0.9)	2	(0.9)
discontinued any drug due to an adverse event	53	(24.4)	56	(25.9)
discontinued pembrolizumab or placebo	12	(5.5)	15	(6.9)
discontinued trastuzumab	12	(5.5)	16	(7.4)
discontinued any chemotherapy	50	(23.0)	52	(24.1)
discontinued all drugs	8	(3.7)	12	(5.6)
discontinued any drug due to a drug-related adverse event	50	(23.0)	44	(20.4)
discontinued pembrolizumab or placebo	11	(5.1)	6	(2.8)
discontinued trastuzumab	10	(4.6)	6	(2.8)
discontinued any chemotherapy	46	(21.2)	40	(18.5)
discontinued all drugs	6	(2.8)	4	(1.9)
discontinued any drug due to a serious adverse event	19	(8.8)	18	(8.3)
discontinued pembrolizumab or placebo	11	(5.1)	15	(6.9)
discontinued trastuzumab	10	(4.6)	15	(6.9)
discontinued any chemotherapy	19	(8.8)	15	(6.9)
discontinued all drugs	8	(3.7)	12	(5.6)
discontinued any drug due to a serious drug-related adverse event	16	(7.4)	8	(3.7)
discontinued pembrolizumab or placebo	10	(4.6)	6	(2.8)
discontinued trastuzumab	8	(3.7)	5	(2.3)
discontinued any chemotherapy	15	(6.9)	5	(2.3)

Adverse Event Summary
(Global Cohort)
(ASaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
discontinued all drugs	6	(2.8)	4	(1.9)

† 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 23.0 preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.

Grades are based on NCI CTCAE version 4.03.

Database Cutoff Date: 17JUN2020.

Source: [P811V01MK3475: adam-adsl; adae]

Deaths

The Applicant's Position:

The frequency of deaths due to AEs was 3.2% in the pembrolizumab + SOC group and 4.6% in the SOC group (Applicant Table 12). Two fatal events in the pembrolizumab + SOC group were considered to be related to study treatment: pneumonitis and hepatitis. Two fatal events in the SOC group were considered to be related to study treatment: myocarditis and cholangitis. Hepatitis is a known risk with pembrolizumab treatment and hepatic toxicity is associated with platinum chemotherapy. Pneumonitis is also a known risk for pembrolizumab, including cases with fatal outcome, and the trastuzumab label specifies fatal cases of pneumonitis have been reported and that patients with interstitial lung disease should be carefully monitored.

Applicant Table 12
Subjects With Adverse Events Resulting in Death by Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
(Global Cohort)
(ASaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Subjects in population	217		216	
with one or more adverse events	7	(3.2)	10	(4.6)
with no adverse events	210	(96.8)	206	(95.4)
Pneumonitis	2	(0.9)	0	(0.0)
Abdominal infection	1	(0.5)	0	(0.0)
Hepatitis	1	(0.5)	0	(0.0)
Multiple organ dysfunction syndrome	1	(0.5)	1	(0.5)
Myocardial infarction	1	(0.5)	0	(0.0)
Pneumonia	1	(0.5)	1	(0.5)
Aspiration	0	(0.0)	1	(0.5)
Cholangitis	0	(0.0)	1	(0.5)
Completed suicide	0	(0.0)	1	(0.5)
Craniocerebral injury	0	(0.0)	1	(0.5)
Death	0	(0.0)	1	(0.5)
Gastric cancer	0	(0.0)	1	(0.5)
Myocarditis	0	(0.0)	1	(0.5)
Respiratory tract infection	0	(0.0)	1	(0.5)
Every subject is counted a single time for each applicable row and column.				
Database Cutoff Date: 17JUN2020.				

Source: [P811V01MK3475: 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 (3.2% and 4.6% in the pembrolizumab and placebo arms respectively). In this reviewer's analysis (not counting deaths due to "malignant neoplasm progression," "death," "gastric cancer," and "completed suicide,") the incidence of deaths due to AE on the placebo arm was identical to the pembrolizumab arm at 3.2%.

After review of the death narratives, this reviewer concludes that in most cases, deaths appear to be related to the underlying gastric adenocarcinoma or other common comorbidities for patients with advanced gastric cancer; of note, however, three patients in the pembrolizumab arm died of possible related autoimmune complications (2 events of pneumonitis and one event of hepatitis), a known toxicity to pembrolizumab. No new safety signal was identified for pembrolizumab.

Serious Adverse Events

The Applicant's Position:

The overall incidence of SAEs in the KEYNOTE-811 treatment groups were similar (31.3% in the pembrolizumab + SOC group compared with 38.4% in the SOC group) (Applicant Table 11). The most frequently reported SAEs (≥4 participants) were diarrhea (2.8%), pneumonia (2.8%), infusion-related reaction (2.3%), vomiting (2.3%), pneumonitis (1.8%), and pulmonary embolism (1.8%) in the pembrolizumab + SOC group, and diarrhea (4.2%), pulmonary embolism (2.3%), dysphagia (1.9%), gastric hemorrhage (1.9%), pneumonia (1.9%), and hypokalemia (1.9%) in the SOC group.

The overall incidence of drug-related SAEs in KEYNOTE-811 was similar in the pembrolizumab + SOC group and SOC group (19.4% vs 17.1%, respectively) (Applicant Table 11). The most frequently reported drug-related SAEs (≥3 participants) were diarrhea (2.8%), infusion-related reaction (2.3%), vomiting (1.8%), colitis (1.4%), pneumonitis (1.4%) and fatigue (1.4%) in the pembrolizumab + SOC group, and diarrhea (3.7%), hypokalemia (1.9%), nausea (1.4%), vomiting (1.4%), dehydration (1.4%), and general physical health deterioration (1.4%) in the SOC group. Of these, pneumonitis and colitis are AEOSIs for pembrolizumab.

The FDA's Assessment:

In FDA's analysis, 33%, and 39% patients in the pembrolizumab and placebo arms, respectively experienced an SAE, including fatal AEs; 26 patients (6%) had a fatal SAE (the dataset included terms such as disease progression, gastric cancer, etc.; see above section for the analysis for deaths). A majority (96%) of the patients with an SAE were hospitalized. The most frequently reported SAEs (≥5%) in both the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group were diarrhea (6% each, grouped terms colitis, diarrhea, enteritis, and enterocolitis), hemorrhage (5% each, grouped terms gastric hemorrhage, gastrointestinal hemorrhage, hemoptysis, lower gastrointestinal hemorrhage, tumor hemorrhage, and upper gastrointestinal hemorrhage), and pneumonia (3% vs. 2% in the pembrolizumab and placebo arms respectively). Grade 1-4 SAEs were experienced in 35% in the pembrolizumab arm, vs 38% in the placebo arm, and 100% of patients requiring hospitalization in both arms.

Immune-related SAEs included colitis, enterocolitis, hepatitis, hypersensitivity, hypophysitis, infusion-related reactions (IRR), pneumonitis, and diabetes mellitus. For additional information on immune-related AEs, please refer to the corresponding section.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

The incidence of AEs and drug-related AEs leading to discontinuation of any drug was similar in the pembrolizumab + SOC group and SOC group (AEs: 24.4% and 25.9%, and drug-related AEs: 23.0% and 20.4%, respectively). The majority of these events resulted in discontinuation of

chemotherapy in both treatment groups (AEs: 23.0% and 24.1%, and drug-related AEs: 21.2% and 18.5% in the pembrolizumab + SOC and SOC groups, respectively). The most common AEs and drug-related AEs (≥1% incidence) leading to discontinuation of any drug in both KEYNOTE-811 treatment groups were peripheral sensory neuropathy, neutrophil count decreased, and neuropathy peripheral .

Discontinuation of pembrolizumab/placebo was reported in 5.5% and 6.9% for all AEs, and: 2.8% and 1.9% for drug-related AEs in the pembrolizumab + SOC group and the SOC group, respectively.

The FDA's Assessment:
FDA agrees with the Applicant's description. Pembrolizumab and placebo were discontinued for adverse reactions in 6% of patients; this incidence is lower than the rate of discontinuation reported in Study KN590 (15%) in patients with esophageal cancer who were treated with a similar chemotherapy backbone (Keytruda USPI). The most common adverse reaction resulting in permanent discontinuation of pembrolizumab (≥1%) was pneumonitis (1.4%).

The treatment discontinuations observed in KEYNOTE-811 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 and drug-related AEs leading to interruption of any drug was similar between the pembrolizumab + SOC and the SOC treatment groups (AEs: 71.0% and 66.2%, and drug-related AEs: 65.0% and 58.8%, respectively). The most common AEs (≥10% incidence) leading to treatment interruption of any drug in both KEYNOTE-811 treatment groups were platelet count decreased, neutrophil count decreased, diarrhea, and neutropenia. The most common drug-related AEs (≥10% incidence) leading to treatment interruption of any drug included the same preferred terms as listed above.

Treatment interruptions of pembrolizumab/placebo were similar in the 2 treatment groups (AEs: 57.6% and 49.5% and drug-related AEs: 50.2% and 42.1% in the pembrolizumab + SOC group and the SOC group, respectively).

The FDA's Assessment:
FDA reproduced the incidence of adverse reactions leading to interruption of pembrolizumab or placebo, which occurred at the same rate as the Applicant's finding: 58% of patients on the pembrolizumab arm vs. 50% of patients on the placebo arm interrupted pembrolizumab or placebo treatment. The most common adverse reactions or laboratory abnormalities leading to interruption of pembrolizumab (≥2%) were neutropenia (18%), thrombocytopenia (12%), diarrhea (6%), anemia (3.7%), hypokalemia (3.7%), fatigue/asthenia (3.2%), decreased appetite (3.2%), increased AST (2.8%), increased blood bilirubin (2.8%), pneumonia (2.8%), increased ALT

(2.3%), and vomiting (2.3%). Of note, these are common adverse reactions to the administration of trastuzumab in combination with chemotherapy and there were no clinically meaningful differences between arms.

The treatment interruption, and dose modifications observed in KEYNOTE-811 are consistent with the known safety profile of pembrolizumab, trastuzumab, and chemotherapy.

Significant Adverse Events

The Applicant's Position:

Events of Special Interest

AEOSI are immune-mediated events and infusion-related reactions known to be associated with pembrolizumab. The overall incidence of AEOSIs was 33.6% in the pembrolizumab + SOC group and 20.8% in the SOC group (Applicant Table 13). No new indication-specific, immune-mediated AEs causally associated with pembrolizumab were identified with the addition of trastuzumab and chemotherapy. Infusion reaction was the most common AEOSI reported in both treatment groups (18.0% in the pembrolizumab + SOC group and 13.0% in the SOC group) (Applicant Table 14). The types and severity of AEOSIs observed with pembrolizumab when used in combination with trastuzumab and chemotherapy remained consistent with the established safety profile of pembrolizumab, with the exception of an increased rate of infusion-related reactions.

Most infusion reactions in the pembrolizumab + SOC group were Grade 1 or 2, 2.8% were Grade 3, and no events were Grade 4 or 5 in severity. No participant discontinued pembrolizumab treatment due to an AEOSI of infusion reaction; however, 4 participants in each KEYNOTE-811 treatment group discontinued SOC treatment as a result of infusion reactions.

A total of 4 participants died due to an AEOSI; 3 in the pembrolizumab + SOC group (2 due to pneumonitis and 1 due to hepatitis) and 1 in the SOC group (due to myocarditis). Those deaths considered to be drug-related by the investigator included single events of pneumonitis and hepatitis in the pembrolizumab + SOC group and 1 event of myocarditis in the SOC group.

Most (71.0%) immune-mediated AEOSIs were Grade 1 or 2 in the pembrolizumab + SOC group and were managed with treatment interruption and/or corticosteroids.

At the time of the data cutoff, 61.6% of participants in the pembrolizumab + SOC group reported resolved events and 24.7% reported unresolved events .

Cardiac Events

Trastuzumab has been associated with cardiomyopathy (see USPI). The frequency of cardiac events, including the proportion of participants with baseline and post-baseline measurements who experienced LVEF <50% and ≥10% decrease from baseline was similar in both KEYNOTE-811 treatment groups. Therefore, the addition of pembrolizumab to the SOC regimen of chemotherapy (FP/CAPOX) and trastuzumab does not appear to increase cardiac toxicity.

Applicant Table 13
Adverse Event Summary
AEOSI
(Global Cohort)
(ASaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Subjects in population	217		216	
with one or more adverse events	73	(33.6)	45	(20.8)
with no adverse event	144	(66.4)	171	(79.2)
with drug-related[†] adverse events	71	(32.7)	40	(18.5)
with toxicity grade 3-5 adverse events	21	(9.7)	7	(3.2)
with toxicity grade 3-5 drug-related adverse events	20	(9.2)	7	(3.2)
with serious adverse events	19	(8.8)	7	(3.2)
with serious drug-related adverse events	18	(8.3)	7	(3.2)
who died	3	(1.4)	1	(0.5)
who died due to a drug-related adverse event	2	(0.9)	1	(0.5)
discontinued any drug due to an adverse event	12	(5.5)	5	(2.3)
discontinued pembrolizumab or placebo	7	(3.2)	2	(0.9)
discontinued trastuzumab	7	(3.2)	2	(0.9)
discontinued any chemotherapy	12	(5.5)	5	(2.3)
discontinued all drugs	6	(2.8)	2	(0.9)
discontinued any drug due to a drug-related adverse event	11	(5.1)	5	(2.3)
discontinued pembrolizumab or placebo	6	(2.8)	2	(0.9)
discontinued trastuzumab	6	(2.8)	2	(0.9)
discontinued any chemotherapy	11	(5.1)	5	(2.3)
discontinued all drugs	5	(2.3)	2	(0.9)
discontinued any drug due to a serious adverse event	9	(4.1)	2	(0.9)
discontinued pembrolizumab or placebo	7	(3.2)	2	(0.9)
discontinued trastuzumab	7	(3.2)	2	(0.9)
discontinued any chemotherapy	9	(4.1)	2	(0.9)
discontinued all drugs	6	(2.8)	2	(0.9)
discontinued any drug due to a serious drug-related adverse event	8	(3.7)	2	(0.9)
discontinued pembrolizumab or placebo	6	(2.8)	2	(0.9)
discontinued trastuzumab	6	(2.8)	2	(0.9)
discontinued any chemotherapy	8	(3.7)	2	(0.9)

Adverse Event Summary
AEOSI
(Global Cohort)
(ASaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
discontinued all drugs	5	(2.3)	2	(0.9)

† 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.
Grades are based on NCI CTCAE version 4.03.
Database Cutoff Date: 17JUN2020.

Source: [P811V01MK3475: adam-adsl; adae]

Applicant Table 14
Subjects With Adverse Events of Special Interest (AEOSI) by AEOSI category
(Incidence > 0% in One or More Treatment Groups)
(Global Cohort)
(ASaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Subjects in population	217		216	
with one or more adverse events	73	(33.6)	45	(20.8)
with no adverse events	144	(66.4)	171	(79.2)
Colitis	10	(4.6)	4	(1.9)
Hepatitis	2	(0.9)	2	(0.9)
Hyperthyroidism	8	(3.7)	7	(3.2)
Hypophysitis	3	(1.4)	0	(0.0)
Hypothyroidism	10	(4.6)	6	(2.8)
Infusion Reactions	39	(18.0)	28	(13.0)
Myocarditis	0	(0.0)	1	(0.5)
Nephritis	1	(0.5)	0	(0.0)
Pneumonitis	11	(5.1)	3	(1.4)
Severe Skin Reactions	2	(0.9)	0	(0.0)
Thyroiditis	1	(0.5)	0	(0.0)
Type 1 Diabetes Mellitus	1	(0.5)	0	(0.0)
Uveitis	1	(0.5)	1	(0.5)

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.
Database Cutoff Date: 17JUN2020.

Source: [P811V01MK3475: adam-adsl; adae]

The FDA's Assessment:

FDA agrees with the Applicant's assessment of AEOSIs. As expected, the incidence of AEOSI was higher in the pembrolizumab arm (34%) compared with the placebo arm (21%). Infusion

reaction was the most common AEOSI reported in both treatment groups (18% in the pembrolizumab arm and 13% in the placebo arm); although 3% of the pembrolizumab-related IRRs were Grade 3 (there were no Grade 4 IRRs), none of these events resulted in treatment discontinuation.

The immune-related AEs observed more frequently were pneumonitis, colitis, and hypothyroidism (5%); of note, pneumonitis, colitis, and hypothyroidism were also reported in the placebo arm (incidences 1.5%, 2%, and 3% respectively), as adverse events that may mimic these autoimmune conditions have been reported with trastuzumab and fluoropyrimidines. There were no new safety signals identified with the addition of pembrolizumab to trastuzumab and chemotherapy. FDA agrees that the types and severity of AEOSIs observed with the pembrolizumab arm remained consistent with the established safety profile of pembrolizumab and chemotherapy.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

The AE profile observed in KEYNOTE-811 for the pembrolizumab + SOC group was generally consistent with the established safety profiles of either SOC regimen alone or pembrolizumab monotherapy. The most frequently reported AEs (>25% incidence) were diarrhea, nausea, anemia, decreased appetite, platelet count decreased, and vomiting in both KEYNOTE-811 treatment groups (Applicant Table 15). A rainfall plot comparing commonly reported AEs (≥10% incidence) is depicted in (Applicant Figure 2). The incidence of AEs of AST increased was 20.7% in the pembrolizumab + SOC group and 13.0% in the SOC group (Applicant Figure 2); however, this was not reflected in laboratory toxicity grade shifts from baseline to worst post-baseline. The incidence of hepatobiliary disorders (system organ class) in the KEYNOTE-811 pembrolizumab + SOC group were 3.7% and 6.5% in the SOC group.

APPEARS THIS WAY ON ORIGINAL

Applicant Table 15
Subjects With Adverse Events by Decreasing Incidence
(Incidence ≥ 10% in One or More Treatment Groups)
(Global Cohort)
(ASaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Subjects in population	217		216	
with one or more adverse events	211	(97.2)	212	(98.1)
with no adverse events	6	(2.8)	4	(1.9)
Diarrhoea	114	(52.5)	96	(44.4)
Nausea	106	(48.8)	96	(44.4)
Anaemia	89	(41.0)	95	(44.0)
Decreased appetite	67	(30.9)	69	(31.9)
Vomiting	67	(30.9)	59	(27.3)
Platelet count decreased	53	(24.4)	61	(28.2)
Fatigue	51	(23.5)	43	(19.9)
Neutrophil count decreased	51	(23.5)	53	(24.5)
Peripheral sensory neuropathy	50	(23.0)	40	(18.5)
Aspartate aminotransferase increased	45	(20.7)	28	(13.0)
Weight decreased	41	(18.9)	37	(17.1)
Palmar-plantar erythrodysaesthesia syndrome	40	(18.4)	35	(16.2)
Neutropenia	34	(15.7)	33	(15.3)
Constipation	33	(15.2)	37	(17.1)
Neuropathy peripheral	33	(15.2)	35	(16.2)
Hypokalaemia	32	(14.7)	25	(11.6)
Alanine aminotransferase increased	31	(14.3)	22	(10.2)
Infusion related reaction	31	(14.3)	20	(9.3)
Pyrexia	31	(14.3)	26	(12.0)
Hypoalbuminaemia	30	(13.8)	32	(14.8)
White blood cell count decreased	27	(12.4)	31	(14.4)
Malaise	24	(11.1)	19	(8.8)
Stomatitis	24	(11.1)	22	(10.2)
Asthenia	22	(10.1)	35	(16.2)
Blood bilirubin increased	22	(10.1)	12	(5.6)

Subjects With Adverse Events by Decreasing Incidence
(Incidence ≥ 10% in One or More Treatment Groups)
(Global Cohort)
(ASaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Thrombocytopenia	20	(9.2)	25	(11.6)

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

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

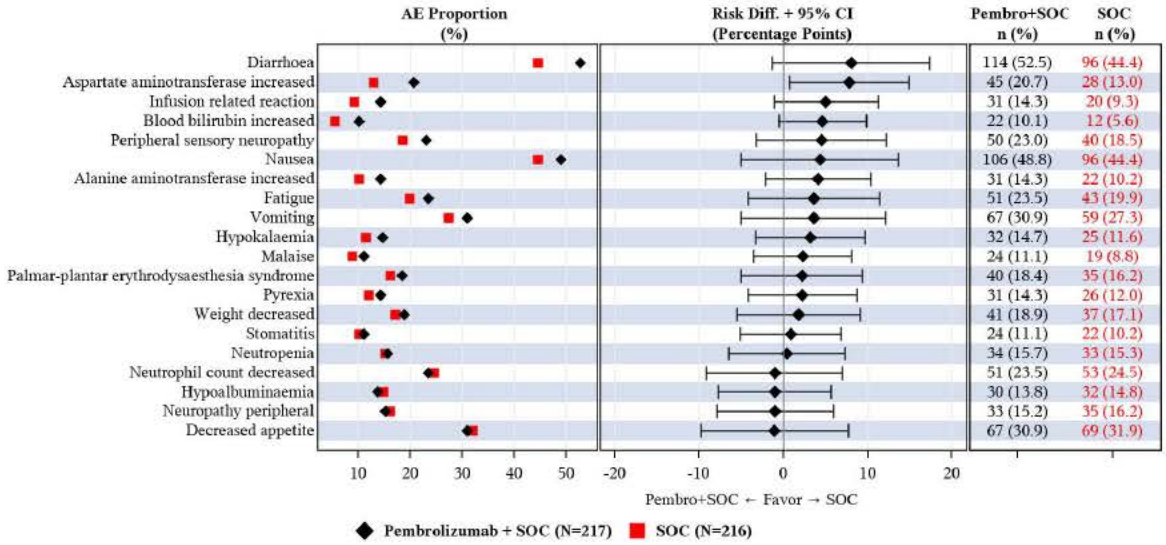
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA 23.0 preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.

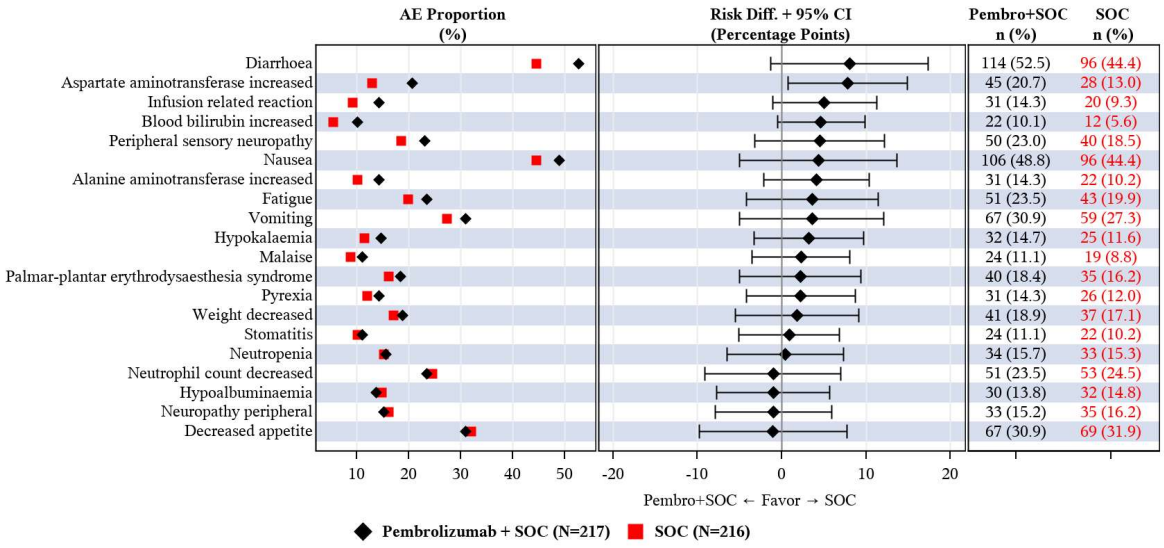
Database Cutoff Date: 17JUN2020.

Source: [P811V01MK3475: adam-adsl; adae]

Applicant Figure 2
Between-treatment Comparisons in Adverse Events
Selected Adverse Events (>=10% Incidence) and Sorted by Risk Difference
(Global Cohort)
(ASaT Population)



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



The FDA's Assessment:

FDA replicated the Applicant's analysis and agrees that the toxicity profile observed in KEYNOTE-811 for the pembrolizumab arm was generally consistent with the established safety profiles of pembrolizumab and chemotherapy (or trastuzumab) alone. The incidence rates of AEs were similar between arms for most AEs; AEs with an increased incidence difference of at least 5% in the pembrolizumab were diarrhea, IRR, AST increased, and nausea. These differences were small in magnitude and not clinically relevant and practitioners are aware of these toxicities and able to manage them.

There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

Laboratory Findings

The Applicant's Position:

No new safety concerns based on laboratory abnormalities were reported in the pembrolizumab + SOC group. The most commonly reported Grade 3 or 4 laboratory abnormalities reported post baseline in the both KEYNOTE-811 treatment groups were neutrophil count decreased (15.1% and 16.6%), platelet count decreased (14.2% and 9.5%), and anemia (13.7% and 11.8%), in the pembrolizumab + SOC group and SOC group, respectively, consistent with the established SOC safety profile.

The FDA's Assessment:

In Merck's analysis, there was a difference of ≥5% between patients treated with pembrolizumab versus standard of care for worsening of ALT (34% vs 29%), and creatinine (20% vs 10%) levels. For most analytes, the incidence of lab abnormalities was similar between arms and most patients on the placebo arm had increased incidence (at least 5%) of alkaline phosphatase (36% vs 30%, respectively) and hyponatremia (28%, 20%, respectively) when compared with patients in the pembrolizumab arm. These are well known and manageable by an oncologist. Table 2 below shows FDA's shift analyses table.

APPEARS THIS WAY ON ORIGINAL

Table 2: Lab abnormalities worsened from baseline in 20% patients in Study KN811

Laboratory Test*	Pembrolizumab 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy		Placebo Trastuzumab Fluoropyrimidine and Platinum Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	64	14	63	12
Neutropenia	60	15	56	17
Decreased platelet count	59	14	60	10
Decreased white blood cells	52	6	52	6
Lymphopenia	46	13	41	9
Chemistry				
Hypoalbuminemia	48	0.5	45	4.3
Hyperglycemia	47	6	48	4.8
Increased AST	47	2.4	44	1.9
Hypocalcemia	43	2.4	39	2.4
Increased ALT	34	1.9	29	0.5
Hypokalemia	32	11	31	10
Increased alkaline phosphatase	30	2.8	36	3.8
Hypophosphatemia	27	8	30	8
Hypomagnesemia	24	1.9	25	1
Hyponatremia	22	5	28	5
Increased blood bilirubin	22	2.4	20	1.4
Increased prothrombin INR	20	1.4	20	2.7
Increased creatinine	20	1.4	10	0.5

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: pembrolizumab/trastuzumab/fluoropyrimidine and platinum chemotherapy (range: 208 to 212 patients) and placebo/trastuzumab/fluoropyrimidine and platinum chemotherapy (range: 207 to 212 patients); increased prothrombin INR: pembrolizumab /trastuzumab/fluoropyrimidine and platinum chemotherapy n=70 and placebo/trastuzumab/fluoropyrimidine and platinum chemotherapy n=75.

† Graded per NCI CTCAE v4.03

The were no clinically meaningful differences in incidence of Grade 3-4 laboratory toxicities between arms.

Vital Signs

The Applicant's Position:

There were no meaningful changes in vital signs measurements, physical examination assessments, or other observations related to safety in both KEYNOTE-811 treatment groups.

The FDA's Assessment:
FDA agrees.

Electrocardiograms (ECGs)

The Applicant's Position:

ECG testing was performed once during screening using local standard procedures. No significant abnormal findings were identified.

The FDA's Assessment:
FDA agrees.

QT

The Applicant's Position:

No meaningful changes in QTc interval were identified in the analyses included in previous submissions.

The FDA's Assessment:
FDA agrees.

Immunogenicity

The Applicant's Position:

No clinically meaningful impact of pembrolizumab and trastuzumab ADA rates on PK, efficacy, and safety was observed.

The FDA's Assessment:
FDA agrees.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 [Name Safety Issue]

The Applicant's Position:

No submission-specific safety issues were identified.

The FDA's Assessment:
FDA agrees.

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

The Applicant's Position:

Not applicable.

The FDA's Assessment:
FDA agrees.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

No new safety concern was observed in the AE profile of the pembrolizumab + SOC group based on age, sex, and ECOG performance status.

The AE profile based on region in the pembrolizumab + SOC group showed 33.3% of US participants with treatment-related SAEs and 18.5% in ex-US participants. Due to the small number of US participants (N=12) compared with non-US participants (N=205) in the pembrolizumab + SOC group, it is not possible to draw conclusions.

The FDA's Assessment:
FDA agrees that the arms were balanced and that there appears to be no confounders or bias that could affect the assessment of safety. FDA has described the demographic and baseline characteristics in detail for the efficacy population in Section 8.1.2. and considers the study results applicable to the U.S. population.

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.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable.

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-811.

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 was summarized in the Periodic Safety Update Report covering the period 04-SEP-2019 through 03-MAR-2020, specifically Appendix 20.3 (Numbers of Adverse Drug Reactions by Preferred Term from Postauthorization Sources).

No revocation or withdrawal of pembrolizumab registration for safety reasons has occurred in any country.

The FDA's Assessment:
FDA agrees.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Postmarketing data for pembrolizumab from the safety reporting database is routinely reviewed. This 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-811. There are no specific safety concerns not already included in pembrolizumab labeling expected from off-label use.

The FDA's Assessment:
FDA agrees.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The results from KEYNOTE-811 demonstrate that pembrolizumab in combination with trastuzumab and chemotherapy has a tolerable and manageable safety profile. Overall, no new safety concerns were identified for the use of pembrolizumab in combination with trastuzumab and chemotherapy in patients with advanced gastric or GEJ adenocarcinoma. No new safety concerns related to the known immune-mediated events associated with pembrolizumab monotherapy were observed with the addition of trastuzumab and chemotherapy.

The FDA's Assessment:
The adverse reaction profile observed in patients receiving pembrolizumab in KEYNOTE-811 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. The types and severity of AEOSIs observed with the pembrolizumab arm remained consistent with the established safety profile of pembrolizumab and chemotherapy.

The proportion of patients with AEs resulting in death was generally similar in the pembrolizumab arm vs placebo arm, 3.2%, and 4.6%, respectively. Based on review, the AEs and resulting fatal outcomes were in most patients likely related to underlying disease or other comorbidities. No new safety concerns were identified for pembrolizumab.

Based on review, the observed SAEs are considered consistent with the established safety profile of pembrolizumab. A generally similar proportion of patients in the pembrolizumab arm experienced SAEs compared with the placebo, with the most frequently reported SAEs including diarrhea, gastrointestinal hemorrhages, and pneumonia.

Discontinuation of any drug in the pembrolizumab arm compared with the placebo arm (24% vs 26%) was similar. A generally similar proportion of patients experienced an AE resulting in treatment interruption of any drug in the pembrolizumab arm compared with the SOC group (71% vs 66%). These results are consistent with the known toxicity of pembrolizumab and SOC components.

FDA agrees with the Applicant's position that pembrolizumab has an acceptable safety profile in patients with first-line locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma. The safety of patients on KEYNOTE-811 were consistent with the RSD (of 2799+ subjects with melanoma or non-small cell lung cancer [NSCLC] who have received pembrolizumab).

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

There were no major statistical issues in the review of this supplemental BLA. This application is based on the results of the first interim analysis where only ORR was tested, and neither PFS nor OS were formally tested. A statistically significant improvement in ORR was observed in the pembrolizumab arm over the placebo arm, and is supported by an improved DOR as well.

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 pembrolizumab for the first-line treatment of patients with metastatic or locally advanced HER2 positive gastric or gastroesophageal adenocarcinoma when combined with trastuzumab and platinum- and fluoropyrimidine- based chemotherapy.

The primary support for the effectiveness of pembrolizumab for this indication was derived from the interim analysis results of the first 264 patients enrolled in a multicenter, randomized, double-blind, randomized trial, Study KEYNOTE 811. The major efficacy outcome measure of this interim analysis is ORR as per blinded independent assessment for patients randomized to pembrolizumab or placebo in combination with trastuzumab and chemotherapy. Treatment continued until unacceptable toxicity or disease progression. The study is ongoing (434 patients of the planned 692 patients have been enrolled as of June 17, 2020) and the primary endpoints are PFS and OS; FDA and Merck agreed that the OS and PFS results will serve as the supportive data to confirm the benefit observed in ORR in this interim analysis.

In the IA1 population, the ORR was 74.4% (95% CI 66.2, 81.6) in the pembrolizumab arm and 51.9% (95% CI 43.0, 60.7) in the placebo arm (one-sided p-value=0.00006, one-sided p-value boundary=0.002). These responses included complete responses in 11.3% and 3.1% patients in the pembrolizumab and placebo arms, respectively. The median DoR estimated using the KM method was 10.6 months (95% CI 1.1; 16.5) in the pembrolizumab arm vs. 9.5 months (95% CI 1.4, 15.4) in the placebo arm; 0.3% and 61.4% patients have responses lasting ≥ 6 months.

The adverse reaction profile observed in patients receiving pembrolizumab in KEYNOTE-811 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-811, only diarrhea, infusion-related reactions, increased AST, and nausea 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 increased ALT and increased creatinine. The rate of immune-related adverse events was consistent with the known incidence for pembrolizumab. Pembrolizumab and placebo were discontinued due to adverse events in 6% of patients. The most common adverse reaction resulting in permanent discontinuation of pembrolizumab (≥1%) was pneumonitis (1.4%). 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 pembrolizumab in combination with trastuzumab and chemotherapy for the treatment of patients with HER2 positive metastatic or locally advanced gastric or gastroesophageal junction adenocarcinoma. The demonstrated improvement in ORR for patients randomized to pembrolizumab in combination with chemotherapy compared to patients randomized to placebo in combination with chemotherapy SOC is clinically meaningful, statistically significant, and supported by the duration of these responses. 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 HER2 positive gastric or GEJ carcinoma. To confirm the clinical benefit observed in ORR, the Applicant will submit the PFS and OS of Study KN811.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

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 ORR and risk-benefit profile of pembrolizumab and chemotherapy as compared to chemotherapy is considered to be favorable.

APPEARS THIS WAY
ON ORIGINAL

10 Pediatrics

The Applicant's Position:

The combination of pembrolizumab plus trastuzumab and chemotherapy was not studied in pediatric patients. The Sponsor has submitted a PREA waiver.

The FDA's Assessment:

Pembrolizumab in gastric cancer including GEJ adenocarcinoma has an orphan drug designation (16 June 2015). A full waiver was requested for all pediatric age groups; clinical studies are impossible or highly impractical because the number of pediatric patients with gastric and GEJ adenocarcinoma is so small.

APPEARS THIS WAY
ON ORIGINAL

11 Labeling Recommendations

The Applicant's Position:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
PRESCRIBING INFORMATION: HIGHLIGHTS OF PRESCRIBING INFORMATION	•Revised Recent Major Changes. •Added indication for patients with locally advanced or metastatic HER2-positive gastric or GEJ cancer. (b) (4) [redacted]	Deleted (b) (4) [redacted]
INDICATIONS AND USAGE	Added indication for patients with locally advanced or metastatic HER2-postive gastric or GEJ cancer	FDA agrees.
DOSAGE AND ADMINISTRATION	Added combination therapy dosing information for patients with gastric cancer	FDA agrees.
ADVERSE REACTIONS	Updated to include study details and present adverse reaction data from KEYNOTE-811	(b) (4) [redacted]
CLINICAL STUDIES	Added study description and efficacy results for KEYNOTE-811	Language was added to highlight that KEYNOTE-811 was designed to enroll 692 patients.
MEDICATION GUIDE: What is KEYTRUDA?	Added indication for patients with HER2-positive gastric cancer	FDA agrees.
What are the possible side effects of KEYTRUDA?	(b) (4) [redacted]	FDA agrees.

The FDA's Assessment:
See notes in the table above.

APPEARS THIS WAY
ON ORIGINAL

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.

APPEARS THIS WAY
ON ORIGINAL

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The Applicant agreed to the following postmarketing requirement to confirm the clinical benefit of pembrolizumab and support regular approval of pembrolizumab for patients with HER2 positive unresectable or metastatic gastric and GEJ adenocarcinoma:

Submit the final progression-free survival and final overall survival analyses and datasets for the ongoing clinical trial KEYNOTE-811, "A Phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants With HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma" to verify and describe the clinical benefit of pembrolizumab with trastuzumab plus chemotherapy for patients with HER2-positive advanced or metastatic gastric or gastroesophageal adenocarcinoma.

Final Protocol Submission: 06/2018
Trial Completion: 03/2024
Final Report Submission: 09/2024

APPEARS THIS WAY
ON ORIGINAL

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

I agree with the overall accelerated approval recommendation by the review teams for this application. Trial KN811 demonstrated substantial evidence of an effect on response rate via a statistically significant effect between arms favoring the pembrolizumab arm. This effect on an intermediate endpoint was deemed reasonably likely to predict benefit which will be further assessed as a PMR by the final results of KN811.

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

X _____

18 Office Director (or designated signatory authority)

Not applicable for this efficacy supplement.

X

19 Appendices

19.1 References

The Applicant's References:

[1] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Stomach Cancer: estimated incidence, mortality and prevalence worldwide in 2012 [Internet]. Lyon: International Agency for Research on Cancer; 2014. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.asp x.

[2] Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: Cancer J Clin. 2018;68:394-424.

[3] American Cancer Society. Cancer Facts & Figures 2020.

[4] National Cancer Institute (NCI). 2020. Cancer stat facts: stomach cancer. Available from: https://seer.cancer.gov/statfacts/html/stomach.html.

[5] Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010 Aug 28;376(9742):687-97.

[6] Ferris RL, Jaffee EM, Ferrone S. Tumor antigen targeted, monoclonal antibody-based immunotherapy: clinical response, cellular immunity, and immunoescape. J Clin Oncol. 2010 Oct 1;28(28):4390-9.

[7] Bellati F, Napoletano C, Ruscito I, Liberati M, Panici PB, Nuti M. Cellular adaptive immune system plays a crucial role in trastuzumab clinical efficacy. J Clin Oncol. 2010 Jul 20;28(21):e369-70.

[8] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines): gastric cancer version 1.2020.

[9] Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2016. 27(Supplement5): v38–v49. doi:10.1093/annonc/mdw350.

[10] Rivera F, Romero C, Jimenez-Fonseca P, Izquierdo-Manuel M, Salud A, Martínez E, et al. Phase II study to evaluate the efficacy of Trastuzumab in combination with Capecitabine and Oxaliplatin in first-line treatment of HER2positive

advanced gastric cancer: HERXO trial. Cancer Chemotherapy and Pharmacology. 2019. 83:1175–1181. https://doi.org/10.1007/s00280-019-03820-7

[11] Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al.

Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Annals of Oncology. 2009. 20: 666–673. doi:10.1093/annonc/mdn717

[12] Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014; 15: 1224–35.

[13] Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, Open-Label, Phase III Study Comparing Irinotecan With Paclitaxel in Patients With Advanced Gastric Cancer Without Severe Peritoneal Metastasis After Failure of Prior Combination Chemotherapy Using Fluoropyrimidine Plus Platinum: WJOG 4007 Trial. J Clin Oncol. 2013. 31:4438-4444.

[14] Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, et al. Salvage Chemotherapy for Pretreated Gastric Cancer: A Randomized Phase III Trial Comparing Chemotherapy Plus Best Supportive Care With Best Supportive Care Alone. J Clin Oncol. 2012. 30:1513-1518

[15] Assersohn L, Brown G, Cunningham D, Ward C, Oates J, Waters JS, et al. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. Annals of Oncology. 2004. 15: 64–69.

The FDA's References:

Ahmadi L, Kamkari S, Mokarram P, Lankarani KB, Tabibi N, Ashktorab A, Vasei M. HER-2/neu and E-cadherin Expression and Microsatellite Instability in Gastric Dysplasia. Middle East J Dig Dis. 2011 Mar; 3(1): 20–27.
Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Ruschoff J, Kang YK, To GATI. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
Beer A, Taghizadeh H, Schiefer A, Puhr HC, Karner AK, Jomrich G, Schoppmann S, Kain R, Presusser M, Ilhan-Mutlu A. PD-L1 and HER2 Expression in Gastroesophageal Cancer: a

Matched Case Control Study. Pathol. Oncol. Res. 2020 (26): 2225–35.

Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, Jeziorski K, Shparyk Y, Hoff PM, Sobrero A, Salman P, Li J, Protsenko SA, Wainberg ZA, Buyse M, Afenjar K, Houe V, Garcia A, Kaneko T, Huang Y, Khan-Wasti S, Santillana S, Press MF, Slamon D. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC--a randomized phase III trial. J Clin Oncol. 2016;34(5):443–51.

https://seer.cancer.gov/statfacts/html/stomach.html accessed on 9 March 2021.

https://www.cancer.org/cancer/stomach-cancer/about/key-statistics.html accessed on 9 March 2021.

Kang YK, Rha SY, Tassone P, Barriuso J, Yu R, Szado T, Garg A, Bang YJ. A phase IIa dose-finding and safety study of first-line pertuzumab in combination with trastuzumab, capecitabine and cisplatin in patients with HER2-positive advanced gastric cancer. Br J Cancer. 2014;111(4):660–6.

Kelly CM and Janjigian YY. The genomics and therapeutics of HER2-positive gastric cancer—from trastuzumab and beyond. J Gastrointest Oncol. 2016 Oct; 7(5): 750–762.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers; version 2.2020. Plymouth Meeting (PA): National Comprehensive Cancer Network (NCCN); 2020. 156 p. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

Pembrolizumab prescribing information. Drugs@FDA [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration. [cited 2021 March 4]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s084lbl.pdf

Press MF, Ellis CE, Gagnon RC, Grob TJ, Buyse M, Villalobos I, Liang Z, Wu S, Bang YJ, Qin SK, Chung HC, Xu J, Park JO, Jeziorski K, Afenjar K, Ma Y, Estrada MC, Robinson DM, Scherer SJ, Sauter G, Hecht JR, Slamon DJ. HER2 status in advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma for entry to the TRIO-013/LOGiC trial of lapatinib. Mol Cancer Ther. 2017;16(1):228–38.

Shah MA, Xu RH, Bang YJ, Hoff PM, Liu T, Herraez-Baranda LA, Xia F, Garg A, Shing M, Tabernero J. HELOISE: Phase IIIb randomized multicenter study comparing standard-of-care and higher-dose trastuzumab regimens combined with chemotherapy as first-line therapy in patients with human epidermal growth factor receptor 2-positive metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol. 2017;35(22):2558–67.

Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, Song C, Wu H, Eng-Wong J, Kim K,

Kang YK. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018;19(10):1372–84.
van Velzena M.J.M., Derksb S, van Griekenc N.C.T., Mohammadd NH, van Laarhovene H.W.M. MSI as a predictive factor for treatment outcome of gastroesophageal adenocarcinoma. Cancer Treatment Reviews. 2020 (86):1-8.
Yamashita K, Iwatsuki M, Harada K, Eto K, Hiyoshi Y, Ishimoto T, Nagai Y, Iwagami S, Miyamoto Y, Yoshida N, Komohara Y, Ajani J, Bab H. Prognostic impacts of the combined positive score and the tumor proportion score for programmed death ligand-1 expression by double immunohistochemical staining in patients with advanced gastric cancer. Gastric Cancer. 2020 Jan;23(1):95-104.
Zhao D, Klempner SJ, Chao J. J Hematol Oncol. 17 May 2019;12(50):1-13.

19.2 Financial Disclosure

The Applicant's Position:

Disclosure of financial interests of the investigators who conducted the KEYNOTE-811 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 on the provided data.

Covered Clinical Study (Name and/or Number):* KEYNOTE-811

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1471		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	N/A ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	N/A ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

19.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No new data are being submitted with this application.

The FDA's Assessment:
N/A

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:
N/A

19.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
N/A

APPEARS THIS WAY ON ORIGINAL

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Blaire Osborn	CDER/OTS/OCP/DCP II	Sections: 6	**Select one:** ☒ Authored ☐ Approved
	Signature: Blaire L. Osborn -S Digitally signed by Blaire L. Osborn -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013312620, cn=Blaire L. Osborn -S Date: 2021.04.29 06:51:35 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	CDER/OTS/OCP/DCP II	Sections:	**Select one:** ☒ Authored ☒ Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Zhao -S, 0.9.2342.19200300.100.1.1=1300136450 Date: 2021.04.28 22:05:21 -04'00'			
Clinical Pharmacology Division Director	Nam A, Rahman	CDER/OTS/OCP/DCP II	Sections:	**Select one:** ☐ Authored ☒ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2021.04.29 14:25:40 -04'00'			
Clinical Reviewer	Leigh Marcus	CDER/OOD/DO3	Sections: parts of 1, 2, 3, 4, 7-14	**Select one:** ☐ Authored ☒ Approved
	Signature: Refer to electronic signature on the final page of this review			
Clinical Team Leader	Sandra Casak	CDER/OOD/DO3	Sections:	**Select one:** ☐ Authored ☐ Approved
	Signature: Refer to electronic signature on the final page of this review			
Statistical Reviewer	Somak Chatterjee	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** ☒ Authored ☐ Approved
	Signature: Somak Chatterjee -S			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Team Leader	Pallavi-Mishra Kalyani	CDER/OTS/DBV	Sections:	**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: 2021.04.28 20:51:57 -04'00'			
Division Director (OB)	Shenghui Tang	CDER/OTS/DBV		**Select one:** ☐ Authored ☒ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2021.04.29 13:32:21 -04'00'			
Associate Director for Labeling (ADL)	William Pierce	OOD/IO		**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: 2021.04.29 16:24:12 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Sandra Casak	CDER/OOD/DO3	Sections:	**Select one:** ☐ Authored ☐ Approved
	Signature: Refer to electronic signature on the final page of this review			
Deputy Division Director (Clinical)	Steven Lemery	CDER/OOD/DO3	Sections:	**Select one:** ☐ Authored ☐ Approved
	Signature: Refer to electronic signature on the final page of this review			

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/

GINA M DAVIS
04/29/2021 07:34:58 PM

LEIGH J MARCUS
04/30/2021 08:24:40 AM

SANDRA J CASAK
04/30/2021 08:28:03 AM

STEVEN J LEMERY
04/30/2021 09:15:16 AM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - MEMO

NDA/BLA #:	BLA 125514 S-97
Drug Name:	KEYTRUDA (Pembrolizumab)
Indication(s):	First-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma
Applicant:	Merck Sharp & Dohme Corp.
Date(s):	Receipt: November 6, 2020 PDUFA date: May 6, 2021
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Somak Chatterjee, Ph.D.
Concurring Reviewers:	Pallavi Mishra-Kalyani, Ph.D., Statistical Team Leader Yuan-Li Shen, Ph.D., Deputy Division Director (Acting)
Medical Division:	Office of Oncologic Diseases, Division of Oncology 3
Clinical Team:	Leigh Marcus, M.D. Sandra Casak, M.D. Steven Lemery, M.D.
Project Manager:	Leah Her, M.S.
Keywords:	Randomized, Double-blind, Response rate,

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. From a statistical standpoint, the supplemental BLA is acceptable to support accelerated approval provided that the Applicant and the FDA reach an agreement regarding the labeling language.

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/

SOMAK CHATTERJEE
04/14/2021 10:41:10 AM

PALLAVI S MISHRA-KALYANI
04/19/2021 02:30:03 PM

YUAN L SHEN
04/19/2021 02:31:30 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s097

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 17, 2021

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

Gina Davis, M.T, Regulatory Project Manager, DO3

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

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

BLA: 125514/Supplement 097

In response to DO3's consult request dated December 7, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for Keytruda (pembrolizumab) injection, for intravenous use (Keytruda). This supplement (S-097) proposes a new indication: Keytruda in combination with trastuzumab and chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma.

OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO3 (Gina Davis) on March 9, 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 March 17, 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.

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

---

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/

KEVIN WRIGHT
03/17/2021 09:50:47 PM

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

PATIENT LABELING REVIEW

Date:	March 17, 2021
To:	Gina Davis, MT Senior Regulatory Project Manager **Division of Oncology 2 (DO2)**
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-097
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On November 6, 2020, Merck Sharp & Dohme Corp. submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved Biologics License Application (BLA) 125514/S-097 for KEYTRUDA (pemrolizumab) injection. With this supplement, the Applicant proposes a new indication for the first-line treatment of patients with locally advanced unresectable or metastatic HER-2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

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 2 (DO2) on December 7, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for KEYTRUDA (pembrolizumab) injection.

2 MATERIAL REVIEWED

- Draft KEYTRUDA (pembrolizumab) injection MG received on November 6, 2020 and November 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on March 9, 2021.
- Draft KEYTRUDA (pembrolizumab) injection Prescribing Information (PI) received on November 6, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on March 9, 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 is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

---

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

/s/

SHARON R MILLS
03/17/2021 09:26:57 AM

KEVIN WRIGHT
03/17/2021 10:52:05 AM

LASHAWN M GRIFFITHS
03/17/2021 11:01:38 AM