CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s170

Trade Name:	KEYTRUDA
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp & Dohme Corp.
Approval Date:	March 19, 2025
Indication:	Keytruda is a programmed death receptor-1 (PD-1)-blocking antibody indicated: Gastric Cancer • in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS≥1) as determined by an FDA approved test.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 125514/S-170

CORRECTED SUPPLEMENT APPROVAL/
FULFILLMENT OF A POSTMARKETING REQUIREMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.
Attention: Anita Lalloo, PhD
Director, Global Regulatory Affairs
351 North Sumneytown Pike, P.O. Box 1000
UG-2D-044
North Wales, PA 19454-2505

Dear Dr. Lalloo:

Please refer to your July 24, 2024, supplemental biologics license application (sBLA) and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab), for injection.

This Prior Approval supplemental biologics license application provides updates to the Keytruda (pembrolizumab) Prescribing Information and traditional approval of Keytruda in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

We also refer to our March 18, 2025, approval letter in which the section entitled, "Subpart E Fulfilled" was inadvertently omitted, and a footnote in the Gastric Cancer section of Highlights of the Prescribing Information was included that was no longer applicable. This corrected action letter includes the "Subpart E Fulfilled" section, and the footnote in the Highlights Gastric Cancer section of the Prescribing Information that was removed. The effective action date will remain March 19, 2025, the date of the original letter.

APPROVAL & LABELING

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

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 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).

SUBPART E FULFILLED

We approved this BLA under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 601.41.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your July 18, 2024, submission containing the final report for the following postmarketing requirement (PMR) listed in the May 5, 2021, approval letter for BLA 125514/S-097.

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

[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 https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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.

We have reviewed your submission and conclude that the above requirement was fulfilled. This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our May 5, 2021, approval letter.

You are not required to report on the status of closed (released or fulfilled) PMRs in your annual report required under 21 CFR 601.70 of the FD&CA.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Gina Davis, Senior Regulatory Health Project Manager at Gina.Davis@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Steven Lemery, MD, MHS
Director
Division of Oncology 3
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s170

LABELING

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

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

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

Indications and Usage (1)	03/2025
Dosage and Administration (2)	01/2025

----------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 adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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)
- for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. (1.2)
- as a single agent, for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC. (1.2)

Malignant Pleural Mesothelioma (MPM)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of adult patients with unresectable advanced or metastatic MPM. (1.3)

Head and Neck Squamous Cell Cancer (HNSCC)

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

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult patients with relapsed or refractory cHL. (1.5)
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy. (1.5)

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

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

Urothelial Cancer

- in combination with enfortumab vedotin, for the treatment of adult patients with locally advanced or metastatic urothelial cancer. (1.7)
- as a single agent for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.7)
- as a single agent for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. (1.7)

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. (1.8, 2.1)

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

- for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test. (1.9, 2.1)

Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. (1.10)
- in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. (1.10)

Esophageal Cancer

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

Cervical Cancer

- in combination with chemoradiotherapy, for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer. (1.12)
- in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. (1.12, 2.1)
- as a single agent 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. (1.12, 2.1)

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen. (1.13)

Biliary Tract Cancer (BTC)

- in combination with gemcitabine and cisplatin, for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer. (1.14)

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. (1.15)

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of adult patients with advanced RCC. (1.16)
- in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC. (1.16)
- for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. (1.16)

Endometrial Carcinoma

- in combination with carboplatin and paclitaxel, followed by KEYTRUDA as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma. (1.17)
- in combination with lenvatinib, for the treatment of adult patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. (1.17, 2.1)
- as a single agent, for the treatment of adult patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. (1.17, 2.1)

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] (1.18, 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 cSCC or locally advanced cSCC that is not curable by surgery or radiation. (1.19)

Triple-Negative Breast Cancer (TNBC)

- for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. (1.20)
- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test. (1.20, 2.1)

Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for Classical Hodgkin Lymphoma and Primary Mediastinal Large B-Cell Lymphoma in adults.[2] (1.21, 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 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 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- NSCLC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- MPM: 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 Cancer: 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)
- BTC: 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 as a single agent in the adjuvant setting, or in the advanced setting with either:
  - axitinib 5 mg orally twice daily or
  - lenvatinib 20 mg orally once daily. (2.2)
- Endometrial Carcinoma: 200 mg every 3 weeks or 400 mg every 6 weeks
  - in combination with carboplatin and paclitaxel regardless of MMR or MSI status, or
  - in combination with lenvatinib 20 mg orally once daily for pMMR or not MSI-H tumors, or
  - as a single agent for MSI-H or dMMR tumors. (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 after dilution. (2.4)
- See Full Prescribing Information for dosage modifications for adverse reactions and preparation and administration instructions. (2.3, 2.4)

---------- 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, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism. (6.1)
- KEYTRUDA in combination with chemotherapy or chemoradiotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, and hypothyroidism. (6.1)
- KEYTRUDA in combination with chemotherapy and bevacizumab: peripheral neuropathy, alopecia, anemia, fatigue/asthenia, nausea, neutropenia, diarrhea, hypertension, thrombocytopenia, constipation, arthralgia, vomiting, urinary tract infection, rash, leukopenia, hypothyroidism, and decreased appetite. (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: hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal disorders, nausea, decreased appetite, vomiting, stomatitis, weight loss, abdominal pain, urinary tract infection, proteinuria, constipation, headache, hemorrhagic events, palmar-plantar erythrodysesthesia, dysphonia, rash, hepatotoxicity, and acute kidney injury. (6.1)
- KEYTRUDA in combination with enfortumab vedotin: rash, peripheral neuropathy, fatigue, pruritus, diarrhea, alopecia, weight loss, decreased appetite, dry eye, nausea, constipation, dysgeusia, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

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

KEYTRUDA is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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.

KEYTRUDA is indicated for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYTRUDA, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC.

1.3 Malignant Pleural Mesothelioma

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

1.4 Head and Neck Squamous Cell Cancer

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

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

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

1.5 Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).

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

1.6 Primary Mediastinal Large B-Cell Lymphoma

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

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

1.7 Urothelial Cancer

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma:

- who are not eligible for any platinum-containing chemotherapy, or
- who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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

1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options *[see Dosage and Administration (2.1)]*.

1.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

1.10 Gastric Cancer

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.

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

1.11 Esophageal Cancer

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

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

1.12 Cervical Cancer

KEYTRUDA, in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer.

KEYTRUDA, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (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 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)]*.

1.13 Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen.

1.14 Biliary Tract Cancer

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

1.15 Merkel Cell Carcinoma

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

1.16 Renal Cell Carcinoma

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

KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of adult patients with advanced RCC.

KEYTRUDA is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions *[see Clinical Studies (14.16)]*.

1.17 Endometrial Carcinoma

KEYTRUDA, in combination with carboplatin and paclitaxel, followed by KEYTRUDA as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not MSI-H as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation *[see Dosage and Administration (2.1)]*.

KEYTRUDA, as a single agent, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation *[see Dosage and Administration (2.1)]*.

1.18 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 (14.18)]*. 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.

1.19 Cutaneous Squamous Cell Carcinoma

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

1.20 Triple-Negative Breast Cancer

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

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

1.21 Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: 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 classical Hodgkin lymphoma and primary mediastinal large B-cell lymphoma in adults *[see Indications and Usage (1.5, 1.6), 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), Clinical Studies (14.21)]*. Continued approval for this dosage may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Information on FDA-approved tests for patient selection is available at: http://www.fda.gov/CcompanionDiagnostics.

Patient Selection for Single-Agent Treatment

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

- Stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.2)]*.
- metastatic NSCLC *[see Clinical Studies (14.2)]*.
- first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.4)]*.
- previously treated recurrent locally advanced or metastatic esophageal cancer *[see Clinical Studies (14.11)]*.
- recurrent or metastatic cervical cancer with disease progression on or after chemotherapy *[see Clinical Studies (14.12)]*.

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

For the TMB-H indication, select patients for treatment with KEYTRUDA as a single agent based on TMB-H status in tumor specimens *[see Clinical Studies (14.18)]*.

Because subclonal dMMR mutations and microsatellite instability may arise in high-grade gliomas during temozolomide therapy, it is recommended to test for TMB-H, MSI-H, and dMMR in the primary tumor specimens obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

Additional Patient Selection Information for MSI-H or dMMR in Patients with non-CRC Solid Tumors

Due to discordance between local tests and FDA-approved tests, confirmation of MSI-H or dMMR status is recommended by an FDA-approved test in patients with MSI-H or dMMR solid tumors, if feasible. If unable to perform confirmatory MSI-H/dMMR testing, the presence of TMB ≥10 mut/Mb, as determined by an FDA-approved test, may be used to select patients for treatment *[see Clinical Studies (14.8)]*.

Patient Selection for Combination Therapy

For use of KEYTRUDA in combination with chemotherapy and trastuzumab, select patients based on the presence of positive PD-L1 expression (CPS ≥1) in locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma *[see Clinical Studies (14.10)].*

For use of KEYTRUDA in combination with chemotherapy, with or without bevacizumab, select patients based on the presence of positive PD-L1 expression in persistent, recurrent, or metastatic cervical cancer *[see Clinical Studies (14.12)].*

For the pMMR/not MSI-H advanced endometrial carcinoma indication, select patients for treatment with KEYTRUDA in combination with lenvatinib based on MMR or MSI status in tumor specimens *[see Clinical Studies (14.17)]*.

For use of KEYTRUDA in combination with chemotherapy, select patients based on the presence of positive PD-L1 expression in locally recurrent unresectable or metastatic TNBC *[see Clinical Studies (14.20)]*.

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, NSCLC, or RCC	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, MSI-H or dMMR Endometrial Carcinoma, 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 or dMMR 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
Pediatric patients (12 years and older) for adjuvant treatment of melanoma	2 mg/kg every 3 weeks (up to a maximum of 200 mg)*	Until disease recurrence, unacceptable toxicity, or up to 12 months
Combination Therapy†		
Adult patients with resectable NSCLC	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemotherapy when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as a single agent after surgery for 39 weeks or until disease recurrence or unacceptable toxicity

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
Adult patients with NSCLC, MPM, HNSCC, HER2-negative Gastric Cancer, Esophageal Cancer, or BTC	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 locally advanced or metastatic urothelial cancer	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA after enfortumab vedotin when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with HER2-positive 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 Cervical Cancer	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemoradiotherapy or prior to chemotherapy with or without bevacizumab when given on the same day.	Until disease progression, unacceptable toxicity, or for KEYTRUDA, 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‡ or 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 Endometrial Carcinoma	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to carboplatin and paclitaxel when given on the same day. or 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 high-risk early-stage TNBC	200 mg every 3 weeks* or 400 mg every 6 weeks* Administer KEYTRUDA prior to chemotherapy when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 24 weeks (8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as a single agent for up to 27 weeks (9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks) or until disease recurrence or unacceptable toxicity§
Adult patients with locally recurrent unresectable or metastatic TNBC	200 mg every 3 weeks* or 400 mg every 6 weeks*	Until disease progression, unacceptable toxicity, or up to 24 months

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
	Administer KEYTRUDA prior to chemotherapy when given on the same day.	

* 30-minute intravenous infusion
† Refer to the Prescribing Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.
‡ When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.
§ Patients who experience disease progression or unacceptable toxicity related to KEYTRUDA with neoadjuvant treatment in combination with chemotherapy should not receive adjuvant single agent KEYTRUDA.

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

Adverse Reaction	Severity*	Dosage Modification
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold†
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
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 KEYTRUDA in Combination with Axitinib

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

Recommended Dose Modifications for Adverse Reactions for KEYTRUDA in Combination with Lenvatinib

When administering KEYTRUDA in combination with lenvatinib, modify the dosage of one or both drugs. Withhold or discontinue KEYTRUDA as shown in Table 2. Refer to lenvatinib prescribing information for additional dose modification 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. For patients with TNBC treated with KEYTRUDA in the neoadjuvant setting, monitor blood cortisol at baseline, prior to surgery, and as clinically indicated. 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.

In a clinical study enrolling 580 adult patients with resected NSCLC (KEYNOTE-091) who received KEYTRUDA as a single agent for adjuvant treatment, pneumonitis occurred in 41 (7%) patients, including fatal (0.2%), Grade 4 (0.3%), and Grade 3 (1%) adverse reactions. Patients received high-dose corticosteroids for a median duration of 10 days (range: 1 day to 2.3 months). Pneumonitis led to discontinuation of KEYTRUDA in 26 (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 63% discontinued KEYTRUDA, and 71% 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.

The incidence of new or worsening hyperthyroidism was higher in 580 patients with resected NSCLC, occurring in 11% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.2%) hyperthyroidism.

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.

The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC, occurring in 22% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) 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, other transplant (including corneal graft) 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 randomized, placebo-controlled trial (KEYNOTE-091), which enrolled 580 patients with resected NSCLC, 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 Stage IIB or IIC Melanoma

Among the 969 patients with Stage IIB or IIC melanoma enrolled in KEYNOTE-716 *[see Clinical Studies (14.1)]* treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 9.9 months (range: 0 to 15.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Adverse reactions occurring in patients with Stage IIB or IIC melanoma were similar to those occurring in 1011 patients with Stage III melanoma from KEYNOTE-054 or the 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Adjuvant Treatment of Stage III 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	25	2.4	15	0.2
Increased AST	22	1.8	14	0.4
Hematology				
Lymphopenia	22	1	15	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: 502 to 505 patients) and placebo (range: 491 to 497 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	65	22	64	25
Neutropenia	50	21	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
Hypophosphatemia	20	4.7	17	4.3
Hematology				
Anemia	43	4.4	79	19
Lymphopenia	30	7	42	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: 585 to 598 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
Hypocalcemia	20	0.9	20	1.8

* 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: 271 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 (32% 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).

Neoadjuvant and Adjuvant Treatment of Resectable NSCLC

The safety of KEYTRUDA in combination with neoadjuvant platinum-containing chemotherapy followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent after surgery was investigated in KEYNOTE-671, a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition *[see Clinical Studies (14.2)].* Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible.

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 10.9 months (range: 1 day to 18.6 months). The study population characteristics were: median age of 64 years (range: 26 to 83), 45% age 65 or older, 7% age 75 or older; 71% male; 61% White, 31% Asian, 2% Black, 4% race not reported; 9% Hispanic or Latino.

Adverse reactions occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum containing chemotherapy, given as neoadjuvant treatment and continued as single agent adjuvant treatment, were generally similar to those occurring in patients in other clinical trials across tumor types receiving KEYTRUDA in combination with chemotherapy.

Neoadjuvant Phase of KEYNOTE-671

A total of 396 patients received at least 1 dose of KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment and 399 patients received at least 1 dose of placebo in combination with platinum-containing chemotherapy as neoadjuvant treatment.

Serious adverse reactions occurred in 34% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥2%) serious adverse reactions were pneumonia (4.8%), venous thromboembolism (3.3%), and anemia (2%). Fatal adverse reactions occurred in 1.3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated lung disease (0.3%).

Permanent discontinuation of any study drug due to an adverse reaction occurred in 18% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of any study drug were acute kidney injury (1.8%), interstitial lung disease (1.8%), anemia (1.5%), neutropenia (1.5%), and pneumonia (1.3%).

Of the 396 KEYTRUDA-treated patients and 399 placebo-treated patients who received neoadjuvant treatment, 6% (n=25) and 4.3% (n=17), respectively, did not receive surgery due to adverse reactions. The most frequent (≥1%) adverse reactions that led to cancellation of surgery in the KEYTRUDA arm was interstitial lung disease (1%).

Of the 325 KEYTRUDA-treated patients who received surgery, 3.1% (n=10) experienced delay of surgery (surgery more than 8 weeks from last neoadjuvant treatment if patient received less than 4 cycles of neoadjuvant therapy or more than 20 weeks after first dose of neoadjuvant treatment if patient received 4 cycles of neoadjuvant therapy) due to adverse reactions. Of the 317 placebo-treated patients who received surgery, 2.5% (n=8) experienced delay of surgery due to adverse reactions.

Of the 325 KEYTRUDA-treated patients who received surgery, 7% (n=22) did not receive adjuvant treatment due to adverse reactions. Of the 317 placebo-treated patients who received surgery, 3.2% (n=10) did not receive adjuvant treatment due to adverse reactions.

Adjuvant Phase of KEYNOTE-671

A total of 290 patients in the KEYTRUDA arm and 267 patients in the placebo arm received at least 1 dose of adjuvant treatment.

Of the patients who received single agent KEYTRUDA as adjuvant treatment, 14% experienced serious adverse reactions; the most frequent serious adverse reaction was pneumonia (3.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of adjuvant KEYTRUDA due to an adverse reaction occurred in 12% of patients; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of adjuvant KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), AST increased (1%), and musculoskeletal pain (1%).

Adjuvant Treatment of Resected NSCLC

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-091, a multicenter, randomized (1:1), triple-blind, placebo-controlled trial in patients with completely resected Stage IB (T2a ≥4 cm), II, or IIIA NSCLC; adjuvant chemotherapy up to 4 cycles was optional *[see Clinical Studies (14.2)]*. A total of 1161 patients received KEYTRUDA 200 mg (n=580) or placebo (n=581) every 3 weeks.

Patients were ineligible if they had active autoimmune disease, were on chronic immunosuppressive agents, or had a history of interstitial lung disease or pneumonitis.

The median duration of exposure to KEYTRUDA was 11.7 months (range: 1 day to 18.9 months). Sixty-eight percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months.

The adverse reactions observed in KEYNOTE-091 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (11%), and pneumonitis (7%). Two fatal adverse reactions of myocarditis occurred.

Malignant Pleural Mesothelioma (MPM)

First-line treatment of unresectable advanced or metastatic MPM with pemetrexed and platinum chemotherapy

The safety of KEYTRUDA in combination with pemetrexed and platinum chemotherapy (either carboplatin or cisplatin) was investigated in KEYNOTE-483, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with previously untreated, unresectable advanced or metastatic MPM *[see Clinical Studies (14.3)]*. A total of 473 patients received KEYTRUDA 200 mg, pemetrexed, and platinum every 3 weeks for up to 6 cycles followed by KEYTRUDA (n=241), or pemetrexed and platinum chemotherapy every 3 weeks for up to 6 cycles (n=232). Patients with autoimmune disease that required systemic therapy within 3 years of treatment or a medical condition that required immunosuppression were ineligible.

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 6.9 months (range: 1 day to 25.2 months). Sixty-one percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months.

Adverse reactions occurring in patients with MPM were generally similar to those in other patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy.

HNSCC

First-line treatment of metastatic or unresectable, recurrent HNSCC

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

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

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

KEYTRUDA was discontinued for adverse reactions in 16% of patients in the combination arm. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). Adverse reactions leading to the interruption of

KEYTRUDA occurred in 45% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (14%), thrombocytopenia (10%), anemia (6%), pneumonia (4.7%), and febrile neutropenia (2.9%).

Tables 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-048.

Table 16: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-048

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

* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

‡ Includes diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis

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

¶ Includes cough, productive cough

Includes dyspnea, exertional dyspnea

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

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

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

Table 17: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-048

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		KEYTRUDA 200 mg every 3 weeks Platinum FU		Cetuximab Platinum FU	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology						
Lymphopenia	54	25	70	35	75	46
Anemia	52	7	89	29	79	20
Thrombocytopenia	12	3.8	73	18	76	18
Neutropenia	8	1.4	68	37	73	43
Chemistry						
Hyperglycemia	47	3.8	54	6	65	4.7
Hyponatremia	46	18	55	20	59	20
Hypoalbuminemia	44	3.5	46	3.9	49	1.1
Increased AST	28	3.1	25	1.9	37	3.6
Increased ALT	25	2.1	22	1.5	38	1.8
Increased alkaline phosphatase	25	2.1	26	1.1	33	1.1
Hypercalcemia	22	4.5	16	4.2	13	2.5
Hypocalcemia	22	1.0	32	3.8	58	6
Hyperkalemia	21	2.8	28	4.2	29	4.6
Hypophosphatemia	20	5	34	12	49	20
Hypokalemia	19	5	33	12	47	15
Increased creatinine	17	1.0	36	2.3	27	2.1
Hypomagnesemia	15	0.4	40	1.7	76	9

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/chemotherapy (range: 240 to 267 patients), KEYTRUDA (range: 245 to 292 patients), cetuximab/chemotherapy (range: 249 to 282 patients).

† Graded per NCI CTCAE v4.0

Previously treated recurrent or metastatic HNSCC

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

The study population characteristics were: median age of 60 years (range: 20 to 84), 35% age 65 or older; 83% male; and 77% White, 15% Asian, and 5% Black. Sixty-one percent of patients had two or more lines of therapy in the recurrent or metastatic setting, and 95% had prior radiation therapy. Baseline ECOG PS was 0 (30%) or 1 (70%) and 86% had M1 disease.

KEYTRUDA was discontinued due to adverse reactions in 17% of patients. Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); therefore, summary safety results are provided in a pooled analysis. The most common adverse reactions (occurring in ≥20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism *[see Warnings and Precautions (5.1)]*.

Relapsed or Refractory cHL

KEYNOTE-204

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

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

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

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

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

Table 18 summarizes adverse reactions in KEYNOTE-204.

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

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

* Graded per NCI CTCAE v4.0
† Adverse reactions in BV arm were Grade 3 only.
‡ Includes acute sinusitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, upper respiratory tract infection, viral upper respiratory tract infection
§ Includes arthralgia, back pain, bone pain, musculoskeletal discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity
¶ Includes diarrhea, gastroenteritis, colitis, enterocolitis
# Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
ᵇ Includes fatigue, asthenia
β Includes dermatitis acneiform, dermatitis atopic, dermatitis allergic, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, eczema, rash, rash erythematous, rash follicular, rash maculo-papular, rash papular, rash pruritic, toxic skin eruption
à Includes cough, productive cough
è Includes pneumonitis, interstitial lung disease
ð Includes dyspnea, dyspnea exertional, wheezing
ø Includes dysesthesia, hypoesthesia, 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	45	4.1	36	2.0
Increased AST	38	4.7	38	2.0
Increased ALT	31	5	43	2.6
Hypophosphatemia	31	4.9	17	2.8
Increased creatinine	26	3.4	13	2.6
Hypomagnesemia	23	0	13	0
Hyponatremia	24	4.1	20	3.3
Hypocalcemia	21	2.0	15	0
Increased alkaline phosphatase	19	2.1	21	2.0
Hypoalbuminemia	16	0.7	18	0.7
Hyperbilirubinemia	15	1.4	8	0.7
Hematology				
Lymphopenia	34	8	32	13
Thrombocytopenia	32	9	24	4.0
Neutropenia	27	8	42	16
Anemia	22	4.1	32	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: 143 to 148 patients) and BV (range: 145 to 152 patients); hypomagnesemia: KEYTRUDA n=52 and BV n=47.

† Graded per NCI CTCAE v4.0

KEYNOTE-087

Among the 210 patients with cHL who received KEYTRUDA in KEYNOTE-087 *[see Clinical Studies (14.5)]*, the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). Serious adverse reactions occurred in 16% of patients who received KEYTRUDA. Serious adverse reactions that occurred in ≥1% of patients included pneumonia, pneumonitis, pyrexia, dyspnea, graft versus host disease (GVHD) and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

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

Table 20: Adverse Reactions (≥10%) in Patients with cHL who Received KEYTRUDA in KEYNOTE-087

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=210	
	All Grades* (%)	Grade 3 (%)
General		
Fatigue†	26	1.0
Pyrexia	24	1.0
Respiratory, Thoracic and Mediastinal		
Cough‡	24	0.5
Dyspnea§	11	1.0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain¶	21	1.0
Arthralgia	10	0.5
Gastrointestinal		
Diarrhea#	20	1.4
Vomiting	15	0
Nausea	13	0
Skin and Subcutaneous Tissue		
Rash Þ	20	0.5
Pruritus	11	0
Endocrine		
Hypothyroidism	14	0.5
Infections		
Upper respiratory tract infection	13	0
Nervous System		
Headache	11	0.5
Peripheral neuropathyβ	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, seborrheic 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‡	35	2.4
Increased alkaline phosphatase	17	0
Increased creatinine	15	0.5
Hematology		
Anemia	30	6
Thrombocytopenia	27	4.3
Neutropenia	25	7

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

† Graded per NCI CTCAE v4.0

‡ Includes elevation of AST or ALT

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

PMBCL

Among the 53 patients with PMBCL who received KEYTRUDA in KEYNOTE-170 *[see Clinical Studies (14.6)],* the median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 22.8 months). Serious adverse reactions occurred in 26% of patients. Serious adverse reactions that occurred in >2% of patients included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment. Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 8% of patients and dosage interruption due to an adverse reaction occurred in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Tables 22 and 23 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-170.

Table 22: Adverse Reactions (≥10%) in Patients with PMBCL who Received KEYTRUDA in KEYNOTE-170

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

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

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

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

Laboratory Abnormality*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Hematology		
Anemia	23	0
Leukopenia	47	12
Lymphopenia	27	10
Neutropenia	39	15
Chemistry		
Hyperglycemia	33	2.2
Hypophosphatemia	24	11
Hypertransaminasemia‡	24	4.4
Hypoglycemia	20	0
Increased creatinine	16	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 (range: 41 to 45 patients)
† Graded per NCI CTCAE v4.0
‡ Includes elevation of AST or ALT

Urothelial Cancer

Patients with urothelial cancer in combination with enfortumab vedotin

The safety of KEYTRUDA in combination with enfortumab vedotin was investigated in KEYNOTE-A39 in patients with locally advanced or metastatic urothelial cancer *[see Clinical Studies (14.7)].* A total of 440 patients received KEYTRUDA 200 mg on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle compared to 433 patients who received gemcitabine on Days 1 and 8 and investigator's choice of cisplatin or carboplatin on Day 1 of each 21-day cycle. Among patients who received KEYTRUDA and enfortumab vedotin, the median duration of exposure to KEYTRUDA was 8.5 months (range: 9 days to 28.5 months).

Fatal adverse reactions occurred in 3.9% of patients treated with KEYTRUDA in combination with enfortumab vedotin including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with enfortumab vedotin. Serious adverse reactions in ≥2% of patients receiving KEYTRUDA in combination with enfortumab vedotin were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%).

Permanent discontinuation of KEYTRUDA occurred in 27% of patients. The most common adverse reactions (≥2%) resulting in permanent discontinuation of KEYTRUDA were pneumonitis/ILD (4.8%) and rash (3.4%).

Dose interruptions of KEYTRUDA occurred in 61% of patients. The most common adverse reactions (≥2%) resulting in interruption of KEYTRUDA were rash (17%), peripheral neuropathy (7%), COVID-19 (5%), diarrhea (4.3%), pneumonitis/ILD (3.6%), neutropenia (3.4%), fatigue (3%), alanine aminotransferase increased (2.7%), hyperglycemia (2.5%), pneumonia (2%), and pruritus (2%).

Tables 24 and 25 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with enfortumab vedotin in KEYNOTE-A39.

Table 24: Adverse Reactions ≥20% (All Grades) in Patients Treated with KEYTRUDA in Combination with Enfortumab Vedotin in KEYNOTE-A39

	KEYTRUDA in combination with Enfortumab Vedotin n=440		Chemotherapy n=433	
Adverse Reaction	**All Grades* %**	**Grades 3-4 %**	**All Grades* %**	**Grades 3-4 %**
Skin and subcutaneous tissue disorders				
Rash†	68	15	15	0
Pruritus	41	1.1	7	0
Alopecia	35	0.5	8	0.2
General disorders and administration site conditions				
Fatigue†	51	6	57	7
Nervous system disorders				
Peripheral neuropathy†	67	8	14	0
Dysgeusia	21	0	9	0
Metabolism and nutrition disorders				
Decreased appetite	33	1.8	26	1.8
Gastrointestinal disorders				
Diarrhea	38	4.5	16	1.4
Nausea	26	1.6	41	2.8
Constipation	26	0	34	0.7
Investigations				
Weight loss	33	3.6	9	0.2
Eye disorders				
Dry eye†	24	0	2.1	0
Infections and infestations				
Urinary tract infection	21	5	19	8

* Graded per NCI CTCAE v4.03
† Includes multiple terms

Clinically relevant adverse reactions (<20%) include pyrexia (18%), dry skin (17%), vomiting (12%), pneumonitis/ILD (10%), hypothyroidism (10%), blurred vision (6%), infusion site extravasation (2%), and myositis (0.5%).

Table 25: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-A39

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Enfortumab Vedotin		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Increased aspartate aminotransferase	75	4.6	39	3.3
Increased creatinine	71	3.2	68	2.6
Hyperglycemia	66	14	54	4.7
Increased alanine aminotransferase	59	5	49	3.3
Hyponatremia	46	13	47	13
Hypophosphatemia	44	9	36	9
Hypoalbuminemia	39	1.8	35	0.5
Hypokalemia	26	5	16	3.1
Hyperkalemia	24	1.4	36	4.0
Hypercalcemia	21	1.2	14	0.2
Hematology				
Lymphopenia	58	15	59	17
Anemia	53	7	89	33
Neutropenia	30	9	80	50

* 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: 407 to 439 patients)

† Graded per NCI CTCAE v4.03

Cisplatin-ineligible patients with urothelial cancer in combination with enfortumab vedotin

The safety of KEYTRUDA in combination with enfortumab vedotin was investigated in KEYNOTE-869 in patients with locally advanced or metastatic urothelial cancer and who are not eligible for cisplatin-based chemotherapy *[see Clinical Studies (14.7)]*. A total of 121 patients received KEYTRUDA 200 mg on Day 1, and enfortumab vedotin 1.25 mg/kg on days 1 and 8 of each 21-day cycle. The median duration of exposure to KEYTRUDA was 6.9 months (range 1 day to 29.6 months).

Fatal adverse reactions occurred in 5% of patients treated with KEYTRUDA in combination with enfortumab vedotin, including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis (0.8%).

Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA and enfortumab vedotin. Serious adverse reactions in ≥2% of patients receiving KEYTRUDA in combination with enfortumab vedotin were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), hematuria (3.3%), pneumonia (3.3%), pneumonitis (3.3%), sepsis (3.3%), anemia (2.5%), diarrhea (2.5%), hypotension (2.5%), myasthenia gravis (2.5%), myositis (2.5%), and urinary retention (2.5%).

Permanent discontinuation of KEYTRUDA occurred in 32% of patients. The most common adverse reactions (≥2%) resulting in permanent discontinuation of KEYTRUDA were pneumonitis (5%), peripheral neuropathy (5%), rash (3.3%), and myasthenia gravis (2.5%).

Dose interruptions of KEYTRUDA occurred in 69% of patients. The most common adverse reactions (≥2%) resulting in interruption of KEYTRUDA were peripheral neuropathy (22%), rash (17%), neutropenia (7%), fatigue (6%), diarrhea (5%), lipase increased (5%), acute kidney injury (3.3%), ALT increased (2.5%), and COVID-19 (2.5%).

Tables 26 and 27 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with enfortumab vedotin in KEYNOTE-869.

Table 26: Adverse Reactions Occurring in ≥20% of Patients Treated with KEYTRUDA in Combination with Enfortumab Vedotin in KEYNOTE-869

Adverse Reaction	KEYTRUDA in combination with Enfortumab Vedotin n=121	
	All Grades* %	Grade 3-4 %
Skin and subcutaneous tissue disorders		
Rash†	71	21
Alopecia	52	0
Pruritus	40	3.3
Dry skin	21	0.8
Nervous system disorders		
Peripheral neuropathy‡	65	3.3
Dysgeusia	35	0
Dizziness	23	0
General disorders and administration site conditions		
Fatigue	60	11
Peripheral edema	26	0
Investigations		
Weight loss	48	5
Gastrointestinal disorders		
Diarrhea	45	7
Nausea	36	0.8
Constipation	27	0
Metabolism and nutrition disorders		
Decreased appetite	38	0.8
Infections and infestations		
Urinary tract infection	30	12
Eye disorders		
Dry eye	25	0
Musculoskeletal and connective tissue disorders		
Arthralgia	23	1.7

* Graded per NCI CTCAE v4.03

† Includes: blister, conjunctivitis, dermatitis, dermatitis bullous, dermatitis exfoliative generalized, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, pemphigoid, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin exfoliation, and stomatitis

‡ Includes: dysesthesia, hypoesthesia, muscular weakness, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and gait disturbance

Clinically relevant adverse reactions (<20%) include vomiting (19.8%), fever (18%), hypothyroidism (11%), pneumonitis/ILD (10%), myositis (3.3%), myasthenia gravis (2.5%), and infusion site extravasation (0.8%).

Table 27: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-869

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Enfortumab Vedotin	
	All Grades† %	Grades 3-4 %
Chemistry		
Hyperglycemia	74	13
Increased aspartate aminotransferase	73	9
Increased creatinine	69	3.3
Hyponatremia	60	19
Increased alanine aminotransferase	60	7
Increased lipase	59	32
Hypoalbuminemia	59	4.2
Hypophosphatemia	51	15
Hypokalemia	35	8
Increased potassium	27	1.7
Increased calcium	27	4.2
Hematology		
Anemia	69	15
Lymphopenia	64	17
Neutropenia	32	12

* 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: 114 to 121 patients)

† Graded per NCI CTCAE v4.03

Platinum-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 had one or more comorbidities. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible *[see Clinical Studies (14.7)]*. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression.

The median duration of exposure to KEYTRUDA was 2.8 months (range: 1 day to 15.8 months).

KEYTRUDA was discontinued due to adverse reactions in 11% of patients. Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with KEYTRUDA experienced sepsis which led to death, and three patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

Immune-related adverse reactions that required systemic glucocorticoids occurred in 8% of patients, use of hormonal supplementation due to an immune-related adverse reaction occurred in 8% of patients, and 5% of patients required at least one steroid dose ≥40 mg oral prednisone equivalent.

Table 28 summarizes adverse reactions in patients on KEYTRUDA in KEYNOTE-052.

Table 28: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=370	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	38	6
Pyrexia	11	0.5
Weight loss	10	0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain‡	24	4.9
Arthralgia	10	1.1
Metabolism and Nutrition		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
Gastrointestinal		
Constipation	21	1.1
Diarrhea§	20	2.4
Nausea	18	1.1
Abdominal pain¶	18	2.7
Elevated LFTs#	13	3.5
Vomiting	12	0
Skin and Subcutaneous Tissue		
Rashᵖ	21	0.5
Pruritus	19	0.3
Edema peripheralᵝ	14	1.1
Infections		
Urinary tract infection	19	9
Blood and Lymphatic System		
Anemia	17	7
Respiratory, Thoracic, and Mediastinal		
Cough	14	0
Dyspnea	11	0.5
Renal and Urinary		
Increased blood creatinine	11	1.1
Hematuria	13	3.0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
§ Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements
¶ Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper
# Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, increased transaminases, hyperbilirubinemia, increased blood bilirubin, increased alanine aminotransferase, increased aspartate aminotransferase, increased hepatic enzymes, increased liver function tests
ᵖ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneiform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized
ᵝ Includes edema peripheral, peripheral swelling

Previously Treated Urothelial Carcinoma

The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in KEYNOTE-045. KEYNOTE-045 was a multicenter, open-label, randomized (1:1), active-controlled trial in which 266 patients received KEYTRUDA 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) *[see Clinical Studies (14.7)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible.

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

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis. Tables 29 and 30 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-045.

Table 29: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=266		Chemotherapy* n=255	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
General				
Fatigue‡	38	4.5	56	11
Pyrexia	14	0.8	13	1.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain§	32	3.0	27	2.0
Skin and Subcutaneous Tissue				
Pruritus	23	0	6	0.4
Rash¶	20	0.4	13	0.4
Gastrointestinal				
Nausea	21	1.1	29	1.6
Constipation	19	1.1	32	3.1
Diarrhea#	18	2.3	19	1.6
Vomiting	15	0.4	13	0.4
Abdominal pain	13	1.1	13	2.7
Metabolism and Nutrition				
Decreased appetite	21	3.8	21	1.2
Infections				
Urinary tract infection	15	4.9	14	4.3
Respiratory, Thoracic and Mediastinal				
Cough‡	15	0.4	9	0
Dyspnea§	14	1.9	12	1.2
Renal and Urinary				
Hematuria à	12	2.3	8	1.6

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

Table 30: 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	55	26
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 31 and 32 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-057.

Table 31: 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▷	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
▷ Includes cough, productive cough

Table 32: 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	7
Increased ALT	25	2.7
Hyponatremia	24	7
Hypophosphatemia	24	6
Hypoalbuminemia	24	1.4
Hyperkalemia	23	1.4
Hypocalcemia	22	0.7
Increased AST	20	2.7
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 Cancer

The safety of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancer enrolled in KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 *[see Clinical Studies (14.8)].* The median duration of exposure to KEYTRUDA was 6.2 months (range: 1 day to 53.5 months). Adverse reactions occurring in patients with MSI-H or dMMR cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

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

Gastric Cancer

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

The safety of KEYTRUDA was evaluated in 696 patients with HER2-positive gastric or GEJ cancer enrolled in KEYNOTE-811, which included 350 patients treated with KEYTRUDA 200 mg, trastuzumab, and CAPOX (n=297) or FP (n=53) every 3 weeks, compared to 346 patients treated with placebo, trastuzumab, and CAPOX (n=298) or FP (n=48) every 3 weeks *[see Clinical Studies (14.10)]*.

The median duration of exposure to KEYTRUDA was 9.2 months (range: 1 day to 33.6 months).

Fatal adverse reactions occurred in 3 patients who received KEYTRUDA in combination with trastuzumab and CAPOX or FP and included pneumonitis in 2 patients and hepatitis in 1 patient.

KEYTRUDA was discontinued due to adverse reactions in 13% of patients. Adverse reactions resulting in permanent discontinuation of KEYTRUDA in ≥1% of patients were pneumonitis (2.0%) and pneumonia (1.1%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 71% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (21%), thrombocytopenia (13%), diarrhea (7%), pneumonia (5%), anemia (4.9%), COVID-19 (3.1%), hypokalemia (3.1%), fatigue/asthenia (4.9%), decreased appetite (4%), increased AST (3.7%), increased blood bilirubin (4.6%), increased ALT (2.9%), vomiting (2.6%), pneumonitis (2.3%), pyrexia (2.3%), increased blood creatinine (2%), and colitis (2%).

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 47%), rash (35% vs. 28%), hypothyroidism (11% vs. 5%), and pneumonia (11% vs. 5%). 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 decreased leukocytes (60% vs. 54%), decreased calcium (56% vs. 46%), decreased lymphocytes (59% vs. 51%), decreased potassium (41% vs. 36%), increased bilirubin (33% vs. 25%), increased creatinine (28% vs 18%), and decreased glucose (17% vs. 11%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Negative Gastric or Gastroesophageal Junction Adenocarcinoma

The safety of KEYTRUDA was evaluated in 1572 patients with HER2-negative gastric or GEJ cancer enrolled in KEYNOTE-859, which included 785 patients treated with KEYTRUDA 200 mg and FP (n=106) or CAPOX (n=674) every 3 weeks, compared to 787 patients who received placebo and FP (n=107) or CAPOX (n=679) every 3 weeks *[see Clinical Studies (14.10)]*.

The median duration of exposure to KEYTRUDA was 6.2 months (range: 1 day to 33.7 months).

Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. Serious adverse reactions in >2% of patients included pneumonia (4.1%), diarrhea (3.9%), hemorrhage (3.9%), and vomiting (2.4%). Fatal adverse reactions occurred in 8% of patients who received KEYTRUDA, including infection (2.3%) and thromboembolism (1.3%).

Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 15% of patients. Adverse reaction resulting in permanent discontinuation of KEYTRUDA in ≥1% were infections (1.8%) and diarrhea (1.0%).

Dosage interruptions of KEYTRUDA due to an adverse reaction occurred in 65% of patients. Adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (21%), thrombocytopenia (13%), diarrhea (5.5%), fatigue (4.8%), infection (4.8%), anemia (4.5%), increased AST (4.3%), increased ALT (3.8%), increased blood bilirubin (3.3%), white blood cell count decreased (2.2%), nausea (2%), palmar-plantar erythrodysesthesia syndrome (2%), and vomiting (2%).

Tables 33 and 34 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-859.

Table 33: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-859

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=785		Placebo and FP or CAPOX n=787	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Nervous System				
Peripheral neuropathy†	47	5	48	6
Gastrointestinal				
Nausea	46	3.7	46	4.4
Diarrhea	36	6	32	5
Vomiting	34	5	27	5
Abdominal Pain‡	26	2.8	24	2.9
Constipation	22	0.5	21	0.8
General				
Fatigue§	40	8	39	9
Metabolism and Nutrition				
Decreased appetite	29	3.3	29	2.5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	25	3.1	22	1.8
Investigations				
Weight loss	20	2.8	19	2.7

* Graded per NCI CTCAE v4.03

† Includes dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy

‡ Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal tenderness, abdominal pain upper, epigastric discomfort, gastrointestinal pain

§ Includes asthenia, fatigue

Table 34: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-859

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX		Placebo and FP or CAPOX	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Hematology				
Anemia	65	15	69	13
Thrombocytopenia	64	12	62	10
Neutropenia	63	25	58	20
Leukopenia	59	7	56	6
Lymphopenia	57	20	51	16
Chemistry				
Increased AST	57	4.7	48	3.6
Hypoalbuminemia	55	4.1	52	2.9
Hyperglycemia	53	6	52	4.6
Hypocalcemia	49	3.6	45	3.3
Increased alkaline phosphatase	48	6	41	5
Hyponatremia	40	13	40	12
Increased ALT	40	4.2	29	2.9
Hypokalemia	35	10	27	9
Bilirubin increased	32	5	30	5
Hypophosphatemia	30	10	27	8
Hypomagnesemia	29	0.3	22	0.7
Increased creatinine	21	3.5	18	1.7
Hyperkalemia	20	3.7	18	2.9
Increased INR	20	1.4	22	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/FP or CAPOX (range: 210 to 766 patients) and placebo/FP or CAPOX (range: 190 to 762 patients)

† Graded per NCI CTCAE v4.03

Esophageal Cancer

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

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

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

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

Tables 35 and 36 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-590.

Table 35: 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 36: 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	84	21	87	25
Neutropenia	77	44	73	41
Leukopenia	73	21	73	17
Lymphopenia	57	23	53	18
Thrombocytopenia	43	5	46	8
Chemistry				
Hyperglycemia	56	7	55	6
Hyponatremia	53	19	53	19
Hypoalbuminemia	53	2.8	52	2.3
Increased creatinine	45	2.5	42	2.5
Hypocalcemia	44	3.9	37	2
Hypophosphatemia	37	9	31	10
Hypokalemia	30	12	34	15
Increased alkaline phosphatase	29	1.9	29	1.7
Hyperkalemia	28	3.6	28	2.5
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: 353 to 365 patients) and placebo/cisplatin/FU (range: 347 to 359 patients)
† Graded per NCI CTCAE v4.03

Previously Treated Recurrent Locally Advanced or Metastatic Esophageal Cancer

Among the 314 patients with esophageal cancer enrolled in KEYNOTE-181 *[see Clinical Studies (14.11)]* treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 24.4 months). Patients with autoimmune disease or a medical condition that required

immunosuppression were ineligible. Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Cervical Cancer

FIGO 2014 Stage III-IVA Cervical Cancer with Chemoradiotherapy

The safety of KEYTRUDA in combination with CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]) was investigated in KEYNOTE-A18, a placebo-controlled, randomized (1:1), multicenter, double-blind trial including 594 patients with FIGO 2014 Stage III-IVA cervical cancer *[see Clinical Studies (14.12)]*. Two hundred ninety-two patients received KEYTRUDA in combination with chemoradiotherapy and 302 patients received placebo in combination with chemoradiotherapy.

The median duration of exposure to KEYTRUDA was 12.1 months (range: 1 day to 27 months).

Fatal adverse reactions occurred in 1.4% of patients receiving KEYTRUDA in combination with chemoradiotherapy, including 1 case each (0.3%) of large intestinal perforation, urosepsis, sepsis, and vaginal hemorrhage.

Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with chemoradiotherapy. Serious adverse reactions occurring in ≥1% of patients included urinary tract infection (2.7%), urosepsis (1.4%), and sepsis (1%).

KEYTRUDA was discontinued for adverse reactions in 7% of patients. The most common adverse reaction (≥1%) resulting in permanent discontinuation was diarrhea (1%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 43% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were anemia (8%), COVID-19 (6%), SARS-CoV-2 test positive (3.1%), decreased neutrophil count (2.7%), diarrhea (2.7%), urinary tract infection (2.7%), and increased ALT (2.4%).

Table 37 and Table 38 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-A18.

Table 37: Adverse Reactions Occurring in ≥10% of Patients with FIGO 2014 Stage III-IVA Cervical Cancer Receiving KEYTRUDA in KEYNOTE-A18

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy n=292		Placebo with chemoradiotherapy n=302	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	56	0	61	2.3
Diarrhea	50	3.8	50	4.3
Vomiting	33	1	34	1.7
Constipation	18	0	18	0.7
Abdominal pain	12	0.7	12	1.7
Infections				
Urinary tract infection†	32	4.1	31	4.6
General				
Fatigue‡	26	1	27	1.3
Pyrexia	12	0.3	13	0
Endocrine				
Hypothyroidism§	20	0.7	5	0
Hyperthyroidism	11	0.3	2.6	0
Metabolism and Nutrition				
Decreased appetite	17	0.7	17	0.3
Investigations				
Weight loss	17	1.4	18	1

Renal and Urinary				
Dysuria	11	0.3	12	0
Skin and Subcutaneous Tissue Disorders				
Rash¶	11	0.7	7	0.3
Reproductive System				
Pelvic pain	10	1	13	1.3

* Graded per NCI CTCAE v5.0
† Includes urinary tract infection, urinary tract infection pseudomonal, pyelonephritis acute, cystitis, Escherichia urinary tract infection
‡ Includes fatigue, asthenia
§ Includes hypothyroidism, autoimmune hypothyroidism
¶ Includes erythema multiforme, dermatitis, drug eruption, eczema, rash, skin exfoliation, dermatitis bullous, rash maculo-papular, lichen planus, dyshidrotic eczema, dermatitis acneiform

Table 38: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with FIGO 2014 Stage III-IVA Cervical Cancer Receiving KEYTRUDA in KEYNOTE-A18

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy		Placebo with chemoradiotherapy	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	99	96	99	92
Leukopenia	96	46	94	49
Anemia	88	31	81	25
Neutropenia	75	32	74	33
Thrombocytopenia	65	8	61	6
Chemistry				
Hypomagnesemia	59	4.2	63	3.4
Hyponatremia	54	3.8	47	4
Increased AST	45	1	39	1.7
Increased ALT	44	2.1	44	1
Hypocalcemia	43	4.8	40	4.3
Hypokalemia	42	14	38	10
Increased creatinine	41	6	43	6
Hypoalbuminemia	37	0.7	35	1.7
Increased alkaline phosphatase	34	0.3	33	0.3

* 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: KEYTRUDA + chemoradiotherapy (range: 286 to 291 patients) and placebo + chemoradiotherapy (range: 298 to 300 patients)
† Graded per NCI CTCAE v5.0

Persistent, Recurrent, or Metastatic Cervical Cancer

The safety of KEYTRUDA in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent *[see Clinical Studies (14.12)]*. A total of 616 patients, regardless of tumor PD-L1 expression, received KEYTRUDA 200 mg and chemotherapy with or without bevacizumab (n=307) every 3 weeks or placebo and chemotherapy with or without bevacizumab (n=309) every 3 weeks.

The median duration of exposure to KEYTRUDA was 9.9 months (range: 1 day to 26 months).

Fatal adverse reactions occurred in 4.6% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab, including 3 cases of hemorrhage, 2 cases of sepsis, 2 cases

due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection.

Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab. Serious adverse reactions in ≥3% of patients included febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), acute kidney injury (3.3%), and sepsis (3.3%).

KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA (≥1%) was colitis (1%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 66% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were thrombocytopenia (15%), neutropenia (14%), anemia (11%), increased ALT (6%), leukopenia (5%), fatigue/asthenia (4.2%), urinary tract infection (3.6%), increased AST (3.3%), pyrexia (3.3%), diarrhea (2.6%), acute kidney injury (2.6%), increased blood creatinine (2.6%), colitis (2.3%), decreased appetite (2%), and cough (2%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=196), the most common (≥20%) adverse reactions were peripheral neuropathy (62%), alopecia (58%), anemia (55%), fatigue/asthenia (53%), nausea (41%), neutropenia (41%), diarrhea (39%), hypertension (35%), thrombocytopenia (35%), constipation (31%), arthralgia (31%), vomiting (30%), urinary tract infection (27%), rash (26%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (21%).

Table 39 and Table 40 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-826.

Table 39: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-826

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and chemotherapy* with or without bevacizumab n=307		Placebo and chemotherapy* with or without bevacizumab n=309	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Nervous System				
Peripheral neuropathy‡	58	4.2	57	6
Skin and Subcutaneous Tissue				
Alopecia	56	0	58	0
Rash§	22	3.6	15	0.3
General				
Fatigue¶	47	7	46	6
Gastrointestinal				
Nausea	40	2	44	1.6
Diarrhea	36	2	30	2.6
Constipation	28	0.3	33	1
Vomiting	26	2.6	27	1.9
Musculoskeletal and Connective Tissue				
Arthralgia	27	0.7	26	1.3
Vascular				
Hypertension	24	9	23	11
Infections				
Urinary tract infection	24	9	26	8

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Graded per NCI CTCAE v4.0
‡ Includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia
§ Includes rash, rash maculo-papular, rash erythematous, rash macular, rash papular, rash pruritic, rash pustular
¶ Includes fatigue, asthenia

Table 40: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-826

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and chemotherapy† with or without bevacizumab n=307		Placebo and chemotherapy† with or without bevacizumab n=309	
	All Grades‡ (%)	Grades 3-4 (%)	All Grades‡ (%)	Grades 3-4 (%)
Hematology				
Anemia	80	35	77	33
Leukopenia	76	27	69	19
Neutropenia	73	43	62	32
Lymphopenia	64	35	59	35
Thrombocytopenia	57	19	53	15
Chemistry				
Hyperglycemia	51	4.7	46	2.3
Hypoalbuminemia	46	1.4	37	5
Hyponatremia	39	14	38	11
Increased ALT	40	7	38	6
Increased AST	40	6	36	3.0
Increased alkaline phosphatase	38	3.4	40	2.3
Hypocalcemia	37	4.1	31	5
Increased creatinine	34	5	32	6
Hypokalemia	29	7	26	7
Hyperkalemia	23	3.7	27	4.7
Hypercalcemia	21	1.0	20	1.3

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA plus chemotherapy (range: 296 to 301 patients) and placebo plus chemotherapy (range: 299 to 302 patients)

† Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

‡ Graded per NCI CTCAE v4.0

Previously Treated Recurrent or Metastatic Cervical Cancer

Among the 98 patients with cervical cancer enrolled in Cohort E of KEYNOTE-158 *[see Clinical Studies (14.12)]*, the median duration of exposure to KEYTRUDA was 2.9 months (range: 1 day to 22.1 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%). Tables 41 and 42 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-158.

Table 41: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=98	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	43	5
Pain‡	22	2.0
Pyrexia	19	1.0
Edema peripheral§	15	2.0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain¶	27	5
Gastrointestinal		
Diarrhea#	23	2.0
Abdominal painÞ	22	3.1
Nausea	19	0
Vomiting	19	1.0
Constipation	14	0
Metabolism and Nutrition		
Decreased appetite	21	0
Vascular		
Hemorrhageß	19	5
Infections		
UTIà	18	6
Infection (except UTI)è	16	4.1
Skin and Subcutaneous Tissue		
Rashð	17	2.0
Endocrine		
Hypothyroidism	11	0
Nervous System		
Headache	11	2.0
Respiratory, Thoracic and Mediastinal		
Dyspnea	10	1.0

* Graded per NCI CTCAE v4.0

† Includes asthenia, fatigue, lethargy, malaise

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

§ Includes edema peripheral, peripheral swelling

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

Includes colitis, diarrhea, gastroenteritis

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

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

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

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

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

Table 42: 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	45	9
Chemistry		
Hypoalbuminemia	44	5
Increased alkaline phosphatase	40	1.3
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 (17% 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 (10% 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

Previously Treated HCC

The safety of KEYTRUDA was investigated in KEYNOTE-394, a multicenter, double-blind, randomized, placebo-controlled trial that enrolled patients with previously treated HCC. Patients were randomized (2:1) and received KEYTRUDA 200 mg (n=299) or placebo (n=153) intravenously every 3 weeks for up to 35 cycles *[see Clinical Studies (14.13)]*.

The median duration of exposure was 3.3 months (range: 1 day to 27.3 months) in the KEYTRUDA arm and 2.2 months (range: 1 day to 15.5 months) in the placebo arm. KEYTRUDA was discontinued due to adverse reactions in 13% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was ascites (2.3%). Adverse reactions leading to interruption of KEYTRUDA occurred in 26% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were increased blood bilirubin (9%), increased AST (5%), and increased ALT (2%).

Tables 43 and 44 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-394.

Table 43: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving KEYTRUDA in KEYNOTE-394

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=299		Placebo n=153	
	All Grades* (%)	Grades 3-5 (%)	All Grades* (%)	Grades 3-5 (%)
General				
Pyrexia	18	0.7	14	0
Skin and Subcutaneous Tissue				
Rash†	18	0.7	7	0
Pruritus	12	0	4	0
Gastrointestinal				
Diarrhea	16	1.7	9	0
Metabolism and Nutrition				
Decreased appetite	15	0.3	9	0
Infections				
Upper respiratory tract infection	11	1.0	7	0.7
Respiratory, Thoracic, and Mediastinal				
Cough	11	0	9	0
Endocrine				
Hypothyroidism	10	0	7	0

* Graded per NCI CTCAE v4.03

† Includes dermatitis, dermatitis allergic, dermatitis bullous, rash, rash erythematous, rash maculo-papular, rash pustular, and blister.

Table 44: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with HCC Receiving KEYTRUDA in KEYNOTE-394

Laboratory Test*	KEYTRUDA		Placebo	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Increased AST	54	14	44	12
Increased bilirubin	47	11	36	7
Increased ALT	47	7	32	4.6
Increased gamma-glutamyl transferase (GGT)	40	20	39	15
Hypoalbuminemia	40	0.7	20	0.7
Increased alkaline phosphatase	39	4.1	34	4
Hyperglycemia	36	3.3	26	1.4
Hyponatremia	36	11	28	5
Hypophosphatemia	30	6	17	4
Hypocalcemia	24	1.4	15	0.7
Hematology				
Lymphopenia	44	11	34	4.6
Anemia	36	7	30	3.3
Decreased platelets	32	4.7	29	2
Leukopenia	30	1.3	21	0.7
Neutropenia	25	4.4	21	2

* 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: 223 to 297 patients) and placebo (range: 144 to 151 patients).

† Graded per NCI CTCAE v4.03

BTC

The safety of KEYTRUDA in combination with gemcitabine and cisplatin, was investigated in KEYNOTE-966, a multicenter, double-blind, randomized, placebo-controlled trial in patients with locally advanced unresectable or metastatic BTC who had not received prior systemic therapy in the advanced disease setting *[see Clinical Studies (14.14)]*. A total of 1063 patients received either KEYTRUDA 200 mg plus gemcitabine and cisplatin chemotherapy (n=529) or placebo plus gemcitabine and cisplatin chemotherapy (n=534) every 3 weeks.

The median duration of exposure to KEYTRUDA was 6 months (range: 1 day to 28 months).

KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA (≥1%) was pneumonitis (1.3%).

Adverse reactions leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were decreased neutrophil count (18%), decreased platelet count (10%), anemia (6%), decreased white blood count (4%), pyrexia (3.8%), fatigue (3.0%), cholangitis (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.3%).

In the KEYTRUDA plus chemotherapy versus placebo plus chemotherapy arms, there was a difference of ≥5% incidence in adverse reactions between patients treated with KEYTRUDA versus placebo for pyrexia (26% vs 20%), rash (21% vs 13%), pruritus (15% vs 10%), and hypothyroidism (9% vs. 2.6%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

There was a difference of ≥5% incidence in laboratory abnormalities between patients treated with KEYTRUDA plus chemotherapy versus placebo plus chemotherapy for decreased lymphocytes (69% vs 61%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

MCC

Among the 105 patients with MCC enrolled in KEYNOTE-017 and KEYNOTE-913 *[see Clinical Studies (14.15)]*, the median duration of exposure to KEYTRUDA was 6.3 months (range 1 day to 28 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 included increased lipase (17%).

RCC

In combination with axitinib in the first-line treatment of advanced RCC (KEYNOTE-426)

The safety of KEYTRUDA in combination with axitinib was investigated in KEYNOTE-426 *[see Clinical Studies (14.16)]*. 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 45 and 46 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 45: 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, seborrheic dermatitis, skin discoloration, skin exfoliation, perineal rash

Table 46: 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	47	9
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 421 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.

In combination with lenvatinib in the first-line treatment of advanced RCC (KEYNOTE-581)

The safety of KEYTRUDA was evaluated in KEYNOTE-581 *[see Clinical Studies (14.16)]*. Patients received KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily (n=352), or lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340). The median duration of exposure to the combination therapy of KEYTRUDA and lenvatinib was 17 months (range: 0.1 to 39).

Fatal adverse reactions occurred in 4.3% of patients treated with KEYTRUDA in combination with lenvatinib, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm, and subarachnoid hemorrhage.

Serious adverse reactions occurred in 51% of patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions in ≥2% of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of either of KEYTRUDA, lenvatinib or both due to an adverse reaction occurred in 37% of patients receiving KEYTRUDA in combination with lenvatinib; 29% KEYTRUDA only, 26% lenvatinib only, and 13% both. The most common adverse reactions (≥2%) resulting in permanent discontinuation of KEYTRUDA, lenvatinib, or the combination were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).

Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse reaction occurred in 78% of patients receiving KEYTRUDA in combination with lenvatinib. KEYTRUDA was interrupted in 55% of

patients and both drugs were interrupted in 39% of patients. The most common adverse reactions (≥3%) resulting in interruption of KEYTRUDA were diarrhea (10%), hepatotoxicity (8%), fatigue (7%), lipase increased (5%), amylase increased (4%), musculoskeletal pain (3%), hypertension (3%), rash (3%), acute kidney injury (3%), and decreased appetite (3%).

Fifteen percent (15%) of patients treated with KEYTRUDA in combination with lenvatinib received an oral prednisone equivalent to ≥40 mg daily for an immune-mediated adverse reaction.

Tables 47 and 48 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in ≥20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

Table 47: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib in KEYNOTE-581

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with Lenvatinib N=352		Sunitinib 50 mg N=340	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue*	63	9	56	8
Gastrointestinal				
Diarrhea†	62	10	50	6
Stomatitis‡	43	2	43	2
Nausea	36	3	33	1
Abdominal pain§	27	2	18	1
Vomiting	26	3	20	1
Constipation	25	1	19	0
Musculoskeletal and Connective Tissue				
Musculoskeletal disorders¶	58	4	41	3
Endocrine				
Hypothyroidism#	57	1	32	0
Vascular				
Hypertensionᵇ	56	29	43	20
Hemorrhagic eventsß	27	5	26	4
Metabolism				
Decreased appetiteª	41	4	31	1
Skin and Subcutaneous Tissue				
Rashᵉ	37	5	17	1
Palmar-plantar erythrodysesthesia syndromeᵟ	29	4	38	4
Investigations				
Weight loss	30	8	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	30	0	4	0
Renal and Urinary				
Proteinuriaᵠ	30	8	13	3
Acute kidney injuryʸ	21	5	16	2
Hepatobiliary				
Hepatotoxicity£	25	9	21	5
Nervous System				
Headache	23	1	16	1

* Includes asthenia, fatigue, lethargy, malaise

† Includes diarrhea, gastroenteritis

‡ Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis

§ Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, upper abdominal pain

¶ Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw

#	Includes hypothyroidism, increased blood thyroid stimulating hormone, secondary hypothyroidism
Þ	Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, labile blood pressure
ß	Includes all hemorrhage terms. Hemorrhage terms that occurred in 1 or more subjects in either treatment group include Anal hemorrhage, aneurysm ruptured, blood blister, blood loss anemia, blood urine present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, contusion, diarrhea hemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye hemorrhage, gastric hemorrhage, gastritis hemorrhagic, gingival bleeding, hemorrhage urinary tract, hemothorax, hematemesis, hematoma, hematochezia, hematuria, hemoptysis, hemorrhoidal hemorrhage, increased tendency to bruise, injection site hematoma, injection site hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, Mallory-Weiss syndrome, melaena, petechiae, rectal hemorrhage, renal hemorrhage, retroperitoneal hemorrhage, small intestinal hemorrhage, splinter hemorrhages, subcutaneous hematoma, subdural hematoma, subarachnoid hemorrhage, thrombotic thrombocytopenic purpura, tumor hemorrhage, traumatic hematoma, upper gastrointestinal hemorrhage
à	Includes decreased appetite, early satiety
è	Includes genital rash, infusion site rash, penile rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular
ð	Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, plantar erythema
ø	Includes hemoglobinuria, nephrotic syndrome, proteinuria
ý	Includes acute kidney injury, azotemia, blood creatinine increased, creatinine renal clearance decreased, hypercreatininemia, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, and nephropathy toxic
£	Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased, gamma-glutamyltransferase increased

Clinically relevant adverse reactions (<20%) that occurred in patients receiving KEYTRUDA with lenvatinib were myocardial infarction (3%) and angina pectoris (1%).

Table 48: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% (All Grades) of Patients Receiving KEYTRUDA with Lenvatinib in KEYNOTE-581

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with Lenvatinib		Sunitinib 50 mg	
	All Grades %†	Grade 3-4 %†	All Grades %†	Grade 3-4 %†
Chemistry				
Hypertriglyceridemia	80	15	71	15
Hypercholesterolemia	64	5	43	1
Increased lipase	61	34	59	28
Increased creatinine	61	5	61	2
Increased amylase	59	17	41	9
Increased AST	58	7	57	3
Hyperglycemia	55	7	48	3
Increased ALT	52	7	49	4
Hyperkalemia	44	9	28	6
Hypoglycemia	44	2	27	1
Hyponatremia	41	12	28	9
Decreased albumin	34	0.3	22	0
Increased alkaline phosphatase	32	4	32	1
Hypocalcemia	30	2	22	1
Hypophosphatemia	29	7	50	8
Hypomagnesemia	25	2	15	3
Increased creatine phosphokinase	24	6	36	5
Hypermagnesemia	23	2	22	3
Hypercalcemia	21	1	11	1
Hematology				
Lymphopenia	54	9	66	15
Thrombocytopenia	39	2	73	13
Anemia	38	3	66	8
Leukopenia	34	1	77	8
Neutropenia	31	4	72	16

* With at least one 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: KEYTRUDA with lenvatinib (range: 343 to 349 patients) and sunitinib (range: 329 to 335 patients).

Grade 3 and 4 increased ALT or AST was seen in 9% of patients. Grade ≥2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received ≥40 mg daily oral prednisone equivalent. Recurrence of Grade ≥2 increased ALT or AST was observed on rechallenge in 10 patients receiving both KEYTRUDA and lenvatinib (n=38) and was not observed on rechallenge with KEYTRUDA alone (n=3).

Adjuvant treatment of RCC

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-564, a randomized (1:1) double-blind placebo-controlled trial in which 984 patients who had undergone nephrectomy for RCC received 200 mg of KEYTRUDA by intravenous infusion every 3 weeks (n=488) or placebo (n=496) for up to one year *[see Clinical Studies (14.16)]*. The median duration of exposure to KEYTRUDA was 11.1 months (range: 1 day to 14.3 months). Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Serious adverse reactions occurred in 20% of these patients receiving KEYTRUDA. Serious adverse reactions (≥1%) were acute kidney injury, adrenal insufficiency, pneumonia, colitis, and diabetic ketoacidosis (1% each). Fatal adverse reactions occurred in 0.2% of those treated with KEYTRUDA, including one case of pneumonia.

Discontinuation of KEYTRUDA due to an adverse reaction occurred in 21% of patients; the most common (≥1%) were increased ALT (1.6%), colitis (1%), and adrenal insufficiency (1%).

Dose interruptions of KEYTRUDA due to an adverse reaction occurred in 26% of patients; the most common (≥1%) were increased AST (2.3%), arthralgia (1.6%), hypothyroidism (1.6%), diarrhea (1.4%),

increased ALT (1.4%), fatigue (1.4%), rash, decreased appetite, and vomiting (1% each). Tables 49 and 50 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-564.

Table 49: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-564

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=488		Placebo n=496	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Musculoskeletal and Connective Tissue				
Musculoskeletal pain‡	41	1.2	36	0.6
General				
Fatigue§	40	1.2	31	0.2
Skin and Subcutaneous Tissue				
Rash¶	30	1.4	15	0.4
Pruritus	23	0.2	13	0
Gastrointestinal				
Diarrhea#	27	2.7	23	0.2
Nausea	16	0.4	10	0
Abdominal painÞ	11	0.4	13	0.2
Endocrine				
Hypothyroidism	21	0.2	3.6	0
Hyperthyroidism	12	0.2	0.2	0
Respiratory, Thoracic and Mediastinal				
Coughß	17	0	12	0
Nervous System				
Headacheà	15	0.2	13	0
Hepatobiliary				
Hepatotoxicityè	14	3.7	7	0.6
Renal and Urinary				
Acute kidney injuryð	13	1.2	10	0.2

* Adverse reactions occurring at same or higher incidence than in placebo arm

† Graded per NCI CTCAE v4.0

‡ Includes arthralgia, back pain, myalgia, arthritis, pain in extremity, neck pain, musculoskeletal pain, musculoskeletal stiffness, spinal pain, musculoskeletal chest pain, bone pain, musculoskeletal discomfort

§ Includes asthenia, fatigue

¶ Includes rash, rash maculo-papular, rash papular, skin exfoliation, lichen planus, rash erythematous, eczema, rash macular, dermatitis acneiform, dermatitis, rash pruritic, Stevens-Johnson Syndrome, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome

\# Includes diarrhea, colitis, enterocolitis, frequent bowel movements, enteritis

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

ß Includes upper-airway cough syndrome, productive cough, cough

à Includes tension headache, headache, sinus headache, migraine with aura

è Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, transaminases increased, gamma-glutamyltransferase increased, bilirubin conjugated increased

ð Includes acute kidney injury, blood creatinine increased, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, nephropathy toxic

Table 50: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-564

Laboratory Test†	KEYTRUDA 200 mg every 3 weeks		Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	48	8	45	4.5
Increased creatinine	39	1.1	28	0.2
Increased INR	29	1.0	20	0.9
Hyponatremia	21	3.3	13	1.9
Increased ALT	20	3.6	11	0.2
Hematology				
Anemia	28	0.5	20	0.4

* 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: 440 to 449 patients) and placebo (range: 461 to 469 patients); increased INR: KEYTRUDA n=199 and placebo n=224.

‡ Graded per NCI CTCAE v4.03

Endometrial Carcinoma

Primary Advanced or Recurrent Endometrial Carcinoma

The safety of KEYTRUDA in combination with chemotherapy (paclitaxel and carboplatin) was investigated in KEYNOTE-868, a randomized (1:1), multicenter, double-blind, placebo-controlled trial that enrolled patients with advanced or recurrent endometrial carcinoma *[see Clinical Studies (14.17)]*. A total of 759 patients received KEYTRUDA 200 mg every 3 weeks and chemotherapy for 6 cycles followed by KEYTRUDA 400 mg every 6 weeks for up to 14 cycles (n=382) or placebo and chemotherapy for 6 cycles followed by placebo for up to 14 cycles (n=377). The median duration of exposure to KEYTRUDA was 5.6 months (range: 1 day to 24.0 months).

Serious adverse reactions occurred in 35% of patients receiving KEYTRUDA in combination with chemotherapy, compared to 19% of patients receiving placebo in combination with chemotherapy.

Fatal adverse reactions occurred in 1.6% of patients receiving KEYTRUDA in combination with chemotherapy, including COVID-19 (0.5%), and cardiac arrest (0.3%).

KEYTRUDA was discontinued for an adverse reaction in 14% of patients. Chemotherapy dose reduction was required in 29% of patients receiving KEYTRUDA in combination with chemotherapy, compared to 23% of patients receiving placebo in combination with chemotherapy. There were no clinically meaningful differences in chemotherapy discontinuations or interruptions between arms.

Adverse reactions occurring in patients treated with KEYTRUDA and chemotherapy were generally similar to those observed with KEYTRUDA alone or chemotherapy alone with the exception of rash (33% all Grades; 2.9% Grades 3-4).

In Combination with Lenvatinib for the Treatment of Advanced Endometrial Carcinoma That Is pMMR or Not MSI-H.

The safety of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings *[see Clinical Studies (14.17)]*. Patients with endometrial carcinoma that is pMMR or not MSI-H received KEYTRUDA 200 mg every 3 weeks in combination with lenvatinib 20mg orally once daily (n=342) or received doxorubicin or paclitaxel (n=325).

For patients with pMMR or not MSI-H tumor status, the median duration of study treatment was 7.2 months (range 1 day to 26.8 months) and the median duration of exposure to KEYTRUDA was 6.8 months (range: 1 day to 25.8 months).

Fatal adverse reactions among these patients occurred in 4.7% of those treated with KEYTRUDA and lenvatinib, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50% of these patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions (≥3%) were hypertension (4.4%) and urinary tract infections (3.2%).

Discontinuation of KEYTRUDA due to an adverse reaction occurred in 15% of these patients. The most common adverse reaction leading to discontinuation of KEYTRUDA (≥1%) was increased ALT (1.2%).

Dose interruptions of KEYTRUDA due to an adverse reaction occurred in 48% of these patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥3%) were diarrhea (8%), increased ALT (4.4%), increased AST (3.8%), and hypertension (3.5%).

Tables 51 and 52 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib in KEYNOTE-775.

Table 51: Adverse Reactions Occurring in ≥20% of Patients with Endometrial Carcinoma in KEYNOTE-775

Adverse Reaction	Endometrial Carcinoma (pMMR or not MSI-H)			
	KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=342		Doxorubicin or Paclitaxel n=325	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Endocrine				
Hypothyroidism†	67	0.9	0.9	0
Vascular				
Hypertension‡	67	39	6	2.5
Hemorrhagic events§	25	2.6	15	0.9
General				
Fatigue¶	58	11	54	6
Gastrointestinal				
Diarrhea#	55	8	20	2.8
Nausea	49	2.9	47	1.5
Vomiting	37	2.3	21	2.2
Stomatitisᵇ	35	2.6	26	1.2
Abdominal painß	34	2.6	21	1.2
Constipation	27	0	25	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal disordersâ	53	5	27	0.6
Metabolism				
Decreased appetiteê	44	7	21	0
Investigations				
Weight loss	34	10	6	0.3
Renal and Urinary				
Proteinuriaô	29	6	3.4	0.3
Infections				
Urinary tract infectionø	31	5	13	1.2
Nervous System				
Headache	26	0.6	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	22	0	0.6	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesiaý	23	2.9	0.9	0
Rash£	20	2.3	4.9	0

* Graded per NCI CTCAE v4.03

† Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, secondary hypothyroidism

‡ Includes hypertension, blood pressure increased, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, blood pressure fluctuation

§ Includes epistaxis, vaginal hemorrhage, hematuria, gingival bleeding, metrorrhagia, rectal hemorrhage, contusion, hematochezia, cerebral hemorrhage, conjunctival hemorrhage, gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, lower gastrointestinal hemorrhage, mouth hemorrhage, petechiae, uterine hemorrhage, anal hemorrhage, blood blister, eye hemorrhage, hematoma, hemorrhage intracranial, hemorrhagic stroke, melena, stoma site hemorrhage, upper gastrointestinal hemorrhage, wound hemorrhage, blood urine present, ecchymosis, hematemesis, hemorrhage subcutaneous, hepatic hematoma, injection site bruising, intestinal hemorrhage, laryngeal hemorrhage, pulmonary hemorrhage, subdural hematoma, umbilical hemorrhage, vessel puncture site bruise

¶ Includes fatigue, asthenia, malaise, lethargy

Includes diarrhea, gastroenteritis

Þ Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, tongue ulceration

ß Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, epigastric discomfort

à Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, pain in jaw

è Includes decreased appetite, early satiety

ð Includes proteinuria, protein urine present, hemoglobinuria

ø Includes urinary tract infection, cystitis, pyelonephritis

ý Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema

£ Includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, rash pustular, rash papular, rash vesicular, application site rash

Table 52: Laboratory Abnormalities Worsened from Baseline* Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients with Endometrial Carcinoma in KEYNOTE-775

Laboratory Test†	Endometrial Carcinoma (pMMR or not MSI-H)			
	KEYTRUDA 200 mg every 3 weeks and Lenvatinib		Doxorubicin or Paclitaxel	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Chemistry				
Hypertriglyceridemia	70	6	45	1.7
Hypoalbuminemia	60	2.7	42	1.6
Increased aspartate aminotransferase	58	9	23	1.6
Hyperglycemia	58	8	45	4.4
Hypomagnesemia	46	0	27	1.3
Increased alanine aminotransferase	55	9	21	1.2
Hypercholesteremia	53	3.2	23	0.7
Hyponatremia	46	15	28	7
Increased alkaline phosphatase	43	4.7	18	0.9
Hypocalcemia	40	4.7	21	1.9
Increased lipase	36	14	13	3.9
Increased creatinine	35	4.7	18	1.9
Hypokalemia	34	10	24	5
Hypophosphatemia	26	8	17	3.2
Increased amylase	25	7	8	1
Hyperkalemia	23	2.4	12	1.2
Increased creatine kinase	19	3.7	7	0
Increased bilirubin	18	3.6	6	1.6
Hematology				
Lymphopenia	51	18	66	23
Thrombocytopenia	50	8	30	4.7
Anemia	49	8	84	14
Leukopenia	43	3.5	83	43
Neutropenia	34	8	80	60

* With at least one 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: KEYTRUDA and lenvatinib (range: 263 to 340 patients) and doxorubicin or paclitaxel (range: 240 to 322 patients).
‡ Graded per NCI CTCAE v4.03

As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma

Among the 90 patients with MSI-H or dMMR endometrial carcinoma enrolled in KEYNOTE-158 *[see Clinical Studies (14.17)]* treated with KEYTRUDA as a single agent, the median duration of exposure to KEYTRUDA was 8.3 months (range: 1 day to 26.9 months). Adverse reactions occurring in patients with endometrial carcinoma were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

TMB-H Cancer

The safety of KEYTRUDA was investigated in 105 patients with TMB-H cancer enrolled in KEYNOTE-158 *[see Clinical Studies (14.18)].* 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 159 patients with advanced cSCC (recurrent or metastatic or locally advanced disease) enrolled in KEYNOTE-629 *[see Clinical Studies (14.19)]*, the median duration of exposure to KEYTRUDA was 6.9 months (range 1 day to 28.9 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 recurrent or metastatic cSCC or locally advanced 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 (10%) and decreased sodium (10%).

TNBC

Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC

The safety of KEYTRUDA in combination with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-522, a randomized (2:1), multicenter, double-blind, placebo-controlled trial in patients with newly diagnosed, previously untreated, high-risk early-stage TNBC.

A total of 778 patients on the KEYTRUDA arm received at least 1 dose of KEYTRUDA in combination with neoadjuvant chemotherapy followed by KEYTRUDA as adjuvant treatment after surgery, compared to 389 patients who received at least 1 dose of placebo in combination with neoadjuvant chemotherapy followed by placebo as adjuvant treatment after surgery *[see Clinical Studies (14.20)].*

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 13.3 months (range: 1 day to 21.9 months).

Fatal adverse reactions occurred in 0.9% of patients receiving KEYTRUDA, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction.

Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA. Serious adverse reactions in ≥2% of patients who received KEYTRUDA included febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%).

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions (≥1%) resulting in permanent discontinuation of KEYTRUDA were increased ALT (2.7%), increased AST (1.5%), and rash (1%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 57% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (26%), thrombocytopenia (6%), increased ALT (6%), increased AST (3.7%), anemia (3.5%), rash (3.2%), febrile neutropenia (2.8%), leukopenia (2.8%), upper respiratory tract infection (2.6%), pyrexia (2.2%), and fatigue (2.1%).

Tables 53 and 54 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-522.

Table 53: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-522

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with chemotherapy*/KEYTRUDA n=778		Placebo with chemotherapy*/Placebo n=389	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
General				
Fatigue‡	70	8	66	3.9
Pyrexia	28	1.3	19	0.3
Gastrointestinal				
Nausea	67	3.7	66	1.8
Constipation	42	0	39	0.3
Diarrhea	41	3.2	34	1.8
Stomatitis§	34	2.7	29	1
Vomiting	31	2.7	28	1.5
Abdominal pain¶	24	0.5	23	0.8
Skin and Subcutaneous Tissue				
Alopecia	61	0	58	0
Rash#	52	5	41	0.5
Nervous System				
Peripheral neuropathyÞ	41	3.3	42	2.3
Headache	30	0.5	29	1
Musculoskeletal and Connective Tissue				
Arthralgia	29	0.5	31	0.3
Myalgia	20	0.5	19	0
Respiratory, Thoracic and Mediastinal				
Coughß	26	0.1	24	0
Metabolism and Nutrition				
Decreased appetite	23	0.9	17	0.3
Psychiatric				
Insomnia	21	0.5	19	0

* Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide
† Graded per NCI CTCAE v4.0
‡ Includes asthenia, fatigue
§ Includes aphthous ulcer, cheilitis, lip pain, lip ulceration, mouth ulceration, mucosal inflammation, oral mucosal eruption, oral pain, stomatitis, tongue blistering, tongue ulceration
¶ Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness
# Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative generalized, drug eruption, eczema, incision site rash, injection site rash, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash rubelliform, skin exfoliation, skin toxicity, toxic skin eruption, urticaria, vasculitic rash, viral rash
Þ Includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy
ß Includes cough, productive cough, upper-airway cough syndrome

Table 54: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-522

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with chemotherapy†/KEYTRUDA		Placebo with chemotherapy†/Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Hematology				
Anemia	97	22	96	19
Leukopenia	93	41	91	32
Neutropenia	88	62	89	62
Lymphopenia	79	28	74	22
Thrombocytopenia	57	10	56	8
Chemistry				
Increased ALT	70	9	67	3.9
Increased AST	65	6	56	1.5
Hyperglycemia	63	4.3	61	2.8
Increased alkaline phosphatase	37	1	35	0.5
Hyponatremia	35	9	25	4.6
Hypoalbuminemia	34	1.0	30	1.3
Hypocalcemia	31	2.2	28	3.1
Hypokalemia	31	6	22	2.8
Hypophosphatemia	20	6	15	4.2

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA in combination with chemotherapy followed by KEYTRUDA as a single agent (range: 762 to 777 patients) and placebo in combination with chemotherapy followed by placebo (range: 381 to 389 patients).

† Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide

‡ Graded per NCI CTCAE v4.0

Locally Recurrent Unresectable or Metastatic 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 (14.20)]*. 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 55 and 56 summarize the adverse reactions and laboratory abnormalities in patients on KEYTRUDA in KEYNOTE-355.

Table 55: 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 56: 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	78	50	79	53
Lymphopenia	73	28	71	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	36	2.0	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 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KEYTRUDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal: Exocrine pancreatic insufficiency

Hepatobiliary: sclerosing cholangitis

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. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to KEYTRUDA are unknown. 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 last 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 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with melanoma, cHL, PMBCL, MCC, MSI-H or dMMR 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 (14.1, 14.5, 14.6, 14.8, 14.15, 14.18)]*.

In KEYNOTE-051, 173 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 pediatric patients aged 12 to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive or MSI-H solid tumors received KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 25 months). Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults included pyrexia (33%), vomiting (29%), headache (25%), abdominal pain (23%), decreased lymphocyte count (13%), and decreased white blood cell count (11%). Laboratory abnormalities that occurred at a ≥10% higher rate in pediatric patients when compared to adults were leukopenia (30%), neutropenia (28%), thrombocytopenia (22%), 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 506 adult patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC following complete resection and platinum-based chemotherapy who were treated with KEYTRUDA in KEYNOTE-091, 242 (48%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and 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.

Of 406 adult patients with endometrial carcinoma who were treated with KEYTRUDA in combination with lenvatinib in KEYNOTE-775, 201 (50%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Of the 564 patients with locally advanced or metastatic urothelial cancer treated with KEYTRUDA in combination with enfortumab vedotin, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years of age or older and younger patients. Patients 75 years of age or older treated with KEYTRUDA in combination with enfortumab vedotin experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 7% in patients 75 years or older.

Of the 432 patients randomized to KEYTRUDA in combination with axitinib in the KEYNOTE-426 trial, 40% were 65 years or older. No overall difference in safety or efficacy was reported between patients who were ≥65 years of age and younger.

Of 292 adult patients with FIGO 2014 Stage III-IVA cervical cancer who were treated with KEYTRUDA in combination with CRT in KEYNOTE-A18, 42 (14%) were 65 years and over. No overall differences in safety or efficacy were observed between elderly 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.

In syngeneic mouse tumor models, combination treatment of a PD-1 blocking antibody and kinase inhibitor lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and reduced tumor growth compared to either treatment alone.

12.2 Pharmacodynamics

There are no clinically significant exposure-response relationships for efficacy or safety at pembrolizumab dosages of 200 mg or 2 mg/kg every 3 weeks regardless of cancer type. There are no clinically significant exposure-response relationships for efficacy or safety at pembrolizumab dosages of 200 mg or 2 mg/kg every 3 weeks and 400 mg every 6 weeks in patients with solid tumors based on observed data in adult patients with melanoma. The exposure-response relationships for efficacy or safety at pembrolizumab dosages of 400 mg every 6 weeks in patients with classical Hodgkin lymphoma or mediastinal large B-cell lymphoma have not been fully characterized.

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 to moderate hepatic impairment (total bilirubin ≤3 times ULN and any AST), or tumor burden. The impact of severe hepatic impairment (total bilirubin >3 times ULN and any AST) 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.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence

of ADA in the studies described in this section with the incidence of ADA in other studies, including those of KEYTRUDA or of other pembrolizumab products.

Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the KEYTRUDA-treated patients with a pembrolizumab concentration below the drug tolerance level of the ADA assay.

In clinical studies in patients treated with KEYTRUDA at a dosage 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 1,289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies of whom 6 (0.5%) patients had neutralizing antibodies against pembrolizumab. There were no identified clinically significant effects of ADA on pembrolizumab pharmacokinetics or on the risk of infusion reactions. Because of the low occurrence of ADA, the effect of these ADA on the effectiveness of KEYTRUDA is unknown.

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/PD-L1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium 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 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-1 and PD-L1 knockout mice and mice receiving PD-L1-blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus. 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.

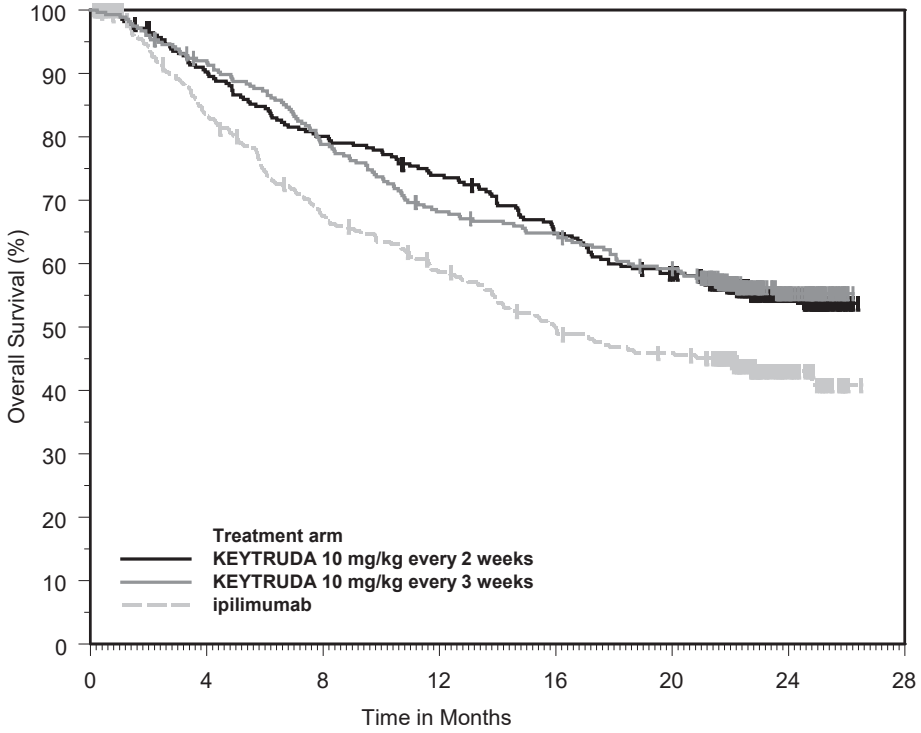
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients 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 57 and Figure 1.

Table 57: 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 58 and Figure 2.

Table 58: Efficacy Results in KEYNOTE-002

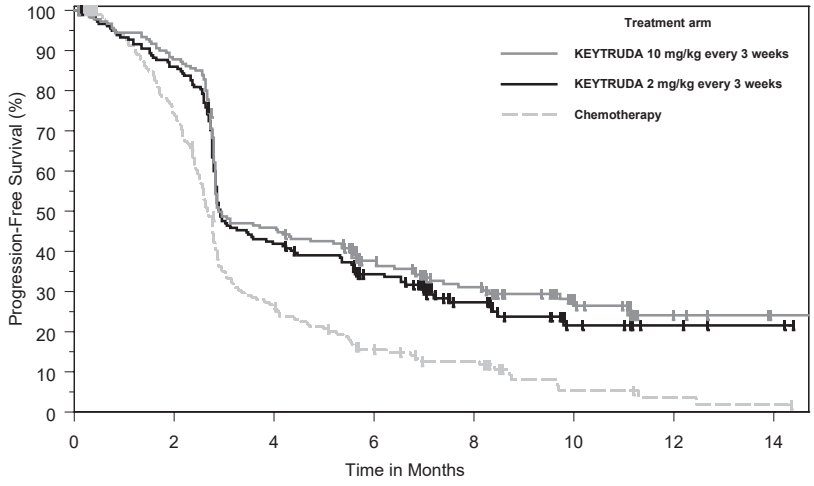
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8,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

The efficacy of KEYTRUDA was investigated in KEYNOTE-716 (NCT03553836), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with completely resected Stage IIB or IIC melanoma. Patients were randomized to KEYTRUDA 200 mg or the pediatric (≥12 years old) dose of KEYTRUDA 2 mg/kg intravenously (up to a maximum of 200 mg) every three weeks or placebo for up to one year until disease recurrence or unacceptable toxicity. Randomization was stratified by AJCC 8th edition T Stage (>2.0-4.0 mm with ulceration vs. >4.0 mm without ulceration vs. >4.0 mm with ulceration). Patients must not have been previously treated for melanoma beyond complete surgical resection for their melanoma prior to study entry. The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) (defined as the time between the date of randomization and the date of first recurrence [local, in-transit or regional lymph nodes or distant recurrence] or death, whichever occurred first). New primary melanomas were excluded from the definition of RFS. Distant metastasis-free survival (DMFS), defined as a spread of tumor to distant organs or distant lymph nodes, was an additional efficacy outcome measure. Patients underwent imaging every six months for one year from randomization, every 6 months from years 2 to 4, and then once in year 5 from randomization or until recurrence, whichever came first.

The study population characteristics were: median age of 61 years (range: 16 to 87), 39% age 65 or older; 60% male; 98% White; and 93% ECOG PS of 0 and 7% ECOG PS of 1. Sixty-four percent had Stage IIB and 35% had Stage IIC.

The trial demonstrated a statistically significant improvement in RFS and DMFS for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 59 and Figure 3.

Table 59: Efficacy Results in KEYNOTE-716

Endpoint	KEYTRUDA 200 mg every 3 weeks n=487	Placebo n=489
RFS		
Number (%) of patients with event	54 (11%)	82 (17%)
Median in months (95% CI)	NR (22.6, NR)	NR (NR, NR)
Hazard ratio*,† (95% CI)	0.65 (0.46, 0.92)	
p-Value†	0.0132‡	
DMFS		
Number (%) of patients with event	63 (13%)	95 (19%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio*,† (95% CI)	0.64 (0.47, 0.88)	
p-Value†	0.0058§	

* Based on the stratified Cox proportional hazard model

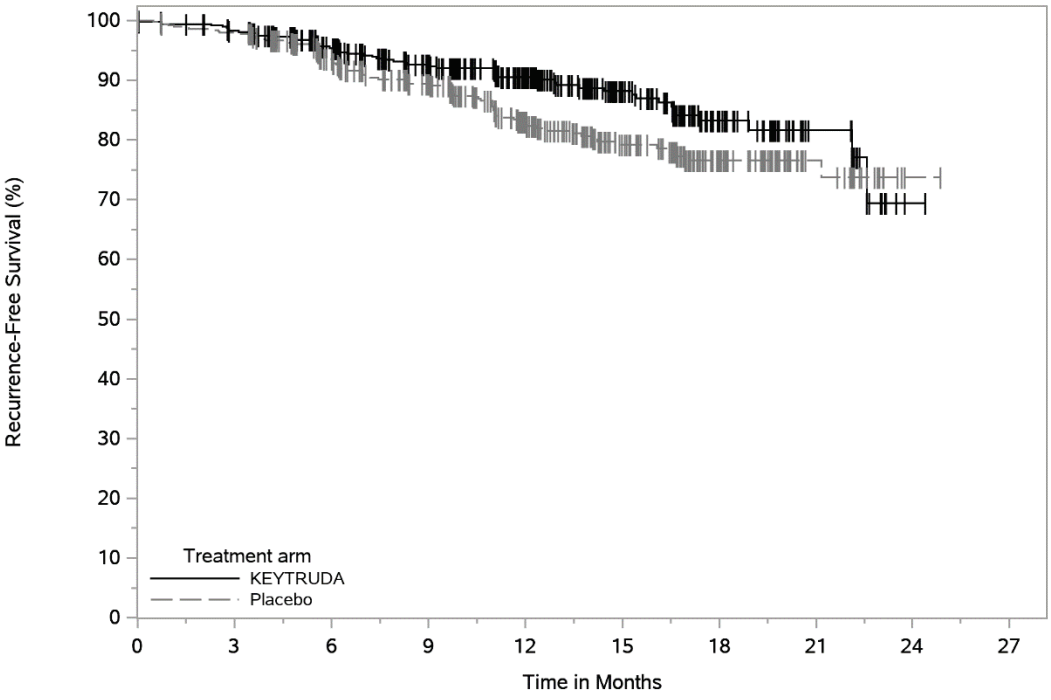
† Based on a log-rank test stratified by American Joint Committee on Cancer 8th edition (AJCC) stage

‡ p-Value is compared with 0.0202 of the allocated alpha for this interim analysis.

§ p-Value is compared with 0.0256 of the allocated alpha for this interim analysis.

NR = not reached

Figure 3: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-716



Number at Risk

KEYTRUDA	487	465	401	340	249	149	71	21	1	0
Placebo	489	475	400	336	229	149	77	27	1	0

Adjuvant Treatment of Stage III 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. New primary melanomas were excluded from the definition of RFS. DMFS in the whole population and in the population with PD-L1 positive tumors were additional efficacy outcome measures. DMFS was defined as a spread of tumor to distant organs or distant lymph nodes. 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 and DMFS for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 60 and Figure 4.

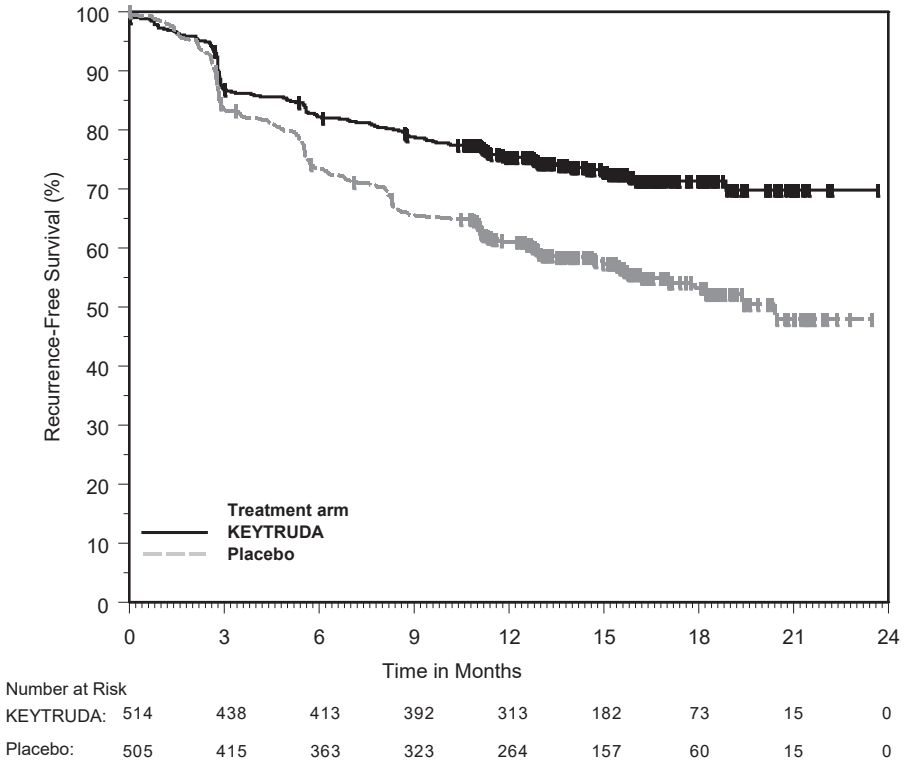
Table 60: Efficacy Results in KEYNOTE-054

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±	
DMFS		
Number (%) of patients with event	173 (34%)	245 (49%)
Median in months (95% CI)	NR (49.6, NR)	40.0 (27.7, NR)
Hazard ratio*,† (95% CI)	0.60 (0.49, 0.73)	
p-Value† (log-rank)	<0.0001§	

* Based on the stratified Cox proportional hazard model
† Stratified by American Joint Committee on Cancer 7th edition (AJCC) stage
± p-Value is compared with 0.016 of the allocated alpha for this interim analysis.
§ p-Value is compared with 0.028 of the allocated alpha for this analysis.
NR = not reached

For patients with PD-L1 positive tumors, the RFS HR was 0.54 (95% CI: 0.42, 0.69); p<0.0001. For patients with PD-L1 positive tumors, the DMFS HR was 0.61 (95% CI: 0.49, 0.76); p<0.0001. The RFS and DMFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression.

Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054



14.2 Non-Small Cell Lung Cancer

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

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1

tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). Patients were randomized (2:1) to one of the following treatment arms:

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

Treatment with KEYTRUDA continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Patients randomized to placebo and chemotherapy were offered KEYTRUDA as a single agent at the time of disease progression. Assessment of tumor status was performed at Week 6, Week 12, and then every 9 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR and DoR, as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

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

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 61 and Figure 5 summarize the efficacy results for KEYNOTE-189.

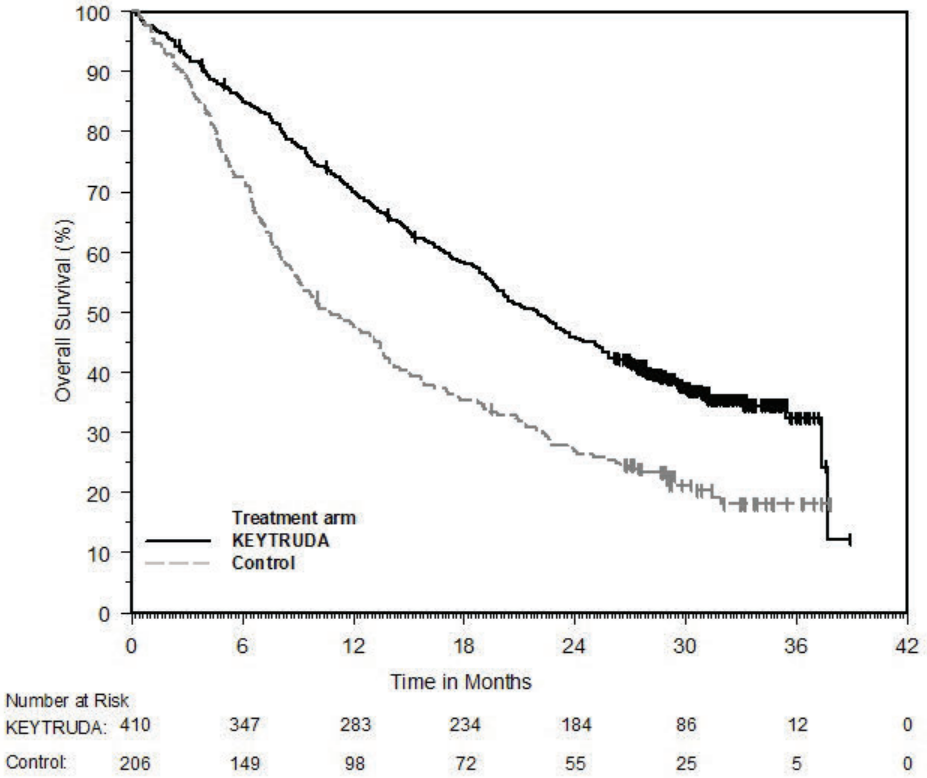
Table 61: Efficacy Results in KEYNOTE-189

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 5: 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 62 and Figure 6 summarize the efficacy results for KEYNOTE-407.

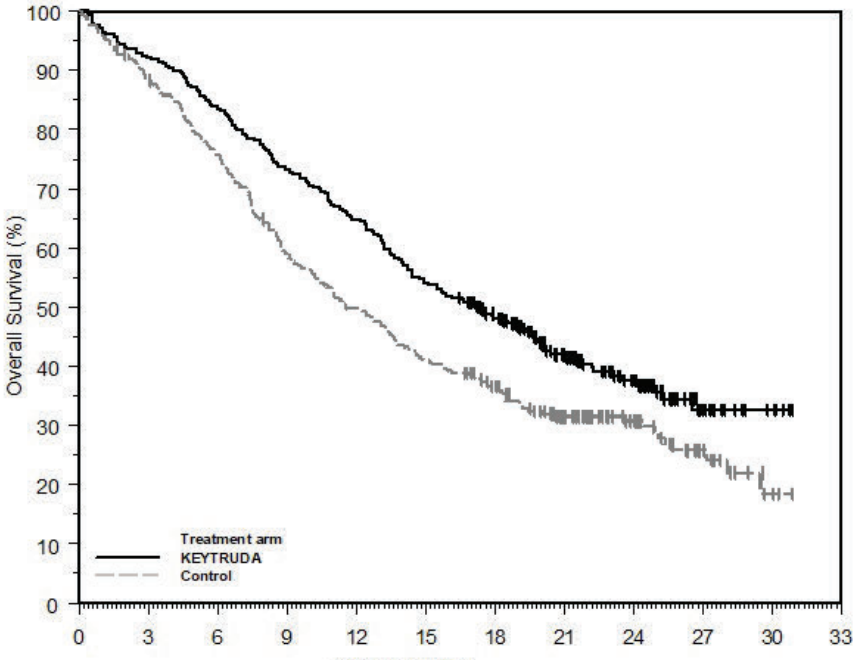
Table 62: Efficacy Results in KEYNOTE-407

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 6: 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 63 and Figure 7 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%.

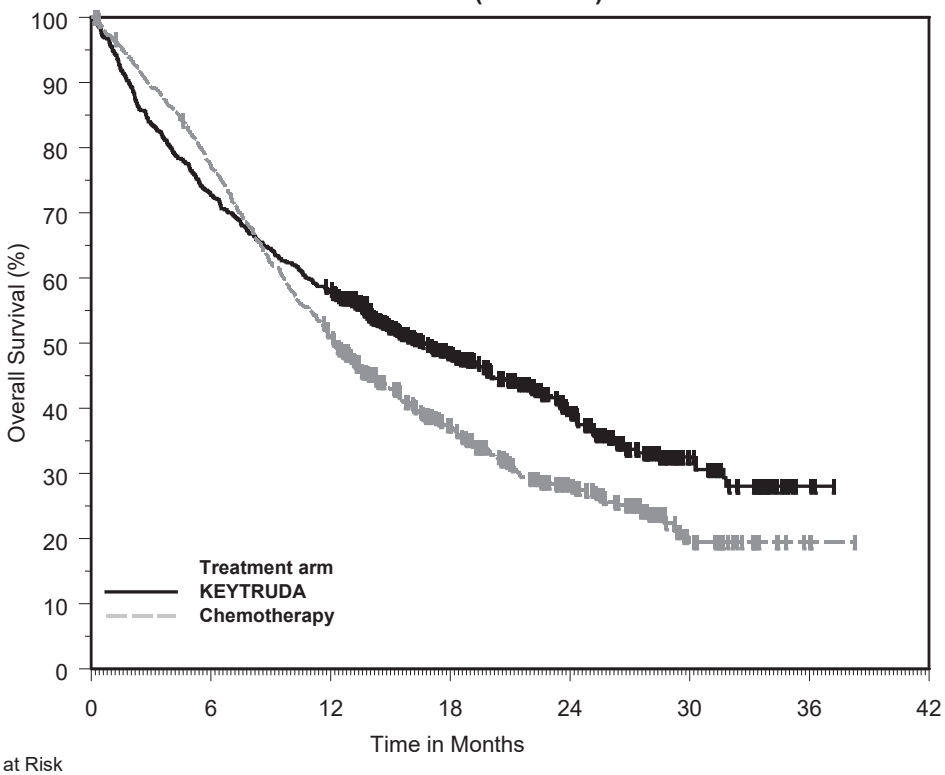
Table 63: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

	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 7: 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 64 and Figure 8 summarize the efficacy results for KEYNOTE-024.

Table 64: 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+)

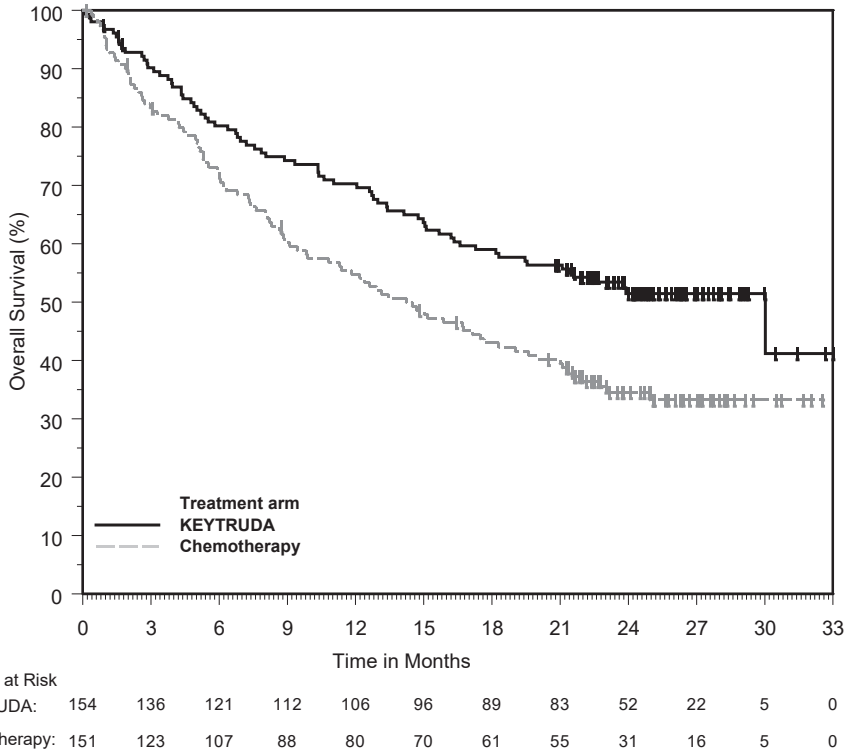
* Based on the stratified Cox proportional hazard model for the interim analysis

† 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 8: Kaplan-Meier Curve for Overall Survival in KEYNOTE-024*



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

Previously treated NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS=1-49%), ECOG PS (0 vs. 1), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1:1) to receive KEYTRUDA 2 mg/kg intravenously every 3 weeks, KEYTRUDA 10 mg/kg intravenously every 3 weeks or docetaxel intravenously 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue until disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or confirmation of progression at 4 to 6 weeks with repeat imaging or for up to 24 months without disease progression. Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%. Additional efficacy outcome measures were ORR and DoR in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%.

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease.

Tables 65 and 66 and Figure 9 summarize efficacy results in the subgroup with TPS ≥50% population and in all patients, respectively.

Table 65: 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 66: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

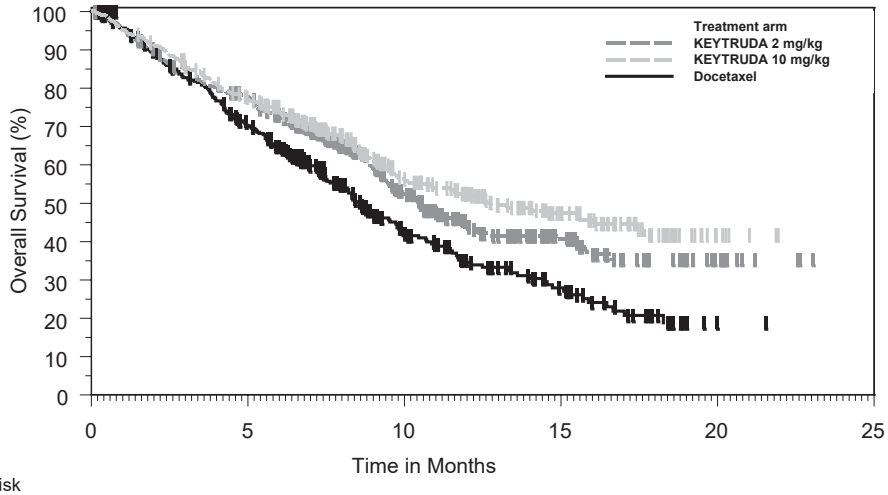
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)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

Neoadjuvant and adjuvant treatment of resectable NSCLC

The efficacy of KEYTRUDA in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-671 (NCT03425643), a multicenter, randomized, double-blind, placebo-controlled trial conducted in 797 patients with previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition. Patients were enrolled regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or a history of interstitial lung disease or pneumonitis that required steroids were ineligible. Randomization was stratified by stage (II vs. III), tumor PD-L1 expression (TPS ≥50% or <50%), histology (squamous vs. nonsquamous), and geographic region (East Asia vs. non-East Asia).

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

- Treatment Arm A: neoadjuvant KEYTRUDA 200 mg on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Within 4-12 weeks following surgery, KEYTRUDA 200 mg was administered every 3 weeks for up to 13 cycles.
- Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Within 4-12 weeks following surgery, placebo was administered every 3 weeks for up to 13 cycles.

All study medications were administered via intravenous infusion. Treatment with KEYTRUDA or placebo continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumor status was performed at baseline, Week 7, and Week 13 in the neoadjuvant phase and within 4 weeks prior to the start of the adjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed every 16 weeks through the end of Year 3, and then every 6 months thereafter.

The trial was not designed to isolate the effect of KEYTRUDA in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measures were OS and investigator-assessed event-free survival (EFS). Additional efficacy outcome measures were pathological complete response (pCR) rate and major pathological response (mPR) rate as assessed by blinded independent pathology review.

The study population characteristics were: median age of 64 years (range: 26 to 83); 45% age 65 or older and 7% age 75 or older; 71% male; 61% White, 31% Asian, 2% Black, 4% race not reported; 9% Hispanic or Latino; 63% ECOG PS of 0 and 37% ECOG PS of 1. Thirty percent had Stage II and 70% had Stage III disease; 33% had TPS ≥50% and 67% had TPS <50%; 43% had tumors with squamous histology and 57% had tumors with non-squamous histology; 31% were from the East Asian region.

Eighty-one percent of patients in the KEYTRUDA in combination with platinum-containing chemotherapy arm received definitive surgery compared to 76% of patients in the placebo in combination with platinum-containing chemotherapy arm.

The trial demonstrated statistically significant improvements in OS and EFS for patients randomized to KEYTRUDA in combination with platinum-containing chemotherapy followed by KEYTRUDA as a single agent compared with patients randomized to placebo in combination with platinum-containing chemotherapy followed by placebo alone.

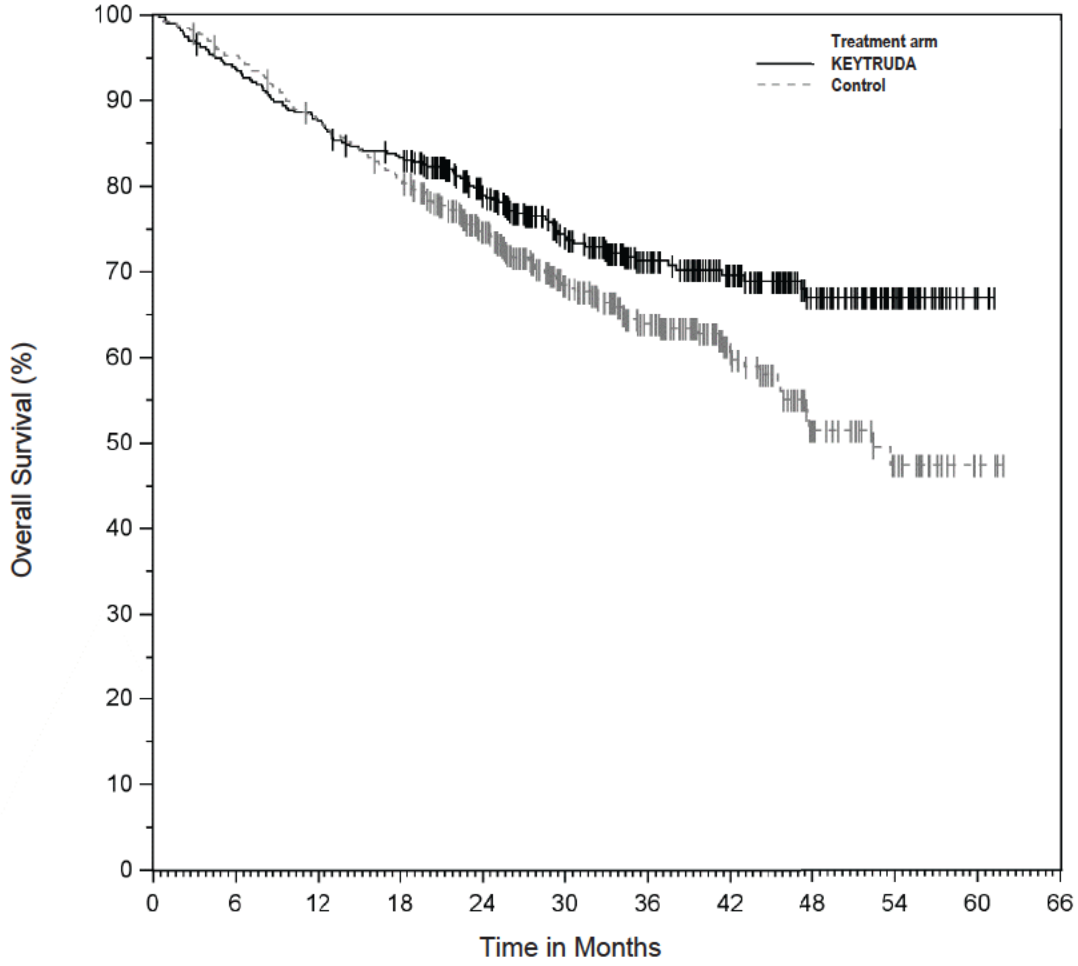
Table 67 and Figure 10 summarize the efficacy results for KEYNOTE-671.

Table 67: Efficacy Results in KEYNOTE-671

Endpoint	KEYTRUDA 200 mg every 3 weeks with chemotherapy/KEYTRUDA n=397	Placebo with chemotherapy/Placebo n=400
OS		
Number of patients with event (%)	110 (28%)	144 (36%)
Median in months* (95% CI)	NR (NR, NR)	52.4 (45.7, NR)
Hazard ratio† (95% CI)	0.72 (0.56, 0.93)	
p-Value‡,§	0.0103	
EFS		
Number of patients with event (%)	139 (35%)	205 (51%)
Median in months* (95% CI)	NR (34.1, NR)	17.0 (14.3, 22.0)
Hazard ratio† (95% CI)	0.58 (0.46, 0.72)	
p-Value‡,¶	<0.0001	

* Based on Kaplan-Meier estimates
† Based on Cox regression model with treatment as a covariate stratified by stage, tumor PD-L1 expression, histology, and geographic region
‡ Based on stratified log-rank test
§ Compared to a two-sided p-Value boundary of 0.0109
¶ Compared to a two-sided p-Value boundary of 0.0092
NR = not reached

Figure 10: Kaplan-Meier Curve for Overall Survival in KEYNOTE-671



The trial demonstrated a statistically significant difference in pCR rate (18.1% vs. 4.0%; p<0.0001) and mPR rate (30.2% vs. 11.0%; p<0.0001).

Adjuvant treatment of resected NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-091 (NCT02504372), a multicenter, randomized, triple-blind, placebo-controlled trial conducted in 1177 patients with completely resected Stage IB (T2a ≥4 cm), II, or IIIA NSCLC by AJCC 7th edition. Patients had not received neoadjuvant radiotherapy or chemotherapy. Adjuvant chemotherapy up to 4 cycles was optional. Patients were ineligible if they had active autoimmune disease, were on chronic immunosuppressive agents, or had a history of interstitial lung disease or pneumonitis. Randomization was stratified by stage (IB vs. II vs. IIIA), receipt of adjuvant chemotherapy (yes vs. no), PD-L1 status (TPS <1% [negative] vs. TPS 1-49% vs. TPS ≥50%), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomized (1:1) to receive KEYTRUDA 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST v1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity or up to one year. Tumor assessments were conducted every 12 weeks for the first year, then every 6 months for years 2 to 3, and then annually through year 5. After year 5, imaging was

performed as per local standard of care. The major efficacy outcome measure was investigator-assessed disease-free survival (DFS). An additional efficacy outcome measure was OS.

Of 1177 patients randomized, 1010 (86%) received adjuvant platinum-based chemotherapy following resection. Among these 1010 patients, the median age was 64 years (range: 35 to 84), 49% age 65 or older; 68% male; 77% White, 18% Asian; 86% current or former smokers; and 39% with ECOG PS of 1. Eleven percent had Stage IB, 57% had Stage II, and 31% had Stage IIIA disease. Thirty-nine percent had PD-L1 TPS <1% [negative], 33% had TPS 1-49%, and 28% had TPS ≥50%. Fifty-two percent were from Western Europe, 20% from Eastern Europe, 17% from Asia, and 11% from Rest of World.

The trial met its primary endpoint, demonstrating a statistically significant improvement in DFS in the overall population for patients randomized to the KEYTRUDA arm compared to patients randomized to the placebo arm. In an exploratory subgroup analysis of the 167 patients (14%) who did not receive adjuvant chemotherapy, the DFS HR was 1.25 (95% CI: 0.76, 2.05). OS results were not mature with only 42% of pre-specified OS events in the overall population.

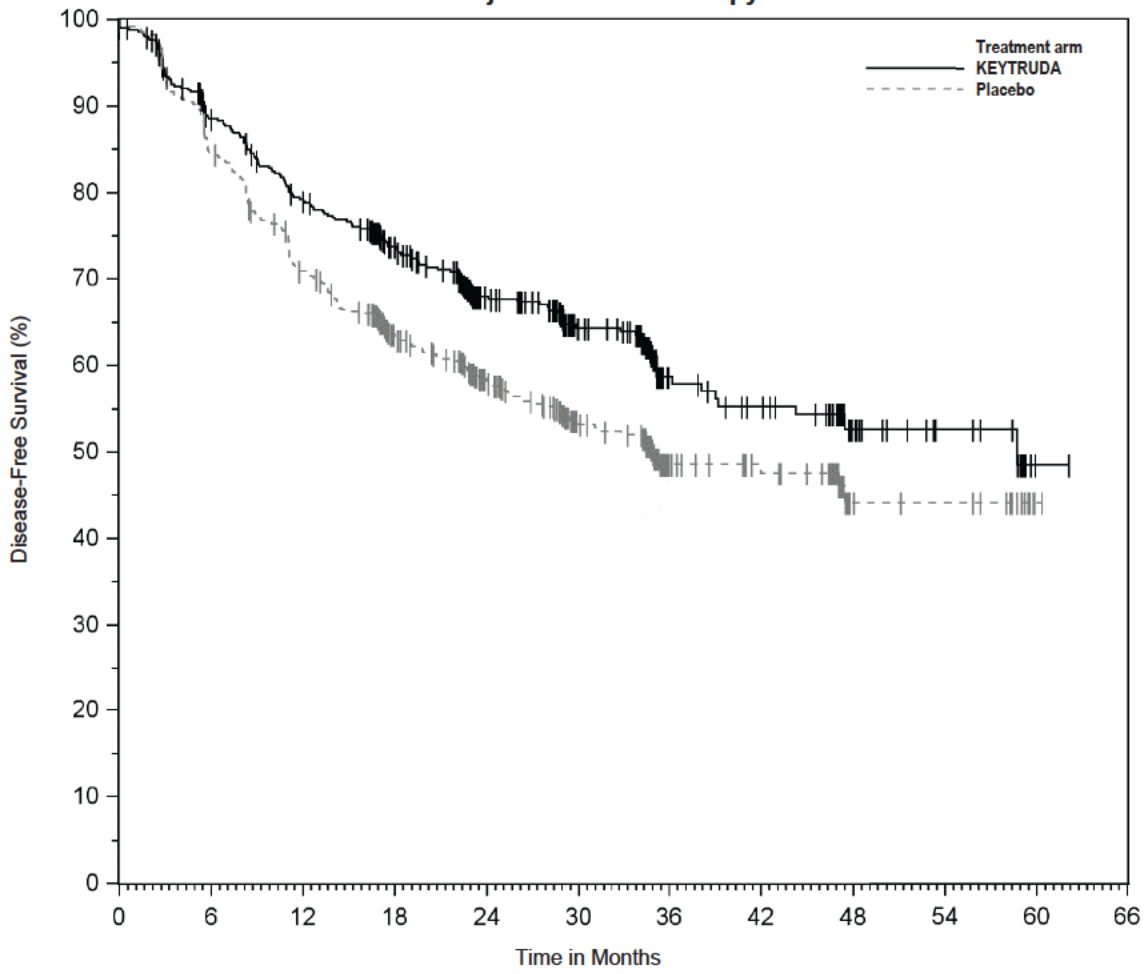
Table 68 and Figure 11 summarize the efficacy results for KEYNOTE-091 in patients who received adjuvant chemotherapy.

Table 68: Efficacy Results in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy

Endpoint	KEYTRUDA 200 mg every 3 weeks n=506	Placebo n=504
DFS		
Number (%) of patients with event	177 (35%)	231 (46%)
Median in months (95% CI)	58.7 (39.2, NR)	34.9 (28.6, NR)
Hazard ratio* (95% CI)	0.73 (0.60, 0.89)	

* Based on the unstratified univariate Cox regression model
NR = not reached

Figure 11: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy



Number at Risk												
KEYTRUDA	506	422	372	308	227	158	71	61	27	16	1	0
Placebo	504	422	349	272	206	134	58	47	17	15	1	0

14.3 Malignant Pleural Mesothelioma

First-line treatment of unresectable advanced or metastatic malignant pleural mesothelioma (MPM) with pemetrexed and platinum chemotherapy

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-483 (NCT02784171), a multicenter, randomized, open-label, active-controlled trial that enrolled 440 patients with unresectable advanced or metastatic MPM and no prior systemic therapy for advanced/metastatic disease. Patients were enrolled regardless of tumor PD-L1 expression. Patients with autoimmune disease that required systemic therapy within 3 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by histological subtype (epithelioid vs. non-epithelioid). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg with pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.

- Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles.

Treatment with KEYTRUDA continued until disease progression as determined by the investigator according to modified RECIST 1.1 for mesothelioma (mRECIST), unacceptable toxicity, or a maximum of 24 months. Assessment of tumor status was performed every 6 weeks for 18 weeks, followed by every 12 weeks thereafter. The main efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR according to mRECIST.

The study population characteristics were: median age of 70 years (77% age 65 or older); 76% male; 79% White, 21% race not reported or unknown; 2% Hispanic or Latino; and 53% ECOG performance status of 1. Seventy-eight percent had epithelioid and 22% had non-epithelioid histology; 60% had tumors with PD-L1 CPS ≥1 and 30% had tumors with PD-L1 CPS <1.

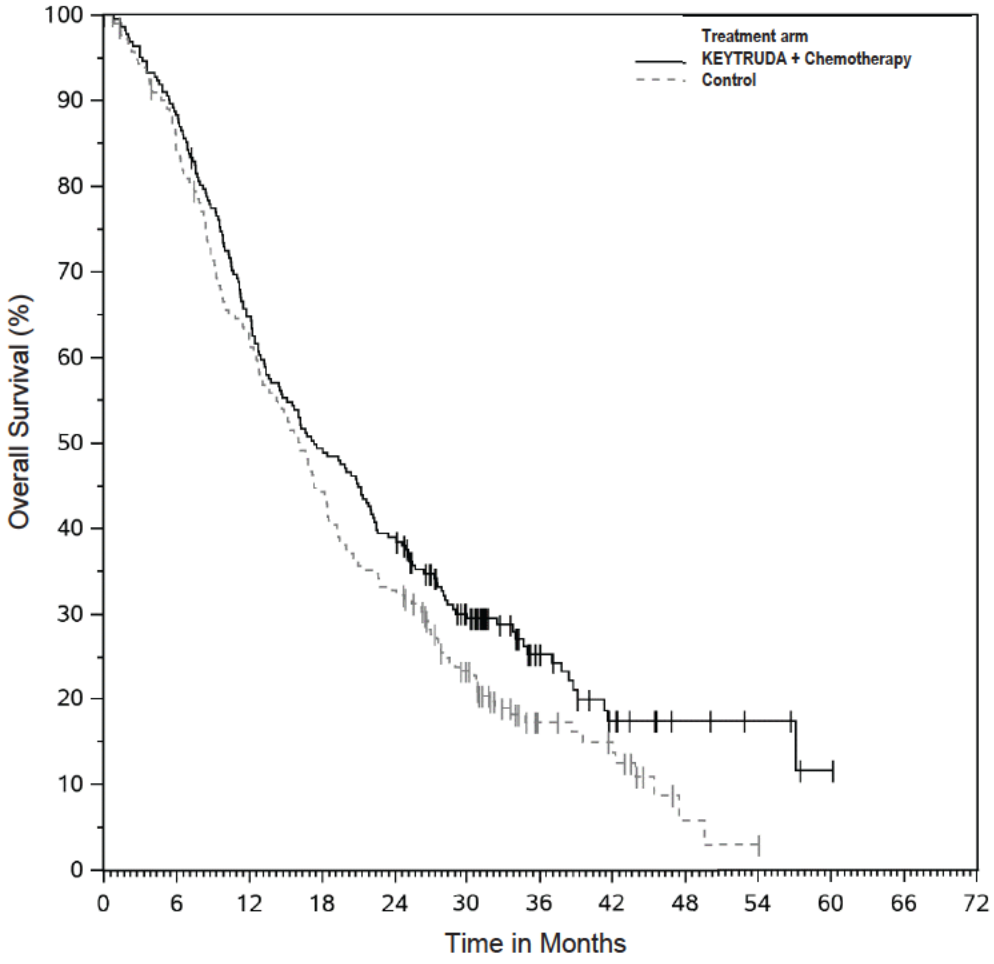
The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomized to KEYTRUDA in combination with chemotherapy compared with patients randomized to chemotherapy alone. Table 69 and Figure 12 summarize the efficacy results for KEYNOTE-483.

Table 69: Efficacy Results in KEYNOTE-483

Endpoint	**KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy (n=222)**	**Pemetrexed Platinum Chemotherapy (n=218)**
OS		
Number (%) of patients with event	167 (75%)	175 (80%)
Median in months (95% CI)	17.3 (14.4, 21.3)	16.1 (13.1, 18.2)
Hazard ratio* (95% CI)	0.79 (0.64, 0.98)	
p-Value†	0.0162	
PFS		
Number (%) of patients with event	190 (86%)	166 (76%)
Median in months (95% CI)	7.1 (6.9, 8.1)	7.1 (6.8, 7.7)
Hazard ratio* (95% CI)	0.80 (0.65, 0.99)	
p-Value†	0.0194	
Objective Response Rate		
ORR % (95% CI)	52% (45.5, 59.0)	29% (23.0, 35.4)
Complete responses	1 (0.5%)	0 (0%)
Partial responses	115 (52%)	63 (29%)
p-Value‡	<0.00001	
Duration of Response§		
Median in months (95% CI)	6.9 (5.8, 8.3)	6.8 (5.5, 8.5)

* Based on stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Based on Miettinen and Nurminen method stratified by histological subtype at randomization (epithelioid vs. non-epithelioid)
§ Based on patients with a best overall response as confirmed complete or partial response; n=116 for patients in the KEYTRUDA combination arm; n=63 for patients in the chemotherapy arm

Figure 12: Kaplan-Meier Curve for Overall Survival in KEYNOTE-483



Number at Risk													
KEYTRUDA + Chemotherapy	222	196	143	109	86	54	25	13	6	4	1	0	0
Control	218	176	128	92	68	40	16	12	2	1	0	0	0

In a pre-specified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology (n=345), the hazard ratio (HR) for OS was 0.89 (95% CI: 0.70, 1.13), with median OS of 19.8 months in KEYTRUDA in combination with chemotherapy and 18.2 months in chemotherapy alone. In the subgroup of patients with non-epithelioid histology (n=95), the HR for OS was 0.57 (95% CI: 0.36, 0.89), with median OS of 12.3 months in KEYTRUDA in combination with chemotherapy and 8.2 months in chemotherapy alone.

14.4 Head and Neck Squamous Cell Cancer

First-line treatment of metastatic or unresectable, recurrent HNSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS ≥50% or <50%) according to the

PD-L1 IHC 22C3 pharmDx kit, HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs. 1). Patients were randomized 1:1:1 to one of the following treatment arms:

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

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

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

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

The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA in combination with chemotherapy compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis in the overall population. Table 70 and Figure 13 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

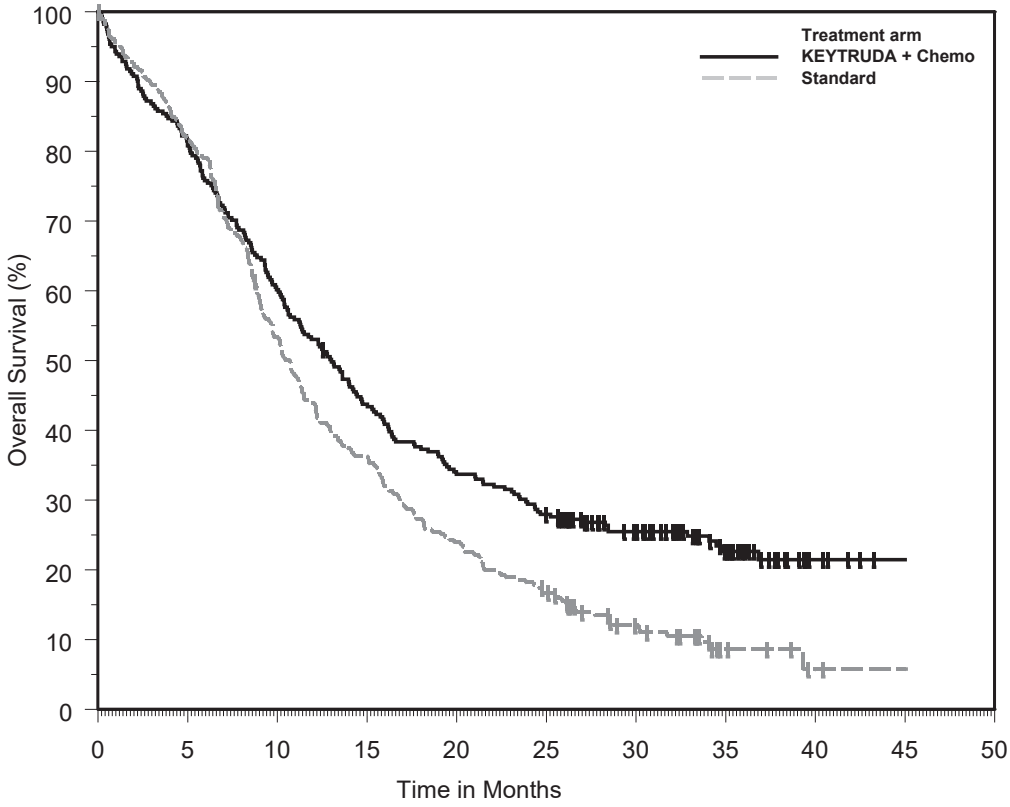
Table 70: Efficacy Results* for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048

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 13: 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 71 summarizes efficacy results for KEYTRUDA as a single agent in the subgroups of patients with CPS ≥1 HNSCC and CPS ≥20 HNSCC. Figure 14 summarizes the OS results in the subgroup of patients with CPS ≥1 HNSCC.

Table 71: Efficacy Results* for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)

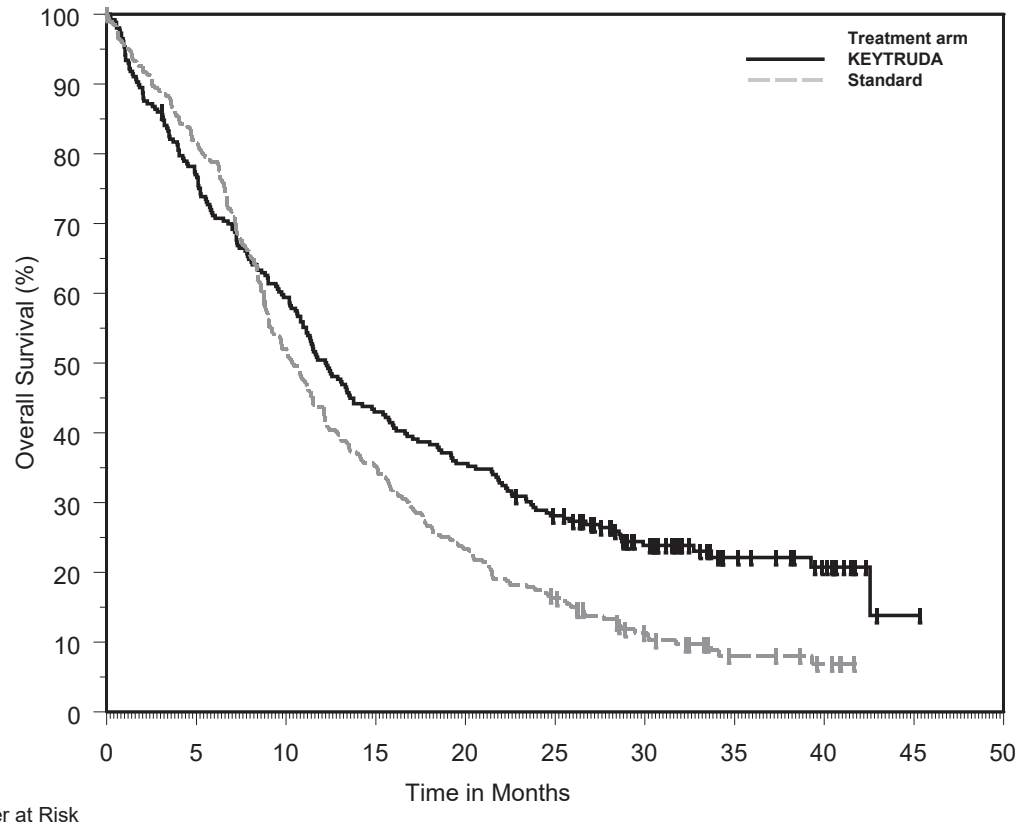
Endpoint	CPS ≥1		CPS ≥20	
	KEYTRUDA 200 mg every 3 weeks n=257	Cetuximab Platinum FU n=255	KEYTRUDA 200 mg every 3 weeks n=133	Cetuximab Platinum FU n=122
OS				
Number of events (%)	177 (69%)	206 (81%)	82 (62%)	95 (78%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)	14.9 (11.6, 21.5)	10.7 (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 14: Kaplan-Meier Curve for Overall Survival for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1)*



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

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

Previously treated recurrent or metastatic HNSCC

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

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

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

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

14.5 Classical Hodgkin Lymphoma

KEYNOTE-204

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

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

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

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

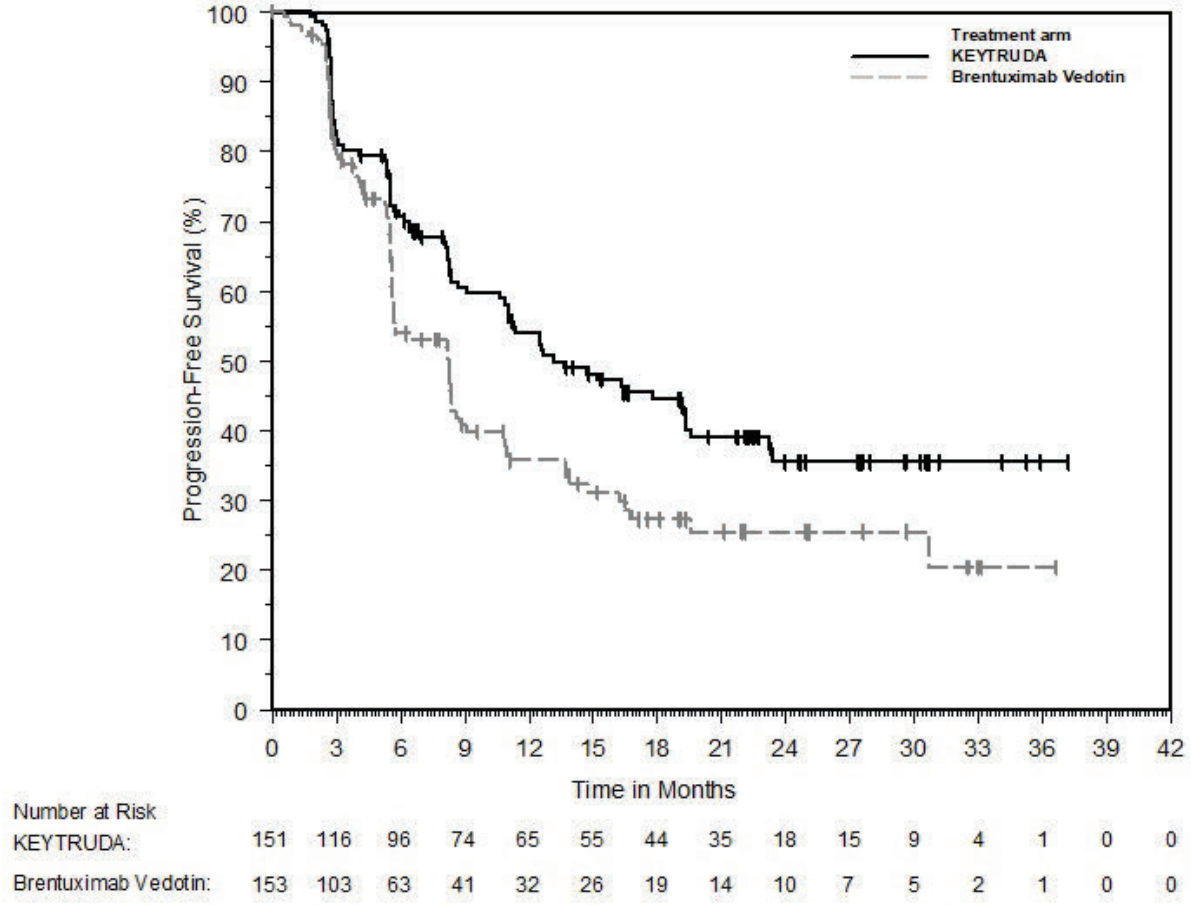
Efficacy is summarized in Table 72 and Figure 15.

Table 72: 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 15: 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 73.

Table 73: Efficacy Results in Patients with cHL in KEYNOTE-087

Endpoint	KEYTRUDA 200 mg every 3 weeks n=210*
Objective Response Rate	
ORR (95% CI)	69% (62, 75)
Complete response rate	22%
Partial response rate	47%
Duration of Response	
Median in months (range)	11.1 (0.0+, 11.1)†

* Median follow-up time of 9.4 months
† Based on patients (n=145) with a response by independent review

14.6 Primary Mediastinal Large B-Cell Lymphoma

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

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

For the 24 responders, the median time to first objective response (complete or partial response) was 2.8 months (range 2.1 to 8.5 months). Efficacy results for KEYNOTE-170 are summarized in Table 74.

Table 74: Efficacy Results in Patients with PMBCL in KEYNOTE-170

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

* Median follow-up time of 9.7 months
† Based on patients (n=24) with a response by independent review
NR = not reached

14.7 Urothelial Cancer

In Combination with Enfortumab Vedotin for the Treatment of Patients with Urothelial Cancer

The efficacy of KEYTRUDA in combination with enfortumab vedotin was evaluated in KEYNOTE-A39 (NCT04223856), an open-label, randomized, multicenter trial that enrolled 886 patients with locally advanced or metastatic urothelial cancer who received no prior systemic therapy for locally advanced or metastatic disease. Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded.

Patients were randomized 1:1 to receive either:

- KEYTRUDA 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle. KEYTRUDA was given approximately 30 minutes after enfortumab vedotin. Treatment was continued until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, KEYTRUDA was continued for up to 2 years.
- Gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m^2 or carboplatin (AUC = 4.5 or 5) on Day 1 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity for up to 6 cycles.

Randomization was stratified by cisplatin eligibility, PD-L1 expression, and presence of liver metastases.

The median age was 69 years (range: 22 to 91); 77% were male; 67% were White, 22% were Asian, 1% were Black or African American, and 10% were unknown or other; 12% were Hispanic or Latino. Patients had a baseline ECOG performance status of 0 (49%), 1 (47%), or 2 (3%). Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 95% of patients had metastatic urothelial cancer, including 72% with visceral and 22% with liver metastases, and 5% had locally advanced urothelial cancer. Eighty-five percent of patients had urothelial carcinoma (UC) histology including 6% with UC mixed squamous differentiation and 2% with UC mixed other histologic variants. Forty-six percent of patients were considered cisplatin-ineligible and 54% were considered cisplatin-eligible at time of randomization.

The major efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1. Additional efficacy outcome measures included ORR as assessed by BICR.

The trial demonstrated statistically significant improvements in OS, PFS, and ORR for patients randomized to KEYTRUDA in combination with enfortumab vedotin as compared to platinum-based chemotherapy. Efficacy results were consistent across all stratified patient subgroups.

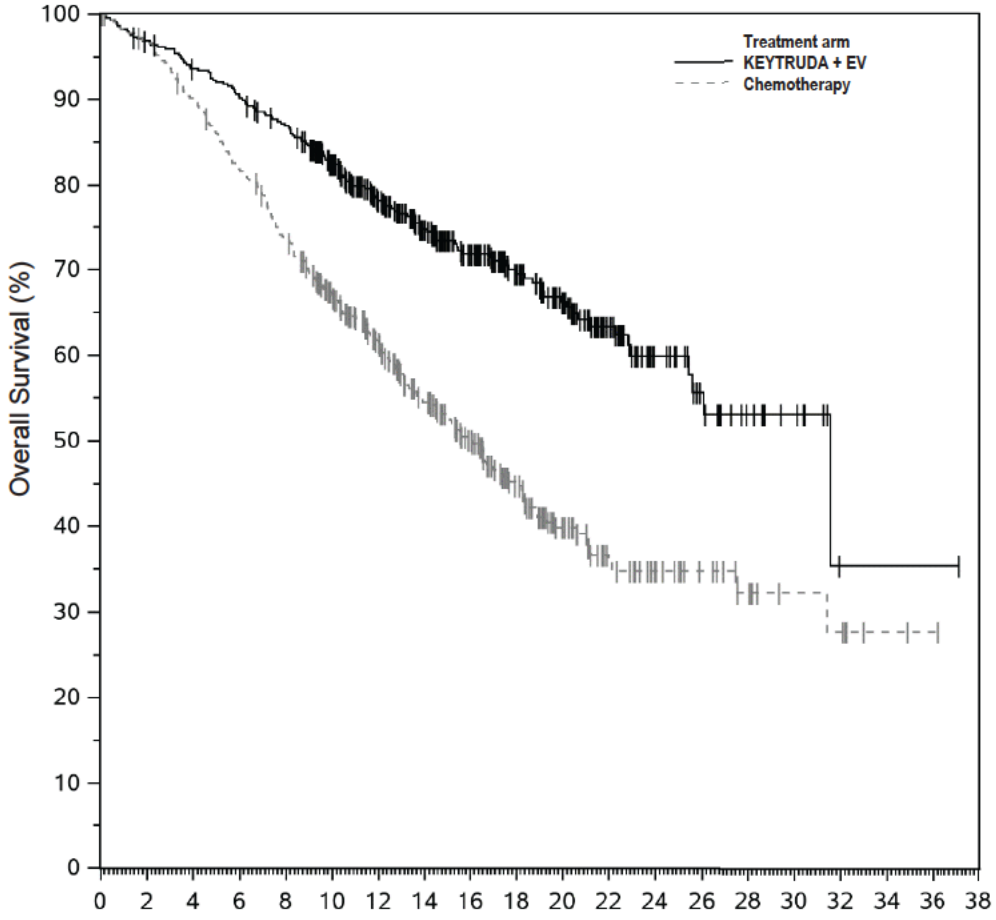
Table 75 and Figures 16 and 17 summarize the efficacy results for KEYNOTE-A39.

Table 75: Efficacy Results in KEYNOTE-A39

Endpoint	KEYTRUDA 200 mg every 3 weeks in combination with Enfortumab Vedotin n=442	Cisplatin or carboplatin with gemcitabine n=444
OS		
Number (%) of patients with event	133 (30%)	226 (51%)
Median in months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)
Hazard ratio* (95% CI)	0.47 (0.38, 0.58)	
p-Value†	<0.0001	
PFS		
Number (%) of patients with event	223 (50%)	307 (69%)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio* (95% CI)	0.45 (0.38, 0.54)	
p-Value†	<0.0001	
Confirmed Objective Response Rate‡		
ORR§ % (95% CI)	68% (63, 72)	44% (40, 49)
p-Value¶	<0.0001	
Complete response	29%	12%
Partial response	39%	32%

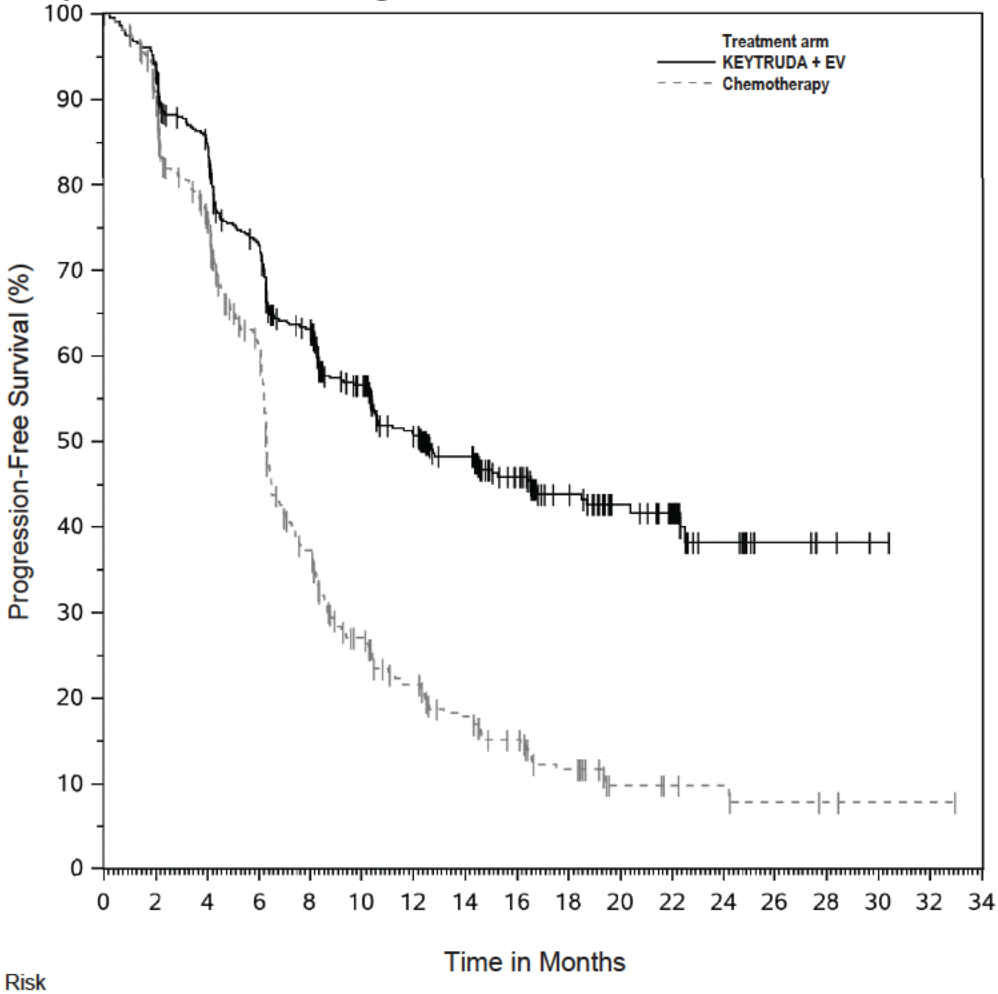
* Based on the stratified Cox proportional hazard regression model
† Two-sided p-Value based on stratified log-rank test
‡ Includes only patients with measurable disease at baseline (n=437 for KEYTRUDA in combination with enfortumab vedotin, n=441 for chemotherapy).
§ Based on patients with a best overall response as confirmed complete or partial response
¶ Two-sided p-Value based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases
NR = not reached

Figure 16: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A39



Number at Risk																			
KEYTRUDA + EV	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1	0
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1	0

Figure 17: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A39



In Combination with Enfortumab Vedotin for the Treatment of Cisplatin-Ineligible Patients with Urothelial Cancer

The efficacy of KEYTRUDA in combination with enfortumab vedotin was evaluated in KEYNOTE-869 (NCT03288545), an open-label, multi-cohort (dose escalation cohort, Cohort A, Cohort K) study in patients with locally advanced or metastatic urothelial cancer who were ineligible for cisplatin-containing chemotherapy and received no prior systemic therapy for locally advanced or metastatic disease. Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded from participating in the study.

Patients in the dose escalation cohort (n=5), Cohort A (n=40), and Cohort K (n=76) received enfortumab vedotin 1.25 mg/kg as an IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by KEYTRUDA 200 mg as an IV infusion on Day 1 of a 21-day cycle approximately 30 minutes after enfortumab vedotin. Patients were treated until disease progression or unacceptable toxicity.

A total of 121 patients received KEYTRUDA in combination with enfortumab vedotin. The median age was 71 years (range: 51 to 91); 74% were male; 85% were White, 5% were Black, 4% were Asian and 6% were other, unknown or not reported. Ten percent of patients were Hispanic or Latino. Forty-five

percent of patients had an ECOG performance status of 1 and 15% had an ECOG performance status of 2. Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. Reasons for cisplatin-ineligibility included: 60% with baseline creatinine clearance of 30-59 mL/min, 10% with ECOG PS of 2, 13% with Grade 2 or greater hearing loss, and 16% with more than one cisplatin-ineligibility criteria.

At baseline, 97.5% of patients had metastatic urothelial cancer and 2.5% of patients had locally advanced urothelial cancer. Thirty-seven percent of patients had upper tract disease. Eighty-four percent of patients had visceral metastasis at baseline, including 22% with liver metastases. Thirty-nine percent of patients had TCC histology; 13% had TCC with squamous differentiation, and 48% had TCC with other histologic variants.

The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1.

The median follow-up time for the dose escalation cohort + Cohort A was 44.7 months (range 0.7 to 52.4) and for Cohort K was 14.8 months (range: 0.6 to 26.2).

Efficacy results are presented in Table 76 below.

Table 76: Efficacy Results in KEYNOTE-869, Combined Dose Escalation Cohort, Cohort A, and Cohort K

Endpoint	KEYTRUDA in combination with Enfortumab Vedotin n=121
Confirmed ORR (95% CI)	68% (58.7, 76.0)
Complete response rate	12%
Partial response rate	55%

The median duration of response for the dose escalation cohort + Cohort A was 22.1 months (range: 1.0+ to 46.3+) and for Cohort K was not reached (range: 1.2 to 24.1+).

Platinum-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 had one or more comorbidities, including patients who were not eligible for any platinum-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. Fifty percent of patients had baseline creatinine clearance of <60 mL/min, 32% had ECOG PS of 2, 9% had ECOG PS of 2 and baseline creatinine clearance of <60 mL/min, and 9% had one or more of 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 11.4 months (range 0.1 to 63.8 months). Efficacy results are summarized in Table 77.

Table 77: Efficacy Results in KEYNOTE-052

Endpoint	KEYTRUDA 200 mg every 3 weeks
	All Subjects n=370
Objective Response Rate	
ORR (95% CI)	29% (24, 34)
Complete response rate	10%
Partial response rate	20%
Duration of Response	
Median in months (range)	33.4 (1.4+, 60.7+)

\+ Denotes ongoing response

Platinum-Eligible Patients with Previously Untreated Urothelial Carcinoma

The efficacy of KEYTRUDA for the first-line treatment of platinum-eligible patients with locally advanced or metastatic urothelial carcinoma was investigated in KEYNOTE-361 (NCT02853305), a multicenter, randomized, open-label, active-controlled study in 1010 previously untreated patients. The safety and efficacy of KEYTRUDA in combination with platinum-based chemotherapy for previously untreated patients with locally advanced or metastatic urothelial carcinoma has not been established.

The study compared KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. Among the patients receiving KEYTRUDA plus platinum-based chemotherapy, 44% received cisplatin and 56% received carboplatin.

The study did not meet its major efficacy outcome measures of improved PFS or OS in the KEYTRUDA plus chemotherapy arm compared to the chemotherapy-alone arm. Additional efficacy endpoints, including improvement of OS in the KEYTRUDA monotherapy arm, could not be formally tested.

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 78 and Figure 18 summarize the efficacy results for KEYNOTE-045.

Table 78: Efficacy Results in KEYNOTE-045

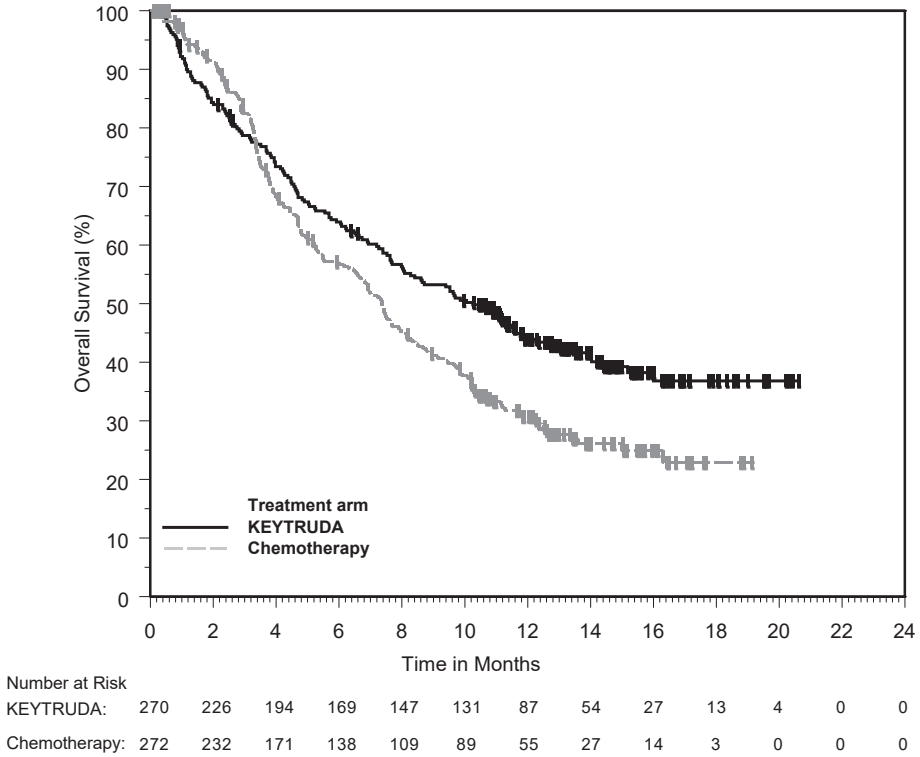
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (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 18: 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 79.

Table 79: Efficacy Results in KEYNOTE-057

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

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

\+ Denotes ongoing response

14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancers enrolled in three multicenter, non-randomized, open-label, multi-cohort trials: KEYNOTE-164 (NCT02460198), KEYNOTE-158 (NCT02628067), and KEYNOTE-051 (NCT02332668). All trials excluded patients with autoimmune disease or a medical condition that required immunosuppression. Regardless of histology, MSI or MMR tumor status was determined using polymerase chain reaction (PCR; local or central) or immunohistochemistry (IHC; local or central), respectively.

- KEYNOTE-164 enrolled 124 patients with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with fluoropyrimidine and either oxaliplatin or irinotecan +/- anti-VEGF/EGFR mAb-based therapy.
- KEYNOTE-158 enrolled 373 patients with advanced MSI-H or dMMR non-colorectal cancers (non-CRC) who had disease progression following prior therapy. Patients were either prospectively

enrolled with MSI-H/dMMR tumors (Cohort K) or retrospectively identified in one of 10 solid tumor cohorts (Cohorts A-J).

- KEYNOTE-051 enrolled 7 pediatric patients with MSI-H or dMMR cancers.

Adult patients received KEYTRUDA 200 mg every 3 weeks (pediatric patients received 2 mg/kg every 3 weeks) until unacceptable toxicity, disease progression, or a maximum of 24 months. In KEYNOTE-164 and KEYNOTE-158, assessment of tumor status was performed every 9 weeks through the first year, then every 12 weeks thereafter. In KEYNOTE-051, assessment of tumor status was performed every 8 weeks for 24 weeks, 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 in KEYNOTE-158) and as assessed by the investigator according to RECIST v1.1 in KEYNOTE-051.

In KEYNOTE-164 and KEYNOTE-158, the study population characteristics were median age of 60 years, 36% age 65 or older; 44% male; 78% White, 14% Asian, 4% American Indian or Alaska Native, and 3% Black; and 45% ECOG PS of 0 and 55% ECOG PS of 1. Ninety-two percent of patients had metastatic disease and 4% had locally advanced, unresectable disease. Thirty-seven percent of patients received one prior line of therapy and 61% received two or more prior lines of therapy.

In KEYNOTE-051, the study population characteristics were median age of 11 years (range: 3 to 16); 71% female; 86% White and 14% Asian; and 57% had a Lansky/Karnofsky Score of 100. Seventy-one percent of patients had Stage IV and 14% had Stage III disease. Fifty-seven percent of patients received one prior line of therapy and 29% received two prior lines of therapy.

Discordant results were observed between local MSI-H or dMMR tests and central testing among patients enrolled in Cohort K of KEYNOTE-158. Among 104 tumor samples that were MSI-H or dMMR by local testing and also tested using the FoundationOne®CDx (F1CDx) test, 59 (56.7%) were MSI-H and 45 (43.3%) were not MSI-H. Among 169 tumor samples that were MSI-H or dMMR by local testing and also tested using the VENTANA MMR RxDx Panel, 105 (62.1%) were dMMR and 64 (37.9%) were pMMR.

Efficacy results are summarized in Tables 80 and 81.

Table 80: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	KEYTRUDA n=504*
Objective Response Rate	
ORR (95% CI)†	33.3% (29.2, 37.6)
Complete response rate	10.3%
Partial response rate	23.0%
Duration of Response	n=168
Median in months (range)	63.2 (1.9+, 63.9+)
% with duration ≥12 months	77%
% with duration ≥36 months	39%

* Median follow-up time of 20.1 months (range 0.1 to 71.4 months)
† Of the 7 pediatric patients from KEYNOTE-051, 1 patient had a radiographic complete response after initial growth of their tumor but is not reflected in the results.
\+ Denotes ongoing response

Table 81: Response by Tumor Type

	N	Objective Response Rate n (%)	95% CI	Duration of Response range (months)
CRC	124	42 (34%)	(26%, 43%)	(4.4, 58.5+)
Non-CRC*	380	126 (33%)	(28%, 38%)	(1.9+, 63.9+)
Endometrial cancer	94	47 (50%)	(40%, 61%)	(2.9, 63.2)
Gastric or GE junction cancer	51	20 (39%)	(26%, 54%)	(1.9+, 63.0+)
Small intestinal cancer	27	16 (59%)	(39%, 78%)	(3.7+, 57.3+)
Brain cancer	27†	1 (4%)‡	(0%, 19%)	18.9
Ovarian cancer	25	8 (32%)	(15%, 54%)	(4.2, 56.6+)
Biliary cancer	22	9 (41%)	(21%, 64%)	(6.2, 49.0+)
Pancreatic cancer	22	4 (18%)	(5%, 40%)	(8.1, 24.3+)
Sarcoma	14	3 (21%)	(5%, 51%)	(35.4+, 57.2+)
Breast cancer	13	1 (8%)	(0%,36%)	24.3+
Other§	13	4 (31%)	(9%, 61%)	(6.2+, 32.3+)
Cervical cancer	11	1 (9%)	(0%, 41%)	63.9+
Neuroendocrine cancer	11	1 (9%)	(0%, 41%)	13.3
Prostate cancer	8	1 (13%)	(0%, 53%)	24.5+
Adrenocortical cancer	7	1 (14%)	(0%, 58%)	4.2
Mesothelioma	7	0 (0%)	(0%, 41%)	
Thyroid cancer	7	1 (14%)	(0%, 58%)	8.2
Small cell lung cancer	6	2 (33%)	(4%, 78%)	(20.0, 47.5)
Bladder cancer	6	3 (50%)	(12%, 88%)	(35.6+, 57.5+)
Salivary cancer	5	2 (40%)	(5%, 85%)	(42.6+, 57.8+)
Renal cell cancer	4	1 (25%)	(0%, 81%)	22.0

* Results include patients in Cohort K of KEYNOTE-158 that were later determined to be pMMR or not MSI-H by central testing

† Includes 6 pediatric patients with brain cancer

‡ In addition to the 1 adult responder, 1 pediatric patient had a radiographic complete response after initial growth of their tumor.

§ Includes tumor type (n): anal (3), HNSCC (1), nasopharyngeal (1), retroperitoneal (1), testicular (1), vaginal (1), vulvar (1), appendiceal adenocarcinoma, NOS (1), hepatocellular carcinoma (1), and carcinoma of unknown origin (1). Includes 1 pediatric patient with abdominal adenocarcinoma.

\+ Denotes ongoing response

Exploratory analysis by TMB

In an exploratory analysis performed in 138 patients (Cohort K of KEYNOTE-158) who were tested retrospectively for tumor mutation burden (TMB) using an FDA-approved test, 45 (33%) had tumors with TMB score of <10 mut/Mb; ORR in these 45 patients was 6.7% (95% CI: 1.4, 18.3). Among the 45 patients with TMB score of <10 mut/Mb, 39 of the patients were pMMR/not MSI-H when tested using an FDA-approved test.

14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

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

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

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

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression. The main efficacy outcome measures were PFS (as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) and OS. Additional efficacy outcome measures were ORR and DoR.

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

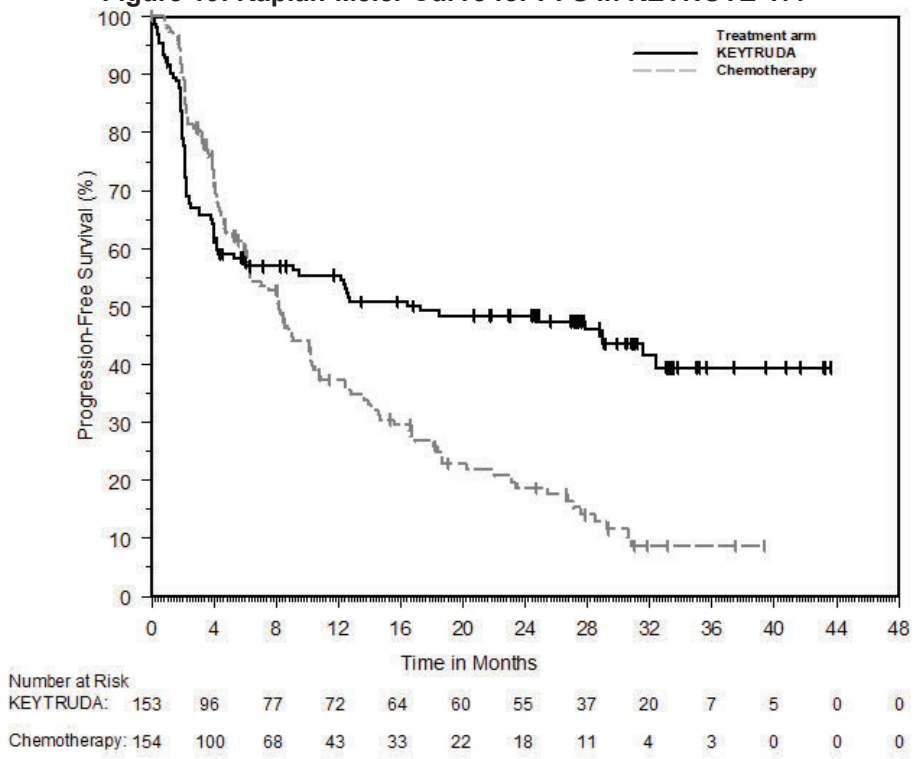
The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis. Sixty percent of the patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including KEYTRUDA. The median follow-up time at the final analysis was 38.1 months (range: 0.2 to 58.7 months). Table 82 and Figure 19 summarize the key efficacy measures for KEYNOTE-177.

Table 82: 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	
OS‡		
Number (%) of patients with event	62 (41%)	78 (51%)
Median in months (95% CI)	NR (49.2, NR)	36.7 (27.6, NR)
Hazard ratio* (95% CI)	0.74 (0.53, 1.03)	
p-Value§	0.0718	
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 monthsᵇ	75%	37%
% with duration ≥24 monthsᵇ	43%	18%

* Based on Cox regression model
† Two-sided p-Value based on log-rank test (compared to a significance level of 0.0234)
‡ Final OS analysis
§ Two-sided p-Value based on log-rank test (compared to a significance level of 0.0492)
¶ 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
ᵇ Based on observed duration of response
\+ Denotes ongoing response
NR = not reached

Figure 19: Kaplan-Meier Curve for PFS in KEYNOTE-177



14.10 Gastric Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction 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 enrolled 698 patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. 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 ≥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 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. The major outcome measures assessed were PFS 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.

Additional outcome measures included ORR and DoR, based on BICR using RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Among the 698 patients, randomized, 594 (85%) had tumors that expressed PD-L1 with a CPS ≥1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. The population characteristics of these 594 patients were: median age of 63 years (range: 19 to 85), 43% age 65 or older; 80% male; 63% White, 33% Asian, and 0.7% Black; 42% ECOG PS of 0 and 58% ECOG PS of 1. Ninety-eight percent of patients had metastatic disease (Stage IV) and 2% had locally advanced unresectable disease. Ninety-five percent (n=562) had tumors that were not MSI-H, 1% (n=8) had tumors that were MSI-H, and in 4% (n=24) the status was not known. Eighty-five percent of patients received CAPOX.

A statistically significant improvement in OS and PFS was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy; however, an exploratory analysis of OS in the PD-L1 CPS <1 population showed a HR of 1.10 (95% CI: 0.72, 1.68), indicating that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1.

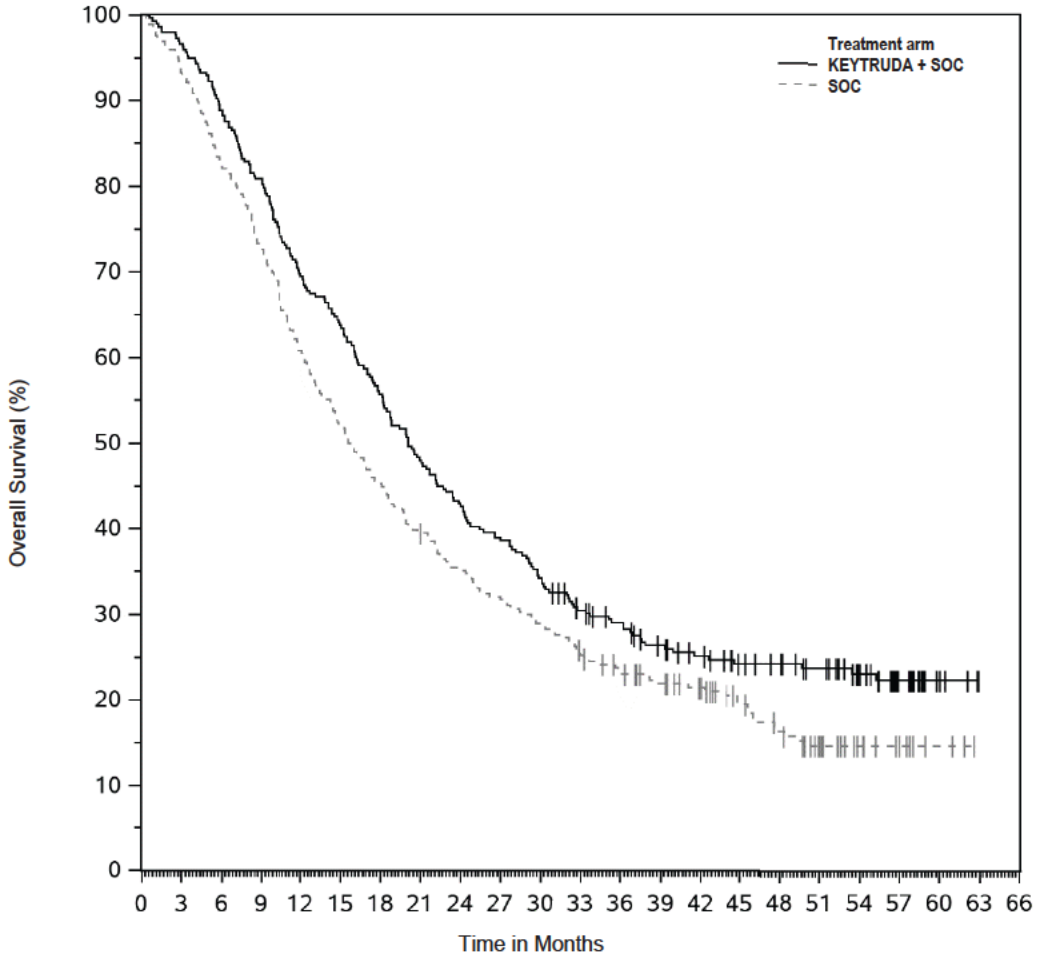
Efficacy results at the final analysis for the subgroup of patients whose tumors expressed PD-L1 with a CPS ≥1 are summarized in Table 83 and Figure 20.

Table 83: Efficacy Results for KEYNOTE-811 with PD-L1 Expression CPS ≥1

Endpoint	**KEYTRUDA 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=298**	**Placebo Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=296**
OS		
Number (%) of patients with event	226 (76%)	244 (82%)
Median in months‡ (95% CI)	20.1 (17.9, 22.9)	15.7 (13.5, 18.5)
Hazard ratio* (95% CI)	0.79 (0.66, 0.95)	
PFS		
Number (%) of patients with event	221 (74%)	226 (76%)
Median in months‡ (95% CI)	10.9 (8.5, 12.5)	7.3 (6.8, 8.4)
Hazard ratio* (95% CI)	0.72 (0.60, 0.87)	
Objective Response Rate		
ORR† (95% CI)	73% (68, 78)	58% (53, 64)
Complete response rate	17%	10%
Partial response rate	56%	48%
Duration of Response	n=218	n=173
Median in months‡ (95% CI) Range in months	11.3 (9.9, 13.7) 1.1+, 60.8+	9.6 (7.1, 11.2) 1.4+, 60.5+

* Based on the unstratified Cox proportional hazard model
† Response: Best objective response as confirmed complete
‡ Based on Kaplan-Meier estimation
\+ Denotes ongoing response

Figure 20: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-811 (CPS ≥1)



Number at Risk																					
KEYTRUDA + SOC	298	288	265	241	207	190	166	143	127	115	102	86	78	67	59	51	48	42	32	18	5	0	0
SOC	296	276	244	215	180	154	135	117	104	93	85	73	63	56	50	38	30	21	13	9	3	0	0

First-line Treatment of Locally Unresectable or Metastatic HER2-Negative Gastric or Gastroesophageal Junction Adenocarcinoma

The efficacy of KEYTRUDA in combination with fluoropyrimidine- and platinum-containing chemotherapy was investigated in KEYNOTE-859 (NCT03675737), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1579 patients with HER2-negative advanced gastric or 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 ≥1 or CPS <1), chemotherapy regimen (FP or 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; treatment was administered prior to chemotherapy on Day 1 of each cycle:

- KEYTRUDA 200 mg, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).
- Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX).

All study medications, except oral capecitabine, were administered as an intravenous infusion every 3-week cycle. Platinum agents could be administered for 6 or more cycles following local guidelines. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. The major efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS, ORR, and DoR 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.

The population characteristics were: median age of 62 years (range: 21 to 86), 39% age 65 or older; 68% male and 32% female; 55% White, 34% Asian, 4.6% Multiple, 4.2% American Indian or Alaskan Native, 1.3% Black, and 0.2% Native Hawaiian or other Pacific Islander; 76% Not Hispanic or Latino and 21% Hispanic or Latino; 37% ECOG PS of 0 and 63% ECOG PS of 1. Ninety-seven percent of patients had metastatic disease (Stage IV) and 3% had locally advanced unresectable disease. Seventy-eight percent had tumors that expressed PD-L1 with a CPS ≥1 and 5% (n=74) had tumors that were MSI-H. Eighty-six percent of patients received CAPOX.

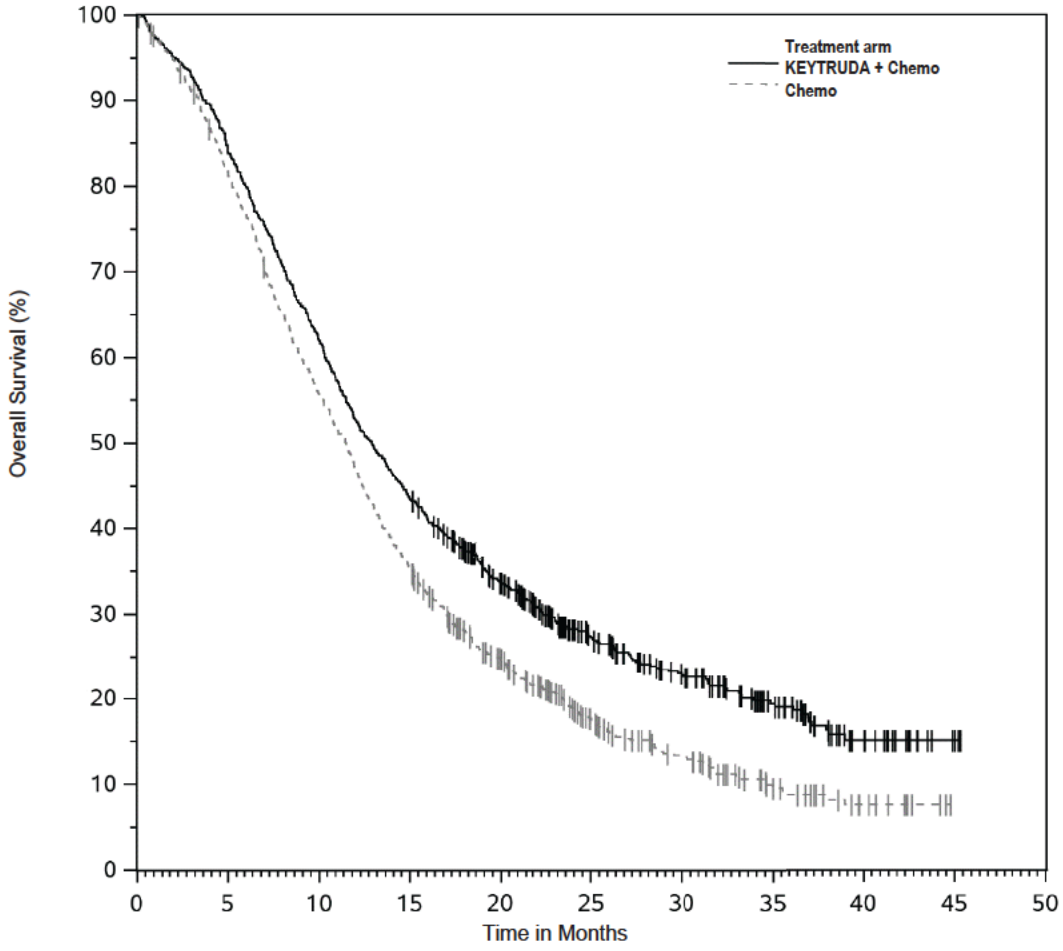
A statistically significant improvement in OS, PFS, and ORR was demonstrated in patients randomized to KEYTRUDA in combination with chemotherapy compared with placebo in combination with chemotherapy at the time of a pre-specified interim analysis of OS. Efficacy results are summarized in Table 84 and Figures 21 and 22.

Table 84: Efficacy Results* for KEYNOTE-859

Endpoint	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=790	Placebo and FP or CAPOX n=789	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=618	Placebo and FP or CAPOX n=617	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=279	Placebo and FP or CAPOX n=272
	All Patients		CPS≥1		CPS≥10	
OS						
Number (%) of patients with event	603 (76)	666 (84)	464 (75)	526 (85)	188 (67)	226 (83)
Median in months (95% CI)	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)	15.7 (13.8, 19.3)	11.8 (10.3, 12.7)
Hazard ratio† (95% CI)	0.78 (0.70, 0.87)		0.74 (0.65, 0.84)		0.65 (0.53, 0.79)	
p-Value (stratified log-rank)‡	<0.0001		<0.0001		<0.0001	
PFS						
Number (%) of patients with event	572 (72)	608 (77)	443 (72%)	483 (78%)	190 (68)	210 (77)
Median in months (95% CI)	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)	8.1 (6.8, 8.5)	5.6 (5.4, 6.7)
Hazard ratio† (95% CI)	0.76 (0.67, 0.85)		0.72 (0.63, 0.82)		0.62 (0.51, 0.76)	
p-Value (stratified log-rank)‡	<0.0001		<0.0001		<0.0001	
Objective Response Rate						
ORR§ (95% CI)	51% (48, 55)	42% (38, 45)	52% (48, 56)	43% (39, 47)	61% (55, 66)	43% (37, 49)
Complete response rate	9%	6%	10%	6%	13%	5%
Partial response rate	42%	36%	42%	37%	48%	38%
p-Value¶	<0.0001		0.0004		<0.0001	
Duration of Response	n=405	n=331	n=322	n=263	n=169	n=117
Median in months# (95% CI)	8.0 (7.0, 9.7)	5.7 (5.5, 6.9)	8.3 (7.0, 10.9)	5.6 (5.4, 6.9)	10.9 (8.0, 13.8)	5.8 (5.3, 7.0)
Range in months	1.2+, 41.5+	1.3+, 34.7+	1.2+, 41.5+	1.3+, 34.2+	1.2+, 41.5+	1.4+, 31.2+

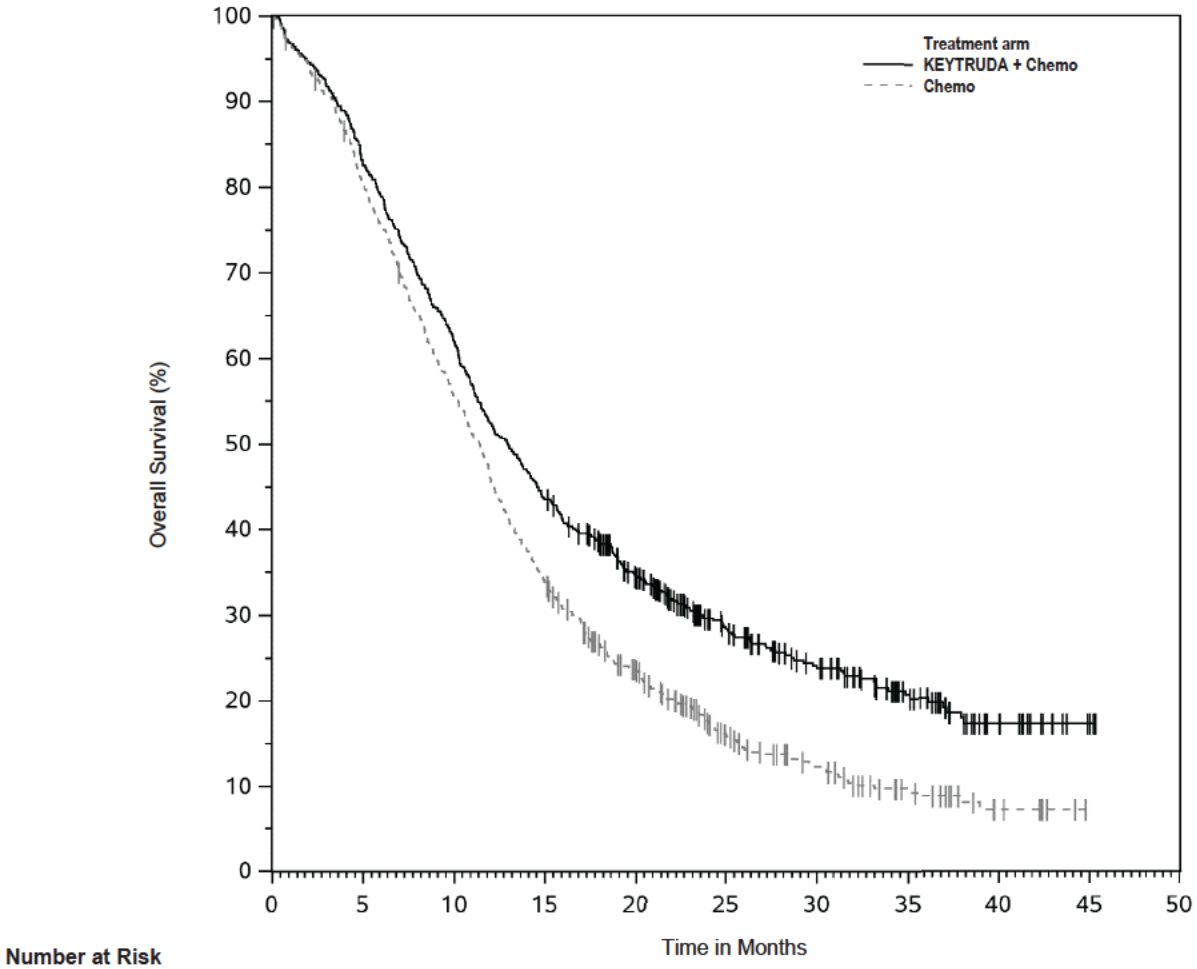
* Based on a pre-specified interim analysis
† Based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ One-sided p-Value based on stratified Miettinen & Nurminen method
# Based on Kaplan-Meier estimates
\+ Denotes ongoing response

Figure 21: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859



Number at Risk											
KEYTRUDA + Chemo	790	663	490	343	240	143	95	55	19	3	0
Chemo	789	636	434	274	169	95	58	26	10	0	0

Figure 22: Kaplan-Meier Curve for Overall Survival in KEYNOTE-859 (CPS≥1)



In an exploratory subgroup analysis in patients with PD-L1 CPS<1 (n=344) at the time of the pre-specified interim analysis of OS, the median OS was 12.7 months (95% CI: 11.4, 15.0) for the KEYTRUDA arm and 12.2 months (95% CI: 9.5, 14.0) for the placebo arm, with a HR of 0.92 (95% CI: 0.73, 1.17).

14.11 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.

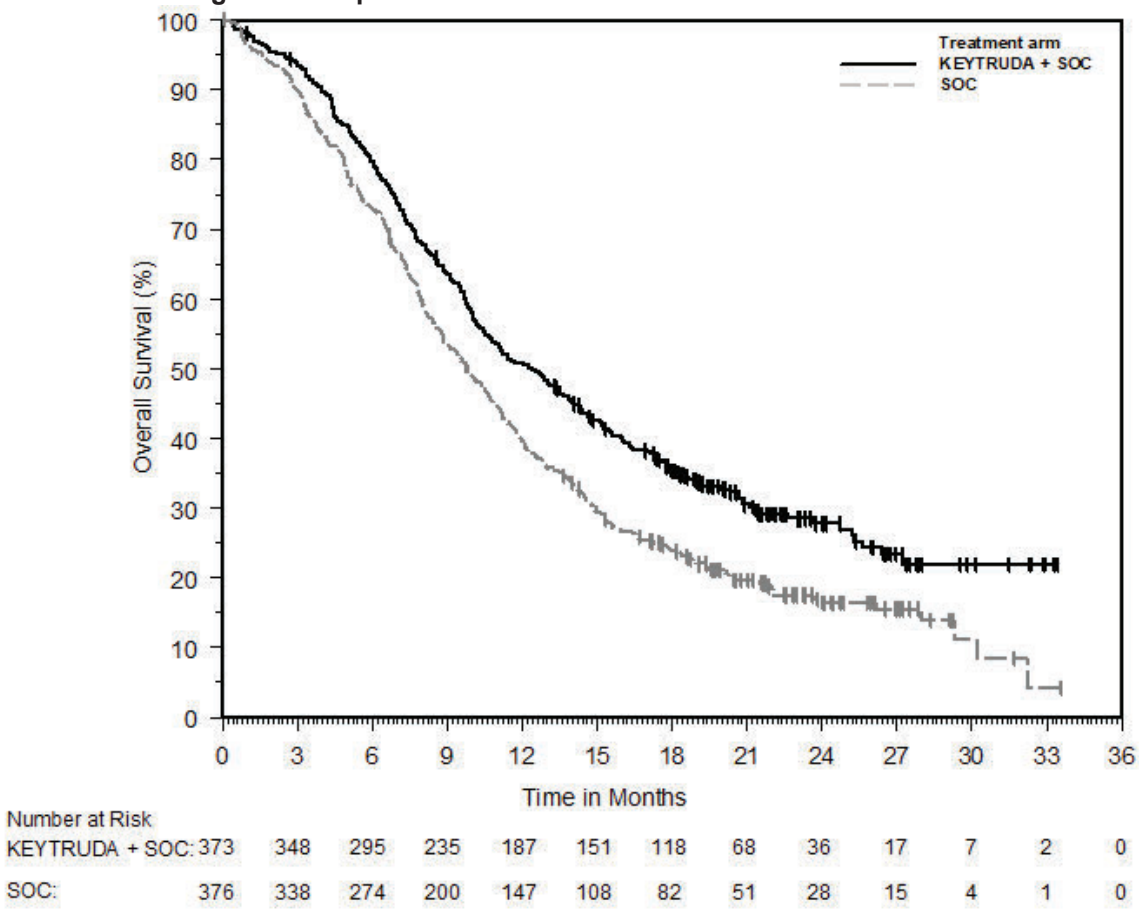
Table 85 and Figure 23 summarize the efficacy results for KEYNOTE-590 in all patients.

Table 85: 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 23: 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.

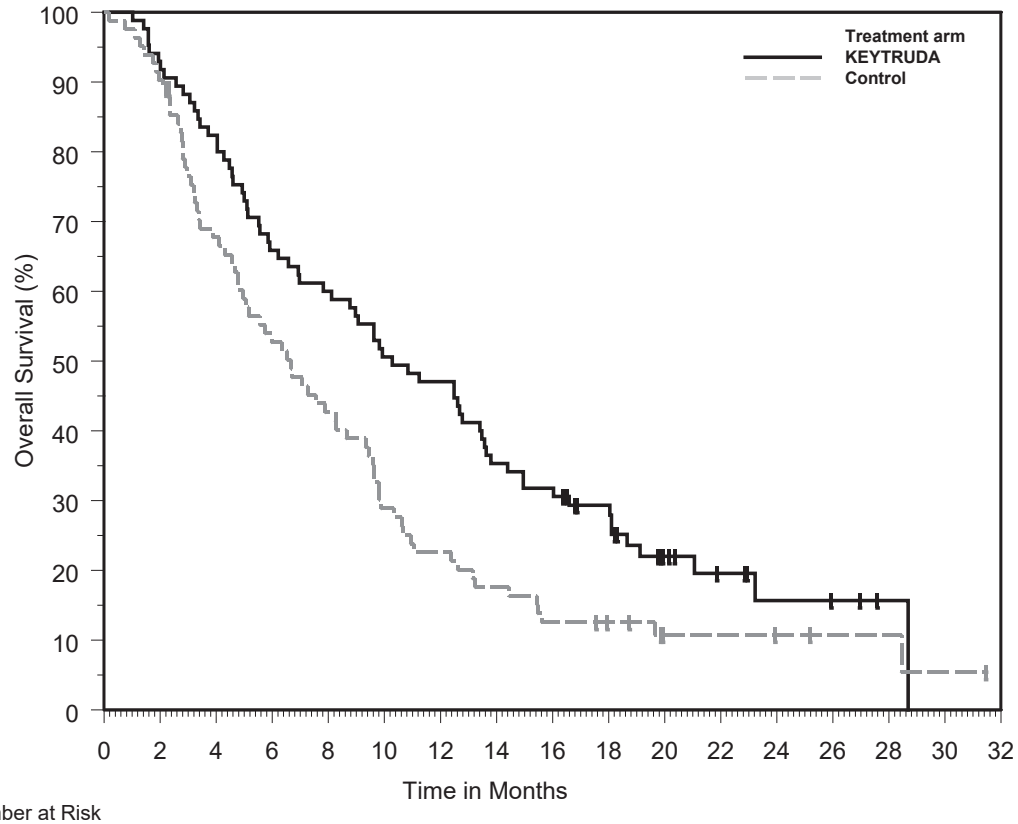
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 86 and Figure 24 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10.

Table 86: 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 24: Kaplan-Meier Curve for Overall Survival in KEYNOTE-181 (ESCC CPS ≥10)



KEYNOTE-180

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

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

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

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

14.12 Cervical Cancer

FIGO 2014 Stage III-IVA Cervical Cancer with Chemoradiotherapy

The efficacy of KEYTRUDA in combination with CRT (cisplatin and external beam radiation therapy [EBRT] followed by brachytherapy [BT]) was investigated in KEYNOTE-A18 (NCT04221945), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1060 patients with cervical

cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. There were 596 patients with FIGO 2014 Stage III-IVA (tumor involvement of the lower vagina with or without extension onto pelvic sidewall or hydronephrosis/non-functioning kidney or has spread to adjacent pelvic organs) with either node-positive or node-negative disease, and 462 patients with FIGO 2014 Stage IB2-IIB (tumor lesions >4 cm or clinically visible lesions that have spread beyond the uterus but have not extended onto the pelvic wall or to the lower third of vagina) with node-positive disease; two patients had FIGO 2014 Stage IVB disease. Randomization was stratified by planned type of EBRT (Intensity-modulated radiation therapy [IMRT] or volumetric modulated arc therapy [VMAT] vs. non-IMRT and non-VMAT), stage at screening of cervical cancer (FIGO 2014 Stage IB2-IIB vs. FIGO 2014 Stage III-IVA), and planned total radiotherapy dose (EBRT + brachytherapy dose of <70 Gy vs. ≥70 Gy as per equivalent dose [EQD2]).

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

- KEYTRUDA 200 mg IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by KEYTRUDA 400 mg IV every 6 weeks (15 cycles)
- Placebo IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by placebo IV every 6 weeks (15 cycles)

Treatment continued until RECIST v1.1-defined progression of disease as determined by investigator or unacceptable toxicity.

Assessment of tumor status was performed every 12 weeks from completion of CRT for the first two years, followed by every 24 weeks in year 3, and then annually. The major efficacy outcome measures were PFS as assessed by investigator according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, or histopathologic confirmation, and OS.

Among the 596 patients with FIGO 2014 Stage III-IVA disease, the baseline characteristics were: median age of 52 years (range: 22 to 87), 17% age 65 or older; 36% White, 34% Asian, 1% Black; 38% Hispanic or Latino; 68% ECOG PS 0 and 32% ECOG PS 1; 93% with CPS ≥1; 70% had positive pelvic and/or positive para-aortic lymph node(s) and 30% had neither positive pelvic nor para-aortic lymph node(s); 83% had squamous cell carcinoma and 17% had non-squamous histology. Regarding radiation, 85% of patients received IMRT or VMAT EBRT, and the median EQD2 dose was 87 Gy (range: 7 to 114).

The trial demonstrated a statistically significant improvement in PFS in the overall population. In an exploratory subgroup analysis for the 462 patients (44%) with FIGO 2014 Stage IB2-IIB disease, the PFS HR estimate was 0.91 (95% CI: 0.63, 1.31), indicating that the PFS improvement in the overall population was primarily attributed to the results seen in the subgroup of patients with FIGO 2014 Stage III-IVA disease. OS data were not mature at the time of PFS analysis, with 10% deaths in the overall population.

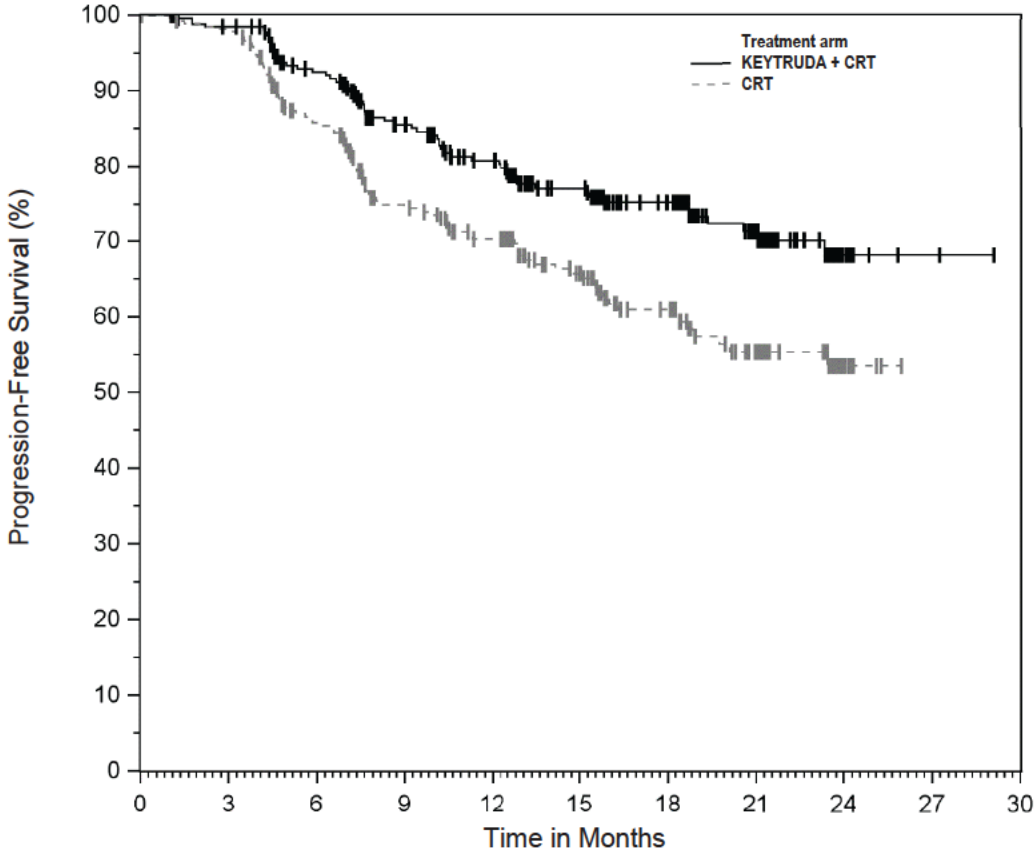
The efficacy results in the exploratory subgroup analysis of 596 patients with FIGO 2014 Stage III-IVA disease are summarized in Table 87 and Figure 25.

Table 87: Efficacy Results in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)

Endpoint	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=293	Placebo with CRT n=303
PFS by Investigator		
Number of patients with event (%)	61 (21%)	94 (31%)
Median in months (95% CI)	NR (NR, NR)	NR (18.8, NR)
12-month PFS rate (95% CI)	81% (75, 85)	70% (64, 76)
Hazard ratio* (95% CI)	0.59 (0.43, 0.82)	

* Based on the unstratified Cox proportional hazard model
CRT = Chemoradiotherapy
NR = not reached

Figure 25: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)



Number at Risk											
KEYTRUDA + CRT	293	254	223	186	163	129	96	62	11	2	0
CRT	303	261	209	163	142	109	78	46	8	0	0

Persistent, Recurrent, or Metastatic Cervical Cancer

The efficacy of KEYTRUDA in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826 (NCT03635567), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent. Patients were enrolled regardless of tumor PD-L1 expression status. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥10). Patients were randomized (1:1) to one of the two treatment groups:

- Treatment Group 1: KEYTRUDA 200 mg plus chemotherapy with or without bevacizumab
- Treatment Group 2: Placebo plus chemotherapy with or without bevacizumab

The investigator selected one of the following four treatment regimens prior to randomization:

1. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2

2. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2 + bevacizumab 15 mg/kg
3. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min + bevacizumab 15 mg/kg

All study medications were administered as an intravenous infusion. All study treatments were administered on Day 1 of each 3-week treatment cycle. Cisplatin could be administered on Day 2 of each 3-week treatment cycle. Treatment with KEYTRUDA continued until RECIST v1.1-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 considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed every 9 weeks for the first year, followed by every 12 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by investigator 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, according to RECIST v1.1, as assessed by investigator.

Of the 617 enrolled patients, 548 patients (89%) had tumors expressing PD-L1 with a CPS ≥1. Among these 548 enrolled patients with tumors expressing PD-L1, 273 patients were randomized to KEYTRUDA in combination with chemotherapy with or without bevacizumab, and 275 patients were randomized to placebo in combination with chemotherapy with or without bevacizumab. Sixty-three percent of the 548 patients received bevacizumab as part of study treatment. The baseline characteristics of the 548 patients were: median age of 51 years (range: 22 to 82), 16% age 65 or older; 59% White, 18% Asian, 6% American Indian or Alaska Native, and 1% Black; 37% Hispanic or Latino; 56% ECOG performance status 0 and 43% ECOG performance status 1. Seventy-five percent had squamous cell carcinoma, 21% adenocarcinoma, and 5% adenosquamous histology, and 32% of patients had metastatic disease at diagnosis. At study entry, 21% of patients had metastatic disease only and 79% had persistent or recurrent disease with or without distant metastases, of whom 39% had received prior chemoradiation only and 17% had received prior chemoradiation plus surgery.

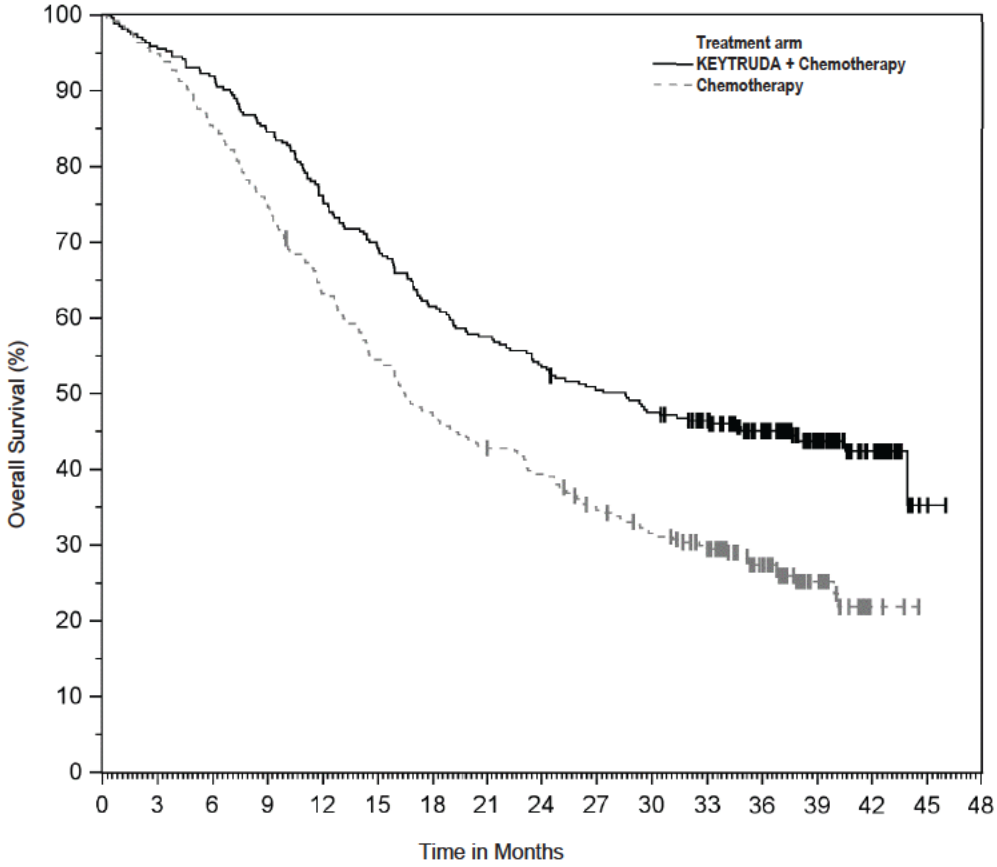
A statistically significant improvement in OS and PFS was demonstrated in patients randomized to receive KEYTRUDA compared with patients randomized to receive placebo. An updated OS analysis was conducted at the time of final analysis when 354 deaths in the CPS ≥1 population were observed. Table 88 and Figure 26 summarize the key efficacy measures for KEYNOTE-826 for patients with tumors expressing PD-L1 (CPS ≥1).

Table 88: Efficacy Results in Patients with Persistent, Recurrent, or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-826

Endpoint	KEYTRUDA 200 mg every 3 weeks and chemotherapy* with or without bevacizumab n=273	Placebo and chemotherapy* with or without bevacizumab n=275
OS		
Number of patients with event (%)	118 (43.2)	154 (56.0)
Median in months (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)
Hazard ratio† (95% CI)	0.64 (0.50, 0.81)	
p-Value‡	0.0001	
Updated OS		
Number of patients with event (%)	153 (56.0%)	201 (73.1%)
Median in months (95% CI)	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
Hazard ratio† (95% CI)	0.60 (0.49, 0.74)	
PFS		
Number of patients with event (%)	157 (57.5)	198 (72.0)
Median in months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
Hazard ratio† (95% CI)	0.62 (0.50, 0.77)	
p-Value§	< 0.0001	
Objective Response Rate		
ORR¶ (95% CI)	68% (62, 74)	50% (44, 56)
Complete response rate	23%	13%
Partial response rate	45%	37%
Duration of Response		
Median in months (range)	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Based on the stratified Cox proportional hazard model
‡ p-Value (one-sided) is compared with the allocated alpha of 0.0055 for this interim analysis (with 72% of the planned number of events for final analysis)
§ p-Value (one-sided) is compared with the allocated alpha of 0.0014 for this interim analysis (with 82% of the planned number of events for final analysis)
¶ Response: Best objective response as confirmed complete response or partial response
\+ Denotes ongoing response
NR = not reached

Figure 26: Kaplan-Meier Curve for Overall Survival in KEYNOTE-826 (CPS ≥1)*,†



Number at Risk																	
KEYTRUDA + Chemotherapy	273	261	251	231	206	189	168	157	146	136	128	116	90	52	22	2	0
Chemotherapy	275	261	235	207	173	149	129	117	107	91	81	68	45	24	3	0	0

*Treatment arms include KEYTRUDA plus chemotherapy, with or without bevacizumab, versus placebo plus chemotherapy, with or without bevacizumab.
†Based on the protocol-specified final OS analysis

Previously Treated Recurrent or Metastatic 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 89 for patients with PD-L1 expression (CPS ≥1).

Table 89: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158

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

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

14.13 Hepatocellular Carcinoma

Previously Treated HCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-394 (NCT03062358), a multicenter, randomized, placebo-controlled, double-blind trial conducted in Asia in patients with Barcelona Clinic Liver Cancer (BCLC) Stage B or C HCC, who were previously treated with sorafenib or oxaliplatin-based chemotherapy and who were not amenable to or were refractory to local-regional therapy. Patients were also required to have Child-Pugh A liver function.

Patients with hepatitis B had treated controlled disease (HBV viral load <2000 IU/mL or $<10^4$ copies/mL). Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Patients with hepatic encephalopathy, main branch portal venous invasion, clinically apparent ascites, or esophageal or gastric variceal bleeding within the last 6 months were also ineligible.

Randomization was stratified by prior treatment: sorafenib vs. oxaliplatin-based chemotherapy, macrovascular invasion, and etiology (active HBV vs. others (active HCV, non-infected)). Patients were randomized (2:1) to receive pembrolizumab 200 mg intravenously every 3 weeks or placebo.

Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Assessment of tumor status was performed every 6 weeks. The main efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, 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.

The study enrolled 453 patients, and 360 (79%) had active hepatitis B. The population characteristics in patients with active hepatitis B were: median age of 52 years (range: 23 to 82), 16% age 65 or older; 86% male; 100% Asian; 42% ECOG PS of 0 and 58% ECOG PS of 1; 90% received prior sorafenib and 10% received prior oxaliplatin-based chemotherapy. Patient characteristics also included extrahepatic disease (77%), macrovascular invasion (10%), BCLC stage C (93%) and B (7%), and baseline AFP ≥200 ng/mL (57%).

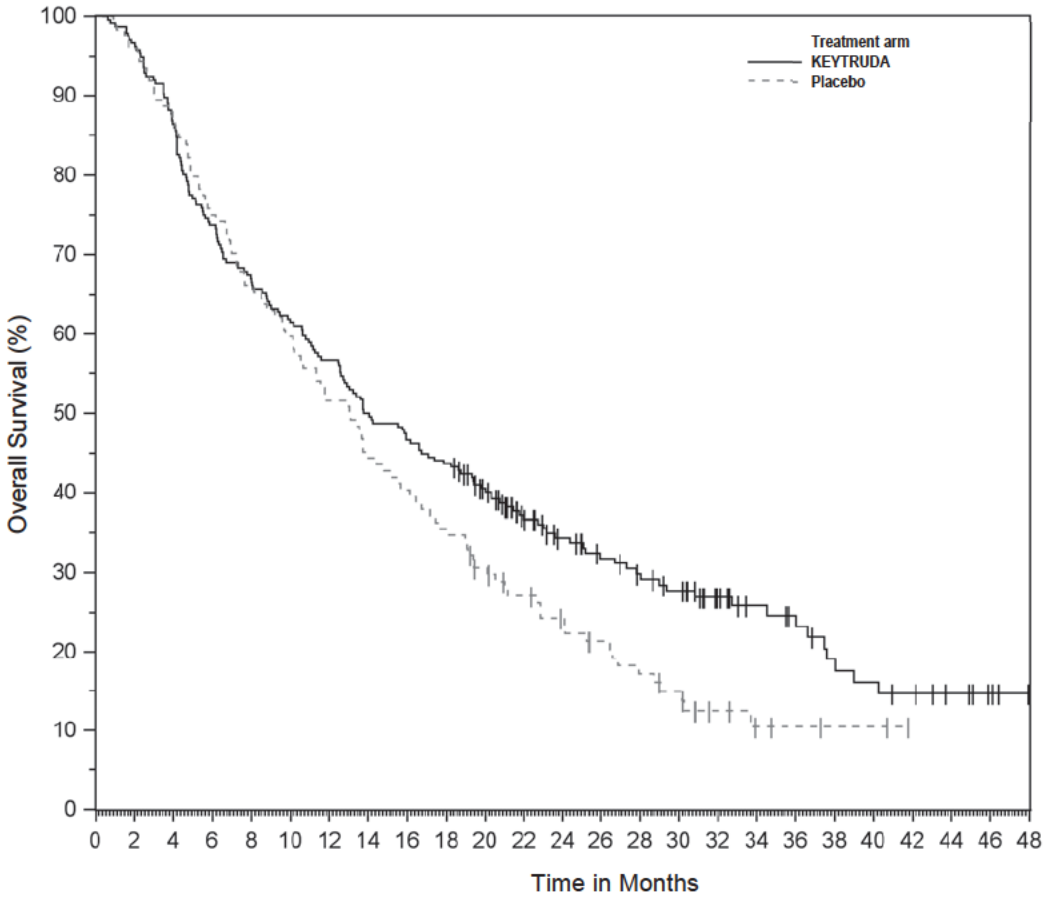
KEYNOTE-394 demonstrated improved OS in patients with HCC secondary to hepatitis B randomized to KEYTRUDA compared with placebo. Efficacy results are summarized in Table 90 and Figure 27.

Table 90: Efficacy Results in Patients with Hepatocellular Carcinoma in KEYNOTE-394

Endpoint	KEYTRUDA 200 mg every 3 weeks n=236	Placebo n=124
OS*		
Number (%) of patients with events	172 (73)	105 (85)
Median in months (95% CI)	13.9 (12.5, 17.9)	13.0 (10.1, 15.6)
Hazard ratio† (95% CI)	0.78 (0.61, 0.99)	
PFS‡		
Number (%) of patients with events	189 (80)	108 (87)
Median in months (95% CI)	2 (1.4, 2.7)	2.3 (1.4, 2.8)
Hazard ratio† (95% CI)	0.78 (0.61, 1.00)	
Objective Response Rate‡		
ORR§ (95% CI)	11% (7, 16)	1.6% (0.2, 5.7)
Number (%) of complete responses	2 (0.9%)	1 (0.8%)
Number (%) of partial responses	24 (10%)	1 (0.8%)
Duration of Response*	n=28	n=2
Median in months¶ (range)	23.9 (2.6+, 44.4+)	5.6 (3.0+, 5.6)

* Results at the pre-specified final OS analysis
† Based on the stratified Cox proportional hazard model
‡ Results at pre-specified interim OS analysis
§ Confirmed complete response or partial response
¶ Based on Kaplan-Meier estimate
\+ Denotes ongoing response

Figure 27: Kaplan-Meier Curve for Overall Survival in KEYNOTE-394



14.14 Biliary Tract Cancer

The efficacy of KEYTRUDA in combination with gemcitabine and cisplatin chemotherapy was investigated in KEYNOTE-966 (NCT04003636), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1069 patients with locally advanced unresectable or metastatic BTC, who had not received prior systemic therapy in the advanced disease setting. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by region (Asia vs. non-Asia), locally advanced versus metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

Patients were randomized (1:1) to KEYTRUDA 200 mg on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks, or placebo on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks. Study medications were administered via intravenous infusion. Treatment continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment continued for a maximum of 35 cycles, or approximately 24 months. For gemcitabine, treatment could be continued beyond 8 cycles while for cisplatin, treatment could be administered for a maximum of 8 cycles.

Administration of KEYTRUDA with chemotherapy was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Assessment of tumor status was performed at baseline and then every 6 weeks through 54 weeks, followed by every 12 weeks thereafter.

Study population characteristics were median age of 64 years (range: 23 to 85), 47% age 65 or older; 52% male; 49% White, 46% Asian, 1.3% Black or African American; 10% Hispanic or Latino; 46% ECOG PS of 0 and 54% ECOG PS of 1; 31% of patients had a history of hepatitis B infection, and 3% had a history of hepatitis C infection.

The major efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, 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.

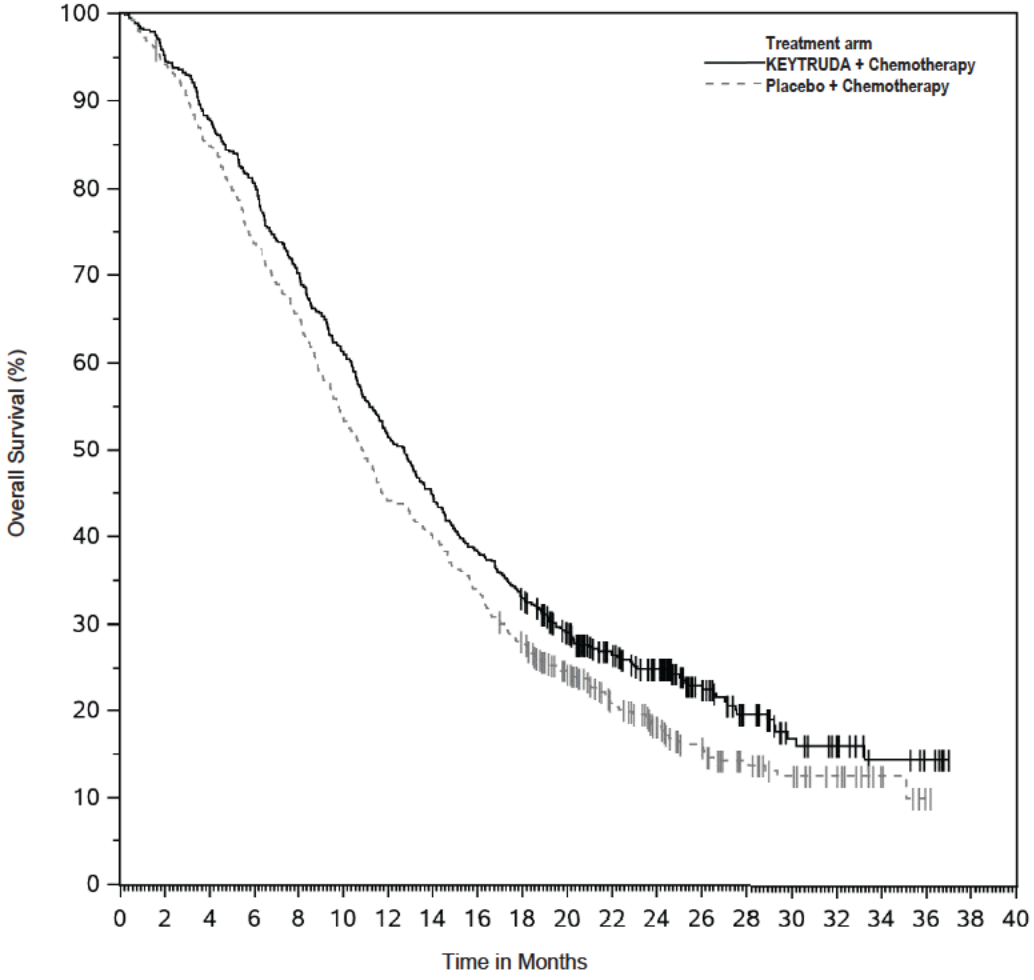
Table 91 and Figure 28 summarize the efficacy results for KEYNOTE-966.

Table 91: Efficacy Results in KEYNOTE-966

Endpoint	KEYTRUDA 200 mg every 3 weeks with gemcitabine/cisplatin n=533	Placebo with gemcitabine/cisplatin n=536
OS*		
Number of patients with event (%)	414 (78%)	443 (83%)
Median in months (95% CI)	12.7 (11.5, 13.6)	10.9 (9.9, 11.6)
Hazard ratio† (95% CI)	0.83 (0.72, 0.95)	
p-Value‡	0.0034	
PFS§		
Number (%) of patients with event	361 (68%)	391 (73%)
Median in months (95% CI)	6.5 (5.7, 6.9)	5.6 (5.1, 6.6)
Hazard ratio† (95% CI)	0.86 (0.75, 1.00)	
p-Value‡	NS	
Objective Response Rate§		
ORR¶ (95% CI)	29% (25, 33)	29% (25, 33)
Number (%) of complete responses	11 (2.1%)	7 (1.3%)
Number (%) of partial responses	142 (27%)	146 (27%)
p-Value #	NS	
Duration of Response*	n=156	n=152
Median in months Þ (95% CI)	8.3 (6.9, 10.2)	6.8 (5.7, 7.1)

* Results at the pre-specified final OS analysis
† Based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on a stratified log-rank test
§ Results at pre-specified final analysis of PFS and ORR
¶ Confirmed complete response or partial response
# One-sided p-Value based on the stratified Miettinen and Nurminen analysis
Þ Based on Kaplan-Meier estimate
NS = not significant

Figure 28: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966



Number at Risk																				
KEYTRUDA + Chemotherapy	533	505	469	430	374	326	275	238	204	175	142	108	88	56	35	21	16	8	5	0	0
Placebo + Chemotherapy	536	504	454	394	349	287	236	213	181	148	115	81	59	43	28	20	14	7	1	0	0

14.15 Merkel Cell Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-017 (NCT02267603) and KEYNOTE-913 (NCT03783078), two multicenter, non-randomized, open-label trials that enrolled 105 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 (KEYNOTE-017) or 200 mg (KEYNOTE-913) 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.

The major efficacy outcome measures were ORR and DoR as assessed by BICR per RECIST v1.1.

Among the 105 patients enrolled, the median age was 73 years (range: 38 to 91), 79% were age 65 or older; 62% were male; 80% were White, race in 19% was unknown or missing, and 1% were Asian; 53% had ECOG PS of 0, and 47% had ECOG PS of 1. Thirteen percent had stage IIIB disease and 84% had stage IV. Seventy-six percent of patients had prior surgery and 51% had prior radiation therapy.

Efficacy results are summarized in Table 92.

Table 92: Efficacy Results in KEYNOTE-017 and KEYNOTE-913

Endpoint	KEYNOTE-017 KEYTRUDA 2 mg/kg every 3 weeks n=50	KEYNOTE-913 KEYTRUDA 200 mg or 2 mg/kg every 3 weeks n=55
Objective Response Rate		
ORR (95% CI)	56% (41, 70)	49% (35, 63)
Complete responses, n (%)	12 (24%)	9 (16%)
Partial responses, n (%)	16 (32%)	18 (33%)
Duration of Response	**n=28**	**n=27**
Median DoR in months (range)	NR (5.9, 34.5+)	NR (4.8, 25.4+)
Patients with duration ≥6 months, n (%)	27 (96%)	25 (93%)
Patients with duration ≥12 months, n (%)	15 (54%)	19 (70%)

\+ Denotes ongoing response
NR = not reached

14.16 Renal Cell Carcinoma

First-line treatment with axitinib

KEYNOTE-426

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; 20% 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 first 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. An updated OS analysis was conducted when 418 deaths were observed based on the planned number of deaths for the pre-specified final analysis. Table 93 and Figure 29 summarize the efficacy results for KEYNOTE-426.

Table 93: 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‡	
Updated OS		
Number of patients with event (%)	193 (45%)	225 (52%)
Median in months (95% CI)	45.7 (43.6, NR)	40.1 (34.3, 44.2)
Hazard ratio* (95% CI)	0.73 (0.60, 0.88)	
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).

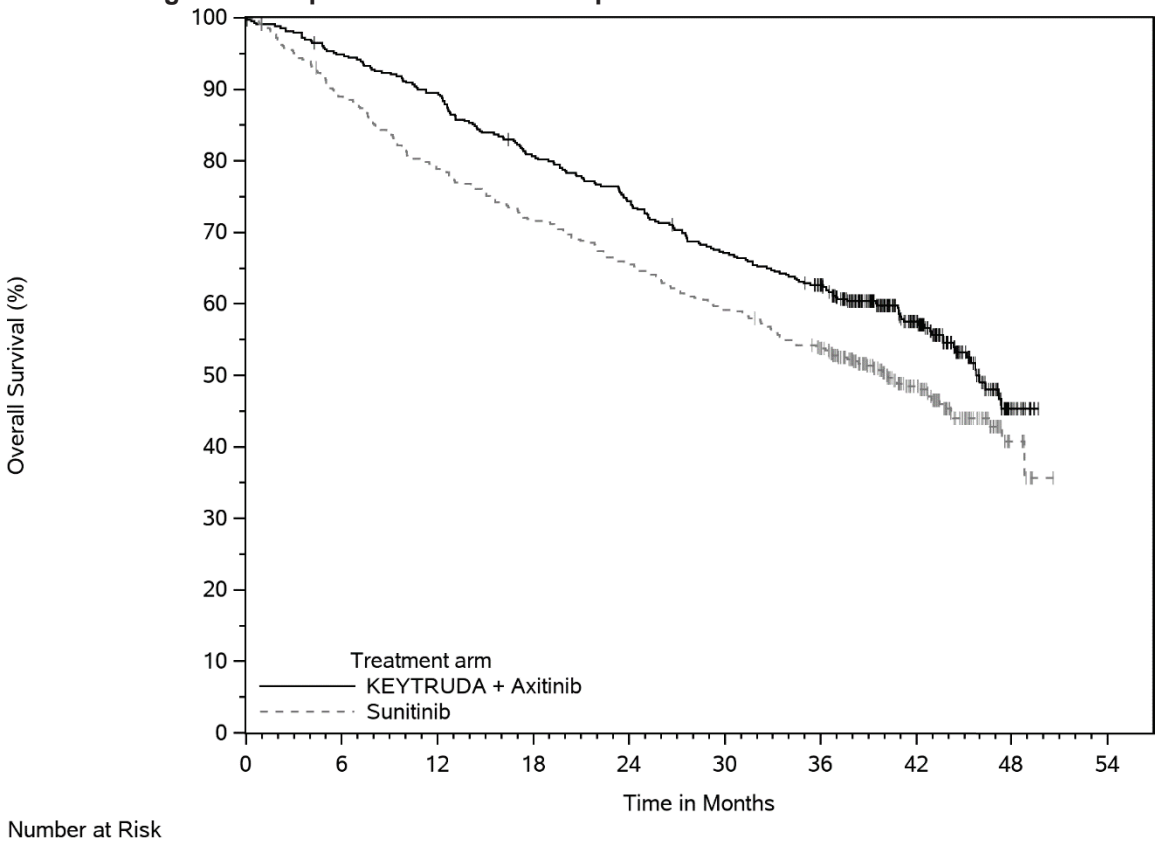
§ p-Value (one-sided) is compared with the allocated alpha of 0.0013 for this interim analysis (with 81% of the planned number of events for final analysis).

¶ 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 29: Kaplan-Meier Curve for Updated Overall Survival in KEYNOTE-426



Number at Risk

KEYTRUDA + Axitinib	432	407	384	345	318	286	259	141	16	0
Sunitinib	429	379	336	306	279	252	224	110	12	0

In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR of 1.17 (95% CI: 0.76, 1.80), 0.67 (95% CI: 0.52, 0.86), 0.64 (95% CI: 0.52, 0.80), and 0.51 (95% CI: 0.32, 0.81), respectively.

First-line treatment with lenvatinib

KEYNOTE-581

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-581 (NCT02811861), a multicenter, open-label, randomized trial conducted in 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified by geographic region (North America versus Western Europe versus “Rest of the World”) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable versus intermediate versus poor risk).

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

- KEYTRUDA 200 mg intravenously every 3 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily.
- Lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily.
- Sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks.

Treatment continued until unacceptable toxicity or disease progression. Administration of KEYTRUDA with 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 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 8 weeks.

The study population characteristics were: median age of 62 years (range: 29 to 88 years), 42% age 65 or older; 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by MSKCC risk categories was 27% favorable, 64% intermediate, and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

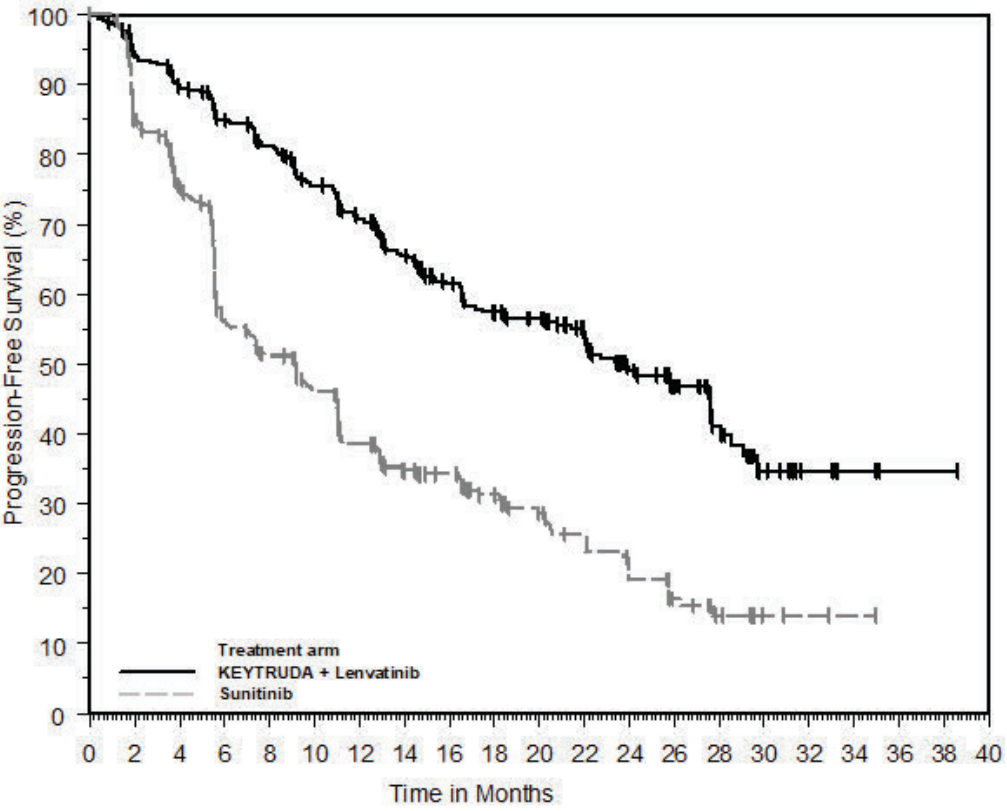
The major efficacy outcome measures were PFS, as assessed by independent radiologic review (IRC) according to RECIST v1.1, and OS. Additional efficacy outcome measures included confirmed ORR as assessed by IRC. KEYTRUDA in combination with lenvatinib demonstrated statistically significant improvements in PFS, OS, and ORR compared with sunitinib. An updated OS analysis was conducted when 304 deaths were observed based on the planned number of deaths for the pre-specified final analysis. Table 94 and Figures 30 and 31 summarize the efficacy results for KEYNOTE-581.

Table 94: Efficacy Results in KEYNOTE-581

Endpoint	**KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=355**	**Sunitinib n=357**
Progression-Free Survival (PFS)		
Number of events, n (%)	160 (45%)	205 (57%)
Progressive disease	145 (41%)	196 (55%)
Death	15 (4%)	9 (3%)
Median PFS in months (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard ratio* (95% CI)	0.39 (0.32, 0.49)	
p-Value†	<0.0001	
Overall Survival (OS)		
Number of deaths, n (%)	80 (23%)	101 (28%)
Median OS in months (95% CI)	NR (33.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.66 (0.49, 0.88)	
p-Value†	0.0049	
Updated OS		
Number of deaths, n (%)	149 (42%)	159 (45%)
Median OS in months (95% CI)	53.7 (48.7, NR)	54.3 (40.9, NR)
Hazard ratio* (95% CI)	0.79 (0.63, 0.99)	
Objective Response Rate (Confirmed)		
ORR, n (%)	252 (71%)	129 (36%)
(95% CI)	(66, 76)	(31, 41)
Complete response rate	16%	4%
Partial response rate	55%	32%
p-Value‡	<0.0001	

Tumor assessments were based on RECIST 1.1; only confirmed responses are included for ORR.
Data cutoff date = 28 Aug 2020, Updated OS cutoff date = 31 July 2022
CI = confidence interval; NR= Not reached
* Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and MSKCC prognostic groups.
† Two-sided p-Value based on stratified log-rank test.
‡ Two-sided p-Value based upon CMH test.

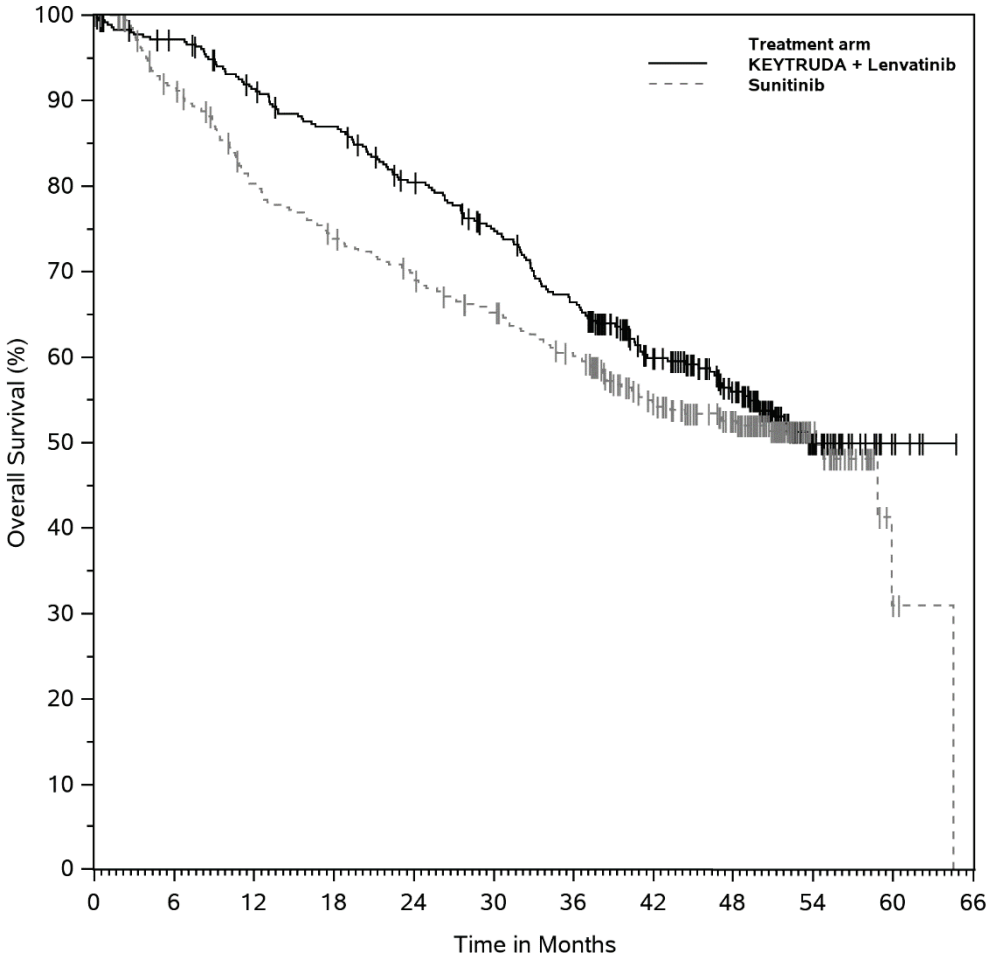
Figure 30: Kaplan-Meier Curve for PFS in KEYNOTE-581



Number at Risk

KEYTRUDA + Lenvatinib:	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Sunitinib:	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0	0	0

Figure 31: Kaplan-Meier Curve for Updated Overall Survival in KEYNOTE-581



Number at Risk

KEYTRUDA + Lenvatinib	355	338	313	296	269	245	216	158	117	34	5	0
Sunitinib	357	308	264	242	226	208	188	145	108	33	3	0

KEYNOTE-B61

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-B61 (NCT04704219), a multicenter, single-arm trial that enrolled 160 patients with advanced or metastatic non-clear cell RCC in the first-line setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 400 mg every 6 weeks in combination with lenvatinib 20 mg orally once daily. KEYTRUDA was continued for a maximum of 24 months; however, lenvatinib could be continued beyond 24 months. Treatment continued until unacceptable toxicity or disease progression. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was considered by the investigator to be deriving clinical benefit.

Among the 158 treated patients, the baseline characteristics were: median age of 60 years (range: 24 to 87 years); 71% male; 86% White, 8% Asian, and 3% Black; <1% Hispanic or Latino; 22% and 78% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; histologic subtypes were 59% papillary, 18% chromophobe, 4% translocation, <1% medullary, 13% unclassified, and 6% other; patient distribution by IMDC risk categories was 35% favorable, 54% intermediate, and 10% poor. Common sites of metastases in patients were lymph node (65%), lung (35%), bone (30%), and liver (21%).

The major efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Additional efficacy outcome measures included DOR as assessed by BICR using RECIST 1.1. Efficacy results are summarized in Table 95.

Table 95: Efficacy Results in KEYNOTE-B61

Endpoint	KEYTRUDA 400 mg every 6 weeks and Lenvatinib n=158
Objective Response Rate (Confirmed)	
ORR (95% CI)	51% (43, 59)
Complete response	8%
Partial response	42%
Duration of Response*	
Median in months (range)	19.5 (1.5+, 23.5+)

CI = confidence interval
* Based on Kaplan-Meier estimates
\+ Denotes ongoing response

Adjuvant Treatment of RCC (KEYNOTE-564)

The efficacy of KEYTRUDA was investigated as adjuvant therapy for RCC in KEYNOTE-564 (NCT03142334), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in 994 patients with intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease (NED). The intermediate-high risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins ≥4 weeks prior to the time of screening. Patients were excluded from the trial if they had received prior systemic therapy for advanced RCC. Patients with active autoimmune disease or a medical condition that required immunosuppression were also ineligible. Patients were randomized to KEYTRUDA 200 mg administered intravenously every 3 weeks or placebo for up to 1 year until disease recurrence or unacceptable toxicity. Randomization was stratified by metastasis status (M0, M1 NED); M0 group was further stratified by ECOG PS (0,1) and geographic region (US, non-US).

The study population characteristics were: median age of 60 years (range: 25 to 84), 33% age 65 or older; 71% male; 75% White, 14% Asian, 9% Unknown, 1% Black or African American, 1% American Indian or Alaska Native, 1% Multiracial; 13% Hispanic or Latino, 78% Not Hispanic or Latino, 8% Unknown; and 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-four percent of patients enrolled had N0 disease; 11% had sarcomatoid features; 86% were intermediate-high risk; 8% were high risk; and 6% were M1 NED. Ninety-two percent of patients had a radical nephrectomy, and 8% had a partial nephrectomy.

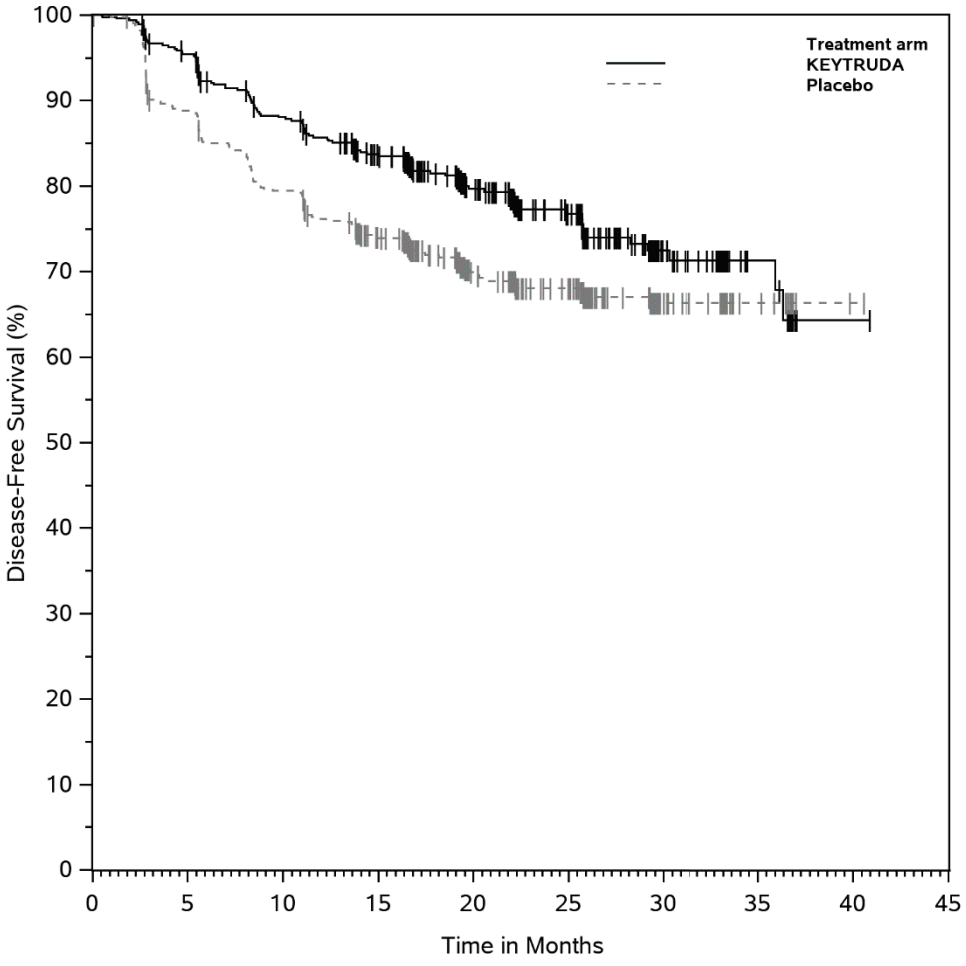
The major efficacy outcome measure was investigator-assessed disease-free survival (DFS), defined as time to recurrence, metastasis, or death. An additional outcome measure was OS. Statistically significant improvements in DFS and OS were demonstrated at pre-specified interim analyses in patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 96 and Figures 32 and 33.

Table 96: Efficacy Results in KEYNOTE-564

Endpoint	KEYTRUDA 200 mg every 3 weeks n=496	Placebo n=498
DFS		
Number (%) of patients with event	109 (22%)	151 (30%)
Median in months (95% CI)	NR	NR
Hazard ratio* (95% CI)	0.68 (0.53, 0.87)	
p-Value†	0.0010‡	
24-month DFS rate (95% CI)	77% (73, 81)	68% (64, 72)
OS		
Number (%) of patients with event	55 (11%)	86 (17%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.62 (0.44, 0.87)	
p-Value†	0.0024§	
48-month OS rate (95% CI)	91% (88, 93)	86% (83, 89)

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ p-Value (one-sided) is compared with a boundary of 0.0114.
§ p-Value (one-sided) is compared with a boundary of 0.0072.
NR = not reached

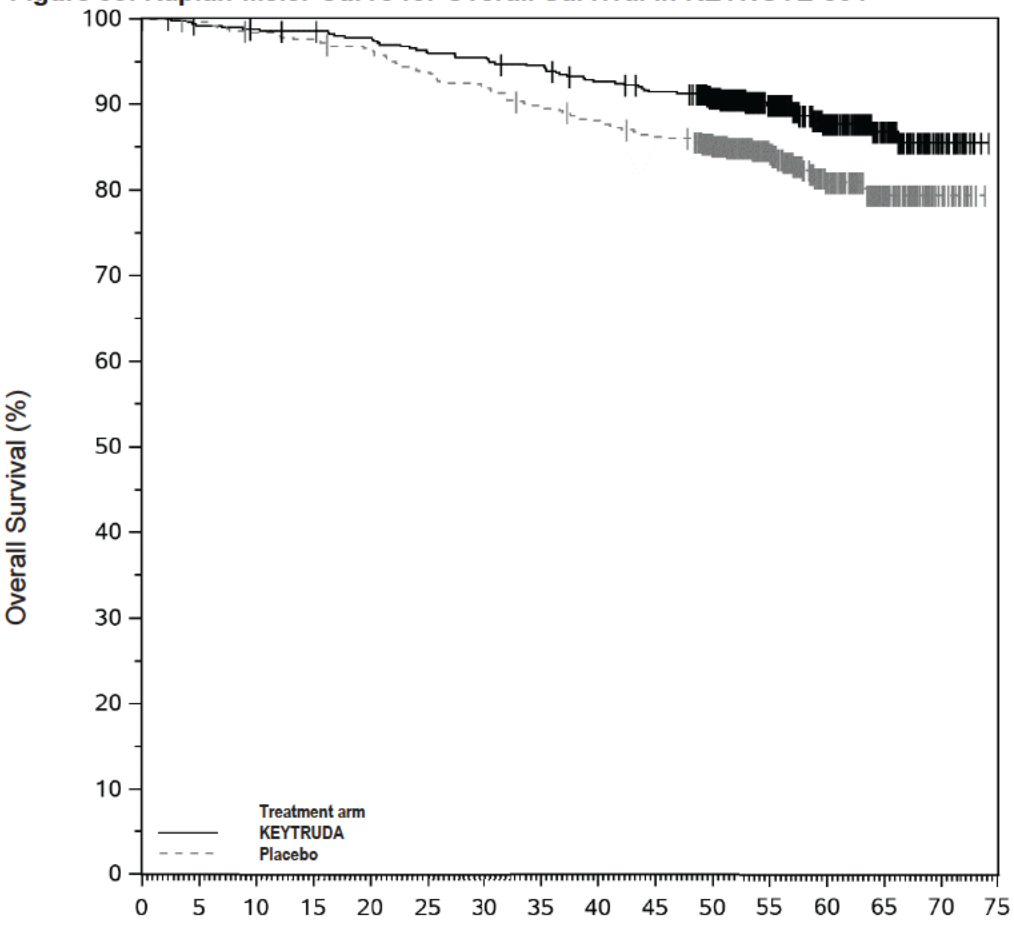
Figure 32: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-564



Number at Risk

KEYTRUDA	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

Figure 33: Kaplan-Meier Curve for Overall Survival in KEYNOTE-564



Number at Risk																
KEYTRUDA	496	489	486	484	479	470	468	462	451	443	397	270	168	81	22	0
Placebo	498	494	487	483	476	463	455	441	433	423	382	248	155	79	22	0

14.17 Endometrial Carcinoma

In Combination with Paclitaxel and Carboplatin for the Treatment of Primary Advanced or Recurrent Endometrial Carcinoma

The efficacy of KEYTRUDA in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868/NRG-GY018 (NCT03914612), a multicenter, randomized, double-blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma. The study design included two separate cohorts based on MMR status; 222 (27%) patients were in dMMR cohort, 588 (73%) patients were in pMMR cohort. The trial enrolled measurable Stage III, measurable Stage IVA, Stage IVB or recurrent endometrial cancer (with or without measurable disease). Patients who had not received prior systemic therapy or had received prior chemotherapy in the adjuvant setting were eligible. Patients who had received prior adjuvant chemotherapy were only eligible if their chemotherapy-free interval was at least 12 months. Patients with endometrial sarcoma, including carcinosarcoma, or patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified according to MMR status, ECOG PS (0 or 1 vs. 2), and prior adjuvant chemotherapy.

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

- KEYTRUDA 200 mg every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by KEYTRUDA 400 mg every 6 weeks for up to 14 cycles.
- Placebo every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by placebo every 6 weeks for up to 14 cycles.

All study medications were administered as an intravenous infusion on Day 1 of each treatment cycle. Treatment continued until disease progression, unacceptable toxicity, or a maximum of 20 cycles (up to approximately 24 months). Patients with measurable disease who had RECIST-defined stable disease or partial response at the completion of cycle 6 were permitted to continue receiving paclitaxel and carboplatin with KEYTRUDA or placebo for up to 10 cycles as determined by the investigator. Assessment of tumor status was performed every 9 weeks for the first 9 months and then every 12 weeks thereafter. The major efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1. An additional efficacy outcome measure was OS.

The dMMR population characteristics were: median age of 66 years (range: 37 to 86), 55% age 65 or older; 79% White, 9% Black, and 3% Asian; 5% Hispanic or Latino; 64% ECOG PS of 0, 33% ECOG PS of 1, and 3% ECOG PS of 2; 61% had recurrent disease and 39% had primary or persistent disease; 5% received prior adjuvant chemotherapy and 43% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (81%), adenocarcinoma NOS (11%), serous carcinoma (2%), and other (6%).

The pMMR population characteristics were: median age of 66 years (range: 29 to 94), 54% age 65 or older; 72% White, 16% Black, and 5% Asian; 6% Hispanic or Latino; 67% ECOG PS of 0, 30% ECOG PS of 1, and 3% ECOG PS of 2; 56% had recurrent disease and 44% had primary or persistent disease; 26% received prior adjuvant chemotherapy and 41% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (52%), serous carcinoma (26%), adenocarcinoma NOS (10%), clear cell carcinoma (7%), and other (5%).

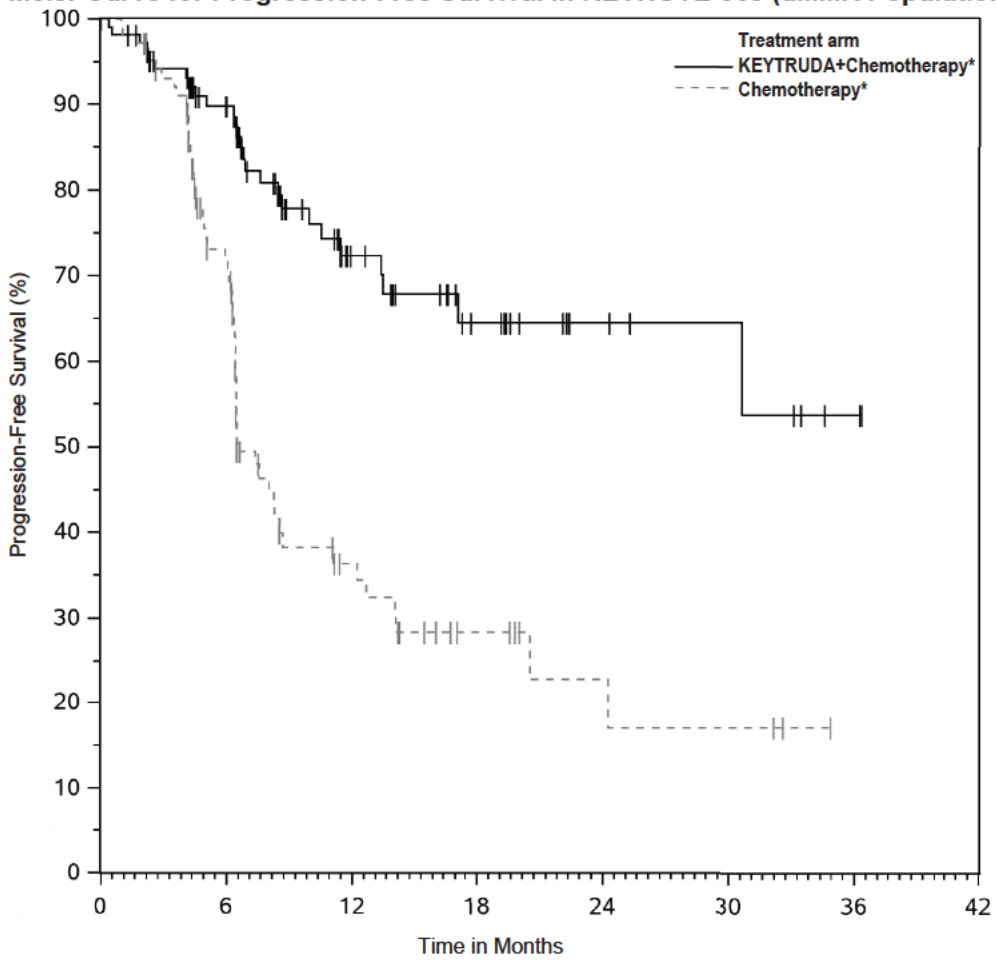
The trial demonstrated statistically significant improvements in PFS for patients randomized to KEYTRUDA in combination with paclitaxel and carboplatin compared to placebo in combination with paclitaxel and carboplatin in both the dMMR and pMMR populations. Table 97 and Figures 34 and 35 summarize the efficacy results for KEYNOTE-868 by MMR status. At the time of the PFS analysis, OS data were not mature with 12% deaths in the dMMR population and 17% deaths in the pMMR population.

Table 97: Efficacy Results in KEYNOTE-868

Endpoint	dMMR Population		pMMR Population	
	KEYTRUDA with paclitaxel and carboplatin n=110	**Placebo with paclitaxel and carboplatin n=112**	**KEYTRUDA with paclitaxel and carboplatin n=294**	**Placebo with paclitaxel and carboplatin n=294**
PFS*				
Number (%) of patients with event	26 (24%)	57 (51%)	91 (31%)	124 (42%)
Median in months (95% CI)	NR (30.7, NR)	6.5 (6.4, 8.7)	11.1 (8.7, 13.5)	8.5 (7.2, 8.8)
Hazard ratio† (95% CI)	0.30 (0.19, 0.48)		0.60 (0.46, 0.78)	
p-Value‡	<0.0001		<0.0001	

* Based on interim PFS analysis; the information fractions for interim analyses were 49% for dMMR and 55% for pMMR.
† Based on the stratified Cox proportional hazard model
‡ Based on the stratified log-rank test
NR = not reached

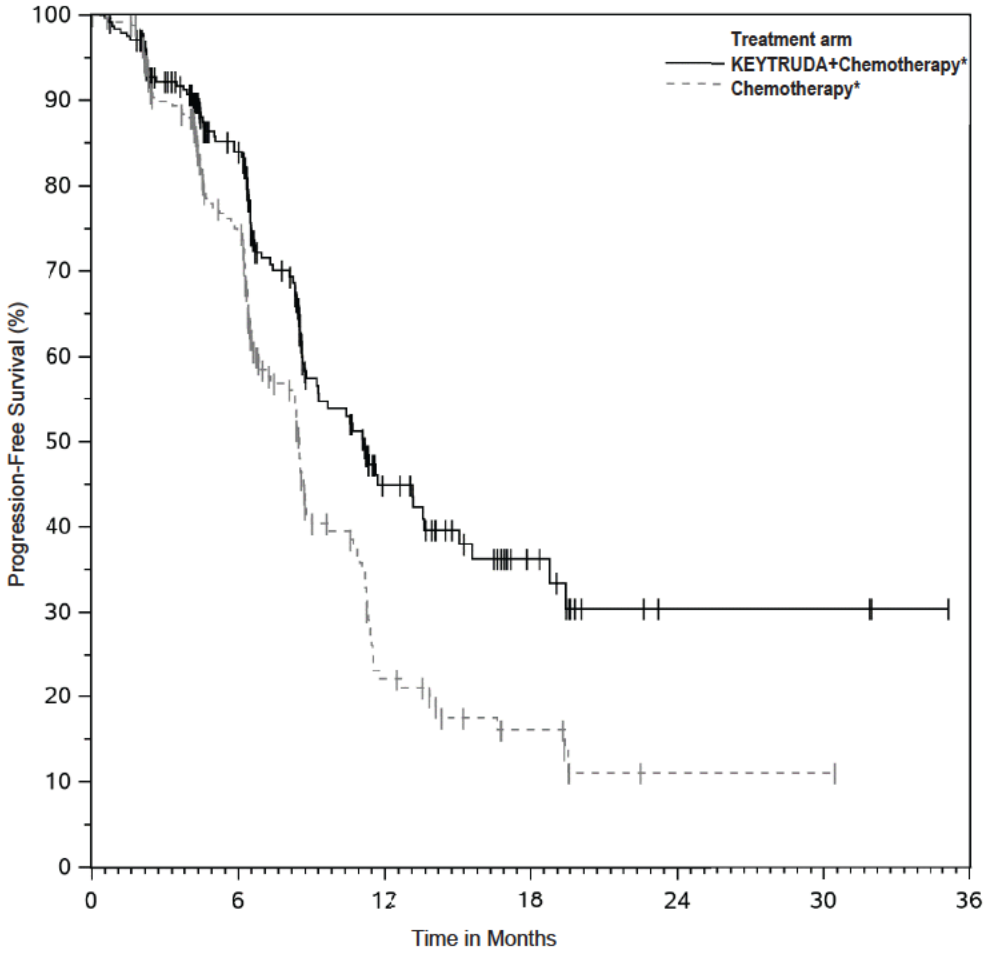
Figure 34: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)



Number at Risk								
KEYTRUDA+Chemotherapy*	110	78	33	17	8	6	2	0
Chemotherapy*	112	58	18	8	4	3	0	0

*Chemotherapy (paclitaxel and carboplatin)

Figure 35: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)



Number at Risk							
KEYTRUDA+Chemotherapy*	294	140	36	14	3	3	0
Chemotherapy*	294	126	22	8	1	1	0

*Chemotherapy (paclitaxel and carboplatin)

In Combination with Lenvatinib for the Treatment of Advanced Endometrial Carcinoma That Is pMMR or Not MSI-H

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775 (NCT03517449), a multicenter, open-label, randomized, active-controlled trial that enrolled 827 patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients with endometrial carcinoma that were pMMR (using the VENTANA MMR RxDx Panel test) or not MSI-H were stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily.
- Investigator's choice, consisting of either doxorubicin 60 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 given weekly, 3 weeks on/1 week off.

Treatment with KEYTRUDA and lenvatinib continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit, and the treatment was tolerated. Assessment of tumor status was performed every 8 weeks. The major 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 and DoR, as assessed by BICR.

Among the 697 pMMR patients, 346 patients were randomized to KEYTRUDA in combination with lenvatinib, and 351 patients were randomized to investigator's choice of doxorubicin (n=254) or paclitaxel (n=97). The pMMR population characteristics were: median age of 65 years (range: 30 to 86), 52% age 65 or older; 62% White, 22% Asian, and 3% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1. The histologic subtypes were endometrioid carcinoma (55%), serous (30%), clear cell carcinoma (7%), mixed (4%), and other (3%). All 697 of these patients received prior systemic therapy for endometrial carcinoma: 67% had one, 30% had two, and 3% had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

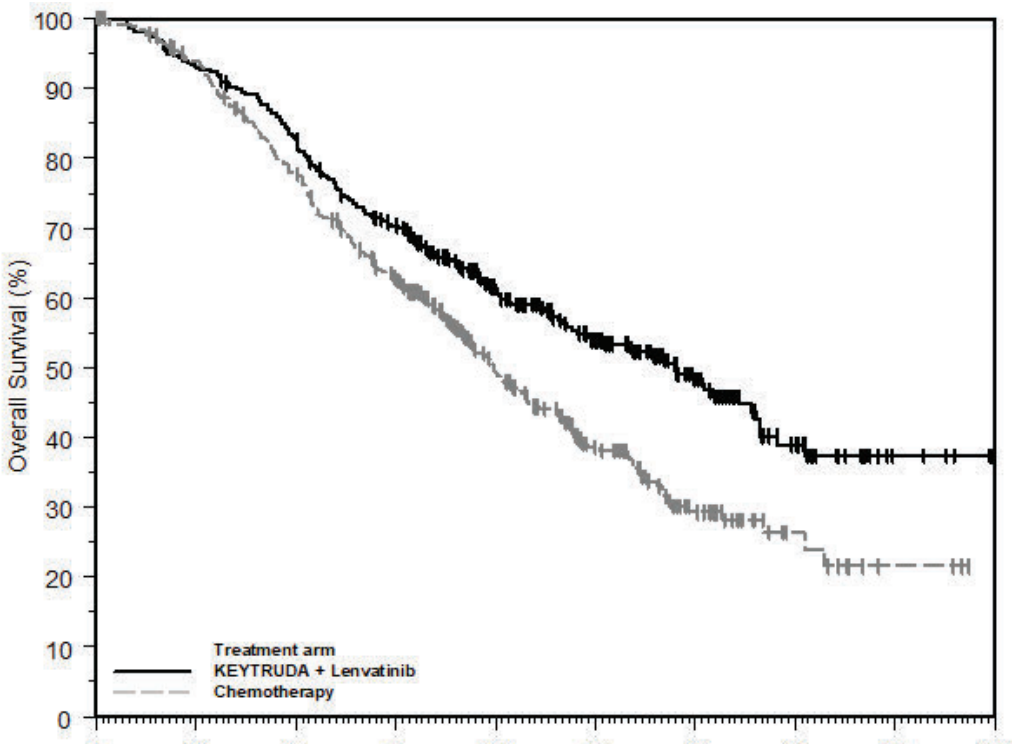
Efficacy results for the pMMR or not MSI-H patients are summarized in Table 98 and Figures 36 and 37.

Table 98: Efficacy Results in KEYNOTE-775

	Endometrial Carcinoma (pMMR or not MSI-H)	
Endpoint	**KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=346**	**Doxorubicin or Paclitaxel n=351**
OS		
Number (%) of patients with event	165 (48%)	203 (58%)
Median in months (95% CI)	17.4 (14.2, 19.9)	12.0 (10.8, 13.3)
Hazard ratio* (95% CI)	0.68 (0.56, 0.84)	
p-Value†	0.0001	
PFS		
Number (%) of patients with event	247 (71%)	238 (68%)
Median in months (95% CI)	6.6 (5.6, 7.4)	3.8 (3.6, 5.0)
Hazard ratio* (95% CI)	0.60 (0.50, 0.72)	
p-Value†	<0.0001	
Objective Response Rate		
ORR‡ (95% CI)	30% (26, 36)	15% (12, 19)
Complete response rate	5%	3%
Partial response rate	25%	13%
p-Value§	<0.0001	
Duration of Response	n=105	n=53
Median in months (range)	9.2 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)

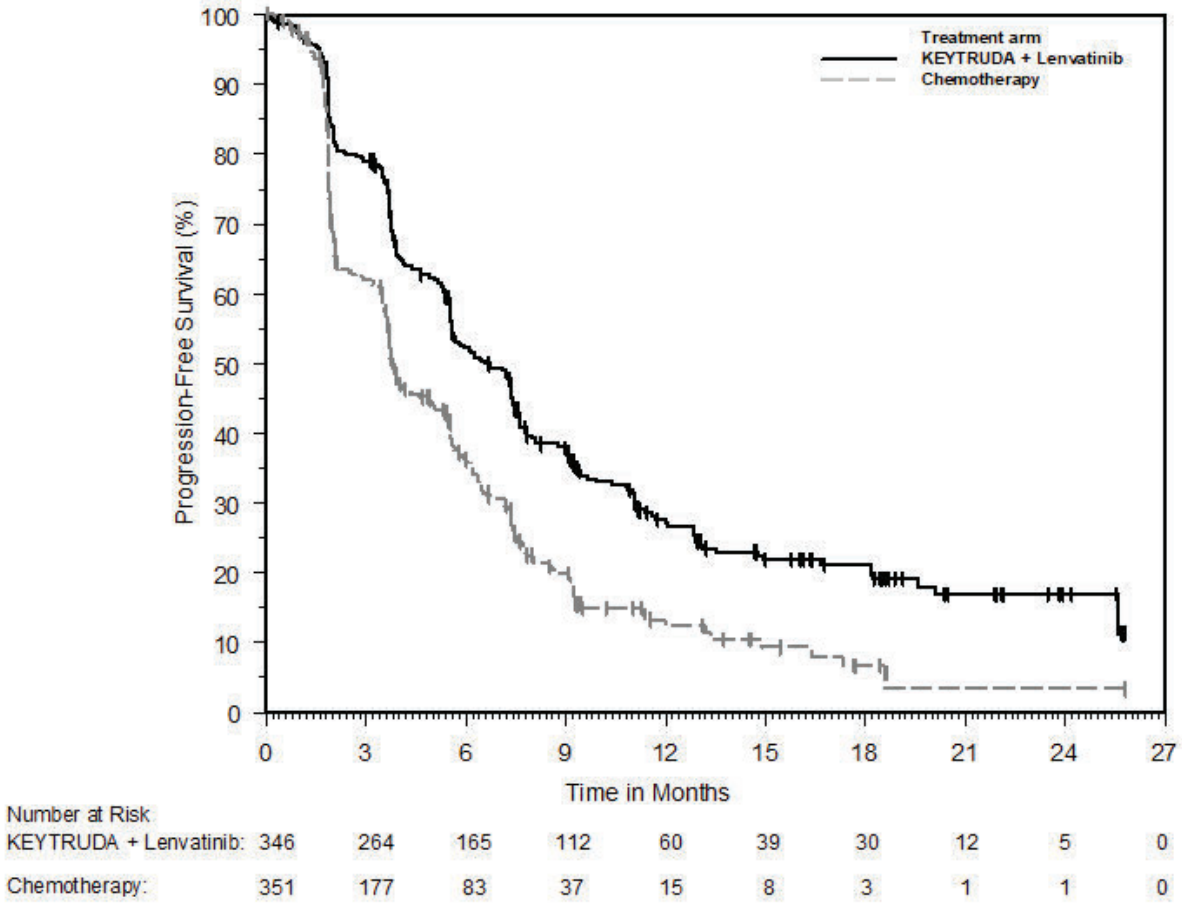
* Based on the stratified Cox regression model
† Based on stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response
§ Based on Miettinen and Nurminen method stratified by ECOG performance status, geographic region, and history of pelvic radiation

Figure 36: Kaplan-Meier Curve for Overall Survival in KEYNOTE-775 (pMMR or Not MSI-H)



Number at Risk										
KEYTRUDA + Lenvatinib:	346	322	285	232	160	109	62	28	5	0
Chemotherapy:	351	319	262	201	120	70	33	11	3	0

Figure 37: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-775 (pMMR or Not MSI-H)



As a Single Agent for the Treatment of Advanced MSI-H or dMMR Endometrial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial enrolled 90 patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma in Cohorts D and K. MSI or MMR tumor status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients treated with KEYTRUDA 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 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 90 patients evaluated, the baseline characteristics were: median age of 64 years (range: 42 to 86); 83% White, 8% Asian, and 3% Black; 12% Hispanic or Latino; 39% ECOG PS of 0 and 61% ECOG PS of 1; 96% had M1 disease and 4% had M0 disease at study entry; and 51% had one and 48% had two or more prior lines of therapy. Nine patients received only adjuvant therapy and one patient received only neoadjuvant and adjuvant therapy before participating in the study.

Efficacy results are summarized in Table 99.

Table 99: Efficacy Results in Patients with Advanced MSI-H or dMMR Endometrial Carcinoma in KEYNOTE-158

Endpoint	KEYTRUDA n=90*
Objective Response Rate	
ORR (95% CI)	46% (35, 56)
Complete response rate	12%
Partial response rate	33%
Duration of Response	n=41
Median in months (range)	NR (2.9, 55.7+)
% with duration ≥12 months	68%
% with duration ≥24 months	44%

* Median follow-up time of 16.0 months (range 0.5 to 62.1 months)
\+ Denotes ongoing response
NR = not reached

14.18 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 100 and 101.

Table 100: 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 101: 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.

14.19 Cutaneous Squamous Cell Carcinoma

The efficacy of KEYTRUDA was investigated in patients with recurrent or metastatic cSCC or locally advanced 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 with recurrent or metastatic cSCC treated, the study population characteristics were: median age of 72 years (range: 29 to 95), 71% age 65 or older; 76% male; 70% 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; 73% received prior radiation therapy.

Among the 54 patients with locally advanced cSCC treated, the study population characteristics were: median age of 76 years (range: 35 to 95), 80% age 65 or older; 72% male; 83% White, 13% race unknown; 41% ECOG PS of 0 and 59% ECOG PS of 1. Twenty-two percent received one or more prior lines of therapy; 63% received prior radiation therapy.

Efficacy results are summarized in Table 102.

Table 102: Efficacy Results in KEYNOTE-629

Endpoint	KEYTRUDA Recurrent or Metastatic cSCC n=105	KEYTRUDA Locally Advanced cSCC n=54
Objective Response Rate		
ORR (95% CI)	35% (26, 45)	52% (38, 66)
Complete response rate	12%	22%
Partial response rate	23%	30%
Duration of Response*	n=37	n=28
Median in months (range)	NR (2.7, 64.2+)	47.2 (1.0+, 49.9+)
% with duration ≥6 months	76%	89%
% with duration ≥12 months	68%	75%

* Median follow-up time: recurrent or metastatic cSCC: 23.8 months; locally advanced cSCC: 48.0 months

\+ Denotes ongoing response

14.20 Triple-Negative Breast Cancer

Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC

The efficacy of KEYTRUDA in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-522 (NCT03036488), a randomized (2:1), multicenter, double-blind, placebo-controlled trial conducted in 1174 patients with newly diagnosed previously untreated high-risk early-stage TNBC (tumor size >1 cm but ≤2 cm in diameter with nodal involvement or tumor size >2 cm in diameter regardless of nodal involvement). Patients were enrolled regardless of tumor PD-L1 expression. 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 nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly).

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

- **Arm 1:**
  - Four cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
    - Carboplatin
      - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen

        -or-

      - AUC 1.5 mg/mL/min every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen

        -and-
    - Paclitaxel 80 mg/m^2 every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen

- Followed by four additional cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
    - Doxorubicin 60 mg/m^2 ***-or-*** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen ***-and-***
    - Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
- Following surgery, nine cycles of KEYTRUDA 200 mg every 3 weeks were administered.

- **Arm 2:**
    - Four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
        - Carboplatin
            - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen

              -or-
            - AUC 1.5 mg/mL/min every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen

              -and-
        - Paclitaxel 80 mg/m^2 every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen
    - Followed by four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
        - Doxorubicin 60 mg/m^2 ***-or-*** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen ***-and-***
        - Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
    - Following surgery, nine cycles of placebo every 3 weeks were administered.

The main efficacy outcomes were pCR rate and EFS. pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. An additional efficacy outcome was overall survival (OS).

The study population characteristics were: median age of 49 years (range: 22 to 80), 11% age 65 or older; 99.9% female; 64% White, 20% Asian, 4.5% Black, and 1.8% American Indian or Alaska Native; 87% ECOG PS of 0 and 13% ECOG PS of 1; 56% were pre-menopausal status and 44% were post-menopausal status; 7% were primary Tumor 1 (T1), 68% T2, 19% T3, and 7% T4; 49% were nodal involvement 0 (N0), 40% N1, 11% N2, and 0.2% N3; 75% of patients were overall Stage II and 25% were Stage III.

Table 103 and Figure 38 summarize the efficacy results for KEYNOTE-522. At the protocol pre-specified IA4 interim analysis of OS, OS data were not mature with 45% of the required events for the final analysis.

Table 103: Efficacy Results in KEYNOTE-522

Endpoint	KEYTRUDA 200 mg every 3 weeks with chemotherapy/KEYTRUDA n=784	Placebo with chemotherapy/Placebo n=390
pCR (ypT0/Tis ypN0)*		
Number of patients with pCR	494	217
pCR Rate (%), (95% CI)	63.0 (59.5, 66.4)	55.6 (50.6, 60.6)
Treatment difference (%) estimate (95% CI)[†,‡]	7.5 (1.6, 13.4)	
EFS		
Number of patients with event (%)	123 (16%)	93 (24%)
Hazard ratio (95% CI)[§]	0.63 (0.48, 0.82)	
p-Value[¶,#]	0.00031	

* Based on the entire intention-to-treat population n=1174 patients

† Based on a pre-specified pCR interim analysis in n=602 patients, the pCR rate difference was statistically significant (p=0.00055 compared to a significance level of 0.003).

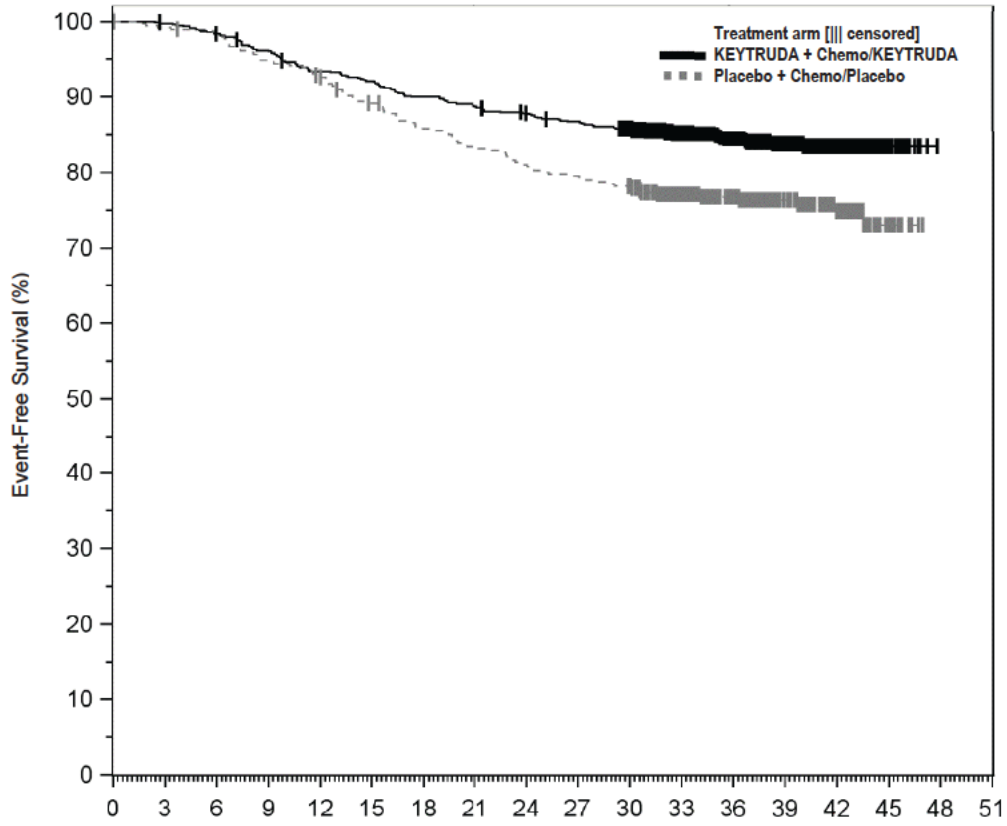
‡ Based on Miettinen and Nurminen method stratified by nodal status, tumor size, and choice of carboplatin

§ Based on stratified Cox regression model

¶ Based on a pre-specified EFS interim analysis (compared to a significance level of 0.0052)

\# Based on log-rank test stratified by nodal status, tumor size, and choice of carboplatin

Figure 38: Kaplan-Meier Curve for Event-Free Survival in KEYNOTE-522



Number at Risk																		
KEYTRUDA + Chemo/KEYTRUDA:	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo + Chemo/Placebo:	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

Locally Recurrent Unresectable or Metastatic TNBC

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 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, tested in the subgroup of patients with CPS ≥10. Additional efficacy outcome measures were 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.

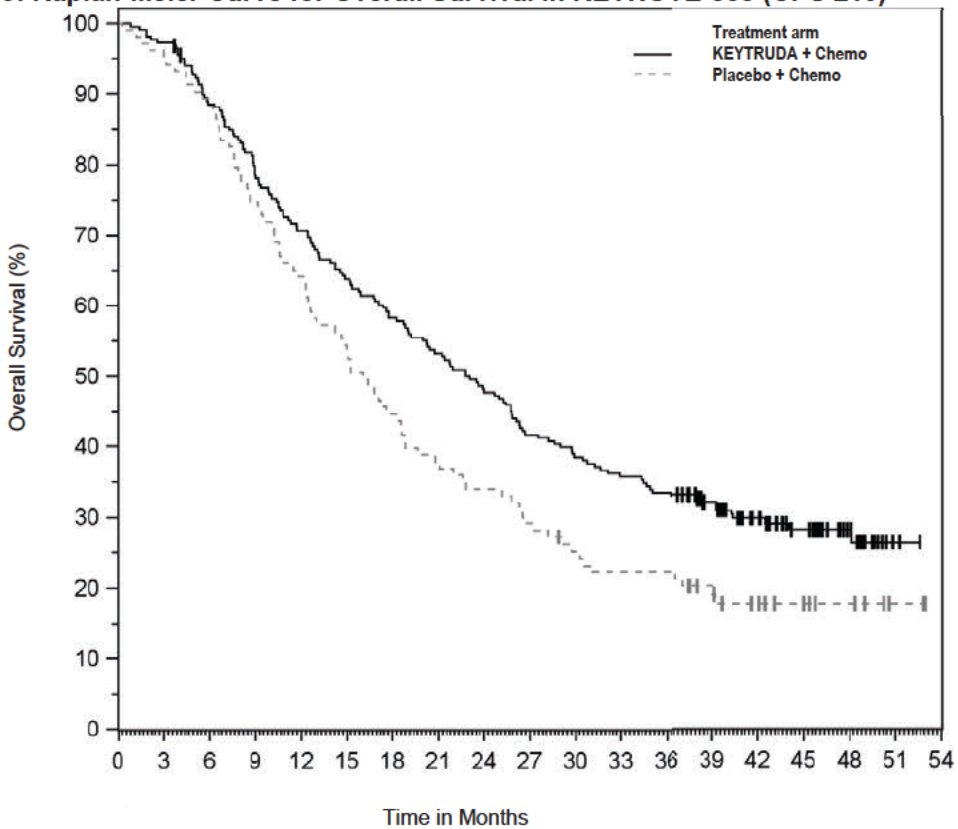
Table 104 and Figures 39 and 40 summarize the efficacy results for KEYNOTE-355.

Table 104: 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
OS*		
Number of patients with event (%)	155 (70%)	84 (82%)
Median in months (95% CI)	23 (19.0, 26.3)	16.1 (12.6, 18.8)
Hazard ratio† (95% CI)	0.73 (0.55, 0.95)	
p-Value‡	0.0093	
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	
Objective Response Rate (Confirmed)*		
ORR (95% CI)	53% (46, 59)	41% (31, 51)
Complete response rate	17%	14%
Partial response rate	35%	27%
Duration of Response*	**n=116**	**n=42**
Median in months (95% CI)	12.8 (9.9, 25.9)	7.3 (5.5, 15.4)

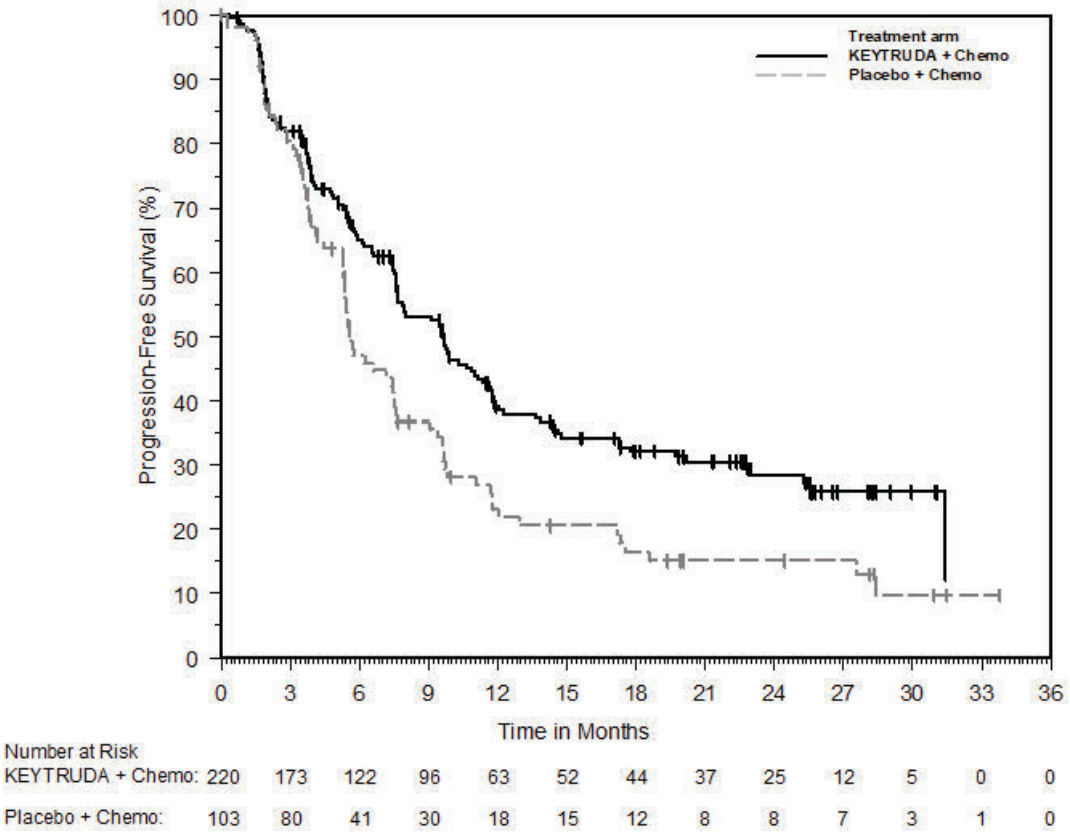
* Based on the pre-specified final analysis
† Based on stratified Cox regression model
‡ One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.0113)
§ Based on a pre-specified interim analysis
¶ One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.00411)

Figure 39: Kaplan-Meier Curve for Overall Survival in KEYNOTE-355 (CPS ≥10)



Number at Risk																		
KEYTRUDA + Chemo	220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
Placebo + Chemo	103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

Figure 40: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-355 (CPS ≥10)



14.21 Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: 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 the classical Hodgkin lymphoma and primary mediastinal large B-cell lymphoma indications for adults was primarily based on the 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 other transplant (including corneal graft) rejection. Advise patients to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection and other transplant (including corneal graft) 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 last 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 LLC
Rahway, NJ 07065, USA
U.S. License No. 0002

For patent information: www.msd.com/research/patent

uspi-mk3475-iv-2503r084

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s170

MULTI-DISCIPLINE REVIEW

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

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	sBLA
Application Number(s)	125514 S-170
Priority or Standard	Standard
Submit Date(s)	July 18, 2024
Received Date(s)	July 18, 2024
PDUFA Goal Date	May 18, 2025
Division/Office	Division of Oncology 3, Office of Oncologic Diseases
Review Completion Date	See electronic stamp date
Established Name	Pembrolizumab
Trade Name	Keytruda
Pharmacologic Class	Programmed death 1(PD-1) receptor blocking antibody
Code name	MK-3475
Applicant	Merck Sharp and Dohme LLC, a subsidiary of Merk
Formulation(s)	Solution for intravenous injection
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 adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test

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Reviewers of Multi-Disciplinary Review and Evaluation

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Division Director (OOD)	Steven J. Lemery
Office Director (or designated signatory authority)	Steven J. Lemery

Glossary

1L	first line
5-FU	5-fluorouracil
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AEOSI	adverse events of special interest
APaT	all participants as treated
BICR	blinded independent central review
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAPOX	capecitabine/oxaliplatin
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2
CPS	combined positive score
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-STO22

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EQ-5D-5L	EuroQoL-5 Dimension Questionnaire Visual Analog Scale
ERC	Ethics Review Committee
ETASU	elements to assure safe use
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FISH	fluorescence in situ hybridization
FP	cisplatin plus 5-fluorouracil
GCP	good clinical practice
GEJ	gastroesophageal junction
GLP	good laboratory practice
GRMP	good review management practice
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
IA1	interim analysis 1
IA2	interim analysis 2
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISH	in situ hybridization
ISS	integrated summary of safety
ITT	intent to treat
KM	Kaplan-Meier
LS	least squares
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSI	microsatellite instability
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCT	National Clinical Trials
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OR	objective response
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PI	prescribing information
PK	Pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
Q3W	every 3 weeks
Q6W	every 6 weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
REMS	risk evaluation and mitigation strategy
RSD	reference safety dataset
S-1	combination product containing tegafur, a prodrug of 5-FU, and 2 types of enzyme inhibitors, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo)
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SOX	S-1 plus oxaliplatin
sSAP	supplemental statistical analysis plan
TEAE	treatment emergent adverse event
ToGA	Trastuzumab for Gastric Cancer
TTR	time to response
USPI	United States Prescribing Information

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 100 mg liquid in single-use vials.

FDA first approved pembrolizumab on September 14, 2014. Prior to action on the current 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), triple negative breast cancer, renal cell cancer 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 review team agrees that the supplement Application for Keytruda (pembrolizumab) meets the statutory standards for approval for the following indication:

in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations.

The data provided is based on the safety and efficacy results of a single trial, KEYNOTE-811 (NCT03615326). KEYNOTE-811 (Study KN811), is an 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 (SOC) first-line treatment with trastuzumab and chemotherapy (fluoropyrimidine/cisplatin [FP] or capecitabine/oxaliplatin [CAPOX]) combined with pembrolizumab or placebo. 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 [ROW]), 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); interim analysis 1 (IA1) had a primary endpoint of overall response rate (ORR) and was conducted when the first 264 patients randomized (133 and 131 in the pembrolizumab and placebo arms, respectively) had been followed up for at least 8.5 months. In the IA1 analysis, a clinically meaningful and statistically significant improvement in a blinded, independent central review (BIRC) of ORR was demonstrated: 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 compared to a one-sided p-value boundary=0.002). 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. These results led to the accelerated approval (May 5, 2021) of pembrolizumab in combination with chemotherapy and trastuzumab for the first-line treatment of HER2+ gastric or GEJ adenocarcinoma, irrespective of PD-L1 expression.

To verify and confirm the benefit of the addition of pembrolizumab to the standard of care chemotherapy and trastuzumab, patients enrolled in KN811 were followed for the study primary endpoints. At the time of IA2 (data cutoff May 25, 2022), the PFS results reached statistical significance. Median PFS was 10.0 months (95% CI 8.6, 11.7) in the pembrolizumab arms and 8.1 months (95% CI 7.0, 8.5) in the control arm, with a HR of 0.72 (95% CI 0.60, 0.87, p 0.0002); OS was not significant at that time. In an OS subgroup analysis of 104 patients (15%) with PD-L1 tumor CPS <1 expression, the survival HR was 1.41 (95% CI 0.90, 2.20), potentially indicating a detriment in OS in this population. Based on this analysis, considering the lack of benefit in any outcome measure and potential detriment in survival, on November 7, 2023, FDA agreed with Merck's proposal to restrict the indication for pembrolizumab in the setting of HER2+ gastric or gastroesophageal cancer to patients whose tumors express PD-L1 CPS ≥1.

At the time of final analysis (data cutoff March 20, 2024), the OS results in the intent-to-treat (ITT) population reached statistical significance. Median OS was 20.0 months (95% CI 17.8, 22.1) in the pembrolizumab arm and 16.8 months (95% CI 14.9, 18.7) in the control arm with a HR of 0.80 (95% CI 0.67, 0.94, p 0.004). In the indicated population (patients with PD-L1 tumor CPS ≥1 expression), the median OS is 20.1 months (95% CI 17.9, 22.9) in the pembrolizumab arm and 15.7 months (95% 13.5, 18.5) in the control arm, with a HR of 0.79 (95% CI 0.66, 0.95).

The observed improvement in survival for patients with HER2-positive, CPS ≥1 advanced gastric or GEJ adenocarcinoma receiving pembrolizumab plus chemotherapy and trastuzumab is statistically robust and clinically meaningful. This finding is supported by consistent results

across clinically relevant subgroups. The study long-term outcomes verify and confirm the benefit observed in response rates in the first-interim analysis and fulfill the terms of the post-marketing requirement (PMR 4033-1) issued upon accelerated approval. The review team recommends conversion to traditional approval.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The substantial evidence of the safety and effectiveness of pembrolizumab for the treatment of adult patients with HER2-positive, PD-L1 CPS ≥ 1 locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma is demonstrated by the results of a single, multicenter, international, double-blinded, randomized controlled trial, KEYNOTE-811 (NCT03615326). KN811 is an international, double-blinded, randomized (1:1) trial comparing pembrolizumab or placebo as add-ons to standard of care (SOC) first-line treatment with trastuzumab and chemotherapy (fluoropyrimidine/cisplatin [FP] or capecitabine/oxaliplatin [CAPOX]). 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 [ROW]), 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); interim analysis 1 (IA1) had a primary endpoint of overall response rate (ORR).

In the IA1 analysis, conducted when the first 264 patients randomized (133 and 131 in the pembrolizumab and placebo arms, respectively) had been followed up for at least 8.5 months, a clinically meaningful and statistically significant improvement in a blinded, independent central review (BIRC) of ORR was demonstrated: 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 compared to a one-sided p-value boundary=0.002). 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. These results led to the accelerated approval (May 5, 2021) of pembrolizumab in combination with chemotherapy and trastuzumab for the first-line treatment of HER2+ gastric or GEJ adenocarcinoma, irrespective of PD-L1 expression.

To verify and confirm the benefit of the addition of pembrolizumab to the standard of care chemotherapy and trastuzumab, patients enrolled in KN811 were followed for the study primary endpoints. At the time of AI2 (data cutoff May 25, 2022), the PFS results reached statistical significance. Median PFS was 10.0 months (95% CI 8.6, 11.7) in the pembrolizumab arms and 8.1 months (95% CI 7.0, 8.5) in the control arm, with a HR of 0.72 (95% CI 0.60, 0.87, p = 0.0002); OS was not significant at that time. In an OS subgroup analysis of 104 patients (15%) with PD-L1 tumor CPS <1 expression conducted at the time of IA3, the survival HR was 1.41 (95% CI 0.90, 2.20), potentially indicating a detriment

in OS in this population. Based on this analysis, considering the lack of benefit in any outcome measure and potential detriment in survival, on November 7, 2023, FDA restricted the indication for pembrolizumab in the setting of HER2+ gastric or gastroesophageal cancer to patients whose tumors express PD-L1 CPS ≥1.

At the time of final analysis (data cutoff March 20, 2024), the OS results in the intent-to-treat (ITT) population reached statistical significance. Median OS was 20.0 months (95% CI 17.8, 22.1) in the pembrolizumab arm and 16.8 months (95% CI 14.9, 18.7) in the control arm with a HR of 0.80 (95% CI 0.67, 0.94, p = 0.004). In the indicated population (patients with PD-L1 tumor CPS ≥1 expression), the median OS is 20.1 months (95% CI 17.9, 22.9) in the pembrolizumab arm and 15.7 months (95% 13.5, 18.5) in the control arm, with a HR of 0.79 (95% CI 0.66, 0.95).

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 13% of patients. Adverse reactions leading to interruption of any of the multidrug component occurred in 82% and 74% of patients in the pembrolizumab and placebo arms, respectively. Twelve percent of patients in the pembrolizumab arm experienced an adverse evet of special interest (AESI) compared with 3.5% patients in the SOC arm. Of these, 3 (0.9%) patients died due to an AESI in the pembrolizumab arm (pneumonitis and hepatitis), while 1 patient (0.3%) died of myocarditis in the SOC arm. The most frequently reported AESI by category (≥5%) incidence were infusion reactions, hypothyroidism, and pneumonitis. This is consistent with the known safety profile of pembrolizumab.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	In the U.S., based on data from the Surveillance, Epidemiology, and End Results (SEER), new cases of gastric cancer in 2024 are expected in 26,890 (7 per 100,000 people) and 10,880 deaths from the disease. Most cases are diagnosed with advanced disease (51%) and the expected 5-yar survival in the US is 36.4% for all stages, but decreases to 7% in patients diagnosed with metastatic disease (https://seer.cancer.gov/statfacts/html/stomach.html). Human epidermal growth factor receptor 2 (ERBB2/HER) is a transmembrane tyrosine kinase receptor and is overexpressed or	Locally advanced or unresectable HER2 positive gastric/GEJ carcinoma is a serious, life-threatening condition with a poor prognosis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	amplified in estimated 7% to 34% of gastric cancer (Bang YJ, 2010). Testing for HER2-positive status is standard of care in all patients considered candidates for combination therapy that includes trastuzumab. Although there is some controversy, HER2 overexpression and amplification in large studies is generally considered an unfavorable prognostic factor (Jørgensen J, 2012). PD-L1 expression is not considered prognostic, but a predictive factor for response to immune checkpoint inhibitors in patients with gastroesophageal cancers (Yoon H, 2022; Klempner S, 2024).	
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 metastatic 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). On May 5, 2021, based on the interim analysis of ORR of Study KEYNOTE-811, FDA granted accelerated approval to pembrolizumab (BLA 125514 S-097) in combination with trastuzumab,	Although trastuzumab is an available effective treatment for patients with HER2-positive gastric and GEJ carcinoma, prognosis is poor with an estimated survival of 14 months. Pembrolizumab received accelerated approval as an add-on to standard of care with trastuzumab and chemotherapy based on an interim analysis of response rates in the overall population; at the time of approval, there were too few patients to characterize the effect in the subpopulation of patients with tumors with PD-L1 CPS<1. Based on long term follow up showing potential detriment in patients with low PD-L1 expression, the indication was revised to restrict the use of pembrolizumab as an add to first line chemotherapy to patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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. The study primary outcomes are PFS and OS. In the first 264 patients (133 and 131 in the pembrolizumab and placebo arms, respectively) consecutively randomized included in the interim analysis, a clinically meaningful and statistically significant improvement in a blinded, independent central review (BIRC) of ORR was demonstrated. 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 compared to a one-sided p-value boundary=0.002). The median duration of response (DoR) 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 had responses lasting ≥ 6 months. At the time of FDA review of IA1, the number of patients with CPS PD-L1 <1% (35) was too low to reliably estimate treatment effect in this subgroup. On November 7, 2023, based on an interim analysis of OS (IA3), where the HR for patients with PD-L1 CPS <1 was 1.41 (95% CI 0.90, 2.20), FDA restricted the indication under accelerated approval to patients with PD-L1 CPS ≥ 1.	with PD-L1 CPS ≥1.
Benefit	KEYNOTE-811, is an 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 (SOC) first-line treatment with trastuzumab and chemotherapy (fluoropyrimidine/cisplatin [FP] or	Results of the final PFS (HR 0.71 [95% CI 0.59, 0.86]) and OS (HR 0.79 [95% CI 0.66, 0.95]) analyses in the indicated population (patients with HER2-positive, CPS ≥ 1 disease) provide clinically meaningful and statistically

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	capecitabine/oxaliplatin [CAPOX]) combined with pembrolizumab or placebo. 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 [ROW]), 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 PFS per modified RECIST v1.1 and OS and the primary endpoint for the interim analysis 1 was ORR. IA1 (described above under "current treatment options") showed a clinically meaningful and statistically significant improvement in ORR. 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 compared to a one-sided p-value boundary=0.002). 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. At the time of AI2 (data cutoff May 25, 2022), the PFS results reached statistical significance. Median PFS was 10.0 months (95% CI 8.6, 11.7) in the pembrolizumab arms and 8.1 months (95% CI 7.0, 8.5) in the control arm, with a HR of 0.72 (95% CI 0.60, 0.87, p = 0.0002); OS was	significant evidence of the benefit of the addition of pembrolizumab to standard of care chemotherapy and trastuzumab for the treatment of patients with advanced gastric and gastroesophageal junction adenocarcinoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	not significant at that time. At the time of final analysis (data cutoff March 20, 2024), the OS results in the intent-to-treat (ITT) population reached statistical significance. Median OS was 20.0 months (95% CI 17.8, 22.1) in the pembrolizumab arm and 16.8 months (95% CI 14.9, 18.7) in the control arm with a HR of 0.80 (95% CI 0.67, 0.94, p = 0.004). Based on subgroup analysis of 104 patients (15%) with PD-L1 tumor CPS <1 expression conducted at the time of IA3 where there was a potential survival detriment (HR 1.41 [95% CI 0.90, 2.20]), on November 7, 2023, FDA restricted the indication for pembrolizumab in the setting of HER2+ gastric or gastroesophageal cancer to patients whose tumors express PD-L1 CPS ≥1. In the final OS analysis in the indicated population (patients with PD-L1 tumor CPS ≥1 expression), the median OS is 20.1 months (95% CI 17.9, 22.9) in the pembrolizumab arm and 15.7 months (95% 13.5, 18.5) in the control arm, with a HR of 0.79 (95% CI 0.66, 0.95).	
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 proportion of patients with AEs resulting in death was generally similar in the pembrolizumab arm vs SOC arm, 6.6%, and 6.4%, respectively. The incidence of SAEs was 46% in both arms, with the most frequently reported SAEs including diarrhea/colitis, pneumonia, and gastrointestinal hemorrhages. Discontinuation of any drug in the pembrolizumab arm compared with the placebo arm (43% vs 39%) was	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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	similar. The most frequently reported adverse events of special interest by category (≥5% incidence) were infusion reactions, hypothyroidism, and pneumonitis. These results are consistent with the known toxicity of pembrolizumab and SOC components and the prior, earlier analysis of the trial.	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 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)

☒	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	☒ Clinical outcome assessment (COA) data, such as	**Section 8.1.2 - Efficacy Results – Secondary or exploratory COA (PRO) 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		
	□	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

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.

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Gastric cancer, also known as stomach cancer, develops from the lining of the stomach and refers to any malignant neoplasm that arises from the region extending between the gastroesophageal junction (GEJ) and the pylorus. The predominant histologic type of gastric cancer is adenocarcinoma, occurring in approximately 95% of diagnosed cases [1]. Gastric cancer is the fifth most common cancer and the fifth leading cause of cancer deaths globally [2]. About 70% of the world's annual new gastric cancer cases occur in Asia and global incidence shows significant geographic variation [3]. In the US, the number of new cases and deaths from gastric cancer in 2024 is estimated to be 26,890 and 10,880, respectively [4]. Incidence increases with age, peaking in those around 70 years of age [5] [6]. Males have a 1.5-fold higher incidence and mortality than females [2] [4]. HER2 (ErbB2) is a transmembrane tyrosine kinase receptor and a key biomarker in gastric cancer that informs treatment decisions [7]. Estimates of HER2-positive prevalence in gastric cancer range widely, generally between 7% and 34% [8]. Patients with gastric cancers that overexpress HER2 represent a distinct population of gastric adenocarcinomas.

In the US, there are differences in gastric cancer incidence and mortality by race/ethnicity, with all racial and ethnic minority groups having a nearly 2-fold greater risk of developing or dying from gastric cancer compared with non-Hispanic White patients [9] [10] [4]. Gastric cancer often goes undetected until an advanced stage. In the US, approximately 36% of new gastric cancer cases are diagnosed at the distant stage, contributing to a poor 5-year relative survival rate of 7% [6].

The FDA's Assessment:

FDA concurs with the Applicant's assessment. 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) (Bang YJ, 2010). 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.

2.2. Analysis of Current Treatment Options

Table 1: Applicant – Summary of FDA Approved First Line Therapies for HER2-positive Gastric or GEJ Adenocarcinoma

Line of Therapy	Approved Therapies	Median Overall Survival	Median Progression-Free Survival	Objective Response Rate	Reference
1L (Phase 3)	Trastuzumab plus SOC chemotherapy (cisplatin plus capecitabine or fluorouracil; investigator's choice) (ToGA)	13.8 months (95% CI: 12.0, 16.0)	6.7 months (95% CI: 6.0, 8.0)	47.0%	[8]
1L (Phase 2)	Trastuzumab + capecitabine + oxaliplatin chemotherapy (HERXO)	13.8 months (95% CI: 10.1, 17.4)	7.1 months (95% CI: 5.5, 8.7)	46.7%	[11]
1L (Phase 3)	Pembrolizumab + trastuzumab + chemotherapy (KEYNOTE-811)	20.5 months[a] (95% CI: 18.2, 24.3)	10.8 months[a] (95% CI: 8.5, 12.5)	74.4%[b]	[12] [13]

Abbreviations: 1L=first-line treatment; CI=confidence interval; CPS=combined positive score; FDA=Food and Drug Administration; GEJ=gastroesophageal junction; HER2=human epidermal growth factor receptor 2; IA1=interim analysis 1; IA2=interim analysis 2; SOC=standard of care; US=United States.

[a] Results are based on IA2 of KEYNOTE-811 in the CPS≥1 population that led to global approvals outside the US.

[b] Based on IA1 of KEYNOTE-811 which led to accelerated approval in the US.

The Applicant's Position:

Historically, the SOC for 1L HER2-positive advanced gastric or GEJ cancer has been trastuzumab in combination with doublet chemotherapy (fluoropyrimidine [5-FU or capecitabine] and platinum [cisplatin or oxaliplatin]) [Table 1]. The SOC was based on the results from the Phase 3, open-label, randomized ToGA trial [8], in which the median OS for patients assigned to trastuzumab in combination with doublet chemotherapy (cisplatin plus capecitabine or 5-FU) was 13.8 months (95% CI: 12, 16) compared with 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). Other studies, including the Phase 2 HERXO study, have yielded similar results to ToGA [11] [14]. Results from the HERXO study extended the chemotherapy backbone from cisplatin-based to oxaliplatin-based; oxaliplatin is the chemotherapy used in KEYNOTE-811. While there are no differences in recommendations across the US population by race, ethnicity, sex, or age, treatment differences for gastric cancer by race and ethnicity have been observed, with Black and Hispanic patients being less likely to receive therapy [15] [16].

In 2021, pembrolizumab and trastuzumab in combination with fluoropyrimidine- and platinum-containing chemotherapy received accelerated approval based on a statistically significant ORR based on BICR assessment per RECIST 1.1, with durable responses, compared with the SOC (22.7% difference [95% CI: 11.2, 33.7]; *p*=0.00006) in the ITT population [17]. Subsequently,

the indication in the US was limited to patients whose tumors express PD-L1 (CPS ≥1), as determined by an FDA-approved test, based on the OS and PFS results from later analyses.

The FDA's Assessment:
The PFS analysis at IA2 of KN811 demonstrated a statistically significant benefit in the ITT and was thus considered as final PFS analysis (see below Section 8.1.2 and Table 12). However, in prespecified exploratory analyses based on PD-L1 expression, no benefit was observed in PFS (HR 1.03, 95% CI 0.65, 1.64) and ORR (69% in both arms) in patients (n: 104) with tumors with CPS <1 compared with patients with tumors with CPS ≥1 (PFS HR 0.71, 95% CI 0.59, 0.86 and ORR 73% vs. 58% in the pembrolizumab and placebo arms respectively). On November 7, 2023, based on an interim analysis of OS (IA3) where the HR for patients with PD-L1 CPS <1 was 1.41 (95% CI 0.90, 2.20), FDA restricted the indication under accelerated approval to patients with PD-L1 CPS ≥ 1.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Pembrolizumab was first approved in the US on 04-SEP-2014 under the trade name KEYTRUDA. KEYTRUDA has been approved globally, including in the US and in Europe. The global registration status of KEYTRUDA is rapidly evolving. Applications are under regulatory agency review worldwide in multiple indications. Please refer to the current KEYTRUDA label for a list of the currently approved indications. The approved doses 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 FDA's Assessment:
Of relevance for this supplement, on May 5, 2021, FDA granted accelerated approval for pembrolizumab, in combination with trastuzumab and fluoropyrimidine- and platinum-based chemotherapy, for the treatment of advanced or metastatic patients with HER2+ gastric/GEJ adenocarcinoma with no prior systemic therapy. On November 7, 2023, FDA restricted the indication under accelerated approval to patients with PD-L1 CPS ≥ 1 (see Section 3.2 below).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
[Table 2] summarizes major regulatory milestones for KEYNOTE-811.

Table 2: Applicant – Major Regulatory Milestones for KEYNOTE-811

IND 123482		
Date	**Serial No.**	**Summary of Communication**
16-JUN-2015	N/A	KEYTRUDA® was granted Orphan Drug Designation (#15-4817) for "gastric cancer, including gastroesophageal junction adenocarcinoma

IND 123482		
Date	**Serial No.**	**Summary of Communication**
02-MAY-2018	N/A	Type B EOP Meeting to discuss the design of KEYNOTE-811
06-JUN-2018	0548	Submission of new protocol KEYNOTE-811-01 for 1L HER2+ gastric cancer
27-AUG-2020	N/A	Teleconference between Merck and FDA to discuss a potential sBLA submission based on KEYNOTE-811 IA1
02-NOV-2020	N/A	Type B pre-sBLA meeting to discuss the KEYNOTE-811 IA1 sBLA
23-MAR-2022	N/A	Advice received from FDA indicating no objection to the proposed change to the triggers for subsequent analyses in KEYNOTE-811
06-SEP-2022	N/A	Informal teleconference between Merck and FDA to discuss a potential sBLA submission based on KEYNOTE-811 IA2
12-JUN-2023	N/A	Informal teleconference between Merck and FDA to discuss a potential sBLA submission based on KEYNOTE-811 IA3
BLA 125514		
06-NOV-2020	1966	Submission of the sBLA based on KEYNOTE-811 at IA1
05-MAY-2021	N/A	FDA grants approval for KEYTRUDA "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."
04-AUG-2023	5199	Submission of KEYNOTE-811 sBLA based on results from IA3 to limit the indication to only those patients whose tumors express PD-L1 with a CPS ≥1.
07-NOV-2023	N/A	FDA grants approval for KEYTRUDA "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 whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Abbreviations: 1L=first-line, BLA=biologics license application; CPS=combined positive score; EOP=end of phase; FDA=Food and Drug Administration; HER2+=human epidermal growth factor receptor 2 positive; IA1=interim analysis 1; IA2=interim analysis 2; IA3=interim analysis 3; IND=Investigational New Drug; N/A=not applicable; PD-L1=programmed cell death ligand 1; sBLA=supplemental biologics license application

The FDA's Assessment:

As stated above, on May 5, 2021, FDA granted accelerated approval to pembrolizumab, in combination with trastuzumab and fluoropyrimidine- and platinum-based chemotherapy, for the first-line treatment of patients with advanced HER2- positive gastric/gastroesophageal junction adenocarcinoma. The approval was based on the interim analysis of the first 264 patients enrolled in Study KEYNOTE-811 based on ORR and DOR. As part of the approval, Merck agreed to the following PMR (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.

In a September 6, 2022, teleconference, FDA and Merck discussed the results of interim analysis 2 (IA2) of Study KN811. The PFS endpoint met statistical significance at IA2 in the intent-to-treat (ITT) population (HR=0.72; 95% CI: 0.60, 0.87; p-value = 0.0002); however, exploratory subgroup results suggested the benefit of treatment appeared to be driven by those patients with a PD-L1 CPS ≥1 (HR=0.70; 95% CI: 0.58, 0.85, nominal p=0.0001). The OS result was not statistically significant in the ITT population (HR=0.87, 95% CI: 0.72, 1.06; p-value = 0.0842), but exploratory subgroup results also suggested the benefit may be driven by the CPS ≥1 population (HR=0.79; 95% CI: 0.64, 0.98, nominal p=0.0143). FDA recommended that Merck to wait for submission of the supplement to convert the approval to regular approval until mature results of the study were available.

On June 12, 2023, FDA and Merck held a teleconference to discuss the results of IA3 of KN811 (data cut-off March 29, 2023). The OS results did not reach statistical significance in the ITT population at IA3 (HR=0.84; 95% CI: 0.70, 1.01; p-value = 0.0292). In this analysis, exploratory subgroup results showed the OS HR in patients whose tumors express PD-L1 with CPS ≥1 is 0.81 (95% CI: 0.67, 0.98); PFS HR=0.71 (95% CI: 0.59, 0.86). In patients whose tumors express PD-L1 with CPS <1, the OS HR was 1.41 (95% CI: 0.9, 2.2) and PFS HR=1.03 (95% CI: 0.65, 1.64). Merck and FDA agreed with the submission of a supplemental BLA to update the labeling and amend the indication from the currently approved ITT (all-comer) indication to a restricted indication only for those patients whose tumors express PD-L1 with CPS ≥1. For conversion to regular approval, FDA requested Merck to submit a sBLA upon availability of the final analysis to allow for an assessment of the mature data.

On August 4, 2023, S-148 was submitted to restrict the indication as discussed above. On September 19, 2023, Agilent submitted sPMA P150013/S027 for the PD-L1 IHC 22C3 pharmDx test, to expand the device intended use for the identification of HER2+, PD-L1 CPS ≥1 gastric or GEJ adenocarcinoma patients who may benefit from treatment with pembrolizumab. On November 7, 2023, FDA restricted the indication under accelerated approval to patients with PD-L1 CPS ≥ 1.

On July 3, 2024, FDA issued preliminary draft responses for a Type B pre-sBLA meeting requested to discuss the format and content of the supplement to be submitted to convert the accelerated approval of the HER2+ gastric cancer indication into regular approval. On July 8, 2024, Merck cancelled the meeting. On July 18, 2024, Merck submitted Supplement 170, which fulfills the PMR 4033-1, described above.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical

Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

In conjunction with OSI, the FDA clinical and statistical review teams determined that inspections were not needed to confirm the integrity of the data submitted with this application. This decision was based upon the extensive clinical experience with pembrolizumab, 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 overall survival as a coprimary endpoint.

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. On November 7, 2023, FDA approved sPMA P150013/S027 for the PD-L1 IHC 22C3 pharmDx test (Agilent) to expand the device intended use for the identification of HER2+, PD-L1 CPS ≥1 gastric or GEJ adenocarcinoma patients who may benefit from treatment with pembrolizumab.

5 Nonclinical Pharmacology/Toxicology

No new data are being submitted.

6 Clinical Pharmacology

No new clinical pharmacology data are being provided in this submission. Data provided with the initial submission of KEYNOTE-811 at IA1 indicated that 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 concurs with the Applicant's assessment.

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

APPEARS THIS WAY ON ORIGINAL

Table 3: Applicant – List of Clinical Studies Relevant to this sBLA

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
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[a] OR Trastuzumab and placebo plus FP or CAPOX[a]	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: 698 APaT: 696	HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma	19 countries 159 sites

Abbreviations: 5-FU=5 fluorouracil; APaT=all participants as treated; BICR=blinded independent central review; CAPOX=oxaliplatin plus capecitabine; DOR=duration of response; FP=cisplatin plus 5-FU; HER2=human epidermal growth factor receptor 2; ITT=intention to treat; NCT=National Clinical Trials; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; sBLA=supplemental biologics license application

[a] Investigators choice of chemotherapy backbone.

The Applicant's Position:

[Table 3] presents details of the pivotal Phase 3 study, KEYNOTE-811, that supports safety and efficacy for the proposed indication.

The FDA's Assessment:
FDA concurs with the description of KN811 in Table 3.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. KEYNOTE-811

Trial Design

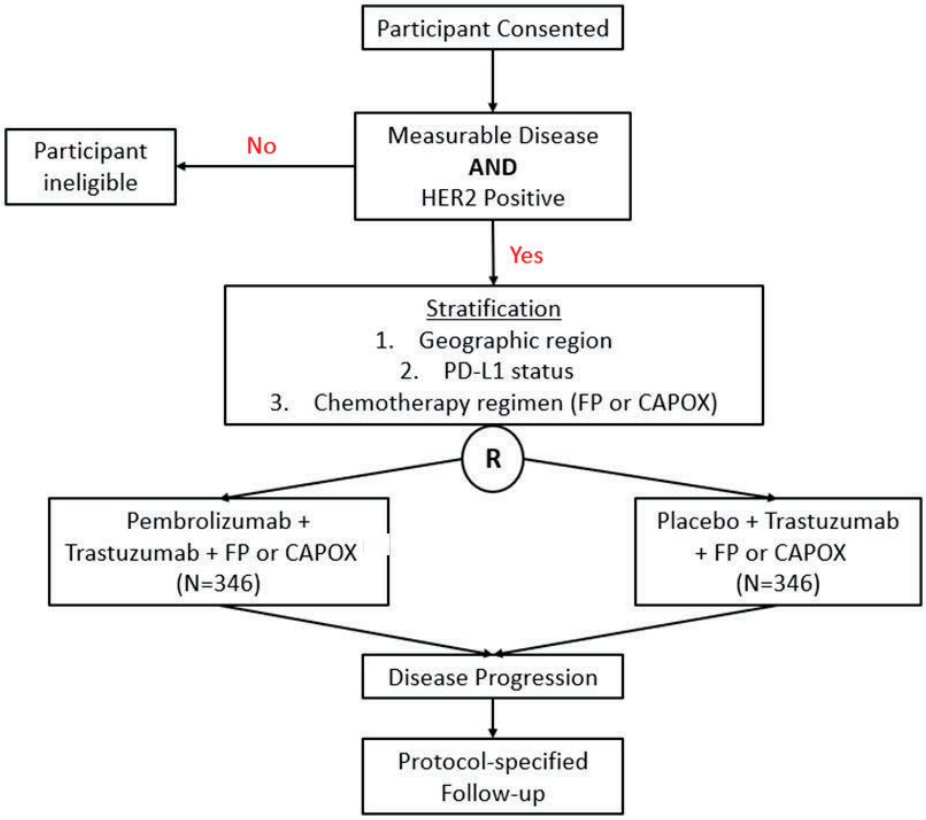
The Applicant's Description:
KEYNOTE-811 is a Phase 3, randomized, placebo-controlled, multicenter, double-blind, efficacy and safety study of pembrolizumab or placebo in combination with standard-of-care (SOC) therapy (trastuzumab plus cisplatin plus 5 fluorouracil [FP] or capecitabine/oxaliplatin [CAPOX]) in participants with previously untreated, locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) positive gastric or GEJ adenocarcinoma. The study design is provided in [Figure 1].

Approximately 692 participants with HER2-positive gastric or GEJ adenocarcinoma were planned to be randomized in the Global Cohort in a 1:1 ratio to receive either pembrolizumab (200 mg Q3W) or placebo each in combination with SOC (trastuzumab plus chemotherapy). The assays used for HER2 testing were the FDA-approved Dako (Agilent) HercepTest (IHC) and Dako (Agilent) HER2 IQFISH pharmDx Kit (Reflex FISH testing for HER2 IHC 2+ samples), and the testing was conducted at a central laboratory.

Participants were stratified by geographic region, PD-L1 status (CPS ≥1 vs CPS <1), and chemotherapy regimen (FP vs CAPOX), which was chosen prior to randomization in the study. The assay used for PD-L1 testing was the Agilent PD-L1 IHC 22C3 pharmDx kit and testing was conducted at a central laboratory. This kit has been analytically validated to determine PD-L1 expression status in gastric tumors.

An additional 40 participants were planned to be randomized in the study as a Japan-specific S-1 plus oxaliplatin (SOX) Cohort in a 1:1 ratio to receive either pembrolizumab or placebo in combination with trastuzumab plus SOX. Randomization was stratified by the participants' PD-L1 status before randomization. Per the prespecified analysis plan, data from the Japan-specific SOX Cohort were not included in the global ITT population and therefore not presented in this Assessment Aid.

Figure 1: Applicant – Study Design (Global Cohort)



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

Study Location: KEYNOTE-811 is an ongoing global study, being conducted at 159 study sites in 19 countries. A total of 95.1% of participants are enrolled outside of the US. Race and ethnicities represented in the study are in [Table 8]. The PK and clinical pharmacology of pembrolizumab were previously shown to be consistent across regions [18].

Choice of Control Group: Trastuzumab plus chemotherapy is the current SOC in previously untreated participants with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma.

Assignment to Treatment: Participants were assigned randomly in a 1:1 ratio to pembrolizumab and placebo after stratification.

Blinding: A double-blinding technique with in-house blinding was used. The participant, investigator, and Sponsor personnel or delegate(s) involved in study intervention, administration,

or clinical evaluation of participants were unaware of study intervention assignments.

Dose Modification, Dose Discontinuation: Treatment with pembrolizumab/placebo and chemotherapy was withheld or discontinued for treatment-related toxicities or life-threatening AEs. Dose modification and toxicity management guidelines were consistent with the approved labels for pembrolizumab, 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 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.

Procedures and Schedules: Screening tests were performed within 28 days prior to enrollment. Pembrolizumab/placebo, trastuzumab, and FP/CAPOX were administered Q3W (1 cycle), during the treatment period, with Cycle 1 beginning at Day 1, for up to 35 cycles. Participants had the option to receive up to 1 additional year of trastuzumab and capecitabine or 5-FU or S-1 beyond 35 administrations of pembrolizumab/placebo at the discretion of the investigator and after Sponsor consultation.

Participants were followed for disease progression until progression occurred, death, withdrawal of consent, or the end of the study, whichever occurred first. Following disease progression, participants entered the Survival Follow-up Period, where they were contacted every 3 months for 2 years and then every 6 months for 3 years until withdrawal of consent, death, or the end of the study, whichever occurred first.

Concurrent 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 days 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: Study treatments were administered by the investigator and/or study staff. The total volume infused was compared with the total volume prepared to determine compliance for each dose administered.

Rescue Medications: Participants received appropriate supportive care measures as deemed necessary by the treating investigator. Supportive care measures for the management of AEs with potential immunologic etiology were consistent with the approved labeling of pembrolizumab. Chemotherapy-related AEs were managed according to local guidelines and practices.

Participant 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 (according to the study flow chart in the KEYNOTE-811 Protocol).

The FDA's Assessment:
FDA concurs with the trial design description. The KEYNOTE-811 study was 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.

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 KN811.

Eligibility Criteria
The Applicant's Description:
Male/female adult (≥18 years of age) 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.

The FDA's Assessment:
Additional key eligibility criteria were as follows:

Inclusion criteria:

- HER2-positive, defined as either IHC 3+ or IHC 2+ in combination with ISH+ (or FISH), as assessed by central review on primary or metastatic tumor. ISH positivity was defined as a ratio of ≥ 2.0 for the number of HER2 gene copies to the number of signals for CEP17. If the ratio is <2.0 but the HER2 gene copy number is >6 the participant could have been considered ISH-positive.
- Adequate cardiac function: left ventricular ejection fraction (LVEF) ≥ 55% and QTcF value ≤470 msec for males and ≤480 msec for females.
- Adequate tumor tissue sample for PD-L1 and MSI biomarker analysis.
- Adequate organ function as follows: ANC ≥1500/mcL, platelets ≥100,000/mcL, hemoglobin ≥9 g/dL; creatinine ≤1.5 × upper limit of normal (ULN) or ≥60 mL/min for participant with creatinine levels >1.5 × ULN; total bilirubin ≤ 1.5 × ULN or direct bilirubin ≤ ULN for participants with total bilirubin levels >1.5 ULN; ALT/AST ≤2.5 × ULN or ≤5 × ULN for participants with liver metastases; albumin ≥2.5 g/dL; INR and aPTT ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.

Exclusion criteria:

- Known active CNS metastases and/or carcinomatous meningitis
- Active autoimmune disease that has required systemic treatment in past 2 years (excluding hormone replacement therapy)
- Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (dosing ≥ 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.
- History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Poorly controlled diarrhea (e.g. Grade ≥2).
- Accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to enrollment (diuretic drugs for other reasons was acceptable)
- Has a history or current evidence of any condition or laboratory abnormality that might confound the results of the trial, including hypokalemia, hypomagnesemia, or hypocalcemia.
- Peripheral neuropathy > Grade 1.

Standard criteria for exclusion of patients in trials and related to the use of checkpoint inhibitors were in place.

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

Key Exploratory Endpoint:

- PRO and utility scores

The FDA's Assessment:

FDA agrees with the Applicant's description.

Statistical Analysis Plan and Amendments

The Applicant's Description:

A summary of the statistical analysis plan is provided in [Table 4].

Table 4: Applicant – Summary of the Statistical Analysis Plan for KEYNOTE-811

Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT) PRO: All participants in the ITT population who had at least 1 PRO assessment and at least 1 dose of study intervention (PRO FAS)
Primary Endpoints	1) Progression-free Survival (PFS) per RECIST 1.1 assessed by BICR 2) Overall survival (OS)
Key Secondary Endpoint	Objective response (OR) per RECIST 1.1 assessed by BICR
Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses on PFS and OS will be evaluated by comparing the experimental arm to the control arm using a stratified log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The stratified Miettinen and Nurminen method [19] with sample size weights will be used for analysis of ORR.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs were to be provided for between-treatment differences in the percentage of participants with events, these analyses were to be performed using the Miettinen and Nurminen method [19].

Interim Analyses	Three interim analyses (IA) were to have been performed in this study based on current projection of enrollment and event accrual rates. Results were reviewed by an external Data Monitoring Committee. • IA1: o Planned timing: was to be performed when ~ 260 participants have been followed up for ~ 8.5 months. o Primary purpose: efficacy analysis for ORR (hypothesis testing). • IA2[a]: o Planned timing: was to be performed after ~ 542 PFS events have occurred AND ~ 9 months after last participant randomized. o Primary purpose: efficacy analysis for PFS and OS. • IA3[a]: o Planned timing: was to be performed when ~ 18 months after the last participant has been randomized AND approximately 606 PFS events have been observed. This was the final PFS analysis. o Primary purpose: efficacy analysis for PFS and OS. • Final analysis[a]: o Planned timing: was to be performed when ~ 28 months after the last participant has been randomized AND ~ 551 deaths have occurred. o Primary purpose: efficacy analysis for OS. [a] Note for IA2, IA3, and FA, if the events had accrued slower than expected, the Sponsor may have conducted the analysis with up to 3 additional months of follow-up than the minimal follow-up as described above, or when the specified number of events are observed, whichever came first.
Multiplicity	The overall Type I error over the primary endpoints (PFS and OS) and the key secondary endpoint (ORR) was strongly controlled at 2.5% (1-sided), with initially 0.2% allocated to ORR, 0.3% to PFS and 2% to OS. By using the graphical approach of Maurer and Bretz, if 1 hypothesis was rejected, the alpha was to be shifted to other hypotheses [20].
Sample Size and Power	The planned sample size was ~ 692 participants. For ORR, with sample size of ~ 260 at IA1, the study had ~ 90% power for detecting a 25% difference in ORR (73% vs 48%) at an initially assigned 0.002 (1-sided) significance level. For PFS, there were estimated to be ~ 606 events at the PFS final analysis. With 606 PFS events, the study had ~ 95% power for detecting a hazard ratio (HR) of 0.7 at an initially assigned 0.003 (1-sided) significance level. For OS, there were estimated to be ~ 551 deaths at the OS final analysis. With 551 deaths, the study had ~ 90% power for detecting a HR of 0.75 at an initially assigned 0.020 (1-sided) significance level.

Abbreviations: APaT=all participants as treated; BICR=blinded independent central review; CI=confidence interval; FA=final analysis; FAS=full analysis set; HR=hazard ratio; IA=interim analysis; IA1=interim analysis 1; IA2=interim analysis 2; IA3=interim analysis 3; ITT=intention- to- treat; OR=objective response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcomes; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1

The FDA's Assessment:

FDA generally agrees with the Applicant's description. FDA adds that according to the statistical

analysis plan, if events accrued more slowly than expected or the same as expected, alpha spending would be based on the actual information fraction. If events accrued more quickly than expected, cumulative spending based on the expected information fraction was to be used to save some alpha for analyses that would be performed with more than the originally planned maximum events. The final analysis was planned to use the remaining Type I error that was not spent at the earlier analyses. The actual event number of OS analysis at IA2, IA3, and FA were 415, 501, and 555 deaths, respectively, which are slightly higher than the expected numbers (401, 488, and 551 deaths for IA2, IA3, and FA, respectively). The p-value boundary for the OS final analysis calculated by this pre-specified approach was one-sided 0.0201 given that the one-sided alpha of 0.025 was allocated to the OS analysis.

Protocol Amendments

The Applicant's Description:

The original protocol was finalized on 11-APR-2018. Changes in the conduct of the study implemented by protocol amendment are summarized in [Table 5].

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

Document	Date of Issue	Overall Rationale
Amendment 8	07-APR-2022	Update SAP language for the flexibility of the timing of the interim and final efficacy analyses in case of significantly slower than anticipated accrual of PFS and/or OS events.
Amendment 7	24-JUN-2021	To update the pembrolizumab dose-modification and toxicity-management guidelines for irAEs and update protocol language to allow option for standard of care treatment beyond 35 cycles.
Amendment 6	07-JUL-2020	Update SAP language to remove PFS analysis at IA1 in response to Regulatory Authority Input.
Amendment 5	20-MAY-2020	Update protocol and SAP language regarding the definition of the curative surgical resection and modification of PFS primary censoring rule associated with the curative surgical resection, remove the ORR futility analysis for IA1, and add a PFS analysis for IA1.
Amendment 4	27-FEB-2019	Updated Biomarker Collection Information and incorporated Amendment 3 changes to apply globally.
Amendment 3	24-JAN-2019	In response to Health Authority input, changes were made regarding safety monitoring procedures for trastuzumab and chemotherapy backbone.
Amendment 2	16-AUG-2018	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.

Document	Date of Issue	Overall Rationale
Amendment 1	31-MAY-2018	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.
Original Protocol	11-APR-2018	N/A

Abbreviations: ECOG=European Cooperative Oncology Group; HIV=human immunodeficiency virus; IA1=interim analysis 1; irAE=immune-related adverse event; MSI=microsatellite instability.; N/A=not applicable; ORR=objective response rate; OS=overall survival; 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 generally agrees with the Applicant's description. In Amendment 8, the revisions allowed for the conduct of IA2, IA3, and the final analyses with up to 3 additional months of follow-up than the minimal follow-up than the one described in Table 4, or when the prespecified number of events were observed (whichever comes first).

An additional protocol revision (Amendment 9, dated September 8, 2022) was conducted to update the Applicant's entity name and address.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:
KEYNOTE-811 was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding IEC review, informed consent, and the protection of human participants in biomedical research. The protocol and any amendments, information provided to participants, and any recruitment materials were reviewed and approved by the IECs (also referred to as an IRB, ERC, or any other ethics committee). Informed consent was obtained from all participants prior to performing any study-related procedures or assessments.

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

Financial Disclosure

The Applicant's Position:
A financial disclosure review of the KEYNOTE-811 study has been conducted. Disclosure of financial interests and/or arrangements, including statements of due diligence for the investigators who conducted the KEYNOTE-811 study, is described in FDA forms 3454, 3455 and Module 1.3.4.

The FDA's Assessment:
FDA verified the information submitted. A total of 26 (3.7%) patients were enrolled at sites where investigators for whom no financial forms were available and only 2 patients were enrolled at a site where the investigator had a financial disclosure. As the coprimary endpoints are blinded-independently assessed progression free survival and overall survival, it is unlikely that the lack of information from financial interests or the potential conflict from one investigator may have biased the trial results. Additional information can be found in Section 19.2.

Patient Disposition

Data:

Table 6: Applicant – Disposition of Participants (Global Cohort) (ITT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		348	
Status for Study Medication of Treatment Phase				
Started	350		346	
Completed	50	(14.3)	30	(8.7)
Discontinued	289	(82.6)	312	(90.2)
Adverse Event	36	(10.3)	33	(9.5)
Associated with COVID-19	2	(0.6)	3	(0.9)
Clinical Progression	27	(7.7)	20	(5.8)
Complete Response	1	(0.3)	0	(0.0)
Non-Study Anti-Cancer Therapy	6	(1.7)	5	(1.4)
Physician Decision	8	(2.3)	5	(1.4)
Progressive Disease	194	(55.4)	235	(67.9)
Associated with COVID-19	0	(0.0)	1	(0.3)
Withdrawal By Subject	17	(4.9)	14	(4.0)
Participants Ongoing	11	(3.1)	4	(1.2)
Status for Trial				
Discontinued	267	(76.3)	290	(83.3)
Death	266	(76.0)	286	(82.2)
Associated with COVID-19	2	(0.6)	3	(0.9)
Lost To Follow-Up	0	(0.0)	1	(0.3)
Not Associated with COVID-19, No Further Information	0	(0.0)	1	(0.3)
Withdrawal By Subject	1	(0.3)	3	(0.9)
Not Associated with COVID-19, No Further Information	0	(0.0)	1	(0.3)
Not Associated with COVID-19, Subsequently Died	1	(0.3)	2	(0.6)
Participants Ongoing	83	(23.7)	58	(16.7)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
For the status for study medication of treatment phase, participants treated with study medication is used as the denominator for percentage calculation.
For the status for trial, participants in population is used as the denominator for percentage calculation.
Database Cutoff Date: 20MAR2024

The Applicant's Position:
As of the database cutoff date of 20-MAR-2024 for FA, 698 participants were randomized in the Global Cohort; 2 patients, who were randomized to the control arm, were not treated [Table 6]. Overall, 86.4% of participants discontinued from study treatment. A total of 82.6% of participants in the pembrolizumab plus SOC group and 90.2% of participants in the SOC group discontinued from study treatment. The most common reason for discontinuation from study treatment in each arm was progressive disease. Discontinuation of study treatment due to progressive disease was higher in the SOC group (67.9%) than in the pembrolizumab plus SOC group (55.4%).

The FDA's Assessment:
The most common cause for treatment discontinuation was disease progression (using grouped terms clinical progression and progressive disease). Disease progression was the cause of treatment discontinuation in 221 (63%) and 255 (73%) patients in the pembrolizumab and placebo arms, respectively. As summarized, the second most common cause for treatment discontinuation was adverse events, which occurred at similar rates between arms (10.3% vs. 9.5%).

Protocol Violations/Deviations
The Applicant's Position:
Important protocol deviations were reported for 48 and 34 participants in the pembrolizumab plus SOC group and SOC group, respectively. Of these, protocol deviations considered clinically important were reported for 2 participants in the pembrolizumab plus SOC group and were related to receiving the incorrect study intervention other than what had been assigned at allocation as summarized below:

- One participant took capecitabine continuously beyond 2 weeks for 3 cycles and experienced multiple Grade 1 to 3 AEs that were considered to be related to capecitabine. The site reported that the participant misunderstood the directions from the investigator and continued taking the capecitabine continuously when they should have paused this treatment.
- One participant took additional doses of capecitabine in Cycle 1. This resulted in a dose interruption in Cycle 2 due to nausea considered related to capecitabine and oxaliplatin and a subsequent dose reduction for capecitabine. An AE of accidental overdose was reported for this participant.

No participant's data were excluded from analysis due to a protocol deviation. No protocol

deviations were classified as a serious GCP compliance issue. None of the important protocol deviations impacted the overall safety or integrity of the study.

The FDA's Assessment:
Overall, 12% of patients had major protocol deviations (Table 7). 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 seven 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 the coprimary endpoints of the trial as independently-assessed progression-free survival and overall survival, it is unlikely that the protocol violations would have an impact on study results.

Table 7. KN811: Major protocol violations

	Pembrolizumab+SOC (N= 350); n (%)	**Placebo+SOC (N= 348); n (%)**
N with major protocol violations	48 (14)	34 (10)
Inclusion/exclusion criteria - Cardiac function - Not HER2+ by central lab	2 (0.6) 0 2 (0.6)	4 (1) 1 (0.3) 3 (1)
Informed Consent issues	4 (1)	5 (1)
Prohibited anticancer medications	1 (0.3)	1 (0.3)
Safety reporting	21 (6)	17 (5)
Study drugs administration - Improperly stored medication - Incorrect medication	19 (5) 15 (4) 5 (1)	9 (3) 7 (2) 2 (0.6)
Trial procedures (failure to conduct safety or efficacy assessments)	8 (2)	4 (1)

In addition, Merck reported that as the data cutoff for the final analysis, 9 (1.2%) patients were inadvertently unblinded to their treatment assignment. Of these participants, 2 were in the pembrolizumab arm and 7 were in the placebo arm; 7 (all in the placebo arm) patients were unblinded after discontinuation from treatment. Each of the 2 events of unblinding involved unblinding of a member of Merck's team who were not responsible for participant care; no site personnel responsible for participant care or headquarters personnel were unblinded. FDA agrees that these events would not have an impact on study results.

KN811 was partly conducted during the COVID-19 pandemic. Table 14.1-13 of the Clinical Study Report (not shown here) summarized the protocol deviations associated with COVID-19, which were all considered minor deviations and are related to visits and assessments delayed, missing, conducted at alternative location/method, etc. FDA agrees with the Applicant's assessment of COVID-19 deviations as minor; given the coprimary endpoint of OS, none of the

delayed or missing scans have an impact on the study outcomes.

Table of Demographic Characteristics

Data:

Table 8: Applicant – Participant Characteristics (Global Cohort) (ITT Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	350		348		698	
Sex						
Male	284	(81.1)	280	(80.5)	564	(80.8)
Female	66	(18.9)	68	(19.5)	134	(19.2)
Age (Years)						
< 65	205	(58.6)	192	(55.2)	397	(56.9)
>= 65	145	(41.4)	156	(44.8)	301	(43.1)
Mean	60.4		61.7		61.0	
SD	11.8		10.8		11.3	
Median	62.0		63.0		63.0	
Range	19 to 85		32 to 85		19 to 85	
Race						
American Indian Or Alaska Native	5	(1.4)	6	(1.7)	11	(1.6)
Asian	119	(34.0)	121	(34.8)	240	(34.4)
Black Or African American	2	(0.6)	2	(0.6)	4	(0.6)
Multiple	6	(1.7)	5	(1.4)	11	(1.6)
White	218	(62.3)	212	(60.9)	430	(61.6)
Missing	0	(0.0)	2	(0.6)	2	(0.3)
Ethnicity						
Hispanic Or Latino	38	(10.9)	45	(12.9)	83	(11.9)
Not Hispanic Or Latino	309	(88.3)	293	(84.2)	602	(86.2)
Not Reported	1	(0.3)	9	(2.6)	10	(1.4)
Unknown	2	(0.6)	1	(0.3)	3	(0.4)
Age Group (Years)						
18-39	19	(5.4)	14	(4.0)	33	(4.7)
40-49	44	(12.6)	30	(8.6)	74	(10.6)
50-59	73	(20.9)	99	(28.4)	172	(24.6)
60-69	135	(38.6)	109	(31.3)	244	(35.0)
70-79	74	(21.1)	88	(25.3)	162	(23.2)
>=80	5	(1.4)	8	(2.3)	13	(1.9)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	113	(32.3)	111	(31.9)	224	(32.1)
Asia	118	(33.7)	119	(34.2)	237	(34.0)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Rest of the World	119	(34.0)	118	(33.9)	237	(34.0)
Geographic Region of Enrolling Site						
US	17	(4.9)	17	(4.9)	34	(4.9)
Ex-US	333	(95.1)	331	(95.1)	664	(95.1)
ECOG Performance Scale						
0	146	(41.7)	146	(42.0)	292	(41.8)
1	204	(58.3)	202	(58.0)	406	(58.2)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	110	(31.4)	122	(35.1)	232	(33.2)
Adenocarcinoma of the stomach	240	(68.6)	226	(64.9)	466	(66.8)
Current Disease Overall Stage						
IIB	1	(0.3)	0	(0.0)	1	(0.1)
IIIA	3	(0.9)	1	(0.3)	4	(0.6)
IIIB	5	(1.4)	2	(0.6)	7	(1.0)
IIIC	1	(0.3)	3	(0.9)	4	(0.6)
IV	340	(97.1)	342	(98.3)	682	(97.7)
Disease Status						
Locally advanced	10	(2.9)	7	(2.0)	17	(2.4)
Metastatic	340	(97.1)	341	(98.0)	681	(97.6)
Number of Metastatic Sites						
0-2	179	(51.1)	198	(56.9)	377	(54.0)
>=3	171	(48.9)	150	(43.1)	321	(46.0)
Histological Subtype (Lauren classification)						
Diffuse	68	(19.4)	51	(14.7)	119	(17.0)
Intestinal	198	(56.6)	188	(54.0)	386	(55.3)
Indeterminate	83	(23.7)	109	(31.3)	192	(27.5)
Unknown	1	(0.3)	0	(0.0)	1	(0.1)
Prior Gastrectomy/Esophagectomy						
Yes	51	(14.6)	63	(18.1)	114	(16.3)
No	299	(85.4)	285	(81.9)	584	(83.7)
CPS>=1						
Y	298	(85.1)	296	(85.1)	594	(85.1)
N	52	(14.9)	52	(14.9)	104	(14.9)
Tumor Burden						
< Median	162	(46.3)	166	(47.7)	328	(47.0)
>= Median	171	(48.9)	170	(48.9)	341	(48.9)
Missing	17	(4.9)	12	(3.4)	29	(4.2)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
HER2 Status						
IHC 1+	1	(0.3)	1	(0.3)	2	(0.3)
IHC 2+ ISH Equivocal	0	(0.0)	1	(0.3)	1	(0.1)
IHC 2+ ISH Negative	1	(0.3)	1	(0.3)	2	(0.3)
IHC 2+ ISH Positive	62	(17.7)	84	(24.1)	146	(20.9)
IHC 3+	286	(81.7)	261	(75.0)	547	(78.4)
MSI Status						
MSI High	6	(1.7)	2	(0.6)	8	(1.1)
non-MSI-High	326	(93.1)	329	(94.5)	655	(93.8)
Unknown	18	(5.1)	17	(4.9)	35	(5.0)
Chemotherapy Regimen						
CAPOX	297	(84.9)	299	(85.9)	596	(85.4)
FP	53	(15.1)	49	(14.1)	102	(14.6)

CAPOX: Backbone chemotherapy oxaliplatin + capecitabine.
FP: Backbone chemotherapy cisplatin + 5-FU.
Database Cutoff Date: 20MAR2024.

The Applicant's Position:
Demographic and baseline characteristics are provided in [Table 8].

The FDA's Assessment:
FDA agrees with Merck's presentation of the patient characteristics in KN811. The median age of diagnosis of patients enrolled in the study is 62 years old, which is slightly younger the median age of diagnosis (non-HER2 selected) in the US (SEER, 2024). The majority (81%) of patients are men, consistent with the disease being more prevalent in men. More patients (82% and 75% in the pembrolizumab and control arms respectively) in the pembrolizumab arm had HER2+ IHC3+ status, which may have had an impact on the efficacy of the backbone regimen; however, the HR for both populations were similar (see Figure 8).

In KN811, the majority (62%) of patients were White; 35% of patients were Asian. Black or African American patients were enrolled at a rate lower than the expected incidence in the US, even when KN811 is a multiregional trial with similar enrollment across regions (only 5% of patients were enrolled in the US). 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.

The majority (85%) of patients had PD-L1-positive tumors (defined as CPS ≥1 as centrally detected using the IHC 22C3 pharmDx™ assay), which represent the population for which pembrolizumab in combination with trastuzumab and chemotherapy is currently approved in the US. Table 9 summarizes the baseline demographic and disease characteristics of the CPS ≥1 population, which are similar to the ITT population. Demographic and disease characteristics in the PD-L1 positive population are well balanced between arms.

Table 9. KN811: Demographic characteristics of patients with CPS ≥1

	Pembrolizumab+SOC (N= 298); n (%)	**Placebo+SOC (N= 296); n (%)**
Sex		
- Male	240 (81)	237 (80)
- Female	58 (19)	59 (20)
Age (years)		
- Median (range)	63 (19, 85)	63 (32, 85)
- ≥ 65 yo	174 (58)	165 (56)
- <65	124 (42)	131 (44)
Race		
- American Indian	5 (2)	6 (2)
- Asian	97 (33)	97 (33)
- Black or African American	2 (<1)	2 (<1)
- Multiple	5 (2)	4 (1)
- White	189 (63)	186 (63)
- Missing	0	1 (<1)
Ethnicity		
- Hispanic or Latino	36 (12)	41 (14)
- Not Hispanic or Latino	259 (87)	250 (84)
- Not reported/unknown	3 (1)	5 (2)
Geographic region		
- Asia	96 (32)	96 (32)
- Rest of the World	105 (35)	104 (35)
- Western Europe/ Israel/ North America/Australia	97 (33)	96 (32)
ECOG PS		
- 0	127 (43)	122 (41)
- 1	171 (57)	174 (59)
Primary tumor location		
- GEJ	97 (33)	99 (33)
- Gastric	201 (67)	197 (67)
Disease status		
- Locally advanced	8 (3)	6 (2)

- Metastatic	290 (97)	290 (98)
Histologic subtype		
- Diffuse	54 (18)	44 (15)
- Intestinal	170 (57)	159 (54)
- Indeterminate/unknown	73 (24)	93 (31)
HER2 status		
- IHC1+/IHC2+ ISH- or equivocal	2 (<1)	3 (1)
- IHC2+/ISH+	51 (17)	68 (23)
- IHC3+	245 (82)	225 (76)
MSI status		
- MSI-H	6 (2)	2 (1)
- Non-MSI-H	282 (95)	280 (95)
- Unknown	10 (3)	14 (5)
Chemotherapy backbone		
- CAPOX	251 (84)	253 (85)
- FP	47 (16)	43 (14)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
The Applicant's Position:
Disease characteristics are provided in [Table 8]. The race and ethnicities represented in the study are provided in [Table 8]. The study population also included participants who identified as multiple races. Diversity in clinical trials has been and continues to be a priority for the Applicant, as an integral component of the Sponsor's broader Diversity and Inclusion strategy and commitments, and in recognition of the clinical value of continued focus on the diversity of our studies.

The FDA's Assessment:
Disease characteristics for the population indicated (HER2+ disease with CPS ≥1) are summarized in Table 9. Black or African American patients were enrolled at lower than the expected incidence rate in the US.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
The Applicant's Position:
Treatment compliance: Study interventions were administered in the clinic by qualified site personnel and recorded in the CRF.
Concomitant Medications and Subsequent Oncological Therapies: Overall, 100% of the participants in the pembrolizumab plus SOC group and all but 1 participant in the SOC group (99.7%) received concomitant medications during the study. A total of 78.0% and 79.5% of participants in the pembrolizumab plus SOC group and the SOC group, respectively, received

steroid medications. Overall, 47.7% and 58.1% of participants in the pembrolizumab plus SOC group and SOC group, respectively, received new oncological medications posttreatment.

The FDA's Assessment:
FDA concurs with the Applicant's assessment. Systemic corticosteroid use was similar across arms (78% vs. 80% in the pembrolizumab and placebo arms, respectively). Fluorouracil, capecitabine, irinotecan, taxanes, ramucirumab, trastuzumab, trastuzumab-deruxtecan, and other immune checkpoint inhibitors were the most frequently used subsequent antineoplastics used, and generally balanced across arms.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)
Data:

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Table 10: Applicant – Summary of Follow-up Duration (Global Cohort) (ITT Population)

	ITT Population			CPS ≥1 Population		
	Pembrolizumab + SOC	**SOC**	**Total**	**Pembrolizumab + SOC**	**SOC**	**Total**
Interim Analysis 1 (first 264 participants randomized)						
Follow-up duration (months)[a]	(N=133)	(N=131)	(N=264)	-	-	-
Median (Range)	11.1 (2.2, 19.0)	10.4 (0.5, 17.9)	10.6 (0.5, 19.0)	-	-	-
Mean (SD)	11.1 (3.7)	10.3 (4.1)	10.7 (3.9)	-	-	-
Interim Analysis 2						
Follow-up duration (months)[a]	(N=350)	(N=348)	(N=698)	(N=298)	(N=296)	(N=594)
Median (Range)	16.1 (0.6, 41.6)	14.8 (0.3, 41.2)	15.4 (0.3, 41.6)	17.0 (0.6, 41.6)	13.9 (0.3, 41.2)	15.3 (0.3, 41.6)
Mean (SD)	17.7 (10.0)	16.4 (10.0)	17.1 (10.0)	18.1 (10.3)	15.9 (9.9)	17.0 (10.2)
Interim Analysis 3						
Follow-up duration (months)[a]	(N=350)	(N=348)	(N=698)	(N=298)	(N=296)	(N=594)
Median (Range)	19.9 (0.6, 51.7)	16.8 (0.3, 51.2)	18.3 (0.3, 51.7)	20.0 (0.6, 51.7)	15.7 (0.3, 51.2)	18.2 (0.3, 51.7)
Mean (SD)	21.3 (13.1)	19.6 (13.1)	20.4 (13.1)	21.9 (13.5)	19.1 (13.2)	20.5 (13.4)
Final Analysis						
Follow-up duration (months)[a]	(N=350)	(N=348)	(N=698)	(N=298)	(N=296)	(N=594)
Median (Range)	20.0 (0.6, 63.4)	16.8 (0.3, 62.9)	18.3 (0.3, 63.4)	20.1 (0.6, 63.4)	15.7 (0.3, 62.9)	18.2 (0.3, 63.4)
Mean (SD)	24.3 (17.0)	22.0 (16.6)	23.2 (16.8)	25.0 (17.5)	21.5 (16.6)	23.3 (17.1)

Abbreviations: CPS=combined positive score; ITT=intention to treat; SD=standard deviation; SOC=standard-of-care.

[a] Follow-up duration is defined as the time from randomization to the date of death or the database cutoff date if the participant is still alive.

N is the number of participants in population.

Database Cutoff Dates: 17-JUN-2020 (IA1), 25-MAY-2022 (IA2), 29-MAR-2023 (IA3), 20-MAR-2024 (FA)

Table 11: Applicant – Summary of Key Efficacy Results (Global Cohort) (ITT Population)

Endpoint	Pembrolizumab + SOC	SOC
OS at FA	**N=350**	**N=348**
Median OS[a], months (95% CI)	20.0 (17.8, 22.1)	16.8 (14.9, 18.7)
HR (95% CI)[b] *p*-value[c]	0.80 (0.67, 0.94) 0.0040	
PFS assessed by BICR at IA2	**N=350**	**N=348**
Median PFS[a], months (95% CI)	10.0 (8.6, 11.7)	8.1 (7.0, 8.5)
HR (95% CI)[b] *p*-value[c]	0.72 (0.60, 0.87) 0.0002	
ORR and DOR assessed by BICR at IA1	**N=133**	**N=131**
ORR, % (95% CI)	74.4 (66.2, 81.6)	51.9 (43.0, 60.7)
ORR Difference % (95% CI)[d] *p*-value[e]	22.7 (11.2, 33.7) 0.00006	
Number of participants with a response[f]	99	68
Median DOR, months (range)[a]	10.6 (1.1+ - 16.5+)	9.5 (1.4+ - 15.4+)

Abbreviations: BICR=blinded independent central review; CAPOX=capecitabine plus oxaliplatin; CI=confidence interval; CPS=combined positive score; DOR=duration of response; FA=final analysis; FP=cisplatin plus 5-fluorouracil; HR=hazard ratio; IA=interim analysis; ITT=intention to treat; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; sSAP=supplemental statistical analysis plan; SOC=standard of care

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

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS ≥1 vs CPS <1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

[c] One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS ≥1 vs CPS <1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

[d] Based on Miettinen & Nurminen method stratified by Geographic region (Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (CPS ≥1 vs CPS <1), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.

[e] One-sided p-value for testing. H0: difference in %=0 vs H1: difference in % > 0.

[f] Includes participants with best objective response as confirmed complete response or partial response.

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.

Endpoints are shown for the analyses at which they reached statistical significance: IA1 for ORR, IA2 for PFS, and FA for OS. DOR was not designed for any formal testing but is presented at IA1 to support ORR.

Database Cutoff Dates: 17-JUN-2020 (IA1), 25-MAY-2022 (IA2), 20-MAR-2024 (FA)

Table 12: Applicant – Summary of Key Efficacy Results at Final Analysis (ITT Population with CPS ≥1)

Endpoint	Pembrolizumab + SOC (N=298)	SOC (N=296)
OS		
Median OS[a], months (95% CI)	20.1 (17.9, 22.9)	15.7 (13.5, 18.5)
HR (95% CI)[b] Nominal *p*-value[c]	0.79 (0.66, 0.95) 0.0062	
PFS assessed by BICR		
Median PFS[a], months (95% CI)	10.9 (8.5, 12.5)	7.3 (6.8, 8.4)
HR (95% CI)[b] Nominal *p*-value[c]	0.72 (0.60, 0.87) 0.0003	
ORR assessed by BICR, % (95% CI)	73.2 (67.7, 78.1)	58.4 (52.6, 64.1)
ORR Difference % (95% CI)[d] Nominal *p*-value[e]	14.7 (7.1, 22.2) 0.00008	
DOR assessed by BICR, (months), median (range)[a]	11.3 (1.1+ - 60.8+)	9.6 (1.4+ - 60.5+)

Abbreviations: BICR=blinded independent central review; CI=confidence interval; CPS=combined positive score; DOR=duration of response; HR=hazard ratio; ITT=intention to treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; SOC=standard-of-care.

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

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

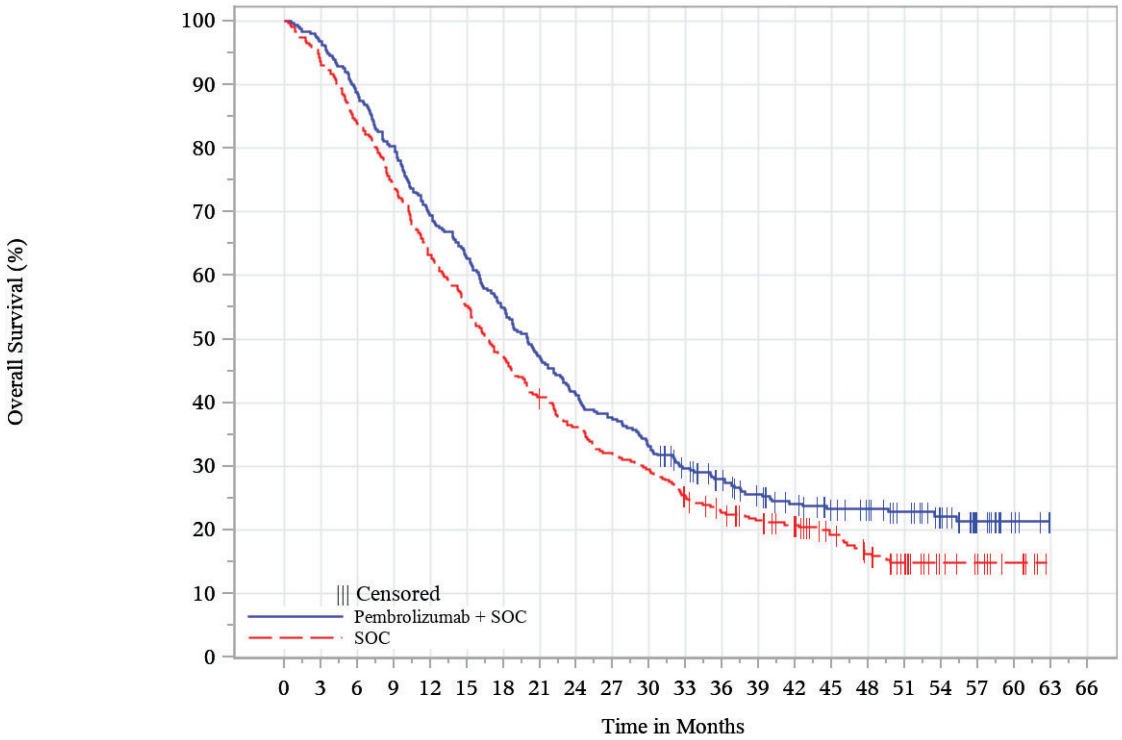
[c] One-sided p-value based on log-rank test.

[d] Based on Miettinen & Nurminen method.

[e] One-sided p-value for testing. H0: difference in %=0 vs H1: difference in % > 0.

Database Cutoff Date: 20-MAR-2024

Figure 2: Applicant – Kaplan-Meier Estimates of Overall Survival at Final Analysis (Global Cohort) (ITT Population)



At Risk

Pembrolizumab + SOC	350	339	311	281	243	220	192	165	144	131	116	97	84	72	62	53	49	42	32	18	5	0	0
SOC	348	326	292	259	220	192	165	142	125	110	102	85	74	66	59	47	37	25	16	12	6	0	0

Database Cutoff Date: 20MAR2024.

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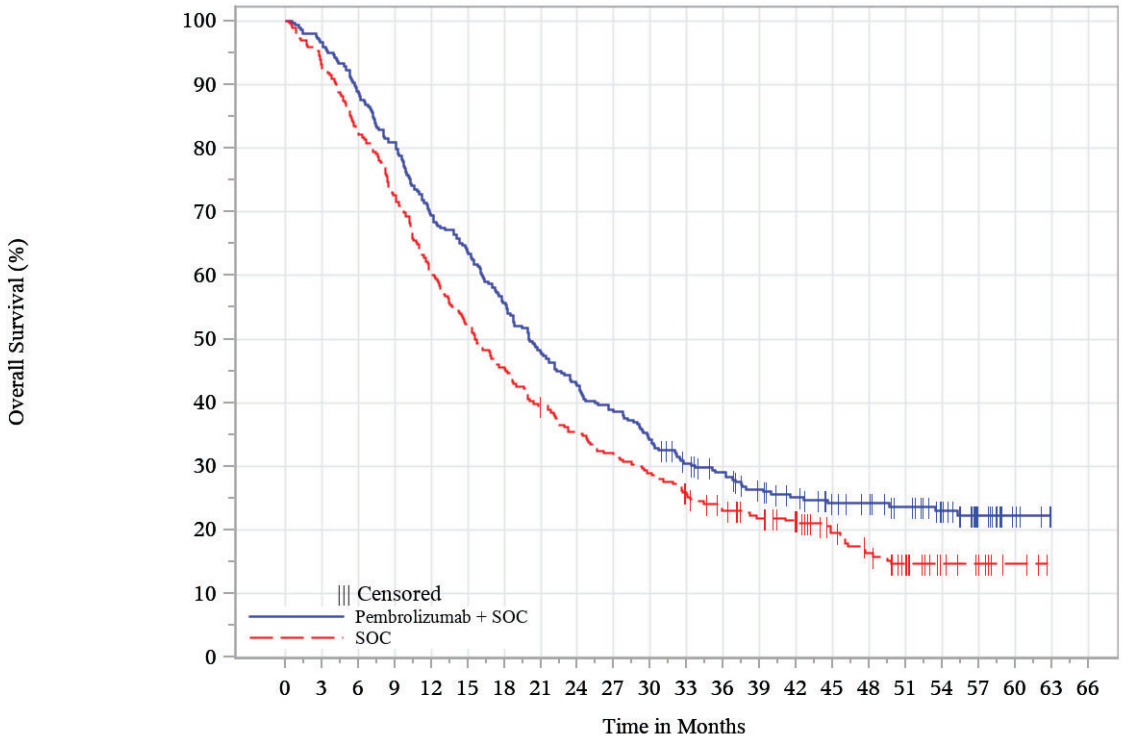
Figure 3: Applicant – Kaplan-Meier Estimates of Overall Survival at Final Analysis (ITT Population with CPS ≥1)



At Risk

Pembrolizumab + SOC	298	288	265	241	207	190	166	143	127	115	102	86	78	67	59	51	48	42	32	18	5	0	0
SOC	296	276	244	215	180	154	135	117	104	93	85	73	63	56	50	38	30	21	13	9	3	0	0

Database Cutoff Date: 20MAR2024.

The Applicant's Position:

The results presented are from IA1 (database cutoff date: 17-JUN-2020), IA2 (database cutoff date: 25-MAY-2022), and the FA (database cutoff date: 20-MAR-2024) for KEYNOTE-811, with the median duration of follow-up at each analysis provided in [Table 10].

OS: At FA, pembrolizumab plus SOC demonstrated a statistically significant improvement in OS compared with SOC [Table 11]:

- The OS HR was 0.80 (95% CI: 0.67, 0.94; *p*=0.0040, which is less than the p-value boundary of 0.0201), representing a 20% reduction in the risk of death [Table 11].
- Results of the analyses of OS by prespecified subgroups were generally consistent with the primary OS analysis in the ITT population; however, HR point estimates for the PD-L1 CPS <1 (HR 1.10 [95% CI: 0.72, 1.68]), Asian race (HR 1.05 [95% CI: 0.77, 1.43]), and Asia region (HR 1.05 [95% CI: 0.77, 1.43]) subgroups were >1 with wide 95% CIs.

- For the PD-L1 CPS ≥1 population at FA, the OS HR was 0.79 (95% CI: 0.66, 0.95; nominal *p*=0.0062). The median OS at FA was 20.1 months (95% CI: 17.9, 22.9) for the pembrolizumab plus SOC group and 15.7 months (95% CI: 13.5, 18.5) for the SOC group [Table 12].
- The KM curves for OS separated at approximately 3 months and remained separated throughout the evaluation period for the ITT population [Figure 2] and for the CPS ≥1 population [Figure 3].

PFS: At IA2, after 484 PFS events had occurred (80% information fraction), pembrolizumab plus SOC demonstrated a statistically significant improvement in PFS compared with SOC [Table 11].

- The PFS HR was 0.72 (95% CI: 0.60, 0.87; *p*=0.0002, which is less than the p-value boundary of 0.0012795), representing a 28% reduction in the risk of disease progression or death.
- PFS results for prespecified subgroups were generally consistent with those of the overall ITT population. The HR point estimate for the PD-L1 CPS <1 subgroup was 1.17 (95% CI: 0.73, 1.89).
- For the PD-L1 CPS ≥1 population at IA2, the PFS HR was 0.70 ([95% CI: 0.58, 0.85], nominal *p*=0.0001). The median PFS was 10.8 months (95% CI: 8.5, 12.5) for the pembrolizumab plus SOC group vs 7.2 months (95% CI: 6.8, 8.4) for the SOC group.

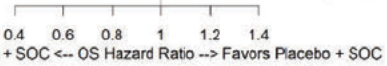
Since the superiority criterion for the primary PFS hypothesis was met at IA2, PFS was not formally tested at FA. With longer follow-up, the results for PFS (HR=0.73; 95% CI: 0.61, 0.87; nominal *p*=0.0002) were consistent with IA2, with the median PFS for the pembrolizumab plus SOC group being 10.0 months (95% CI: 8.6, 12.2) compared with 8.1 months (95% CI: 7.0, 8.5) in the SOC group. For the PD-L1 CPS ≥1 population at FA, the PFS HR was 0.72 (95% CI: 0.60, 0.87; nominal *p*=0.0003) [Table 12].

The FDA's Assessment:
FDA generally agrees with the Applicant's analyses of the dual primary endpoints. The primary analyses of KEYNOTE-811 demonstrated statistically significant improvements in PFS assessed by BICR at IA2 (stratified PFS HR = 0.72; 95% CI: 0.60, 0.87; one-sided p-value = 0.0002, p-value boundary = 0.00128) and OS at the FA (stratified OS HR = 0.80; 95% CI: 0.67, 0.94; one-sided p-value = 0.004; p-value boundary = 0.0201) in the ITT population. The PFS results with longer follow-up at FA appear to be consistent with IA2, showing a robust estimate of the treatment benefit in PFS. However, FDA notes that the nominal p-values of the analyses other than the hypothesis tests pre-specified in the multiple testing plan (i.e., ORR comparison at IA1, PFS comparison at IA2, and OS comparison at FA in the ITT population) should be considered exploratory and interpreted with caution.

FDA performed additional exploratory analyses to assess the efficacy results of OS in different PD-L1 expression subgroups using the FA data set with data cutoff date on 20-MAR-2024. As shown in the forest plot in Figure 4 and the Kaplan-Meier curves in Figure 5, the OS HRs were similar in various PD-L1 positive subgroups such as CPS 1-<5, CPS 5-<10, and CPS ≥10. However, the subgroup of patients with CPS < 1, accounting for 15% of the total population, had Kaplan-Meier curves with the SOC arm generally indicated better survival than the pembrolizumab+SOC arm with a point estimate of the OS HR greater than 1 (HR = 1.1 [95% CI: 0.72, 1.68]). Therefore, the OS results of the ITT population may be attributable to the benefit in patients with PD-L1 positive expression, and it appears that the addition of pembrolizumab may not provide additional OS benefit to the standard of care chemotherapy and trastuzumab in the CPS < 1 patient population. The OS benefit of adding pembrolizumab in the CPS ≥ 1 subgroup was demonstrated by the unstratified OS HR of 0.79 (95% CI: 0.66, 0.95), with the estimated median OS of 20.1 months in the pembrolizumab+SOC arm vs 15.7 months in the SOC arm.

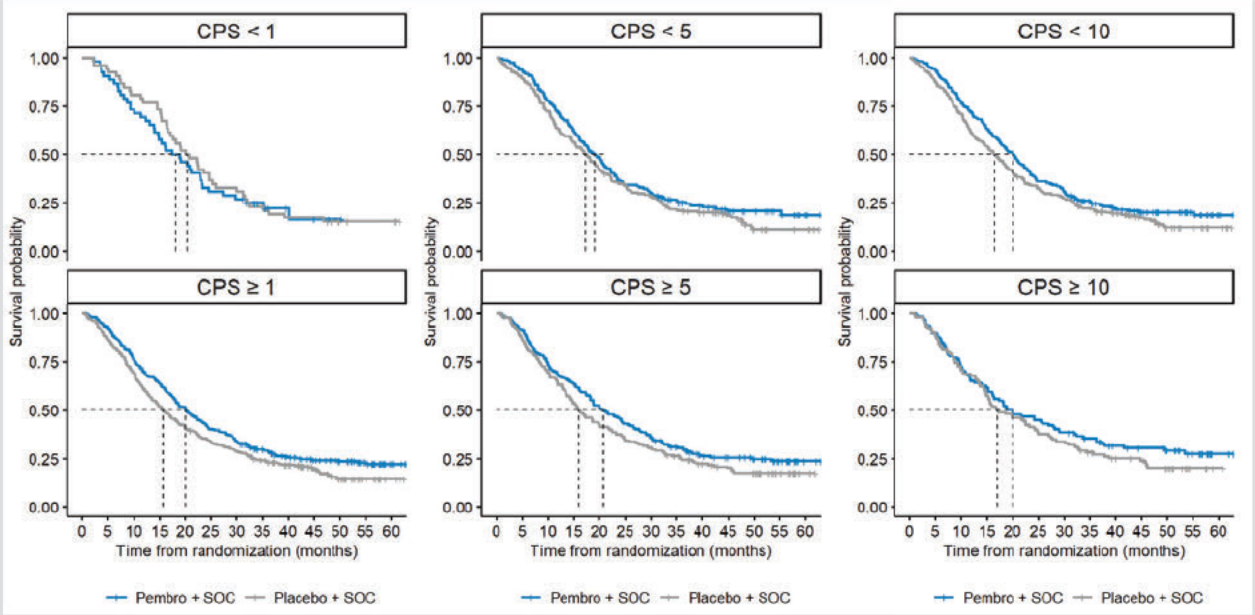
Figure 4. KEYNOTE-811: Overall Survival in PD-L1 Expression Subgroups

		Pembro + SOC	SOC			Pembro + SOC	SOC
Subgroup	**% of Pts**	**Evt / N**	**Evt / N**	**HR (95% CI)**		**Median (95% CI)**	**Median (95% CI)**
Overall	**100**	**267/350**	**288/348**	**0.83 (0.7 ,0.98)**		**20 (17.8, 22.1)**	**16.8 (14.9, 18.7)**
CPS >=1	85	226/298	244/296	0.79 (0.66 ,0.95)		20.1 (17.9, 22.9)	15.7 (13.5, 18.5)
CPS >=5	51	139/186	138/171	0.82 (0.65 ,1.04)		20.8 (18.1, 24.5)	16 (13.7, 19.9)
CPS >=10	31	77/109	83/106	0.84 (0.62 ,1.15)		19.9 (15.2, 28.2)	17.1 (14.6, 24.2)
CPS <1	15	41/52	44/52	1.1 (0.72 ,1.68)		18.2 (13.9, 22.9)	20.4 (16.4, 24.7)
CPS <5	49	128/164	150/177	0.85 (0.67 ,1.08)		19 (16.1, 22.1)	17.3 (14.6, 19.9)
CPS <10	69	190/241	205/242	0.83 (0.68 ,1.01)		20.1 (17.5, 22.2)	16.5 (14.2, 18.6)
CPS 1-<5	34	87/112	106/125	0.75 (0.57 ,1)		19.7 (16.3, 22.2)	14.7 (11.4, 19)
CPS 5-<10	20	62/77	55/65	0.77 (0.53 ,1.1)		21.7 (17.4, 26.6)	13.7 (11.2, 16.6)
CPS 1-<10	54	149/189	161/190	0.76 (0.61 ,0.96)		20.5 (17.8, 22.9)	14.4 (11.8, 18.1)



Hazard Ratios were estimated using unstratified Cox regression model with treatment as the only covariate.
Source: Reviewer generated analysis based on Applicant submitted data; adsl.xpt, adtte.xpt.

Figure 5. FDA- KEYNOTE-811: Kaplan-Meier Curves of Overall Survival in PD-L1 Expression Subgroups



Source: Reviewer generated analysis based on Applicant submitted data; adsl.xpt, adtte.xpt.

The PD-L1 subgroups analyses of PFS assessed by BICR using the FA data set shown in the forest plot in Figure 6 and the Kaplan-Meier curves in Figure 7 demonstrated similar trending as the OS analyses. The PFS results also show that the ITT analysis results may be attributable to the benefit in patients with PD-L1 positive expression, and the addition of pembrolizumab may not provide additional PFS benefit to standard of care chemotherapy and trastuzumab in the CPS <1 patient population.

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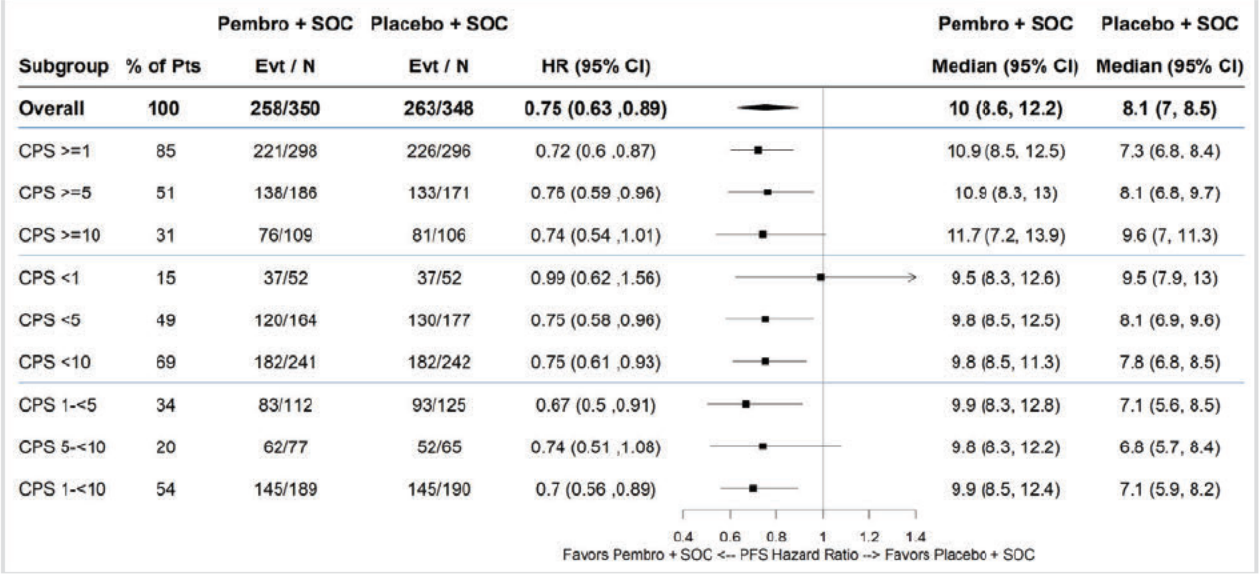
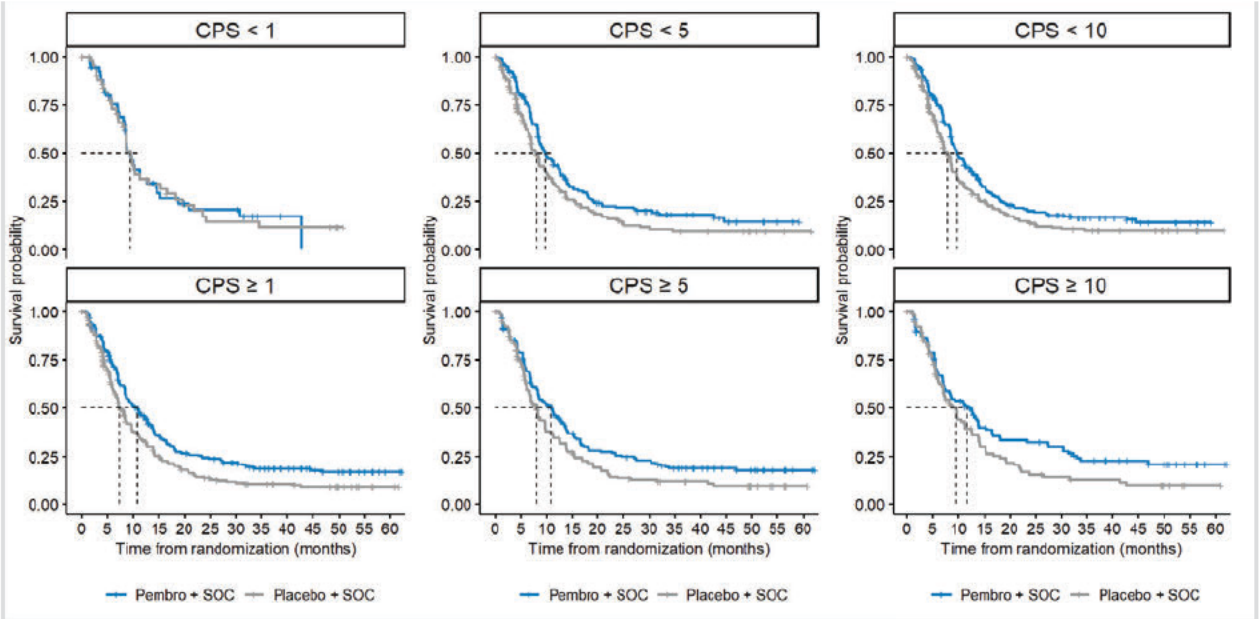
Figure 6. FDA - KEYNOTE-811: Progression-free Survival Assessed by BICR in PD-L1 Expression Subgroups

Subgroup	% of Pts	Pembro + SOC Evt / N	Placebo + SOC Evt / N	HR (95% CI)	Pembro + SOC Median (95% CI)	Placebo + SOC Median (95% CI)
Overall	**100**	**258/350**	**263/348**	**0.75 (0.63 ,0.89)**	**10 (8.6, 12.2)**	**8.1 (7, 8.5)**
CPS >=1	85	221/298	226/296	0.72 (0.6 ,0.87)	10.9 (8.5, 12.5)	7.3 (6.8, 8.4)
CPS >=5	51	138/186	133/171	0.76 (0.59 ,0.96)	10.9 (8.3, 13)	8.1 (6.8, 9.7)
CPS >=10	31	76/109	81/106	0.74 (0.54 ,1.01)	11.7 (7.2, 13.9)	9.6 (7, 11.3)
CPS <1	15	37/52	37/52	0.99 (0.62 ,1.56)	9.5 (8.3, 12.6)	9.5 (7.9, 13)
CPS <5	49	120/164	130/177	0.75 (0.58 ,0.96)	9.8 (8.5, 12.5)	8.1 (6.9, 9.6)
CPS <10	69	182/241	182/242	0.75 (0.61 ,0.93)	9.8 (8.5, 11.3)	7.8 (6.8, 8.5)
CPS 1-<5	34	83/112	93/125	0.67 (0.5 ,0.91)	9.9 (8.3, 12.8)	7.1 (5.6, 8.5)
CPS 5-<10	20	62/77	52/65	0.74 (0.51 ,1.08)	9.8 (8.3, 12.2)	6.8 (5.7, 8.4)
CPS 1-<10	54	145/189	145/190	0.7 (0.56 ,0.89)	9.9 (8.5, 12.4)	7.1 (5.9, 8.2)



Hazard Ratios were estimated using unstratified Cox regression model with treatment as the only covariate.
Source: Reviewer generated analysis based on Applicant submitted data; adsl.xpt, adtte.xpt.

Figure 7. FDA - KEYNOTE-811: Kaplan-Meier Curves of Progression-free Survival Assessed by BICR in PD-L1 Expression Subgroups.



Source: Reviewer generated analysis based on Applicant submitted data; adsl.xpt, adtte.xpt.

FDA further performed the OS subgroup analyses of baseline characteristics using unstratified HRs in the PD-L1 CPS ≥ 1 population. As shown in the forest plot in Figure 8, the results were consistent across various subgroups. OS HR point estimates for Asian race (HR 1.03 [95% CI: 0.73, 1.46]), and Asia region (HR 1.03 [95% CI: 0.73, 1.46]) subgroups were >1 with wide 95% Cis, which is similar to the subgroup analyses results in the ITT population as described by the Applicant. This subgroup effect in Asian patients was not replicated in the ITT population in (HER2 negative) gastric cancer trial KN-859. The HR for OS in Asian patients in the ITT population in KN859 was 0.72 (0.59, 0.86) vs 0.80 (0.70, 0.92) in non-Asian patients (refer to FDA review dated Nov 16, 2023).

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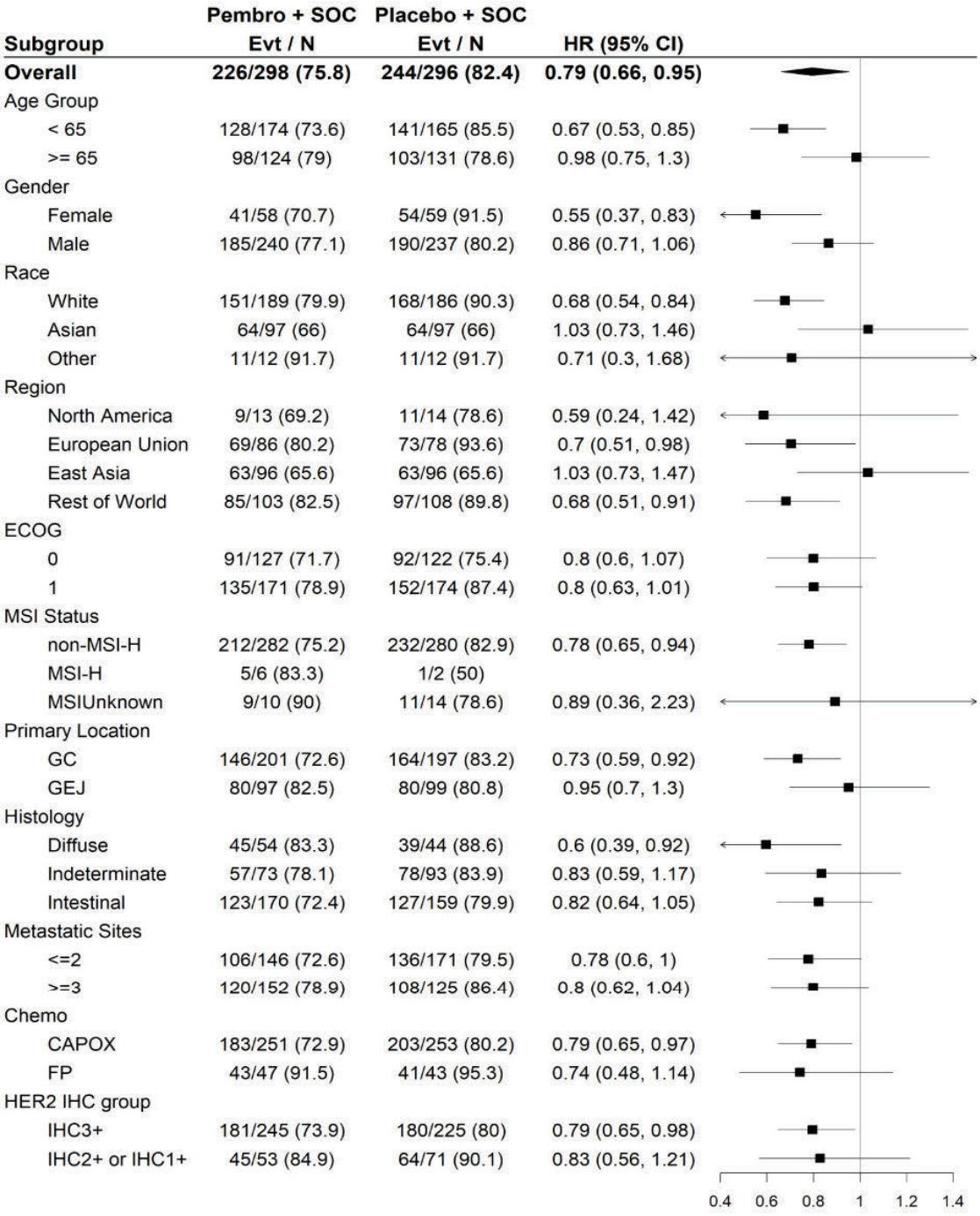
Figure 8. FDA - KEYNOTE-811: Subgroup Analysis for Overall Survival in the PD-L1 CPS ≥ 1 Population



Source: Reviewer generated analysis based on Applicant submitted data; adsl.xpt, adtte.xpt.

Data Quality and Integrity

The Applicant's Position:

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

The clinical study program was conducted in accordance with GCP guidelines. Merck Research Laboratory Quality Assurance 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.

Part of this study was conducted during the COVID-19 pandemic. There were no changes in the planned conduct of the study or planned analyses due to the COVID-19 pandemic. No serious GCP compliance issues were identified for this study. Audit information is available on request. There are no potential issues concerning the submitted data quality or integrity that raise questions about the reported efficacy results.

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:

ORR: At IA1 (based on first 264 participants randomized in the ITT population), pembrolizumab plus SOC demonstrated a statistically significant improvement in ORR compared with SOC.

- The ORR in the pembrolizumab plus SOC group was 74.4% (95% CI: 66.2, 81.6) vs 51.9% (95% CI: 43.0, 60.7) in the SOC group, resulting in a 22.7% difference (95% CI: 11.2, 33.7; p=0.00006, which is less than the p-value boundary of 0.002) [Table 11].
- The CR and PR rates were 11.3% and 63.2% in the pembrolizumab plus SOC group and 3.1% and 48.9% in the SOC group.
- ORR results for prespecified subgroups were generally consistent with those of the overall ITT population.

Since the superiority criterion for the ORR hypothesis was met at IA1, ORR was not formally tested at FA. With longer follow-up, ORR results were consistent with IA1. At FA, ORR for pembrolizumab plus SOC compared with SOC treatment was 72.6% (95% CI: 67.6, 77.2) vs 60.1% (95% CI: 54.7, 65.2), nominal p=0.00020. At FA in the ITT population, 17.1% vs 11.8% participants in the pembrolizumab plus SOC group vs the SOC group achieved a CR and 55.4% vs 48.3% participants in the pembrolizumab plus SOC group vs the SOC group achieved a PR.

For the CPS ≥1 subgroup at IA1, ORR was 76.1% (95% CI: 67.3, 83.5) for the pembrolizumab plus SOC group and 50.9% (95% CI: 41.3, 60.5) in the SOC group, resulting in a difference of 25.2% (95% CI: 12.8, 36.9). ORR results for the CPS ≥1 population at FA remained generally consistent with that of the ITT population at FA [Table 12].

The FDA's Assessment:
FDA agrees with the Applicant's analyses of ORR. FDA notes that the ORR comparison at the final analysis was not included in the multiple testing plan and the nominal p-value should be interpreted with caution.

Dose/Dose Response
The Applicant's Position: Not applicable

The FDA's Assessment:
FDA concurs.

Durability of Response
The Applicant's Position:
DOR and TTR: The DOR for the pembrolizumab plus SOC compared with the SOC at IA1 based on the first 264 participants (with a confirmed response) randomized in the ITT population are below [Table 11].

- The median DOR was 10.6 months (range: 1.1+ to 16.5+) in the pembrolizumab plus SOC group compared to 9.5 months (range: 1.4+ to 15.4+) in the SOC group.
- The median TTR was 1.4 months (range: 1.2 to 5.6) in the pembrolizumab plus SOC group and 1.5 months (range: 1.0 to 5.5) in the SOC group.

At FA, DOR results were consistent with IA1. The median DOR was 11.3 months (range: 1.1+ to 60.8+) for the pembrolizumab plus SOC group vs 9.5 months (range: 1.4+ to 60.5+) in the SOC group.

For the CPS ≥1 subgroup at FA, the median DOR was 11.3 months (range: 1.1+ to 60.8+) for the pembrolizumab plus SOC group vs 9.6 months (range: 1.4+ to 60.5+) in the SOC group [Table 12].

The FDA's Assessment:
FDA agrees with the Applicant's analysis. FDA adds that the 95% CIs of median DOR for the CPS ≥1 subgroup at FA were (9.9, 13.7) for the pembrolizumab + SOC arm and (7.1, 11.2) for the SOC arm.

Persistence of Effect
The Applicant's Position:
The persistence of effect for pembrolizumab plus chemotherapy is discussed in the OS and PFS

results (Efficacy Results – Primary Endpoint) and in the ORR and DOR results (Efficacy Results – Secondary and other relevant endpoints).

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:
Based on prespecified criteria as outlined in the sSAP prior to IA2, Week 24 was selected as the time point for analyzing changes from baseline for the prespecified scales in the 3 PRO questionnaires: EORTC QLQ-C30, EORTC QLQ-STO22, and EQ-5D-5L. The FA results reported below were similar between the PRO FAS and CPS ≥1 populations and consistent with the results at IA2.

Compliance rates for the 3 questionnaires were >90% at baseline and >80% at Week 24. Completion rates decreased at each time point as more participants discontinued the study and ranged between 55.7% and 67.0% at Week 24:

- LS mean changes from baseline at Week 24 were similar between the pembrolizumab plus SOC and the SOC groups for all the prespecified scales analyzed.
- Median time to deterioration was not reached for either of the groups for all the scales analyzed.
- At Week 24, the proportion of participants with "improved/stable" or "improved" in the EORTC QLQ-STO22 pain symptom scale was 82.7% and 40.4%, respectively, in the pembrolizumab plus SOC group compared with 78.3% and 32.1%, respectively, in the SOC group. For other scales analyzed, the proportion of participants who were "improved/stable" or "improved" were similar between groups.

The FDA's Assessment:
Since there is no pre-specified statistical testing procedure to control the Type-1 error for PROs; all PRO analyses are considered to be exploratory. As such, there is not substantial evidence of effectiveness to support efficacy claims (either superiority or non-inferiority) based on these PRO analyses.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position: Not applicable

The FDA's Assessment:
FDA concurs.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
See Integrated Assessment of Effectiveness Section 8.1.5.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:
KEYNOTE-811 is a standalone study to support the efficacy and safety in the proposed indication.

The FDA's Assessment:
FDA agrees.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:
The results of KEYNOTE-811 demonstrate that pembrolizumab plus SOC provides a statistically significant improvement in OS, PFS, and ORR compared with SOC in the ITT population, meeting the pre-specified success criteria.

- Regarding the analyses of OS:
  - At FA, pembrolizumab plus SOC demonstrated a statistically significant improvement in OS compared with SOC (HR=0.80 [95% CI: 0.67, 0.94]; *p*=0.0040). Results were consistent in patients with PD-L1 CPS ≥1 (HR=0.79 [95% CI: 0.66, 0.95], nominal *p*=0.0062).
  - At IA2, while OS did not reach statistical significance in the ITT population, the OS HR in the CPS <1 subgroup (14.9% of the ITT population) was 1.61 (95% CI: 0.98, 2.64). Based on these data, the Sponsor proposed an indication in patients whose tumors express PD-L1 with CPS ≥1. The FDA updated the indication to restrict the population to patients whose tumors express PD-L1 (CPS ≥1) as determined by an approved test at IA3. The USPI includes the HR for PFS and OS in patients with PD-L1 CPS <1 based on IA3.
- Analyses of PFS at FA were consistent with the results observed at IA2 where pembrolizumab plus SOC provided a statistically significant improvement in the ITT population (HR=0.72 [95% CI: 0.60, 0.87]; *p*=0.0002). Results were also consistent in patients with PD-L1 CPS ≥1 at FA (HR=0.72 [95% CI: 0.60, 0.87], nominal *p*=0.0003).
- Analyses of ORR at FA were consistent with the results observed at IA1 where pembrolizumab plus SOC provided a statistically significant improvement in ORR in the ITT population. Results were also consistent in patients with PD-L1 CPS ≥1.
- At FA, the DOR was longer in the pembrolizumab plus SOC group compared to SOC group in both the ITT population and CPS ≥1 subgroup.

The FDA's Assessment:
The effectiveness of pembrolizumab for the treatment of patients with HER2-positive unresectable or metastatic gastric/GEJ adenocarcinoma is supported by KN811, a double-

blinded, randomized (1:1) trial comparing pembrolizumab or placebo in combination with standard of care chemotherapy and trastuzumab. KN811 trial was designed to provide preliminary evidence of benefit and within the same trial, to verify this benefit through assessment of long-term outcomes. Upon readout of ORR in the first interim analysis, where a clinically meaningful and statistically significant improvement was demonstrated, FDA-granted accelerated approval for the proposed population (i.e., the indication was granted to all HER2-positive patients, irrespective of tumor PD-L1 expression).

At the time of the second interim analysis, the PFS results (coprimary endpoint) reached statistical significance. Median PFS was 10.0 months (95% CI 8.6, 11.7) in the pembrolizumab arms and 8.1 months (95% CI 7.0, 8.5) in the control arm, with a HR of 0.72 (95% CI 0.60, 0.87, p 0.0002); OS was not significant at that time.

At the time of the third interim analysis, OS was not statistically significant. In an OS subgroup analysis of 104 patients (15%) with PD-L1 tumor CPS <1 expression, the survival HR was 1.41 (95% CI 0.90, 2.20), potentially indicating a detriment in OS in this population. Based on this analysis, considering the lack of benefit in any outcome measure and potential detriment in survival, on November 7, 2023, FDA approved an application submitted by Merck to restrict the indication for pembrolizumab in the setting of HER2+ gastric or gastroesophageal cancer to patients whose tumors express PD-L1 CPS ≥1.

This submission provides the results of the final OS analysis. OS results in the intent-to-treat (ITT) population reached statistical significance: the median OS was 20.00 months (95% CI 17.8, 22.1) in the pembrolizumab arm and 16.8 months (95% CI 14.9, 18.7) in the control arm with a HR of 0.80 (5% CI 0.67, 0.94), p 0.004. In the indicated population (patients with PD-L1 tumor CPS ≥1 expression), the median OS is 20.1 months (95% CI 17.9, 22.9) in the pembrolizumab arm and 15.7 months (95% 13.5, 18.5) in the control arm, with a HR of 0.79 (95% CI 0.66, 0.95). As the results are driven by patients with PD-L1-positive expression, there appears that the addition of pembrolizumab to standard of care chemotherapy and trastuzumab does not provide benefit in the CPS negative population (HR for patients with CPS <1 in the final analysis was 1.10 [95% CI 0.72, 1.68]); the review team considers that overall, for patients with HER2+ CPS ≥1 gastric/GEJ adenocarcinoma, KN811 provides robust evidence of statistical significance and clinically meaningful benefit.

8.2. Review of Safety

The Applicant's Position:
The safety results from KEYNOTE-811 demonstrate that pembrolizumab in combination with trastuzumab and chemotherapy had a safety profile that generally reflects the known safety profiles of the components. No new safety concerns were identified.

The FDA's Assessment:
FDA agrees with the Applicant's position. While there were some differences between the as treated safety population and the population represented in the pembrolizumab RSD, FDA did not consider these differences to be clinically important as this is expected given the heterogenous patient populations represented in both groups. Overall, a review of the safety profile of the KN811 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:
Safety analyses were based on the APaT population, which included all 696 randomized participants who received at least 1 dose of study intervention, according to the study intervention they received.

The FDA's Assessment:
FDA agreed with Merck's approach to the safety review, as discussed in the pre-sBLA correspondence issued on July 3, 2024. Although the indication is restricted to patients with CPS ≥ 1, as previously stated in the reviews of S-97 and S-148, there are no differences in safety related to PD-L1 expression status (Table 23). Therefore, for completeness, this review and labeling will assess the all treated population.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 13: Applicant – Summary of Drug Exposure (Global Cohort) (APaT Population)

	Pembrolizumab + SOC (N=350)	SOC (N=346)
Number of Months on Therapy (months)		
Mean	13.4	11.0
Median	9.8	7.3
SD	10.9	9.9
Range	0.3 to 42.1	0.0 to 41.9
Number of Cycles		
Mean	18.3	15.1
Median	14.0	10.0
SD	14.6	13.2
Range	1.0 to 55.0	1.0 to 53.0
Database Cutoff Date: 20MAR2024.		

The Applicant's Position:

The median duration of exposure to study intervention was longer in the pembrolizumab plus SOC group compared with the SOC group (9.8 vs 7.3 months) [Table 13]. Overall, 21.1% and 14.2% of participants remained on study intervention for ≥24 months in the pembrolizumab plus SOC group and SOC group, respectively.

The FDA's Assessment:
FDA concurs with the Applicant's position. The median duration of exposure to treatment summarized above reflects exposure to pembrolizumab and chemotherapy. Median duration of exposure to pembrolizumab was 9.2 months (range: 1 day to 33.6 months). Table 14 provides additional information on duration of exposure. Although similar proportion of patients received at least 3 months of treatment, differences between arms are more pronounced after 6 or more months of treatment.

Table 14. KN811: Duration of exposure

Duration of exposure	**Pembro+SOC N = 350; n (%)**	**Placebo+SOC N= 346; n (%)**
Study treatment		
≥ 3 months	299 (85)	283 (82)
≥ 6 months	241 (69)	206 (60)
≥ 12 months	151 (43)	108 (31)
≥ 18 months	100 (29)	71 (21)
≥ 24 months	74 (21)	49 (14)
Median number of treatments by drug		
Pembrolizumab/placebo	13.0 (1, 35)	10.0 (1, 36)
Trastuzumab	13.0 (1, 54)	10.0 (1, 53)

Relevant characteristics of the safety population:
The Applicant's Position:
Baseline demographic and disease characteristics of participants in the APaT population were similar to those of the ITT population and generally representative of a patient population with previously untreated, HER2-positive, advanced gastric or GEJ adenocarcinoma [Table 8].

The FDA's Assessment:
A summarized in Table 6, only two patients (both the placebo+SOC arm) did not receive treatment. Therefore, the safety population and the ITT population characteristics are very similar.

Adequacy of the safety database:
The Applicant's Position:
The safety database is of an adequate size, considering exposure to appropriate dose, duration of treatment, patient demographics, and disease characteristics with reference to a US target population.

The FDA's Assessment:
FDA concurs with the Applicant's assessment regarding safety database size, duration of treatment, and disease characteristics. Pembrolizumab was first approved in 2014, and currently approved in combination with trastuzumab and fluoropyrimidine- and platinum-based regimens for the proposed indication. In addition, it is approved in combination with fluoropyrimidine- and platinum-based regimens for the treatment of HER2-negative gastric cancer and esophageal cancer.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
The Applicant's Position:
There were no issues with data integrity or analysis that precluded the inclusion of data in the safety analysis.

The FDA's Assessment:
FDA concurs with the Applicant's assessment.

Categorization of Adverse Event
The Applicant's Position:
Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints, including, but not limited to, the incidence, severity, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values.

All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment were reported by the investigator. All AEs meeting serious criteria, 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 is earlier, were reported by the investigator. AEs and SAEs whether or not assessed as related to the Sponsor or Comparator's product were recorded. AEs were graded by the investigator using NCI CTCAE version 4.0.

MedDRA version 26.1 was used at the time of table generation. The following MedDRA PTs were excluded from the statistical safety tables if the AEs were reported as not related to study intervention: neoplasm progression, malignant neoplasm progression, and disease progression.

AEOSI are immune-mediated events and infusion-related reactions associated with

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

The FDA's Assessment:
FDA concurs with the Applicant'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:
Participants were evaluated at scheduled study visits based on a 21-day (3-week) cycle. Key assessments included laboratory testing, vital sign measurements, physical examination, and AE monitoring as provided in the study protocol.

The FDA's Assessment:
FDA concurs with the description of laboratory testing, vital sign measurements, physical examinations and AE monitoring.

8.2.4. Safety Results

Deaths
Data:

Table 15: Applicant – Participants with Adverse Events Resulting in Death by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups) (Global Cohort) (APaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		346	
with one or more adverse events	23	(6.6)	22	(6.4)
with no adverse events	327	(93.4)	324	(93.6)
Death	3	(0.9)	1	(0.3)
Pneumonia	3	(0.9)	2	(0.6)
Pneumonitis	2	(0.6)	0	(0.0)
Abdominal infection	1	(0.3)	0	(0.0)
Acute respiratory failure	1	(0.3)	1	(0.3)
COVID-19	1	(0.3)	0	(0.0)
Cardiac failure chronic	1	(0.3)	0	(0.0)
Cerebral infarction	1	(0.3)	0	(0.0)
Gastric haemorrhage	1	(0.3)	0	(0.0)
Hepatitis	1	(0.3)	0	(0.0)
Multiple organ dysfunction syndrome	1	(0.3)	1	(0.3)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Myocardial infarction	1	(0.3)	0	(0.0)
Peritonitis	1	(0.3)	0	(0.0)
Pneumonia aspiration	1	(0.3)	0	(0.0)
Pulmonary embolism	1	(0.3)	1	(0.3)
Respiratory distress	1	(0.3)	0	(0.0)
Sepsis	1	(0.3)	1	(0.3)
Sudden death	1	(0.3)	1	(0.3)
Aspiration	0	(0.0)	2	(0.6)
COVID-19 pneumonia	0	(0.0)	2	(0.6)
Cerebellar haemorrhage	0	(0.0)	1	(0.3)
Cholangitis	0	(0.0)	1	(0.3)
Completed suicide	0	(0.0)	1	(0.3)
Craniocerebral injury	0	(0.0)	1	(0.3)
Intestinal ischaemia	0	(0.0)	1	(0.3)
Ischaemic stroke	0	(0.0)	1	(0.3)
Myocarditis	0	(0.0)	1	(0.3)
Respiratory tract infection	0	(0.0)	1	(0.3)
Subdural haematoma	0	(0.0)	1	(0.3)
Upper gastrointestinal haemorrhage	0	(0.0)	1	(0.3)

Every participant is counted a single time for each applicable row and column.
Database Cutoff Date: 20MAR2024.

The Applicant's Position:

The number of participants with AEs resulting in death was similar in the pembrolizumab plus SOC group (23 [6.6%] participants) and SOC group (22 [6.4%] participants) [Table 15]. Four AEs resulting in death in the pembrolizumab plus SOC group were considered drug-related by the investigator: pneumonitis, hepatitis, sepsis, and cerebral infarction. Three AEs resulting in death in the SOC group were considered drug-related by the investigator: myocarditis, pulmonary embolism, and cholangitis. Based on medical review by the Sponsor, the AEs with fatal outcomes were likely related to underlying disease, other comorbidities, and/or known risks associated with the treatments. No new safety concerns were identified for pembrolizumab.

The FDA's Assessment:

FDA replicated the results summarized in Table 15. When grouped by similar pathophysiology (Table 16), pneumonia was the most frequent cause of death in both arms. This reviewer agrees that pneumonitis and hepatitis can be attributed to pembrolizumab; all other causes of death are common in the setting of advanced disease and chemotherapy.

Table 16. KN811: Deaths (grouped terms)

Cause of death	Pembro+SOC N = 350; n (%)	Placebo+SOC N= 346; n (%)
Pneumonia[1]	4	7
Death[2]	4	2
CNS ischemic or hemorrhagic event[3]	1	2
Acute respiratory failure[4]	2	1
Abdominal infection[5]	2	1
Pneumonitis	2	0
Multiple organ dysfunction syndrome	1	1
Pulmonary embolism	1	1
Sepsis	1	1
Gastric haemorrhage[6]	1	1
Cardiac failure chronic	1	0
COVID-19	1	0
Hepatitis	1	0
Myocardial infarction	1	0
Completed suicide	0	1
Craniocerebral injury	0	1
Intestinal ischaemia	0	1
Myocarditis	0	1
Subdural hematoma	0	1

[1]Pneumonia, COVID-19 pneumonia, pneumonia aspiration, aspiration, respiratory tract infection
[2]Death, sudden death
[3]Cerebellar haemorrhage, cerebral infarction, ischaemic stroke
[4]Acute respiratory failure, respiratory distress
[5]Abdominal infection, cholangitis, peritonitis
[6]Gastric haemorrhage, upper gastrointestinal haemorrhage

Serious Adverse Events
Data:

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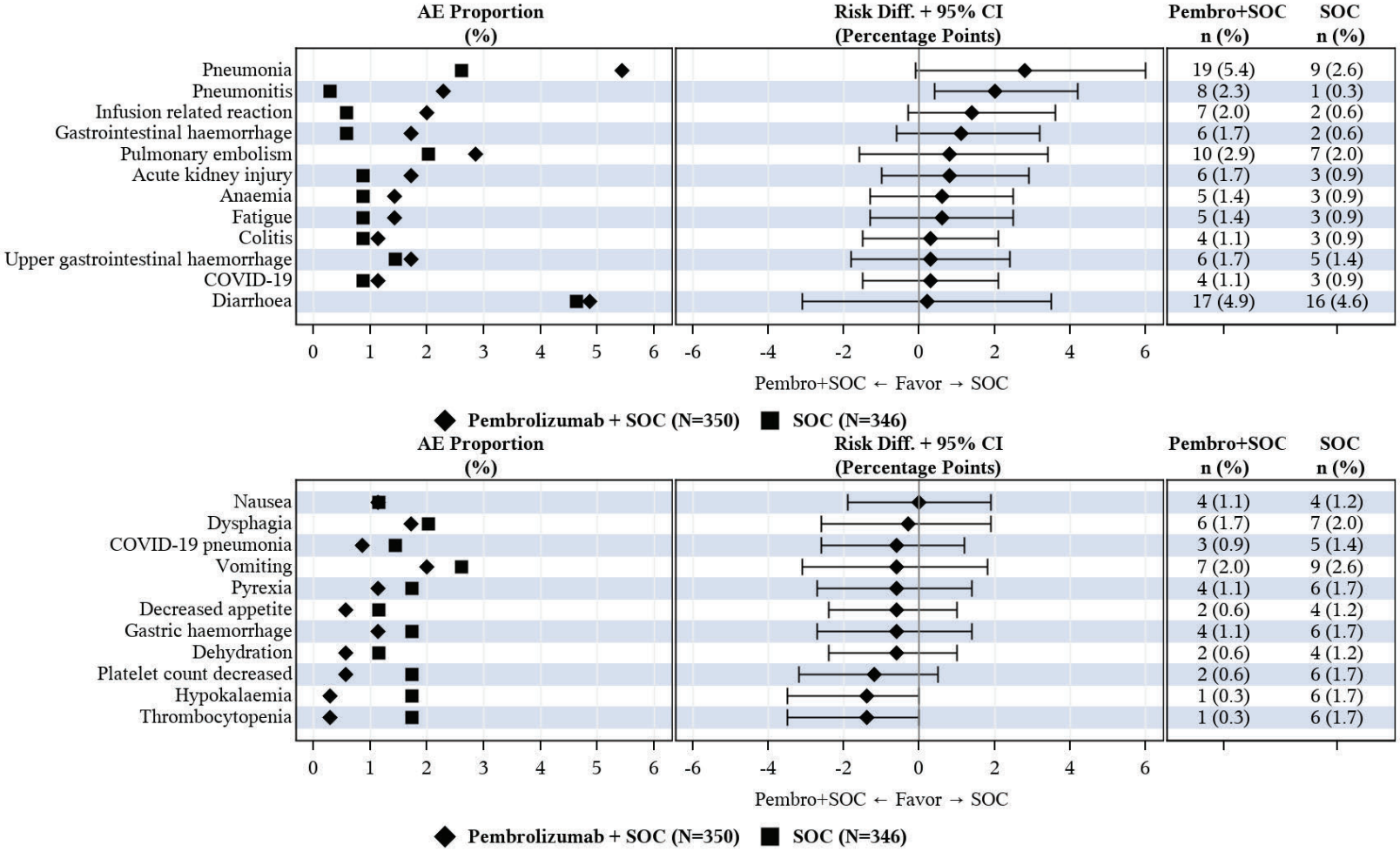
Figure 9: Applicant – Between-treatment Comparisons in Serious Adverse Events
Selected Adverse Events (>=1% Incidence) and Sorted by Risk Difference (Global Cohort) (APaT Population)



Database Cutoff Date: 20MAR2024

The Applicant's Position:

The percentage of participants who experienced SAEs was 46.6% in the pembrolizumab plus SOC group and 46.0% in the SOC group. The most frequently reported SAEs (≥2.0% of participants) in the pembrolizumab plus SOC group were pneumonia, diarrhea, pulmonary embolism, pneumonitis, infusion-related reaction, and vomiting. The most frequently reported SAEs (≥2.0% of participants) in the SOC group were diarrhea, pneumonia, vomiting, dysphagia, and pulmonary embolism.

- SAEs of pneumonitis had a greater risk difference for the pembrolizumab plus SOC group (i.e., the lower bound of the 95% CI is >0) [Figure 9]. SAEs of pneumonitis were reported for 8 (2.3%) participants in the pembrolizumab plus SOC group and 1 (0.3%) participant in the SOC group. Pneumonitis is a known ADR for pembrolizumab.
- SAEs of hypokalemia and thrombocytopenia had a greater risk difference for the SOC group (i.e., the upper bound of the 95% CI is <0) [Figure 9]. In the pembrolizumab plus SOC group, 1 (0.3%) participant each experienced SAEs of hypokalemia and thrombocytopenia. In the SOC group, 6 (1.7%) participants each experienced SAEs of hypokalemia and thrombocytopenia.

The FDA's Assessment:

Non-fatal SAEs were reported in 158 (45%) patients and 152 (44%) patients in the pembrolizumab and SOC arms, respectively. Table 17 summarizes FDA's analysis of non-fatal SAEs. Overall, the incidence of non-fatal SAEs is similar between arms.

Table 17. KN811: Non-fatal SAEs (incidence ≥ 2%)

AE	Pembro+SOC N = 350; n (%)	Placebo+SOC N= 346; n (%)
Diarrhea/colitis[1]	27 (8)	23 (7)
Pneumonia[2]	20 (6)	12 (3)
GI hemorrhage[3]	18 (5)	20 (6)
Pulmonary embolism	8 (2)	7 (2)
Pneumonitis[4]	8 (2)	1 (<1)
Vomiting	7 (2)	9 (3)
Anemia[5]	7 (2)	3 (1)
Dysphagia	6 (2)	7 (2)
Infusion related reaction	6 (2)	2 (1)
Thrombocytopenia[6]	3 (1)	12 (3)
Pyrexia	4 (1)	6 (2)
Hypokalemia	3 (1)	6 (2)

[1] Grouped term includes colitis, diarrhea, enteritis, enterocolitis, gastroenteritis, immune-mediated enterocolitis.
[2] Grouped terms include pneumonia, infectious pleural effusion, COVID19 pneumonia

[3]Grouped term includes diarrhea hemorrhagic, gastric hemorrhage, gastric ulcer hemorrhage, gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, melena, tumor hemorrhage, and upper gastrointestinal hemorrhage.
[4] Grouped terms include pneumonitis and interstitial lung disease.
[5] Grouped terms include anemia and iron deficient anemia
6 Grouped terms platelet count decreased and thrombocytopenia

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

The percentage of participants who experienced AEs leading to discontinuation of any treatment intervention or discontinuation of all treatment interventions, respectively, was 42.9% and 6.3% in the pembrolizumab plus SOC group and 39.3% and 6.9% in the SOC group. Most types of AEs and drug-related AEs resulting in discontinuation of any drug were generally similar between the groups. Exceptions included AEs (≥1% difference) in the pembrolizumab plus SOC group compared with the SOC group, respectively, of palmar-plantar erythrodysesthesia syndrome (13 [3.7%] vs 8 [2.3%] participants), pneumonitis (7 [2.0%] vs 1 [0.3%] participants), neurotoxicity (1 [0.3%] vs 5 [1.4%] participants), and blood creatinine increased (5 [1.4%] vs no participants).

The FDA's Assessment:

FDA replicated the results summarized below in Table 18.

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

The Applicant's Position:

The percentage of participants who experienced AEs leading to interruption of any treatment intervention was 81.7% in the pembrolizumab plus SOC group and 74.3% in the SOC group, and a similar percentage of participants in the pembrolizumab plus SOC group (44.0%) and SOC group (40.2%) experienced AEs leading to interruption of all treatment interventions. Most of the types of AEs resulting in treatment interruption of any drug were generally similar in both groups. These results are consistent with the known toxicity of the SOC components.

The FDA's Assessment:

FDA replicated the results summarized below in Table 18.

Significant Adverse Events

Data:

Table 18: Applicant – Adverse Event Summary – AEOSI (Global Cohort) (APaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		346	
with one or more adverse events	140	(40.0)	86	(24.9)
with no adverse event	210	(60.0)	260	(75.1)
with drug-related adverse events	129	(36.9)	80	(23.1)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
with toxicity grade 3-5 adverse events	41	(11.7)	12	(3.5)
with toxicity grade 3-5 drug-related adverse events	38	(10.9)	12	(3.5)
with serious adverse events	37	(10.6)	15	(4.3)
with serious drug-related adverse events	33	(9.4)	15	(4.3)
who died	3	(0.9)	1	(0.3)
who died due to a drug-related adverse event	2	(0.6)	1	(0.3)
discontinued any drug due to an adverse event	27	(7.7)	14	(4.0)
discontinued pembrolizumab or placebo	17	(4.9)	6	(1.7)
discontinued trastuzumab	10	(2.9)	4	(1.2)
discontinued any chemotherapy	20	(5.7)	12	(3.5)
discontinued all drugs	8	(2.3)	4	(1.2)
discontinued any drug due to a drug-related adverse event	26	(7.4)	14	(4.0)
discontinued pembrolizumab or placebo	16	(4.6)	6	(1.7)
discontinued trastuzumab	9	(2.6)	4	(1.2)
discontinued any chemotherapy	19	(5.4)	12	(3.5)
discontinued all drugs	7	(2.0)	4	(1.2)
discontinued any drug due to a serious adverse event	18	(5.1)	6	(1.7)
discontinued pembrolizumab or placebo	15	(4.3)	6	(1.7)
discontinued trastuzumab	10	(2.9)	4	(1.2)
discontinued any chemotherapy	13	(3.7)	4	(1.2)
discontinued all drugs	8	(2.3)	4	(1.2)
discontinued any drug due to a serious drug-related adverse event	17	(4.9)	6	(1.7)
discontinued pembrolizumab or placebo	14	(4.0)	6	(1.7)
discontinued trastuzumab	9	(2.6)	4	(1.2)
discontinued any chemotherapy	12	(3.4)	4	(1.2)
discontinued all drugs	7	(2.0)	4	(1.2)

[a] 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.
NCI CTCAE version 4.03.
Database Cutoff Date: 20MAR2024.

Table 19: Applicant – Participants With Adverse Events of Special Interest (AEOSI) by AEOSI Category (Incidence > 0% in One or More Treatment Groups) (Global Cohort) (APaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		346	
with one or more adverse events	140	(40.0)	86	(24.9)
with no adverse events	210	(60.0)	260	(75.1)
Adrenal Insufficiency	**5**	**(1.4)**	**0**	**(0.0)**
Arthritis	**1**	**(0.3)**	**0**	**(0.0)**
Colitis	**17**	**(4.9)**	**10**	**(2.9)**
Gastritis	**5**	**(1.4)**	**3**	**(0.9)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**1**	**(0.3)**
Haemolytic Anaemia	**1**	**(0.3)**	**0**	**(0.0)**
Hepatitis	**2**	**(0.6)**	**4**	**(1.2)**
Hyperthyroidism	**15**	**(4.3)**	**11**	**(3.2)**
Hypophysitis	**5**	**(1.4)**	**0**	**(0.0)**

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Hypothyroidism	**37**	**(10.6)**	**16**	**(4.6)**
Infusion Reactions	**58**	**(16.6)**	**45**	**(13.0)**
Myocarditis	**0**	**(0.0)**	**1**	**(0.3)**
Myositis	**1**	**(0.3)**	**0**	**(0.0)**
Nephritis	**4**	**(1.1)**	**0**	**(0.0)**
Pancreatitis	**0**	**(0.0)**	**1**	**(0.3)**
Pneumonitis	**22**	**(6.3)**	**5**	**(1.4)**
Severe Skin Reactions	**3**	**(0.9)**	**0**	**(0.0)**
Thyroiditis	**4**	**(1.1)**	**0**	**(0.0)**
Type 1 Diabetes Mellitus	**1**	**(0.3)**	**0**	**(0.0)**
Uveitis	**1**	**(0.3)**	**1**	**(0.3)**
Vasculitis	**4**	**(1.1)**	**1**	**(0.3)**

Every participant 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: 20MAR2024.

Table 20: Applicant – Participants With Adverse Events of Special Interest (AEOSI) by Maximum Toxicity Grade (Incidence > 0% in One or More Treatment Groups) (Global Cohort) (APaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		346	
with one or more AEOSI	140	(40.0)	86	(24.9)
Grade 1	34	(9.7)	30	(8.7)
Grade 2	65	(18.6)	44	(12.7)
Grade 3	34	(9.7)	11	(3.2)
Grade 4	4	(1.1)	0	(0.0)
Grade 5	3	(0.9)	1	(0.3)
with no AEOSI	210	(60.0)	260	(75.1)
Adrenal Insufficiency	**5**	**(1.4)**	**0**	**(0.0)**
Adrenal insufficiency	5	(1.4)	0	(0.0)
Grade 1	1	(0.3)	0	(0.0)
Grade 2	2	(0.6)	0	(0.0)
Grade 3	2	(0.6)	0	(0.0)
Arthritis	**1**	**(0.3)**	**0**	**(0.0)**
Immune-mediated arthritis	1	(0.3)	0	(0.0)
Grade 2	1	(0.3)	0	(0.0)
Colitis	**17**	**(4.9)**	**10**	**(2.9)**
Colitis	13	(3.7)	6	(1.7)
Grade 1	2	(0.6)	1	(0.3)
Grade 2	5	(1.4)	1	(0.3)
Grade 3	6	(1.7)	4	(1.2)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Enterocolitis	2	(0.6)	2	(0.6)
Grade 3	2	(0.6)	2	(0.6)
Immune-mediated enterocolitis	2	(0.6)	2	(0.6)
Grade 2	1	(0.3)	1	(0.3)
Grade 3	1	(0.3)	1	(0.3)
Gastritis	**5**	**(1.4)**	**3**	**(0.9)**
Gastritis	5	(1.4)	3	(0.9)
Grade 2	2	(0.6)	1	(0.3)
Grade 3	1	(0.3)	0	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**1**	**(0.3)**
Demyelinating polyneuropathy	0	(0.0)	1	(0.3)
Grade 2	0	(0.0)	1	(0.3)
Haemolytic Anaemia	**1**	**(0.3)**	**0**	**(0.0)**
Autoimmune haemolytic anaemia	1	(0.3)	0	(0.0)
Grade 4	1	(0.3)	0	(0.0)
Hepatitis	**2**	**(0.6)**	**4**	**(1.2)**
Hepatitis	2	(0.6)	3	(0.9)
Grade 1	0	(0.0)	1	(0.3)
Grade 2	0	(0.0)	1	(0.3)
Grade 3	0	(0.0)	1	(0.3)
Grade 4	1	(0.3)	0	(0.0)
Grade 5	1	(0.3)	0	(0.0)
Immune-mediated hepatitis	0	(0.0)	1	(0.3)
Grade 3	0	(0.0)	1	(0.3)
Hyperthyroidism	**15**	**(4.3)**	**11**	**(3.2)**
Hyperthyroidism	15	(4.3)	11	(3.2)
Grade 1	11	(3.1)	8	(2.3)
Grade 2	4	(1.1)	3	(0.9)
Hypophysitis	**5**	**(1.4)**	**0**	**(0.0)**
Hypophysitis	4	(1.1)	0	(0.0)
Grade 1	1	(0.3)	0	(0.0)
Hypophysitis	4	(1.1)	0	(0.0)
Grade 2	1	(0.3)	0	(0.0)
Grade 3	2	(0.6)	0	(0.0)
Hypopituitarism	1	(0.3)	0	(0.0)
Grade 3	1	(0.3)	0	(0.0)
Hypothyroidism	**37**	**(10.6)**	**16**	**(4.6)**
Hypothyroidism	37	(10.6)	16	(4.6)
Grade 1	18	(5.1)	8	(2.3)
Grade 2	18	(5.1)	8	(2.3)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Grade 3	1	(0.3)	0	(0.0)
Infusion Reactions	**58**	**(16.6)**	**45**	**(13.0)**
Anaphylactic reaction	1	(0.3)	0	(0.0)
Grade 3	1	(0.3)	0	(0.0)
Drug hypersensitivity	5	(1.4)	4	(1.2)
Grade 1	1	(0.3)	3	(0.9)
Grade 2	3	(0.9)	1	(0.3)
Grade 3	1	(0.3)	0	(0.0)
Hypersensitivity	10	(2.9)	7	(2.0)
Grade 1	4	(1.1)	1	(0.3)
Grade 2	5	(1.4)	6	(1.7)
Grade 3	1	(0.3)	0	(0.0)
Infusion related reaction	43	(12.3)	35	(10.1)
Grade 1	7	(2.0)	9	(2.6)
Grade 2	30	(8.6)	24	(6.9)
Grade 3	5	(1.4)	2	(0.6)
Grade 4	1	(0.3)	0	(0.0)
Myocarditis	**0**	**(0.0)**	**1**	**(0.3)**
Myocarditis	0	(0.0)	1	(0.3)
Grade 5	0	(0.0)	1	(0.3)
Myositis	**1**	**(0.3)**	**0**	**(0.0)**
Rhabdomyolysis	1	(0.3)	0	(0.0)
Grade 3	1	(0.3)	0	(0.0)
Nephritis	**4**	**(1.1)**	**0**	**(0.0)**
Nephritis	3	(0.9)	0	(0.0)
Grade 1	1	(0.3)	0	(0.0)
Grade 2	1	(0.3)	0	(0.0)
Grade 3	1	(0.3)	0	(0.0)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)
Grade 2	1	(0.3)	0	(0.0)
Pancreatitis	**0**	**(0.0)**	**1**	**(0.3)**
Pancreatitis	0	(0.0)	1	(0.3)
Grade 2	0	(0.0)	1	(0.3)
Pneumonitis	**22**	**(6.3)**	**5**	**(1.4)**
Autoimmune lung disease	1	(0.3)	0	(0.0)
Grade 2	1	(0.3)	0	(0.0)
Immune-mediated lung disease	1	(0.3)	0	(0.0)
Grade 2	1	(0.3)	0	(0.0)
Interstitial lung disease	2	(0.6)	0	(0.0)
Grade 2	2	(0.6)	0	(0.0)
Pneumonitis	19	(5.4)	5	(1.4)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Grade 1	4	(1.1)	1	(0.3)
Grade 2	8	(2.3)	4	(1.2)
Grade 3	4	(1.1)	0	(0.0)
Grade 4	1	(0.3)	0	(0.0)
Grade 5	2	(0.6)	0	(0.0)
Severe Skin Reactions	**3**	**(0.9)**	**0**	**(0.0)**
Dermatitis exfoliative generalised	1	(0.3)	0	(0.0)
Grade 3	1	(0.3)	0	(0.0)
Pruritus	1	(0.3)	0	(0.0)
Grade 3	1	(0.3)	0	(0.0)
Rash maculo-papular	1	(0.3)	0	(0.0)
Grade 3	1	(0.3)	0	(0.0)
Thyroiditis	**4**	**(1.1)**	**0**	**(0.0)**
Autoimmune thyroiditis	1	(0.3)	0	(0.0)
Grade 2	1	(0.3)	0	(0.0)
Thyroid disorder	2	(0.6)	0	(0.0)
Grade 1	2	(0.6)	0	(0.0)
Thyroiditis	1	(0.3)	0	(0.0)
Grade 2	1	(0.3)	0	(0.0)
Type 1 Diabetes Mellitus	**1**	**(0.3)**	**0**	**(0.0)**
Type 1 diabetes mellitus	1	(0.3)	0	(0.0)
Grade 3	1	(0.3)	0	(0.0)
Uveitis	**1**	**(0.3)**	**1**	**(0.3)**
Uveitis	1	(0.3)	1	(0.3)
Grade 1	0	(0.0)	1	(0.3)
Grade 2	1	(0.3)	0	(0.0)
Vasculitis	**4**	**(1.1)**	**1**	**(0.3)**
Vasculitis	4	(1.1)	1	(0.3)
Grade 1	2	(0.6)	1	(0.3)
Vasculitis	4	(1.1)	1	(0.3)
Grade 2	2	(0.6)	0	(0.0)

Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.
Only the highest reported grade of a given adverse event is counted for the individual participant.
Grades are based on NCI CTCAE version 4.03.
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: 20MAR2024.

The Applicant's Position:

AEOSI are immune-mediated events and infusion-related reactions causally associated with pembrolizumab. The percentage of participants who experienced AEOSI was higher in the

pembrolizumab plus SOC group (40.0%) compared with the SOC group (24.9%), which was expected due to the addition of pembrolizumab [Table 18]. Most AEOSI were Grade 1 or 2 in severity [Table 20], nonserious [Table 18], and managed by standard clinical practice, including corticosteroid administration.

- A total of 41 (11.7%) participants in the pembrolizumab plus SOC group and 12 (3.5%) participants in the SOC group reported AEOSI with a maximum toxicity of Grade 3 to 5 [Table 18].
- Overall, 3 (0.9%) participants died due to an AEOSI in the pembrolizumab plus SOC group (pneumonitis [2 participants] and hepatitis [1 participant]), and 1 (0.3%) participant died due to an AEOSI of myocarditis in the SOC group [Table 18] [Table 20].
- A higher percentage of participants discontinued any study intervention due to an AEOSI in the pembrolizumab plus SOC group (7.7%) compared with the SOC group (4.0%) [Table 18].
- A higher percentage of participants had a serious AEOSI in the pembrolizumab plus SOC group (10.6%) compared with the SOC group (4.3%) [Table 18].
- The most frequently reported AEOSI by category (≥5.0% of participants) in the pembrolizumab plus SOC group were infusion reactions, hypothyroidism, and pneumonitis [Table 19].
- The most frequently reported AEOSI by category (≥5.0% of participants) in the SOC group was infusion reactions [Table 19].

The FDA's Assessment:
FDA replicated the analyses in Table 18, Table 19, and Table 20. The addition of pembrolizumab to standard of care trastuzumab in combination with chemotherapy resulted in an increase in immune mediated adverse events, treatment discontinuation, AESIs and infusion related reactions. These are toxicities expected with treatment with pembrolizumab and no new additional safety signals were detected.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 21: Applicant – Adverse Event Summary (Global Cohort) (APaT Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	350		346	
with one or more adverse events	348	(99.4)	346	(100.0)
with no adverse event	2	(0.6)	0	(0.0)
with drug-relateda adverse events	341	(97.4)	334	(96.5)
with toxicity grade 3-5 adverse events	253	(72.3)	228	(65.9)
with toxicity grade 3-5 drug-related adverse events	206	(58.9)	176	(50.9)
with serious adverse events	163	(46.6)	159	(46.0)
with serious drug-related adverse events	91	(26.0)	79	(22.8)
who died	23	(6.6)	22	(6.4)
who died due to a drug-related adverse event	4	(1.1)	3	(0.9)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
discontinued any drug due to an adverse event	150	(42.9)	136	(39.3)
discontinued pembrolizumab or placebo	46	(13.1)	37	(10.7)
discontinued trastuzumab	46	(13.1)	33	(9.5)
discontinued any chemotherapy	141	(40.3)	135	(39.0)
discontinued all drugs	22	(6.3)	24	(6.9)
discontinued any drug due to a drug-related adverse event	130	(37.1)	117	(33.8)
discontinued pembrolizumab or placebo	30	(8.6)	17	(4.9)
discontinued trastuzumab	27	(7.7)	12	(3.5)
discontinued any chemotherapy	120	(34.3)	116	(33.5)
discontinued all drugs	11	(3.1)	9	(2.6)
discontinued any drug due to a serious adverse event	49	(14.0)	44	(12.7)
discontinued pembrolizumab or placebo	36	(10.3)	36	(10.4)
discontinued trastuzumab	33	(9.4)	32	(9.2)
discontinued any chemotherapy	40	(11.4)	40	(11.6)
discontinued all drugs	20	(5.7)	24	(6.9)
discontinued any drug due to a serious drug-related adverse event	32	(9.1)	21	(6.1)
discontinued pembrolizumab or placebo	22	(6.3)	16	(4.6)
discontinued trastuzumab	17	(4.9)	11	(3.2)
discontinued any chemotherapy	25	(7.1)	18	(5.2)
discontinued all drugs	10	(2.9)	9	(2.6)

[a] 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 26.1 preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.

NCI CTCAE version 4.03.

Database Cutoff Date: 20MAR2024.

APPEARS THIS WAY ON ORIGINAL

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

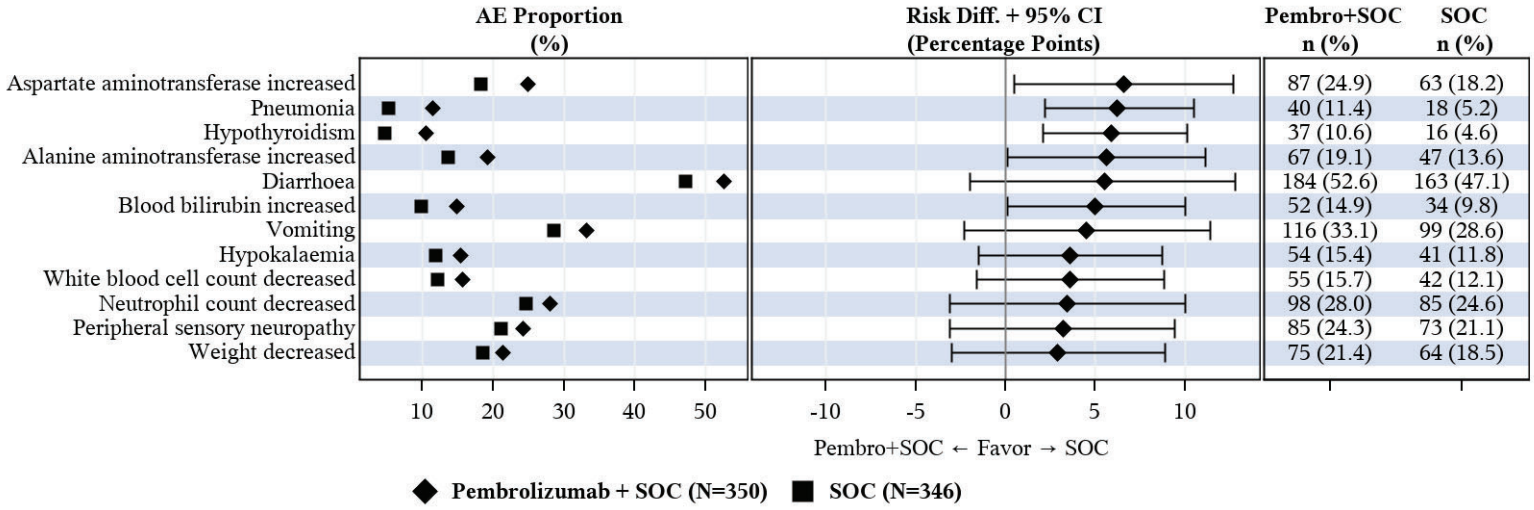


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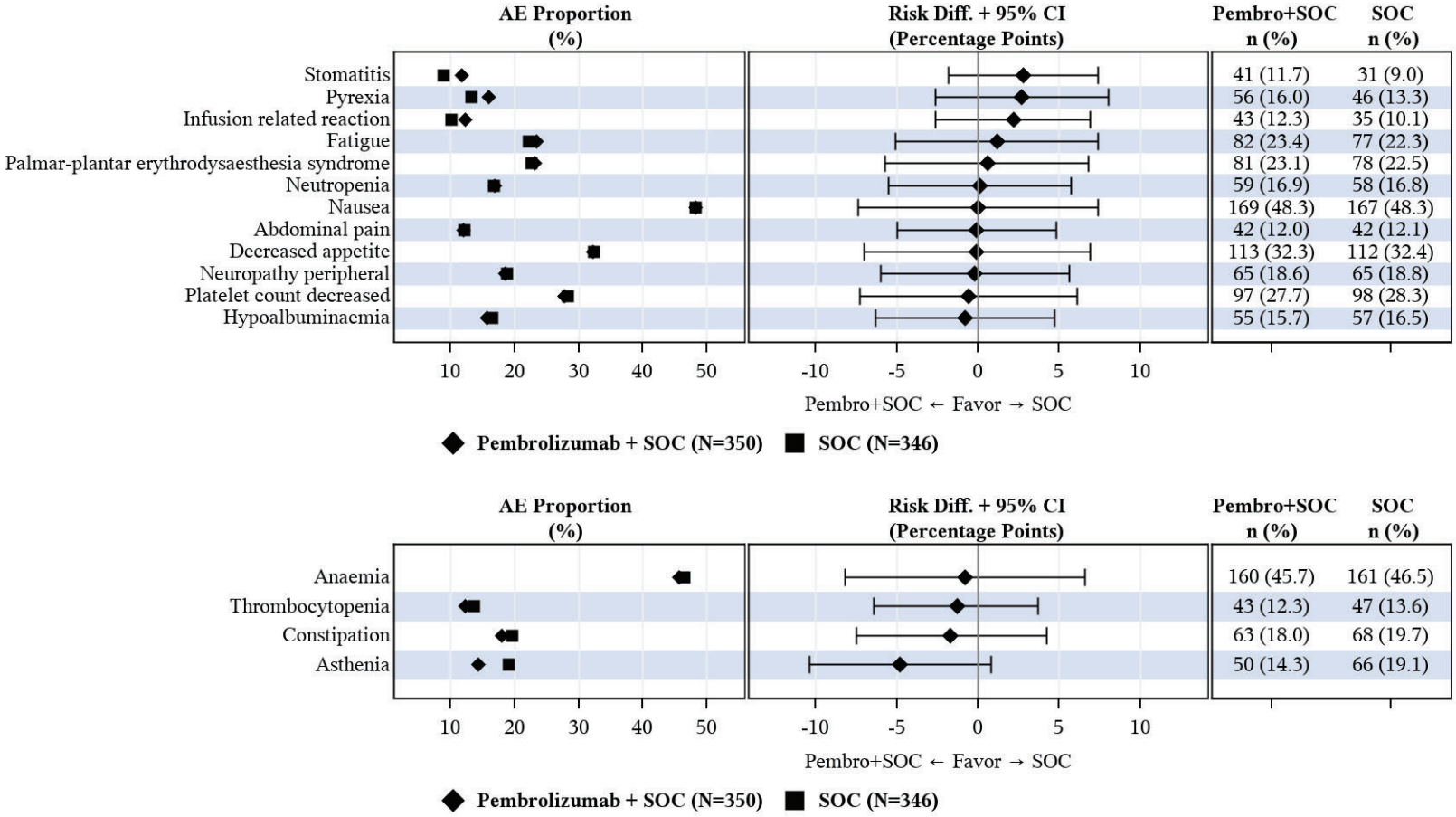
Figure 11 Applicant – Between-treatment Comparisons in Adverse Events - Selected Adverse Events (>=10% Incidence) and Sorted by Risk Difference (Global Cohort) (APaT Population) (Continued)



Database Cutoff Date: 20MAR2024

The Applicant's Position:
The safety profile of pembrolizumab plus SOC was generally consistent with prior analyses and the known safety profiles of either SOC regimen or pembrolizumab alone. The participant incidences in each AE category in the pembrolizumab plus SOC group were generally similar with those in the SOC group [Table 21]. A total of 45 participants died due to an AE: 23 (6.6%) in the pembrolizumab plus SOC group and 22 (6.4%) in the SOC group. Of these deaths, 7 were considered related to study treatment per investigator assessment: 4 (1.1%) in the pembrolizumab plus SOC group (pneumonitis, hepatitis, sepsis, and cerebral infarction) and 3 (0.9%) in the SOC group (myocarditis, pulmonary embolism, and cholangitis).

The frequency and types of AEs (by PT) in the pembrolizumab plus SOC group were generally similar to the SOC group. Diarrhea, nausea, and anemia were the most frequently reported (incidence ≥40%) AEs in both the pembrolizumab plus SOC and SOC groups [Figure 10].

The safety results in the KEYNOTE-811 pembrolizumab plus SOC dataset by region were generally consistent with the study population and the known established safety profiles of the chemotherapy components, trastuzumab, and pembrolizumab monotherapy.

The FDA's Assessment:
FDA agrees with the Applicants analysis. Grade 3-4 AEs were observed in 63% and 56% patients in the pembrolizumab and SOC arms, respectively; Grade 4 AEs were reported in 7% and 10% patients in the pembrolizumab and SOC arms, respectively. Review of the datasets did not result in the identification of new safety signals. As stated above, the addition of pembrolizumab to standard of care trastuzumab in combination with chemotherapy resulted in an increase in immune mediated adverse events, treatment discontinuation, AESIs and infusion related reactions; these are toxicities commonly managed by the treating oncologist and the risk:benefit analysis of the overall population of KN811 is consistent with the analysis conducted upon submission of the results of the first 264 patients (BLA 125514 S97).

Laboratory Findings

The Applicant's Position:
For most laboratory tests, a generally similar proportion of participants experienced laboratory abnormalities postbaseline in both groups. A generally similar rate of clinically relevant laboratory findings (defined as Grade 3 to 4 events) was observed in the pembrolizumab plus SOC group compared with the SOC group.

The FDA's Assessment:
Table 22 summarizes the laboratory abnormalities occurring in at least 10% of patients in KN811.

Table 22. KN811: Lab abnormalities (incidence ≥10%)

	Pembrolizumab + SOC N = 350		SOC N = 346	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
Hemoglobin decreased	247/346 (71)	59/346 (17)	223/339 (66)	45/339 (13)
Platelets decreased	225/347 (65)	40/347 (12)	211/337 (63)	36/337 (11)
Neutrophils decreased	213/343 (62)	59/343 (17)	187/332 (56)	58/332 (17)
Leukocytes decreased	206/346 (60)	21/346 (6)	185/338 (55)	23/338 (7)
Albumin decreased	190/345 (55)	8/345 (2.3)	169/335 (50)	9/335 (2.7)
Calcium decreased	187/345 (54)	6/345 (1.7)	150/335 (45)	7/335 (2.1)
Lymphocytes decreased	184/326 (56)	46/326 (14)	152/314 (48)	34/314 (11)
Glucose increased	182/343 (53)	28/343 (8)	187/333 (56)	19/333 (6)
Glucose decreased	54/343 (16)	0/343 (0.0)	36/333 (11)	0/333 (0.0)
AST increased	181/344 (53)	17/344 (4.9)	174/335 (52)	8/335 (2.4)
ALT increased	140/344 (41)	11/344 (3.2)	122/335 (36)	5/335 (1.5)
Potassium decreased	139/349 (40)	46/349 (13)	119/340 (35)	38/340 (11)
Potassium increased	58/349 (17)	4/349 (1.1)	65/340 (19)	5/340 (1.5)
ALK increased	129/344 (38)	8/344 (2.3)	126/335 (38)	15/335 (4.5)
Sodium decreased	116/346 (34)	27/346 (8)	103/338 (30)	27/338 (8)
Sodium increased	41/346 (12)	1/346 (0.3)	34/338 (10)	0/338 (0.0)
Phosphate decreased	114/340 (34)	35/340 (10)	115/332 (35)	31/332 (9)
Bilirubin increased	112/343 (33)	13/343 (3.8)	84/335 (25)	7/335 (2.1)
Magnesium decreased	94/343 (27)	4/343 (1.2)	97/331 (29)	2/331 (0.6)
Magnesium increased	37/343 (11)	5/343 (1.5)	35/331 (11)	2/331 (0.6)
Creatinine increased	92/346 (27)	7/346 (2.0)	54/338 (16)	5/338 (1.5)
INR increased	22/124 (18)	0/124 (0.0)	28/122 (23)	3/122 (2.5)
aPTT increased	15/120 (13)	1/120 (0.8)	13/116 (11)	0/116 (0.0)

The addition of pembrolizumab to standard of care treatment with trastuzumab and chemotherapy resulted in an overall increase in lab abnormalities; however, the only Grade 3-4 abnormalities that increased at least 3% in the pembrolizumab arm were decreased hemoglobin (17% vs. 13% in the pembrolizumab and SOC arms, respectively) and lymphopenia (14% vs. 11% in the pembrolizumab and SOC arms respectively). Anemia is a treatable condition and the

increase was observed in a small percentage, which can be attributed to the prolonged exposure to treatment in the pembrolizumab arm or the inherent variability observed in large randomized studies. The small increase in lymphopenia (related to pembrolizumab mechanism of action) did not translate into an increase in infections and therefore does not appear to be of clinical significance.

Vital Signs
The Applicant's Position:
No clinically meaningful findings were reported.

The FDA's Assessment:
FDA concurs.

Electrocardiograms (ECGs)
The Applicant's Position:
No clinically meaningful findings were reported.

The FDA's Assessment:
Not applicable.

QT
The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

Immunogenicity
The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:
The safety results were generally consistent with the established safety profiles of pembrolizumab and SOC components, and no new safety issues were identified.

The FDA's Assessment:
Analyses of AESI are summarized in Section 8.2.4. Twelve percent of patients in the pembrolizumab arm experienced one of these events compared with 3.5% patients in the SOC arm. Of these, 3 (0.9%) patients died due to an AESI in the pembrolizumab arm (pneumonitis and hepatitis), while 1 patient (0.3%) died of myocarditis in the SOC arm. The most frequently reported AESI by category (≥5%) incidence were infusion reactions, hypothyroidism, and pneumonitis. This is consistent with the known safety profile of pembrolizumab.

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

The Applicant's Position:
Results from patient-reported outcomes are provided in Section 8.1.2.

The FDA's Assessment:
The study was not designed to assess tolerability through COA.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:
No safety concerns for pembrolizumab plus SOC were identified based on the AE profile by age, sex, or ECOG performance status.

The FDA's Assessment:
FDA concurs. Table 23 summarizes the major safety results by PD-L1 status. Consistently with other pembrolizumab and immune checkpoint applications, there are no differences in the toxicity profile based on PD-L1 positivity.

Table 23. KN811: Summary of safety by PD-L1 status

	Pembrolizumab + SOC N= 350; n(%)		**SOC N= 346; n (%)**	
	PD-L1+ (n= 298)	**PD-L1- (n=52)**	**PD-L1+ (n=295)**	**PD-L1- (n= 51)**
N patients with events	296 (99)	52 (100)	295 (100)	51 (100)
SAEs	154 (52)	21 (40)	141 (48)	18 (35)
Grade 3-4 AEs	218 (73)	31 (60)	186 (63)	34 (67)
Grade 5 AEs	20 (7)	3 (7)	20 (7)	2 (4)

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Not applicable

The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

Human Reproduction and Pregnancy

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
No pembrolizumab overdose was reported. The potential for drug abuse or dependence is not expected for an anti-PD-1 mAb, and no reports of drug abuse with pembrolizumab have occurred. No withdrawal or rebound effects are expected with an anti-PD-1 mAb, and none have been observed in pembrolizumab clinical studies to date.

There were 2 clinically important deviations of overdose, described below.

One participant took capecitabine continuously beyond 2 weeks for 3 cycles and experienced multiple Grade 1 to 3 AEs that were considered to be related to capecitabine. The site reported that the participant misunderstood the directions from the investigator and continued taking the capecitabine continuously when they should have paused this treatment.

The second participant took additional doses of capecitabine in Cycle 1. This resulted in a dose interruption in Cycle 2 due to nausea considered related to capecitabine and oxaliplatin and a subsequent dose reduction for capecitabine. An AE of accidental overdose was reported.

The FDA's Assessment:
FDA concurs with the Applicant's assessment.

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 PSUR covering the period 04-SEP-2022 through 03-SEP-2023. There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

The FDA's Assessment:
The observed safety profile in Study KN811 is consistent with the known safety profile of pembrolizumab. No new safety signals were found.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:
Postmarketing data from the safety reporting database are routinely reviewed for pembrolizumab. The Sponsor's AE reporting system contains all data from postmarketing sources, including health care providers, consumers, and scientific literature, as well as competent authorities worldwide. The Sponsor continues to monitor postmarketing data associated with pembrolizumab.

There are no specific safety concerns associated with subpopulations not adequately represented in the safety database for KEYNOTE-811. No difference in pembrolizumab administration in the postmarketing 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 concurs with the Applicant's assessment.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:
The safety profile for pembrolizumab in combination with SOC in previously untreated participants with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma was generally consistent with the known profiles of either SOC regimen alone or pembrolizumab monotherapy, as shown by:

- The addition of pembrolizumab to the SOC regimen of chemotherapy plus trastuzumab did not increase the incidence or severity of common chemotherapy-related toxicities and did not increase treatment discontinuation of SOC in the pembrolizumab plus SOC group when compared with the SOC group. Additionally, the discontinuation of pembrolizumab due to AEs in the pembrolizumab plus SOC group was consistent with the pembrolizumab

monotherapy reference safety dataset (RSD), which is the pooled safety data of 2799 participants from pembrolizumab monotherapy studies.

- Overall, the incidences, severity, and types of the most frequently reported AEs and SAEs in KEYNOTE-811 were similar between the pembrolizumab plus SOC and SOC groups.
- AEs observed for the combination of pembrolizumab plus SOC were managed with dose modifications and appropriate use of supportive care as applicable for pembrolizumab and SOC.
- The addition of pembrolizumab to the SOC regimen of chemotherapy (FP/CAPOX) and trastuzumab did not appear to increase the frequency and severity of cardiac AEs and LVEF decrease associated with the established safety profile of trastuzumab.
- The overall incidences of AEOSI observed in KEYNOTE-811 were higher than the pembrolizumab monotherapy RSD, driven primarily by infusion reactions and pneumonitis. This was expected with the addition of trastuzumab and oxaliplatin to pembrolizumab since these are known risks of the SOC combination. The longer median duration of exposure to these treatments in the pembrolizumab plus SOC group (9.8 months) compared with the pembrolizumab monotherapy RSD (4.17 months) may also have contributed to the observed higher incidence of these AEOSI. These events were managed by standard clinical practice, including administration of systemic corticosteroids or treatment interruption.
- The types and severity of AEOSI observed with pembrolizumab when used in combination with trastuzumab and chemotherapy remained generally consistent with the established safety profile of pembrolizumab.
- No new indication-specific, immune-mediated AEs were identified with the addition of trastuzumab and chemotherapy to pembrolizumab, and no new safety concerns were identified.

The FDA's Assessment:

The adverse reaction profile observed in patients receiving pembrolizumab in KEYNOTE-811 is consistent with the known pembrolizumab safety profile. Incidence rates 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 SOC arm, 6.6%, and 6.4%, respectively; 3 patients in the pembrolizumab arm died of immune-related adverse reactions (pneumonitis and hepatitis) and one patient in the SOC arm died of myocarditis. 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. The incidence of SAEs was 46% in both arms, with the most frequently reported SAEs including diarrhea/colitis, pneumonia, and gastrointestinal hemorrhages.

Discontinuation of any drug in the pembrolizumab arm compared with the placebo arm (43% vs 39%) 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 (82% vs 74%). These results are consistent with the known toxicity of pembrolizumab and SOC components and the prior, earlier analysis of the trial.

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:

The primary efficacy evaluation for this application was based on the final analysis of the pivotal study KEYNOTE-811. This study is a double-blind, placebo-controlled, randomized study of 698 patients comparing the efficacy of pembrolizumab to placebo in combination with standard of care chemotherapy and trastuzumab in participants with previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma. The dual-primary endpoints include PFS assessed by BICR and OS, and the trial formally tested ORR assessed by BICR at the first interim analysis to support the filing of a marketing application for accelerated approval.

KEYNOTE-811 showed a statistically significant improvement in OS in favor of the pembrolizumab + SOC arm in the final analysis (stratified HR = 0.80; 95% CI: 0.67, 0.94; stratified log-rank test p-value = 0.004 passing the p-value boundary at 0.0201). However, based on the exploratory subgroup analysis for PD-L1 expression, the statistically significant improvement in OS in the ITT population may be attributable to the results in the PD-L1 high subgroups, as the PD-L1 CPS <1 subgroup, accounting for 15% of the total population, had a point estimate of OS HR at 1.1 (95% CI: 0.72, 1.68) demonstrating no benefit from the addition of pembrolizumab in this subgroup. The PFS HR estimate also demonstrated a similar trend of no benefit for adding pembrolizumab in this subgroup (PFS HR = 0.99; 95% CI: 0.62, 1.56) in the PD-L1 CPS <1 subgroup.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The effectiveness of pembrolizumab for the treatment of patients with HER2-positive, CPS ≥1, unresectable or metastatic gastric/GEJ adenocarcinoma is supported by KN811, a double-blinded, randomized (1:1) trial comparing pembrolizumab or placebo in combination with standard of care chemotherapy and trastuzumab.

This submission is the third supplemental application for KN811. Results of the first interim analysis supported accelerated approval of pembrolizumab in the HER2+ disease setting (BLA 125514 S-097). The trial was designed to provide preliminary evidence of benefit and within the same trial, to verify this benefit through assessment of long-term outcomes. Upon readout of ORR in the first interim analysis, where a clinically meaningful and statistically significant improvement was demonstrated, FDA-granted accelerated approval for the proposed population (i.e., the indication was granted to all HER2-positive patients, irrespective of tumor PD-L1 expression).

At the time of the second interim analysis, the PFS results (coprimary endpoint) reached statistical significance. At the time of the third interim analysis, OS was not statistically significant but a subgroup analysis of patients with PD-L1 tumor CPS <1 expression that indicated a potential for detrimental survival in this population, FDA restricted the pembrolizumab indication for pembrolizumab in the setting of HER2+ gastric or gastroesophageal cancer to patients whose tumors express PD-L1 CPS ≥1.

The current submission contains the final, statistically significant analysis of OS. OS in the ITT population are statistically significant, but results appear to be driven by the CPS ≥ 1 population. In patients with HER2+, CPS ≥1 gastric or gastroesophageal junction adenocarcinoma with no prior systemic treatment, the results of KN811 provide for a robust, statistically significant and clinically meaningful benefit in all studied endpoints.

This submission provides the results of the final OS analysis. OS results in the intent-to-treat (ITT) population reached statistical significance: the median OS was 20.00 months (95% CI 17.8, 22.1) in the pembrolizumab arm and 16.8 months (95% CI 14.9, 18.7) in the control arm with a HR of 0.80 (5% CI 0.67, 0.94), p 0.004. In the indicated population (patients with PD-L1 tumor CPS ≥1 expression), the median OS is 20.1 months (95% CI 17.9, 22.9) in the pembrolizumab arm and 15.7 months (95% 13.5, 18.5) in the control arm, with a HR of 0.79 (95% CI 0.66, 0.95). As the results are driven by patients with PD-L1-positive expression, there appears that the addition of pembrolizumab to standard of care chemotherapy and trastuzumab does not provide benefit in the PD-L1 negative population (HR for patients with CPS <1 in the final analysis was 1.10 [95% CI 0.72, 1.68]); the review team considers that overall, for patients with HER2+ CPS ≥1 gastric/GEJ adenocarcinoma, KN811 provides robust evidence of statistical and clinical benefit.

The review team recommends conversion to traditional approval.

8.4.1. Approach to Substantial Evidence of Effectiveness

1. Verbatim indication:

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

2. SEE was established with
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☒ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

   OR

   b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

   OR

   c. ☐ Evidence that supported SEE from a prior approval *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[2]

3. Complete response, if applicable
   a. ☒ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)
[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)
[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

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

10 Pediatrics

The Applicant's Position:
Pembrolizumab in combination with 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.

11 Labeling Recommendations

Data:

Table 24: Applicant – Summary of Significant Proposed Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1 INDICATIONS AND USAGE	The Sponsor deleted the accelerated approval paragraph associated with KEYNOTE-811.	FDA agrees
6.1 CLINICAL TRIALS EXPERIENCE	The Sponsor deleted duplicate information contained in the Clinical Studies section.	Changed to update safety data as per final analysis

14 CLINICAL STUDIES	The Sponsor updated the efficacy results from KEYNOTE-811, final analysis.	Minor changes to comply with current labeling policies

The Applicant's Position:
The Sponsor has provided the proposed labeling separately. [Table 24] summarizes the significant proposed labeling changes at a high level.

The FDA's Assessment:
FDA and Merck agreed on final labeling for this indication.

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 since 2014.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
This supplemental application fulfills the PMR requirement to verify and describe the benefit and safety issued upon de accelerated approval of pembrolizumab in combination with trastuzumab and chemotherapy for the first-line treatment of patients with HER2+ gastric or GEJ adenocarcinoma dated May 5, 2021.

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 recommendation from the review teams to approve this Application. The Application is supported by substantial evidence of effectiveness and a favorable risk-benefit assessment (improved OS) in the proposed indication.

X

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.

18 Appendices

18.1. References

The Applicant's References:

[1] Nagini S. Carcinoma of the stomach: a review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol. 2012 Jul 15;4(7):156-69. [05GF0M]

[2] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. In press 2024. [08KHPG]

[3] Global Cancer Observatory (GCO): Cancer Today [Internet]. Lyon (France): International Agency for Research on Cancer (IARC); c1965-2024. Stomach; [cited 2024 Mar 4]; 2 p. Available from: https://gco.iarc.who.int/media/globocan/factsheets/cancers/7-stomach-fact-sheet.pdf. [08JJK6]

[4] Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74:12-49. [08HZXM]

[5] Zhang T, Chen H, Zhang Y, Yin X, Man J, Yang X, et al. Global changing trends in incidence and mortality of gastric cancer by age and sex, 1990-2019: findings from Global Burden of Disease Study. J Cancer. 2021;12(22):6695-705. [08097V]

[6] Surveillance, Epidemiology, and End Results Program [Internet]. Bethesda (MD): National Cancer Institute (NCI). Cancer stat facts: stomach cancer; [cited 2024 Apr 26]; [about 17 screens]. Available from: https://seer.cancer.gov/statfacts/html/stomach.html. [08KSQF]

[7] Boku N. HER2-positive gastric cancer. Gastric Cancer. 2014;17:1-12. [08BFZJ]

[8] 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 HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010 Aug 28;376(9742):687-97. [042MMY]

[9] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022 Jan/Feb;72(1):7-33. [07YSZM]

[10] Bui A, Yang L, Soroudi C, May FP. Racial and ethnic disparities in incidence and mortality for the five most common gastrointestinal cancers in the United States. J Natl Med Assoc. 2022 Aug;114(4):426-9. [0847WT]

[11] Rivera F, Romero C, Jimenez-Fonseca P, Izquierdo-Manuel M, Salud A, Martinez E, et al. Phase II study to evaluate the efficacy of trastuzumab in combination with capecitabine and oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial. Cancer Chemother Pharmacol. 2019;83:1175-81. Erratum in: Cancer Chemother Pharmacol. 2019;84:1365. [05LV2S]

[12] Janjigian YY, Kawazoe A, Bai Y, Xu J, Lonardi S, Metges JP, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. Lancet. In press 2023. [08GCSZ]

[13] Janjigian YY, Kawazoe A, Yanez P, Li N, Lonardi S, Kolesnik O, et al. Combined PD-1 and HER2 blockade for HER2-positive gastric cancer [manuscript]. Nature. 2021. 19 p. [08LVC2]

[14] Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, et al. 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 Oct;19:1372-84. [05KDNZ]

[15] Zhang C, Zhang C, Wang Q, Li Z, Lin J, Wang H. Differences in stage of cancer at diagnosis, treatment, and survival by race and ethnicity among leading cancer types. JAMA Netw Open. 2020 Apr 8;3(4):e202950. [06FPRR]

[16] Tseng J, Miller JP, Johnson J, Waters K, Gangi A, Gong J, et al. Disparities and survival in newly diagnosed gastric cancer in Hispanic patients in the United States: a propensity score matched analysis. J Gastrointest Oncol. 2021 Aug;12(4):1308-25. [0874J4]

[17] Janjigian YY, Kawazoe A, Yanez P, Li N, Lonardi S, Kolesnik O, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature. 2021 Dec 20/30;600:727-30. Additional material; 12 p. [07YVL8]

[19] Miettinen O and Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26. [00QHZT]

[20] Maurer W and Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20. [03XQVB]

FDA's Additional References:

- Jørgensen JT and Hersom M. HER2 as a Prognostic Marker in Gastric Cancer - A Systematic Analysis of Data from the Literature. J Cancer, 2012; 3: 137-144.
- Klempner S, Cowden E, Cytryn S, Fassan M, Kawakami H. et al. PD-L1 Immunohistochemistry in Gastric Cancer: Comparison of Combined Positive Score and Tumor Area Positivity Across 28-8, 22C3, and SP263 Assays. JCO Precision Oncology. Volume 8 https://doi.org/10.1200/PO.24.00230
- SEER: https://seer.cancer.gov/statfacts/html/stomach.html
- Yoon H, Zhaohui J, Kour O, Kankeu Fonkoua LA, et al. Association of PD-L1 Expression and Other Variables With Benefit From Immune Checkpoint Inhibition in Advanced Gastroesophageal Cancer: Systematic Review and Meta-analysis of 17 Phase 3 Randomized Clinical Trials. JAMA Oncol 2022 Oct 1;8(10):1456-1465

18.2. Financial Disclosure

The Applicant's Position:
Disclosure of financial interests and/or arrangements, including statements of due diligence for the investigators who conducted KEYNOTE-811 are described in FDA forms 3454, 3455 and Module 1.3.4.

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: 1802		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 2		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		

Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: MSD		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6		
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.

The FDA's Assessment:
FDA verified the contents of the table above with documentation submitted on Module 1.3.4 of the submission. Of the 1802 total number of investigators and subinvestigators, 1795 certified absence of financial interests or arrangements; 6 investigators did not return the requested information despite the Applicant's due diligence. The sites employing these subinvestigators enrolled patients as follows:

- Site (b) (6) randomized (b) (6) participants
- Site 0500 randomized 1 participant
- Site 1505 randomized 9 participants
- Site 1508 randomized 6 participants
- Site 1510 randomized 1 participants
- Site 1512 screened 1 but did not randomize any participants
- Site 2202 randomized 7 participants

One subinvestigator (b) (6) (b) (6) enrolled one patient into the trial. One subinvestigator's (b) (6) enrolled (b) (6) patients into the trial and in all the investigator was another physician (b) (6)

One Investigator, (b) (6) received $35,000.00 in consulting fees. (b) (6) (b) (6) enrolled (b) (6) patients in KN811.

In summary, 26 (3.7%) patients were enrolled in sites where investigators for whom no financial forms were available and only (b) (6) patients were enrolled in a site where the investigator had a financial disclosure. As the coprimary endpoints are blinded-independently assessed progression

free survival and overall survival, it is unlikely that the lack of information from financial interests or the potential conflict from one investigator may have biased the trial results.

sBLA 125514.170 Merck Sharp and Dohme, LLC
Prior Approval Supplement – Efficacy

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Sandra Casak	Division of Oncology 3	Sections: All	**Select one:** __X__Authored __X__Approved
	Signature: See Signature in DARRTs			
Clinical Team Leader	Sandra Casak	Division of Oncology 3	Sections: All	**Select one:** __X__Authored __X__Approved
	Signature: See Signature in DARRTs			
Biostatistics Reviewer	Yiming Zhang	Division of Biometrics V	Sections: 8.1, 8.3	**Select one:** __X__Authored ____Approved
	Signature: Yiming Zhang -S Digitally signed by Yiming Zhang -S Date: 2025.03.17 11:50:15 -04'00'			
Biostatics Team Lead	Chi Song	Division of Biometrics V	Sections: 8.1, 8.3	**Select one:** __X__Authored __X__Approved
	Signature: Chi Song -S Digitally signed by Chi Song -S Date: 2025.03.17 15:06:53 -04'00'			
Deputy Director, Division of Biostatistics	Pallavi Mishra-Kalyani	Division of Biometrics V	Sections: 8.1, 8.3	**Select one:** __Authored __X__Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2025.03.17 19:19:37 -04'00'			

Associate Director for Labeling (ADL)	Doris Auth	Oncology Center for Excellence	Sections: All	**Select one:** ___Authored __X_Approved
	Signature: DORIS AUTH -S Digitally signed by DORIS AUTH -S Date: 2025.03.18 08:06:05 -04'00'			
Cross Discipline Team Lead	Sandra Casak	Division of Oncology 3	Sections: All	**Select one:** X Authored X Approved
	Signature: See signature in DARRTs			
Division Director (Clinical)	Steven Lemery	Division of Oncology 3	Sections: All	**Select one:** X Approved
	Signature: See signature in DARRTs			

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/

SANDRA J CASAK
03/18/2025 07:23:50 PM

STEVEN J LEMERY
03/19/2025 12:27:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

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

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

Memorandum

Date: February 7, 2025

To: Gina Davis, MT, Regulatory Project Manager
Division of Oncology 3 (DO3)

From: Andrew Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, Team Leader, OPDP

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

BLA: 125514, Supplement 170

Background:

In response to DO3's consult request dated October 18, 2024, OPDP has reviewed the proposed Prescribing Information (PI) for supplement 170 for KEYTRUDA® (pembrolizumab) injection, for intravenous use. This supplement proposes updates to the labeling to include information from the KEYNOTE-811 final analysis and IA2 clinical study reports to fulfill PMR 4033-1.

PI:

OPDP's review of the proposed PI is based on the draft labeling sent by electronic mail to OPDP and received on January 28, 2025, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Andrew Nguyen at 240-402-0512 or andrew.nguyen@fda.hhs.gov.

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

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/s/

ANDREW D NGUYEN
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