

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s180

Trade Name: KEYTRUDA

Generic or Proper Name: pembrolizumab

Sponsor: Merck Sharp & Dohme Corp.

Approval Date: June 12, 2025

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

Head and Neck Squamous Cell Cancer (HNSCC)

- for the treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumors express PD-L1 [Combined Positive Score (CPS $\geq$ 1)as determined by an FDA approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin and then as a single agent.

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APPROVAL LETTER



BLA 125514/S-180

SUPPLEMENT APPROVAL

Merck Sharp & Dohme LLC
Attention: Steven S. Mundt, M.S.
Director, Global Regulatory Affairs
126 East Lincoln Avenue, P.O. Box 2000
RY34-2014
Rahway, NJ 07065

Dear Steven S. Mundt:

Please refer to your supplemental biologics license application (sBLA) received December 23, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Keytruda (pembrolizumab) injection.

This Prior Approval supplemental biologics license application provides for a new indication for Keytruda (pembrolizumab) for the treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin and then as a single agent.

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 Effectuated" (CBE) supplements.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable to conduct due to the rarity of this condition in all pediatric age groups.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

- 4859-1 Complete clinical trial, KEYNOTE-689 (NCT03765918), titled, “Study of Pembrolizumab Given Prior to Surgery and in Combination With Radiotherapy Given Post-surgery for Advanced Head and Neck Squamous Cell Carcinoma (MK-3475-689)” to provide long-term efficacy data. Provide the final overall survival (OS) analysis once the required number of events for OS, as prespecified in the statistical analysis plan, have occurred in the intention-to-treat population.

The timetable you submitted on June 4, 2025, states that you will conduct this study according to the following schedule:

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>.

Trial Completion: 11/2026

Final Report Submission: 05/2027

Submit the final OS analysis and datasets with the final report submission.

Submit clinical protocols to your IND 122325 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

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

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 601.12(f)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(f)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA

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>

(in 21 CFR 600.80 and in 21 CFR 600.81).

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

Sincerely,

{See appended electronic signature page}

Erin Larkins, M.D.
Director (Acting)
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide

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/

PAZ J VELLANKI

06/12/2025 03:57:29 PM

I am the Acting Supervisory Associate Director of Division of Oncology 2 (DO2) and the designated signatory authority for this application, signing on behalf of the DO2 Division Director, Dr. Erin Larkins.

**CENTER FOR DRUG EVALUATION AND
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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) 06/2025
Dosage and Administration (2) 06/2025

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) $\geq 1\%$] 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 $\geq 1\%$) 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)

- for the treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent. (1.4)
- 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 whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test. (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 for patients whose tumors express PD-L1 (CPS ≥ 1), 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 locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA). (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, hypothyroidism, radiation skin injury, dysphagia, dry mouth, and musculoskeletal pain. (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: 06/2025

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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) $\geq 1\%$] 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 $\geq 1\%$) 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 is indicated for the treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test [see *Dosage and Administration* (2.1)], as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.

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 whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA approved test [see *Dosage and Administration* (2.1)].

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 for patients with tumors that express PD-L1 (CPS ≥ 1) [see *Dosage and Administration* (2.1)], 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 locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA).

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/CompanionDiagnostics>.

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 as a single agent as neoadjuvant treatment, then in combination with radiotherapy (RT) with or without chemotherapy then continued as a single agent as adjuvant treatment, select patients based on presence of positive PD-L1 expression (CPS ≥ 1) in resectable locally advanced HNSCC [see *Clinical Studies* (14.4)].

For use of KEYTRUDA in combination with chemotherapy, select patients based on the presence of positive PD-L1 expression (CPS ≥ 1) in locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma, and esophageal or gastroesophageal junction (GEJ) carcinoma [see *Clinical Studies* (14.10), (14.11)].

- An FDA-approved test for the detection of PD-L1 for the selection of patients with PD-L1 (CPS ≥ 1) expression in esophageal carcinoma in combination with platinum- and fluoropyrimidine-based chemotherapy is not available.

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

Administer KEYTRUDA as a 30-minute intravenous infusion. The recommended dosages of KEYTRUDA are presented in Table 1.

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	Until disease recurrence, unacceptable toxicity, or up to 12 months

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
	400 mg every 6 weeks	
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
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 locally advanced HNSCC	200 mg every 3 weeks or 400 mg every 6 weeks Administer KEYTRUDA prior to cisplatin when given on the same day.	Neoadjuvant: - Administer KEYTRUDA for 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity. Adjuvant: - Administer KEYTRUDA in combination with RT with or without cisplatin. - Continue KEYTRUDA as a single agent. - Continue KEYTRUDA until disease recurrence or unacceptable toxicity or up to one year
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

Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
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 Administer KEYTRUDA prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months

* 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	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†
For liver enzyme elevations in patients treated with combination therapy with axitinib, see Table 3.	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver‡	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold†
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold†
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold†
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
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 (temperatures at or below 25°C) 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 ($\geq 1\%$) 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 maculopapular, 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 IIC 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 IIC (1-3 positive lymph nodes), and 20% had Stage IIC (≥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 ($\geq 2\%$) 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 $\geq 20\%$ 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 $\geq 20\%$ 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 ($\geq 2\%$) were thrombocytopenia (20%), neutropenia (11%), anemia (6%), asthenia (2%), and diarrhea (2%). The most frequent ($\geq 2\%$) 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/m² 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 ($\geq 2\%$) 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 ($\geq 1\%$) 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 ($\geq 1\%$) 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 ($\geq 1\%$) 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

Neoadjuvant and Adjuvant Treatment of Locally Advanced HNSCC

The safety of KEYTRUDA as neoadjuvant and adjuvant treatment added to standard of care (SOC) therapy was evaluated in KEYNOTE-689, a multicenter, randomized (1:1), open-label, active-controlled trial in patients with resectable locally advanced (Stage III-IVA by AJCC 8th edition) head and neck squamous cell carcinoma (HNSCC) [see *Clinical Studies* (14.4)]. KEYTRUDA was administered as single-agent neoadjuvant therapy before definitive surgery, during adjuvant radiotherapy (RT) with or without concurrent cisplatin, and then as single agent adjuvant therapy. Concurrent cisplatin was added to KEYTRUDA and adjuvant RT for high-risk disease pathology. A total of 361 patients received treatment on the KEYTRUDA arm and 315 patients received treatment on the SOC therapy arm.

The median duration of exposure to KEYTRUDA in the neoadjuvant phase was 3.1 weeks (range: 1 day to 4.9 weeks). The median duration of exposure to KEYTRUDA in the adjuvant phase was 42 weeks (range: 1 day to 82 weeks).

The median age of patients who received KEYTRUDA was 60 years (range: 29 to 82), 32% age 65 or older, 6% age 75 or older; 79% male; 78% White, 14% Asian, 2.2% Black or African American, 2% Other races, 2.7% unknown race; and 15% Hispanic or Latino.

The most common adverse reactions ($\geq 20\%$) on the KEYTRUDA arm were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), dysphagia (29%), constipation (27%), hypothyroidism (26%), nausea (24%), rash (22%), dry mouth (22%), diarrhea (22%), and musculoskeletal pain (22%).

Table 16 and Table 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-689.

Table 16: Adverse Reactions in $\geq 20\%$ of Patients with HNSCC Who Received KEYTRUDA in KEYNOTE-689

Adverse Reaction	KEYTRUDA Neoadjuvant then adjuvant beginning with RT with or without cisplatin n=361		Standard of Care Adjuvant RT with or without cisplatin n=315	
	All Grades* (%)	Grade 3 or 4 (%)	All Grades* (%)	Grade 3 or 4 (%)
Gastrointestinal				
Stomatitis [†]	48	14	60	13
Dysphagia	29	12	32	11
Constipation	27	0.3	22	0.3
Nausea	24	1.9	28	2.9
Dry mouth	22	1.4	26	1.6
Diarrhea [‡]	22	4.2	11	0.6
Injury, poisoning and procedural complications				
Radiation skin injury	40	4.2	48	5.7
Investigations				
Weight loss	36	14	27	10
Endocrine disorders				
Hypothyroidism [§]	26	0	6	0
General				
Fatigue [¶]	33	2.2	27	1.6
Skin and subcutaneous tissue disorders				
Rash [#]	22	1.9	10	1.9
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [Ⓟ]	22	1.9	16	0.6

* Graded per NCI CTCAE v4.03

† Includes pharyngeal inflammation, cheilitis, oral mucosal erythema, mucosal inflammation, glossitis, mouth ulceration, tongue ulceration

‡ Includes colitis, enteritis, hemorrhagic diarrhea

§ Includes blood thyroid stimulating hormone increased

¶ Includes asthenia

Includes dermatitis, skin exfoliation, dermatitis acneiform, eczema, rash macular, rash maculo-papular, erythema multiforme, dermatitis exfoliative, urticarial dermatitis, eczema asteatotic, exfoliative rash, rash pruritic, rash pustular

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

Table 17: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with HNSCC Who Received KEYTRUDA in KEYNOTE-689

Laboratory Test*	KEYTRUDA Neoadjuvant then adjuvant beginning with radiation with or without cisplatin		Radiation with or without cisplatin	
	All Grades [†] (%)	Grades 3-4 (%)	All Grades [†] (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	76	50	86	55
Anemia	75	12	74	12
Neutropenia	32	13	35	19
Thrombocytopenia	22	1.7	29	1.9
Chemistry				
Hyperglycemia	57	5.7	47	2.7
Hyponatremia	47	16	36	11
Increased ALT	42	6.2	37	2.0
Hypoalbuminemia	40	1.4	38	1.0
Increased AST	38	4.8	23	2.0
Hypomagnesemia	34	1.2	22	1.3
Hypokalemia	29	6.8	20	7.4
Hyperkalemia	29	3.4	24	2.3
Increased alkaline phosphatase	27	2.5	19	0.0
Hypocalcemia	27	2.6	26	3.3
Hypophosphatemia	23	6.1	15	7.0
Increased creatinine	22	2.0	27	2.9
Hypercalcemia	21	2.0	14	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 + CRT/RT (range: 342 to 357 patients) and CRT/RT (range: 300 to 309 patients)

† Graded per NCI CTCAE v4.03

Neoadjuvant Phase of KEYNOTE 689

Of the 361 patients who received at least one dose of single agent KEYTRUDA as neoadjuvant treatment, 11% of patients experienced serious adverse reactions. Serious adverse reactions that occurred in more than one patient were pneumonia (1.4%), tumor hemorrhage (0.8%), dysphagia (0.6%), immune mediated hepatitis (0.6%), cellulitis (0.6%), and dyspnea (0.6%). Fatal adverse reactions occurred in 1.1% of patients who received neoadjuvant KEYTRUDA including respiratory failure, clostridium infection, septic shock, and myocardial infarction (one patient each).

Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 2.8% of patients who received KEYTRUDA as neoadjuvant treatment. The most frequent adverse reaction which resulted in permanent discontinuation of neoadjuvant KEYTRUDA in more than one patient was arthralgia (0.6%).

Of the 361 patients who received KEYTRUDA as neoadjuvant treatment, 11% (n=38) did not receive surgery. Surgical cancellation on the KEYTRUDA arm was due to disease progression in 4% (n=15), patient decision in 3% (n=10), adverse reactions in 1.4% (n=5), physician's decision in 1.1% (n=4), unresectable tumor in 0.6% (n=2), loss of follow-up in 0.3% (n=1), and use of non-study anti-cancer therapy in 0.3% (n=1).

Of the 351 patients randomized to SOC, 12% (n=43) did not receive surgery. Surgical cancellation on the SOC arm was due to patient decision in 7% (n=24), physician's decision in 2.3% (n=8), disease progression in 1.7% (n=6), and adverse reactions in 1.4% (n=5).

Of the 323 KEYTRUDA-treated patients who received surgery, 1.2% (n=4) experienced delay of surgery (defined as on-study surgery occurring ≥ 9 weeks after initiation of neoadjuvant KEYTRUDA) due to adverse reactions. Of the 307 patients randomized to SOC who received surgery on study, 0.3% (n=1) experienced delay of surgery (defined as surgery occurring ≥ 6 weeks after randomization) due to adverse reactions

Among the KEYTRUDA-treated patients who received surgery, 2.8% (n=9) did not receive adjuvant treatment due to adverse reactions. Among the SOC-treated patients who received surgery, 3.6% (n=11) did not receive adjuvant RT or chemoradiation due to adverse reactions.

Adjuvant Phase of KEYNOTE 689

A total of 275 patients in the KEYTRUDA arm and 275 patients in the SOC arm started the adjuvant phase of treatment. On the KEYTRUDA arm, 100 patients received KEYTRUDA and cisplatin with concurrent RT, 154 patients received KEYTRUDA alone with concurrent RT, 7 patients received cisplatin alone with concurrent RT, and 13 patients received RT alone. One patient received KEYTRUDA alone. On the SOC arm, 139 patients received cisplatin with concurrent RT while 136 patients received RT alone. For the KEYTRUDA arm, a total of 222 patients received single-agent KEYTRUDA following RT.

Of the 255 patients who received at least one dose of KEYTRUDA in the adjuvant phase, 38% experienced serious adverse reactions. The most frequent serious adverse reactions reported in $\geq 1\%$ of KEYTRUDA-treated patients were pneumonia (2.7%), pyrexia (2.4%), stomatitis (2.4%), acute kidney injury (2.0%), pneumonitis (1.6%), COVID-19 (1.2%), death not otherwise specified (1.2%), diarrhea (1.2%), dysphagia (1.2%), gastrostomy tube site complication (1.2%), and immune-mediated hepatitis (1.2%).

Fatal adverse reactions occurred in 5% including death not otherwise specified (1.2%), acute renal failure (0.4%), hypercalcemia (0.4%), pulmonary hemorrhage (0.4%), dysphagia/malnutrition (0.4%), mesenteric thrombosis (0.4%), sepsis (0.4%), pneumonia (0.4%), COVID-19 (0.4%), respiratory failure (0.4%), cardiovascular disorder (0.4%) and gastrointestinal hemorrhage (0.4%).

Permanent discontinuation of adjuvant KEYTRUDA due to an adverse reaction occurred in 17% of patients. The most frequent ($\geq 1\%$) adverse reactions that led to permanent discontinuation of adjuvant KEYTRUDA were pneumonitis, colitis, immune-mediated hepatitis and death not otherwise specified. Of the 275 patients who received SOC in the adjuvant phase, 23% experienced serious adverse reactions.

The most frequent serious adverse reactions reported in $>1\%$ of SOC-treated patients were pneumonia (3.6%) and acute kidney injury (3.3%). Fatal adverse reactions occurred in 4.7% including pneumonia (0.7%), septic shock (0.4%), death not otherwise specified (0.4%), sudden death (0.4%), myocardial infarction (0.4%), pancreatic neoplasm (0.4%) and other infections (2.9%).

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 ($\geq 2\%$) 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 ($\geq 2\%$) were neutropenia (14%), thrombocytopenia (10%), anemia (6%), pneumonia (4.7%), and febrile neutropenia (2.9%).

Tables 18 and 19 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-048.

Table 18: 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 [Ⓟ]	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 [Ⓟ]	1	0	14	1.1	7	1
Musculoskeletal						
Myalgia [ⓐ]	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

[Ⓟ] Includes pneumonia, atypical pneumonia, bacterial pneumonia, staphylococcal pneumonia, aspiration pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal

[Ⓟ] Includes peripheral sensory neuropathy, peripheral neuropathy, hypoesthesia, dysesthesia

[ⓐ] Includes back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia

Table 19: 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 $\geq 1000/\mu\text{L}$, platelet count $\geq 75,000/\mu\text{L}$, 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 $\geq 1\%$ 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 $\geq 3\%$ 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 20 summarizes adverse reactions in KEYNOTE-204.

Table 20: 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
Fatigue␣	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
Pneumonitisé	11	5	3	1.3
Dyspneað	11	0.7	7	0.7
Endocrine				
Hypothyroidism	19	0	3	0
Nervous System				
Peripheral neuropathyº	11	0.7	43	7
Headacheÿ	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

␣ 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

é Includes pneumonitis, interstitial lung disease

ð Includes dyspnea, dyspnea exertional, wheezing

º Includes dysesthesia, hypoesthesia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy

ÿ 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 21 summarizes laboratory abnormalities in KEYNOTE-204.

Table 21: 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 22 and 23 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-087.

Table 22: 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 [▷]	20	0.5
Pruritus	11	0
Endocrine		
Hypothyroidism	14	0.5
Infections		
Upper respiratory tract infection	13	0
Nervous System		
Headache	11	0.5
Peripheral neuropathy ^β	10	0

* Graded per NCI CTCAE v4.0

[†] Includes fatigue, asthenia

[‡] Includes cough, productive cough

[§] Includes dyspnea, dyspnea exertional, wheezing

[¶] Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain

[#] Includes diarrhea, gastroenteritis, colitis, enterocolitis

[▷] 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 23: 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 24 and 25 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-170.

Table 24: 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 [▷]	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

▷ 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 25: 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 $\geq 2\%$ 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 ($\geq 2\%$) 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 ($\geq 2\%$) 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 26 and 27 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with enfortumab vedotin in KEYNOTE-A39.

Table 26: Adverse Reactions ≥20% (All Grades) in Patients Treated with KEYTRUDA in Combination with Enfortumab Vedotin in KEYNOTE-A39

Adverse Reaction	KEYTRUDA in combination with Enfortumab Vedotin n=440		Chemotherapy n=433	
	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 27: 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 28 and 29 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with enfortumab vedotin in KEYNOTE-869.

Table 28: 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 29: 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 30 summarizes adverse reactions in patients on KEYTRUDA in KEYNOTE-052.

Table 30: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

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

* Graded per NCI CTCAE v4.0

[†] Includes fatigue, asthenia

[‡] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain

[§] Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements

[¶] Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper

[#] Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, increased transaminases, hyperbilirubinemia, increased blood bilirubin, increased alanine aminotransferase, increased aspartate aminotransferase, increased hepatic enzymes, increased liver function tests

[Ⓟ] 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

[Ⓟ] 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 ($\geq 1\%$) 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 ($\geq 2\%$) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis. Tables 31 and 32 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-045.

Table 31: Adverse Reactions Occurring in $\geq 10\%$ 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 [Ⓢ]	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

[Ⓢ] Includes blood urine present, hematuria, chromaturia

Table 32: Laboratory Abnormalities Worsened from Baseline Occurring in $\geq 20\%$ 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 ($\geq 2\%$) were diarrhea (4%) and urinary tract infection (2%). Serious adverse reactions occurred in 28% of KEYTRUDA-treated patients. The most frequent serious adverse reactions ($\geq 2\%$) in KEYTRUDA-treated patients were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). Tables 33 and 34 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-057.

Table 33: 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 34: 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 $\geq 1\%$ 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 ($\geq 2\%$) 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 $\geq 5\%$ 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 $\geq 5\%$ 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 35 and 36 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-859.

Table 35: 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 36: Laboratory Abnormalities Worsened from Baseline Occurring in $\geq 20\%$ 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 ($\geq 1\%$) 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 ($\geq 2\%$) 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 37 and 38 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-590.

Table 37: 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 38: 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 597 patients with FIGO 2014 Stage III-IVA cervical cancer [see *Clinical Studies* (14.12)]. Two hundred ninety-four patients received KEYTRUDA in combination with chemoradiotherapy and 303 patients received placebo in combination with chemoradiotherapy.

The median duration of exposure to KEYTRUDA was 20 months (range: 1 day to 32 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 34% of patients receiving KEYTRUDA in combination with chemoradiotherapy. Serious adverse reactions occurring in $\geq 1\%$ of patients included urinary tract infection (3.1%), urosepsis (1.4%), and sepsis (1%).

KEYTRUDA was discontinued for adverse reactions in 9% of patients. The most common adverse reaction ($\geq 1\%$) resulting in permanent discontinuation was diarrhea (1%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 47% of patients; the most common adverse reactions leading to interruption of KEYTRUDA ($\geq 2\%$) were anemia (7%), COVID-19 (7%), SARS-CoV-2 test positive (4.8%), diarrhea (4.1%), increased ALT (4.1%), increased AST (3.4%) decreased neutrophil count (3.1%), and urinary tract infection (2.7%).

Table 39 and Table 40 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-A18.

Table 39: Adverse Reactions Occurring in $\geq 10\%$ 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=294		Placebo with chemoradiotherapy n=303	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	56	0	62	2.3
Diarrhea	51	4.4	50	4.3
Vomiting	34	1.0	35	1.7
Constipation	20	0	19	0.7
Abdominal pain	13	1.0	14	1.7
Infections				
Urinary tract infection [†]	35	4.8	34	5
COVID-19	10	0	7	1.0
General				
Fatigue [‡]	28	1.0	28	1.3
Pyrexia	14	0.7	15	0
Endocrine				
Hypothyroidism [§]	23	0.7	8	0
Hyperthyroidism	13	0.3	3.3	0
Investigations				
Weight loss	19	2.4	19	1.0
Metabolism and Nutrition				

Decreased appetite	18	0.7	17	0.3
Renal and Urinary				
Dysuria	12	0.3	12	0
Skin and Subcutaneous Tissue Disorders				
Rash [¶]	12	1.0	8	0.3
Musculoskeletal and Connective Tissues Disorders				
Back pain	11	0.7	11	0.7
Reproductive System				
Pelvic pain	11	1.0	14	1.7

* 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 40: 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	48	94	49
Anemia	87	33	82	27
Neutropenia	76	33	76	33
Thrombocytopenia	64	9	62	7
Chemistry				
Hypomagnesemia	61	4.2	63	3.7
Hyponatremia	56	4.8	50	4.7
Increased AST	50	1.7	44	2.3
Increased ALT	49	3.1	46	1
Hypocalcemia	45	5	43	5
Hypokalemia	44	15	41	11
Increased creatinine	44	7	46	6
Hypoalbuminemia	38	2.4	37	2.3
Increased alkaline phosphatase	38	0.3	35	0.3
Hyperkalemia	21	2.0	16	1

* 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: 288 to 293 patients) and placebo + chemoradiotherapy (range: 299 to 301 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 $\geq 3\%$ 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 ($\geq 1\%$) 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 ($\geq 2\%$) 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 ($\geq 20\%$) 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 41 and Table 42 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-826.

Table 41: Adverse Reactions Occurring in $\geq 20\%$ 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 42: 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 43 and 44 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-158.

Table 43: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=98	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue [†]	43	5
Pain [‡]	22	2.0
Pyrexia	19	1.0
Edema peripheral [§]	15	2.0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain [¶]	27	5
Gastrointestinal		
Diarrhea [#]	23	2.0
Abdominal pain [▷]	22	3.1
Nausea	19	0
Vomiting	19	1.0
Constipation	14	0
Metabolism and Nutrition		
Decreased appetite	21	0
Vascular		
Hemorrhage [Ⓡ]	19	5
Infections		
UTI [Ⓐ]	18	6
Infection (except UTI) [Ⓔ]	16	4.1
Skin and Subcutaneous Tissue		
Rash [Ⓛ]	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

[▷] Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper

[Ⓡ] Includes epistaxis, hematuria, hemoptysis, metrorrhagia, rectal hemorrhage, uterine hemorrhage, vaginal hemorrhage

[Ⓐ] Includes bacterial pyelonephritis, pyelonephritis acute, urinary tract infection, urinary tract infection bacterial, urinary tract infection pseudomonal, urosepsis

[Ⓔ] 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

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

Table 44: 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 45 and 46 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-394.

Table 45: 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 46: 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 ($\geq 1\%$) 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 ($\geq 2\%$) 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 $\geq 5\%$ 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 $\geq 5\%$ 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 $\geq 1\%$ 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 47 and 48 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 47: 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 acneiform, 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 48: Laboratory Abnormalities Worsened from Baseline Occurring in $\geq 20\%$ 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 $\geq 2\%$ 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 ($\geq 2\%$) 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 ($\geq 3\%$) 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 49 and 50 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in $\geq 20\%$ of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

Table 49: Adverse Reactions Occurring in $\geq 20\%$ 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				
Hypertension ^b	56	29	43	20
Hemorrhagic events ^b	27	5	26	4
Metabolism				
Decreased appetite ^a	41	4	31	1
Skin and Subcutaneous Tissue				
Rash ^e	37	5	17	1
Palmar-plantar erythrodysesthesia syndrome ^d	29	4	38	4
Investigations				
Weight loss	30	8	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	30	0	4	0
Renal and Urinary				
Proteinuria ^g	30	8	13	3
Acute kidney injury ^h	21	5	16	2
Hepatobiliary				
Hepatotoxicity ^f	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
▷	Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, labile blood pressure
Ⓕ	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
ø	Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, plantar erythema
ÿ	Includes hemoglobinuria, nephrotic syndrome, proteinuria
Ÿ	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 50: Laboratory Abnormalities Worsened from Baseline Occurring in $\geq 20\%$ (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 ($\geq 1\%$) 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 ($\geq 1\%$) 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 ($\geq 1\%$) 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 51 and 52 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-564.

Table 51: 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 pain [▷]	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				
Cough [℞]	17	0	12	0
Nervous System				
Headache ^à	15	0.2	13	0
Hepatobiliary				
Hepatotoxicity ^è	14	3.7	7	0.6
Renal and Urinary				
Acute kidney injury ^ò	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

[▷] Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, gastrointestinal pain

[℞] 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

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

Table 52: 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 ($\geq 3\%$) 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 ($\geq 1\%$) 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 ($\geq 3\%$) were diarrhea (8%), increased ALT (4.4%), increased AST (3.8%), and hypertension (3.5%).

Tables 53 and 54 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib in KEYNOTE-775.

Table 53: Adverse Reactions Occurring in $\geq 20\%$ 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
Stomatitis [¶]	35	2.6	26	1.2
Abdominal pain [§]	34	2.6	21	1.2
Constipation	27	0	25	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal disorders ^a	53	5	27	0.6
Metabolism				
Decreased appetite [§]	44	7	21	0
Investigations				
Weight loss	34	10	6	0.3
Renal and Urinary				
Proteinuria [§]	29	6	3.4	0.3
Infections				
Urinary tract infection [§]	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 erythrodysesthesia [¶]	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
Ⓟ	Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, tongue ulceration
Ⓠ	Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, epigastric discomfort
Ⓡ	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
Ⓢ	Includes decreased appetite, early satiety
Ⓣ	Includes proteinuria, protein urine present, hemoglobinuria
Ⓤ	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 54: 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 $\geq 2\%$ 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 ($\geq 1\%$) 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 ($\geq 2\%$) 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 55 and 56 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-522.

Table 55: 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 neuropathy [Ⓟ]	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				
Cough [Ⓛ]	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

Ⓟ Includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy

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

Table 56: Laboratory Abnormalities Worsened from Baseline Occurring in $\geq 20\%$ 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 $\geq 2\%$ 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 ($\geq 1\%$) 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 ($\geq 2\%$) 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 57 and 58 summarize the adverse reactions and laboratory abnormalities in patients on KEYTRUDA in KEYNOTE-355.

Table 57: 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 58: 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 $\geq 10\%$ 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 $\geq 10\%$ 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 294 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 difference in safety was observed between patients ≥ 65 years of age 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 ($eGFR \geq 15$ mL/min/1.73 m²), 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 ($\geq 1\%$ 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.

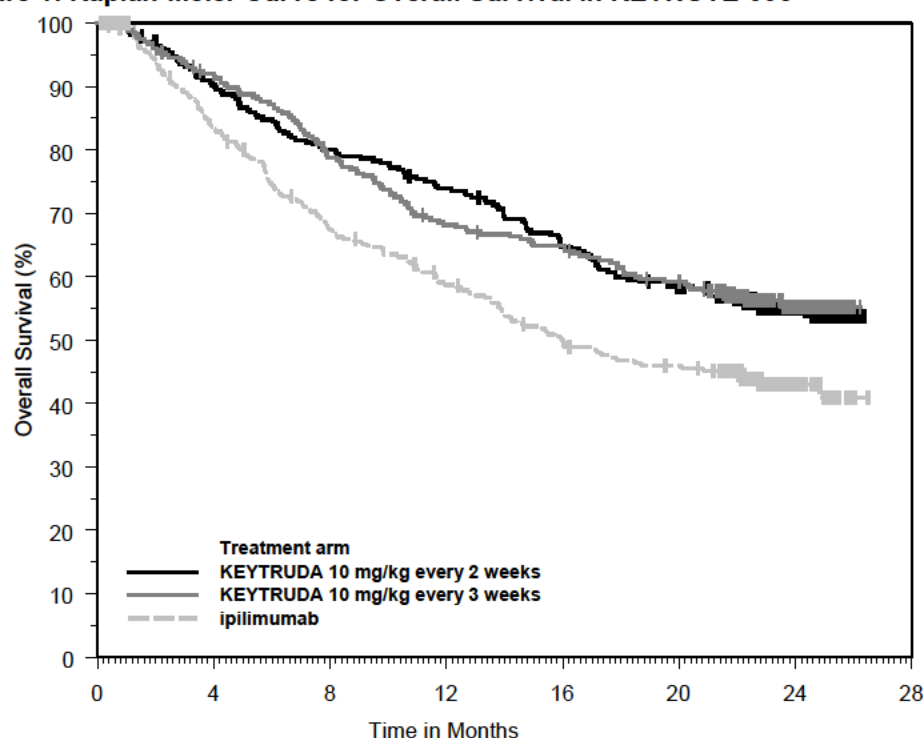
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients 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 59 and Figure 1.

Table 59: 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		Time in Months						
		0	4	8	12	16	20	24
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/m² intravenously every 3 weeks (26%), temozolomide 200 mg/m² orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 mg/mL/min intravenously plus paclitaxel 225 mg/m² intravenously every 3 weeks for four cycles then carboplatin AUC of 5 mg/mL/min plus paclitaxel 175 mg/m² every 3 weeks (25%), paclitaxel 175 mg/m² 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 [$\geq 110\%$ 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 60 and Figure 2.

Table 60: Efficacy Results in KEYNOTE-002

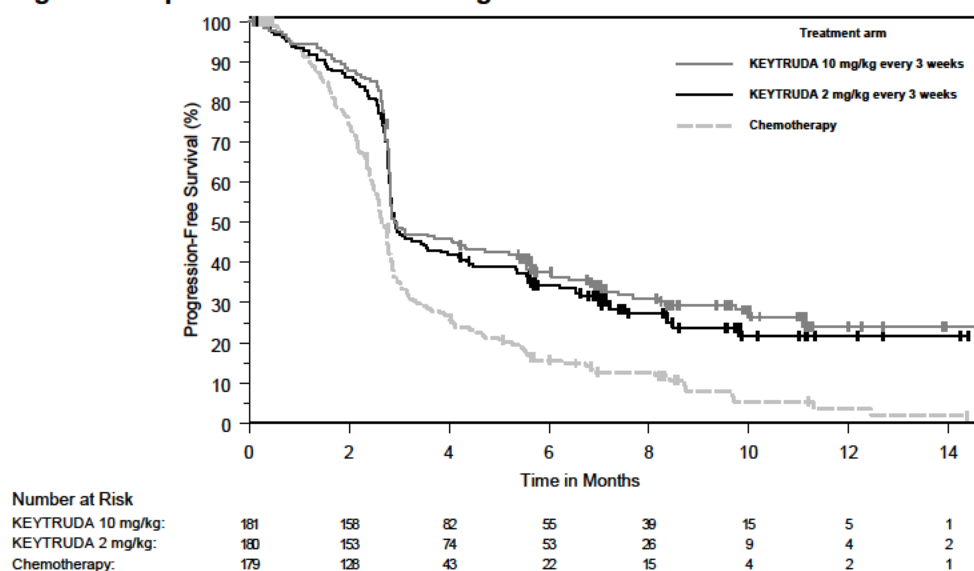
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8,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



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 61 and Figure 3.

Table 61: 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

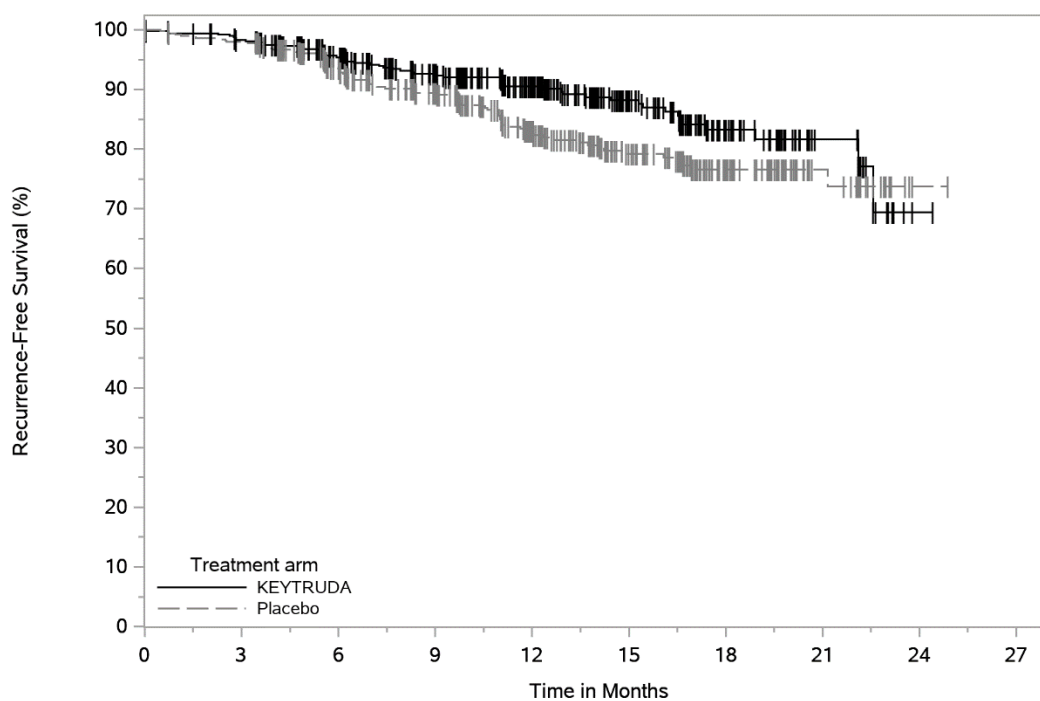
[†] Based on a log-rank test stratified by American Joint Committee on Cancer 8th edition (AJCC) stage

[‡] 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 62 and Figure 4.

Table 62: 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

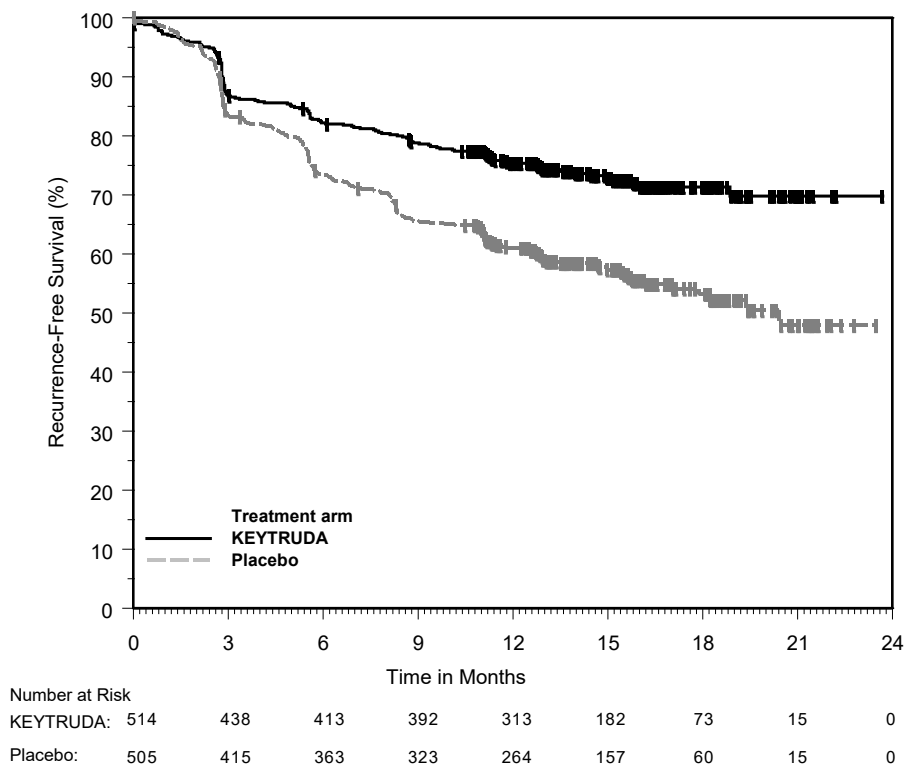
‡ p-Value is compared with 0.016 of the allocated alpha for this interim analysis.

§ 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/m², and investigator's choice of cisplatin 75 mg/m² 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/m² intravenously every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Placebo, pemetrexed 500 mg/m², and investigator's choice of cisplatin 75 mg/m² 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/m² 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 63 and Figure 5 summarize the efficacy results for KEYNOTE-189.

Table 63: 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

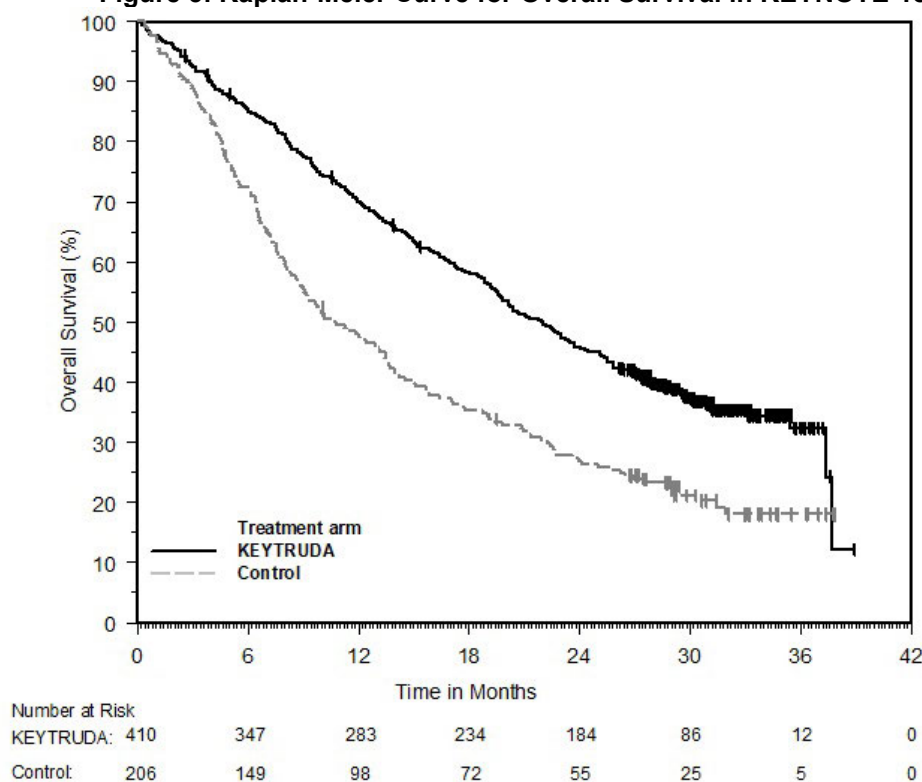
‡ Response: Best objective response as confirmed complete response or partial response

§ 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/m² on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m² 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/m² on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m² 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 64 and Figure 6 summarize the efficacy results for KEYNOTE-407.

Table 64: 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

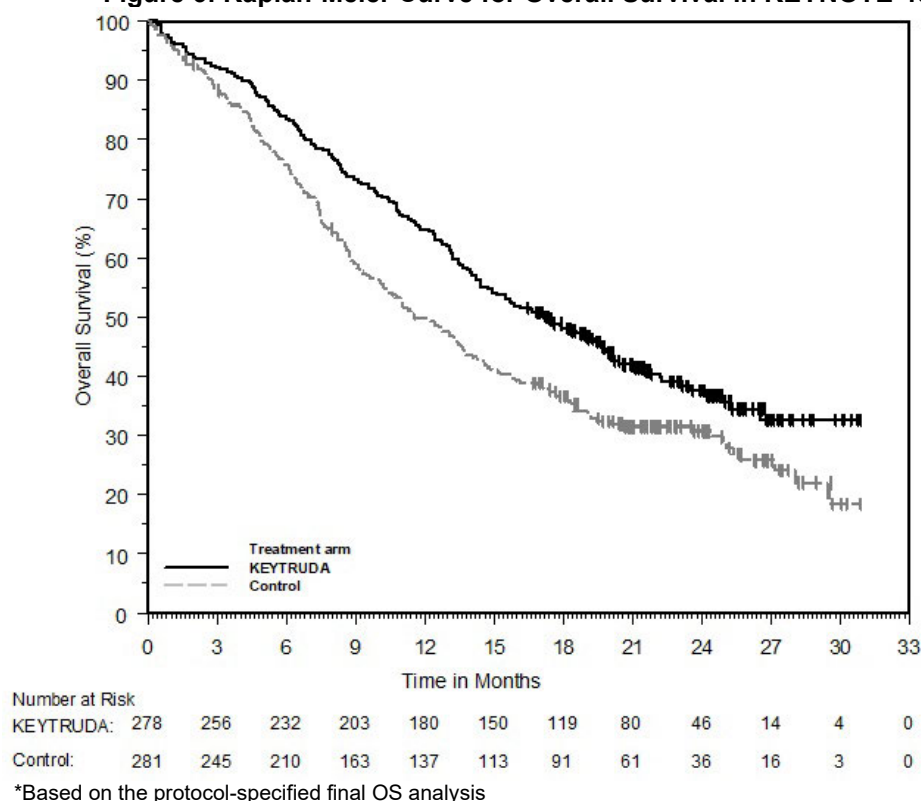
‡ ORR primary analysis and DoR analysis were conducted with the first 204 patients enrolled.

§ 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*



First-line treatment of metastatic NSCLC with PD-L1 expression (TPS $\geq$ 1%) 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 $\geq$ 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 $\geq$ 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/m² 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/m² every 3 weeks for patients with nonsquamous histologies;
- Paclitaxel 200 mg/m² 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/m² 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 $\geq 50\%$ NSCLC, the subgroup of patients with TPS $\geq 20\%$ NSCLC, and the overall population with TPS $\geq 1\%$ NSCLC. Additional efficacy outcome measures were PFS and ORR in the subgroup of patients with TPS $\geq 50\%$ NSCLC, the subgroup of patients with TPS $\geq 20\%$ NSCLC, and the overall population with TPS $\geq 1\%$ 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 $\geq 50\%$ NSCLC and 53% had TPS 1 to 49% NSCLC.

The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS $\geq 50\%$, TPS $\geq 20\%$, TPS $\geq 1\%$) randomized to KEYTRUDA as compared with chemotherapy. Table 65 and Figure 7 summarize the efficacy results in the subgroup of patients with TPS $\geq 50\%$ and in all randomized patients with TPS $\geq 1\%$.

Table 65: Efficacy Results of All Randomized Patients (TPS $\geq 1\%$ and TPS $\geq 50\%$) 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

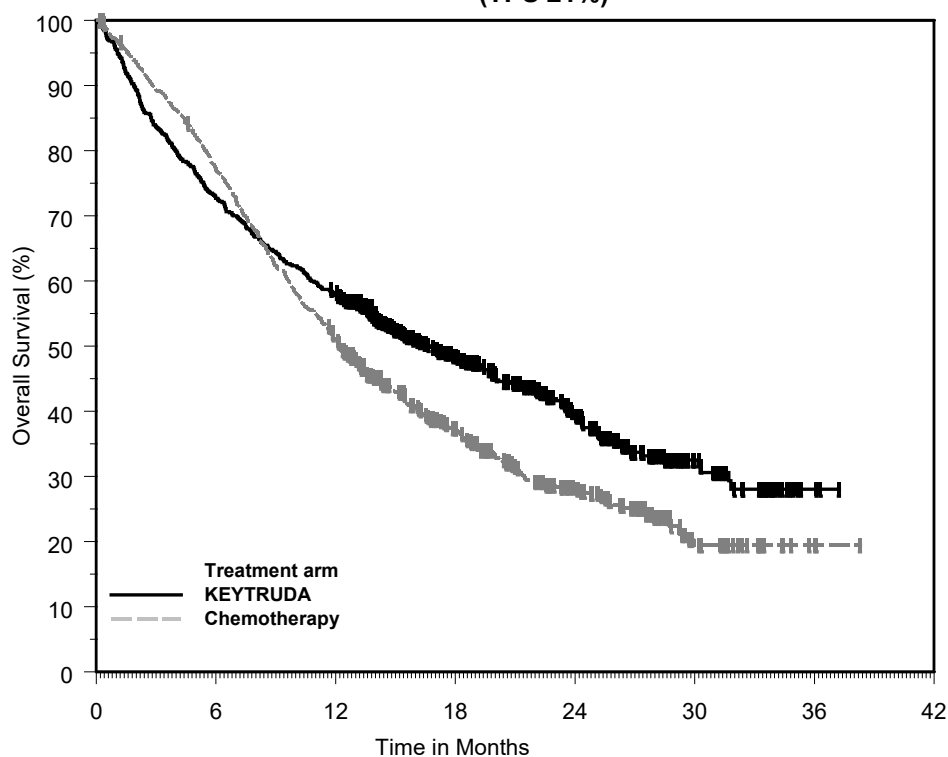
‡ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints

§ 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 $\geq 20\%$ NSCLC were intermediate between the results of those with PD-L1 TPS $\geq 1\%$ and those with PD-L1 TPS $\geq 50\%$. 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 $\geq 1\%$)



		Time in Months						
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/m² 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/m² every 3 weeks for patients with nonsquamous histologies;
- Pemetrexed 500 mg/m² every 3 weeks and cisplatin 75 mg/m² every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m² every 3 weeks for patients with nonsquamous histologies;
- Gemcitabine 1250 mg/m² on days 1 and 8 and cisplatin 75 mg/m² every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m² 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/m² 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 66 and Figure 8 summarize the efficacy results for KEYNOTE-024.

Table 66: 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+)

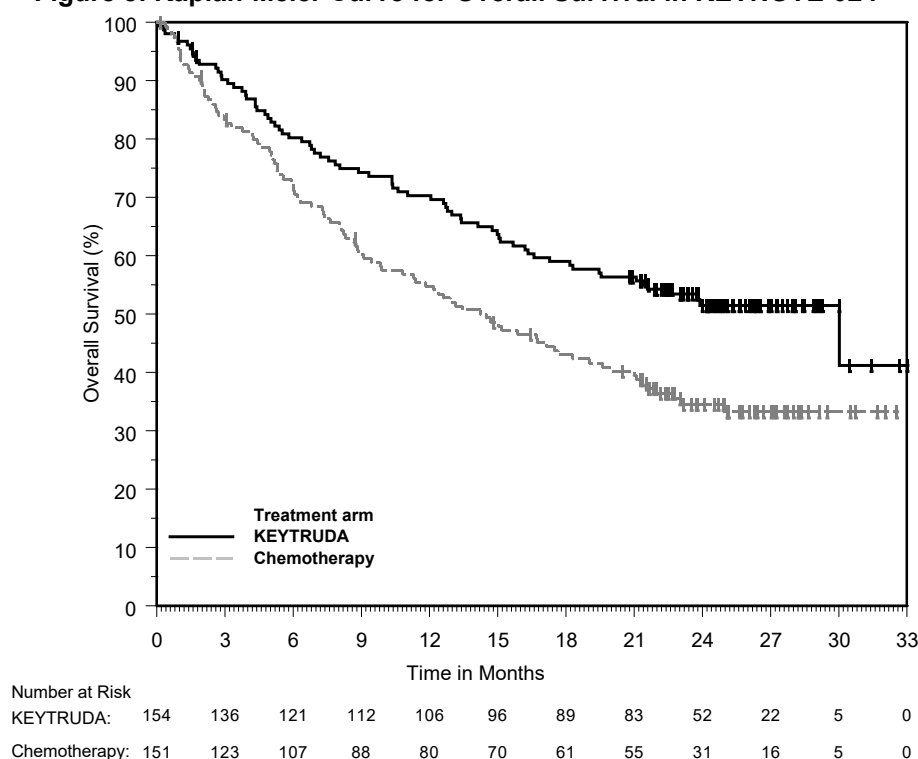
* Based on the stratified Cox proportional hazard model for the interim analysis

[†] 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 with PD-L1 expression (TPS ≥ 1%)

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/m² 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 67 and 68 and Figure 9 summarize efficacy results in the subgroup with TPS $\geq 50\%$ population and in all patients, respectively.

Table 67: Efficacy Results of the Subgroup of Patients with TPS $\geq 50\%$ 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 68: Efficacy Results of All Randomized Patients (TPS $\geq 1\%$) in KEYNOTE-010

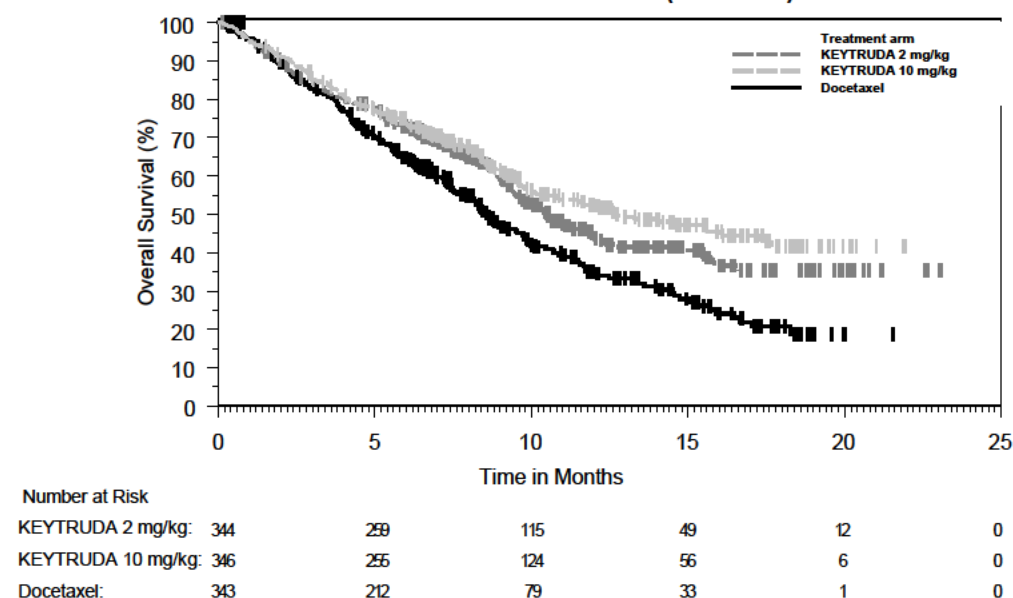
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m ² every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)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



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/m² and either pemetrexed 500 mg/m² on Day 1 or gemcitabine 1000 mg/m² 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/m² and either pemetrexed 500 mg/m² on Day 1 or gemcitabine 1000 mg/m² 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 $\geq$ 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 69 and Figure 10 summarize the efficacy results for KEYNOTE-671.

Table 69: 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

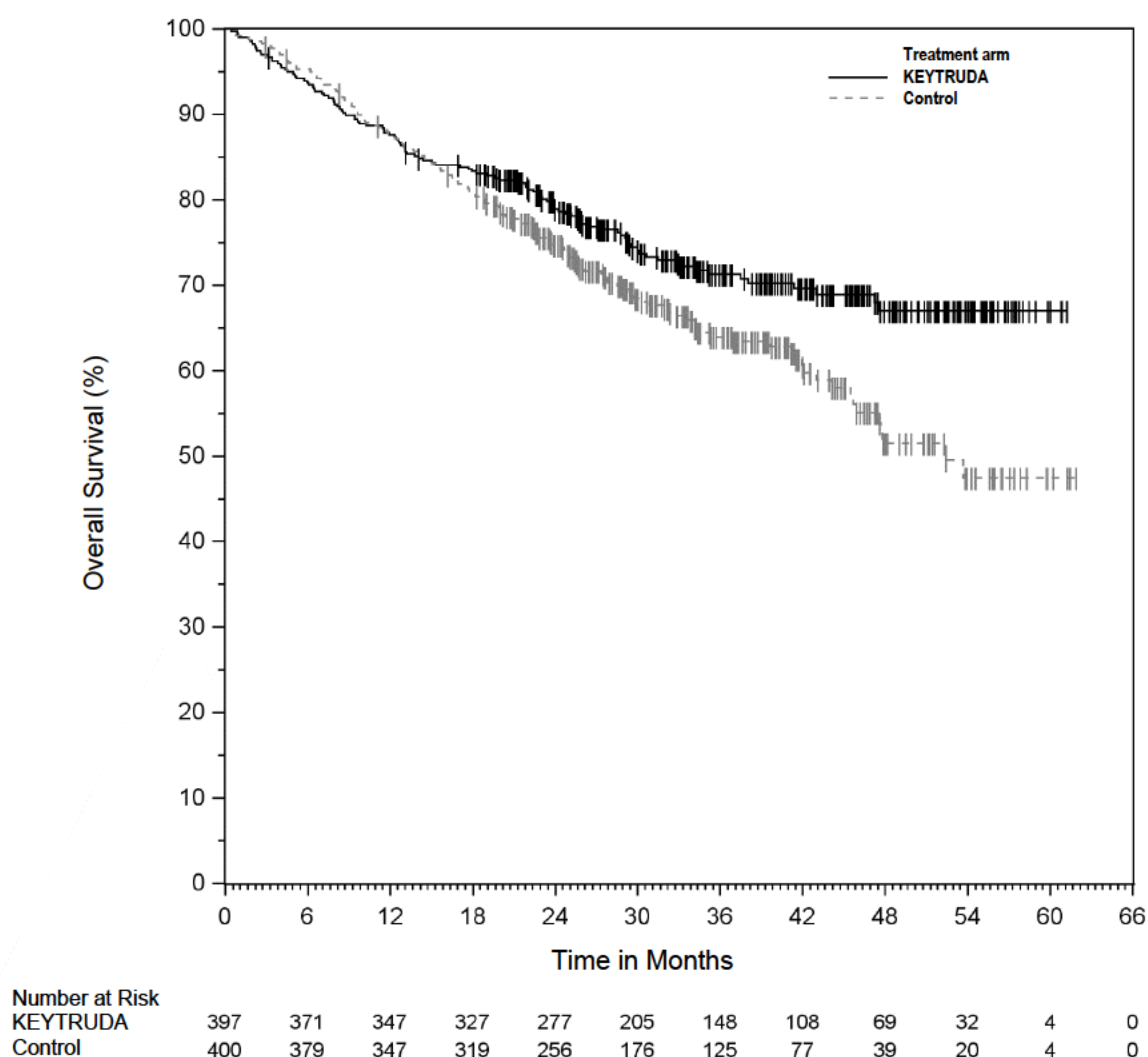
‡ Based on stratified log-rank test

§ 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 $\geq 50\%$), 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.

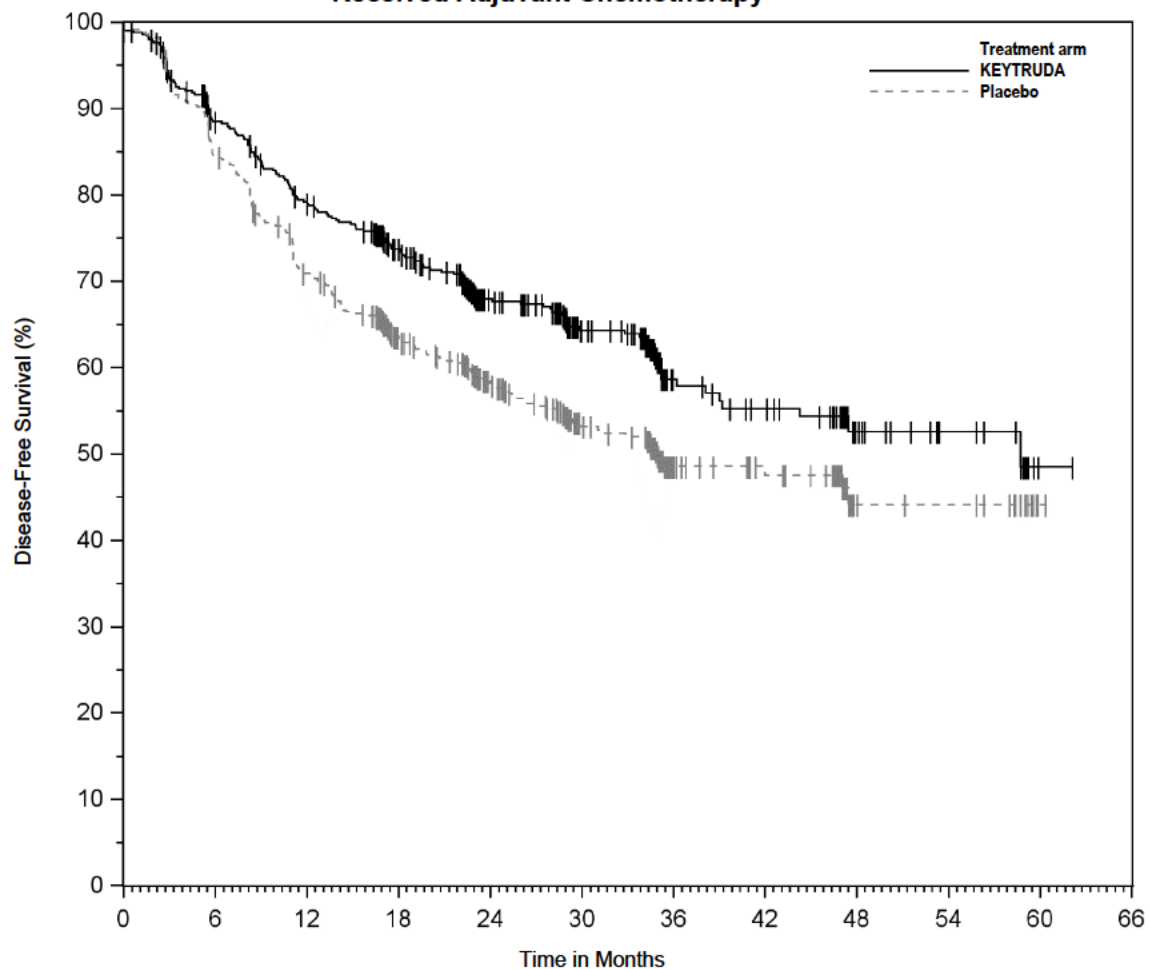
Table 70 and Figure 11 summarize the efficacy results for KEYNOTE-091 in patients who received adjuvant chemotherapy.

Table 70: 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/m² and cisplatin 75 mg/m² 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/m² and cisplatin 75 mg/m² 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 71 and Figure 12 summarize the efficacy results for KEYNOTE-483.

Table 71: 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)

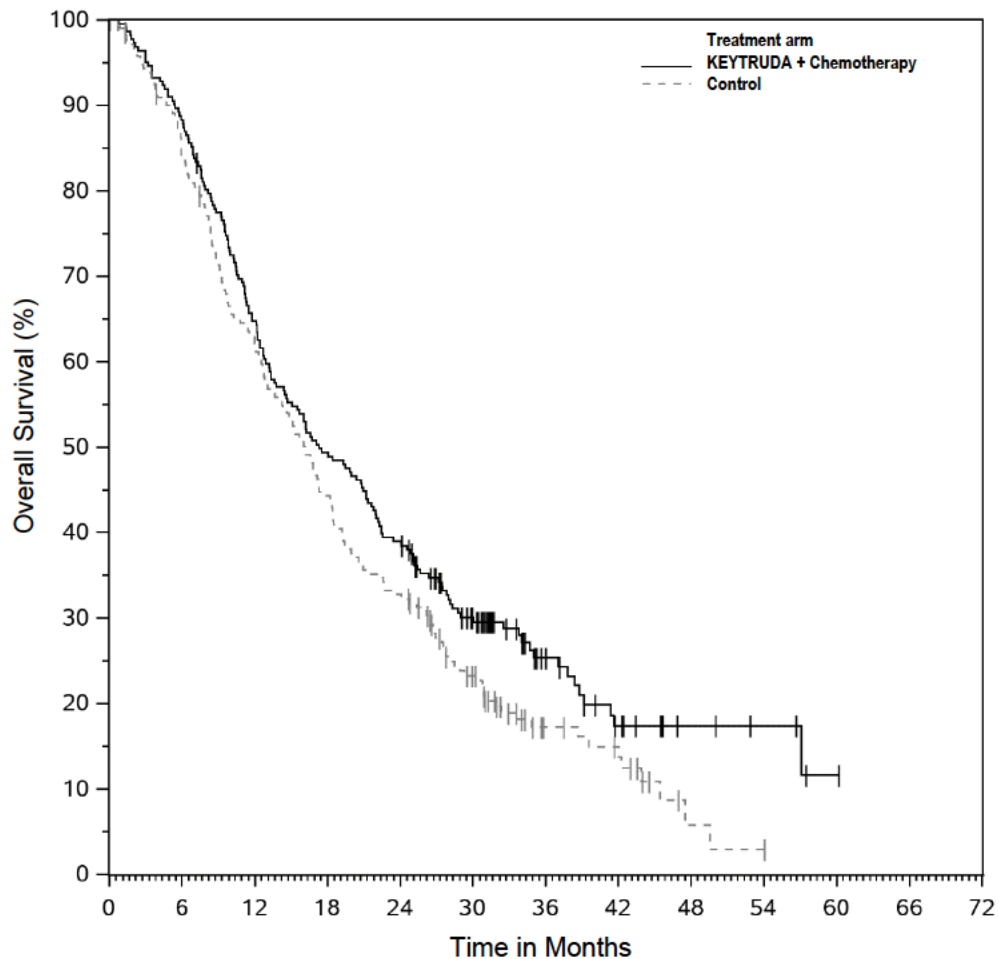
* Based on stratified Cox proportional hazard model

† 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

Neoadjuvant and Adjuvant Treatment of Locally Advanced HNSCC for Tumors Expressing PD-L1 (CPS $\geq$ 1)

The efficacy of KEYTRUDA was investigated in KEYNOTE-689 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 714 patients with resectable locally advanced (Stage III-IVA) HNSCC [AJCC, 8th edition]. Patients with active autoimmune disease requiring systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs.

hypopharynx), tumor stage (III vs. IVA) and PD-L1 status (TPS $\geq$ 50% vs. TPS < 50%) according to the PD-L1 IHC 22C3 pharmDx kit.

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

- neoadjuvant KEYTRUDA 200 mg for 2 cycles prior to surgical resection. Within 6 weeks following surgery, 3 cycles of adjuvant KEYTRUDA 200 mg every 3 weeks in combination with radiotherapy (RT) with or without 3 cycles of cisplatin 100 mg/m² every 3 weeks. This was followed by KEYTRUDA 200 mg every 3 weeks for up to 12 cycles.
- no neoadjuvant treatment prior to surgery. Within 6 weeks following surgery, adjuvant RT with or without 3 cycles of concurrent cisplatin 100 mg/m² every 3 weeks.

On both treatment arms, patients received cisplatin with adjuvant RT if high-risk pathological features (i.e., positive margins <1 mm or extranodal extension) were present at surgery.

Treatment with KEYTRUDA continued until disease progression by RECIST v1.1 per BICR during the neoadjuvant phase that precluded surgery, local or metastatic recurrence during the adjuvant phase, completion of treatment, or unacceptable toxicity. Assessment of tumor status was performed prior to surgery at Week 6 in the neoadjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed 12 weeks after end of RT with or without cisplatin treatment and then every 3 months until the end of year 3; then every 6 months thereafter up to the end of year 5.

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

The major efficacy outcome measure was event-free survival (EFS) by BICR 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 disease progression or recurrence, or death due to any cause. Additional efficacy outcome measures were major pathological response (mPR) as assessed by BIPR, and overall survival (OS).

The demographic and baseline characteristics in the 682 patients with PD-L1 expression of CPS $\geq$ 1 were: median age of 60 years (range: 22 to 87), 33% age 65 or older; 79% male; 78% White, 13% Asian and 2.5% Black or African American, 14% were Hispanic or Latino; 43% had ECOG PS of 1, and 79% were former/current smokers. Four percent of patients' tumors were HPV-positive, and 26% had Stage III disease, 74% had Stage IVA disease. Sixty-eight percent of patients' tumors had PD-L1 expression of CPS $\geq$ 10.

Eighty-eight percent of patients received definitive surgery in both the KEYTRUDA and the SOC arm.

Seventy-six percent of patients in the KEYTRUDA arm and 78% of patients in the SOC arm started the radiation phase of treatment. In the KEYTRUDA arm, 35% of patients received KEYTRUDA and cisplatin with concurrent RT, 57% of patients received KEYTRUDA alone with concurrent RT, 3% of patients received cisplatin alone with concurrent RT, 5% of patients received RT alone and one patient (0.4%) received KEYTRUDA alone without concurrent RT. On the SoC arm, 52% of patients received cisplatin with concurrent RT while 48% patients received RT alone.

The trial demonstrated a statistically significant improvement in EFS for patients randomized to the KEYTRUDA arm compared to those randomized to the standard of care (SOC) arm at the first pre-specified interim analysis. Table 72 and Figure 13 summarize efficacy results in KEYNOTE-689 for patients with HNSCC CPS $\geq$ 1.

Table 72 Efficacy Results for Perioperative KEYTRUDA with adjuvant RT with or without cisplatin in Patients with HNSCC CPS $\geq$ 1 in KEYNOTE-689

Endpoint	KEYTRUDA 200 mg every 3 weeks with RT with or without cisplatin n=347	RT with or without cisplatin n=335
EFS		
Number of events, n (%)	128 (37%)	156 (47%)
Median in months* (95% CI)	59.7 (37.9, NR)	29.6 (19.5, 41.9)
Hazard ratio† (95% CI)	0.70 (0.55, 0.89)	
p-Value‡	0.00140	

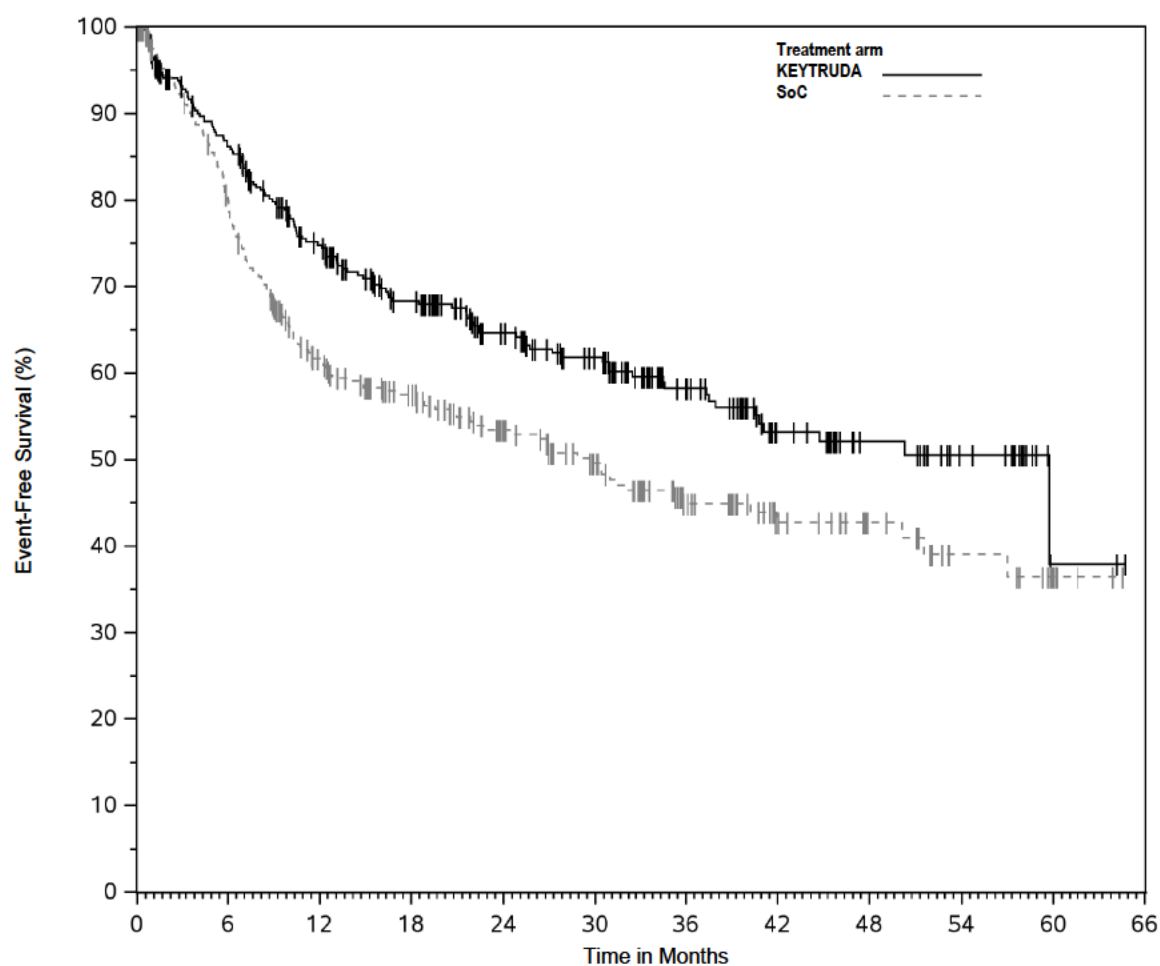
* From product-limit (Kaplan-Meier) method for censored data.

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site and tumor stage.

‡ One-sided p-value based on log-rank test stratified by primary tumor site and tumor stage. Compared to a one-sided p-value boundary of 0.0124

NR = not reached

Figure 13: Kaplan-Meier Curve for Event-free Survival for KEYTRUDA in Patients with HNSCC CPS ≥1 in KEYNOTE-689



Number at Risk												
KEYTRUDA	347	274	220	181	147	122	83	51	33	21	2	0
SoC	335	245	170	140	104	82	56	36	25	15	7	0

While OS results were not mature at this interim analysis, with 76% of pre-specified OS events in the CPS≥1 population, no trend towards a detriment was observed.

Hypopharyngeal Tumors

In an exploratory subgroup analysis of patients with PD-L1-positive (CPS ≥ 1) hypopharyngeal tumors who were randomized (n=51), the EFS HR was 2.28 (95% CI: 0.79, 6.56). Among these patients, 23 patients in the KEYTRUDA arm received surgery, of which 17 patients (74%) had R0 resections. On the SOC arm, 23 patients received surgery, of which 20 (87%) had R0 resections.

Oral Cavity, Oropharyngeal and Laryngeal Tumors

In an exploratory subgroup analysis of patients with PD-L1 positive (CPS ≥ 1) oral cavity, oropharyngeal and laryngeal tumors who received surgery (n=555), 91% of patients on the KEYTRUDA arm had R0 resections while 85% of patients on the SOC arm had R0 resections.

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 $\geq 50\%$ 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/m² intravenously every 3 weeks, and FU 1000 mg/m²/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)
- Cetuximab 400 mg/m² intravenously as the initial dose then 250 mg/m² intravenously once weekly, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m² intravenously every 3 weeks, and FU 1000 mg/m²/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 $\geq 50\%$, 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 73 and Figure 14 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

**Table 73: 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

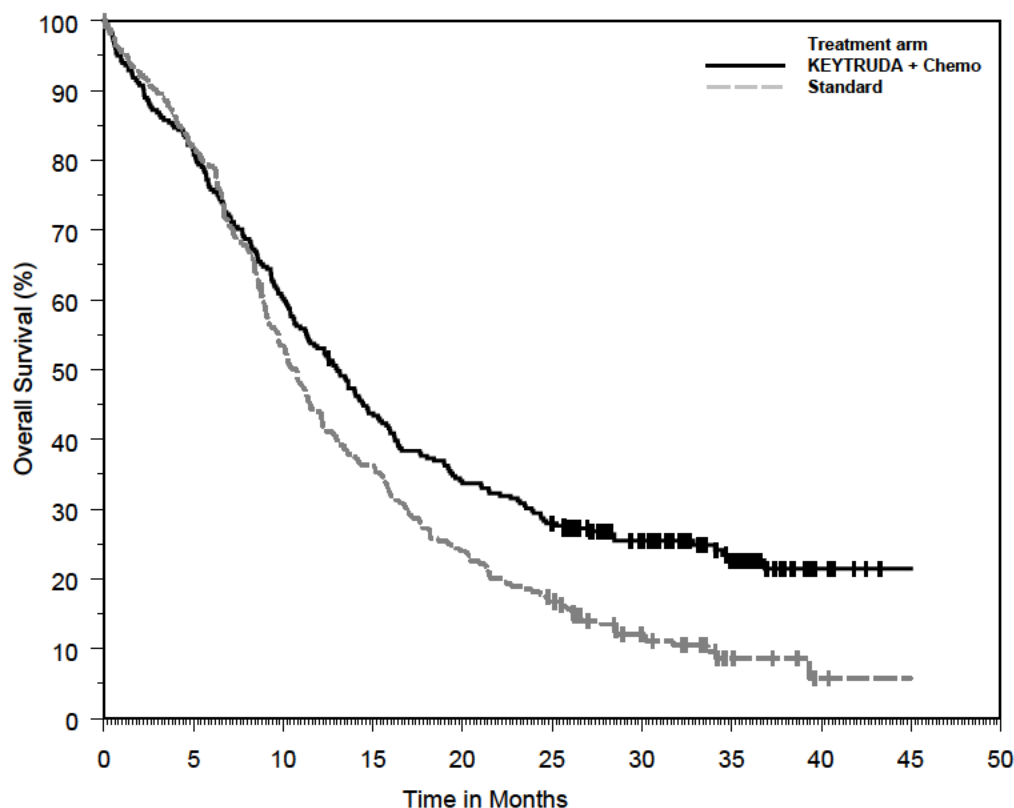
† Based on the stratified Cox proportional hazard model

‡ 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 14: 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
Standard:	278	227	147	100	66	45	23	6	1	0

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

First-line treatment of metastatic or unresectable, recurrent HNSCC for Tumors Expressing PD-L1 (CPS ≥ 1) as a single agent

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 74 summarizes efficacy results for KEYTRUDA as a single agent in the subgroups of patients with CPS ≥ 1 HNSCC and CPS ≥ 20 HNSCC. Figure 15 summarizes the OS results in the subgroup of patients with CPS ≥ 1 HNSCC.

Table 74: 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	Cetuximab Platinum FU	KEYTRUDA 200 mg every 3 weeks	Cetuximab Platinum FU
	n=257	n=255	n=133	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

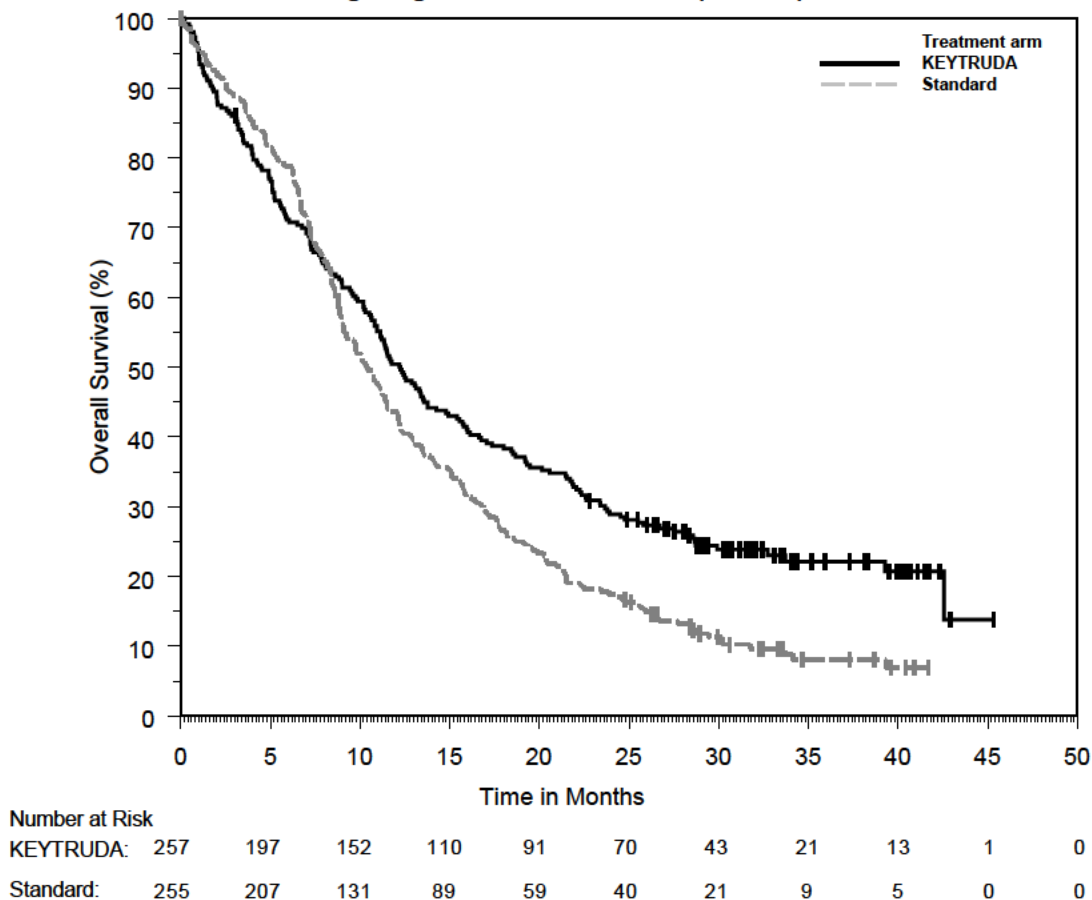
[‡] Based on a stratified log-rank test

[§] 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 15: Kaplan-Meier Curve for Overall Survival for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥ 1)*



* 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 75 and Figure 16.

Table 75: 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.

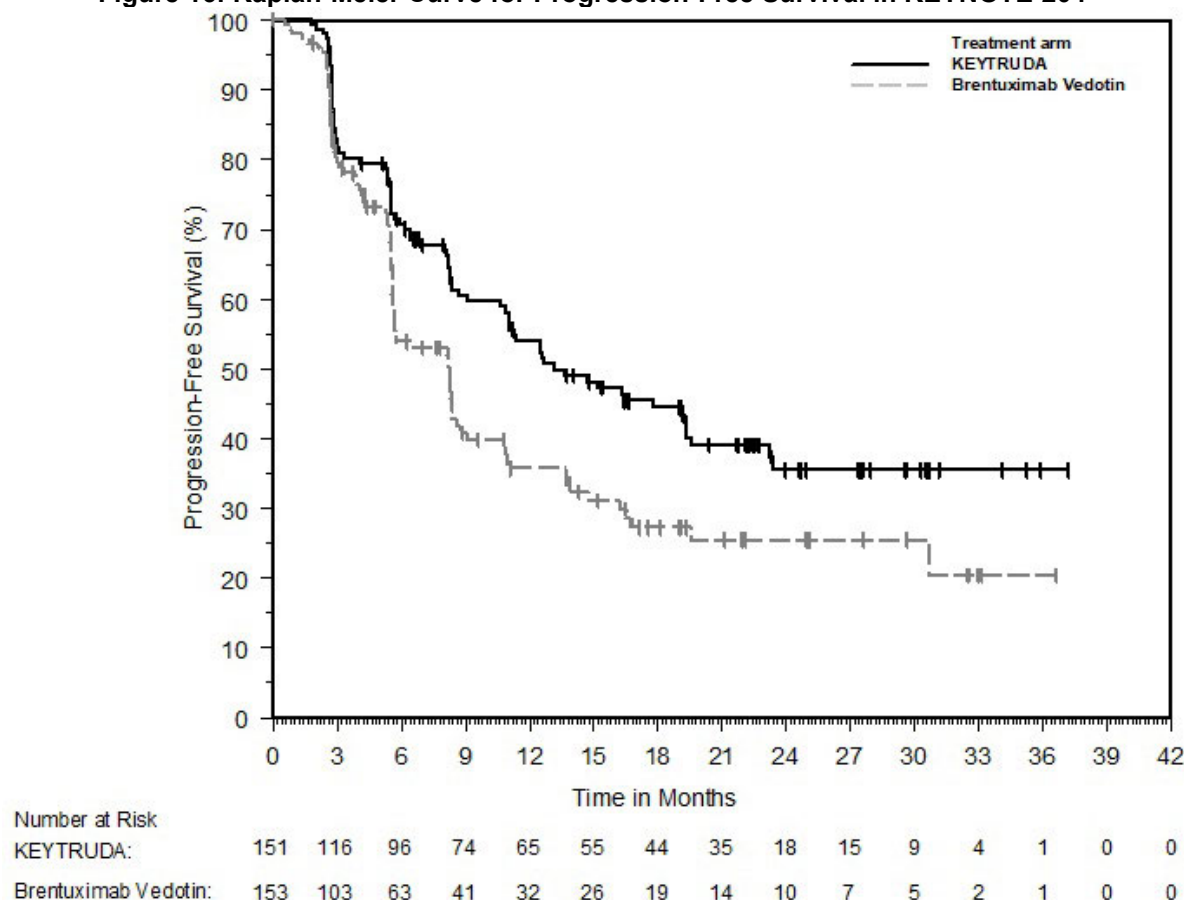
† Based on the stratified Cox proportional hazard model.

‡ 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 16: 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 76.

Table 76: 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 77.

Table 77: 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/m² on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m² 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 78 and Figures 17 and 18 summarize the efficacy results for KEYNOTE-A39.

Table 78: 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 17: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A39

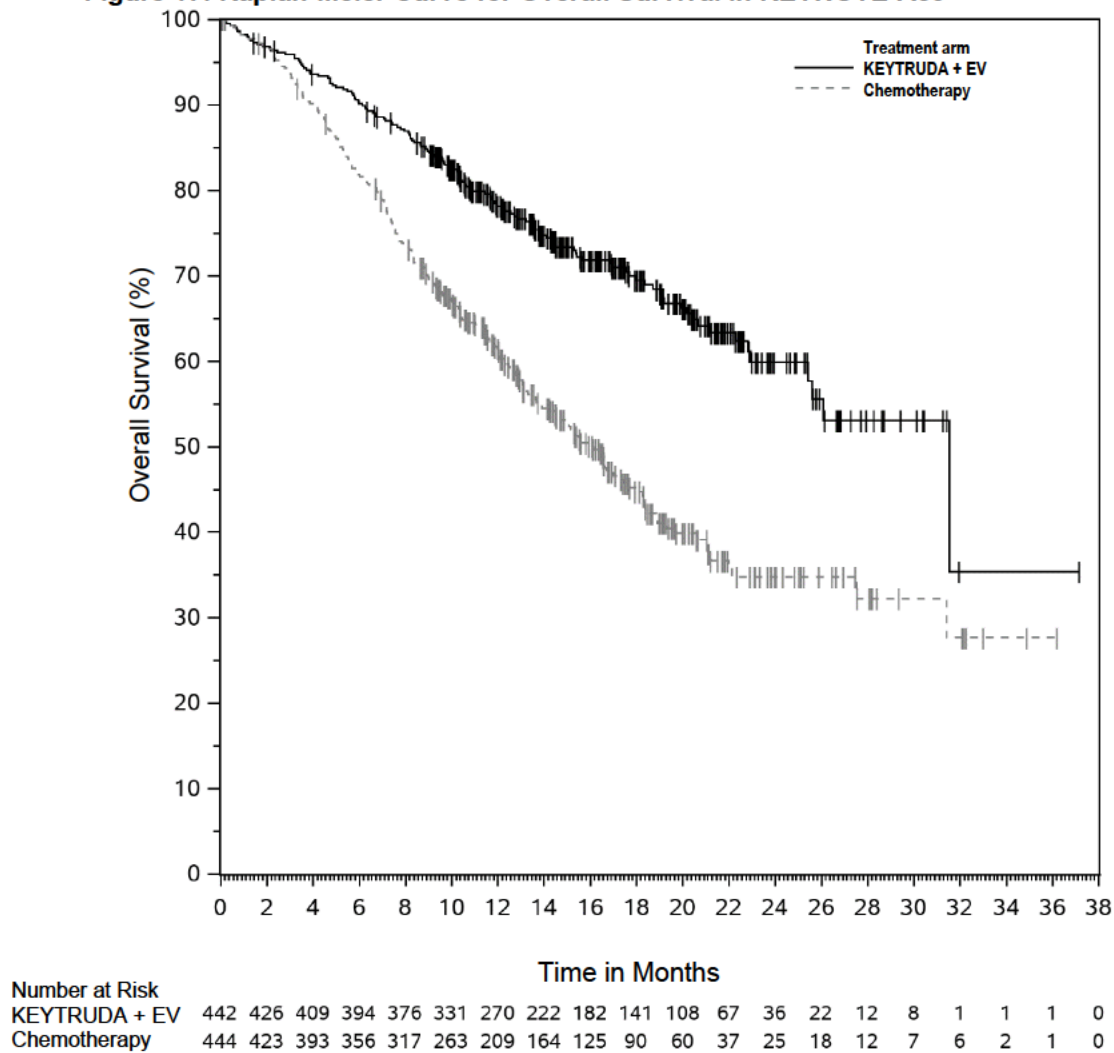
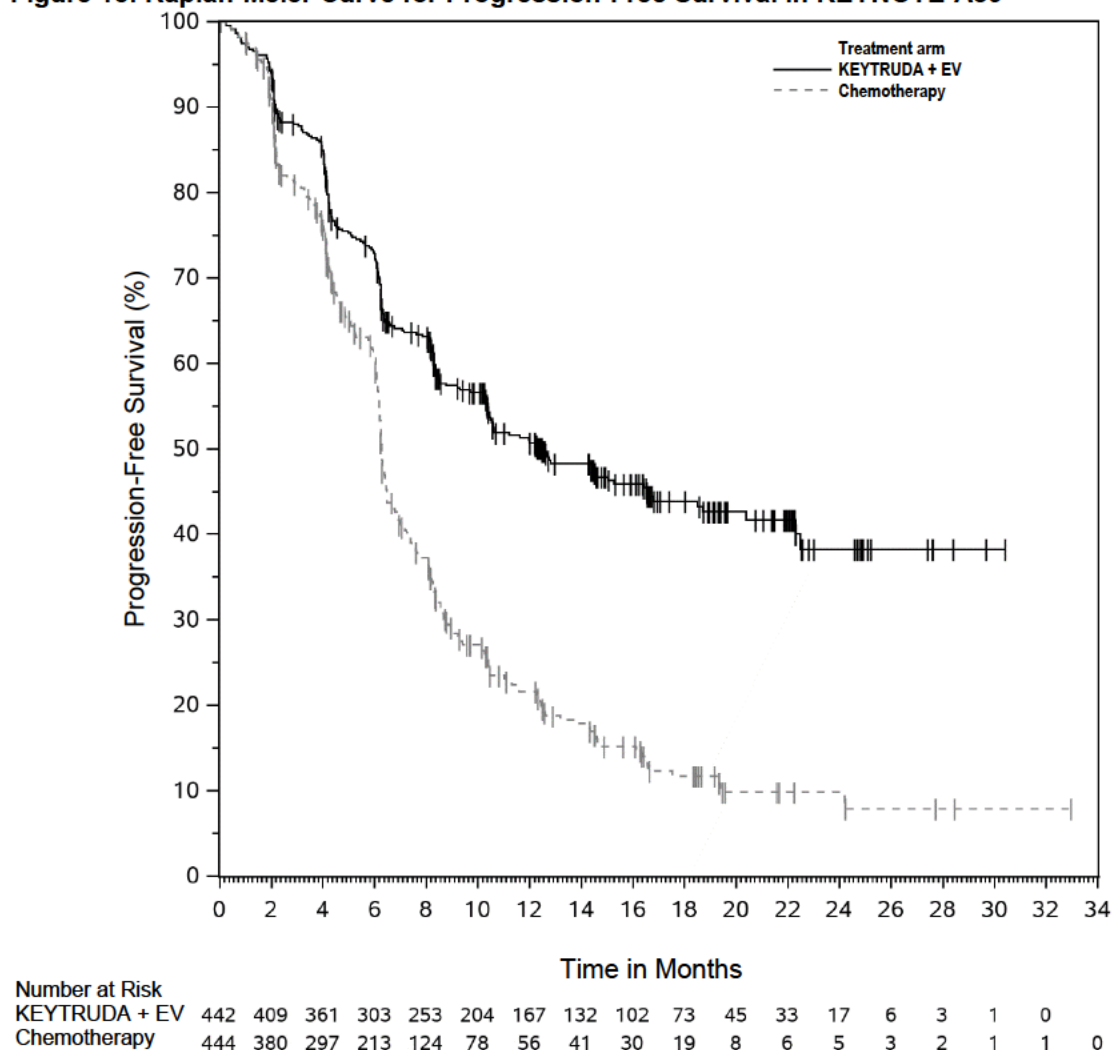


Figure 18: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A39



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) $\geq 8\%$ or HbA1c $\geq 7\%$ 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 79 below.

Table 79: 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 80.

Table 80: 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/m² (n=90), docetaxel 75 mg/m² (n=92), or vinflunine 320 mg/m² (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 81 and Figure 19 summarize the efficacy results for KEYNOTE-045.

Table 81: Efficacy Results in KEYNOTE-045

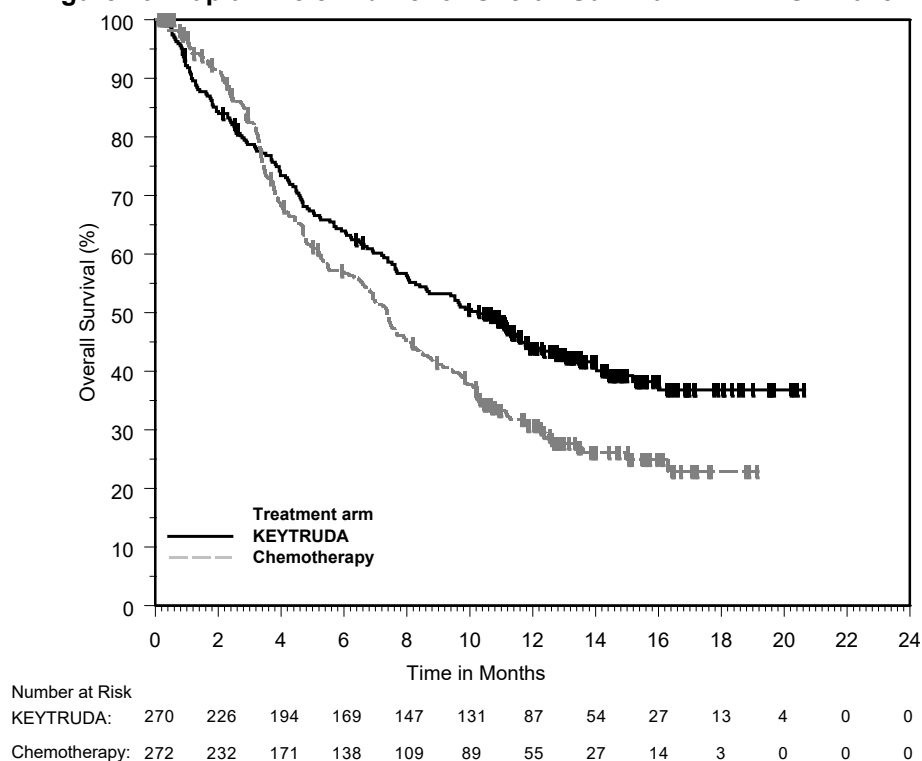
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (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 19: 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 82.

Table 82: 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 83 and 84.

Table 83: 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 84: 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/m², leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²), and FU 400 mg/m² bolus on Day 1, then FU 2400 mg/m² over 46–48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m² on first infusion, then 250 mg/m² weekly.
- FOLFIRI (irinotecan, leucovorin, and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m², leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²), and FU 400 mg/m² bolus on Day 1, then FU 2400 mg/m² over 46–48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m² on first infusion, then 250 mg/m² 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 85 and Figure 20 summarize the key efficacy measures for KEYNOTE-177.

Table 85: 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 months ^p	75%	37%
% with duration ≥24 months ^p	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

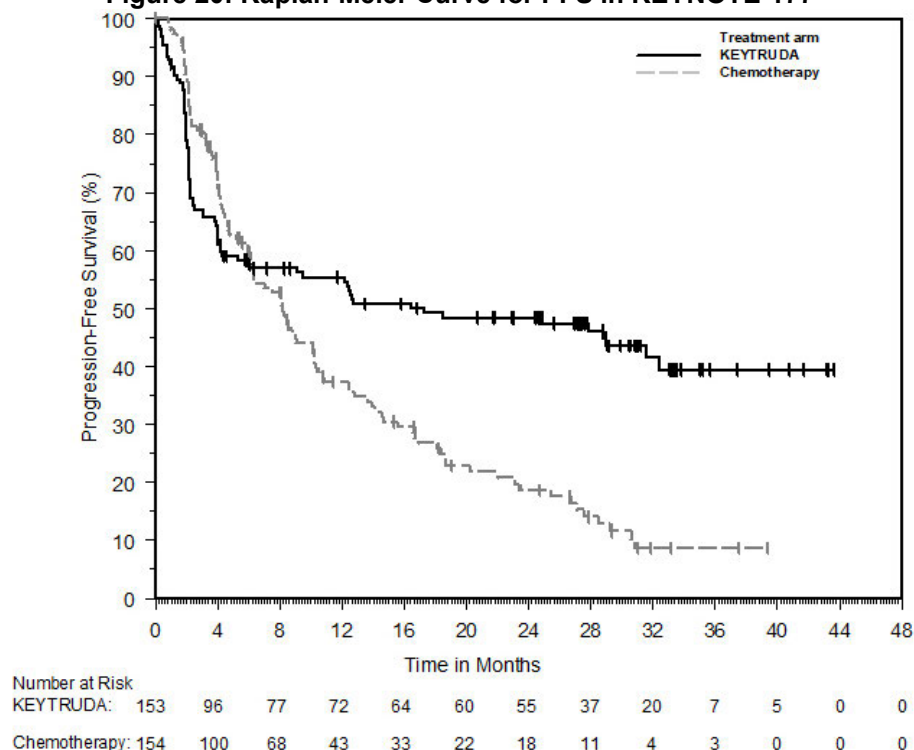
Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm

^p Based on observed duration of response

+ Denotes ongoing response

NR = not reached

Figure 20: 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 for Tumors Expressing PD-L1 (CPS $\geq$ 1)

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 $\geq$ 1 or CPS <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m² for up to 6 cycles and 5-FU 800 mg/m²/day for 5 days (FP) or oxaliplatin 130 mg/m² up to 6-8 cycles and capecitabine 1000 mg/m² 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/m² for up to 6 cycles and 5-FU 800 mg/m²/day for 5 days (FP) or oxaliplatin 130 mg/m² up to 6-8 cycles and capecitabine 1000 mg/m² 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 .

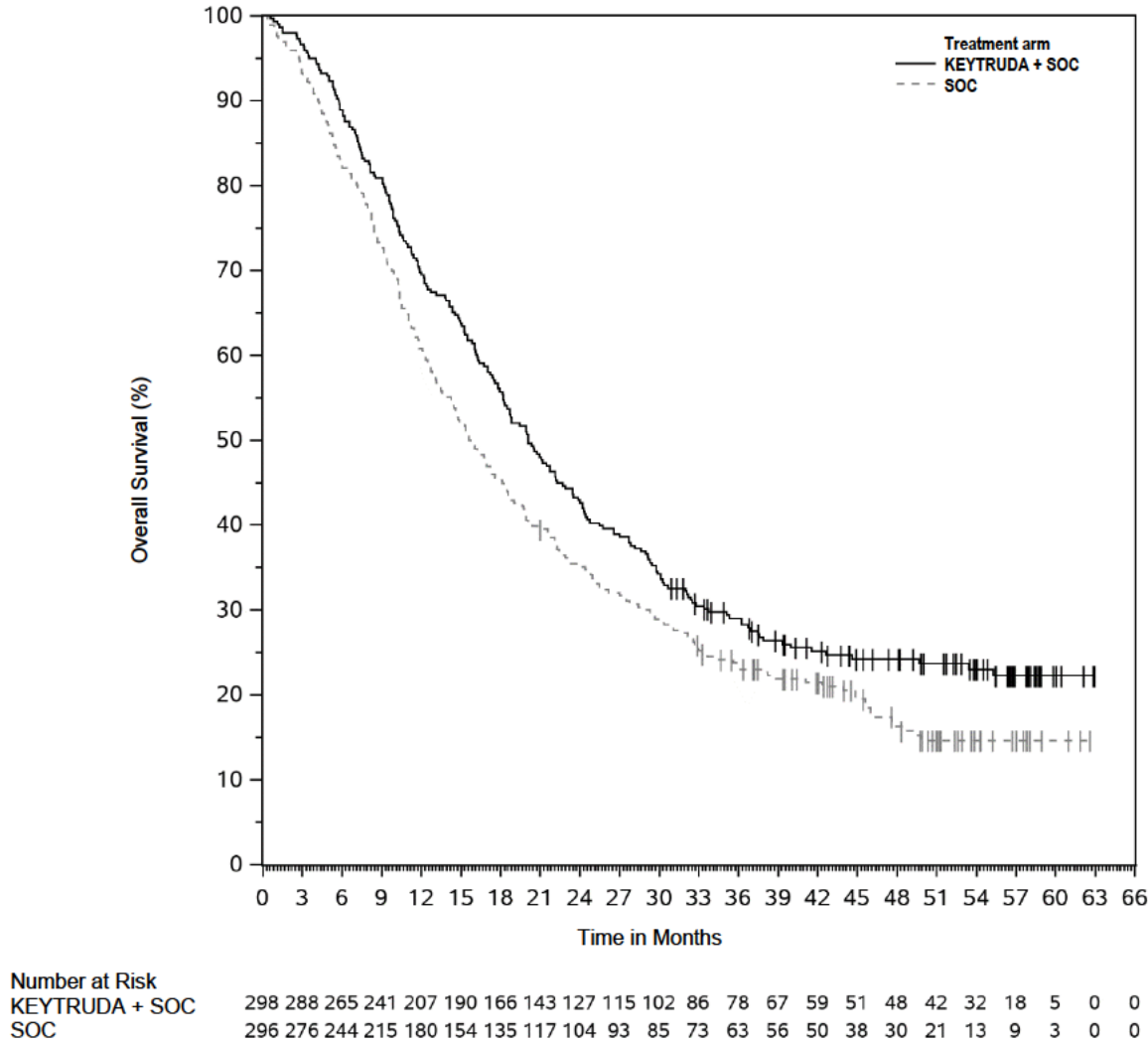
Efficacy results at the final analysis for the subgroup of patients whose tumors expressed PD-L1 with a CPS ≥ 1 are summarized in Table 86 and Figure 21.

Table 86: 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)	11.3 (9.9, 13.7)	9.6 (7.1, 11.2)
Range in months	1.1+, 60.8+	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 21: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-811 (CPS ≥ 1)



First-line Treatment of Locally Unresectable or Metastatic HER2-Negative Gastric or Gastroesophageal Junction Adenocarcinoma for Tumors Expressing PD-L1 (CPS ≥ 1)

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/m² and 5-FU 800 mg/m²/day for 5 days (FP) or oxaliplatin 130 mg/m² and capecitabine 1000 mg/m² bid for 14 days (CAPOX).
- Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m² and 5-FU 800 mg/m²/day for 5 days (FP) or oxaliplatin 130 mg/m² and capecitabine 1000 mg/m² 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.

Among 1,579 patients, 1,235 (78%) had tumors expressing PD-L1 CPS ≥ 1. The population characteristics in patients with PD-L1 CPS ≥ 1 expressing tumors were: median age of 62 years (range: 24 to 86), 40% age 65 or older; 70% male and 30% female; 55% White, 33% Asian, 4.6% Multiple, 4.3% 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-six percent of patients had metastatic disease (Stage IV) and 3% had locally advanced unresectable disease. Five percent (n=66) 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; however, an exploratory analysis of OS in the PD-L1 CPS <1 population showed a HR of 0.92 (95% CI 0.73, 1.17) 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 for patients whose tumors expressed PD-L1 CPS ≥1 and CPS ≥10 are summarized in Table 87 and Figures 22 and 23.

Table 87: Efficacy Results* for KEYNOTE-859

Endpoint	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
	CPS ≥1		CPS ≥10	
OS				
Number (%) of patients with event	464 (75)	526 (85)	188 (67)	226 (83)
Median in months (95% CI)	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)	0.74 (0.65, 0.84)		0.65 (0.53, 0.79)	
p-Value (stratified log-rank) [‡]	<0.0001		<0.0001	
PFS				
Number (%) of patients with event	443 (72%)	483 (78%)	190 (68)	210 (77)
Median in months (95% CI)	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)	0.72 (0.63, 0.82)		0.62 (0.51, 0.76)	
p-Value (stratified log-rank) [‡]	<0.0001		<0.0001	
Objective Response Rate				
ORR [§] (95% CI)	52% (48, 56)	43% (39, 47)	61% (55, 66)	43% (37, 49)
Complete response rate	10%	6%	13%	5%
Partial response rate	42%	37%	48%	38%
p-Value [¶]	0.0004		<0.0001	
Duration of Response	n=322	n=263	n=169	n=117
Median in months [#] (95% CI)	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+, 34.2+	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 22: Kaplan-Meier Curve for Overall Survival in KEYNOTE-859 (CPS≥1)

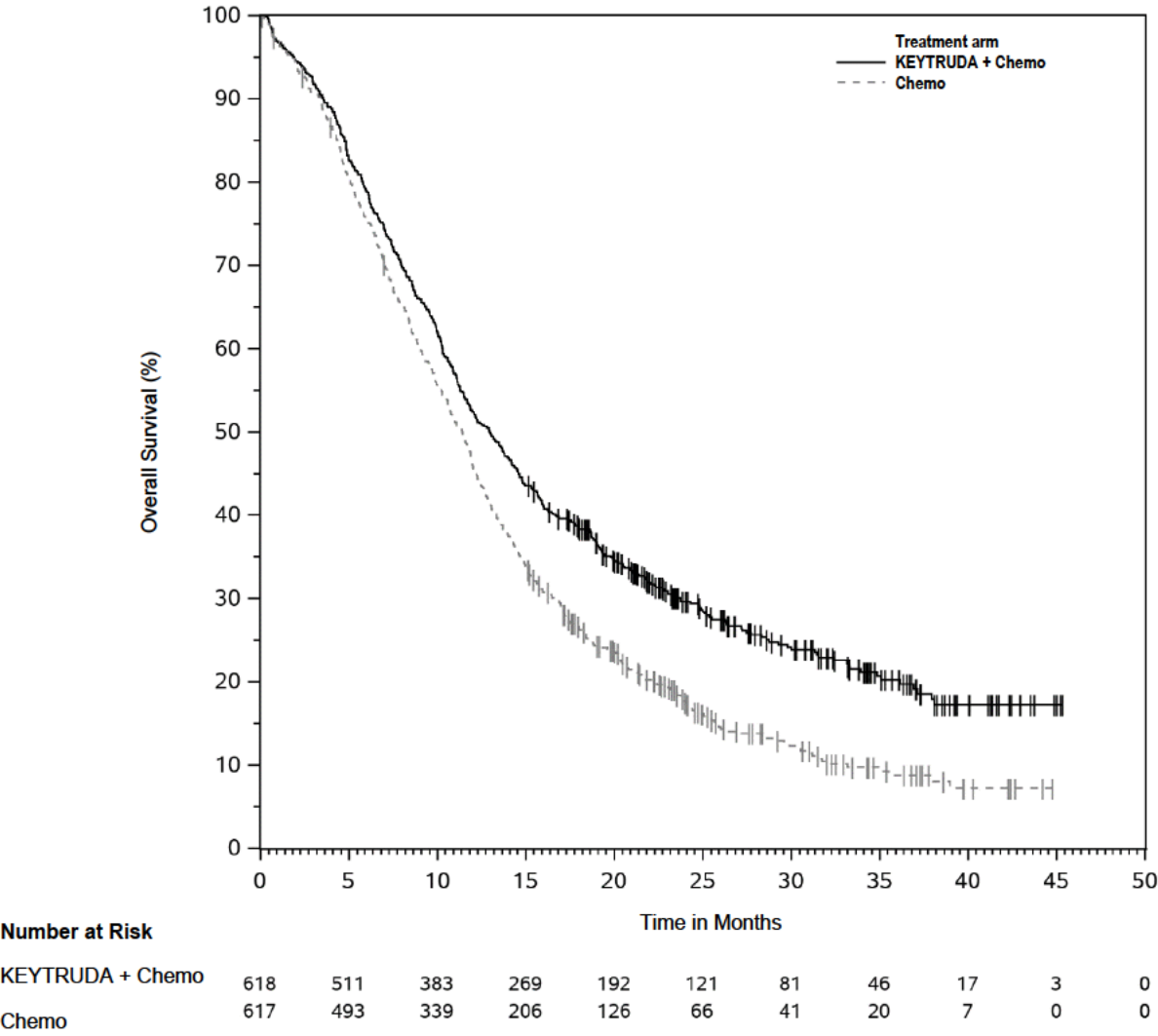
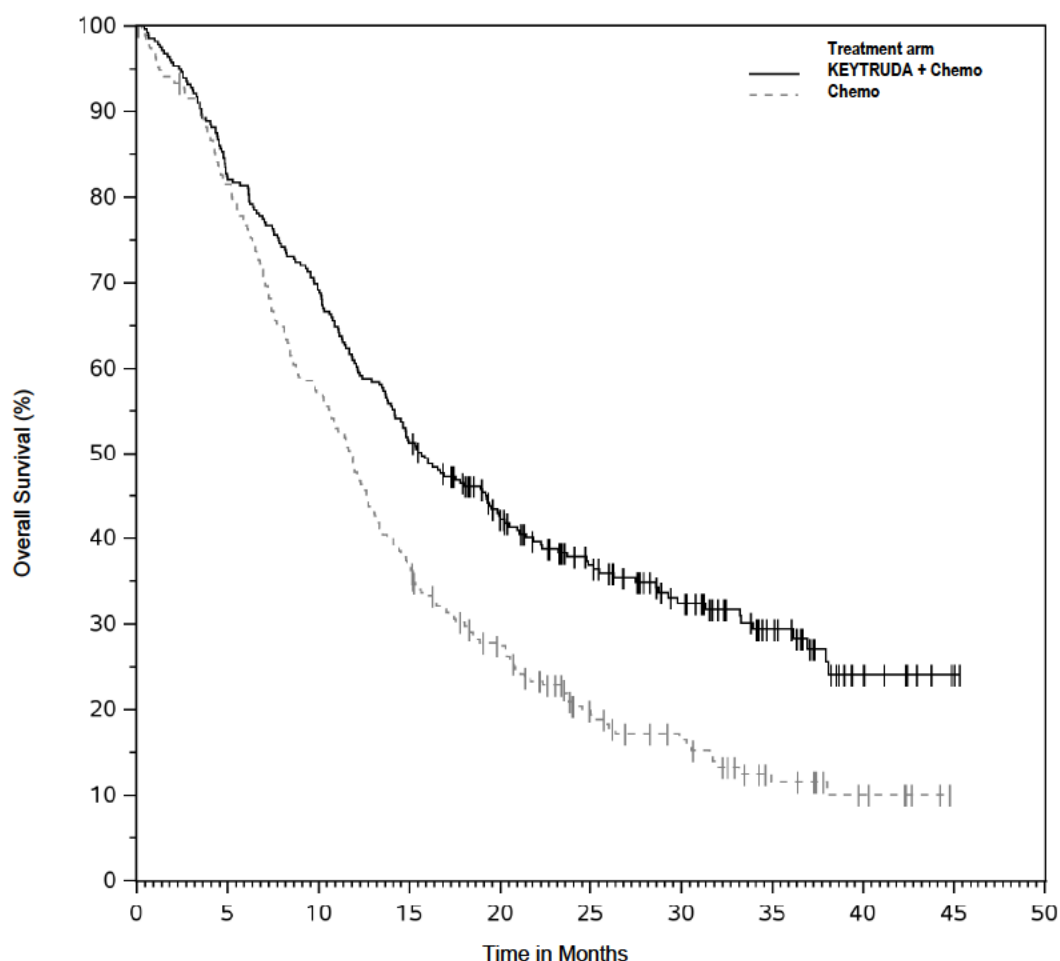


Figure 23: Kaplan-Meier Curve for Overall Survival in KEYNOTE-859 (CPS $\geq$ 10)



Number at Risk											
KEYTRUDA + Chemo	279	230	193	143	104	76	52	30	10	2	0
Chemo	272	220	154	99	67	37	26	12	6	0	0

An exploratory analysis of OS in the 74 patients with MSI-H tumors irrespective of PD-L1 status showed a HR of 0.34 (95% CI: 0.18, 0.66).

14.11 Esophageal Cancer

First-line Treatment of Locally Advanced Unresectable or Metastatic Esophageal/Gastroesophageal Junction Cancer for Tumors Expressing PD-L1 (CPS $\geq$ 1)

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

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. Additional analyses of efficacy outcome measures were also conducted based on PD-L1 CPS ≥ 1 .

Among 749 patients, 647 (86%) had tumors expressing PD-L1 CPS ≥ 1 . The study population characteristics in patients with PD-L1 CPS ≥ 1 expressing tumors were: median age of 63 years (range: 27 to 89), 41% age 65 or older; 83% male; 36% White, 54% Asian, and 1% Black; 40% had an ECOG PS of 0 and 59% had an ECOG PS of 1. Ninety-one percent had M1 disease and 9% had M0 disease. Seventy-four percent had a tumor histology of squamous cell carcinoma, and 26% 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; however, an exploratory analysis of OS in the PD-L1 CPS < 1 population showed an HR of 0.96 (0.59, 1.55), 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 .

Table 88 and Figures 24 and 25 summarize the efficacy results for KEYNOTE-590 in patients whose tumors expressed PD-L1 CPS ≥ 1 and CPS ≥ 10 .

Table 88: 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=320	Placebo Cisplatin FU n=327	KEYTRUDA 200 mg every 3 weeks Cisplatin FU n=186	Placebo Cisplatin FU n=197
CPS ≥ 1			CPS ≥ 10	
OS				
Number (%) of events	222 (69)	271 (83)	124 (67)	165 (84)
Median in months (95% CI)	12.7 (10.5, 14.4)	9.8 (8.8, 10.8)	13.5 (11.1, 15.6)	9.4 (8.0, 10.7)
Hazard ratio* (95% CI)	0.71 (0.59, 0.84)		0.62 (0.49, 0.78)	
p-Value†			<0.0001	
PFS				
Number of events (%)	252 (79)	291 (89)	140 (75)	174 (88)
Median in months (95% CI)	6.3 (6.2, 7.1)	5.7 (4.6, 6.0)	7.5 (6.2, 8.2)	5.5 (4.3, 6.0)
Hazard ratio* (95% CI)	0.62 (0.52, 0.73)		0.51 (0.41, 0.65)	
p-Value†			<0.0001	
Objective Response Rate				
ORR, %‡ (95% CI)	45 (40, 51)	29 (24, 34)	51 (44, 59)	27 (21, 34)
Number (%) of complete responses	19 (6)	9 (2.8)	11 (6)	5 (2.5)
Number (%) of partial responses	126 (39)	85 (26)	84 (45)	48 (24)
Duration of Response				
Median in months (range)	8.6 (1.2+, 31.0+)	5.8 (1.5+, 25.0+)	10.4 (1.9+, 28.9+)	5.6 (1.5+, 25.0+)

* Based on the stratified Cox proportional hazard model

† Based on a stratified log-rank test; p-Value for CPS ≥ 1 not included (not pre-specified subgroup)

‡ Confirmed complete response or partial response

Figure 24: Kaplan-Meier Curve for Overall Survival in KEYNOTE-590 (CPS ≥ 1)

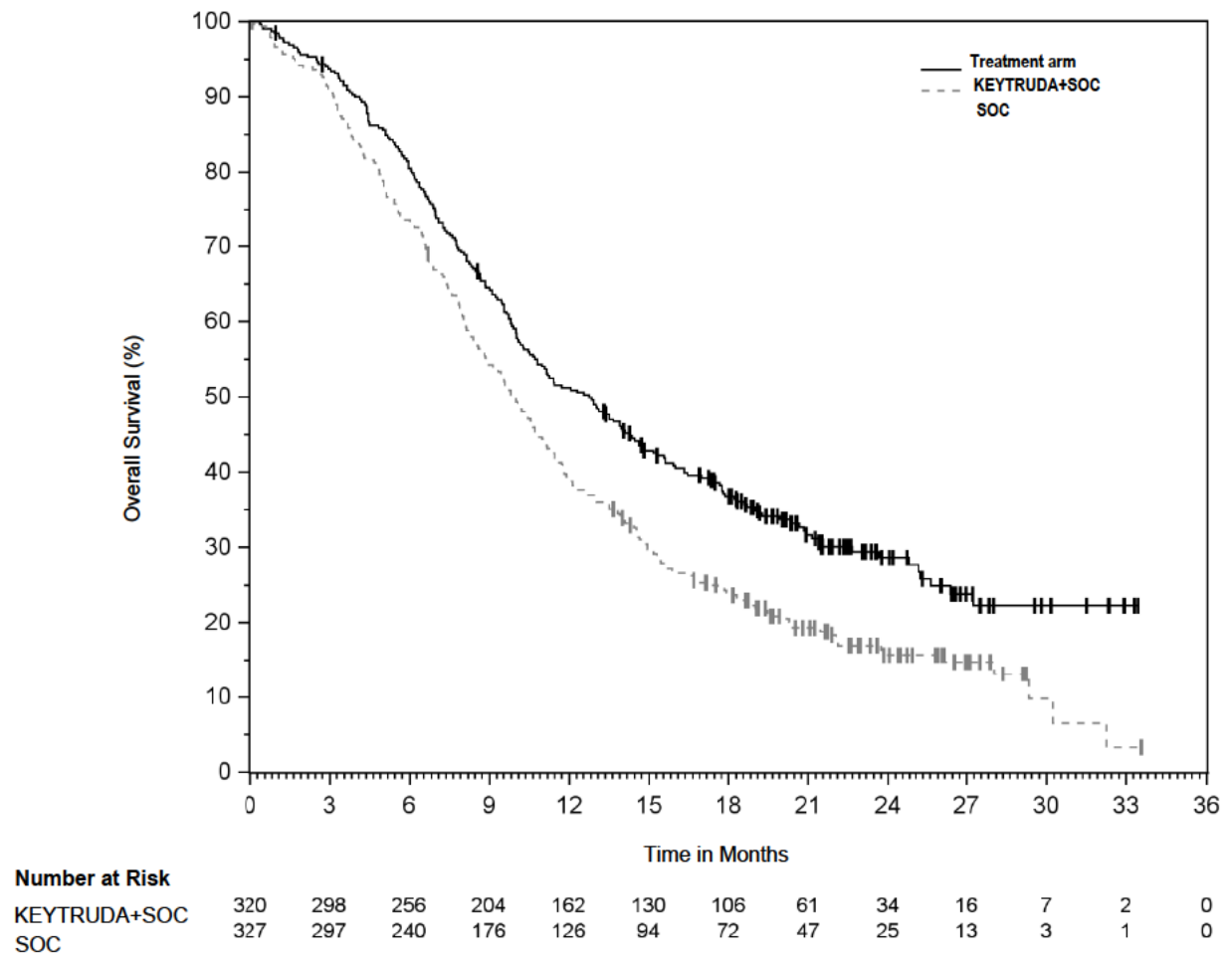
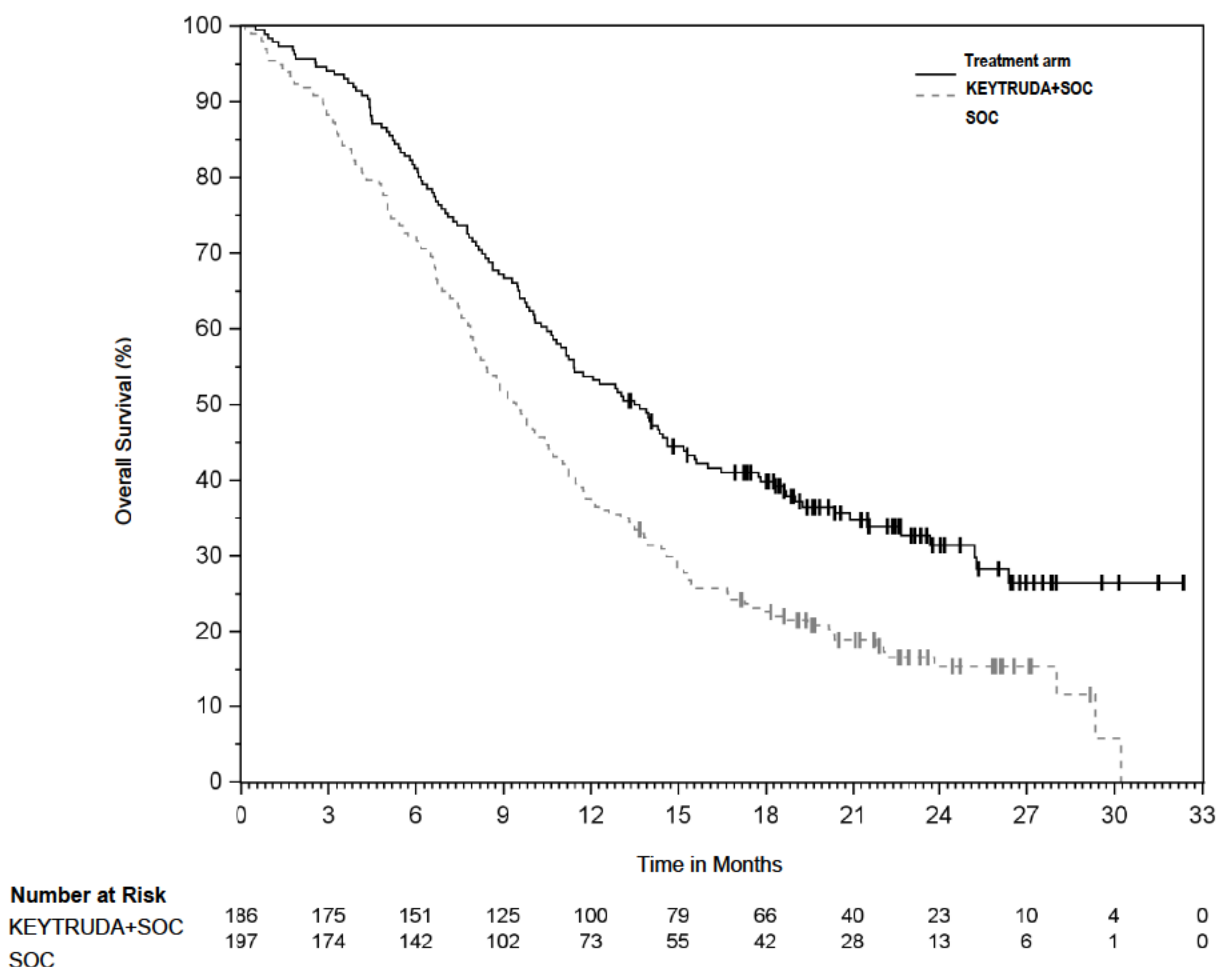


Figure 25: Kaplan-Meier Curve for Overall Survival in KEYNOTE-590 (CPS ≥ 10)



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 for Tumors Expressing PD-L1 (CPS ≥ 10)

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/m² on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m² every 3 weeks, or irinotecan 180 mg/m² 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.

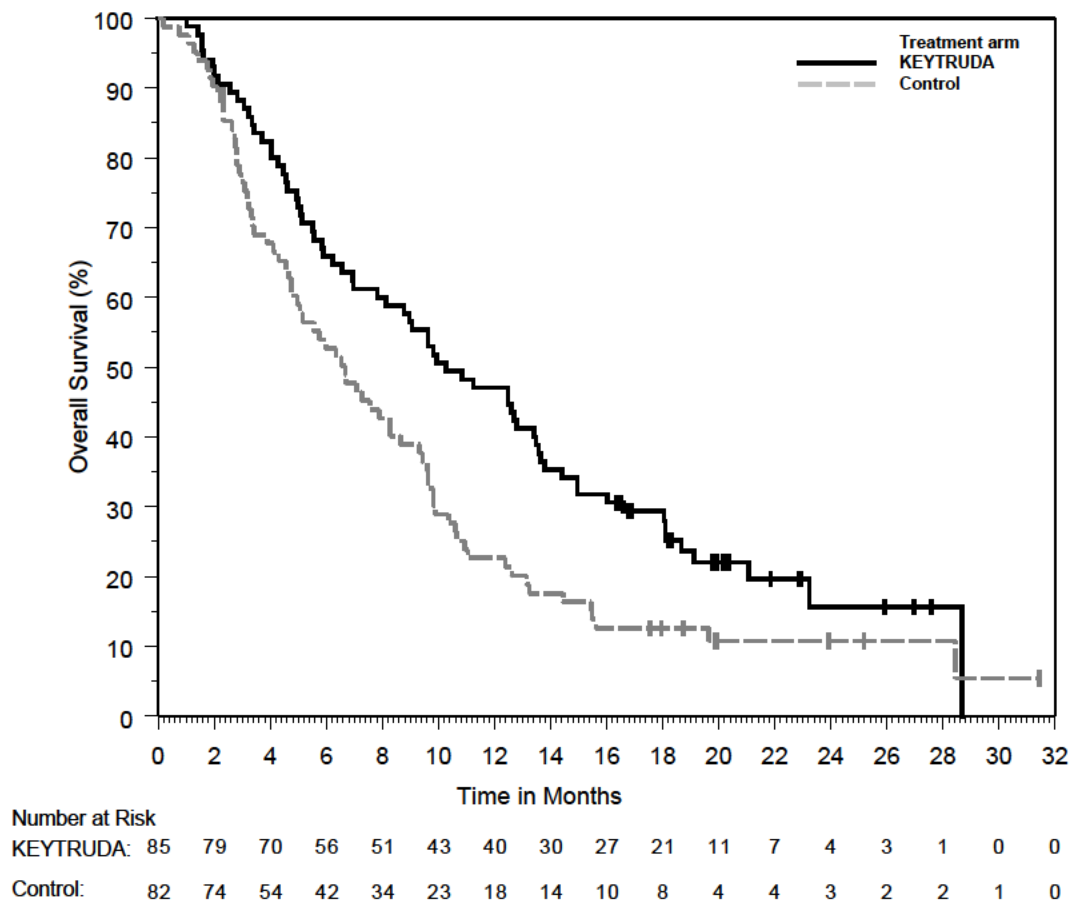
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 89 and Figure 26 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10.

Table 89: 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 26: 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

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 599 patients with FIGO 2014 Stage III-IVA disease (tumor involves the lower third of the vagina or the pelvic sidewall, or there is hydronephrosis/non-functioning kidney or spread to adjacent pelvic organs, all without spread to distant organs), and 459 patients with FIGO 2014 Stage IB2-IIB disease (clinical lesion >4 cm confined to the cervix, or clinical lesion of any size with extension beyond the uterus, but which has not extended to the pelvic wall or lower third of the vagina) with positive nodes. 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/m² 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/m² 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 599 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, 2% Black; 38% Hispanic or Latino; 68% ECOG PS 0 and 32% ECOG PS 1; 93% with CPS ≥1; 71% had positive pelvic and/or positive para-aortic lymph node(s) and 29% had neither positive pelvic nor para-aortic lymph node(s); 83% had squamous cell carcinoma and 17% had non-squamous histology. Regarding radiation, 86% of patients received IMRT or VMAT EBRT, and the median EQD2 dose was 87 Gy (range: 7 to 114).

The trial demonstrated statistically significant improvements in PFS and OS in the ITT population. Exploratory analyses of PFS and OS by the stratification factor of FIGO 2014 stage showed that the improvement in the ITT population was primarily attributed to the results seen in the patients with FIGO 2014 Stage III-IVA disease. Table 90 and Figures 27 and 28 summarize the results in exploratory subgroup analyses of 599 patients with FIGO 2014 Stage III-IVA disease.

Table 90: 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=295	Placebo with CRT n=304
OS*		
Number of patients with event (%)	61 (21)	90 (30)
Hazard ratio [†] (95% CI)	0.65 (0.47, 0.90)	
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, 0.81)	

*Results at the time of pre-specified final analysis for OS

[†] Based on the unstratified Cox proportional hazard model

[‡] Results at the time of first pre-specified interim analysis for PFS

CRT = Chemoradiotherapy

NR = not reached

Figure 27: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)

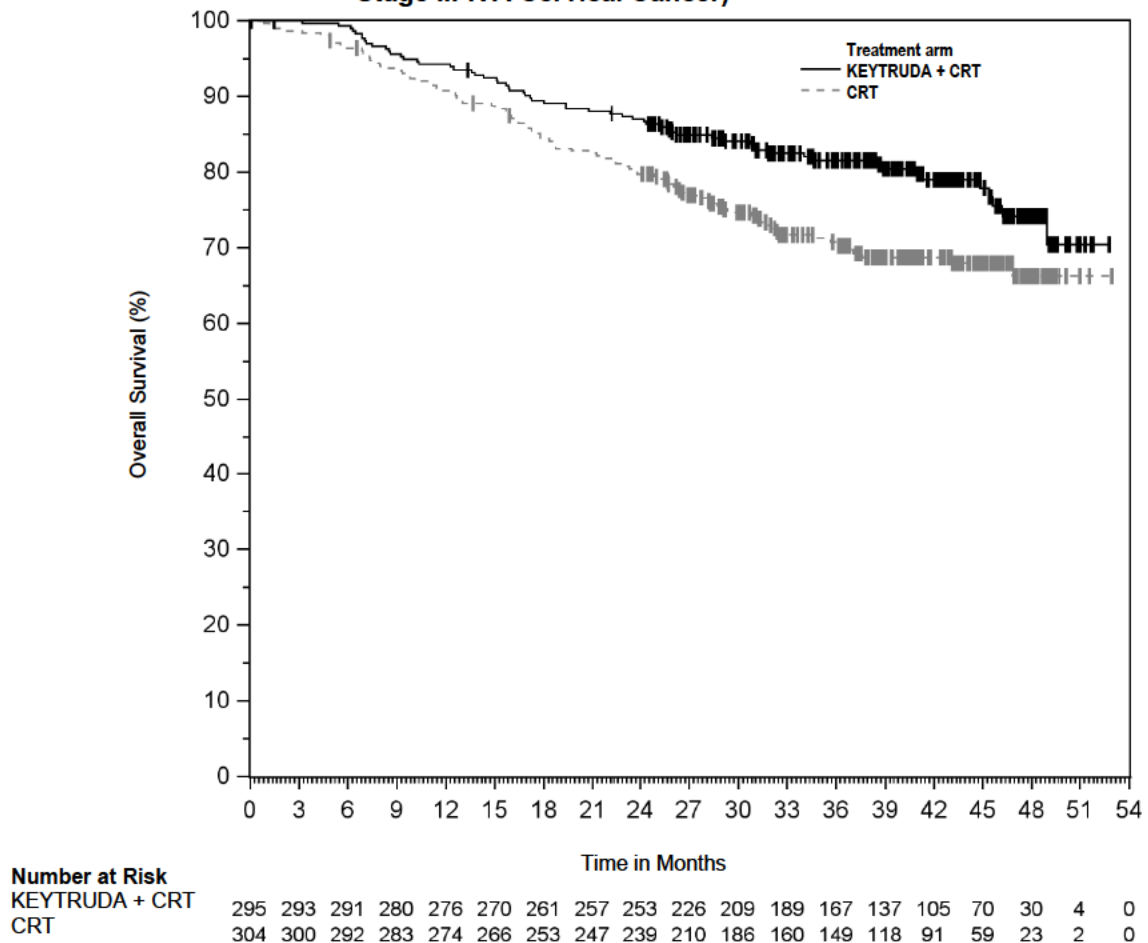
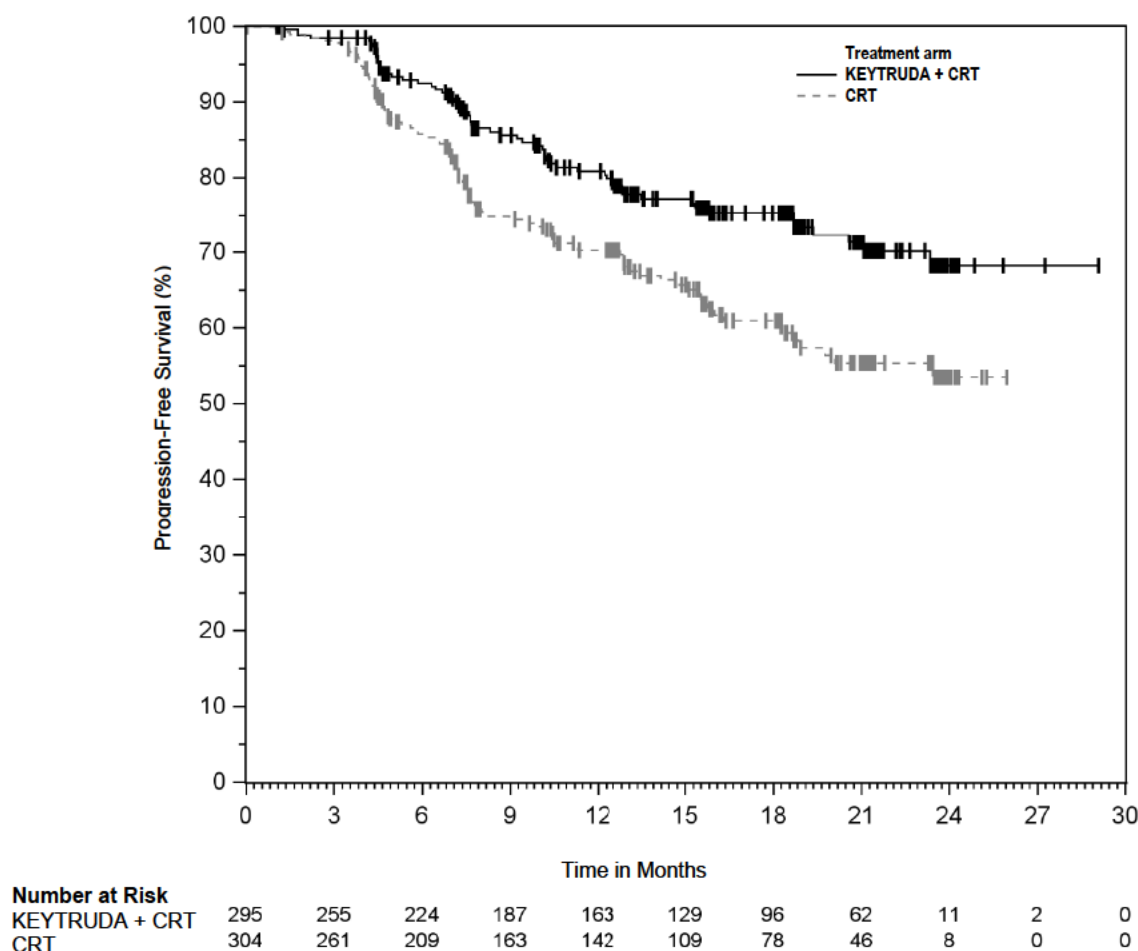


Figure 28: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)



Persistent, Recurrent, or Metastatic Cervical Cancer for Tumors Expressing PD-L1 (CPS ≥ 1)

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/m² + cisplatin 50 mg/m²
2. Paclitaxel 175 mg/m² + cisplatin 50 mg/m² + bevacizumab 15 mg/kg

3. Paclitaxel 175 mg/m² + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m² + 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 91 and Figure 29 summarize the key efficacy measures for KEYNOTE-826 for patients with tumors expressing PD-L1 (CPS ≥ 1).

Table 91: 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)

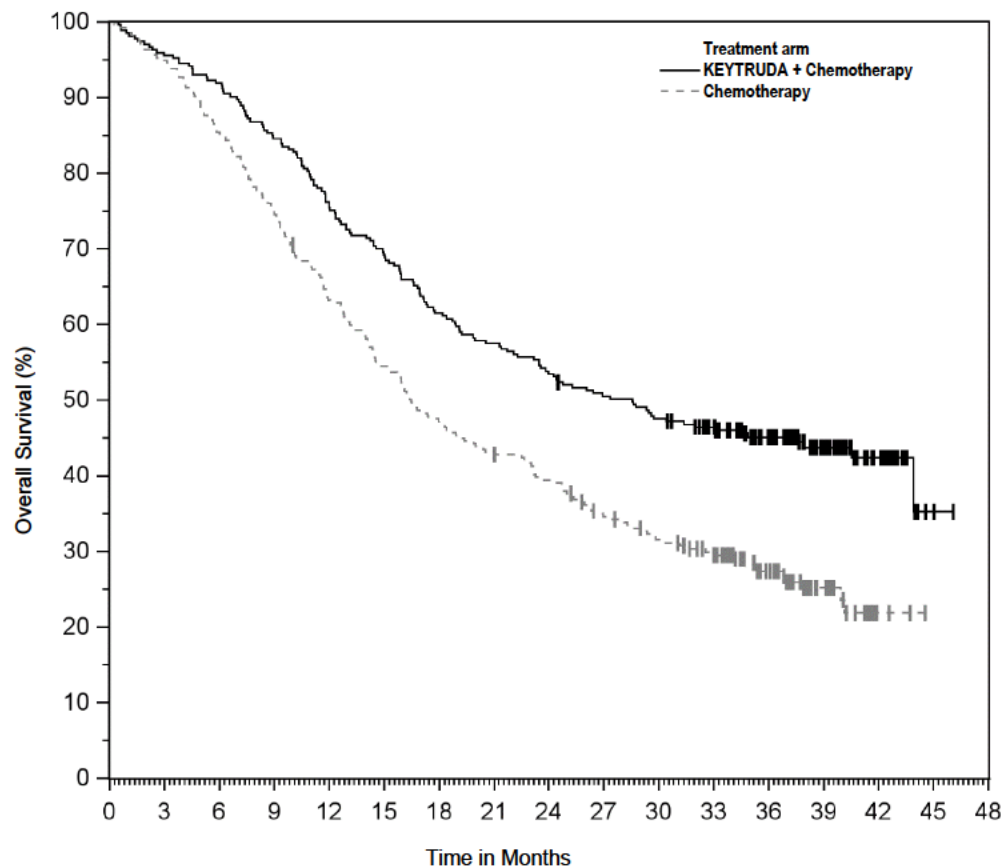
[§] p-Value (one-sided) is compared with the allocated alpha of 0.0014 for this interim analysis (with 82% of the planned number of events for final analysis)

[¶] Response: Best objective response as confirmed complete response or partial response

+ Denotes ongoing response

NR = not reached

Figure 29: 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 for Tumors Expressing PD-L1 (CPS ≥ 1)

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

Table 92: 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 <10⁴ 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%).

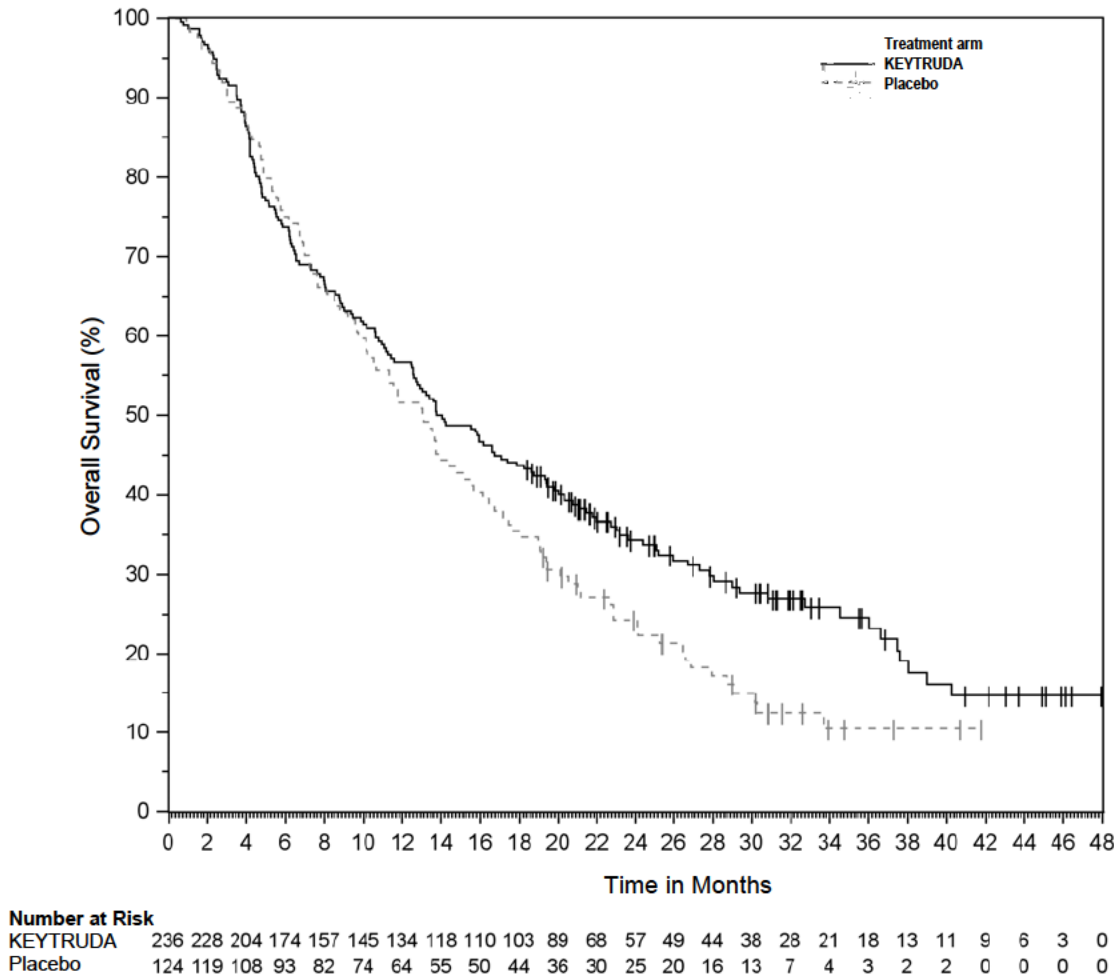
KEYNOTE-394 demonstrated improved OS in patients with HCC secondary to hepatitis B randomized to KEYTRUDA compared with placebo. Efficacy results are summarized in Table 93 and Figure 30.

Table 93: 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 30: 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/m² and cisplatin 25 mg/m² on Day 1 and Day 8 every 3 weeks, or placebo on Day 1 plus gemcitabine 1000 mg/m² and cisplatin 25 mg/m² 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 94 and Figure 31 summarize the efficacy results for KEYNOTE-966.

Table 94: 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 [Ⓟ] (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

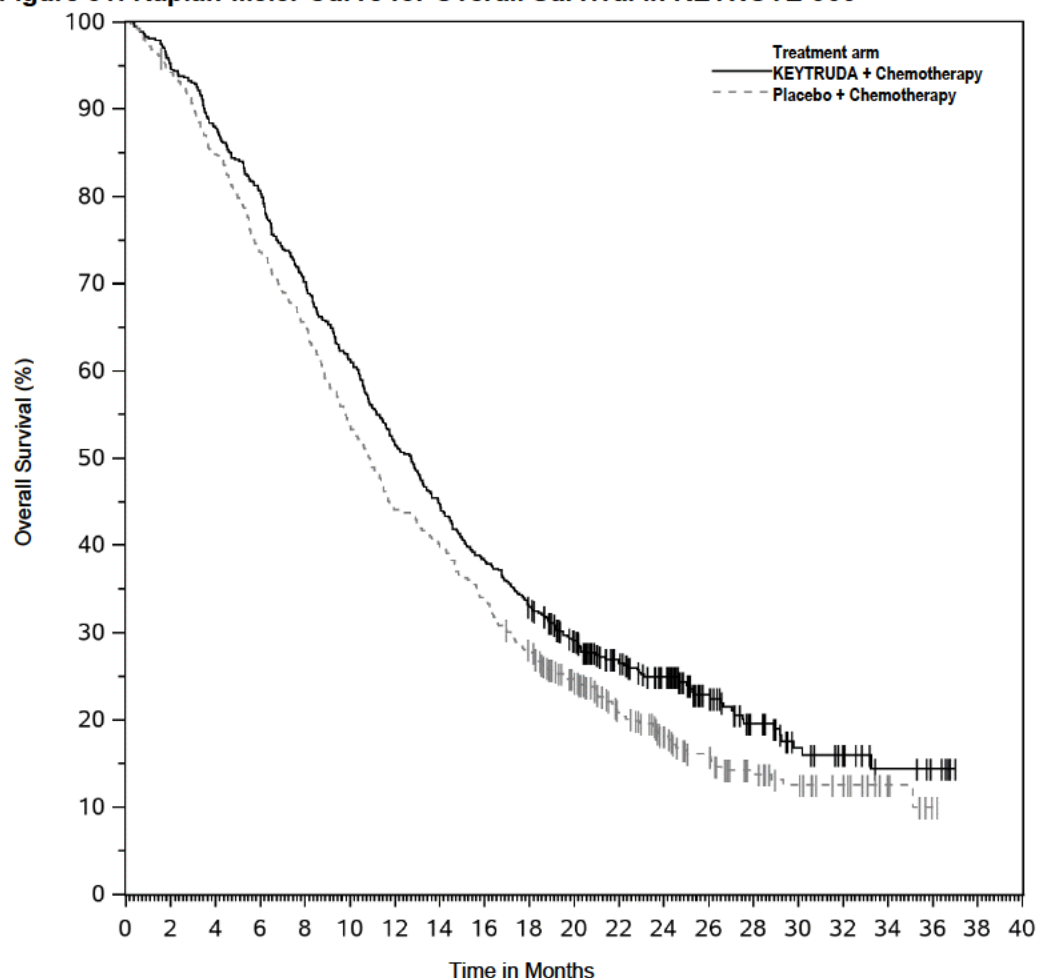
¶ Confirmed complete response or partial response

One-sided p-Value based on the stratified Miettinen and Nurminen analysis

Ⓟ Based on Kaplan-Meier estimate

NS = not significant

Figure 31: 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 95.

Table 95: 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 96 and Figure 32 summarize the efficacy results for KEYNOTE-426.

Table 96: 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).

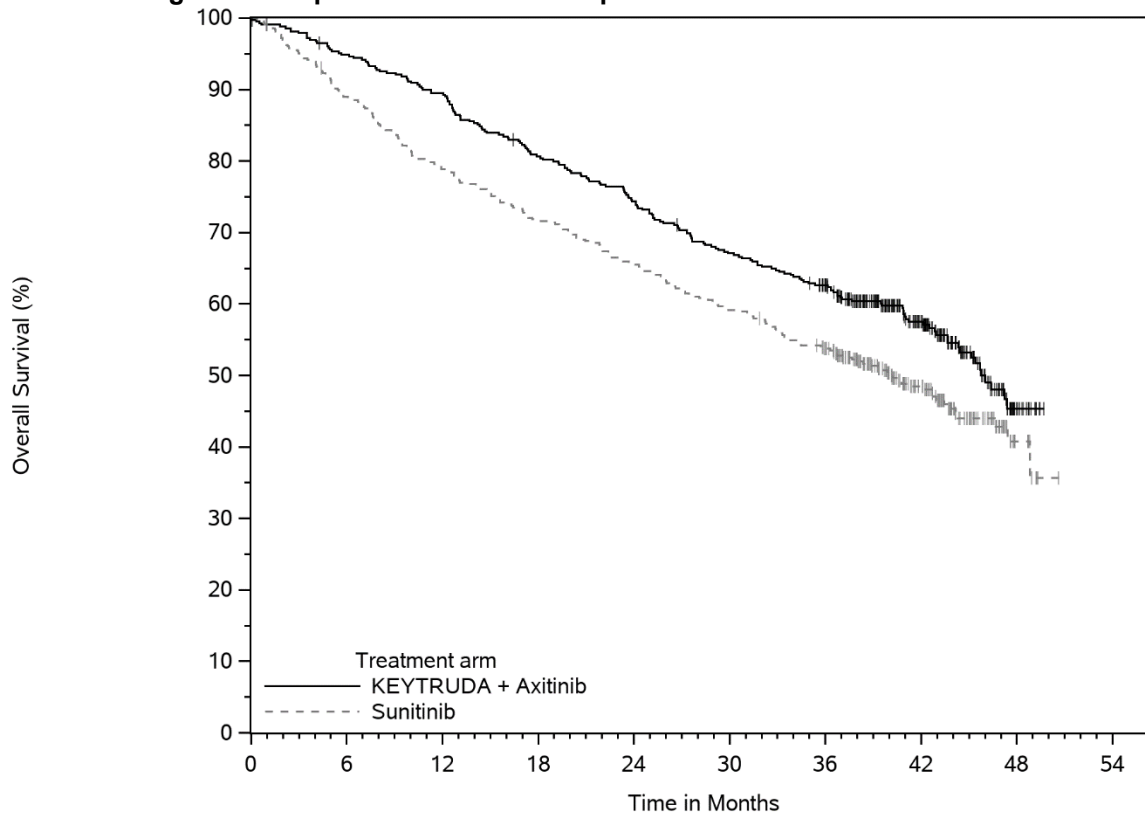
[§] p-Value (one-sided) is compared with the allocated alpha of 0.0013 for this interim analysis (with 81% of the planned number of events for final analysis).

[¶] 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 32: 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 97 and Figures 33 and 34 summarize the efficacy results for KEYNOTE-581.

Table 97: 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

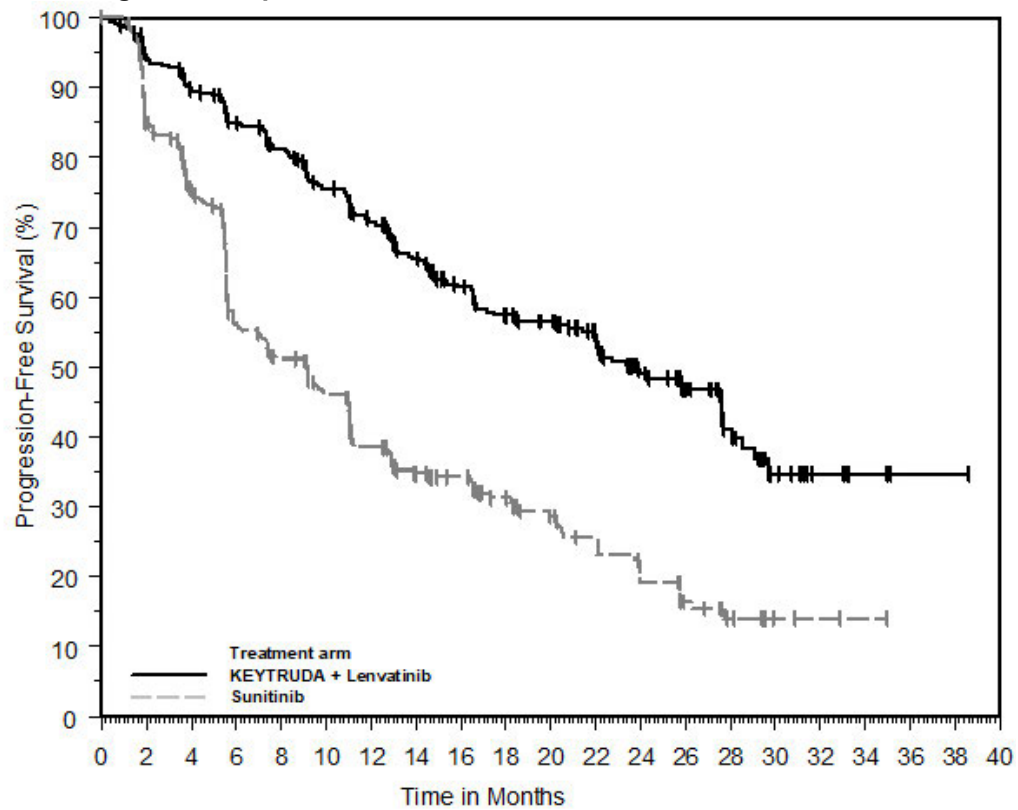
CI = confidence interval; NR= Not reached

* 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 33: Kaplan-Meier Curve for PFS in KEYNOTE-581

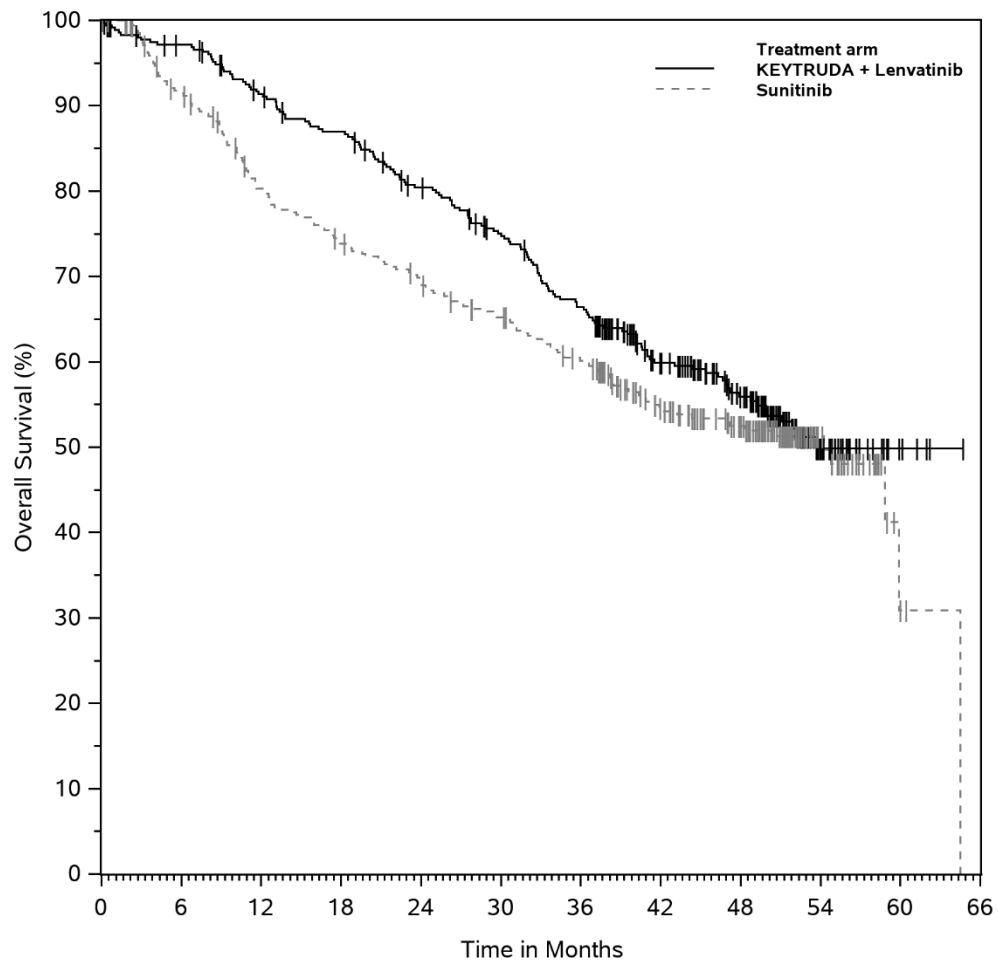


Number at Risk

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 34: 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 98.

Table 98: 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 nephrectomy 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 99 and Figures 35 and 36.

Table 99: 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

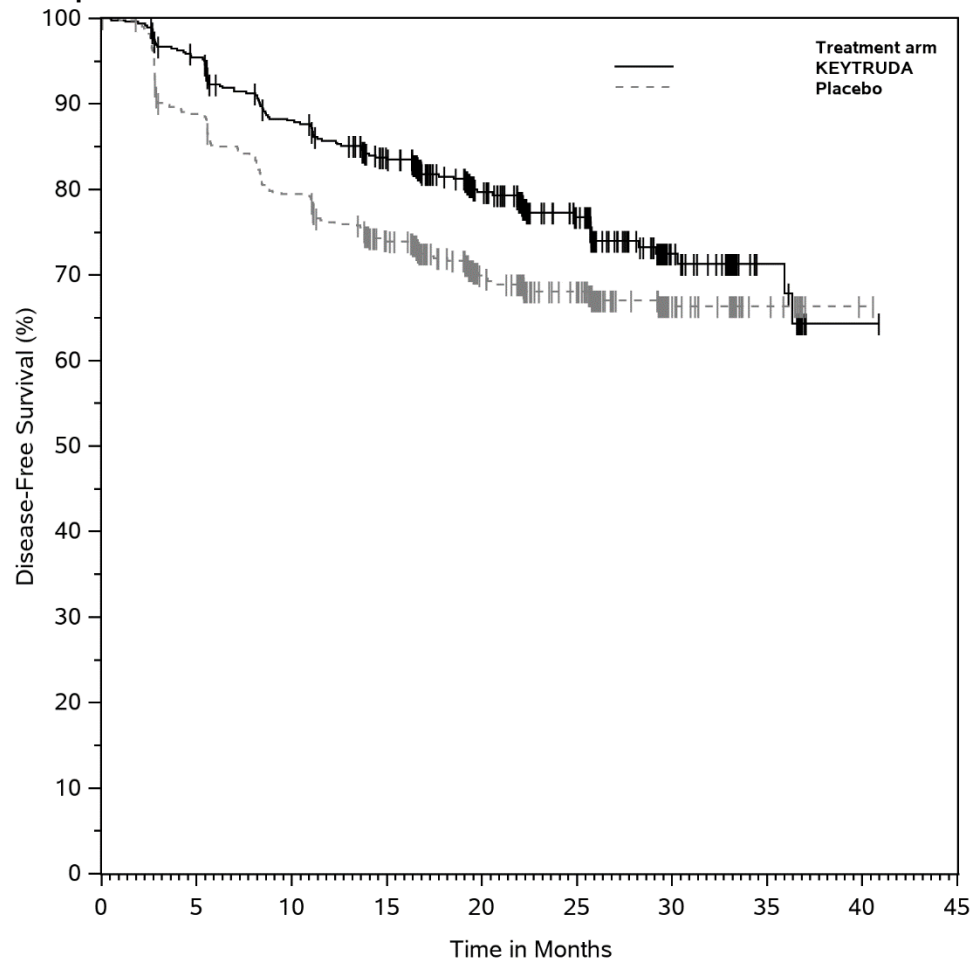
[†] Based on stratified log-rank test

[‡] 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

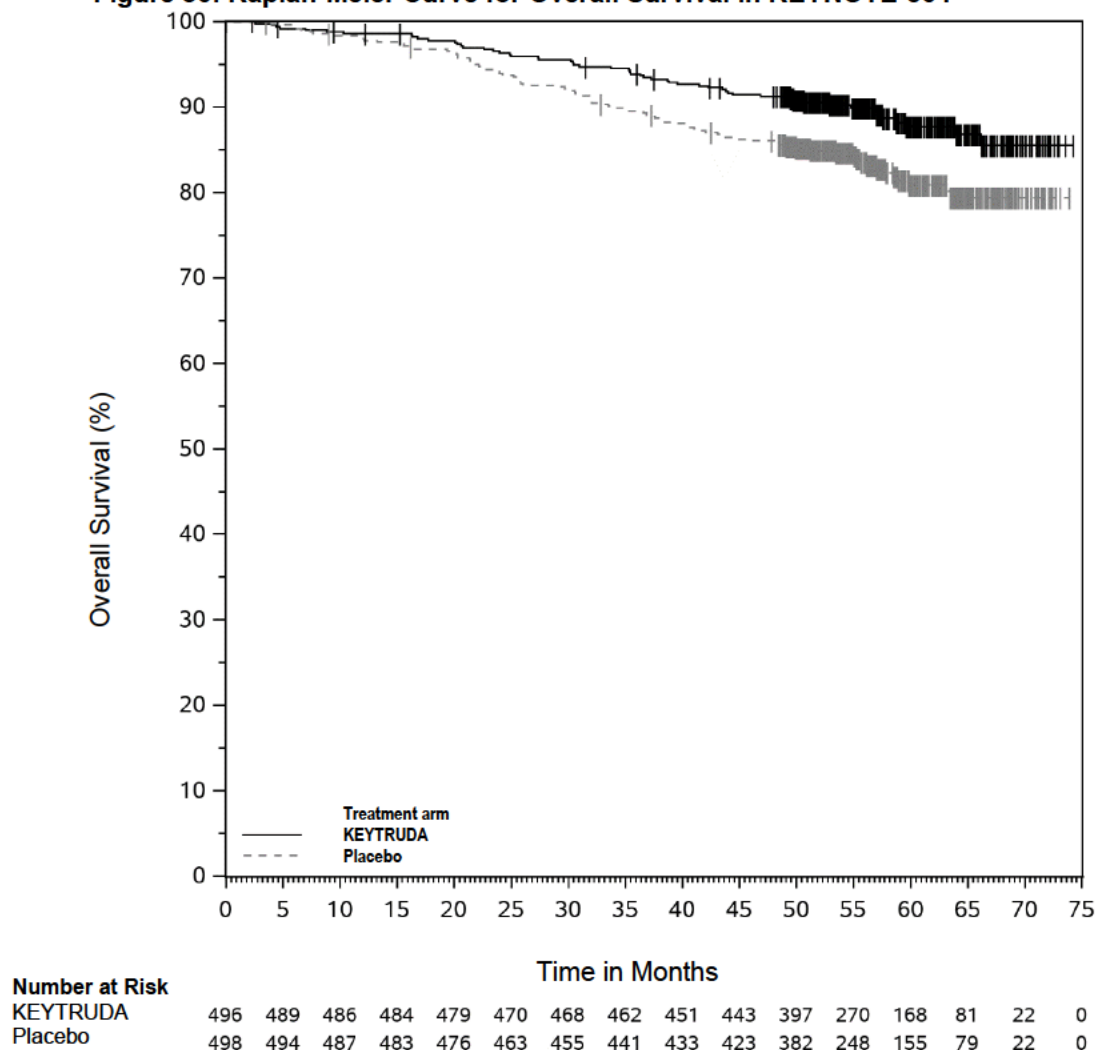
Figure 35: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-564



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 36: Kaplan-Meier Curve for Overall Survival in KEYNOTE-564



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/m² 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/m² 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 100 and Figures 37 and 38 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 100: 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 37: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)

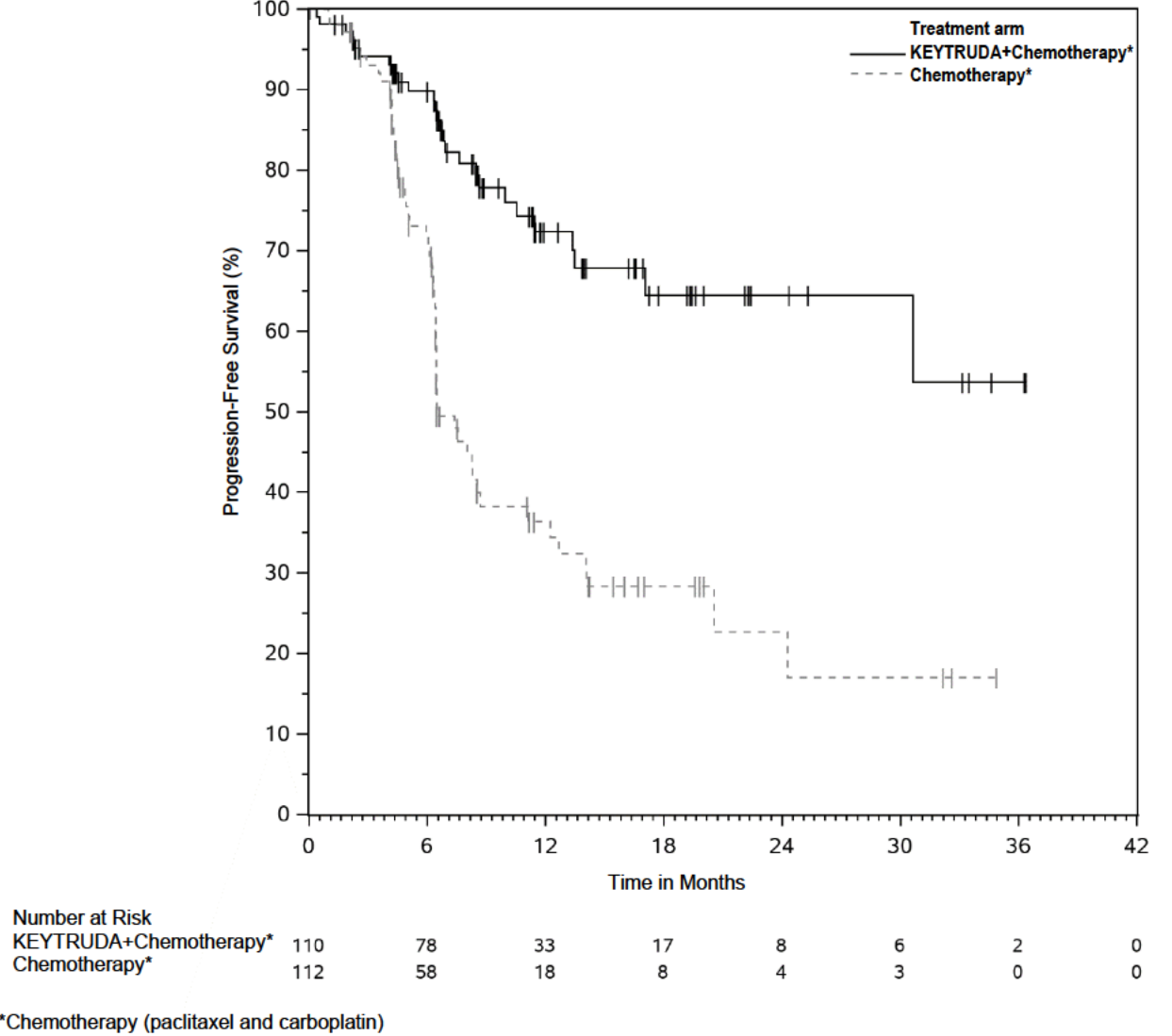
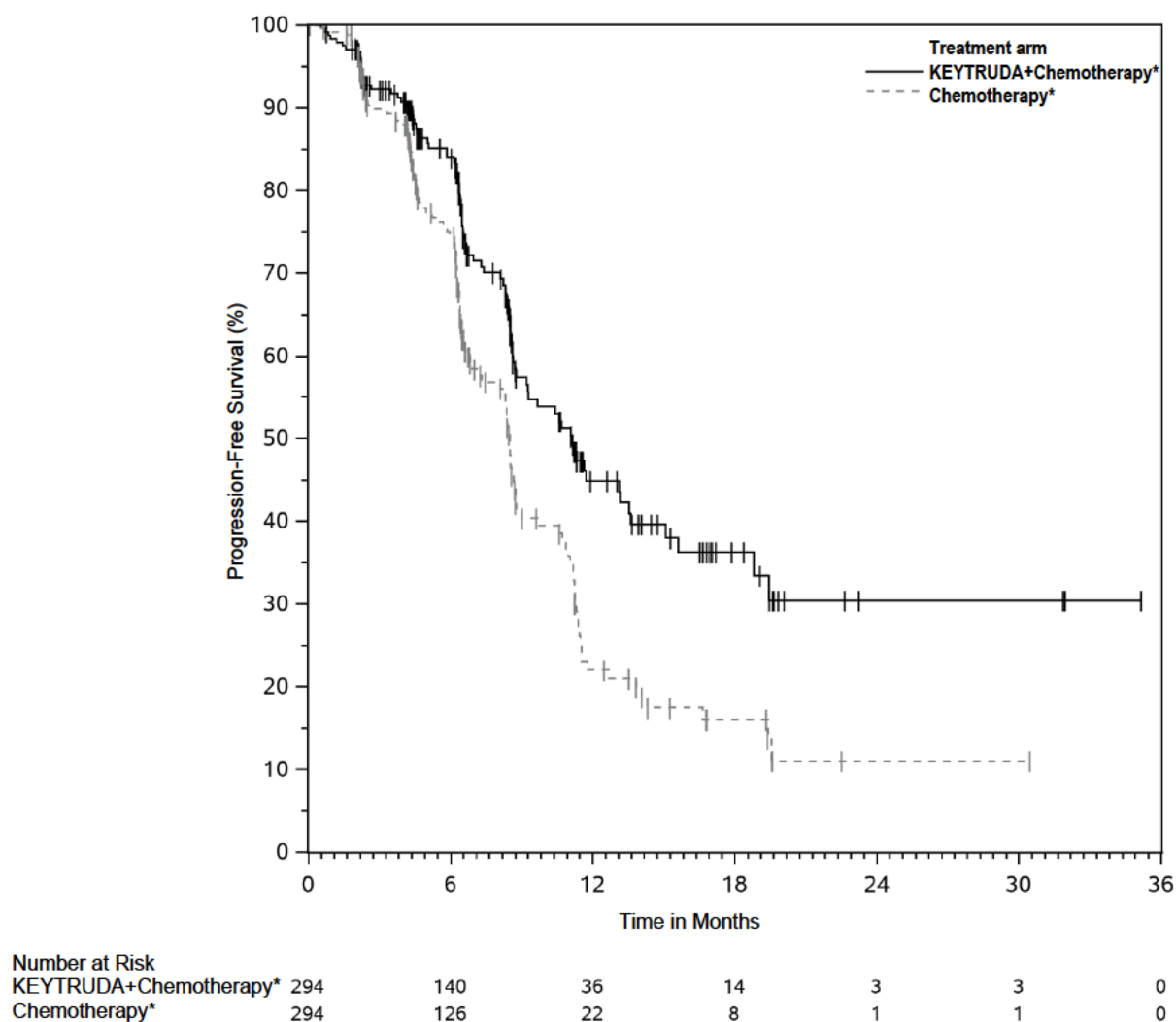


Figure 38: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)



*Chemotherapy (paclitaxel and carboplatin)

Lack of Effectiveness for Adjuvant Treatment of Patients with Endometrial Carcinoma

The efficacy of KEYTRUDA in combination with carboplatin and paclitaxel, with or without radiation, was investigated in KEYNOTE-B21 (NCT04634877), a randomized, multicenter, double-blind, placebo-controlled trial in 1,095 patients with newly-diagnosed, high-risk endometrial cancer with no evidence of disease on imaging following curative intent surgery. High-risk disease was defined as any of the following (staging per FIGO 2009): Stage I/II with myometrial invasion and either non-endometrioid histology or aberrant p53 expression or p53 mutation, or Stage III/IVA. The trial did not meet the prespecified primary endpoint for investigator-assessed DFS, with a HR of 1.02 (95% CI: 0.79, 1.32).

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/m² every 3 weeks or paclitaxel 80 mg/m² 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 101 and Figures 39 and 40.

Table 101: Efficacy Results in KEYNOTE-775

Endpoint	Endometrial Carcinoma (pMMR or not MSI-H)	
	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 39: Kaplan-Meier Curve for Overall Survival in KEYNOTE-775 (pMMR or Not MSI-H)

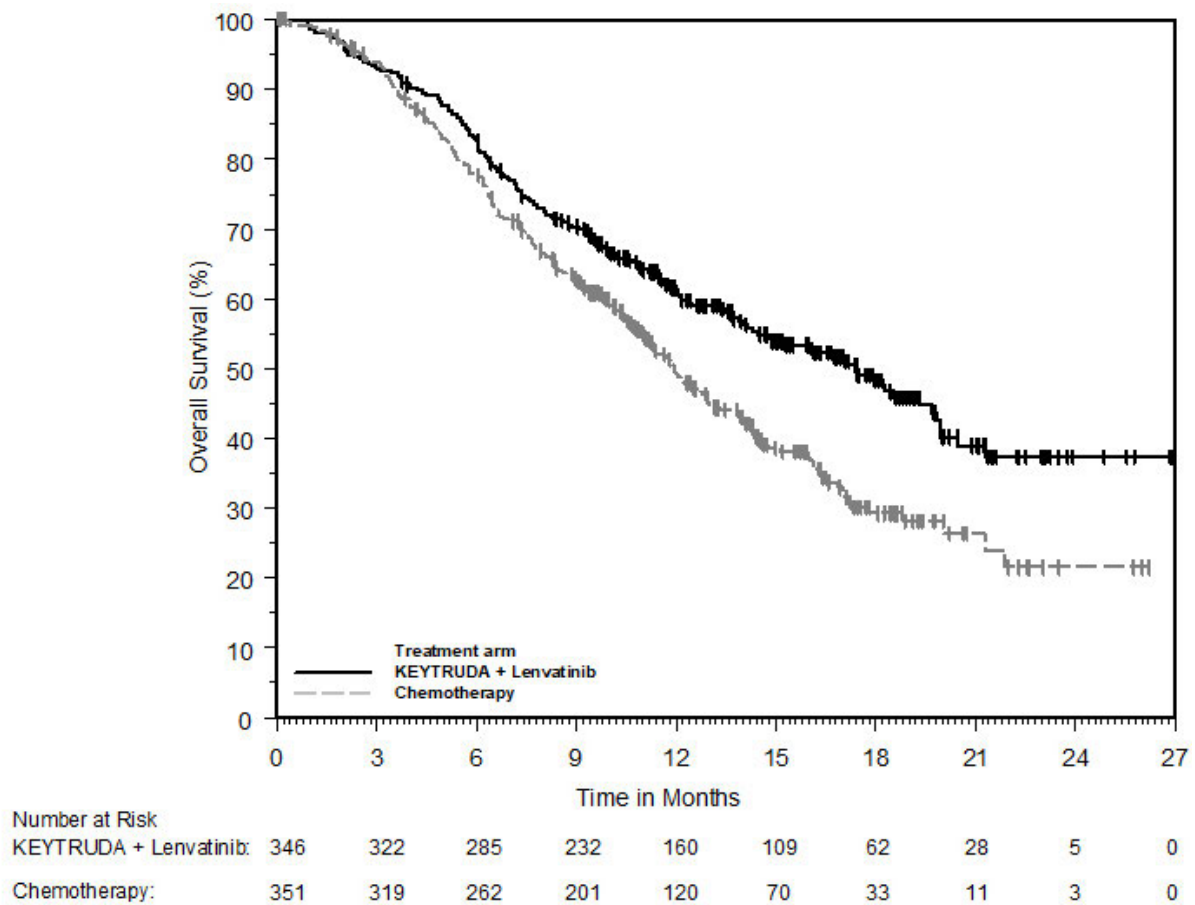
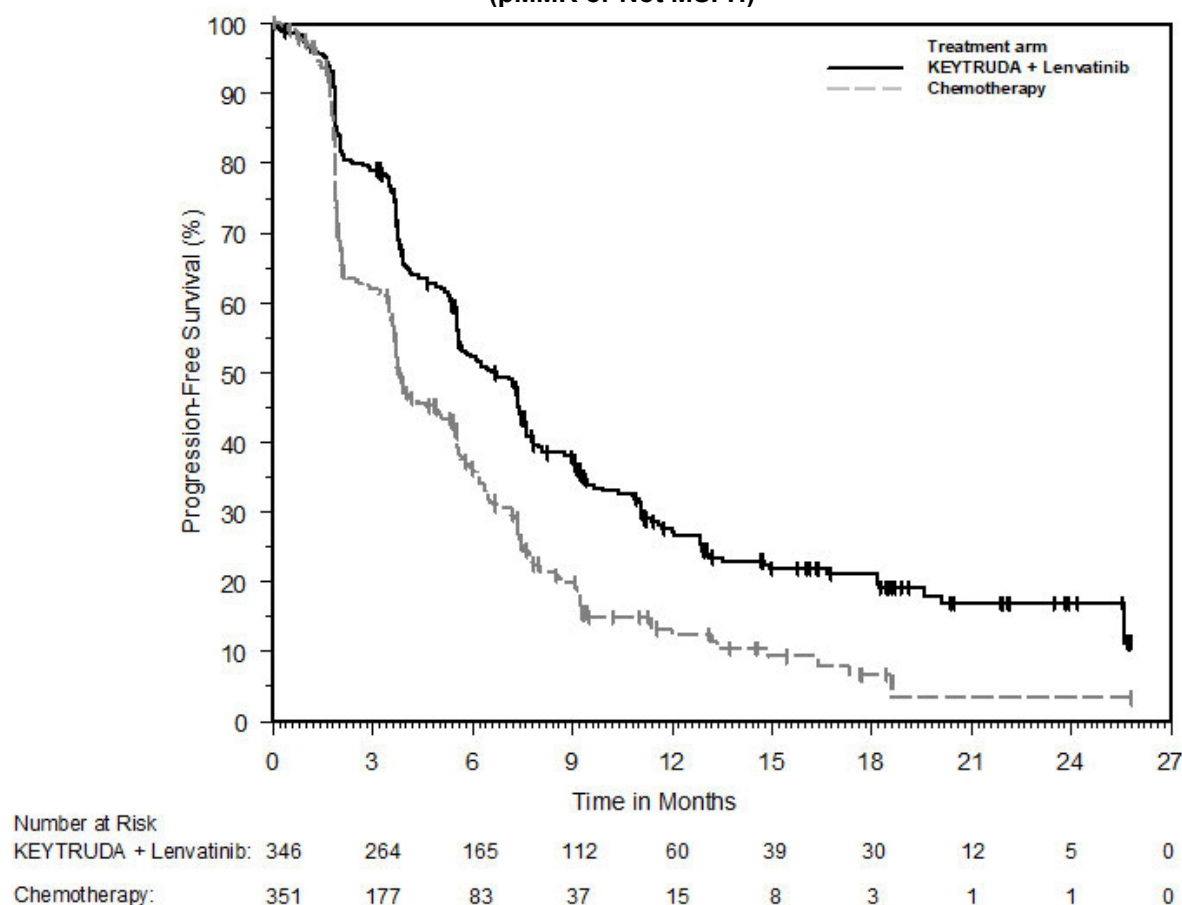


Figure 40: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-775 (pMMR or Not MSI-H)



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 102.

Table 102: 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 103 and 104.

Table 103: 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 104: 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 105.

Table 105: 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/m² 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/m² **-or-** epirubicin 90 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **-and-**
 - Cyclophosphamide 600 mg/m² 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/m² 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/m² **-or-** epirubicin 90 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **-and-**
 - Cyclophosphamide 600 mg/m² 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 trial was not designed to isolate the effect of KEYTRUDA in each phase (neoadjuvant or adjuvant) of treatment.

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.

Statistically significant improvements in pCR, EFS, and OS were demonstrated at pre-specified interim analyses for patients randomized to KEYTRUDA in combination with chemotherapy followed by KEYTRUDA as a single agent compared with patients randomized to placebo in combination with chemotherapy followed by placebo alone.

Table 106 and Figures 41 and 42 summarize the efficacy results for KEYNOTE-522.

Table 106: 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	
OS		
Number of patients with event (%)	115 (15%)	85 (22%)
Hazard ratio (95% CI) [§]	0.66 (0.50, 0.87)	
p-Value ^{#,‡}	0.00150	

* 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

‡ Based on a pre-specified OS interim analysis (compared to a significance level of 0.0050)

Figure 41: Kaplan-Meier Curve for Event-Free Survival in KEYNOTE-522

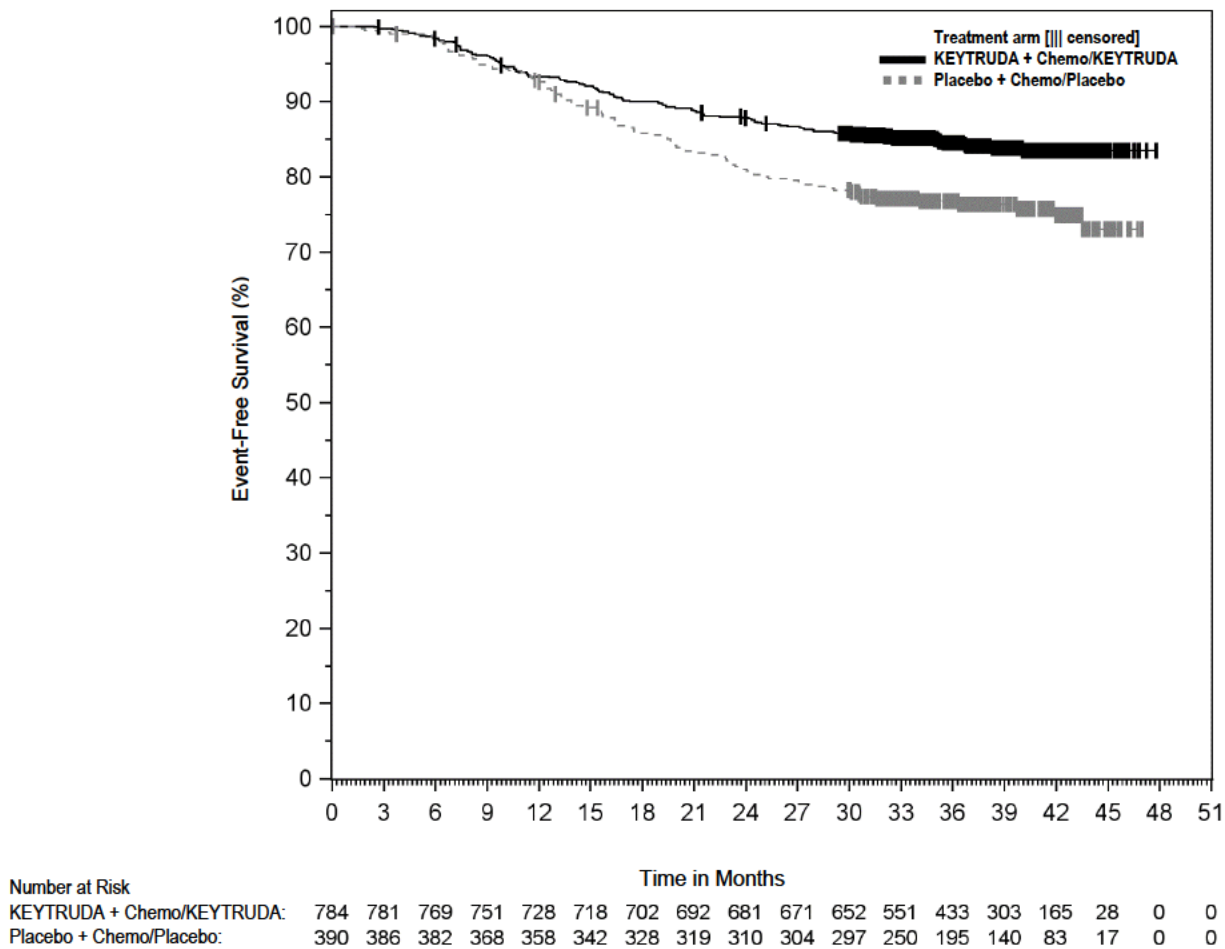
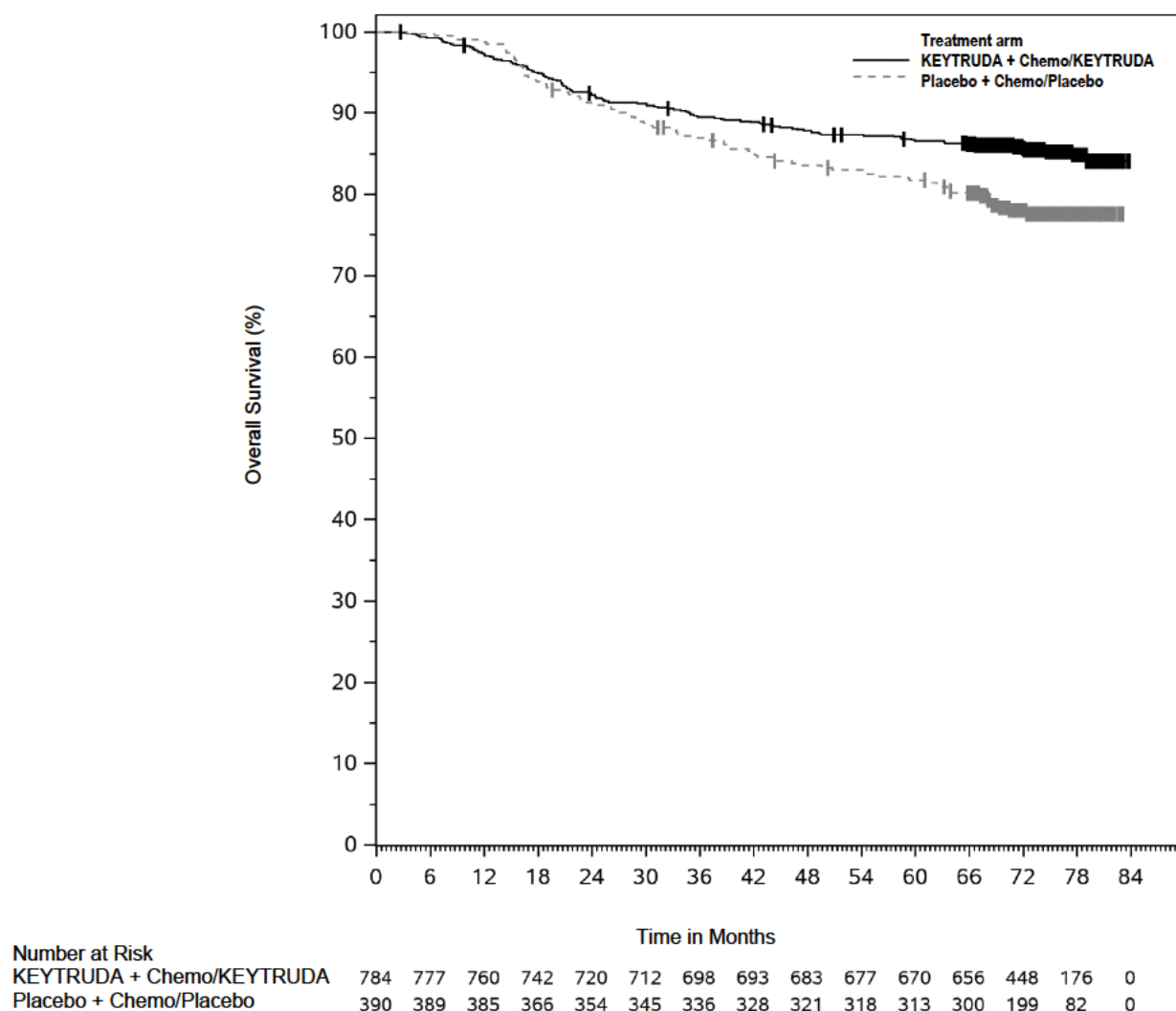


Figure 42: Kaplan-Meier Curve for Overall Survival in KEYNOTE-522



Locally Recurrent Unresectable or Metastatic TNBC for Tumors Expressing PD-L1 (CPS $\geq$ 10)

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 $\geq$ 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/m² on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m² on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m² 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/m² on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m² on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m² 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 107 and Figures 43 and 44 summarize the efficacy results for KEYNOTE-355.

Table 107: 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 43: Kaplan-Meier Curve for Overall Survival in KEYNOTE-355 (CPS ≥ 10)

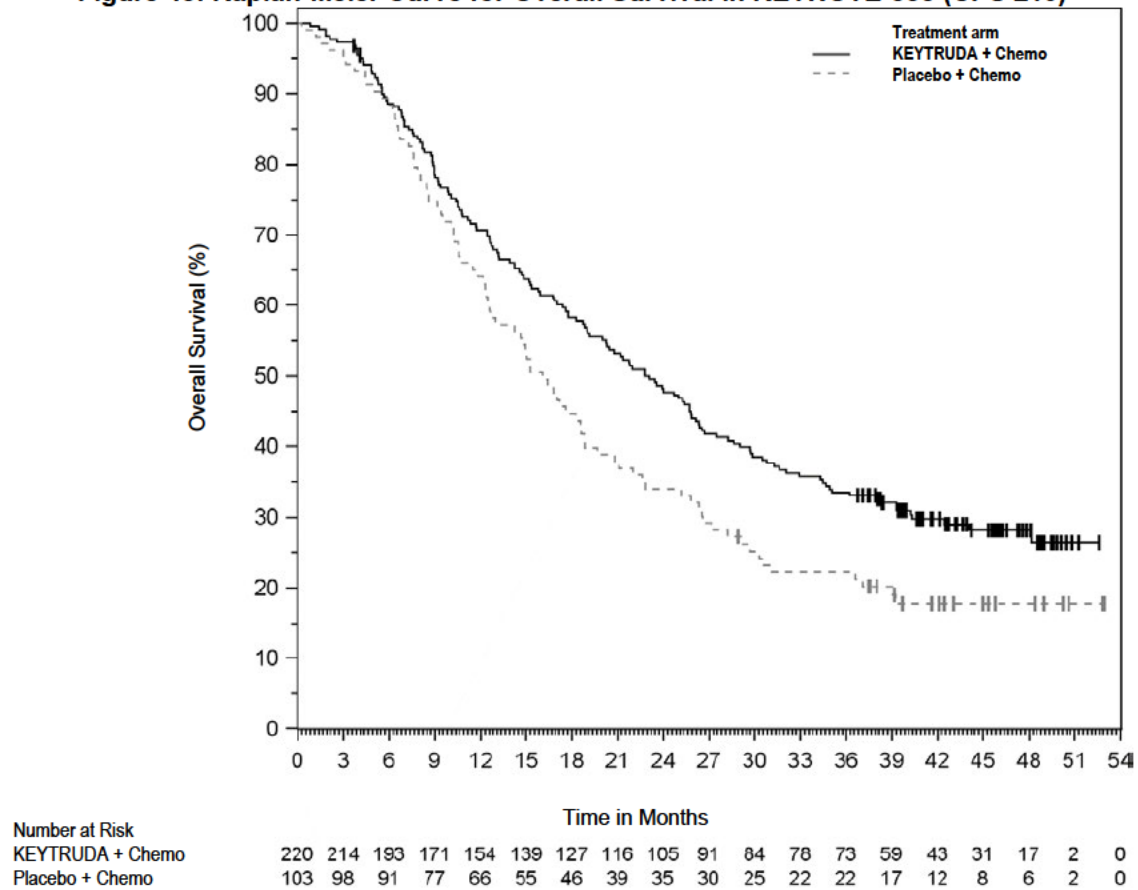
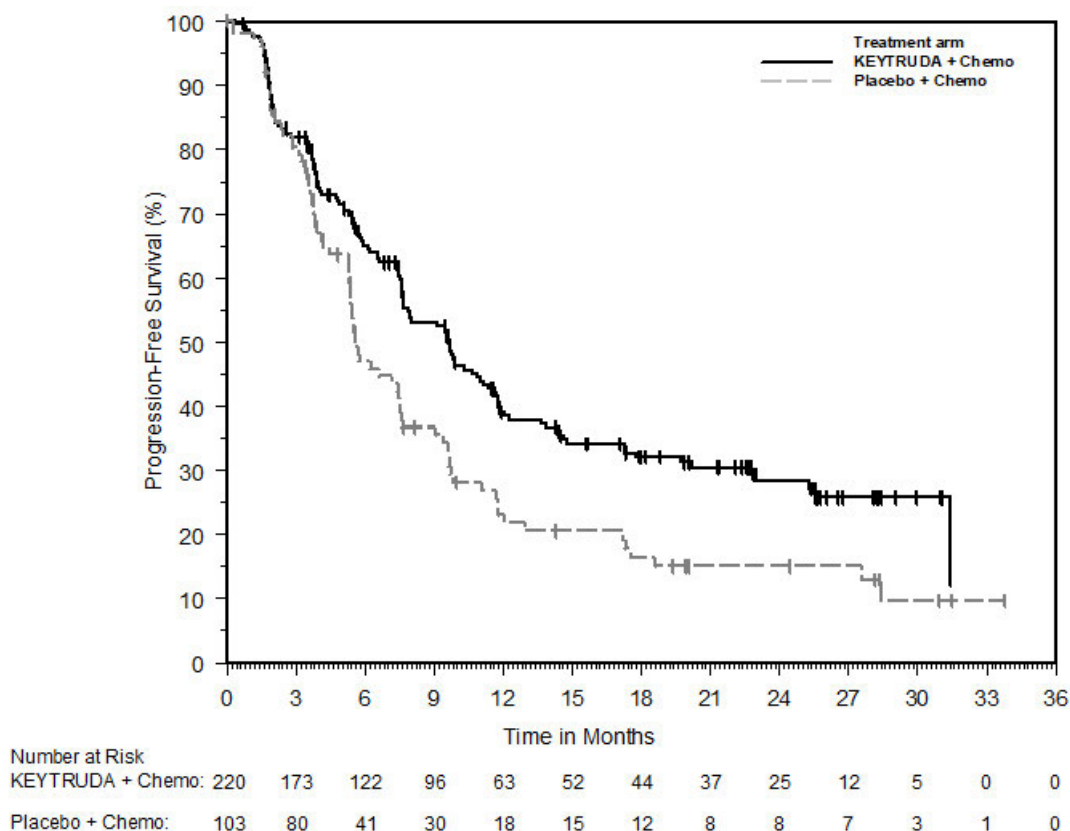


Figure 44: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-355 (CPS ≥ 10)



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

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uspi-mk3475-iv-2506r089

MEDICATION GUIDE
KEYTRUDA® (key-true-duh)
(pembrolizumab)
injection

What is the most important information I should know about KEYTRUDA?

KEYTRUDA is a medicine that may treat certain cancers by working with your immune system. KEYTRUDA can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

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

Lung problems

- cough
- shortness of breath
- chest pain

Intestinal problems

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

Liver problems

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

Hormone gland problems

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

Kidney problems

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

Skin problems

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

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

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

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

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

Rejection of a transplanted organ or tissue. Your healthcare provider should tell you what signs and symptoms you should report and monitor you depending on the type of organ or tissue transplant that you have had.

Complications, including graft-versus-host-disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with KEYTRUDA. Your healthcare provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during treatment with KEYTRUDA. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with KEYTRUDA if you have severe side effects.

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat:

- a kind of skin cancer called melanoma. KEYTRUDA may be used:
 - when your melanoma has spread or cannot be removed by surgery (advanced melanoma), **or**
 - in adults and children 12 years of age and older with Stage IIB, Stage IIC, or Stage III melanoma, to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.
- a kind of lung cancer called non-small cell lung cancer (NSCLC).
 - KEYTRUDA may be used with the chemotherapy medicines pemetrexed and a platinum as your first treatment when your lung cancer:
 - has spread (advanced NSCLC), **and**
 - is a type called “nonsquamous”, **and**
 - your tumor does not have an abnormal “EGFR” or “ALK” gene.
 - KEYTRUDA may be used with the chemotherapy medicines carboplatin and either paclitaxel or paclitaxel protein-bound as your first treatment when your lung cancer:
 - has spread (advanced NSCLC), **and**
 - is a type called “squamous”.
 - KEYTRUDA may be used alone as your first treatment when your lung cancer:
 - has not spread outside your chest (Stage III) and you cannot have surgery or chemotherapy with radiation **or**
 - your NSCLC has spread to other areas of your body (advanced NSCLC), **and**
 - your tumor tests positive for “PD-L1”, **and**
 - does not have an abnormal “EGFR” or “ALK” gene.
 - KEYTRUDA may also be used alone when:
 - you have received chemotherapy that contains platinum to treat your advanced NSCLC, and it did not work or it is no longer working, **and**
 - your tumor tests positive for “PD-L1”, **and**
 - if your tumor has an abnormal “EGFR” or “ALK” gene, you have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.
 - KEYTRUDA may be used in combination with chemotherapy that contains platinum and another chemotherapy medicine:
 - before surgery when you have early-stage NSCLC which can be removed by surgery, **and**
 - then continued alone after surgery to help prevent your lung cancer from coming back.
 - KEYTRUDA may be used alone as a treatment in adults for your lung cancer:
 - to help prevent your lung cancer from coming back after your tumor(s) has been removed by surgery and you have received platinum-based chemotherapy, **and**
 - you have Stage IB and your tumor(s) is 4 cm or greater in size, Stage II, or Stage IIIA NSCLC.
- a kind of cancer in adults called malignant pleural mesothelioma (MPM) that affects the lining of the lungs and chest wall.
 - KEYTRUDA may be used in combination with the chemotherapy medicines pemetrexed and a platinum as your first treatment when your cancer has spread or cannot be removed by surgery (advanced MPM).
- a kind of cancer called head and neck squamous cell cancer (HNSCC).
 - KEYTRUDA may be used alone in adults with HNSCC before surgery:
 - when your cancer can be removed by surgery, has spread to nearby tissues, and your tumor tests positive for “PD-L1”, **and**
 - then continued in combination with radiation with or without cisplatin after surgery, **and**
 - then continued alone to help prevent your head and neck cancer from coming back.
 - KEYTRUDA may be used with the chemotherapy medicines fluorouracil and a platinum as your first treatment when your head and neck cancer has spread or returned and cannot be removed by surgery.
 - KEYTRUDA may be used alone as your first treatment when your head and neck cancer:
 - has spread or returned and cannot be removed by surgery, **and**

- your tumor tests positive for “PD-L1”.
- KEYTRUDA may be used alone when your head and neck cancer:
 - has spread or returned, **and**
 - you have received chemotherapy that contains platinum and it did not work or is no longer working.
- a kind of cancer called classical Hodgkin lymphoma (cHL):
 - in adults when:
 - your cHL has returned **or**
 - you have tried a treatment and it did not work, **or**
 - in children when:
 - you have tried a treatment and it did not work **or**
 - your cHL has returned after you received 2 or more types of treatment.
- a kind of cancer called primary mediastinal B-cell lymphoma (PMBCL) in adults and children when:
 - you have tried a treatment and it did not work **or**
 - your PMBCL has returned after you received 2 or more types of treatment.
- a kind of bladder and urinary tract cancer called urothelial cancer.
 - KEYTRUDA may be used with the medicine enfortumab vedotin in adults when your bladder or urinary tract cancer has spread or cannot be removed by surgery (advanced urothelial cancer).
 - KEYTRUDA may be used alone when your bladder or urinary tract cancer:
 - has spread or cannot be removed by surgery (advanced urothelial cancer), **and**
 - you are not able to receive chemotherapy that contains platinum (medicines called either cisplatin or carboplatin), **or**
 - you have received chemotherapy that contains platinum, and it did not work or is no longer working.
 - KEYTRUDA may be used alone when your cancer has not spread to nearby tissue in the bladder, but is at high-risk for spreading (high-risk non-muscle-invasive bladder cancer [NMIBC]) when:
 - your tumor is a type called “carcinoma in situ” (CIS), **and**
 - you have tried treatment with Bacillus Calmette-Guerin (BCG) and it did not work, **and**
 - you are not able to or have decided not to have surgery to remove your bladder.
- a kind of cancer that is shown by a laboratory test to be a microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumor. KEYTRUDA may be used in adults and children to treat:
 - cancer that has spread or cannot be removed by surgery (advanced cancer), **and**
 - has progressed following treatment, and you have no satisfactory treatment options.
- a kind of cancer called colon or rectal cancer. KEYTRUDA may be used when your cancer:
 - has spread or cannot be removed by surgery (advanced colon or rectal cancer), **and**
 - has been shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).
- a kind of stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma.
 - KEYTRUDA may be used in adults in combination with the medicine trastuzumab along with fluoropyrimidine and platinum chemotherapy as your first treatment when your stomach cancer:
 - is HER2-positive, **and** your tumor tests positive for “PD-L1”, **and**
 - has spread or cannot be removed by surgery (advanced gastric cancer).
 - KEYTRUDA may be used in adults in combination with fluoropyrimidine and platinum chemotherapy as your first treatment when your stomach cancer:
 - is HER2-negative, **and** your tumor tests positive for “PD-L1”, **and**
 - has spread or cannot be removed by surgery (advanced gastric cancer).
- a kind of cancer called esophageal or certain gastroesophageal junction (GEJ) carcinomas that cannot be cured by surgery or a combination of chemotherapy and radiation therapy.
 - KEYTRUDA may be used in combination with platinum- and fluoropyrimidine-based chemotherapy medicines when your tumor tests positive for “PD-L1”.
 - KEYTRUDA may be used alone when:
 - you have received one or more types of treatment, and it did not work or it is no longer working, **and**
 - your tumor is a type called “squamous”, **and**
 - your tumor tests positive for “PD-L1”.
- a kind of cancer called cervical cancer.
 - KEYTRUDA may be used with chemotherapy and radiation therapy when your cervical cancer has spread nearby to the lower part of your vagina or to pelvic organs or has affected your kidneys (Stage III to IVA FIGO 2014 classification).
 - KEYTRUDA may be used with chemotherapy medicines, with or without the medicine bevacizumab, when:
 - your cervical cancer does not go away (persistent), has returned, or has spread (advanced cervical cancer), **and**
 - your tumor tests positive for “PD-L1”.
 - KEYTRUDA may be used alone when your cervical cancer:
 - has returned, or has spread (advanced cervical cancer), **and**

- you have received chemotherapy, and it did not work or is no longer working, **and**
 - your tumor tests positive for “PD-L1”.
- a kind of liver cancer called hepatocellular carcinoma (HCC). KEYTRUDA may be used when:
 - you have HCC after having hepatitis B, **and**
 - you have received anti-cancer treatment that did not contain a “PD-1” or “PD-L1” blocking medicine.
- a kind of bile duct or gallbladder cancer called biliary tract cancer (BTC). KEYTRUDA may be used with chemotherapy medicines gemcitabine and cisplatin when your biliary tract cancer has spread or cannot be removed by surgery.
- a kind of skin cancer called Merkel cell carcinoma (MCC) in adults and children. KEYTRUDA may be used to treat your skin cancer when it has spread or returned.
- a kind of kidney cancer called renal cell carcinoma (RCC).
 - KEYTRUDA may be used in adults with the medicine axitinib as your first treatment when your kidney cancer has spread or cannot be removed by surgery (advanced RCC).
 - KEYTRUDA may be used in adults with the medicine lenvatinib as your first treatment when your kidney cancer has spread or cannot be removed by surgery (advanced RCC).
 - KEYTRUDA may be used alone if you are at intermediate-high or high risk of your kidney cancer (RCC) coming back after surgery to:
 - remove all or part of your kidney, **or**
 - remove all or part of your kidney and also surgery to remove cancer that has spread to other parts of the body (metastatic lesions).
- a kind of uterine cancer called advanced endometrial carcinoma.
 - KEYTRUDA may be used with the chemotherapy medicines carboplatin and paclitaxel, and then KEYTRUDA may be used alone, in adults:
 - when your cancer has spread (advanced), **or**
 - if your cancer has returned.
 - KEYTRUDA may be used with the medicine lenvatinib in adults:
 - when a laboratory test shows that your tumor is mismatch repair proficient (pMMR) or not microsatellite instability-high (MSI-H), **and**
 - you have received anti-cancer treatment, and it is no longer working, **and**
 - your cancer cannot be cured by surgery or radiation.
 - KEYTRUDA may be used alone in adults:
 - if your cancer is shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), **and**
 - you have received anti-cancer treatment and it is no longer working, **and**
 - your cancer cannot be cured by surgery or radiation.
- a kind of cancer that is shown by a test to be tumor mutational burden-high (TMB-H). KEYTRUDA may be used in adults and children to treat:
 - solid tumors that have spread or cannot be removed by surgery (advanced cancer), **and**
 - you have received anti-cancer treatment, and it did not work or is no longer working, **and**
 - you have no satisfactory treatment options.

It is not known if KEYTRUDA is safe and effective in children with TMB-H cancers of the brain or spinal cord (central nervous system cancers).
- a kind of skin cancer called cutaneous squamous cell carcinoma (cSCC). KEYTRUDA may be used when your skin cancer:
 - has returned or spread, **and**
 - cannot be cured by surgery or radiation.
- a kind of cancer called triple-negative breast cancer (TNBC).
 - KEYTRUDA may be used with chemotherapy medicines as treatment before surgery and then continued alone after surgery when you:
 - have early-stage breast cancer, **and**
 - are at high risk of your breast cancer coming back.
 - KEYTRUDA may be used with chemotherapy medicines when your breast cancer:
 - has returned and cannot be removed by surgery or has spread, **and**
 - tests positive for “PD-L1”.

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

- have immune system problems such as Crohn’s disease, ulcerative colitis, or lupus
- have received an organ or tissue transplant, including corneal transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome

- are pregnant or plan to become pregnant. KEYTRUDA can harm your unborn baby.
- Females who are able to become pregnant:**
- Your healthcare provider will give you a pregnancy test before you start treatment with KEYTRUDA.
 - You should use an effective method of birth control during treatment with KEYTRUDA and for 4 months after the last dose of KEYTRUDA. Talk to your healthcare provider about birth control methods that you can use during this time.
 - Tell your healthcare provider right away if you think you may be pregnant or if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed. It is not known if KEYTRUDA passes into your breast milk. Do not breastfeed during treatment with KEYTRUDA and for 4 months after your last dose of KEYTRUDA.

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

How will I receive KEYTRUDA?

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

What are the possible side effects of KEYTRUDA?

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

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

Side effects of KEYTRUDA when used alone that are more common in children than in adults include: fever, vomiting, headache, stomach area (abdominal) pain, and low levels of white blood cells.

Common side effects of KEYTRUDA when given with certain chemotherapy or chemotherapy with radiation therapy medicines include: feeling tired or weak, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, trouble breathing, fever, hair loss, inflammation of the nerves that may cause pain, weakness, and paralysis in the arms and legs, swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina, mouth sores, headache, weight loss, stomach-area (abdominal) pain, joint and muscle pain, trouble sleeping, blisters or rash on the palms of your hands and soles of your feet, urinary tract infection, low levels of thyroid hormone, skin irritation in the radiation area, trouble swallowing and dry mouth.

Common side effects of KEYTRUDA when given with chemotherapy and bevacizumab include: tingling or numbness of the arms or legs, hair loss, low red blood cell count, feeling tired or weak, nausea, low white blood cell count, diarrhea, high blood pressure, decreased platelet count, constipation, joint aches, vomiting, urinary tract infection, rash, low levels of thyroid hormone, and decreased appetite.

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

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

Common side effects of KEYTRUDA when given with enfortumab vedotin include: rash, tingling or numbness of the arms or legs, feeling tired, itching, diarrhea, hair loss, weight loss, decreased appetite, dry eye, nausea, constipation, changes in sense of taste, and urinary tract infection.

These are not all the possible side effects of KEYTRUDA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of KEYTRUDA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about KEYTRUDA that is written for health professionals.

What are the ingredients in KEYTRUDA?**Active ingredient:** pembrolizumab**Inactive ingredients:** KEYTRUDA injection: L-histidine, polysorbate 80, sucrose, and Water for Injection.

Manufactured by: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

U.S. License No. 0002

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

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usmg-mk3475-iv-2506r070

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: June 2025

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s180

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

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NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	Supplemental BLA (Efficacy Supplement)
Application Number(s)	BLA
Priority or Standard	Standard
Submit Date(s)	December 23, 2024
Received Date(s)	December 23, 2024
PDUFA Goal Date	June 23, 2025
Division/Office	Division of Oncology 2 / Office of Oncologic Diseases
Review Completion Date	June 12, 2025
Established Name	Pembrolizumab
(Proposed) Trade Name	KEYTRUDA
Pharmacologic Class	Programed death receptor ligand-1 (PD-L1) blocking agent
Code name	MK-3475
Applicant	Merck Sharp & Dohme LLC
Formulation(s)	Intravenous
Dosing Regimen	200 mg as a single agent every 3 weeks for 2 cycles or 1 dose of 400 mg prior to surgical resection. Within 6 weeks following surgery, KEYTRUDA 200 mg for 3 cycles every 3 weeks or 2 doses of 400 mg every 6 weeks in combination with either radiation with or without 3 cycles of cisplatin 100 mg/m ² every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery. Followed by KEYTRUDA 200 mg every 3 weeks for up to 12 cycles or KEYTRUDA 400 mg every 6 weeks for up to 6 cycles.
Applicant Proposed Indication(s)/Population(s)	KEYTRUDA is indicated for the treatment of adult patients with resectable locally advanced HNSCC as neoadjuvant treatment, continued as adjuvant treatment in combination with

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	radiotherapy (RT) with or without platinum-containing chemotherapy and then as a single agent.
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	KEYTRUDA is indicated for the treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1], as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without platinum-containing chemotherapy and then as a single agent.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Ashley Lane
Pharmacology/Toxicology Reviewer(s)	Not Applicable
Pharmacology/Toxicology Team Leader(s)	Not Applicable
Office of Clinical Pharmacology Reviewer(s)	Not Applicable
Office of Clinical Pharmacology Team Leader(s)	Not Applicable
Clinical Reviewer	Yun Oh
Clinical Team Leader	Justin Malinou
Associate Director for Patient Outcomes	Vishal Bhatnagar
Safety Analyst (if applicable)	Not Applicable
Statistical Reviewer	Michelle Marcovitz
Statistical Team Leader	Flora Mulkey
Associate Director for Labeling (ADL)	Barbara Scepura
Cross-Disciplinary Team Leader	Justin Malinou
Division Director (DHOT)	Not Applicable
Division Director (OCP)	Not Applicable
Supervisory Mathematical Statistician (OB)	Anup Amatya
Supervisory Associate Director, Acting (Designated Signatory Authority)	Paz Vellanki

Additional Reviewers of Application

OPDP	Kelle Caruso (reviewer); Rachael Conklin (team lead)
OSI	Lee Pai-Scherf (reviewer), Michele Fedowitz (team lead)

OSI=Office of Scientific Investigations

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Glossary

AC	advisory committee
ADA	Antidrug antibodies
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEOSI	adverse event(s) of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
APaT	All Participants as Treated
BICR	Blinded Independent Central Review
BIPR	Blinded Independent Pathological Review
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
B/R	benefit risk
BRA	Benefit Risk Assessment
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPS	combined positive score
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff

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CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DFS	disease-free survival
DILI	drug-induced liver injury
DMC	data monitoring committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EFS	event-free survival
EOC	Executive Oversight Committee
EOP2	end of Phase 2
EORTC	European Organization for Research and Treatment of Cancer
ERC	Ethics Review Committee
ETASU	elements to assure safe use
EU	European Union
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
HNC	head and neck cancer
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR	hazard ratio
HRQOL	health-related quality of life
IA	interim analysis
ICH	International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human use
IEC	Independent Ethics Committee

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IHC	Immunohistochemistry
IND	Investigational New Drug
irAE	immune-related adverse event
IRB	Independent Review Board
irRECIST	immune-based RECIST
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	Intravenous
KM	Kaplan-Meier
LA	locoregionally advanced
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mPR	major pathological response
MSD	Merck Sharp & Dohme, Corp., a subsidiary of Merck & Co., Inc.
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NR	Not reached
NSCLC	non-small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
pCR	pathological complete response
PD	Pharmacodynamics
PD-L1	programmed cell death ligand 1
PET	positron emission tomography

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PI	prescribing information
PK	Pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PS	performance score
PSUR	Periodic Safety Update report
PT	preferred term
Q3W	every 3 weeks
Q6W	every 6 weeks
QA	quality assurance
QC	quality control
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
R/M	recurrent or metastatic
RT	radiation therapy
SAE	serious adverse event
SAP	statistical analysis plan
SCC	squamous cell carcinoma
SGE	special government employee
SoC	standard of care
sSAP	Supplemental Statistical Analysis Plan
TC	tumor cell
TEAE	treatment-emergent adverse event
TPS	tumor proportion score
UK	United Kingdom
US	United States

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vs	Versus
WOCBP	women of childbearing potential

1 Executive Summary

1.1. Product Introduction

Pembrolizumab (KEYTRUDA®) is a humanized antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with programmed-death ligand 1 (PD-L1) and programmed-death ligand 2 (PD-L2), releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Pembrolizumab is approved for multiple oncologic indications, including the following head and neck squamous cell carcinoma (HNSCC) indications:

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

1.2. Conclusions on the Substantial Evidence of Effectiveness

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The primary trial supporting this supplemental biologic licensing application (sBLA) is KEYNOTE-689, a randomized, multicenter, open label, active controlled trial in patients with resectable locally advanced (Stage III-IVA) HNSCC [AJCC, 8th edition]. A total of 714 patients were randomized 1:1 to receive either:

- Neoadjuvant pembrolizumab 200 mg every 3 weeks (Q3W) for 2 cycles prior to surgical resection; followed by 3 cycles of adjuvant pembrolizumab 200 mg Q3W in combination with radiotherapy (RT) with or without 3 cycles of cisplatin 100 mg/m² Q3W; followed by pembrolizumab 200 mg Q3W as a single agent for up to 12 cycles.
- No neoadjuvant treatment prior to surgery; followed by adjuvant RT with or without 3 cycles of concurrent cisplatin 100 mg/m² Q3W (SoC Arm).

On both treatment arms, patients received cisplatin with adjuvant RT if high-risk pathological features (i.e., positive margins <1 mm or extranodal extension) were present at surgery.

Randomization was stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor stage (III vs. IVA) and PD-L1 status (tumor proportion score, TPS $\geq 50\%$ vs. TPS <50%). For the purposes of this review, we will define treatment that includes both neoadjuvant and adjuvant phases of therapy as “perioperative” therapy.

The primary endpoint of KEYNOTE-689 was event-free survival (EFS) as assessed by blinded independent central review (BICR) analyzed hierarchically in patients with tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , then the intention-to-treat (ITT) population. Major pathological response (MPR) by blinded independent pathological review (BIPR) and overall survival (OS) were key secondary endpoints. Major pathological response was defined as having less than or equal to 10% invasive SCC within the resected primary tumor specimen and all sampled regional lymph nodes. The initial alpha allocation was as follows: the primary endpoint of EFS was to be tested at a one-sided alpha of 0.025, with one-sided alpha of 0.0005 recycled to MPR and one-sided alpha of 0.0245 recycled to OS if EFS is significant.

At the first EFS interim analysis (IA1), with a data cutoff date of July 25, 2024, the study met the pre-specified boundary for statistical significance favoring the pembrolizumab arm in patients with tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT populations with EFS hazard ratios (HR) of 0.66 (95% CI: 0.49, 0.88; p=0.00217), 0.70 (95% CI: 0.55, 0.89; p=0.00140), and 0.73 (95% CI: 0.58, 0.92; p=0.00411), respectively.

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At the first MPR interim analysis (IA1), with a data cutoff date of July 25, 2024, the study met the pre-specified boundary for statistical significance favoring the pembrolizumab arm in patients with tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT population with a difference in MPR rates of 13.7% (95% CI: 9.7, 18.7), 9.8% (95% CI: 7.0, 13.3), and 9.3% (95% CI: 6.7, 12.8), favoring the pembrolizumab arm. As expected, no major pathological responses were observed in patients on the SoC control arm as they did not receive any neoadjuvant therapy. While this secondary endpoint was statistically significant, mPR is not a validated endpoint and the clinical meaningfulness of mPR has not been established for resectable, locally advanced HNSCC (LA HNSCC).

At the time of the first EFS interim analysis (IA1), the OS results did not cross the one-sided p-value boundary of 0.0104 for statistical significance in patients with PD-L1 CPS ≥ 10 ; however, there was a numerical difference in OS favoring the pembrolizumab arm. Because the hierarchical testing strategy requires OS to reach statistical significance in the patients with PD-L1 CPS ≥ 10 before proceeding with testing OS in other populations, OS was not tested in patients with PD-L1 CPS ≥ 1 or in the ITT population. The descriptive analysis of OS in patients with tumor PD-L1 CPS ≥ 10 at EFS IA1 included 73 (31%) deaths in the pembrolizumab arm and 89 (39%) deaths in the SoC arm. The median OS was not reached (95% CI: NR, NR) in the pembrolizumab arm and was 61.8 months (95% CI: 49.2, NR) in the SoC arm corresponding to a HR of 0.72 (95% CI: 0.52, 0.98). In an additional descriptive analysis of OS in patients with PD-L1 CPS ≥ 1 , the OS HR estimate favored pembrolizumab versus SoC with a HR of 0.72 (95% CI: 0.56, 0.94). These descriptive analyses suggest a potential trend in improved OS with the pembrolizumab-based regimen for patients with PD-L1 positive (CPS ≥ 1) LA HNSCC.

In an exploratory subgroup analysis at IA1, the EFS results for patients with PD-L1 negative tumors (CPS < 1) disfavored the pembrolizumab arm (n=13) over the SoC arm (n=14) with an observed HR of 2.57 (95% CI: 0.5, 13.36). An exploratory analysis of OS for patients with PD-L1 negative tumors also showed a trend toward potential detriment with pembrolizumab with an OS HR of 1.73 (95% CI: 0.32, 9.54). In contrast, for patients with PD-L1 positive (CPS ≥ 1) tumors, there was a statistically significant, 30.1 month-improvement in median EFS with pembrolizumab, with a median EFS of 59.7 months (95% CI: 37.9, NR) for the pembrolizumab arm vs 29.6 months (95% CI: 19.5, 41.9) for the SoC arm (EFS HR 0.70, 95% CI: 0.55, 0.89; p=0.00140). In addition, though median OS has not yet been reached, the point estimate of OS HR favored the pembrolizumab arm over the SoC arm (HR 0.72; 95% CI: 0.56, 0.94) among patients with PD-L1 positive tumors. Given these exploratory EFS and OS results, and taken together with prior data of pembrolizumab monotherapy demonstrating a potential detriment for patients with PD-L1 negative recurrent or metastatic HNSCC, the FDA review team recommends that the current indication is limited to patients with PD-L1 positive (CPS ≥ 1) tumors.

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The submitted evidence meets the statutory evidentiary standard for traditional approval of pembrolizumab for adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test, as neoadjuvant treatment, continued as adjuvant treatment in combination with RT with or without cisplatin, and then as a single agent. For patients with PD-L1 positive (CPS ≥ 1) HNSCC in KEYNOTE-689, the median EFS was 59.7 months (95% CI: 37.9, not reached [NR]) for the pembrolizumab arm and 29.6 months (95% CI: 19.5, 41.9) for the SoC control arm. The observed improvement in EFS, with a HR of 0.70 (95% CI: 0.55, 0.89; $p=0.00140$) and 30.1-month difference in median EFS favoring the pembrolizumab arm, is statistically robust and clinically meaningful. EFS is an acceptable and clinically meaningful endpoint which has supported approval of other perioperative immunotherapy regimens for other solid tumors (e.g., breast cancer, non-small cell lung cancer). These results are supported by a trend towards improved OS for the pembrolizumab arm.

This is the first approval of a systemic regimen for combined neoadjuvant and adjuvant treatment for resectable, LA HNSCC.

1.3. **Benefit-Risk Assessment (BRA)**

Benefit-Risk Summary and Assessment

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. In the U.S., HNSCC accounts for approximately 3% of new cancer cases and 2% of all cancer-related deaths. Approximately 50 to 60% of patients have resectable, locally advanced (LA) HNSCC at diagnosis (Stage III-IVB: T3-4 and/or N1-3) (Wang H, et al. 2023). Currently, approximately 40% of these patients undergo surgery for resectable (Stage III-IVA) HNSCC followed by adjuvant radiation therapy (RT) or cisplatin chemoradiation (CRT) therapy, with the remaining 60% of patients with LA HNSCC receiving definitive CRT therapy alone (Black C, et al. 2023; Barsouk A, et al. 2023).

The standard of care (SoC) treatment for patients with LA HNSCC is complex and generally involves multi-modality therapy. Multiple retrospective studies including systematic reviews and meta-analyses have demonstrated 5-year overall survival of 40 to 50% for LA HNSCC depending on stage, site of tumor, and tumor characteristics, with similar or better outcomes with surgery followed by RT/CRT compared to definitive CRT (Park JO, et al. 2020; Zimmerman PH, et al. 2021; Kim YJ, et al. 2018; Zheng L, et al. 2023; Tsai T-Y, et al. 2024). However, more than half of patients with resectable HNSCC do not receive surgery due to its morbidity. Previous clinical trials of neoadjuvant or induction chemotherapy prior to either surgery and adjuvant RT/CRT, or definitive CRT with curative intent have failed to demonstrate improved survival

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or reduced morbidity in the intention to treat (ITT) populations (Cohen EE, et al. 2014; Bossi P, et al. 2014). For the purposes of this review, we will define “perioperative” as therapy that includes both neoadjuvant and adjuvant phases of therapy.

Pembrolizumab is a humanized antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with programmed-death ligand 1 (PD-L1) and programmed-death ligand 2 (PD-L2), releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Pembrolizumab is approved for numerous oncologic indications including for HNSCC in the advanced/metastatic setting, and in the perioperative setting for other types of solid tumors.

The primary trial supporting this sBLA is KEYNOTE-689, a multicenter, global, open-label, randomized trial in patients with resectable Stage III to IVA HNSCC, per the AJCC 8th edition staging system. A total of 714 patients were randomized 1:1 to receive either:

- Neoadjuvant pembrolizumab 200 mg every 3 weeks (Q3W) for 2 cycles prior to surgical resection; followed by 3 cycles of adjuvant pembrolizumab 200 mg Q3W in combination with RT with or without 3 cycles of cisplatin 100 mg/m² Q3W; followed by pembrolizumab 200 mg Q3W as a single agent for up to 12 cycles.
- No neoadjuvant treatment prior to surgery; followed by adjuvant RT with or without 3 cycles of concurrent cisplatin 100 mg/m² Q3W (SoC Arm).

On both treatment arms, patients received cisplatin with adjuvant RT if high-risk pathological features (i.e., positive margins <1 mm or extranodal extension) were present at surgery.

Randomization was stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor stage (III vs. IVA) and PD-L1 status (tumor proportion score, TPS ≥ 50% vs. TPS <50%). The primary endpoint of KEYNOTE-689 was event-free survival (EFS) as assessed by blinded independent central review (BICR) analyzed hierarchically in patients with tumor PD-L1 CPS ≥10, then CPS ≥1, then the intention-to-treat (ITT) population. Major pathological response (MPR) by blinded independent pathological review (BIPR) and overall survival (OS) were key secondary endpoints. Major pathological response was defined as having less than or equal to 10% invasive squamous cell carcinoma (SCC) within the resected primary tumor specimen and all sampled regional lymph nodes. The initial alpha allocation was as follows: the primary endpoint of EFS was to be tested at a one-sided alpha of 0.025, with one-sided alpha of 0.0005 recycled to MPR and one-sided alpha of 0.0245 recycled to OS if EFS was significant.

At the first EFS interim analysis (IA1) with a data cutoff date of July 25, 2024, the study met the pre-specified boundary for significance in the

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tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT populations with EFS hazard ratios (HR) of 0.66 (95% CI: 0.49, 0.88; $p=0.00217$), 0.70 (95% CI: 0.55, 0.89; $p=0.00140$), and 0.73 (95% CI: 0.58, 0.92; $p=0.00411$), respectively. In the population of patients with PD-L1 CPS ≥ 1 tumors, the median EFS was 59.7 months (CI 95%: 37.9, NR) in the pembrolizumab arm and 29.6 (CI 95%: 19.5, 41.9) in the SoC arm, corresponding to a 30.1-month improvement in median EFS. At the first MPR interim analysis (IA1), with a data cutoff date of July 25, 2024, the study met the pre-specified boundary for statistical significance favoring the pembrolizumab arm in patients with tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT population with a difference in MPR rates of 13.7% (95% CI: 9.7, 18.7), 9.8% (95% CI: 7.0, 13.3), and 9.3% (95% CI: 6.7, 12.8), favoring the pembrolizumab arm. As expected, there were no major pathological responses observed in patients on the SoC control arm as they did not receive any neoadjuvant therapy. While the secondary endpoint was statistically significant, mPR is not a validated endpoint and the clinical meaningfulness of mPR has not been established for patients with resectable HNSCC.

At IA1, OS in patients with tumor PD-L1 CPS ≥ 10 had not reached statistical significance, although there was a numerical difference in OS favoring the pembrolizumab arm. The median OS was not reached (NR) (95% CI: NR, NR) in the pembrolizumab arm and was 61.8 months (95% CI: 49.2, NR) in the SoC arm, corresponding to a HR of 0.72 (95% CI: 0.52, 0.98). Because the hierarchical testing strategy requires OS to reach statistical significance in the patients with PD-L1 CPS ≥ 10 before proceeding with testing OS in other populations, OS was not tested in patients with PD-L1 CPS ≥ 1 or in the ITT population. However, in a descriptive analysis of OS in patients with PD-L1 CPS ≥ 1 , the OS HR estimate also favored pembrolizumab versus SoC with a HR of 0.72 (95% CI: 0.56, 0.94). These descriptive analyses suggest a potential trend in improved OS with the pembrolizumab-based regimen for patients with PD-L1 positive (CPS ≥ 1) LA HNSCC. Overall survival will be tested again at interim analysis 2 (IA2), when approximately 187 patients with PD-L1 CPS ≥ 10 have had OS events (93% information fraction of the final OS analysis).

The EFS treatment effect was largely preserved across subgroups except for patients with PD-L1 negative (CPS < 1) tumors and patients with primary tumors originating in the hypopharynx. The trial was not designed to detect a statistically significant difference in patients with PD-L1 negative (CPS < 1) tumors ($n=27$); however, in an exploratory subgroup analysis, the EFS for patients with PD-L1 negative disease demonstrated an EFS HR of 2.57 (95% CI 0.50, 13.36) with the median EFS not reached in either the pembrolizumab ($n=13$) arm or the SoC ($n=14$) arm. An exploratory analysis of OS for patients with PD-L1 negative tumors also showed a trend toward potential detriment with pembrolizumab with an OS HR of 1.73 (95% CI: 0.32, 9.54). Pembrolizumab monotherapy has also previously demonstrated a potential detriment for patients with PD-L1 negative recurrent or metastatic HNSCC, both in the first-line treatment setting (i.e., in the KEYNOTE-048 trial) and the refractory treatment setting (i.e., in KEYNOTE-040). The mechanism of action of pembrolizumab also provides scientific rationale that the efficacy of pembrolizumab monotherapy may be limited in patients with PD-L1 negative tumors. Taken together, the FDA review team recommends that the

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current indication is limited to patients with PD-L1 positive (CPS ≥ 1) tumors.

In an exploratory subgroup analysis by primary tumor site in patients with PD-L1 positive (CPS ≥ 1) hypopharyngeal tumors, the median EFS was 44.7 months (95% CI 10.3, NR) in the pembrolizumab arm (n=26) and NR (95% CI NR, NR) in the SoC arm (n=25) with an EFS HR of 2.28 (95% CI: 0.79, 6.56). For all other primary tumor site subgroups in patients with PD-L1 positive (CPS ≥ 1) tumors, including oral cavity (n=415), oropharyngeal (n=71), and laryngeal (n=144) tumors, EFS in the pembrolizumab arm compared to the SoC arm was 0.71 (95% CI: 0.53, 0.95), 0.32 (95% CI: 0.15, 0.68), and 0.62 (95% CI: 0.36, 1.06), respectively. In addition, for patients with PD-L1 positive primary hypopharyngeal tumors who received surgery, only 74% patients on the pembrolizumab arm (n=17/23) had complete surgical resections (R0) compared to 87% of patients with R0 resections on the SoC arm (n=20/23). For all other PD-L1 positive primary tumor site subgroups, the R0 resection rate was higher on the pembrolizumab arm compared to the SoC arm, at 93% vs 88% for laryngeal tumors (n=137), 89% vs 85% for oral cavity tumors (n=383), and 97% vs 82% for oropharyngeal tumors (n=61), respectively. The clinical review team recommends that the results of these exploratory analyses in patients with hypopharyngeal tumors are included in Section 14 of the USPI for pembrolizumab.

The observed safety profile of pembrolizumab is considered acceptable in the context of a life-threatening disease. The primary safety population was of 361 patients who received at least one dose of therapy in the pembrolizumab arm and 351 patients in the SoC arm. The most common AEs observed in the pembrolizumab arm ($\geq 20\%$) were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), dysphagia (29%), constipation (27%), hypothyroidism (26%), nausea (24%), rash (22%), musculoskeletal pain (22%), dry mouth (22%) and diarrhea (22%). In the neoadjuvant phase, rates of surgical cancellation were similar (11% vs 12%) for patients on the pembrolizumab arm compared to the SoC arm. Surgical cancellation due to adverse reactions on the pembrolizumab arm was 1.4% compared to 1.4% on the SoC arm. Fatal adverse reactions during the neoadjuvant phase of treatment occurred in 1.1% of patients who received pembrolizumab due to respiratory failure, clostridium infection, septic shock, and myocardial infarction (one patient each). There were 255 patients on the pembrolizumab arm who received at least one dose of pembrolizumab in the adjuvant phase and 275 patients on the SoC arm who started the adjuvant phase of therapy. In the adjuvant phase, there were slightly higher rates of serious adverse events (SAEs) (38% vs 23%), however there were similar rates of fatal AEs (5% vs 4.7%) in the pembrolizumab arm compared to the SoC arm. On the pembrolizumab arm, fatal AEs occurring during the adjuvant phase of therapy were due to death not otherwise specified (1.2%), acute renal failure (0.4%), hypercalcemia (0.4%), pulmonary hemorrhage (0.4%), dysphagia/malnutrition (0.4%), mesenteric thrombosis (0.4%), sepsis (0.4%), pneumonia (0.4%), COVID-19 (0.4%), respiratory failure (0.4%), cardiovascular disorder (0.4%) and gastrointestinal hemorrhage (0.4%).

No new safety signals were identified in the pembrolizumab arm, and the observed safety profile including immune-related adverse events

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(irAEs) was generally consistent with that described for pembrolizumab as a single agent in current product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure the safe use of perioperative pembrolizumab for HNSCC.

A major limitation of the design of KEYNOTE-689 is the inability of this two-arm trial to isolate the contribution of effect of the neoadjuvant, adjuvant radiation, and adjuvant post-radiation phases to the overall regimen, raising the concern for overtreatment. The inability to isolate the contribution of treatment phase in perioperative regimens for non-small cell lung cancer (NSCLC), another solid tumor, was the subject of an Oncologic Drugs Advisory Committee (ODAC) meeting on July 25, 2024. Although the perioperative regimen with durvalumab, another anti-PD-(L)1 antibody, evaluated for NSCLC in the AEGEAN trial was unable to isolate the effect of each phase of therapy, the ODAC members generally agreed that an additional trial prior to approval was not necessary. Since KEYNOTE-689 was initiated in 2017 prior to this ODAC, FDA will similarly not require an additional trial prior to approval of perioperative pembrolizumab for resectable HNSCC, despite the uncertainty surrounding the need for the adjuvant phase of treatment. Based on additional discussions at the July 25, 2024, ODAC, future perioperative trials in solid tumors including resectable HNSCC should be designed to improve the ability to demonstrate the contribution of each phase of therapy. Based on the available data, the FDA clinical review team does not consider that the lack of demonstration of clinical benefit of each phase of treatment significantly alters the overall benefit-risk evaluation of the regimen given the safety profile of single agent pembrolizumab in the adjuvant setting.

In summary, the results from KEYNOTE-689 meet the statutory evidentiary standard for traditional approval and provide substantial evidence of effectiveness of pembrolizumab for adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test, as neoadjuvant treatment, continued as adjuvant treatment in combination with RT with or without cisplatin, and then as a single agent. The magnitude of treatment effect on EFS, with a HR of 0.70 corresponding to a difference of 30.1 months in median EFS, is statistically significant and clinically meaningful, representing a major improvement for the treatment of patients with resectable, locally advanced HNSCC. These results are supported by a trend towards improved OS with pembrolizumab.

In conclusion, the results of KEYNOTE-689 support a favorable benefit-risk profile and meet the statutory evidentiary standard for traditional approval for the following indication:

Pembrolizumab for adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.

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The application was reviewed under Project Orbis, Assessment Aid, and Summary Review Programs. The Summary Review Program relies on qualified data summaries from the Applicant to support approval of a supplemental application, without independent verification of the data analyses.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 3% of new cancer cases and 2% of all cancer-related deaths in the U.S. At diagnosis, 50 to 60% of cases are locally advanced (LA) HNSCC (Stage III-IVa), treatable with curative-intent therapy, but with considerable morbidity that can include dysfunction of breathing, swallowing, and speech. - For LA HNSCC, the 5-year recurrence rate is 34% and the 5-year OS is 40 to 50%.	Resectable LA HNSCC is a serious and life-threatening disease, and patients experience high rates of disease recurrence or death after standard treatment.
Current Treatment Options	Standard of care (SoC) therapy for resectable LA HNSCC (Stage III-IVA) includes: - Surgical resection followed by adjuvant radiation or concurrent chemoradiation with cisplatin, (i.e., in patients with high-risk pathologic features) OR - Definitive chemoradiation therapy with concurrent cisplatin	No immune checkpoint inhibitor-based regimen is currently FDA approved for neoadjuvant, adjuvant, or perioperative therapy in patients with resectable LA HNSCC.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	- KEYNOTE-689 is a multicenter, international, open label, randomized, trial in patients with resectable LA HNSCC. In total, 714 patients were randomized 1:1 to receive either: - Single-agent pembrolizumab 200 mg every 3 weeks (Q3W) as neoadjuvant therapy for 2 cycles prior to surgical resection; then within 6 weeks after surgery; for 3 cycles during radiation with or without cisplatin; then as a single agent for 12 cycles. - No neoadjuvant therapy prior to surgery followed by adjuvant radiation with or without concurrent cisplatin In both treatment arms, patients received concurrent cisplatin with radiation if high-risk features were identified at the time of surgery (i.e., positive margins <1 mm or extranodal extension). - The primary endpoint of KEYNOTE-689 is EFS as assessed by BICR analyzed hierarchically in patients with tumor PD-L1 CPS ≥ 10, then CPS ≥ 1, then in the ITT population. Key secondary endpoints are mPR by BIPR and OS. - At the first EFS interim analysis (IA1), the study met the pre-specified boundary for significance in the tumor PD-L1 CPS ≥ 10, then CPS ≥ 1, and then in the ITT populations with EFS hazard ratios (HR) of 0.66 (95% CI: 0.49, 0.88; $p=0.00217$), 0.70 (95% CI: 0.55, 0.89; $p=0.00140$), and 0.73 (95% CI: 0.58, 0.92; $p=0.00411$), respectively. For patients with PD-L1 positive (CPS	This perioperative pembrolizumab regimen demonstrated a statistically significant improvement in EFS when compared to standard of care therapy. In an exploratory subgroup analysis, the EFS results for patients with PD-L1 negative tumors (CPS <1) disfavored the pembrolizumab arm. Taken together with findings of pembrolizumab monotherapy for patients with HNSCC with recurrent or metastatic disease, the review team recommends limiting the indication to patients with PD-L1 positive (CPS ≥ 1) tumors. The 30.1-month improvement in EFS with pembrolizumab for patients with PD-L1 positive tumors was statistically significant and clinically meaningful. While mPR was statistically significant in favor of the pembrolizumab arm, the relationship between mPR and direct clinical benefit in patients with LA HNSCC has not been established. At this time, OS has not reached statistical significance; however, there is a trend favoring pembrolizumab.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	≥1) tumors, the median EFS was 59.7 months (CI 95%: 37.9, NR) in the pembrolizumab arm and 29.6 (CI 95%: 19.5, 41.9) in the SoC arm. • Also at IA1, the study met the pre-specified boundary for statistical significance for mPR in patients with tumor PD-L1 CPS ≥10, then CPS ≥1, and then in the ITT population with MPR rates of 13.7% (95% CI: 9.7, 18.7), 9.8% (95% CI: 7.0, 13.3), and 9.3% (95% CI: 6.7, 12.8), respectively on the pembrolizumab arm, with no major pathological responses observed in patients on the SoC control arm. • At IA1, OS in patients with PD-L1 CPS ≥10 had not reached statistical significance. Median OS was not reached (95% CI: NR, NR) in the pembrolizumab arm and was 61.8 months (95% CI: 49.2, NR) in the SoC arm, corresponding to a HR of 0.72 (95% CI: 0.52, 0.98). • In an exploratory subgroup analysis of patients with tumor PD-L1 CPS <1, median EFS was not reached in the pembrolizumab arm (n=13) or SoC arm (n=14). The EFS HR was 2.57 (95% CI: 0.50, 13.36) suggesting a potential detriment with pembrolizumab. • In an additional exploratory subgroup analysis by primary tumor site in patients with PD-L1 positive (CPS≥1) hypopharyngeal primary tumors, median EFS was 44.7 months (95% CI 10.3, NR) in the pembrolizumab arm (n=26) and NR (95% CI NR, NR) in the SoC arm (n=25) with an EFS HR of 2.28 (95% CI: 0.79, 6.56).	The clinical review team recommends that the results of the exploratory analyses in patients with hypopharyngeal tumors are included in Section 14 of the USPI for pembrolizumab.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	For patients with PD-L1 positive hypopharyngeal tumors who received surgery, the rate of R0 resections in the pembrolizumab arm was 74% (n=17/23) compared to 87% (n=20/23) on the SoC arm.	
<u>Risk and Risk Management</u>	- The addition of perioperative pembrolizumab to SoC therapy in KEYNOTE-689 did not appear to compromise the ability for patients with LA HNSCC to receive surgery, have R0 resections (other than in patients with hypopharyngeal tumors as described above), or receive adjuvant radiation or chemoradiation. - The most common AEs observed in the pembrolizumab arm ($\geq 20\%$) were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), dysphagia (29%), constipation (27%), hypothyroidism (26%), nausea (24%), rash (22%), musculoskeletal pain (22%), dry mouth (22%) and diarrhea (22%). - No new safety signals were identified in the pembrolizumab arm, and the observed safety profile including irAEs, was generally consistent with the current USPI.	The observed safety profile of perioperative pembrolizumab as neoadjuvant therapy followed by surgery and continued as adjuvant therapy with pembrolizumab during and after adjuvant radiation or chemoradiation for resectable LA HNSCC is acceptable when assessed in the context of treatment for a life-threatening disease. The incidence of adverse reactions leading to cancellation or delay of surgery and of surgery-related complications were similar between study arms. A similar proportion of patients in the pembrolizumab arm were able to undergo definitive surgery compared to patients in the SoC arm. The KEYNOTE-689 design did not isolate the contribution of either the neoadjuvant or adjuvant treatment phases with the greatest uncertainty related to the need for additional adjuvant treatment with pembrolizumab. This raised the risk of overtreatment and its attendant toxicities; however, the safety profile

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		of single agent adjuvant immunotherapy is relatively well tolerated and the overall risk and uncertainties around the perioperative regimen were considered acceptable at the time of trial initiation in 2017. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of perioperative pembrolizumab for LA HNSCC.

1.4. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
☒	Patient reported outcome (PRO)	Section 8.1.2

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

X

Cross-Disciplinary Team Leader

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

HNC is the sixth most common cancer worldwide [1] [2]. HNSCC accounts for over 90% of HNC. The most frequent tumor sites of HNSCC are the oral cavity, pharynx, and larynx [3] [4]. Based on GLOBOCAN estimates, in 2022 there were 771,694 new cases and 385,004 deaths of HNC located in the lip, oral cavity, oropharynx, hypopharynx, and larynx [5] [6]. In the US, it is projected that in 2024 there will be 71,100 new cases and 16,110 deaths of HNC located in the oral cavity, pharynx, and larynx [7]. Among newly diagnosed cases, around 50% are locally advanced (Stages III-IVB), and 15% have distant metastases (Stage IVC). The 5-year OS rate of resectable LA HNSCC remains low (40-50%), despite multimodal treatment consisting of surgery followed by postoperative RT with or without platinum-containing chemotherapy [8] [9] [10]. Patients with HPV-positive Stage III-IV (as per AJCC 7th edition) oropharyngeal cancer have a better prognosis, with a 5-year survival rate of 71% to 74% (independently of their age and smoking status), except for patients with T4 or N3 disease for which the 5-year OS is around 50% to 60% [11].

Alcohol and tobacco consumption are the main risk factors for oral cavity, larynx, oropharynx, and hypopharynx cancers [12] [13]. In addition, the oncogenic HPV infection, mainly HPV-16, has been established as a known independent cause of oropharyngeal cancer (tonsils and base of tongue) [14] [15], and is associated with significantly improved survival [14] [16] [17] [18].

The FDA's Assessment:

FDA agrees with the Applicant's position.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

The current SoC treatment for patients with newly diagnosed Stage III-IV resectable LA HNSCC consists of surgical resection of the tumor and neck lymph node dissection, followed by either RT alone or in combination with cisplatin, based on the presence of post-surgical high-risk pathologic features of extranodal extension and/or positive surgical margins [19] [9] [10] [20]

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[21]. Neoadjuvant therapy is not part of the standard of care for Stage III-IV resectable LA HNSCC.

Since it was demonstrated approximately 20 years ago that the addition of cisplatin to RT was superior to RT alone in patients with high-risk pathologic features, the SoC for this patient population has not changed and there continues to be no approved adjuvant therapies that can be administered after completion of postoperative locoregional treatment [22]. Furthermore, should the disease progress, the median survival for R/M HNSCC is only approximately 12 months [23] [24]. Accordingly, new treatment strategies to decrease rates of recurrence and distant metastases of HNSCC are needed to improve outcomes for this patient population with newly diagnosed resectable Stage III-IV LA HNSCC.

The FDA's Assessment:

FDA agrees with the Applicant's position.

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 of KEYTRUDA®. In the US, the 400 mg Q6W regimen for adult patients was approved on 28-APR-2020 for all approved monotherapy and combination indications. At the time of the submission of this application, KEYTRUDA is registered and approved for at least 1 oncology indication in at least 100 countries worldwide, including the US, EU, and Japan. For a complete list of indications for KEYTRUDA, please refer to the product labeling.

The FDA's Assessment:

FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position: [Table 1] summarizes key regulatory interactions for KEYNOTE-689.

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Table 1: Applicant – Key Regulatory Interactions Related to KEYNOTE-689

<i>Date</i>	<i>Type of Meeting/ Correspondence</i>	<i>Key Outcomes or Recommendations</i>
17-JUL-2017	FDA Type B EOP2 (Preliminary Comments Reference ID: 4123673)	The Agency considered the overall trial design to be largely acceptable, but emphasized the trial would not be able to differentiate between the neoadjuvant and adjuvant phases. The Agency recommended refinements for the eligible patient population and the proposed stratification factors. FDA recommended that risk categorization be based on central pathology review. Following consultation with vendors, Merck requested a follow-up Type C meeting to align with FDA.
06-SEP-2017	Original submission (Serial No. 0563)	Study KN-689 was submitted to FDA as a new protocol to existing IND 122325.
25-JUN-2018	FDA Type C Meeting (Reference ID: 4279704)	Focused consideration of central pathological assessment for determination of risk categorization for adjuvant phase.
09-FEB-2021	Submission of Agreed iPSP (Serial No. 0731)	Submission of Agreed Initial Pediatric Study Plan indicating Merck's intention to submit a waiver request from the requirements of PREA for pediatric population <18 years of age.
03-OCT-2024	Teleconference to review Top-Line results from IA1 of KN-689. (Ad-hoc teleconference, no minutes generated)	Merck and FDA had an informal teleconference to discuss the acceptability of the efficacy and safety results from IA1 of KN-689 to support a supplemental efficacy application for Keytruda.
25-NOV-2024	FDA Type B pre-sBLA Meeting (Preliminary Comments Reference ID: 5482815; Final Meeting Minutes pending)	FDA agreed with Merck's proposals provided to FDA in response to Preliminary Comments, included generation of an ISE and exploratory analyses to address Contribution of Phase to be included in the dossier.

The FDA's Assessment:

FDA agrees with the Applicant's position.

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

4.1. Office of Scientific Investigations (OSI)

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Clinical data from KEYNOTE-689 (Study MK-3475-689) were submitted to the Agency in support of supplemental Biologics License Application (sBLA) 125514 S-180 for pembrolizumab given prior to surgery and in combination with radiotherapy given post-surgery for advanced head and neck squamous cell cancer (HNSCC). Two clinical investigators, Drs. Irene Brana Garcia (Site # 1200) and Anupama Nehra (Site # 2053), as well as the Sponsor, Merck Sharp & Dohme Corp. (thereafter Merck), and the imaging Contract Research Organization (CRO), (b) (4) were inspected.

Inspections of Drs. Garcia and Nehra, Merck, and (b) (4) did not find significant concerns regarding the study conduct, data discrepancies or integrity, Good Clinical Practice (GCP), or regulatory compliance. Based on these inspections, KEYNOTE-689 appears to have been conducted adequately, and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

For additional details, refer to the Clinical Inspection Summary uploaded to DARRTS on May 24, 2025.

4.2. Product Quality

No new CMC information was submitted in this supplemental application.

4.3. Clinical Microbiology

No clinical microbiology data were submitted in this supplemental application.

4.4. No clinical microbiology data were submitted in this supplemental application. Devices and Companion Diagnostic Issues

There was no device or companion diagnostic test reviewed as part of this supplemental application.

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

5.2. Not applicable Referenced NDAs, BLAs, DMFs

The Applicant's Position: No new data are being submitted in the current application.

The FDA's Assessment:

Not applicable

X

X

Primary Reviewer

Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

KEYTRUDA was utilized at the FDA-approved dose and schedule, and no new clinical pharmacology evaluation was needed.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

No new data are being submitted in the current application.

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

X	X
<u>Primary Reviewer</u>	<u>Team Leader</u>

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Table 2: Applicant – List of Clinical Trials Relevant to This BLA

<i>Controlled Studies to Support Efficacy and Safety</i>	
Trial Identity/NCT no.	KEYNOTE-689 / NCT03765918
Trial Design	Phase 3, randomized, open-label, active-controlled, multicenter study
Regimen/Schedule/Route	Neoadjuvant pembrolizumab (200 mg, Q3W, IV infusion) followed by surgery and adjuvant pembrolizumab plus RT ± cisplatin followed by pembrolizumab monotherapy OR no neoadjuvant treatment followed by surgery and adjuvant RT ± cisplatin
Study Endpoints	
Primary	EFS per BICR in CPS ≥ 10, CPS ≥ 1, and all participants
Secondary	- mPR per BIPR in CPS ≥ 10, CPS ≥ 1, and all participants - OS in CPS ≥ 10, CPS ≥ 1, and all participants - pCR per BIPR in CPS ≥ 10, CPS ≥ 1, and all participants - HRQoL (EORTC QLQ-C30, EORTC QLQ-H&N35) in CPS ≥ 10, CPS ≥ 1, and all participants - Toxicity according to CTCAE version 4.03
Exploratory/Tertiary	- Local Regional Control - Distant Metastases-Free Survival (DMFS) - Incidence of second Head and Neck and Other Cancers - EFS and OS in high-risk and low-risk participants - EuroQol-5 dimensions (EQ-5D-5L) in all study populations - Identification of molecular biomarkers - Correlation of clinical response to tumor/circulating markers - Efficacy endpoints in CPS ≥ 50 participants - Rate of in situ carcinoma/dysplasia observed in surgically resected specimens
Treatment Duration, Follow-Up	- Treatment Duration: Neoadjuvant phase: Pembrolizumab group: 2 cycles, SoC group: No study treatment. - Adjuvant phase: Pembrolizumab group: 15 cycles, and RT +/- cisplatin (3 cycles), SoC group: RT +/- cisplatin (3 cycles) - Post-Treatment Follow-up: Assessed through Year 5.
No. of Patients Enrolled	Pembrolizumab (n=363); SoC (n=351) – ITT Population
Study Population	Adults with newly diagnosed treatment-naïve Stage III-IVA, resectable, locoregionally advanced head and neck squamous cell carcinoma (LA HNSCC)
No. of Centers, Countries	192 centers, 24 countries
Abbreviations: BIPR= blinded independent pathologist review; CPS=combined positive score; CTCAE=Common Terminology Criteria for Adverse Events; EFS=event-free survival; HNSCC=head and neck squamous cell carcinoma; HRQoL=health-related quality of life; ITT=intent to treat; IV=intravenous; LA=locally advanced; mPR=major pathological response; NCT=National Clinical Trial; pCR=pathological complete response; OS=overall survival; Q3W=every 3 weeks; RT=radiotherapy; SoC=standard of care. Database Cutoff Date: 25-JUL-2024	

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The Applicant's Position: The efficacy and safety results from IA1 of KEYNOTE-689 support the proposed indication of the use of KEYTRUDA for the treatment of patients with resectable locally advanced HNSCC as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without platinum-containing chemotherapy and then as a single agent. The study is summarized in [Table 2].

The FDA's Assessment:

FDA generally agrees with the Applicant's position that KEYNOTE-689 is the pivotal trial providing efficacy and safety data to support this supplemental application. The data submitted represent the first interim analysis (IA1) of trial data and are from a data cut off (DCO) date of July 25, 2024.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. KEYNOTE-689

Trial Design

The Applicant's Description:

This is a Phase 3, randomized, active-controlled, multisite, open-label study of pembrolizumab as neoadjuvant therapy and pembrolizumab in combination with RT ± cisplatin as post-surgical adjuvant therapy followed by pembrolizumab monotherapy OR no neoadjuvant treatment followed by surgery and adjuvant RT ± cisplatin in newly diagnosed treatment-naïve participants with Stage III-IVA resectable LA HNSCC. AEs were monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE Version 4.03. The study design is summarized in [Figure 1].

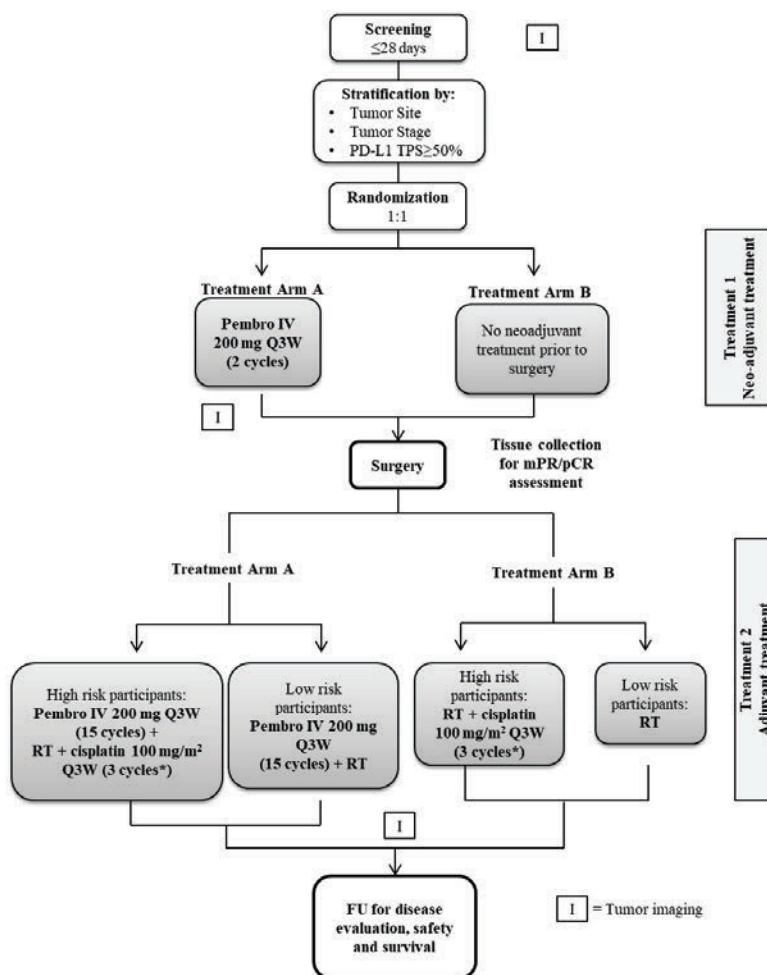
In this document, efficacy analyses are based on the ITT population (in CPS ≥ 10, CPS ≥ 1, and all participants), in which participants are analyzed based on the treatment group to which they were randomized, and safety analyses are based on the APaT population, in which participants are analyzed based on the study treatment they received. The PRO analyses are based on the PRO FAS population, defined as participants who have received treatment and have at least 1 PRO assessment available. For simplicity, the treatment groups for both efficacy and safety analyses are designated “pembrolizumab” and “SoC”.

For efficacy and PRO analyses, the “pembrolizumab” treatment group refers to study participants who were randomized to receive the 17 dose regimen of pembrolizumab as

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neoadjuvant therapy for 2 doses and then continued to complete 15 doses as adjuvant treatment in combination with RT ± cisplatin followed by pembrolizumab monotherapy. The “SoC” treatment group refers to study participants who were randomized to receive RT ± cisplatin during the adjuvant phase (following surgical resection), with no neoadjuvant treatment prior to surgery. The same definitions apply for safety analyses with the exception that the treatment group to which a pembrolizumab or SoC participant is assigned is determined by the treatment the participant actually received rather than the treatment to which the participant was randomized.

Figure 1 Applicant – KEYNOTE-689 Study Design



*If there are delays in cisplatin treatment, cisplatin may continue for up to 1 week following completion of RT.

FU = follow-up; IV = intravenous; mPR = major pathological response; pCR = pathological complete response; PD-L1 = programmed cell death ligand 1; Pembro = pembrolizumab; Q3W = every 3 weeks; RT = radiotherapy; TPS = tumor proportion score.

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Trial Location: 192 centers, 24 countries.

There were 39 sites in the US. Demographic factors, such as median age and disease characteristics (eg, histology, stage), were similar to previously conducted studies in participants with Stage III-IVA, resectable LA HNSCC [25] [26] [10]. Demographic and baseline characteristics were generally balanced between the treatment groups.

Dose Selection: The dose of pembrolizumab for this study was 200 mg Q3W.

Blinding: Open-label

Dose Modification and Dose Discontinuation: Treatment with pembrolizumab was withheld or discontinued based on guidelines described in the protocol, which included treatment-related toxicities or life-threatening AEs. Dose modification and toxicity management guidelines were consistent with the approved labels for pembrolizumab. Dosing interruptions were permitted for reasons not related to study therapy.

Summary of Trial Governance and Oversight: The study uses an external DMC to provide independent review and assessment of efficacy and safety data to safeguard the interest and safety of the participants and the continued ethical integrity of the study. The DMC reviews ongoing study data periodically and makes recommendations to the EOC to continue or stop the trial. The EOC will receive and decide upon any recommendations made by the DMC or Trial Steering Committee regarding the study.

Procedures and Schedule: An overview of the schedules of activities for the neoadjuvant and adjuvant phase for the pembrolizumab group are in [Table 3] and [Table 4]. Schedules of activities for the neoadjuvant and adjuvant phase for SoC are in [Table 5] and [Table 6].

Table 3: Applicant – Schedule of Activities – Preoperative (neoadjuvant) for Pembrolizumab

Study Period	Screening	Treatment randomization	Treatment 1		Presurgery Imaging/ Safety ^c	Surgery ^c	Post-surgery Safety Follow-up
Visit Number/Title			Pembro neoadjuvant				
Treatment Cycle			1	2			
Week			1	4	6		
Scheduled Day (s)			1	1	1		
Scheduling Window (Days, unless noted)			-28 to -1	+3	±3		±10
Administrative Procedures							
Inclusion/Exclusion Criteria	X						
Demographics, Disease Details and Complete Medical History (includes substance usage)	X						
Prior/Concomitant Medication Review	X		X	X	X		X

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Treatment Randomization via IVRS		X					
Pembrolizumab Administration			X	X			
Surgery						X	
Efficacy Procedures							
CT/MRI head & neck, chest, upper abdomen	X				X		(X) optional
FDG-PET or FDG-PET/CT	X						
Tissue Collection for Histopathology (mPR and pCR assessment)						X	
Patient Reported Outcomes							
EQ-5D-5L			X	X	X		
EORTC QLQ-C30			X	X	X		
EORTC QLQ-H&N35			X	X	X		
Safety Procedures							
Full physical examination including neurological exam and Height	X						X
Directed physical examination			X	X	X		
ECOG Performance Status	X		X	X	X		X
Weight and Vital Signs	X		X	X	X		X
12-lead ECG (local)	X						
Urine or Serum β -hCG Pregnancy Test (WOCBP only) – as per local SOP	X		X	(x)			(x)
HIV, hepatitis B and C screen (testing optional per site SOP)	X						
Hematology	X		X	X	X		X
Chemistry	X		X	X	X		X
Urinalysis	X		X	X	X		X
Coagulation tests (PT/INR and aPTT/PTT)	X		-----If Clinically Indicated----				--If Clinically Indicated--
Thyroid Function (TSH)	X			X	--If Clinically Indicated--		--If Clinically Indicated--
AE/SAE review	X		---Continuous Reporting---				
Oral and dental check-up	X						
Audiometric Testing	X						
Fiber optic examination of primary tumor site	X		--If Clinically Indicated				
Tumor Tissue Sample Collection							
Histology, PD-L1 and p16 biomarker analysis prior to randomization for stratification	X						

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Tissue Collection for Biomarker Analysis	X					X	
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APPEARS THIS WAY ON ORIGINAL

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Table 4: Applicant –Schedule of Activities – Postoperative (adjuvant) for Pembrolizumab

Study Period	Treatment 2 (adjuvant)											
Visit Number/Title												
Treatment Cycle	1			2			3	4	5	6	7	8-15
Week	1	2	3	4	5	6	7	10	13	16	19	22-43
Scheduled Day(s)	1	8	15	1	8	15	1	1	1	1	1	1
Scheduling Window (Days, unless noted)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Administrative Procedures												
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X
Pembrolizumab Administration	X			X			X	X	X	X	X	X
Radiotherapy (IMRT/IGRT)	X	X	X	X	X	X	(X)					
Conditional Cisplatin Treatment (100 mg/m ²)	X			X			X					
Efficacy Procedures												
CT/MRI head and neck, chest, upper abdomen										X		X
FDG-PET or FDG-PET/CT										X		
Patient Reported Outcomes												
EQ-5D-5L	X			X						X		X
EORTC QLQ-C30	X			X						X		X
EORTC QLQ-H&N35	X			X						X		X
Safety Procedures												
Full physical examination including neurological exam	X											
Directed physical examination		X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X
Weight and Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Urine or Serum β-hCG Pregnancy Test (WOCBP only) – as per local SOP	X			(x)			(x)	(x)	(x)	(x)	(x)	(x)
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X							X			X	X
Coagulation tests (PT/INR and aPTT/PTT)	-----As Clinically Indicated-----											
Thyroid Function (TSH)				X					X			X
AE/SAE review	-----Continuous Reporting-----											
Oral and dental check-up	-----Recommended Every 6 months-----											
Audiometric Testing	-----As Clinically Indicated-----											
Fiber optic exam of primary tumor site									X			X
Tumor Tissue Sample Collection												
Tissue Collection for Biomarker Analysis (tested centrally)												
Neck Dissection (per site discretions) ± biopsy/photography								-----If Clinically Indicated----				

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Table 5: Applicant –Schedule of Activities – Preoperative (neoadjuvant) for the SoA Group

Study Period	Screening	Treatment randomization	Presurgery	Surgery	Post-surgery Safety Follow-up 7-30 days post-surgery	Treatment 2						
Visit Number/Title			SoC RT ± cisplatin adjuvant									
Week			1			2	3	4	5	6	7	
Scheduled Day (s)	1		8			15	1	8	15	1		
Scheduling Window (Days, unless noted)	±3		±3			±3	±3	±3	±3	±3		
Administrative Procedures												
Inclusion/Exclusion Criteria	X											
Demographics, Disease Details and Complete Medical History (includes substance usage)	X											
Prior/Concomitant Medication Review	X		X		X	X	X	X	X	X	X	X
Treatment Randomization via IVRS		X										
Radiotherapy (IMRT/IGRT)						X	X	X	X	X	X	(X*)
Conditional Cisplatin Treatment (100 mg/m²)						X			X			X
Surgery				X								
Efficacy Procedures												
CT/MRI head and neck, chest, upper abdomen	X		X*		(X) optional at site discretion							
FDG-PET or FDG-PET/CT	X											
Tissue Collection for Histopathology (mPR and pCR assessment)				X								
Patient Reported Outcomes												

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EQ-5D-5L			X			X*			X*			
EORTC QLQ-C30			X			X*			X*			
EORTC QLQ-H&N35			X			X*			X*			
Safety Procedures												
Full physical examination including neurological exam and Height	X				X							
Directed physical examination			X			X	X	X	X	X	X	X
ECOG Performance Status	X		X		X	X	X	X	X	X	X	X
Weight and Vital Signs	X		X		X	X	X	X	X	X	X	X
12-lead ECG (local)	X											
Urine or Serum β -hCG Pregnancy Test (WOCBP only) – as per local SOP	X				(x)	X			(x)			(x)
HIV, hepatitis B and C screen (testing optional per site SOP)	X											
Hematology	X		X*		X	X	X	X	X	X	X	X
Chemistry	X		X*		X	X	X	X	X	X	X	X
Urinalysis	X		--If Clinically Indicated--		X	X	--If Clinically Indicated--					
Coagulation tests (PT/INR and aPTT/PTT)	X				----If Clinically Indicated----							
Thyroid Function (TSH)	X		X*						X			
AE/SAE review	X		-----Continuous Reporting-----									
Oral and dental check-up	X					---Recommended Every 6 months---						
Audiometric Testing	X					----If Clinically Indicated----						
Fiber optic examination of primary tumor site	X					----If Clinically Indicated----						
Future Biomedical Research/Biomarkers												

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Blood for Genetic Analysis			X										
Blood for RNA Analysis			X			X							
Blood for Plasma Biomarker Analyses			X			X							
Blood for Serum Biomarker Analyses			X			X							
Blood for ctDNA			X			X						X*	X*
Tumor Tissue Sample Collection													
Histology, including PD-L1 and p16 biomarker analysis on all participants prior to randomization for stratification, p16 evaluations	X												
Tissue Collection for Biomarker Analysis	X			X*									
Neck Dissection (per site discretions) ± biopsy/photography						-----If Clinically Indicated-----							

Table 6: Applicant –Schedule of Activities – Postoperative (adjuvant) for the SoA Group

Study Period	End of Treatment	Post-Treatment Follow-up ^a				
Visit Number/Title	Discontinuation	Safety FU	Post-Treatment FU			Survival FU
Treatment Cycle/Day			Up to end of Year 3	Years 4-5		
Scheduling Window (Days (unless noted))	At time of Treatment Discontinuation	30 days from last dose +14 days	Every 3 months from last scan ±7 days	Q6M ±14 days	Q12M ±14 days	Every 3 months ±14 days
Administrative Procedures						
Prior/Concomitant Medication Review	X	X	----If Clinically Indicated---			
Post-study Anticancer Therapy Status						X
Survival status						X

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Efficacy Procedures						
CT/MRI head and neck, chest, upper abdomen			X	X		[X]
EQ-5D-5L	X	X	X		X	
EORTC QLQ-C30	X	X	X		X	
EORTC QLQ-H&N35	X	X	X		X	
Safety Procedures						
Full physical examination	X					
Directed physical examination		X	X	X		
ECOG Performance Status	X	X	X	X		
Weight and Vital Signs	X	----If Clinically Indicated-----				
Urine or Serum β -hCG Pregnancy Test (WOCBP only) – as per local SOP	X*	X				
Hematology, Chemistry, Urinalysis	X	X	--If Clinically Indicated--			
Coagulation tests (PT/INR and aPTT/PTT)		-----If Clinically Indicated----- -				
Thyroid Function (TSH)	X	X	---If Clinically Indicated---			
AE/SAE review	-----Continuous Reporting-----					
Oral and dental check-up			--Recommended every 6 months--			
Audiometric Testing	-----If Clinically Indicated-----					
Fiber optic examination of primary tumor site			-----Every 12 months----- or as per site discretion			
Future Biomedical Research/Biomarkers						
Blood for RNA Analysis	X					
Blood for Plasma Biomarker Analyses	X					
Blood for Serum Biomarker Analyses	X					
Blood for ctDNA	X		X	X		
Tumor Tissue Sample Collection						
Tissue Collection for Biomarker Analysis (tested centrally)						

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Concomitant Medications: Concomitant medications received within 28 days of the first dose through 30 days after the last dose of study treatment were to be recorded. Prohibited medications included antineoplastic systemic chemotherapy or biological therapy, immunotherapy, chemotherapy and RT not specified in this protocol, investigational agents other than pembrolizumab, live or live attenuated vaccines within 30 days prior to the first dose of study treatment and while receiving study treatment, systemic corticosteroids except for AE management, and prophylactic growth factor support such as erythropoietin or granulocyte-colony stimulating factor was not permitted while receiving RT.

Treatment Compliance: The total volume of pembrolizumab infused was compared with the total volume prepared to determine compliance with each dose of pembrolizumab administered. Study treatments were administered by the investigator and/or study staff, ensuring compliance.

Participant Completion, Discontinuation, or Withdrawal: Participants could withdraw consent or discontinue from study intervention at any time and for any reason or be discontinued from treatment at the discretion of the investigator if any untoward effect occurred. In addition, a participant could be discontinued from treatment by the investigator or the Sponsor if the treatment was inappropriate, the trial plan was violated, or for administrative and/or other safety reasons. After discontinuation of study intervention, participants remained in the study for follow-up, unless consent was withdrawn. Once discontinued from study intervention, study intervention was not restarted (except for infusion/treatment interruptions due to AEs). Reasons for study intervention discontinuation included: disease recurrence, unacceptable AEs, progression/recurrence of any malignancy, occurrence of another malignancy that requires active treatment, a confirmed positive serum pregnancy test, completion of 17 doses of treatments with pembrolizumab if in the pembrolizumab group, intercurrent illness, study intervention-related toxicity, medical conditions, personal circumstances, or noncompliance with study intervention or procedure requirements. Participants who withdrew from the study were not replaced.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the study design. Of note, the experimental arm contains pembrolizumab in both the neoadjuvant and adjuvant phase, while the control arm does not include neoadjuvant therapy and only standard of care adjuvant therapy. The trial design lacks additional experimental arms evaluating the addition of pembrolizumab in the neoadjuvant phase only or the adjuvant phase only, therefore the contribution of pembrolizumab in both the neoadjuvant and adjuvant settings to the overall treatment effect cannot be assessed.

Eligibility Criteria

The Applicant's Description:

Summary of Key Inclusion Criteria Key inclusion criteria included:

- Male/female participants who were at least 18 years of age on the day of informed consent

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with histologically confirmed new diagnosis of resectable, nonmetastatic, squamous cell carcinoma as assessed by the investigator based on baseline imaging and clinical assessment that is either:

- a. Stage III oropharyngeal p16 positive that is T4 (N0-N2), M0 OR
 - b. Stage III or IVA oropharyngeal p16 negative
OR
 - c. Stage III or IVA larynx/hypopharynx/oral cavity (independent of p16).
- Able to undergo protocol therapy, including necessary surgery.
 - ECOG performance status 0 or 1 within 10 days of randomization.
 - Had adequate organ function as defined in the study protocol.

Summary of Key Exclusion Criteria Key exclusion criteria excluded participants who:

- Have Stage T4B and/or N3 LA HNSCC and/or distant metastases.
- Had a history of (noninfectious) pneumonitis that required steroids or had current pneumonitis.
- Had active autoimmune disease that had required systemic treatment in the past 2 years.
- Had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
- Had received prior radiotherapy treatment or systemic anticancer therapy including investigational agents for the HNC under study prior to randomization/allocation. Note: RT to treat a prior HNC is also grounds for exclusion.
- Had Grade ≥ 2 audiometric hearing loss. Note: Audiometric abnormalities without corresponding clinical symptoms of Grade ≥ 2 hearing loss were not grounds for exclusion. Note: Participants with complete nontumor-related hearing loss (ie, congenital deafness) are eligible for this study.
- Had Grade ≥ 2 neuropathy.
- Had Grade 3-4 bleeding due to the underlying malignancy.

The FDA's Assessment:

FDA agrees with the Applicant's description of the eligibility criteria.

Study Endpoints

The Applicant's Description: The primary study endpoint was EFS assessed by BICR. Key secondary study efficacy endpoints were mPR assessed by BIPR, and OS. Other secondary endpoints and exploratory study endpoints are detailed in [Table 2]. Key efficacy analyses were conducted in the PD-L1 CPS ≥ 10 , PD-L1 CPS ≥ 1 , and all participants populations.

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The FDA's Assessment:

FDA agrees with the Applicant's description of the primary and secondary endpoints. An EFS event is defined by the Applicant as radiographic disease progression per RECIST 1.1 (with the exception of patients who undergo a definitive biopsy of the progressed lesion and are found to have no histologic evidence of invasive cancer), radiographic disease progression during the neoadjuvant phase that precludes surgery, local or distant progression or recurrence (as assessed with imaging or biopsy as indicated), or death due to any cause. The EFS and OS endpoints incorporate the effect of the entire neoadjuvant and adjuvant pembrolizumab regimen. As further described in Section 8.1.2, mPR was defined as having less than or equal to 10% invasive SCC within the resected primary tumor specimen and all sampled regional lymph nodes, as assessed by BIPR. While statistically tested, the mPR endpoint is not a currently validated endpoint to demonstrate clinical benefit in patients with resectable HNSCC.

Statistical Analysis Plan and Amendments

The Applicant's Description: Key elements of the SAP are summarized in [Table 7].

Table 7: Applicant – KEYNOTE-689 Statistical Analysis Plan Summary

Analysis Populations	Efficacy: Intent to Treat (ITT) Safety: All Participants as Treated (APaT) Patient reported outcome (PRO): Full Analysis Set (FAS) population
Study Endpoints	Refer to [Table 2]. KEYNOTE-689 was designed with the primary endpoint of EFS. If the primary endpoint meets statistical significance, then the study can be declared positive.
Statistical Methods for Key Efficacy Analyses	The primary hypothesis for EFS and key secondary hypothesis for OS will be evaluated by comparing the pembrolizumab arm to the SoC arm using a stratified log-rank test. Estimation of the HR will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The key secondary hypothesis for mPR will be evaluated by comparing the pembrolizumab arm to the SoC arm with respect to the rate of mPR using the stratified Miettinen and Nurminen method with strata weighting by sample size. The between-treatment difference in percentages, its 95% CI and p value will be provided.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, the analyses will be provided using the Miettinen and Nurminen method.
Interim Analyses (IAs)	<u>Efficacy:</u> Two IAs will be performed. Results will be reviewed by an eDMC. These IAs and the final analysis (FA) are summarized below. Details are provided in Protocol Section 10.7. IA1:

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	- Timing: ~207 EFS events in participants whose tumors express PD-L1 CPS ≥ 10 and ~6 months after last participant randomized (estimated to be 64 months after the first participant is randomized) - Testing: Inferential analysis for EFS, mPR, and OS will be provided - IA2: - Timing: ~232 EFS events in participants whose tumors express PD-L1 CPS ≥ 10 and ~22 months after last participant randomized (estimated to be 80 months after the first participant is randomized) - Testing: Inferential analysis for EFS and OS will be provided - FA: - Timing: ~201 deaths in participants whose tumors express PD-L1 CPS ≥ 10 and ~34 months after last participant randomized (estimated to be 92 months after the first participant is randomized). - Testing: Inferential analysis for OS will be provided Note that for IA1, IA2, and FA, if the EFS events or the OS events in participants whose tumors express PD-L1 CPS ≥ 10 accrue slower than expected, the analysis can be delayed up to 3 months after the projected timing. For IA2 and FA, if the EFS events or OS events in participants whose tumors express PD-L1 CPS ≥ 10 accrue faster than expected (ie, ~targeted number of events have been observed prior to the projected timing of analysis), the analysis may be conducted at least ~10 months after the timing of prior IA. Safety: An interim safety analysis will be performed and reviewed by the eDMC when the first 15 participants in the pembrolizumab arm have completed RT during the post-surgery adjuvant treatment phase. Afterwards, the eDMC will review safety data periodically in the study.
Multiplicity	The overall Type I error across the primary endpoint (EFS) and the key secondary endpoints (mPR and OS) and across multiple populations is strongly controlled at $\alpha = 2.5\%$ (one-sided), with $\alpha = 2.5\%$ initially allocated to the hypothesis for EFS in participants whose tumors express PD-L1 CPS ≥ 10 (H1). Alpha can be reallocated using the graphical approach of Mauer and Bretz [27] as described in the protocol. Group-sequential methods will be used to allocate alpha among the interim and final analyses for EFS and OS.
Sample Size and Power	The planned sample size is 714 participants, which will result in approximately 462 participants whose tumors express PD-L1 CPS ≥ 10 and approximately 680 participants whose tumors express PD-L1 CPS ≥ 1. For testing EFS in participants whose tumors express PD-L1 CPS ≥ 10, the study has ~94.9% power to demonstrate that the pembrolizumab arm is superior to the SoC arm at a one-sided 2.5% alpha-level, if the underlying HR of EFS is 0.62. For the mPR endpoint, the study has >99.9% power to detect a true mPR rate improvement from 2% to 27% (ie, a difference of 25 percentage points) at $\alpha = 0.05\%$ (one-sided) with ~462 participants whose tumors express PD L1 CPS ≥ 10. For testing OS in participants whose tumors express PD-L1 CPS ≥ 10, the study has ~84.9% power to demonstrate that the pembrolizumab arm is superior to the SoC arm at a one-sided 2.45% alpha-level, if the underlying HR of OS is 0.65.

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Abbreviations: APaT=all participants as treated; CI=confidence interval; CPS=combined positive score; EFS=event-free survival; FA=final analysis; FAS=full analysis set; HR=hazard ratio; IA=interim analysis; IA1=first interim analysis; IA2=second interim analysis; ITT=intent to treat; mPR=major pathological response; OS=overall survival; PD-L1=programmed cell death ligand 1; PRO=patient reported outcome; SoC=standard of care.

The FDA's Assessment:

In general, FDA agrees with the Applicant's summary of key elements of the SAP. The primary and key secondary endpoints are tested with appropriate control for multiple comparisons using a hierarchical testing procedure with a graphical approach. EFS and OS were analyzed using appropriate group sequential procedures and the interim analysis was conducted when the pre-specified number of events were accrued in the CPS ≥ 10 subpopulation. Although mPR was included in the hypothesis testing scheme with appropriate type I error control, FDA considers this endpoint to be exploratory only for resectable HNSCC. EFS, OS, and mPR were each planned to be tested across 3 populations with appropriate multiplicity control: patients with tumors expressing PD-L1 CPS ≥ 10 , patients with tumors expressing PD-L1 CPS ≥ 1 , and the ITT population.

The study was appropriately powered to assess outcomes in patients with PD-L1 CPS ≥ 1 with the following statistical assumptions: for testing EFS in patients with PD-L1 CPS ≥ 1 , the study was designed to have approximately 91% power to detect a true average hazard ratio of 0.70 based on a total of 354 EFS events across the two arms. For testing OS in the population of patients with PD-L1 CPS ≥ 1 , the study was designed to have approximately 69.7% power to detect a true average hazard ratio of 0.75 based on a total of 309 OS events across the two arms.

Protocol Amendments

The Applicant's Description: [Table 8] summarizes amendments to the database cutoff.

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Table 8: Applicant – Summary of Key Changes to the KEYNOTE-689 Protocol

Protocol ^a	Date of Issue	Key Changes and Rationale
3475-689-09	29-MAR-2024	To update the assumptions of the survival distribution of the control group based on historical data and update with more conservative HR assumption for EFS in CPS ≥ 10 population based on study data from KEYNOTE-412.
3475-689-08	07-SEP-2023	To amend the SAP, update the EFS definition, update the endpoint of mPR from a primary endpoint to a secondary endpoint and remove original efficacy IA1 (inferential analysis of mPR only), and to modify CPS cutoff to add evaluation of pCR for CPS ≥ 10 .
3475-689-07	07-JUN-2022	To update contraception language for required duration of contraception for males and WOCBP after RT. Additional minor updates, corrections, and clarifications were made.
3475-689-06	03-MAR-2022	1) To add pregnancy testing for WOCBP at monthly intervals during study treatment until 120 days after the last dose of pembrolizumab and 180 days after the last dose of cisplatin, including at the end of treatment visit. 2) To allow imaging and/or biopsy assessments to continue for participants who have not experienced an event. 3) To update the contraception requirements and make additional minor corrections and clarifications throughout the protocol.
3475-689-05	13-MAY-2021	To update the dose modification and toxicity management guidelines for irAEs.
3475-689-04	17-JUN-2019	To add both biomarker-driven hypotheses and the stratification factor of TPS $\geq 50\%$. The rationale for these modifications is that higher PD-L1 expression was associated with improved response to pembrolizumab for patients with R/M HNSCC enrolled on the KN040 and KN048 randomized phase III studies. It is reasonable to expect that biomarker enrichment effects are also likely to be seen in locally advanced HNC.
3475-689-03	02-AUG-2018	To clarify the definitions of residual disease used in the pathological assessment used for this study and to clarify the roles of the local and central pathologists, to align the pembrolizumab dose modification table with the most current safety information, and to remove iRECIST assessment which is not relevant for this study. Additional clarifications and corrections were also made.
3475-689-02	10-MAY-2018	To align with regulatory requirements at German and French sites as well as to align with the cisplatin SmPC as required for German and French sites.
3475-689-01	13-JAN-2018	To provide for more frequent pregnancy testing and to extend the prohibition of live vaccines to 3 months after the end of study treatment.
3475-689-00	24-AUG-2017	Initial protocol
Abbreviations: CPS=combined positive score; EFS=event-free survival; HNC=head and neck cancer; HR=hazard ratio; IA1=Interim Analysis 1; irAEs=immune-related AE; iRECIST=modified RECIST; pCR=pathological complete response; R/M HNSCC=recurrent or metastatic head and neck squamous cell carcinoma; RT=radiotherapy; SAP=Statistical analysis plan; SmPC=Summary of Product Characteristics; TPS=tumor proportion score; WOCBP= women of childbearing potential.		

The FDA's Assessment:

FDA agrees with the Applicant's description of the protocol amendments.

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KEYNOTE-689 was initially designed with mPR and EFS as dual primary endpoints, with randomization stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx), tumor stage (III vs IVA) and HPV p16 expression status (either oropharynx– p16 positive vs oropharynx-p16 negative or larynx/hypopharynx/oral cavity HNSCC).

On June 21, 2019, the study was amended (amendment 4) to include biomarker-driven hypotheses and the stratification factor of tumor proportion score (TPS) $\geq 50\%$ was added based on external data from the KEYNOTE-040 and KEYNOTE-048 studies showing that higher PD-L1 expression is a predictive biomarker for response to pembrolizumab in recurrent or metastatic HNSCC. Prior to initiation of amendment 4, 103 patients (14.4%) had been randomized on the study.

On September 13, 2023, the study was amended (amendment 8) to update the definition of the EFS endpoint to include events that preclude surgery, and to change mPR from a dual primary endpoint to a secondary endpoint.

On March 29, 2024, the study was amended (amendment 9) to update the number of expected patients with PD-L1 CPS ≥ 10 from 458 to 462 and the number of patients with PD-L1 CPS ≥ 1 from 662 to 680. Sample size and power calculations for EFS and OS were updated for the PD-L1 CPS ≥ 10 and PD-L1 CPS ≥ 1 populations as follows: for the EFS analysis at IA2 (final EFS), the study was updated to have 94.9% power at one-sided alpha of 0.025 to detect a HR of 0.62 based on 232 EFS events across the two arms for patients with PD-L1 CPS ≥ 10 and to have 91.2% power at one-sided alpha of 0.025 to detect a true average hazard ratio of 0.70 based on a total of 354 events across the two arms for patients with PD-L1 CPS ≥ 1 . For both populations, the anticipated number of EFS events at IA2 increased from the assumptions given in protocol v8.0 (i.e., in protocol v8.0, 193 EFS events were expected for the CPS ≥ 10 population and 294 EFS events were expected for the CPS ≥ 1 population). For the final OS analysis, the assumptions were updated as follows: at one-sided alpha of 0.0245, the study was powered at 69.7% in the patients with PD-L1 CPS ≥ 10 to detect a HR of 0.75 based on a total of 309 deaths across the two arms, and in patients with PD-L1 CPS ≥ 1 , the study had 71.9% power to detect a HR of 0.75 based on a total of 324 deaths.

Given that the amendments to KEYNOTE-689 occurred prior to analysis of any efficacy data from the ongoing study and were based on external data alone, the revisions to the statistical analysis plan and study design are unlikely to have impacted the trial outcome.

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8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position: KEYNOTE-689 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 and documented in accordance with the principles and provisions in Section 4.8 of the ICH E6 Guideline for Good Clinical Practice, US CFR Title 21 Part 50, Protection of Human Subjects, and/or local country/cultural consent practices and/or requirements where applicable. Informed consent was obtained from all participants before performing study-related procedures or assessments. The IRB/IECs consulted for this study met the definition as outlined in US CFR Title 21, Part 56 or equivalent country-specific regulations.

The FDA's Assessment:

FDA agrees with the Applicant's position. Based on the information provided in this application, the conduct of KEYNOTE-689 was consistent with the International Council for Harmonization guidelines for Good Clinical Practice, U.S. Federal regulations and requirements by other applicable regulatory authorities.

Financial Disclosure

The Applicant's Position: Disclosure of financial interests of the investigators who conducted KEYNOTE-689 is described in this submission and a summary is provided in [Appendix 19.2], including statements of due diligence in cases where the Applicant was unable to obtain a signed form from the investigator. Seven investigators had disclosable financial interests/arrangements. Details of the disclosable financial interests/arrangements and a description of the steps taken to minimize potential bias are provided (FDA forms 3454 and 3455).

The FDA's Assessment:

FDA reviewed the financial disclosure information provided by the Applicant. Refer to FDA's assessment of this information in Appendix 19.2.

Patient Disposition

Data:

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Figure 2: Applicant – Consort Diagram – Disposition of All Participants

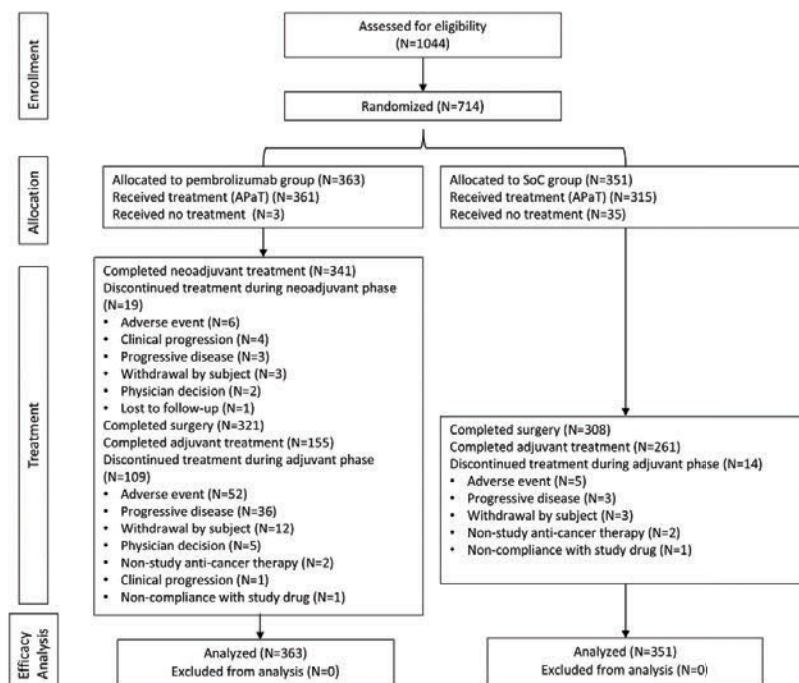


Table 9: Applicant – Disposition of Participants (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		351		714	
Status for Neoadjuvant Study Treatment						
Started	360		2		362	
Completed	341	(94.7)	0	(0.0)	341	(94.2)
Discontinued	19	(5.3)	0	(0.0)	19	(5.2)
Adverse Event	6	(1.7)	0	(0.0)	6	(1.7)
Clinical Progression	4	(1.1)	0	(0.0)	4	(1.1)
Lost To Follow-Up	1	(0.3)	0	(0.0)	1	(0.3)
Physician Decision	2	(0.6)	0	(0.0)	2	(0.6)
Associated with COVID-19	1	(0.3)	0	(0.0)	1	(0.3)
Progressive Disease	3	(0.8)	0	(0.0)	3	(0.8)
Withdrawal By Subject	3	(0.8)	0	(0.0)	3	(0.8)
Status Not Recorded	0	(0.0)	2	(100.0)	2	(0.6)
Status for In-study Surgery						
Started	322		308		630	
Completed	321	(99.7)	308	(100.0)	629	(99.8)
Discontinued	1	(0.3)	0	(0.0)	1	(0.2)

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Tumor Found To Be Surgically Unresectable	1	(0.3)	0	(0.0)	1	(0.2)
Status for Adjuvant Study Treatment						
Started	275		275		550	
Completed	155	(56.4)	261	(94.9)	416	(75.6)
Discontinued	109	(39.6)	14	(5.1)	123	(22.4)
Adverse Event	52	(18.9)	5	(1.8)	57	(10.4)
Associated with COVID-19	1	(0.4)	0	(0.0)	1	(0.2)
Clinical Progression	1	(0.4)	0	(0.0)	1	(0.2)
Non-Compliance With Study Drug	1	(0.4)	1	(0.4)	2	(0.4)
Non-Study Anti-Cancer Therapy	2	(0.7)	2	(0.7)	4	(0.7)
Physician Decision	5	(1.8)	0	(0.0)	5	(0.9)
Associated with COVID-19	1	(0.4)	0	(0.0)	1	(0.2)
Progressive Disease	36	(13.1)	3	(1.1)	39	(7.1)
Withdrawal By Subject	12	(4.4)	3	(1.1)	15	(2.7)
Participants Ongoing	11	(4.0)	0	(0.0)	11	(2.0)
Status for Study Treatment (Overall)						
Started	360		316		676	
Completed	155	(43.1)	261	(82.6)	416	(61.5)
Discontinued	194	(53.9)	55	(17.4)	249	(36.8)
Adverse Event	65	(18.1)	16	(5.1)	81	(12.0)
Associated with COVID-19	2	(0.6)	0	(0.0)	2	(0.3)
Status for Study Treatment (Overall)						
Clinical Progression	3	(0.8)	1	(0.3)	4	(0.6)
Lost To Follow-Up	1	(0.3)	0	(0.0)	1	(0.1)
Non-Compliance With Study Drug	2	(0.6)	3	(0.9)	5	(0.7)
Non-Study Anti-Cancer Therapy	4	(1.1)	3	(0.9)	7	(1.0)
Physician Decision	13	(3.6)	9	(2.8)	22	(3.3)
Associated with COVID-19	2	(0.6)	0	(0.0)	2	(0.3)
Progressive Disease	79	(21.9)	10	(3.2)	89	(13.2)
Withdrawal By Subject	27	(7.5)	13	(4.1)	40	(5.9)
Participants Ongoing	11	(3.1)	0	(0.0)	11	(1.6)
Status for Trial						
Discontinued	123	(33.9)	146	(41.6)	269	(37.7)
Death	109	(30.0)	127	(36.2)	236	(33.1)
Associated with COVID-19	2	(0.6)	4	(1.1)	6	(0.8)
Lost To Follow-Up	2	(0.6)	3	(0.9)	5	(0.7)
Withdrawal By Subject	12	(3.3)	16	(4.6)	28	(3.9)
COVID-19 association unspecified, Subsequently died	4	(1.1)	4	(1.1)	8	(1.1)
Participants Ongoing	240	(66.1)	205	(58.4)	445	(62.3)
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 Database Cutoff Date: 25JUL2024						

Source: [P689V01MK3475: adam-adsl]

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

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The Applicant's Position:

A total of 714 participants were randomized and included in the ITT population (363 in the pembrolizumab group, 351 in the SoC group). All nonrandomized participants (330) were screen failures. A total of 155 (43.1%) participants in the pembrolizumab group and 261 (82.6%) participants in the SoC group completed overall study treatment [Table 9] [Figure 2].

In the neoadjuvant phase, 360 participants in the pembrolizumab group started study treatment, of which 341 (94.7%) completed neoadjuvant study treatment [Table 9]. A total of 321 (88.4%) participants in the pembrolizumab group and 308 (87.7%) participants in the SoC group completed in-study surgery; 1 (0.3%) tumor was found to be unresectable (pembrolizumab group). In the adjuvant phase following surgery, 275 participants in the pembrolizumab group started study treatment, of which 155 (56.4%) completed study treatment. In the SoC group, 275 participants started study treatment, and 261 (94.9%) participants completed study treatment.

For participants who underwent surgery, 266 (82.4%) participants in the pembrolizumab group and 267 (87.0%) participants in the SoC group received in-study surgery and RT. The proportion of participants who underwent surgery for both treatment groups is consistent with clinical experience. Of these participants who underwent surgery, 100 (31.0%) of participants in the pembrolizumab group and 132 (43.0%) participants in the SoC group received in-study surgery and RT + cisplatin.

The median follow-up duration was longer in the pembrolizumab group compared with the SoC group (30.0 months vs 23.4 months).

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition in KEYNOTE-689.

Protocol Violations/Deviations

Data:

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Table 10: Applicant – Summary of Important Protocol Deviations Considered to be Clinically Important (ITT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	363		351	
with one or more clinically important protocol deviations	17	(4.7)	12	(3.4)
with no clinically important protocol deviations	346	(95.3)	339	(96.6)
Discontinuation Criteria	1	(0.3)	0	(0.0)
Participant developed study intervention discontinuation criteria, but was not discontinued from study intervention.	1	(0.3)	0	(0.0)
Inclusion/ Exclusion Criteria	0	(0.0)	1	(0.3)
Primary tumor location is not oropharynx, oral cavity, hypopharynx, or larynx.	0	(0.0)	1	(0.3)
Safety Reporting	1	(0.3)	1	(0.3)
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	1	(0.3)	1	(0.3)
Study Intervention	5	(1.4)	1	(0.3)
Participant was administered improperly stored study intervention that was deemed unacceptable for use.	5	(1.4)	0	(0.0)
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	0	(0.0)	1	(0.3)
Trial Procedures	11	(3.0)	9	(2.6)
Post surgery specimens sufficient for central review of mPR/pCR/HRPF were not submitted.	11	(3.0)	9	(2.6)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 25JUL2024.				

Source: [P689V01MK3475: adam-ads1] [P689V01MK3475: sdtm-dv; suppdv]

The Applicant's Position: Important protocol deviations were reported for 78 (21.5%) participants in the pembrolizumab group and 51 (14.5%) in the SoC group. Of these participants, 17 (4.7%) in the pembrolizumab group and 12 (3.4%) in the SoC group had important protocol deviations that were clinically important (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) [Table 10]. No participant's data were excluded from analyses due to an important protocol deviation.

The FDA's Assessment:

FDA acknowledges the Applicant's enumeration of protocol deviations. The most common protocol deviation was the "[failure to submit] post-surgery specimens sufficient for central review of mPR/pCR" and the second most common protocol deviation was "administration of improperly stored study intervention deemed unacceptable for use". Protocol deviations were

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relatively balanced between both arms and unlikely to have biased the study results in any meaningful way.

Table of Demographic Characteristics

Data:

Table 11: Applicant – Participant Characteristics (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		351		714	
Sex						
Male	286	(78.8)	277	(78.9)	563	(78.9)
Female	77	(21.2)	74	(21.1)	151	(21.1)
Age (Years)						
< 65	249	(68.6)	227	(64.7)	476	(66.7)
≥ 65	114	(31.4)	124	(35.3)	238	(33.3)
Mean	59.4		60.6		59.9	
SD	10.0		10.0		10.0	
Median	60.0		61.0		60.0	
Range	29 to 82		22 to 87		22 to 87	
Race						
American Indian Or Alaska Native	0	(0.0)	1	(0.3)	1	(0.1)
Asian	51	(14.0)	44	(12.5)	95	(13.3)
Black Or African American	9	(2.5)	9	(2.6)	18	(2.5)
Multiple	9	(2.5)	20	(5.7)	29	(4.1)
American Indian Or Alaska Native, Black Or African American, White	2	(0.6)	4	(1.1)	6	(0.8)
American Indian Or Alaska Native, White	1	(0.3)	8	(2.3)	9	(1.3)
Black Or African American, White	4	(1.1)	7	(2.0)	11	(1.5)
Native Hawaiian Or Other Pacific Islander, Asian	1	(0.3)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific Islander, White	0	(0.0)	1	(0.3)	1	(0.1)
White, Asian	1	(0.3)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific Islander	1	(0.3)	1	(0.3)	2	(0.3)
White	284	(78.2)	270	(76.9)	554	(77.6)
Missing	9	(2.5)	6	(1.7)	15	(2.1)

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Ethnicity					
Hispanic Or Latino	55	(15.2)	46	(13.1)	101 (14.1)
Not Hispanic Or Latino	300	(82.6)	298	(84.9)	598 (83.8)
Not Reported	4	(1.1)	4	(1.1)	8 (1.1)
Unknown	0	(0.0)	2	(0.6)	2 (0.3)
Missing	4	(1.1)	1	(0.3)	5 (0.7)
Region					
North America	64	(17.6)	49	(14.0)	113 (15.8)
European Union	138	(38.0)	145	(41.3)	283 (39.6)
Rest of World	161	(44.4)	157	(44.7)	318 (44.5)
PD-L1 Status by TPS Score					
TPS <50%	257	(70.8)	242	(68.9)	499 (69.9)
TPS ≥50%	103	(28.4)	107	(30.5)	210 (29.4)
Missing	3	(0.8)	2	(0.6)	5 (0.7)
PD-L1 Status by CPS Score (CPS50)					
CPS <50	244	(67.2)	224	(63.8)	468 (65.5)
CPS ≥50	116	(32.0)	125	(35.6)	241 (33.8)
Missing	3	(0.8)	2	(0.6)	5 (0.7)
PD-L1 Status by CPS Score (CPS10)					
CPS <10	126	(34.7)	118	(33.6)	244 (34.2)
CPS ≥10	234	(64.5)	231	(65.8)	465 (65.1)
Missing	3	(0.8)	2	(0.6)	5 (0.7)
PD-L1 Status by CPS Score (CPS1)					
CPS <1	13	(3.6)	14	(4.0)	27 (3.8)
CPS ≥1	347	(95.6)	335	(95.4)	682 (95.5)
Missing	3	(0.8)	2	(0.6)	5 (0.7)
Primary Tumor Site					
Oropharynx	35	(9.6)	38	(10.8)	73 (10.2)
Oral Cavity	219	(60.3)	213	(60.7)	432 (60.5)
Larynx	81	(22.3)	73	(20.8)	154 (21.6)
Hypopharynx	28	(7.7)	26	(7.4)	54 (7.6)
Missing	0	(0.0)	1	(0.3)	1 (0.1)
ECOG PS					
0	199	(54.8)	209	(59.5)	408 (57.1)
1	164	(45.2)	142	(40.5)	306 (42.9)
HPV Status					
Positive	12	(3.3)	15	(4.3)	27 (3.8)
Negative	351	(96.7)	335	(95.4)	686 (96.1)
Unknown	0	(0.0)	1	(0.3)	1 (0.1)
Overall Cancer Staging at Baseline					

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III	90	(24.8)	93	(26.5)	183	(25.6)
IVA	271	(74.7)	257	(73.2)	528	(73.9)
IVB	2	(0.6)	0	(0.0)	2	(0.3)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Cancer T Staging at Baseline						
T1	9	(2.5)	4	(1.1)	13	(1.8)
T2	49	(13.5)	47	(13.4)	96	(13.4)
T3	110	(30.3)	113	(32.2)	223	(31.2)
T4	11	(3.0)	15	(4.3)	26	(3.6)
T4A	184	(50.7)	170	(48.4)	354	(49.6)
T4B	0	(0.0)	1	(0.3)	1	(0.1)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Cancer N Staging at Baseline						
N0	94	(25.9)	88	(25.1)	182	(25.5)
N1	81	(22.3)	72	(20.5)	153	(21.4)
N2	32	(8.8)	31	(8.8)	63	(8.8)
N2A	12	(3.3)	7	(2.0)	19	(2.7)
N2B	83	(22.9)	88	(25.1)	171	(23.9)
N2C	58	(16.0)	64	(18.2)	122	(17.1)
N3	1	(0.3)	0	(0.0)	1	(0.1)
N3B	2	(0.6)	0	(0.0)	2	(0.3)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Cancer M Staging at Baseline						
M0	363	(100.0)	350	(99.7)	713	(99.9)
Missing	0	(0.0)	1	(0.3)	1	(0.1)
Smoking Status						
Never Smoker	64	(17.6)	81	(23.1)	145	(20.3)
Former Smoker	176	(48.5)	144	(41.0)	320	(44.8)
Current Smoker	117	(32.2)	123	(35.0)	240	(33.6)
Unknown	6	(1.7)	3	(0.9)	9	(1.3)
Cigarette use (packs per year)						
0 (No Cigarette use)	64	(17.6)	81	(23.1)	145	(20.3)
<=10	67	(18.5)	73	(20.8)	140	(19.6)
>10	216	(59.5)	186	(53.0)	402	(56.3)
Unknown	16	(4.4)	11	(3.1)	27	(3.8)
Alcohol use						
Yes	250	(68.9)	238	(67.8)	488	(68.3)
No	107	(29.5)	110	(31.3)	217	(30.4)
Unknown	6	(1.7)	3	(0.9)	9	(1.3)
SD=Standard deviation. European Union category in this table includes European Economic Area, United Kingdom and Switzerland. Database Cutoff Date: 25JUL2024.						

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Source: [P689V01MK3475: adam-adsl]

The Applicant's Position:

No significant differences were observed in demographic characteristics and efficacy data between regions. The pharmacokinetics of pembrolizumab have been shown to be consistent across ethnicity and region.

In the KEYNOTE-689 study population, the demographic and baseline characteristics of participants were generally similar between the treatment groups for the CPS ≥ 10 population, CPS ≥ 1 population, and for all participants [Table 11]. The majority of participants were male (78.9%), white (77.6%), and of not Hispanic or Latino ethnicity (83.8%). The median age was 60.0 (22 to 87) years. Most participants across both groups had an overall cancer staging at baseline of IVA (73.9%), and 57.1% of participants across both groups had an ECOG-PS score of 0. PD-L1 status by CPS score was similar across both groups. Of the 714 participants enrolled in the study, there were 465 (65.1%) of participants whose tumors expressed PD-L1 CPS ≥ 10 and 682 (95.5%) participants whose tumors express PD-L1 CPS ≥ 1 .

The FDA's Assessment:

FDA generally agrees that the distribution of the efficacy population across relevant patient demographics and baseline patient and tumor related characteristics was generally similar between the two arms in both the ITT population and the primary efficacy population for the approval consisting of the 682 patients (96%) who have tumors expressing PD-L1 CPS ≥ 1 .

There was a total of 27 patients (3.8%) enrolled across the two arms whose tumors were PD-L1 negative (CPS < 1), markedly underrepresenting the prevalence of PD-L1 negative tumors in HNSCC patient populations as reported in CheckMate 141, KEYNOTE-048, and in HNSCC tumor tissue array analyses (15% to 43%) (Burtneess, et al. JCO 2022; Ferris, et al. NEJM 2016; Deuss, et al. Cancers 2024). The small size of the PD-L1 CPS < 1 subpopulation complicates the interpretation of the EFS and OS results in this subgroup making it difficult to fully assess the benefit:risk profile for these patients.

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)

The Applicant's Position:

Participant characteristics in the APaT population were generally consistent with the ITT population. The reported medical history conditions were generally as expected for participants with Stage III-IVA resectable LA HNSCC and were generally balanced between the treatment groups. Participant characteristics in the overall study population are representative of participants with resectable locoregionally advanced HNSCC.

The FDA's Assessment:

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Version date: March 1, 2024 (ALL NDA/ BLA reviews)

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FDA agrees with the applicant's description of the other baseline characteristics.

Of note, in the ITT population (n=714), HPV positivity was found in 3.3% (n=12) of the patients on the pembrolizumab arm and in 4.3% (n=15) of the patients on the SoC arm. HPV positivity was defined by p16 immunohistochemistry (IHC), with strong and diffuse nuclear and cytoplasmic staining in $\geq 70\%$ of tumor cells using the Ventana CINtec p16 Histology assay. The p16 IHC testing was performed locally, or if local testing was not possible or indeterminate, was performed at a central lab.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Pembrolizumab was administered in the clinic by qualified site personnel. Rescue medication was not applicable.

Concomitant medications were generally balanced between the treatment groups for most reported medications. Subsequent oncologic therapy use (therapies received following discontinuation of study treatment) was balanced across treatment group. The most common (>10% of participants) subsequent oncologic therapy in the pembrolizumab group compared with the SoC group was cisplatin (11.0% vs 10.8%).

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 12: Applicant – Summary of KEYNOTE-689 Primary Efficacy Endpoint Results

Endpoints (pembrolizumab vs. SoC)	Number of events observed (IF ^a)	Median in months (95% CI)	Observed HR (95% CI)	p-Value ^b crossing boundary	Observed p-Value ^b	Outcome
PRIMARY ENDPOINT: EFS per RECIST 1.1, BICR assessed						
CPS ≥ 10	192 (83%)	59.7 (41.1, NR) vs. 26.9 (18.3, 51.5)	0.66 (0.49, 0.88)	0.0138	0.00217	Statistically significant
CPS ≥ 1	284 (80%)	59.7 (37.9, NR) vs. 29.6 (19.5, 41.9)	0.70 (0.55, 0.89)	0.0124	0.00140	Statistically significant
All participants	295 (80%)	51.8 (37.5, NR) vs. 30.4 (21.8, 50.1)	0.73 (0.58, 0.92)	0.0120	0.00411	Statistically significant

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^a Information fraction, the number of observed events / the target events for the EFS final analysis.
^b One-sided p-value.
 Analyses of EFS are based on stratified analyses.
 BICR=blinded independent central review; CI=Confidence Interval; CPS=Combined Positive Score; EFS=Event Free Survival;
 HR=Hazard Ratio; IF=Information Fraction
 :: NR=Not Reached; RECIST=Response Evaluation Criteria in Solid Tumors; SoC=Standard of Care.

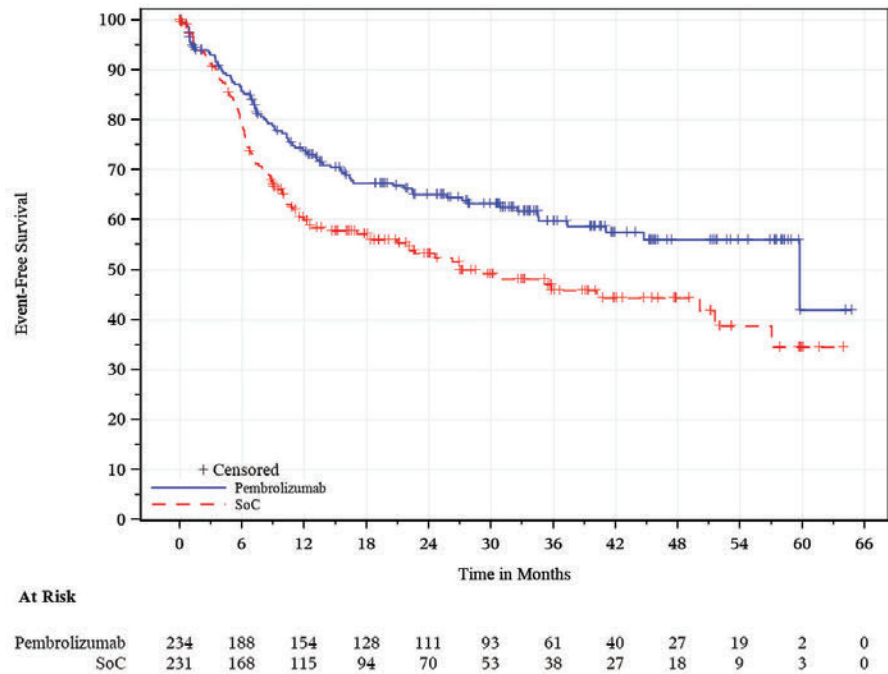
Table 13: Applicant – Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (Participants with CPS $\geq$ 10, ITT Population)

	Pembrolizumab (N=234)	SoC (N=231)
Number of Events (%)	85 (36.3)	107 (46.3)
Death	43 (18.4)	37 (16.0)
Distant PD	15 (6.4)	39 (16.9)
Local And Distant PD	2 (0.9)	2 (0.9)
Local PD/Recurrence	25 (10.7)	29 (12.6)
Number of Censored (%)	149 (63.7)	124 (53.7)
Last assessment showing no progression	148 (63.2)	116 (50.2)
Randomization	1 (0.4)	8 (3.5)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	59.7 (41.1, NR)	26.9 (18.3, 51.5)
[Q1, Q3]	[10.9, NR]	[6.5, NR]
Person-months	5605.3	4244.6
Event Rate / 100 Person-months	1.5	2.5
vs SoC		
Hazard Ratio (95% CI) ^b	0.66 (0.49, 0.88)	
p-value ^c	0.00217	
EFS Rate at month 6 (%) (95% CI)	85.7 (80.4, 89.7)	79.4 (73.3, 84.2)
EFS Rate at month 12 (%) (95% CI)	74.0 (67.6, 79.3)	60.0 (53.0, 66.3)
EFS Rate at month 24 (%) (95% CI)	65.1 (58.2, 71.2)	53.2 (45.9, 59.9)
EFS Rate at month 36 (%) (95% CI)	59.8 (52.3, 66.5)	45.9 (38.0, 53.4)
EFS Rate at month 48 (%) (95% CI)	55.9 (47.7, 63.4)	44.4 (36.3, 52.2)
^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 primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
^c One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
NR = Not reached.		
Database Cutoff Date: 25JUL2024		

Source: [P689V01MK3475: adam-adsl; adtte]

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Figure 3: Applicant – Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule)
Based on BICR per RECIST 1.1 (Participants with CPS≥10, ITT Population)



Database Cutoff Date: 25JUL2024.

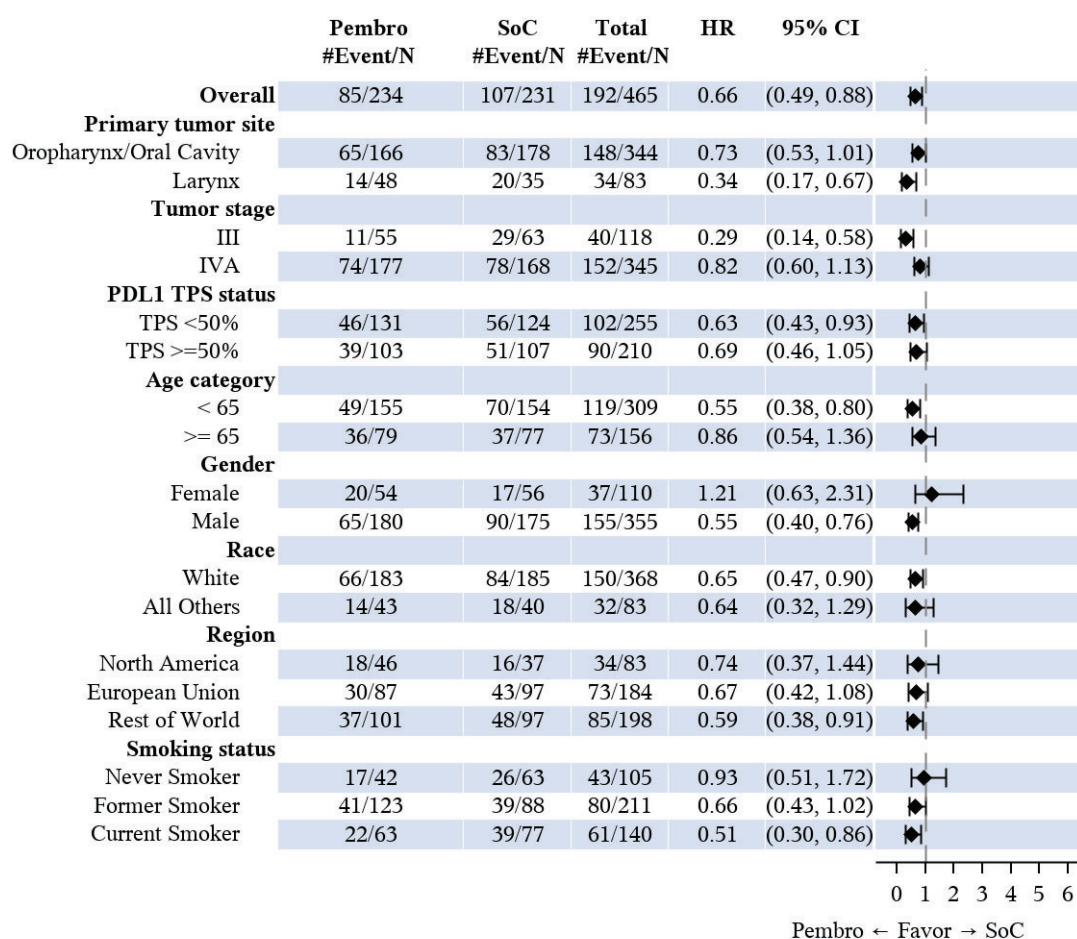
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Figure 4: Applicant – Forest Plot of EFS Hazard Ratio by Subgroup Factors Based on BICR per RECIST 1.1 (Primary Censoring Rule) (Participants with CPS $\geq$ 10, ITT Population)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <10% of the CPS $\geq$ 10 population, that particular level will not be displayed.

European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.

Database Cutoff Date: 25JUL2024

Source: [P689V01MK3475: adam-adsl; adtte]

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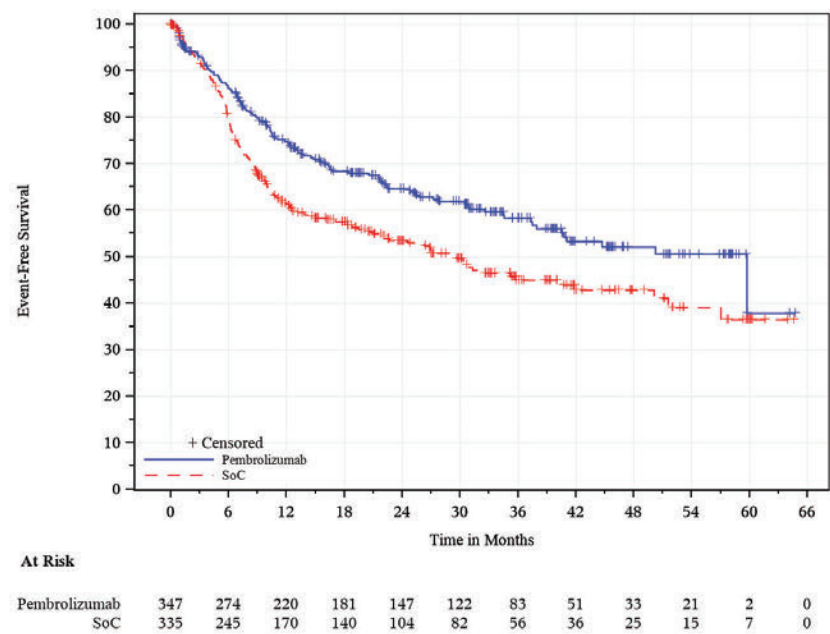
Table 14: Applicant – Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (Participants with CPS $\geq$ 1, ITT Population)

	Pembrolizumab (N=347)	SoC (N=335)
Number of Events (%)	128 (36.9)	156 (46.6)
Death	63 (18.2)	62 (18.5)
Distant PD	24 (6.9)	51 (15.2)
Local And Distant PD	4 (1.2)	6 (1.8)
Local PD/Recurrence	37 (10.7)	37 (11.0)
Number of Censored (%)	219 (63.1)	179 (53.4)
Last assessment showing no progression	216 (62.2)	168 (50.1)
Randomization	3 (0.9)	11 (3.3)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	59.7 (37.9, NR)	29.6 (19.5, 41.9)
[Q1, Q3]	[11.9, NR]	[6.9, NR]
Person-months	7751.6	6245.2
Event Rate / 100 Person-months	1.7	2.5
vs SoC		
Hazard Ratio (95% CI) ^b	0.70 (0.55, 0.89)	
p-value ^c	0.00140	
EFS Rate at month 6 (%) (95% CI)	86.2 (82.0, 89.5)	80.0 (75.1, 84.0)
EFS Rate at month 12 (%) (95% CI)	74.8 (69.6, 79.2)	61.3 (55.5, 66.5)
EFS Rate at month 24 (%) (95% CI)	64.6 (58.8, 69.8)	53.4 (47.4, 59.1)
EFS Rate at month 36 (%) (95% CI)	58.2 (51.9, 64.0)	44.9 (38.4, 51.2)
EFS Rate at month 48 (%) (95% CI)	52.1 (45.0, 58.8)	42.8 (35.9, 49.4)
^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 primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
^c One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
NR = Not reached.		
Database Cutoff Date: 25JUL2024		

Source: [P689V01MK3475: adam-adsl; adtte]

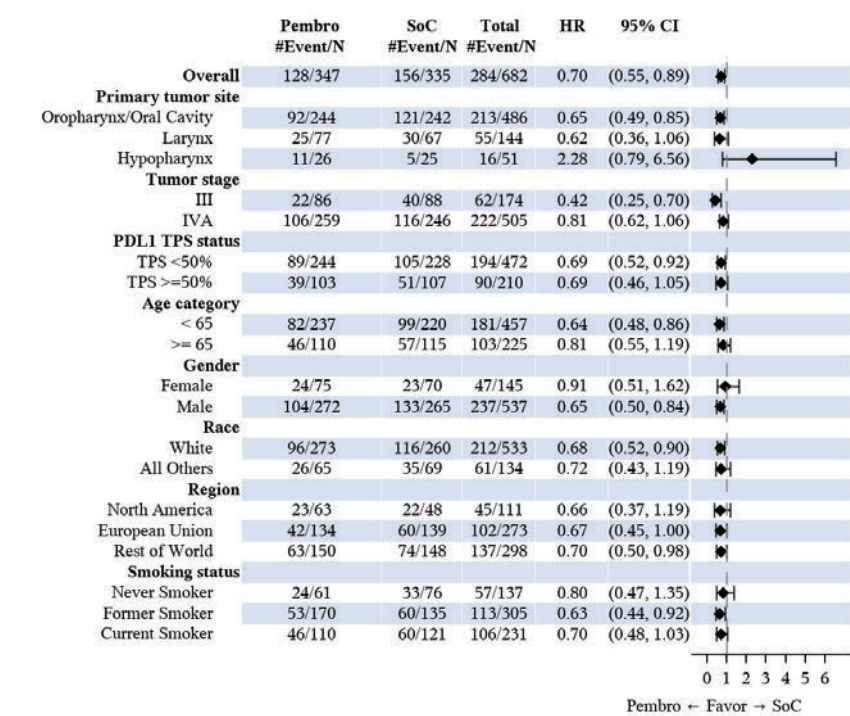
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Figure 5: Applicant – Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (Participants with CPS≥1, ITT Population)



Database Cutoff Date: 25JUL2024.
Source: [P689V01MK3475: adam-adsl; adtte]

Figure 6: Applicant – Forest Plot of EFS Hazard Ratio by Subgroup Factors Based on BICR per RECIST 1.1 (Primary Censoring Rule) (Participants with CPS≥1, ITT Population)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <10% of the CPS≥10 population, that particular level will not be displayed. European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.

Database Cutoff Date: 25JUL2024 Source: [P689V01MK3475: adam-adsl; adtte]

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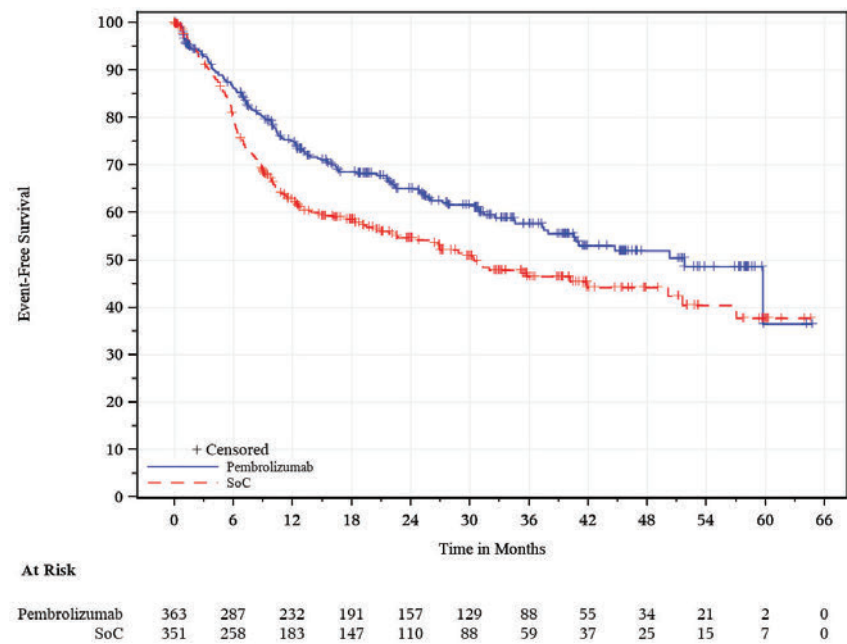
Table 15: Applicant – Analysis of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)

	Pembrolizumab (N=363)	SoC (N=351)
Number of Events (%)	136 (37.5)	159 (45.3)
Death	67 (18.5)	64 (18.2)
Distant PD	26 (7.2)	51 (14.5)
Local And Distant PD	4 (1.1)	7 (2.0)
Local PD/Recurrence	39 (10.7)	37 (10.5)
Number of Censored (%)	227 (62.5)	192 (54.7)
Last assessment showing no progression	224 (61.7)	181 (51.6)
Randomization	3 (0.8)	11 (3.1)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	51.8 (37.5, NR)	30.4 (21.8, 50.1)
[Q1, Q3]	[12.1, NR]	[6.9, NR]
Person-months	8166.9	6588.2
Event Rate / 100 Person-months	1.7	2.4
vs SoC		
Hazard Ratio (95% CI) ^b	0.73 (0.58, 0.92)	
p-value ^c	0.00411	
EFS Rate at month 6 (%) (95% CI)	86.3 (82.1, 89.5)	80.3 (75.5, 84.2)
EFS Rate at month 12 (%) (95% CI)	75.1 (70.0, 79.4)	62.5 (56.9, 67.5)
EFS Rate at month 24 (%) (95% CI)	65.0 (59.4, 70.1)	54.6 (48.7, 60.1)
EFS Rate at month 36 (%) (95% CI)	57.6 (51.5, 63.3)	46.4 (40.0, 52.5)
EFS Rate at month 48 (%) (95% CI)	52.0 (45.1, 58.4)	44.2 (37.5, 50.8)
^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 primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
^c One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
NR = Not reached.		
Database Cutoff Date: 25JUL2024		

Source: [P689V01MK3475: adam-adsl; adtte]

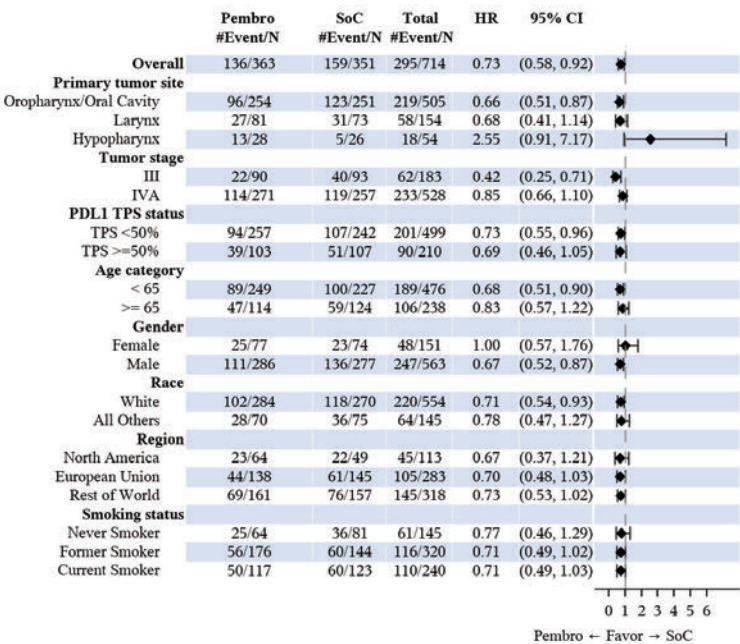
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Figure 7: Applicant – Kaplan-Meier Plot of Event-Free Survival (Primary Censoring Rule) Based on BICR per RECIST 1.1 (ITT Population)



Database Cutoff Date: 25JUL2024.
Source: [P689V01MK3475: adam-adsl; adtte]

Figure 8: Applicant – Forest Plot of EFS Hazard Ratio by Subgroup Factors Based on BICR per RECIST 1.1 (Primary Censoring Rule) (ITT Population)

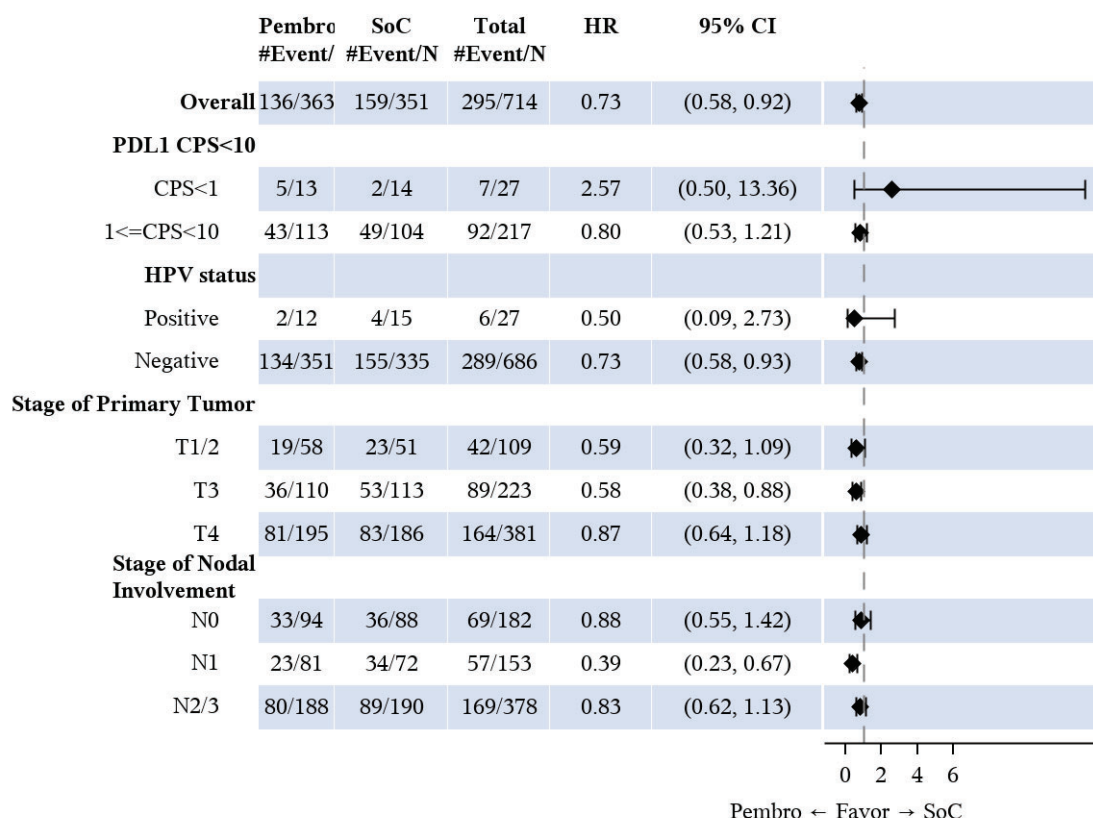


For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <10% of the CPS≥10 population, that particular level will not be displayed. European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.
Database Cutoff Date: 25JUL2024
Source: [P689V01MK3475: adam-adsl; adtte]

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Figure 9: Applicant – Forest Plot of EFS Hazard Ratio by Subgroup Factors (Post-hoc) Based on BICR per RECIST 1.1 (Primary Censoring Rule) (ITT Population)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. Thirteen participants were classified as T Stage T1. Three participants were classified as N Stage N3 or N3B. Database Cutoff Date: 25JUL2024

Source: [P689V01MK3475: adam-adsl; adtte]

The Applicant's Position:

The results presented are from the IA1 for KEYNOTE-689, with a database cutoff date of 25-JUL-2024. The study had a primary analysis and a sensitivity analysis of EFS by BICR (in the CPS ≥ 10 , CPS ≥ 1 , and all participants populations) based on censoring rules outlined in the study protocol. The study met the success criterion for EFS. A statistically significant and clinically meaningful improvement in EFS was seen in the CPS ≥ 10 , CPS ≥ 1 , and all participants populations.

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EFS in the CPS ≥ 10 Population

- A statistically significant and clinically meaningful improvement in EFS per RECIST 1.1 as assessed by BICR was observed in the pembrolizumab group compared with the SoC group (HR: 0.66; 95% CI: 0.49, 0.88; $p=0.00217$, which is below the p-value boundary of 0.0138), representing a 34% reduction in the risk of an EFS event in the pembrolizumab group versus the SoC group [Table 12][Table 13].
- Median EFS was 59.7 months in the pembrolizumab group compared with the median EFS of 26.9 months in the SoC group [Table 13]. The EFS rates by KM estimation were higher in the pembrolizumab group than in the SoC group at all timepoints analyzed.
- The KM plot for EFS shows that the pembrolizumab curve separated from the SoC curve at approximately 3 months and remained separated throughout the evaluation period [Figure 3].
- The EFS improvement of pembrolizumab over SoC was generally consistent across prespecified subgroups. Note that the small sample sizes in some subgroups result in wide CIs and the results should therefore be interpreted with caution [Figure 4].

EFS in the CPS ≥ 1 Population

- A statistically significant and clinically meaningful improvement in EFS per RECIST 1.1 as assessed by BICR was observed in the pembrolizumab group compared with the SoC group (HR: 0.70; 95% CI: 0.55, 0.89; $p=0.00140$, which is below the p-value boundary of 0.0124), representing a 30% reduction in the risk of an EFS event in the pembrolizumab group versus the SoC group [Table 14].
- Median EFS was 59.7 months in the pembrolizumab group compared with the median EFS of 29.6 months in the SoC group [Table 14]. The EFS rates by KM estimation were higher in the pembrolizumab group than in the SoC group at all timepoints analyzed.
- The KM plot for EFS shows that the pembrolizumab group curve separated from the SoC curve at approximately 3 months and remained separated throughout the evaluation period [Figure 5].
- The EFS improvement of pembrolizumab over SoC was generally consistent across prespecified subgroups [Figure 6]. Note that the small sample sizes in some subgroups result in wide CIs and the results should therefore be interpreted with caution.

EFS in All Participants

- A statistically significant and clinically meaningful improvement in EFS per RECIST 1.1 as assessed by BICR was observed in the pembrolizumab group compared with the SoC group (HR: 0.73; 95% CI: 0.58, 0.92; $p=0.00411$, which is below the p-value boundary of

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0.0120), representing a 27% reduction in the risk of an EFS event in the pembrolizumab group versus the SoC group [Table 15].

- Median EFS was 51.8 months in the pembrolizumab group compared with 30.4 months in the SoC group [citation]. The EFS rates by KM estimation were higher in the pembrolizumab group than in the SoC group at all timepoints analyzed [Table 15].
- The KM plot for EFS showed that the pembrolizumab group curve separated from the SoC group curve at approximately Month 3 and remained separated through approximately Month 57. Results beyond 57 months should be interpreted with caution due to the small numbers of participants at risk beyond this timepoint in both treatment groups [Figure 7].
- The EFS improvement of pembrolizumab over SoC was generally consistent across prespecified subgroups, including tumor stage, PD-L1 TPS status, age, race, smoking status, and geographical region [Figure 8]. Note that the small sample sizes in some subgroups result in wide CIs and the results should therefore be interpreted with caution.

Post-hoc Analysis of EFS in the CPS <1 and CPS 1-9 Populations

- The HR of EFS in the CPS <1 population was 2.57 (95% CI: 0.50, 13.36), but note that the small sample sizes in the CPS <1 subgroup (n=27) resulted in wide CIs, limiting definitive conclusions [Figure 9]. The HR of EFS in the CPS 1-9 population observed was 0.80 (95% CI: 0.53, 1.21) and was consistent with EFS results for all participants (HR: 0.73; 95% CI: 0.58, 0.92).

The FDA's Assessment:

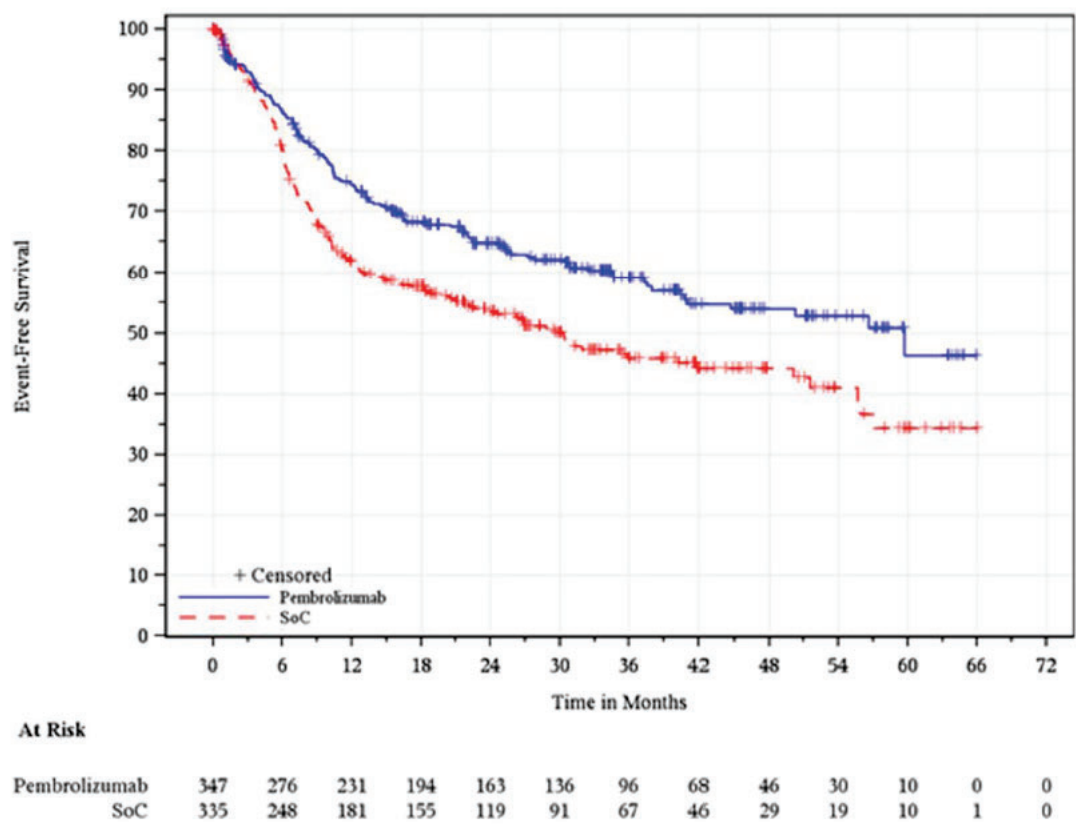
FDA agrees with the Applicant's position that KEYNOTE-689 met the primary endpoint of EFS in the PD-L1 CPS ≥ 10 , CPS ≥ 1 , and ITT populations. Statistical significance in EFS was demonstrated at IA1 in each of these populations. At the time of these analyses, 83% (CPS ≥ 10), 80% (CPS ≥ 1), and 80% (ITT population) of the number of EFS events needed for the final analyses had occurred. Among patients in the PD-L1 CPS ≥ 1 population, there were fewer EFS events in the pembrolizumab arm compared to the SOC arm (37% vs 47%), with the largest difference in EFS events being related to distant progression in the pembrolizumab arm compared to the standard of care arm (7% vs 15%). The observed rates of other event categories, including local progression/recurrence, local and distant progression, and deaths, were generally similar between treatment arms.

While the medians for EFS were reached for both treatment arms in the PD-L1 CPS ≥ 10 , PD-L1 CPS ≥ 1 , and ITT populations, the median estimate for the pembrolizumab arm occurs at timepoints when there are only a few patients left in follow-up and, thus appear unstable. In response to an information request (IR) for updated EFS in the PD-L1 CPS ≥ 1 population, the Applicant provided an updated Kaplan-Meier curve and median estimates for EFS with corresponding 95% confidence intervals for each treatment arm based on a safety update

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with a data cutoff date of January 3, 2025, providing an additional 4 months of follow-up for the estimates of the medians. The updated Kaplan-Meier estimates of the median EFS were 59.7 months (95% CI: 40.5, NR) in the pembrolizumab arm and 30.3 months (95% CI: 20.5, 50.1) in the SoC arm.

Figure 7A: FDA - Updated EFS in the PD-L1 CPS ≥ 1 Population (January 3, 2025, data cutoff)



Source: Applicant response on April 7, 2025, to an FDA information request

The effect on EFS was generally consistent across subgroups presented by the Applicant in the PD-L1 CPS ≥10, PD-L1 CPS ≥1, and ITT populations with three notable exceptions found on exploratory subgroup analyses. First, in patients with tumors that had PD-L1 CPS <1 (n=27), the EFS HR was 2.57 (95% CI: 0.50, 13.36) and the OS HR was 1.3 (95% CI: 0.32, 9.54), favoring the standard of care (SoC) arm. Second, in female patients with tumor PD-L1 CPS ≥1 (n=75), the EFS HR was 0.91 (95% CI: 0.51, 1.62) in the pembrolizumab arm versus the SoC arm. Third, among patients with PD-L1-positive CPS ≥1 hypopharyngeal tumors who were

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randomized (n=51), the EFS HR was 2.28 (95% CI: 0.79, 6.56), favoring the SoC arm (see Table 16 below). The small sample sizes make it difficult to draw definitive conclusions regarding the benefit:risk profile for patients in these subgroups. For female patients, an EFS benefit in the pembrolizumab arm might have been overshadowed by a higher frequency of radiation related toxicities and complications in women, as discussed in Sections 8.2.4 and 8.2.7. For the CPS<1 and hypopharyngeal cancer subgroups, potential explanations for the decreased EFS and OS are discussed below. In general, we agreed with the Applicant on the data presented in Table 16 with one exception. In total, the sum of the HNSCC subtypes patients in the SoC arm were 334 rather than 335 as indicated in Table 16 by the Applicant.

For patients with PD-L1 negative (CPS <1) HNSCC in the recurrent or metastatic disease setting, post-hoc subgroup analyses from two prior randomized studies, KEYNOTE-040 and KEYNOTE-048, suggest a potential detriment in OS with pembrolizumab as a single agent compared to other therapies. Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU was evaluated in KEYNOTE-048 for the first-line treatment of patients with recurrent or metastatic HNSCC (R/M HNSCC) (Burtness, et al. 2022). In KEYNOTE-048, OS was sequentially tested in patients with PD-L1 CPS ≥ 20 , then CPS ≥ 1 , and then in the ITT population (including 15% of patients with PD-L1 negative tumors). OS was positive in the PD-L1 CPS ≥ 20 and CPS ≥ 1 populations but not the ITT population. In an exploratory analysis of patients with PD-L1 CPS <1, the OS HR was 1.07 (95% CI: 0.66, 1.74). Based on these results, the indication for pembrolizumab monotherapy was limited to patients with PD-L1 positive (CPS ≥ 1) tumors.

Pembrolizumab monotherapy versus investigator's choice of docetaxel, cetuximab, and methotrexate was evaluated in KEYNOTE-040 for the treatment of patients with refractory, PD-L1 negative R/M HNSCC (Cohen, et al. 2019). In an exploratory analysis of 104 patients (21%) with PD-L1 negative (CPS <1) tumors, the OS HR was 1.28 (95% CI: 0.80, 2.10). KEYNOTE-048 and KEYNOTE-040 appear to have congruent findings, suggesting a potential detriment with pembrolizumab monotherapy for patients with PD-L1 negative HNSCC. The mechanism of action of pembrolizumab also provides scientific rationale that the efficacy of pembrolizumab monotherapy may be limited in patients with PD-L1 negative tumors. Taken together, the FDA review team is recommending that the current indication based on the KEYNOTE-689 trial is limited to patients with PD-L1 positive (CPS ≥ 1) tumors.

To better understand the EFS results in the PD-L1 CPS ≥ 1 population across different primary tumor sites, the FDA sent an IR to the Applicant to compare EFS, OS, and rates of R0, R1, and R2 resections across the primary tumor sites of hypopharyngeal, laryngeal, oral cavity, and oropharyngeal tumors. For PD-L1 positive, hypopharyngeal tumors, complete (R0) resections occurred in a smaller percentage of patients in the pembrolizumab arm (74%) compared to the SoC arm (87%), whereas for all other primary tumor sites, R0 resections were more common in the pembrolizumab arm. The results of these analyses are presented in the two tables below.

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Table 16: FDA – EFS at IA1 by Tumor Subtypes with PD-L1 CPS $\geq$ 1

	Tumor Site				
	Hypopharyngeal Pembro (N=26) SoC (N=25)	Laryngeal Pembro (N=77) SoC (N=67)	Oral Pembro (N=210) SoC (N=205)	Oropharyngeal Pembro (N=34) SoC (N=37)	All Tumor Sites Pembro (N=347) SoC (N=335)
EFS HR (95% CI)	2.28 (0.79, 6.56)	0.62 (0.36, 1.06)	0.71 (0.53, 0.95)	0.32 (0.15, 0.68)	0.70 (0.55, 0.89)
Median in months (95% CI)	44.7 (10.3, NR) vs NR (NR, NR)	59.7 (30.5, NR) vs 30.3 (12.8, NR)	NR (34.5, NR) vs 26.9 (12.6, 40.2)	NR (21.7, NR) vs 12.0 (6.1, 31.3)	59.7 (37.9, NR) vs 29.6 (19.5, 41.9)
OS HR (95% CI)	2.03 (0.62, 6.60)	0.65 (0.38, 1.14)	0.74 (0.54, 1.02)	0.38 (0.15, 0.93)	0.72 (0.56, 0.94)
Median in months (95% CI)	47.4 (27.2, NR) vs NR (NR, NR)	NR (48.6, NR) vs 49.2 (30.3, NR)	NR (NR, NR) vs 61.8 (42.6, NR)	NR (40.6, NR) vs 57.0 (16.1, NR)	NR (NR, NR) vs 61.8 (49.2, NR)

Source: Adapted from Information Request (IR) Response from Sponsor, April 18, 2025 – 1.11. CLINICAL INFORMATION AMENDMENT

Table 17: FDA – Extent of Resection by Tumor Subtype with PD-L1 CPS $\geq$ 1

	Hypopharyngeal		Laryngeal		Oral		Oropharyngeal		All Tumor sites	
Resections	Pembro N = 23	SoC N=23	Pembro N = 68	SoC N=60	Pembro N = 186	SoC N=182	Pembro N = 31	SoC N=28	Pembro N = 308	SoC N=293
R0, n (%)	17 (73.9)	20 (87.0)	63 (92.6)	52 (86.7)	165 (88.7)	154 (84.6)	30 (96.8)	23 (82.1)	275 (89.3)	249 (85.0)
R1, n (%)	6 (26.1)	2 (8.7)	4 (5.9)	5 (8.3)	16 (8.6)	21 (11.5)	1 (3.2)	4 (14.3)	27 (8.8)	32 (10.9)
R2, n (%)	0 (0.0)	1 (4.3)	1 (1.5)	3 (5.0)	4 (2.2)	7 (3.8)	0 (0.0)	1 (3.6)	5 (1.6)	12 (4.1)
Aborted Resection n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

Source: Information Request (IR) Response from Sponsor, April 18, 2025 – 1.11. CLINICAL INFORMATION AMENDMENT

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Two other factors may have limited therapeutic benefit from pembrolizumab among patients with hypopharyngeal tumors in KEYNOTE-689. Among patients with hypopharyngeal cancer in KEYNOTE-689, the prevalence of tumor PD-L1 CPS $\geq$ 10 was lower in the pembrolizumab arm compared to the SoC arm (0% vs 66%), reflecting the lower PD-L1 expression of hypopharyngeal cancers also reported in other studies (Deuss, et al. 2024; Harrington, et al. 2023; Cohen, et al. 2019). Additionally, patients with hypopharyngeal cancer in the pembrolizumab arm compared to the SoC arm also had higher stage tumors, i.e., T4a tumors (n=16, 57% vs n=11, 42%, respectively), which could compromise complete resectability (See 1.11.3 CLINICAL INFORMATION AMENDMENT, Applicant's response to information request on March 19, 2025).

Given a potential detriment with pembrolizumab for patients with PD-L1 positive, hypopharyngeal tumors, the EFS and R0 resection results for this subgroup of patients in KEYNOTE-689 are included in Section 14 of the USPI for pembrolizumab.

Data Quality and Integrity

The Applicant's Position:

KEYNOTE-689 was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding IEC review, informed consent, and the protection of human participants in biomedical research, as stated in the Sponsor's Code of Conduct for Interventional Clinical Trials in the study protocol. The Code of Conduct includes a description of how the study was monitored to ensure compliance with GCP.

There was one serious breach of GCP, which was identified by a site in the UK. The ALT blood test reference ranges were identified as having been incorrect since March 2019 due to a change in the analyzer and assay for ALT without an accompanying change in the ALT lab reference range. The final study impact assessment was completed on 07-APR-2022 with the conclusion that a total of 3 participants were affected without impact to participant safety or overall data integrity.

The FDA's Assessment:

FDA acknowledges the breach of GCP described as an outdated ALT lab reference range affecting 3 patients. FDA agrees that there were no major issues that impacted data quality and integrity.

Efficacy Results – Secondary and other relevant endpoints

Data:

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Table 18: Applicant – Summary of KEYNOTE-689 Key Secondary Endpoint mPR

Endpoints (pembrolizumab vs. SoC)	Observed difference in response rate (%) (95% CI)	p-Value ^a crossing boundary	Observed p- Value ^a	Outcome
KEY SECONDARY ENDPOINT: mPR				
CPS ≥10	13.7 (9.7, 18.7)	0.0005	<0.00001	Statistically significant
CPS ≥1	9.8 (7.0, 13.3)	0.0005	<0.00001	Statistically significant
All participants	9.3 (6.7, 12.8)	0.0005	<0.00001	Statistically significant
^a One-sided p-value. Analyses of mPR are based on stratified analyses. CI=Confidence Interval; CPS=Combined Positive Score; mPR=Major Pathological Response; SoC=Standard of Care.				

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Table 19: Applicant – Analysis of Overall Survival (Participants with CPS $\geq$ 10, ITT Population)

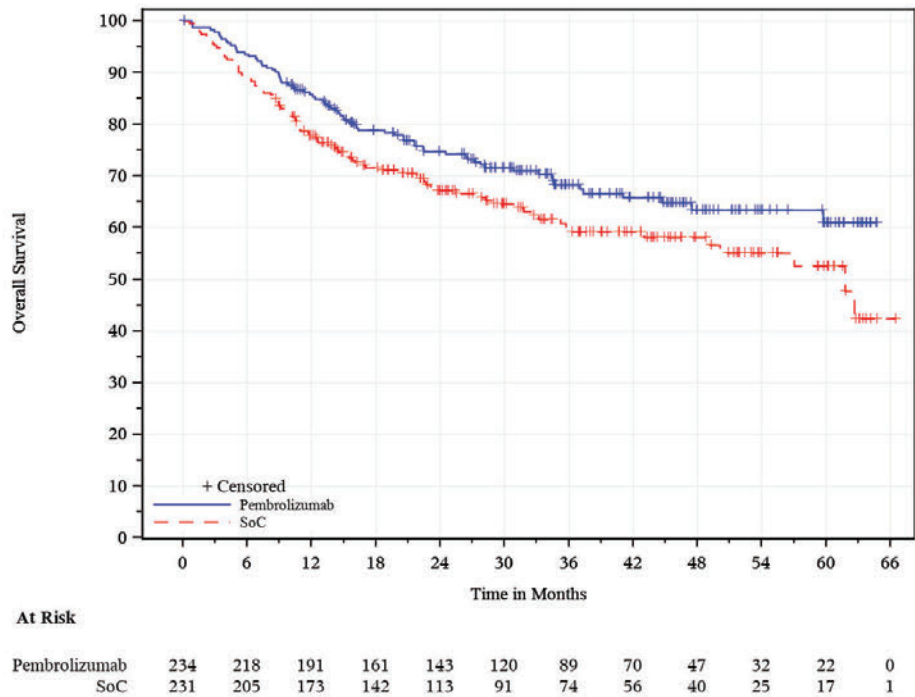
	Pembrolizumab (N=234)	SoC (N=231)
Number of Events (%)	73 (31.2)	89 (38.5)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	NR (NR, NR)	61.8 (49.2, NR)
[Q1, Q3]	[22.4, NR]	[14.6, NR]
Person-months	7314.8	6337.5
Event Rate / 100 Person-months	1.0	1.4
vs SoC		
Hazard Ratio (95% CI) ^b	0.72 (0.52, 0.98)	
p-value ^c	0.01793	
OS Rate at month 6 (%) (95% CI)	93.6 (89.5, 96.1)	88.7 (83.9, 92.2)
OS Rate at month 12 (%) (95% CI)	85.8 (80.6, 89.7)	77.8 (71.9, 82.7)
OS Rate at month 24 (%) (95% CI)	74.8 (68.5, 80.0)	67.1 (60.4, 73.0)
OS Rate at month 36 (%) (95% CI)	68.2 (61.3, 74.2)	59.2 (51.7, 65.9)
OS Rate at month 48 (%) (95% CI)	63.5 (55.7, 70.2)	58.1 (50.4, 65.0)
OS Rate at month 60 (%) (95% CI)	61.0 (52.0, 68.8)	52.5 (42.9, 61.1)
^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 primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
^c One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
NR = Not reached.		
Database Cutoff Date: 25JUL2024		

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Figure 10: Applicant – Kaplan-Meier Plot of Overall Survival (Participants with CPS≥10, ITT Population)



Database Cutoff Date: 25JUL2024.

Source: [P689V01MK3475: adam-adsl; adtte]

Table 20: Applicant – Analysis of Overall Survival (Participants with CPS≥1, ITT Population)

	Pembrolizumab (N=347)	SoC (N=335)
Number of Events (%)	106 (30.5)	128 (38.2)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	NR (NR, NR)	61.8 (49.2, NR)
[Q1, Q3]	[24.5, NR]	[14.2, NR]
Person-months	10621.2	9081.0
Event Rate / 100 Person-months	1.0	1.4
vs SoC		
Hazard Ratio (95% CI) ^b	0.72 (0.56, 0.94)	
p-value ^c	0.00666	
OS Rate at month 6 (%) (95% CI)	94.2 (91.2, 96.2)	88.4 (84.4, 91.4)

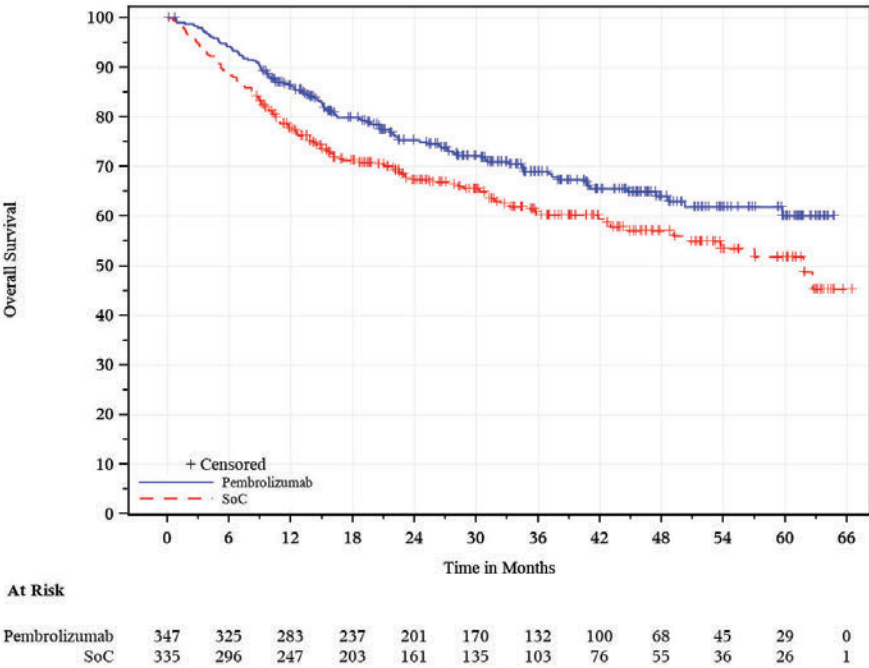
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OS Rate at month 12 (%) (95% CI)	86.3 (82.2, 89.5)	77.5 (72.6, 81.6)
OS Rate at month 24 (%) (95% CI)	75.3 (70.2, 79.7)	67.3 (61.7, 72.2)
OS Rate at month 36 (%) (95% CI)	69.0 (63.3, 74.0)	60.2 (54.1, 65.8)
OS Rate at month 48 (%) (95% CI)	64.0 (57.6, 69.6)	57.0 (50.4, 63.0)
OS Rate at month 60 (%) (95% CI)	60.1 (52.4, 66.8)	51.7 (43.8, 59.1)
^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 primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
^c One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP.		
NR = Not reached.		
Database Cutoff Date: 25JUL2024		

Source: [P689V01MK3475: adam-adsl; adtte]

Figure 11: Applicant – Kaplan-Meier Plot of Overall Survival (Participants with CPS≥1, ITT Population)



Database Cutoff Date: 25JUL2024.

Source: [P689V01MK3475: adam-adsl; adtte]

Table 21: Applicant – Analysis of Overall Survival (ITT Population)

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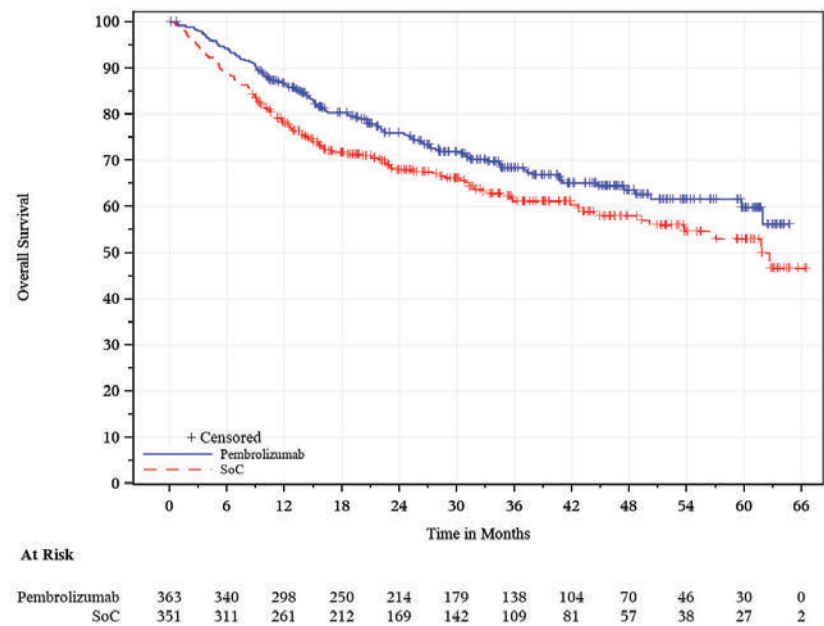
	Pembrolizumab (N=363)	SoC (N=351)
Number of Events (%)	113 (31.1)	131 (37.3)
Kaplan-Meier Estimates (months) ^a		
Median (95% CI)	NR (61.9, NR)	61.8 (50.1, NR)
[Q1, Q3]	[25.2, NR]	[14.4, NR]
Person-months	11133.5	9550.7
Event Rate / 100 Person-months	1.0	1.4
vs SoC		
Hazard Ratio (95% CI) ^b	0.76 (0.59, 0.98)	
p-value ^c	0.01529	
OS Rate at month 6 (%) (95% CI)	94.2 (91.2, 96.2)	88.6 (84.8, 91.5)
OS Rate at month 12 (%) (95% CI)	86.7 (82.7, 89.8)	77.9 (73.2, 81.9)
OS Rate at month 24 (%) (95% CI)	75.9 (70.9, 80.1)	67.9 (62.5, 72.7)
OS Rate at month 36 (%) (95% CI)	68.4 (62.9, 73.3)	61.1 (55.1, 66.5)
OS Rate at month 48 (%) (95% CI)	63.6 (57.4, 69.1)	58.0 (51.6, 63.9)
OS Rate at month 60 (%) (95% CI)	59.8 (52.4, 66.4)	52.9 (45.2, 60.0)
^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 primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. ^c One-sided p-value based on log-rank test stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. NR = Not reached. Database Cutoff Date: 25JUL2024		

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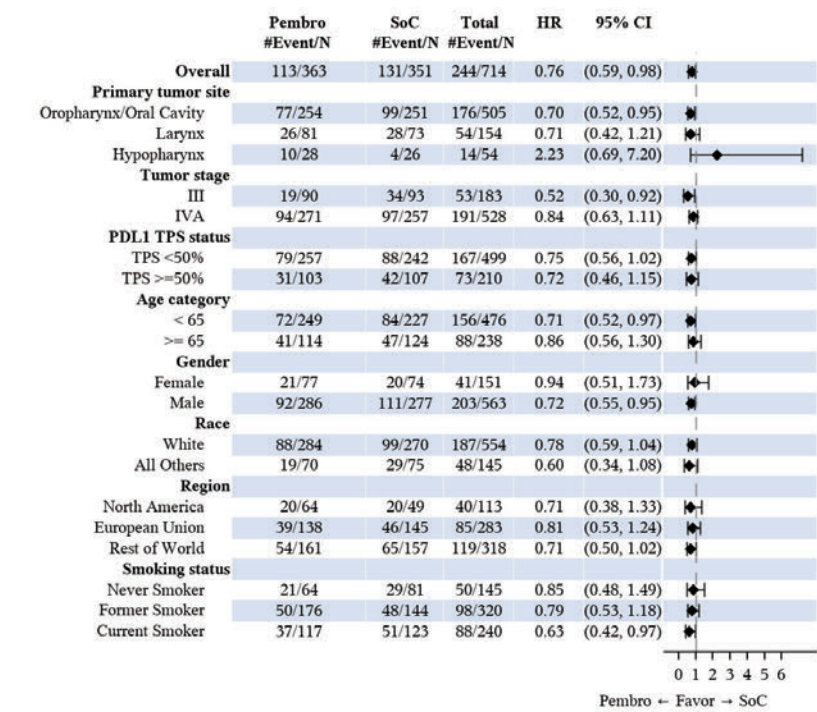
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Figure 12: Applicant – Kaplan-Meier Plot of Overall Survival (ITT Population)



Database Cutoff Date: 25JUL2024.
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Figure 13: Applicant –Forest Plot of OS Hazard Ratio by Subgroup Factors (ITT Population)

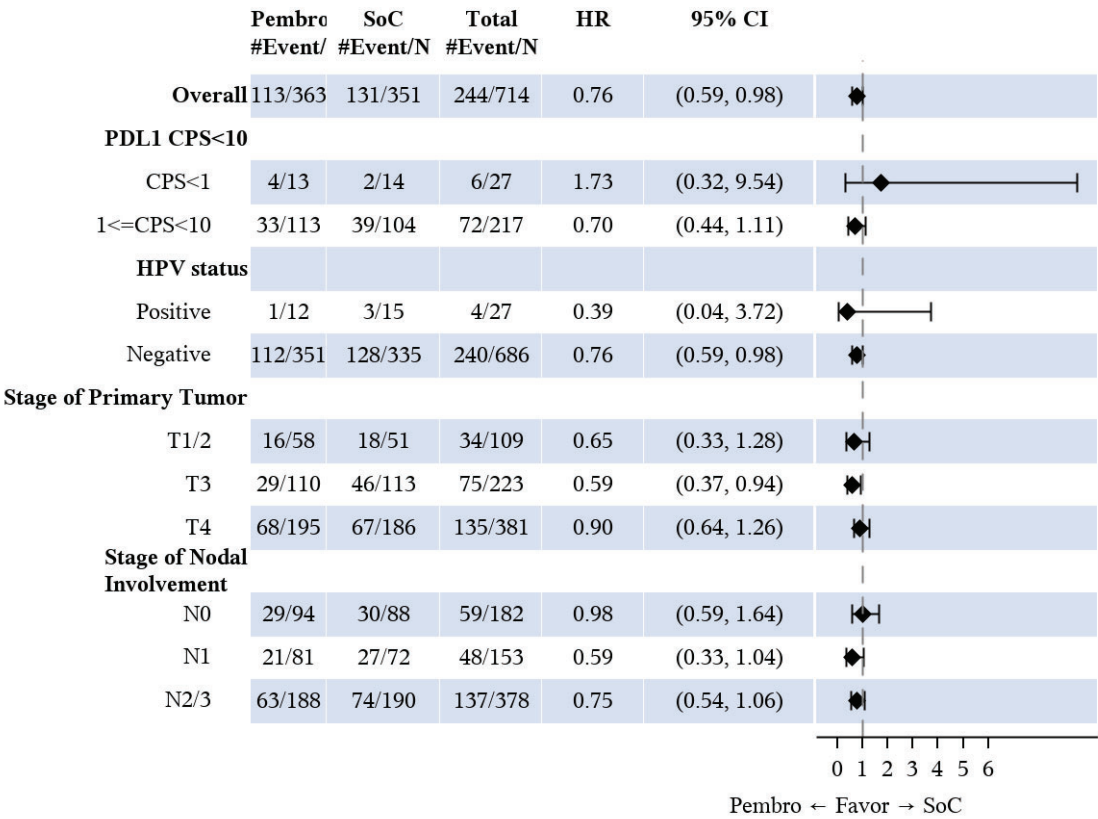


For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. If total number of participants in one level of a subgroup is <10% of the CPS≥10 population, that particular level will not be displayed. European Union category in this graph includes European Economic Area, United Kingdom and Switzerland.
Database Cutoff Date: 25JUL2024
Source: [P689V01MK3475: adam-adsl; adtte]

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Figure 14: Applicant – Forest Plot of OS Hazard Ratio by Subgroup Factors (Post-hoc) (ITT Population)



For overall population, analysis is based on Cox regression model with treatment as a covariate stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx) and tumor stage (III vs IVA) with small strata collapsed as pre-specified in the sSAP. For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate. Thirteen participants were classified as T Stage T1. Three participants were classified as N Stage N3 or N3B. Database Cutoff Date: 25JUL2024

Source: [P689V01MK3475: adam-adsl; adtte]

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Table 22: Applicant – Summary of KEYNOTE-689 Other Secondary Efficacy Endpoint pCR

Endpoints (pembrolizumab vs. SoC)	Observed difference in response rate (%) (95% CI)	p-Value ^a crossing boundary	Observed p- Value ^a	Outcome
SECONDARY ENDPOINT: pCR				
CPS ≥10	4.2 (2.1, 7.6)	NA	Nominal 0.0011	No hypothesis
CPS ≥1	3.1 (1.6, 5.6)	NA	Nominal 0.0006	No hypothesis
All participants	3.0 (1.5, 5.3)	NA	Nominal 0.0006	No hypothesis
^a One-sided P-value Analyses of pCR are based on stratified analyses. CI=Confidence Interval; CPS=Combined Positive Score; NA=Not Applicable; pCR=Pathological Complete Response; SoC=Standard of Care.				

Table 23: Applicant – Summary of Post-Surgical Risk Categorization (ITT Population)

	Pembrolizumab		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	363		351		714	
Risk Category by Central Assessment						
HIGH RISK	118	(32.5)	156	(44.4)	274	(38.4)
LOW RISK	196	(54.0)	148	(42.2)	344	(48.2)
Missing	49	(13.5)	47	(13.4)	96	(13.4)
Post-surgical pathological risk categorization of participants as either high or low risk was completed based on central (BIPR) pathological assessment of the surgically resected specimens from the primary tumor site and neck lymph nodes. Database Cutoff Date: 25JUL2024.						

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Table 24: Applicant – Exploratory Event-free Survival in High and Low-risk Category

Endpoints (pembrolizumab vs. SoC)	Median in months (95% CI)	Observed HR (95% CI)
EXPLORATORY ENDPOINT: EFS per RECIST 1.1, BICR assessed		
High-Risk Population (Pembrolizumab n= 118, SoC n= 156)	41.1 (22.1, NR) vs. 19.5 (11.3, 57.0)	0.73 (0.52, 1.05)
Low Risk Population (Pembrolizumab n= 196, SoC= 148)	NR (44.7, NR) vs. 51.5 (35.3, NR)	0.74 (0.51, 1.08)
Analyses of EFS are based on unstratified analyses. BICR=blinded independent central review; CI=Confidence Interval; EFS=Event Free Survival; HR=Hazard Ratio; NR=Not Reached; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SoC=Standard of Care.		

Table 2165: Applicant – Exploratory Overall Survival in High and Low-risk Category

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Endpoints (pembrolizumab vs. SoC)	Median in months (95% CI)	Observed HR (95% CI)
High-Risk Population	61.9 (48.6, NR) vs. 49.2 (33.2, NR)	0.79 (0.53, 1.16)
Low Risk Population	NR (NR, NR) vs. NR (62.6, NR)	0.79 (0.52, 1.20)
Analyses of OS are based on unstratified analyses. CI=Confidence Interval; HR=Hazard Ratio; NR=Not Reached; SoC=Standard of Care.		

The Applicant’s Position:

Major Pathological Response (mPR):

mPR was defined as having less than or equal to 10% invasive SCC within the resected primary tumor specimen and all sampled regional lymph nodes, as assessed by BIPR. There was a statistically significant improvement in mPR based on BIPR in the pembrolizumab group compared to the SoC group in the CPS ≥10, CPS ≥1, and all participants populations noting that the SOC treatment group did not receive neoadjuvant therapy[Table 16].

Post-hoc Analysis of mPR in the CPS <1 and CPS 1-9 Populations

- No mPR rate difference was observed in the CPS <1 population (mPR rate difference=0%; 95% CI: -22.2, 23.5), but the number of participants was small (n=27). Note that the small sample sizes in some subgroups resulted in wide CIs, limiting definitive conclusions. The mPR rate difference between treatment groups in the CPS 1-9 population was 1.8% (95% CI: -1.8, 6.2), lower than the mPR results for all participants (mPR rate difference: 9.3%; 95% CI: 6.7, 12.8).

Overall Survival (OS):

The point estimate of OS HR favors the pembrolizumab group versus the SoC group in the CPS ≥10, CPS ≥1, and all participant populations. However, the observed p-value did not cross the p-value boundary in the CPS ≥10 population at IA1. Per the multiplicity strategy prespecified in the SAP, OS in CPS ≥1 and subsequently in all participants can only be formally tested after statistical significance is established in CPS ≥10. Therefore, OS was not formally tested at CPS ≥1 or in all participants at IA1.

Overall Survival in the CPS ≥10 Population

- As of the data cutoff for IA1, a total of 73 OS events were observed in the pembrolizumab group, and the median OS was not reached (95% CI: NR, NR). A total of 89 OS events were observed in the SoC group and the median OS was 61.8 months (95% CI: 49.2, NR). The point estimate of OS HR favored the pembrolizumab group over the SoC group (HR: 0.72; 95% CI: 0.52, 0.98; p=0.01793). However, the observed

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p -value did not cross the p -value boundary (0.0104) at IA1 (information fraction of approximately 81%) [162 of the 201 events needed for the final analysis] [Table 17].

- The KM curves separated within the first 2 months and remained separated throughout the evaluation period in favor of pembrolizumab [Figure 10]. OS rates were higher in the pembrolizumab group than in the SoC group at all timepoints analyzed [Table 17].
- The OS improvement of pembrolizumab over SoC was generally consistent across prespecified subgroups.

Overall Survival in the CPS ≥ 1 Population and All Participants

- Per multiplicity strategy prespecified in the SAP, OS in CPS ≥ 1 and subsequently in all participants can only be formally tested after statistical significance is established in CPS ≥ 10 . Therefore, OS was not formally tested at CPS ≥ 1 and in all participants. The OS HR estimates favored pembrolizumab versus SoC at CPS ≥ 1 and in all participants, with HRs of 0.72 (95% CI: 0.56, 0.94; nominal $p=0.00666$) and 0.76 (95% CI: 0.59, 0.98; nominal $p=0.01529$). Median OS was not reached in the pembrolizumab group compared with a median OS of 61.8 months in the SoC group in both CPS ≥ 1 and all participants [Table 18] [Table 19].
- In both the CPS ≥ 1 and all participant populations, the KM curves separated within the first 2 months and remained separated throughout the evaluation period in favor of pembrolizumab [Figure 11] [Figure 12]. OS rates in both the CPS ≥ 1 and all participant populations were higher in pembrolizumab group at all timepoints analyzed [Table 18] [Table 19].
- In both the CPS ≥ 1 and all participant populations, the OS improvement of pembrolizumab over SoC was generally consistent across prespecified subgroups [Figure 13].

OS will continue to be tested at the next IA.

Post-hoc Analysis of Overall Survival in the CPS < 1 and CPS 1-9 Populations

- The HR of OS in the CPS < 1 population was 1.73 (95% CI: 0.32, 9.54), but note that the small sample size in the CPS < 1 subgroup ($n=27$) resulted in wide CIs, limiting definitive conclusions. The HR of OS in the CPS 1-9 population was 0.70 (95% CI: 0.44, 1.11) and was consistent with OS results for all participants (HR: 0.76; 95% CI: 0.59, 0.98) [Figure 14].

Analysis of pCR

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pCR was defined as having no residual invasive SCC within the resected primary tumor specimen and all sampled regional lymph nodes, as assessed by BIPR.

There is no hypothesis for pCR since it is not included in the multiplicity strategy.

In the CPS ≥ 10 , CPS ≥ 1 , and all participant populations, there was an improvement in pCR rate based on BIPR in the pembrolizumab group compared with the SoC group noting that the SoC group did not receive neoadjuvant therapy.

pCR in the CPS ≥ 10 Population: response rate difference of 4.2% (95% CI: 2.1, 7.6; nominal $p=0.0011$). The pCR rate was 4.3% for the pembrolizumab group; there were no participants with pCR in the SoC group for all 3 populations [Table 20].

pCR in the CPS ≥ 1 Population: response rate difference of 3.1% (95% CI: 1.6, 5.6; nominal $p=0.0006$). The pCR rate was 3.2% for the pembrolizumab group [Table 20].

pCR in All Participants: response rate difference of 3.0% (95% CI: 1.5, 5.3; nominal $p=0.0006$). The pCR rate was 3.0% for the pembrolizumab group [Table 20].

The FDA's Assessment:

FDA generally agrees with the Applicant's position regarding the OS endpoint. OS in the PD-L1 CPS ≥ 10 population did not meet the statistical boundary for early stopping; therefore, OS in the PD-L1 CPS ≥ 1 and ITT populations could not be tested, and the trial will continue to collect OS data. OS data is currently immature, though no numerical detriment in OS was observed in the PD-L1 CPS ≥ 10 , PD-L1 CPS ≥ 1 and ITT populations. As discussed above in the EFS data section, definitive conclusions regarding OS in the PD-L1 CPS < 1 patient population cannot be determined due to the small sample size of this subgroup.

(b) (4)

(b) (4) In KEYNOTE-689, patients on the standard of care arm did not receive neoadjuvant treatment, further adding to the challenge in establishing correlation between mPR and pCR with long-term clinical outcomes. Therefore, despite the fact that mPR was an alpha allocated endpoint in this study, the clinical meaningfulness of this result in patients with resectable HNSCC is unknown.

Dose/Dose Response

The Applicant's Position: Not applicable for this study.

The FDA's Assessment:

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Not applicable.

Durability of Response

The Applicant's Position: Not applicable for this study.

The FDA's Assessment:

Not applicable.

Persistence of Effect

The Applicant's Position: Not applicable for this study.

The FDA's Assessment:

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

PROs were evaluated using the EORTC QLQ-C30 and EORTC QLQ-H&N 35 (secondary endpoints). Analysis of mean change from baseline in the EORTC QLQ-C30 global health status/QoL and physical functioning scores and swallowing, speech, and pain symptoms using the EORTC QLQ-H&N35 was calculated in all participants at IA1. Analyses in this PRO section for all participants, CPS $\geq$ 1, and CPS $\geq$ 10 are based on the PRO FAS population.

Mean Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL in Physical Functioning Scores and QLQ-H&N35 Swallowing, Speech, and Pain Scores in the Pembrolizumab Group (Neoadjuvant and Presurgery) at Weeks 4 and 6

Mean change from baseline in the EORTC QLQ-C30 global health status/QoL scores were similar in all 3 populations in the pembrolizumab group at Week 4 (neoadjuvant phase) and Week 6.

Mean change from baseline in the EORTC QLQ-C30 physical functioning domain, QLQ-H&N35 swallowing, speech, and pain scores remained stable over time in all participants in the pembrolizumab group at Week 4 (neoadjuvant phase) and Week 6.

Mean Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL in Physical Functioning Scores, QLQ-H&N35 Swallowing, Speech, and Pain Scores in the Pembrolizumab Group and SoC Group at Post-Adjuvant Weeks 25 and 51

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In all participants, mean change from baseline global health status/QoL scores were similar between the pembrolizumab and SoC groups in all 3 populations at postadjuvant RT $\pm$ cisplatin Week 25 and Week 51.

No differences were observed in the change in baseline for physical functioning scores at postadjuvant RT $\pm$ cisplatin Week 25 and Week 51 between the pembrolizumab and the SoC groups in all participants.

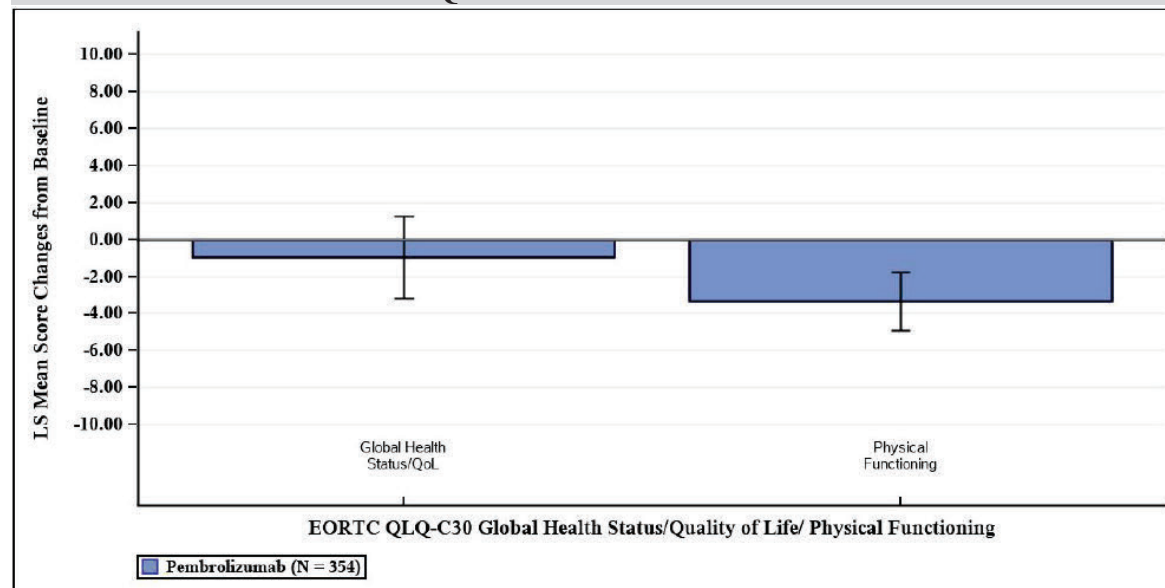
In all participants, mean change from baseline EORTC QLQ-H&N35 swallowing, speech, and pain symptom scores were generally similar between the pembrolizumab and SoC groups at postadjuvant RT $\pm$ cisplatin Week 25 and Week 51. Mean change from baseline pain scores were observed to improve in both groups.

The FDA's Assessment:

The Applicant's position references figures that were omitted from the submitted Assessment Aid and are provided here. These figures have been reproduced from Clinical Study Report, Section 11.2.

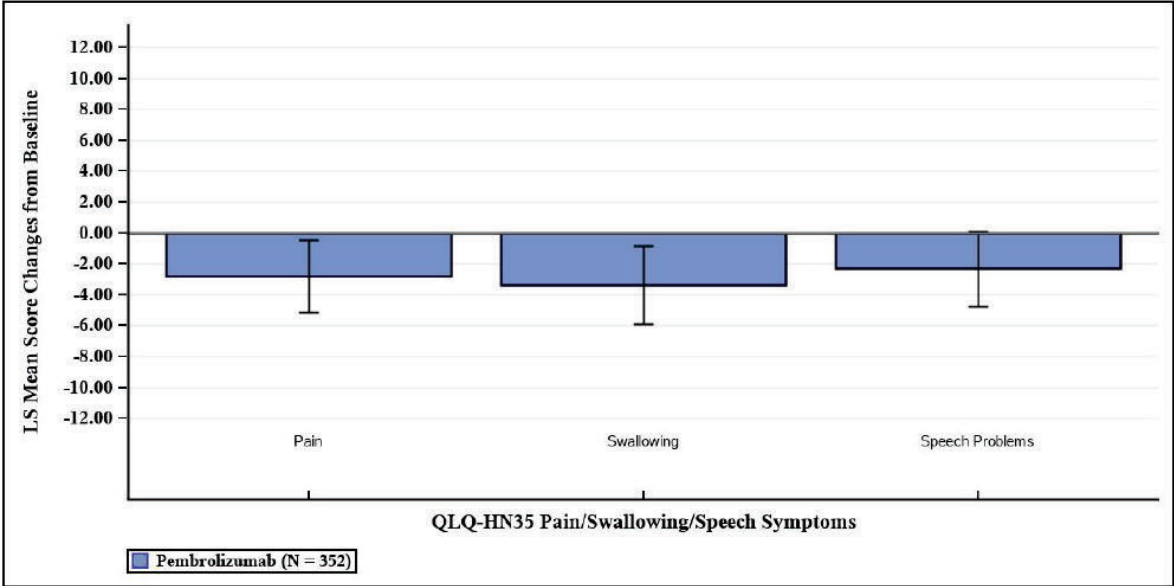
Figure 15: FDA - Mean Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL in Physical Functioning Scores and QLQ-H&N35 Swallowing, Speech, and Pain Scores in the Pembrolizumab Group (Neoadjuvant and Presurgery) at Weeks 4 and 6

Week 4 - Global Health Status/QoL Physical Functioning Scores in Pembrolizumab Arm

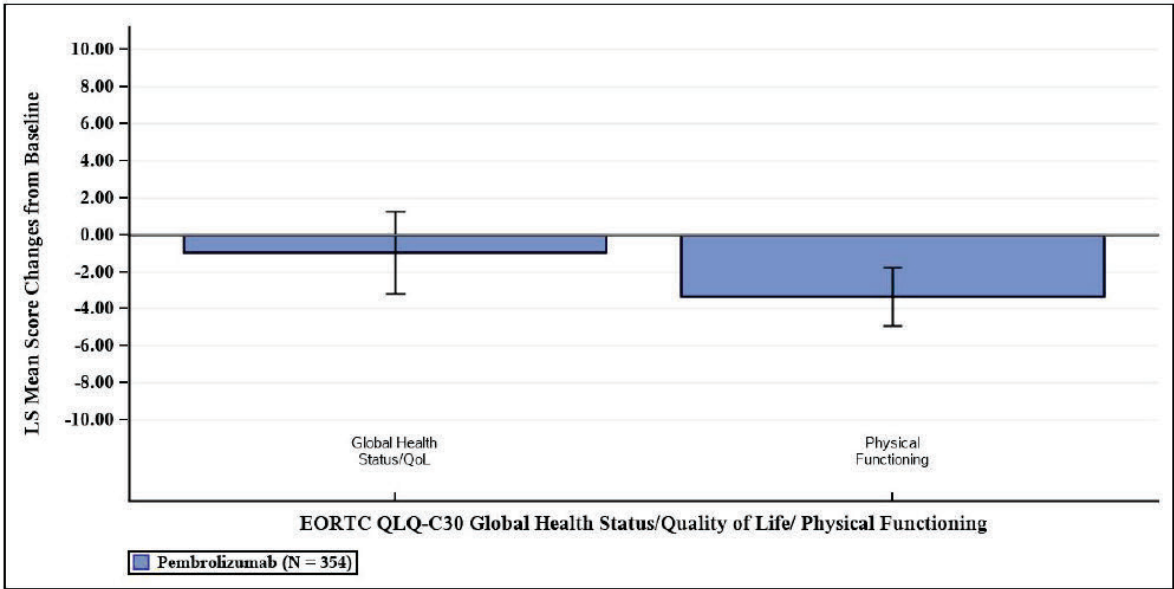


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Week 4 - Swallowing, Speech, and Pain Scores in the Pembrolizumab Arm



Week 6 - Global Health Status/QoL Physical Functioning Scores in Pembrolizumab Arm



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Week 6 - Swallowing, Speech, and Pain Scores in the Pembrolizumab Arm

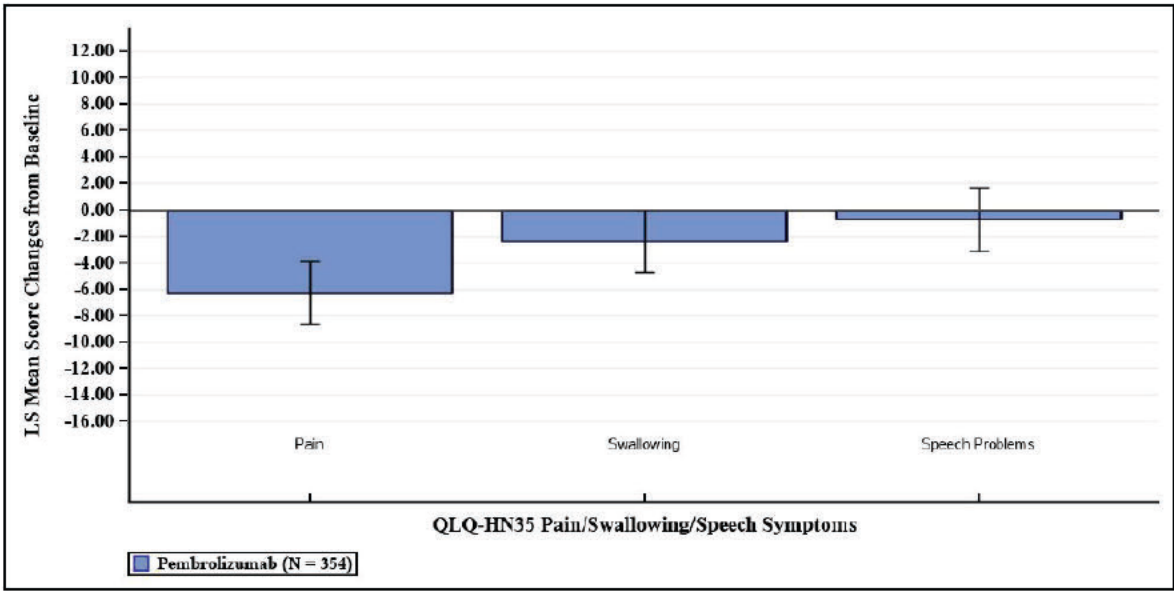
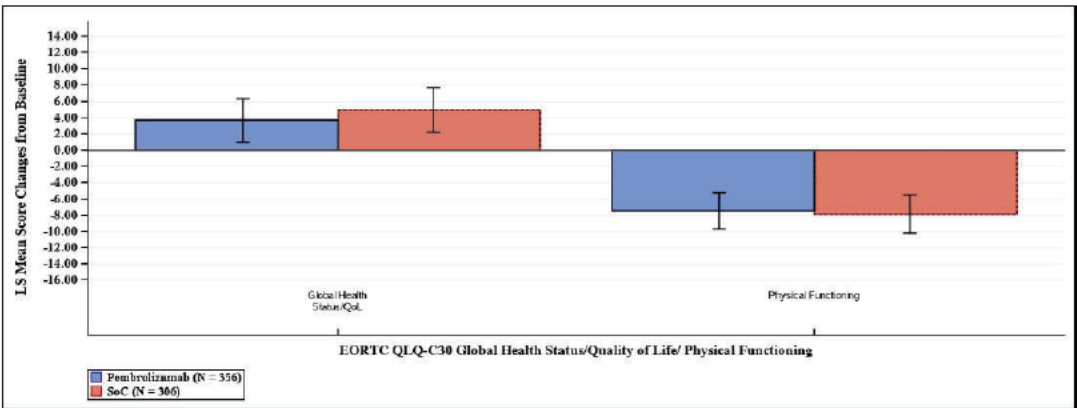


Figure 16: FDA - Mean Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL in Physical Functioning Scores, QLQ-H&N35 Swallowing, Speech, and Pain Scores in the Pembrolizumab Group and SoC Group at Post-Adjuvant Weeks 25 and 51

The data summarized above by the Applicant are presented graphically below as reproduced from Clinical Study Report, Section 11.2.

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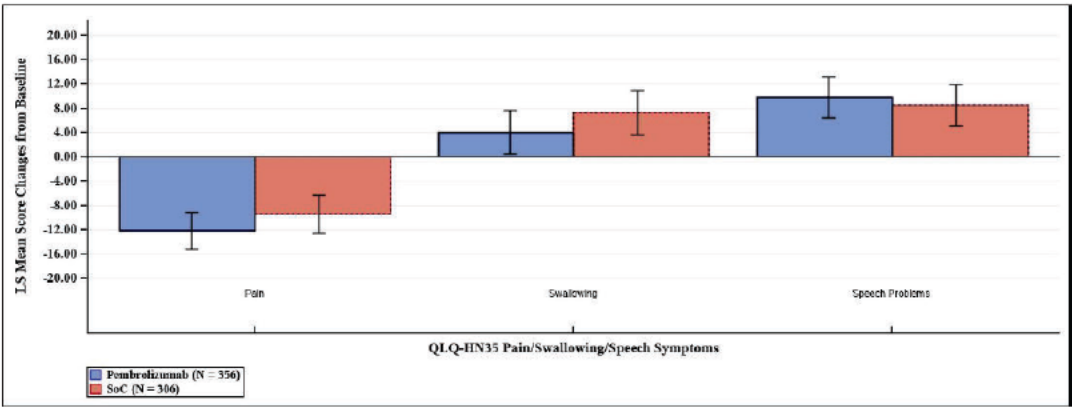
Week 25 - Global Health Status/QoL in Physical Functioning Scores in the Pembrolizumab and SoC arms



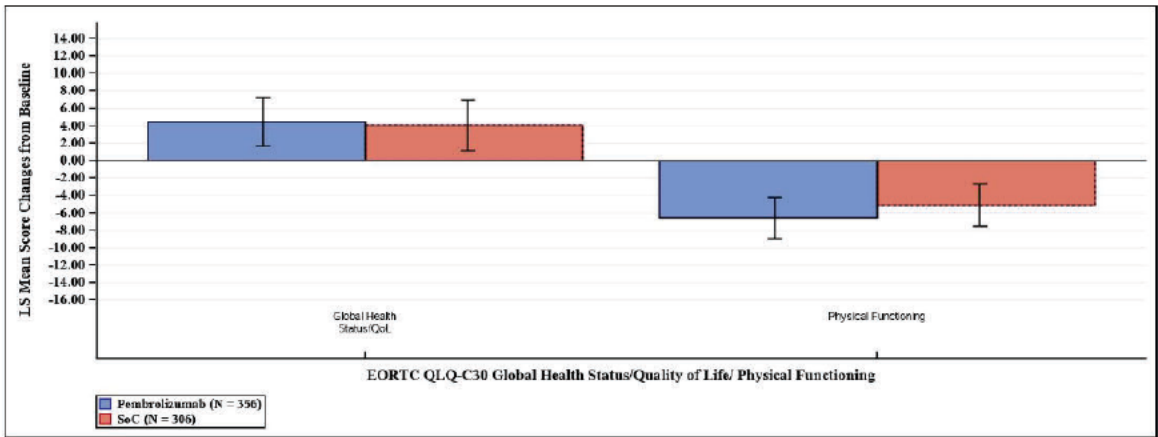
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Week 25 - Pain/Swallowing/Speech Symptoms Scores in Pembrolizumab and SoC arms



Week 51 - Global Health Status/QoL in Physical Functioning Scores in the Pembrolizumab and SoC arms



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Week 51 - Pain/Swallowing/Speech Symptoms Scores in Pembrolizumab and SoC arms

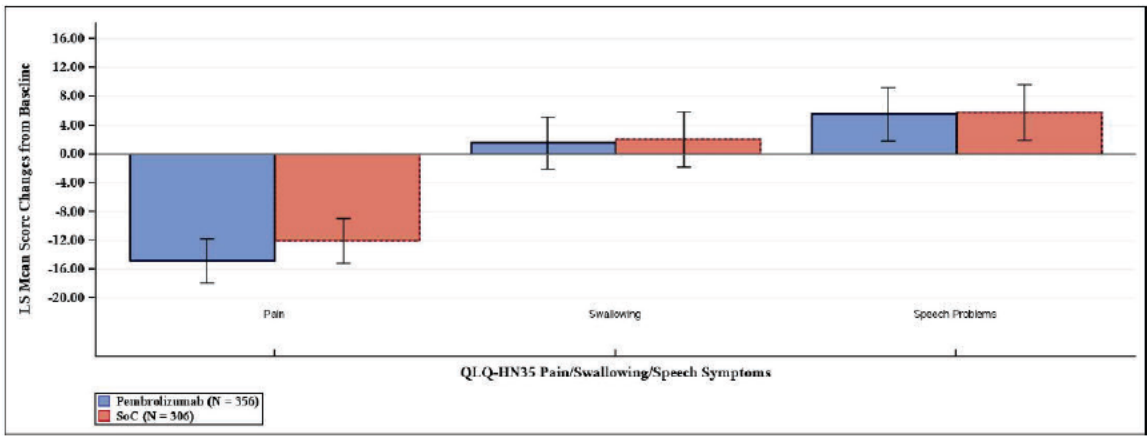
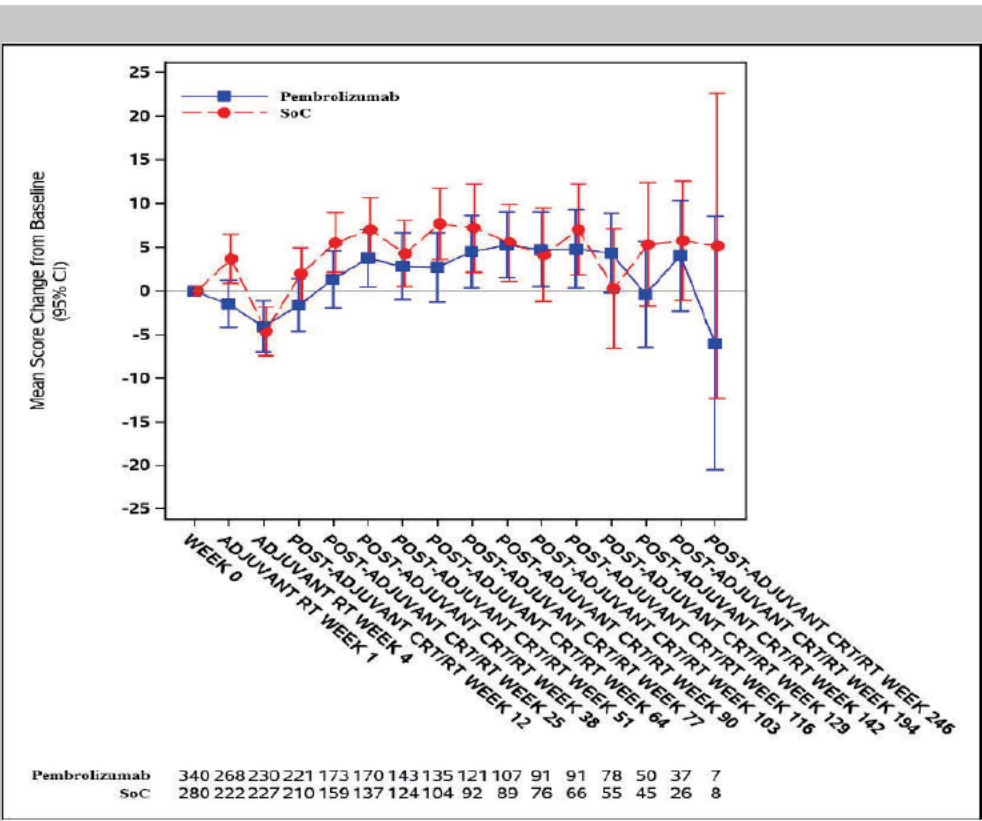


Figure 17: FDA - Line Plot of Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time by Treatment Group (PRO FAS Population) From Clinical Summary Report, Section 11.2



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According to the Applicant's analysis in Section 11.2.1 of the CSR, compliance rates during the neoadjuvant portion of the study for the pembrolizumab arm at Weeks 4 and 6 were >94.0% for the EORTC QLQ-C30, >93.0% for the EORTC QLQ-H&N 35 and >94.0% for the EQ-5D-5L. In the post-adjuvant portion of the study, compliance rates for the EORTC-QLQ-C30 were 81.7% in the pembrolizumab arm and 91.0% in the SOC arm at Week 25 and 88.5% for the pembrolizumab arm and 89.9% for the SoC arm at Week 51; similar rates were observed at these timepoints for the EORTC-QLQ-H&N35 and EQ-5D-5L.

Patient-reported outcomes (PRO) endpoints are considered exploratory for KEYNOTE-689. FDA agrees with the Applicant that the PRO scores for core domains were generally similar between arms at most timepoints, however definitive conclusions cannot be drawn based on the trial results. Similar PRO scores between arms are not considered as evidence of tolerability.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Post-Surgery Pathological Risk Assessment

After 2 cycles of neoadjuvant pembrolizumab administration and surgical resection in participants in the pembrolizumab group, and after surgical resection in participants in the SoC group, pathological risk categorization of participants as either high- or low-risk was completed based on central (BIPR) pathological assessment of the surgically resected specimens from the primary tumor site and neck lymph nodes. Post-surgical treatment decisions involving cisplatin were guided based on local pathology results.

In the all participants population, based on central post-surgical pathological risk assessment of the resected primary tumor and lymph node specimens, a total of 54.0% of participants in the pembrolizumab group were categorized as low-risk compared with 42.2% of participants in the SoC group, while 32.5% of participants in the pembrolizumab group were categorized as high-risk compared with 44.4% of participants in the SoC group [Table 21]. A total of 13.5% of participants in the pembrolizumab group and 13.4% of participants in the SoC group did not undergo surgery or did not get post-surgical risk assessment. These results suggest that response to neoadjuvant pembrolizumab may lead to a decrease in the rate of high-risk pathologic features as baseline characteristics were well balanced between treatment arms.

EFS in the High-Risk Population (Exploratory Analysis as per Protocol)

- In the high-risk population, the EFS HR estimate was 0.73 (CI: 0.52, 1.05). The median EFS based on BICR was 41.1 months in the pembrolizumab group compared with the median EFS of 19.5 months in the SoC group. The EFS rates were higher in the pembrolizumab group than in the SoC group [Table 22].

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EFS in the Low-Risk Population (Exploratory Analysis as per Protocol)

- In the low-risk population, the EFS HR estimate was 0.74 (CI: 0.51, 1.08). The median EFS was not reached in the pembrolizumab group compared with the median EFS of 51.5 months in the SoC group. The EFS rates were higher in the pembrolizumab group than in the SoC group [Table 22].

Overall Survival in the High-Risk Population (Exploratory Analysis as per Protocol)

- The OS HR estimate was 0.79 (95% CI: 0.53, 1.16). The median OS was longer in the pembrolizumab group than in the SoC group (61.9 months vs 49.2 months, respectively) [Table 23].

Overall Survival in the Low-Risk Population (Exploratory Analysis as per Protocol)

- The OS HR estimate was 0.79 (95% CI: 0.52, 1.20). The median OS was not reached in the pembrolizumab group or in the SoC group [Table 23].

The treatment effect of pembrolizumab was consistent regardless of the risk population as defined post-surgery.

The FDA's Assessment:

High-risk and low-risk populations are identified based on post-surgical pathological features assessment after initial randomization. Therefore, EFS and OS results from these post-randomization subgroup analyses should be interpreted with caution due to the potential for bias and the loss of randomization.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

KEYNOTE-689 met its primary objective of improving EFS with the pembrolizumab-based perioperative regimen. At EFS interim analysis 1 (IA1), with an approximate information fraction of 80% in the ITT population, the study met the pre-specified boundary for significance in the tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT populations with EFS hazard ratios (HR) of 0.66 (95% CI: 0.49, 0.88; $p=0.00217$), 0.70 (95% CI: 0.55, 0.89; $p=0.00140$), and 0.73 (95% CI: 0.58, 0.92; $p=0.00411$), respectively. In the subgroup of patients with PD-L1 positive (CPS ≥ 1) tumors, the median EFS was 59.7 months (CI 95%: 37.9, NR) in the pembrolizumab arm and 29.6 months (CI 95%: 19.5, 41.9) in the SoC arm, corresponding to a 30.1-month improvement in median EFS.

At IA1, the study met the pre-specified boundary for statistical significance for mPR favoring the pembrolizumab arm in patients with tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT population with MPR rates of 13.7% (95% CI: 9.7, 18.7), 9.8% (95%

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CI: 7.0, 13.3), and 9.3% (95% CI: 6.7, 12.8), respectively, on the pembrolizumab arm, with no major pathological responses observed in patients on the SoC control arm.

At IA1, OS in patients with tumor PD-L1 CPS ≥ 10 had not reached statistical significance, although there was a numerical difference in OS favoring the pembrolizumab arm. The median OS was not reached (NR) (95% CI: NR, NR) in the pembrolizumab arm and was 61.8 months (95% CI: 49.2, NR) in the SoC arm, corresponding to a HR of 0.72 (95% CI: 0.52, 0.98). Because the hierarchical testing strategy requires OS to reach statistical significance in the patients with PD-L1 CPS ≥ 10 before proceeding with testing OS in other populations, OS was not tested in patients with PD-L1 CPS ≥ 1 or in the ITT population. However, in a descriptive analysis of OS in patients with PD-L1 CPS ≥ 1 , the OS HR estimate favored pembrolizumab versus SoC with a HR of 0.72 (95% CI: 0.56, 0.94). Overall survival will be tested again at interim analysis 2 (IA2), when approximately 187 patients with PD-L1 CPS ≥ 10 have had OS events (93% information fraction of the final OS analysis).

The EFS treatment effect was largely preserved across subgroups except for patients with PD-L1 negative (CPS < 1) tumors and patients with primary tumors originating from the hypopharynx. In exploratory subgroup analyses of patients with PD-L1 CPS < 1 (n=27), the EFS HR was 2.57 (95% CI: 0.50, 13.36) and the OS HR of 1.73 (95% CI: 0.32, 9.54), favoring the SoC arm.

In an exploratory subgroup analysis in patients with PD-L1 positive (CPS ≥ 1) hypopharyngeal primary tumors, the EFS HR was 2.28 (95% CI: 0.79, 6.56), favoring the SoC arm. For patients with all other primary tumor subsites (i.e., oral cavity, oropharyngeal and laryngeal tumors), the EFS results favored the pembrolizumab arm over the SoC arm. In addition, the rate of complete (R0) surgical resection, a predictor of HNSCC overall survival, was lower in the pembrolizumab arm compared to the SoC arm for patients with PD-L1 positive (CPS ≥ 1) hypopharyngeal tumors, at 74% vs 87%, respectively. For all other PD-L1 positive (CPS ≥ 1) primary tumors subsites, the R0 resection rate was higher in the pembrolizumab arm compared to the SoC arm at 91% vs 85%, respectively.

Although the trial was not designed to determine the contribution of effect of the neoadjuvant and adjuvant phases of therapy, the overall perioperative pembrolizumab-based regimen evaluated in KEYNOTE-689 demonstrated a large EFS treatment effect and a trend towards improved OS for patients with resectable, PD-L1 positive (CPS ≥ 1) LA HNSCC.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position: Not Applicable

The FDA's Assessment: Not applicable.

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Not Applicable Secondary and Other Endpoints

The Applicant's Position: Not Applicable

The FDA's Assessment: Not applicable.

Not Applicable Subpopulations

The Applicant's Position: Not Applicable

The FDA's Assessment: Not applicable.

Additional Efficacy Considerations

The Applicant's Position:

This section is not applicable because the current application presents efficacy results from a single study, KEYNOTE-689.

The FDA's Assessment: Not Applicable.

8.1.5. Integrated Assessment of Effectiveness

The FDA's Assessment:

This sBLA is primarily supported by results from KEYNOTE-689, a randomized, multicenter, open label, active controlled trial conducted in patients with resectable locally advanced (Stage III-IVA) HNSCC [AJCC, 8th edition]. KEYNOTE-689 was conducted globally with patients enrolled and randomized across North America, South America, Europe, Russia, Australia, and Asia; approximately 13% of the efficacy population in this application was enrolled in the U.S. The primary endpoint of KEYNOTE-689 was EFS as assessed by BICR analyzed hierarchically in patients with tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , then the ITT population. Major pathological response by BIPR and OS were key secondary endpoints. Major pathological response was defined as having less than or equal to 10% invasive SCC within the resected primary tumor specimen and all sampled regional lymph nodes.

The study met its primary EFS endpoint, meeting the pre-specified boundary for significance in the tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT populations, with EFS hazard ratios (HR) of 0.66 (95% CI: 0.49, 0.88; $p=0.00217$), 0.70 (95% CI: 0.55, 0.89; $p=0.00140$), and 0.73 (95% CI: 0.58, 0.92; $p=0.00411$), respectively.

However, in an exploratory subgroup analysis of patients with PD-L1 CPS ≥ 1 ($n=27$), the EFS HR was 2.57 (95% CI: 0.50, 13.36). An exploratory analysis of OS for patients in this PD-L1 negative subgroup also showed a trend toward potential detriment with pembrolizumab with an OS HR of 1.73 (95% CI: 0.32, 9.54). The small sample size makes it difficult to draw definitive conclusions regarding the benefit:risk profile of perioperative pembrolizumab for patients with PD-L1 negative, LA HNSCC. However, this trend in a potential detriment in patients with PD-L1 negative tumors is consistent with prior findings with pembrolizumab monotherapy for patients with PD-L1 negative recurrent or metastatic HNSCC, both in the first-line treatment setting (i.e., in the KEYNOTE-048 trial) and the refractory treatment setting (i.e., in KEYNOTE-040). The mechanism of action of pembrolizumab also provides scientific rationale that the efficacy of pembrolizumab monotherapy may be limited in patients with PD-L1 negative tumors. Taken together, the FDA review team recommends that the current indication is limited to patients with PD-L1 positive (CPS ≥ 1) tumors.

For patients with PD-L1 positive (CPS ≥ 1) HNSCC, there was a statistically significant and clinically meaningful 30% reduction in risk of an EFS event in the pembrolizumab arm vs the SoC arm with a HR of 0.70 (95% CI: 0.55, 0.89; one-sided p-value of 0.00140, compared with the pre-specified one-sided boundary of 0.0124). In patients with PD-L1 positive (CPS ≥ 1) HNSCC, the median EFS was 59.7 months (CI 95%: 37.9, NR) in the pembrolizumab arm and 29.6 months (CI 95%: 19.5, 41.9) in the SoC arm, corresponding to a 30.1-month improvement in median EFS.

The observed improvement in EFS appeared to be driven by fewer events of distant disease progression compared to events of local recurrence. Among patients in the PD-L1 CPS ≥ 1 population, disease progression accounted for 37% of EFS events on the pembrolizumab arm compared to 47% of EFS events on the SoC arm, with the largest difference in EFS events being related to distant progression (7% for the pembrolizumab arm vs 15% for the SoC arm). In the PD-L1 CPS ≥ 1 subgroup, the pembrolizumab arm also had a higher rate of R0 surgical resections at 91% compared to 85% R0 resections for the SoC arm.

At the first mPR interim analysis (IA1), the study also met the pre-specified boundary for statistical significance of this secondary endpoint in patients with tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT population with difference in mPR rates of 13.7% (95% CI: 9.7, 18.7; $p < 0.00001$), 9.8% (95% CI: 7.0, 13.3; $p < 0.00001$), and 9.3% (95% CI: 6.7, 12.8; $p < 0.00001$), respectively on the pembrolizumab arm, with no major pathological responses observed in patients on the SoC control arm. Of note, patients on the SoC arm did not receive any neoadjuvant therapy and were therefore not expected to have a pathologic response at the time of surgery. Additionally, mPR is not a validated endpoint and the clinical meaningfulness of mPR has not been established for patients with resectable HNSCC.

At IA1, the key secondary endpoint of OS in patients with tumor PD-L1 CPS ≥ 10 had not reached statistical significance, although there was a numerical difference in OS favoring the

pembrolizumab arm. The median OS was not reached (NR) (95% CI: NR, NR) in the pembrolizumab arm and was 61.8 months (95% CI: 49.2, NR) in the SoC arm, corresponding to a HR of 0.72 (95% CI: 0.52, 0.98). Because the hierarchical testing strategy requires OS to reach statistical significance in the patients with PD-L1 CPS ≥ 10 before proceeding with testing OS in other populations, OS was not tested in patients with PD-L1 CPS ≥ 1 or in the ITT population. However, in a descriptive analysis of OS in patients with PD-L1 CPS ≥ 1 , the OS HR estimate favored pembrolizumab versus SoC with a HR of 0.72 (95% CI: 0.56, 0.94). This descriptive analysis suggests a potential trend in improved OS with the pembrolizumab-based regimen for patients with PD-L1 positive (CPS ≥ 1) LA HNSCC. Overall survival will be tested again at interim analysis 2 (IA2), when approximately 187 patients with PD-L1 CPS ≥ 10 have had OS events (93% information fraction of the final OS analysis).

Exploratory subgroup analyses in KEYNOTE-689 of patients with PD-L1 positive (CPS ≥ 1) tumors demonstrated generally consistent EFS results favoring the pembrolizumab arm, except for patients with hypopharyngeal tumors. In exploratory subgroup analyses by primary tumor site in patients with CPS ≥ 1 , the EFS HR for patients with hypopharyngeal tumors (n=51) was 2.28 (95% CI: 0.79, 6.56) favoring the SoC arm. For patients with PD-L1 positive disease for all other primary tumor sites, EFS results favored the pembrolizumab arm over the SoC arm. Specifically, for patients with PD-L1 positive oral cavity (n=415), oropharyngeal (n=71), and laryngeal (n=144) primary tumor sites, the EFS HRs were 0.71 (95% CI: 0.53, 0.95), 0.32 (95% CI: 0.15, 0.68), and 0.62 (95% CI: 0.36, 1.06), respectively. In addition, the rate of complete (R0) surgical resection, a predictor of HNSCC overall survival, was lower in the pembrolizumab arm compared to the SoC arm for patients with PD-L1 positive (CPS ≥ 1) hypopharyngeal tumors, at 74% vs 87%, respectively. For all other primary tumor subsites, the R0 resection rate was higher in the pembrolizumab arm compared to the SoC arm at 91% vs 85%, respectively.

The potential detriment of perioperative pembrolizumab for patients with hypopharyngeal tumors in KEYNOTE-689 may in part be driven by more advanced disease at presentation, with a higher percentage of patients with hypopharyngeal tumors having T4a tumors. Some real-world data suggest a potential detriment for induction therapies followed by surgery compared to upfront surgery for advanced, particularly T4a, hypopharyngeal cancer (Zheng, et al. 2023; Tsai, et al. 2024). In addition, hypopharyngeal tumors in KEYNOTE-689 had lower levels of PD-L1 expression by CPS compared to other HNSCC anatomic subsites, reducing the potential benefit of pembrolizumab therapy.

Given a potential detriment with pembrolizumab for patients with PD-L1 positive, hypopharyngeal tumors, the EFS and R0 resection results for this subgroup of patients in KEYNOTE-689 are included in Section 14 of the USPI for pembrolizumab. We acknowledge this potential detriment for perioperative pembrolizumab for patients with PD-L1 positive, hypopharyngeal tumors was found in an exploratory subgroup analysis that only included 51 patients and therefore this exploratory analysis should be interpreted with caution. Therefore, the FDA review team recommends approval of the KEYNOTE-689

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perioperative pembrolizumab regimen for the entire PD-L1 positive population, without a limitation of use for patients with hypopharyngeal cancer.

A major limitation of the design of KEYNOTE-689 is its inability to isolate the contribution of effects from the neoadjuvant and adjuvant phases. As designed, KEYNOTE-689 does not distinguish whether the effect on the primary endpoint of EFS is due to pembrolizumab given in the neoadjuvant phase, in the adjuvant phase, or in both treatment phases. There is the potential for increased toxicity with no additional improvement in efficacy with adjuvant pembrolizumab (with concurrent radiation and as a single agent), compared to receiving pembrolizumab in the neoadjuvant phase of therapy alone. This potential overtreatment in KEYNOTE-689 comes with increased treatment burden and additional toxicities for patients, some of whom may be cured following SoC surgery and adjuvant radiation or chemoradiation alone. Further mature OS data from remaining prespecified analyses in KEYNOTE-689 will be important to provide assurance of the current trend indicating that treatment with pembrolizumab is not resulting in more deaths due to toxicity than in the control arm.

Notably, the inability to isolate the contribution of treatment phase in perioperative regimens for non-small cell lung cancer (NSCLC), another solid tumor, was the subject of an Oncologic Drugs Advisory Committee (ODAC) meeting on July 25, 2024. Although the perioperative regimen with durvalumab, another anti-PD-(L)1 antibody, evaluated for NSCLC in the AEGEAN trial was unable to isolate the effect of each phase of therapy, the ODAC members generally agreed that an additional trial prior to approval was not necessary. Since KEYNOTE-689 was initiated in 2017 prior to this ODAC, FDA will similarly not require an additional trial prior to approval of perioperative pembrolizumab for resectable HNSCC, despite the uncertainty surrounding the need for the adjuvant phase of treatment. Based on currently available data, the FDA clinical review team does not consider that the lack of demonstration of clinical benefit of each phase of treatment significantly alters the overall benefit-risk evaluation of the regimen particularly given the observed safety profile of pembrolizumab in the adjuvant setting.

Overall, KEYNOTE-689 demonstrated substantial evidence of effectiveness of a perioperative regimen of pembrolizumab as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without cisplatin after surgery, and then as a single agent for patients with LA HNSCC. The EFS HR of 0.70 (95% CI: 0.55, 0.89; $p=0.00140$) corresponding to a 30.1-month improvement in median EFS with perioperative pembrolizumab over SoC, is statistically significant and clinically meaningful. These results are supported by a trend towards improved OS for the pembrolizumab arm.

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8.2. Review of Safety

The Applicant’s Position: Pembrolizumab, as neoadjuvant therapy and continued as adjuvant therapy in combination with RT, with or without cisplatin followed by pembrolizumab monotherapy, has a manageable safety profile that is generally consistent with the established safety profile of pembrolizumab monotherapy, and the individual safety profiles of RT and cisplatin.

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

8.2.1. Safety Review Approach

Data:

Table 26: Applicant – Datasets for Presentation of Safety Results

Dataset	Population	Nomenclature in Tables	Nomenclature in Text
KEYNOTE-689 pembrolizumab	(N=361): Safety data from participants with resectable Stage III-IVA LA HNSCC who received pembrolizumab as neoadjuvant therapy and pembrolizumab in combination with SoC RT ± cisplatin as post-surgical adjuvant therapy followed by pembrolizumab monotherapy in KEYNOTE-689	KN689: Pembrolizumab	pembrolizumab group
KEYNOTE-689 SoC	(N=315): Safety data from participants with resectable Stage III-IVA LA HNSCC who received no neoadjuvant treatment prior to surgery and who received SoC RT ± cisplatin in the adjuvant phase in KEYNOTE-689	KN689: SoC	SoC group
Abbreviations: HNSCC=head and neck squamous cell carcinoma; LA=locally advanced; N=number; RT=radiation therapy; SoC=standard-of-care			

The Applicant’s Position: The safety data in this submission are based on IA1 of KEYNOTE-689 from the protocol-prespecified IA1 (data cutoff date: 25-JUL-2024). The specific efficacy and safety, and/or other variables to be assessed, their schedule, and measurement/collection methods, are displayed in the Schedule of Activities [Table 3] [Table 4] [Table 5] [Table 6]. AEs were reported according to NCI CTCAE Version 4.03 and coded using MedDRA (Version 27.0). The safety endpoints used in this study were standard, generally reliable, and relevant to the objectives set forth in the protocol. Safety analyses are presented for the participants who comprise the APaT populations [Table 24]. Safety comparisons for KEYNOTE-689 are based on the combined safety analysis group, ie, neoadjuvant/surgery phase plus the adjuvant phase.

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The overall approach to evaluate the safety data in this study was adequate.

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

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 27: Applicant – Summary of Drug Exposure Adjuvant Phase (Participants Who Received Adjuvant Treatment)

	Pembrolizumab (N=275)	SoC (N=275)
Study Days on Therapy (months)		
n	275	275
Mean (SD)	7.3 (3.7)	1.5 (0.2)
Median	9.7	1.5
Range	0.03 to 18.9	0.1 to 2.4
Treatment includes study drugs and in-study radiotherapy. Database Cutoff Date: 25JUL2024		

Source: [P689V01MK3475: adam-adsl; adexsum]

The Applicant’s Position:

KEYNOTE-689 is an ongoing study. Safety analyses were based on the APaT population, which included all 676 randomized participants (pembrolizumab group 361; SoC group 315) who received at least 1 dose of study intervention or at least 1 surgery according to the study intervention they received. There were 118 (32.5%) categorized as high-risk and 196 (54.0%) categorized as low-risk in the pembrolizumab group versus 156 (44.4%) high-risk and 148 (42.2%) low-risk in the SoC group. Post-surgical treatment decisions involving cisplatin were guided based on local pathology results. The median duration of exposure to study treatments was longer in the pembrolizumab group (9.1 months) compared with the SoC group (2.9 months) [Table 25].

Overall exposure was adequate to support the characterization of the safety profile in the proposed patient population.

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

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Relevant characteristics of the safety population:

The Applicant's Position: The demographic and other baseline characteristics in KEYNOTE-689 were generally similar in both treatment groups in the APaT population and were representative of participants with resectable LA HNSCC.

The FDA's Assessment:

FDA generally agrees with the Applicant's position, with one exception. There was a total of 27 patients (3.8%) enrolled across the two arms whose tumors were PD-L1 negative (CPS <1), markedly underrepresenting the prevalence of PD-L1 negative tumors in HNSCC patient populations as reported in CheckMate 141, KEYNOTE-048, and in HNSCC tumor tissue array analyses (15% to 43%) (Burtneiss, et al. JCO 2022; Ferris, et al. NEJM 2016; Deuss, et al. Cancers 2024).

Adequacy of the safety database:

The Applicant's Position:

The clinical safety data supporting this submission are derived from KEYNOTE-689. The study design, number of participants treated in each study arm, and duration of exposure to study treatment were adequate to support the characterization of the safety profile in the proposed patient population [Table 25].

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

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

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

The FDA's Assessment:

FDA agrees with the Applicant's assessment. No quality issues were identified during FDA review.

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Categorization of Adverse Event

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

AEs and SAEs were collected through the protocol-specified time period (all AEs occurring up until 30 days following end of study treatment and SAEs occurring up until 90 days following end of treatment or 30 days if the participant initiates new anticancer therapy, whichever is earlier, and treatment-related late toxicity for up to 5 years). AEs and SAEs, whether assessed as related to the Sponsor or comparator's product, were recorded.

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

The overall approach to categorize AEs in this study was adequate and consistent with prior submissions for pembrolizumab.

The FDA's Assessment:

FDA acknowledges the Applicant's approach of reporting AEs in KEYNOTE-689 based on preferred terms according to MedDRA version 27.0. However, FDA's clinical review team used grouped terms (GTs) comprised of related preferred terms (PTs) in their analysis of the safety outcomes of this study. FDA agrees with the Applicant's grading of AEs according to NCI CTCAE version 5.0. FDA also agrees with the Applicant's description of adverse event categorization.

Routine Clinical Tests

The Applicant's Position: The schedule of activities from KEYNOTE-689 is provided in the study protocol, including key laboratory assessments such as the frequency of laboratory testing, vital signs, physical examination, and AE monitoring.

The clinical tests were appropriate for the safety monitoring of the population under study and for the known safety profiles of pembrolizumab, RT and cisplatin.

The FDA's Assessment:

FDA agrees with the Applicant's description of the schedule and evaluation of standard

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laboratory tests as part of the safety assessment.

8.2.4. Safety Results

Deaths

Data:

Table 28: Applicant – Participants With Adverse Events Resulting in Death (Sorted by Decreasing Incidence) (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	25	(6.9)	24	(7.6)
with no adverse events	336	(93.1)	291	(92.4)
Death	3	(0.8)	2	(0.6)
Pneumonia	2	(0.6)	3	(1.0)
Post procedural complication	2	(0.6)	0	(0.0)
Respiratory failure	2	(0.6)	1	(0.3)
Atypical pneumonia	1	(0.3)	0	(0.0)
COVID-19	1	(0.3)	1	(0.3)
COVID-19 pneumonia	1	(0.3)	1	(0.3)
Cardiovascular disorder	1	(0.3)	0	(0.0)
Clostridial infection	1	(0.3)	0	(0.0)
Disseminated intravascular coagulation	1	(0.3)	0	(0.0)
Dysphagia	1	(0.3)	0	(0.0)
Gastrointestinal haemorrhage	1	(0.3)	0	(0.0)
Hypercalcaemia	1	(0.3)	0	(0.0)
Myocardial infarction	1	(0.3)	1	(0.3)
Pneumonia aspiration	1	(0.3)	0	(0.0)
Pneumonitis	1	(0.3)	0	(0.0)
Pulmonary haemorrhage	1	(0.3)	0	(0.0)
Renal failure	1	(0.3)	0	(0.0)
Sepsis	1	(0.3)	0	(0.0)
Septic shock	1	(0.3)	3	(1.0)
Thrombosis mesenteric vessel	1	(0.3)	0	(0.0)
Acute kidney injury	0	(0.0)	2	(0.6)
Acute respiratory distress syndrome	0	(0.0)	1	(0.3)
Acute respiratory failure	0	(0.0)	1	(0.3)
Bradyarrhythmia	0	(0.0)	1	(0.3)
Brain oedema	0	(0.0)	1	(0.3)
Cardiac arrest	0	(0.0)	1	(0.3)
Inferior vena caval occlusion	0	(0.0)	1	(0.3)
Multiple organ dysfunction syndrome	0	(0.0)	2	(0.6)
Pancreatic neoplasm	0	(0.0)	1	(0.3)
Postoperative wound infection	0	(0.0)	1	(0.3)

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Pulmonary sepsis	0	(0.0)	1	(0.3)
Respiratory arrest	0	(0.0)	1	(0.3)
Sudden death	0	(0.0)	2	(0.6)
Urosepsis	0	(0.0)	1	(0.3)
Every participant is counted a single time for each applicable row and column. Serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded. Database Cutoff Date: 25JUL2024.				

Source: [P689V01MK3475: adam-adsl; adae]

The Applicant’s Position: The incidence of AEs resulting in death was generally similar in both treatment groups (6.9% in the pembrolizumab group compared to 7.6% in the SoC group) [Table 26]. Most fatal events in both treatment groups were not considered drug-related by investigator assessment. The most common AEs resulting in death was recorded as “death” 3 (0.8%) in the pembrolizumab group and pneumonia and septic shock, 3 (1.0%) participants each in the SoC group. The 3 pembrolizumab participants for whom the term “death” was reported included a participant with cardiovascular failure as a result of electrolyte disorder, a participant with excessive alcohol consumption, and a participant with no cause cited for the death. In all 3 cases, the investigator considered the death unrelated to pembrolizumab administration.

One fatal drug-related AE of pneumonitis was reported, which is a known risk of pembrolizumab. The remaining AEs leading to death were generally consistent with the known risks of cisplatin/RT, underlying disease, or intercurrent illnesses associated with this patient population. No new safety concerns were identified upon review of these fatal events.

The FDA’s Assessment:

FDA reviewed the narratives for patients who experienced fatal AEs in KEYNOTE-689. FDA generally agrees with the summary statistics described by the Applicant. However, as there may be heterogeneity between investigators and difficulty in accurately assigning attribution of adverse events to study therapy, FDA generally does not report drug-related adverse events and did not complete an independent review of drug-related fatal adverse events. FDA’s review of AEs leading to death did not identify any new safety signals. Fatal adverse reactions occurred in 1.1% of patients who received neoadjuvant pembrolizumab including respiratory failure, clostridium infection, septic shock, and myocardial infarction (one patient each). For patients who started the adjuvant phase of study therapy, fatal adverse reactions occurred in 5% of patients on the pembrolizumab arm including death not otherwise specified (1.2%), acute renal failure (0.4%), hypercalcemia (0.4%), pulmonary hemorrhage (0.4%), dysphagia/malnutrition (0.4%), mesenteric thrombosis (0.4%), sepsis (0.4%), pneumonia (0.4%), COVID-19 (0.4%), respiratory failure (0.4%), cardiovascular disorder (0.4%) and gastrointestinal hemorrhage (0.4%).

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Serious Adverse Events

Data:

Table 29: Applicant – Participants With Serious Adverse Events (Sorted by Decreasing Incidence) (Incidence $\geq 5\%$ in One or More Treatment Groups) (APaT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	179	(49.6)	116	(36.8)
with no adverse events	182	(50.4)	199	(63.2)
Pneumonia	13	(3.6)	18	(5.7)
Every participant is counted a single time for each applicable row and column. A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. Serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded. Database Cutoff Date: 25JUL2024.				

Source: [P689V01MK3475: adam-adsl; adac]

The Applicant's Position: The incidence of SAEs was 49.6% in the pembrolizumab group and 36.8% in the SoC group [Table 27]. After adjusting for exposure, event rates were generally similar between treatment groups. The most frequently reported SAE (incidence $\geq 3\%$) was pneumonia in both groups (pembrolizumab 3.6%; SoC group 5.7%).

The incidence of drug-related SAE was 19.1% in the pembrolizumab group vs 10.5% in the SoC group. The most frequently reported (incidence $\geq 1\%$) drug-related SAEs were colitis (1.7%), stomatitis (1.7%), immune-mediated hepatitis (1.4%), pneumonitis (1.4%) and adrenal insufficiency (1.1%) in the pembrolizumab group and acute kidney injury (1.9%), febrile neutropenia (1.3%), and nausea (1.0%) in the SoC group.

The most frequently reported SAEs are known risks of pembrolizumab monotherapy, RT, or cisplatin.

The FDA's Assessment:

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FDA generally agrees with the Applicant's position. SAEs were assessed separately during the neoadjuvant and adjuvant phases of the trial. Of patients who received pembrolizumab in the neoadjuvant phase of KEYNOTE-689, SAEs that occurred in more than one patient were pneumonia (1.4%), tumor hemorrhage (0.8%), dysphagia (0.6%), immune mediated hepatitis (0.6%), cellulitis (0.6%), and dyspnea (0.6%). Of the 255 patients who received pembrolizumab in the adjuvant phase, the most frequent serious adverse reactions reported in $\geq 1\%$ of patients were pneumonia (2.7%), pyrexia (2.4%), stomatitis (2.4%), acute kidney injury (2.0%), pneumonitis (1.6%), COVID-19 (1.2%), death not otherwise specified (1.2%), diarrhea (1.2%), dysphagia (1.2%), gastrostomy tube site complication (1.2%), and immune-mediated hepatitis (1.2%).

SAEs were more frequent in female than male patients treated in the pembrolizumab arm (58% vs 47%) but similar in the SoC arm (33% vs 38%). Specific SAEs with higher incidence in female patients in the pembrolizumab arm compared to the SoC arm included: wound infection, skin infection, wound dehiscence, skin necrosis, flap necrosis, dysphagia, and dehydration in 1 (1.3%) or 2 (2.6%) patients each.

Table 30: FDA – Safety Summary by Patient Sex

	Pembrolizumab N=361				SoC N=305			
	M N=284		F N=77		M N=248		F N=67	
	n	(%)	n	(%)	n	(%)	n	(%)
All TEAEs	272	(96)	76	(99)	240	(97)	65	(97)
Grade 3-4 TEAEs	201	(71)	69	(90)	181	(73)	45	(67)
Grade 5 AEs	19	(7)	6	(8)	19	(8)	5	(7)
SAEs	134	(47)	45	(58)	94	(38)	22	(33)

Source: Adapted from 1.11.3 CLINICAL INFORMATION AMENDMENT, applicant's response to information request of 03/12/2025.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 31: Applicant – Participants With Adverse Events Resulting in Any Treatment Discontinuation (Sorted by Decreasing Incidence) (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	

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with one or more adverse events	88	(24.4)	45	(14.3)
with no adverse events	273	(75.6)	270	(85.7)
Neutrophil count decreased	7	(1.9)	10	(3.2)
Pneumonitis	7	(1.9)	0	(0.0)
Colitis	6	(1.7)	0	(0.0)
Acute kidney injury	4	(1.1)	7	(2.2)
Immune-mediated hepatitis	4	(1.1)	0	(0.0)
Stomatitis	4	(1.1)	4	(1.3)
White blood cell count decreased	4	(1.1)	1	(0.3)
Alanine aminotransferase increased	3	(0.8)	1	(0.3)
Arthralgia	3	(0.8)	0	(0.0)
Death	3	(0.8)	0	(0.0)
Fatigue	3	(0.8)	0	(0.0)
Pneumonia	3	(0.8)	0	(0.0)
Blood creatinine increased	2	(0.6)	4	(1.3)
COVID-19 pneumonia	2	(0.6)	1	(0.3)
Deafness	2	(0.6)	1	(0.3)
Diarrhoea	2	(0.6)	0	(0.0)
Dysphagia	2	(0.6)	0	(0.0)
Interstitial lung disease	2	(0.6)	0	(0.0)
Pancreatitis	2	(0.6)	0	(0.0)
Post procedural complication	2	(0.6)	0	(0.0)
Adenocarcinoma of colon	1	(0.3)	0	(0.0)
Anaemia	1	(0.3)	1	(0.3)
Atypical pneumonia	1	(0.3)	0	(0.0)
Clostridial infection	1	(0.3)	0	(0.0)
Dermatitis	1	(0.3)	0	(0.0)
Dermatitis exfoliative	1	(0.3)	0	(0.0)
Enteritis	1	(0.3)	0	(0.0)
Gastrointestinal haemorrhage	1	(0.3)	0	(0.0)
Hepatitis acute	1	(0.3)	0	(0.0)
Hypercalcaemia	1	(0.3)	0	(0.0)
Hypoacusis	1	(0.3)	1	(0.3)
Immune-mediated nephritis	1	(0.3)	0	(0.0)
Metabolic disorder	1	(0.3)	0	(0.0)
Myocardial infarction	1	(0.3)	1	(0.3)
Nausea	1	(0.3)	1	(0.3)
Neutropenia	1	(0.3)	0	(0.0)
Obstructive airways disorder	1	(0.3)	0	(0.0)
Orocutaneous fistula	1	(0.3)	0	(0.0)
Pancreatitis acute	1	(0.3)	0	(0.0)
Platelet count decreased	1	(0.3)	0	(0.0)
Pneumonia aspiration	1	(0.3)	0	(0.0)
Primary adrenal insufficiency	1	(0.3)	0	(0.0)
Psoriasis	1	(0.3)	0	(0.0)
Pulmonary haemorrhage	1	(0.3)	0	(0.0)
Pulmonary sepsis	1	(0.3)	0	(0.0)

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Radiation skin injury	1	(0.3)	0	(0.0)
Rash	1	(0.3)	0	(0.0)
Renal failure	1	(0.3)	0	(0.0)
Sepsis	1	(0.3)	0	(0.0)
Septic shock	1	(0.3)	0	(0.0)
Skin infection	1	(0.3)	0	(0.0)
Staphylococcal infection	1	(0.3)	0	(0.0)
Thrombosis mesenteric vessel	1	(0.3)	0	(0.0)
Tinnitus	1	(0.3)	1	(0.3)
Tubulointerstitial nephritis	1	(0.3)	0	(0.0)
Type 2 diabetes mellitus	1	(0.3)	0	(0.0)
Vomiting	1	(0.3)	2	(0.6)
Weight decreased	1	(0.3)	1	(0.3)
Wound dehiscence	1	(0.3)	0	(0.0)
Asthenia	0	(0.0)	2	(0.6)
Chronic kidney disease	0	(0.0)	1	(0.3)
Feeding intolerance	0	(0.0)	1	(0.3)
General physical health deterioration	0	(0.0)	1	(0.3)
Oral candidiasis	0	(0.0)	1	(0.3)
Pharyngeal inflammation	0	(0.0)	1	(0.3)
Pulmonary embolism	0	(0.0)	1	(0.3)
Renal injury	0	(0.0)	1	(0.3)
	Pembrolizumab		SoC	
	n	(%)	n	(%)
Upper respiratory tract infection	0	(0.0)	1	(0.3)
Every participant is counted a single time for each applicable row and column. Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded. Database Cutoff Date: 25JUL2024.				

Source: [P689V01MK3475: adam-adsl; adae]

The Applicant's Position: The types of AEs and incidence of participants with AEs that led to discontinuation of any study drug in the pembrolizumab group were generally consistent with the established profile of pembrolizumab and the individual safety profiles of RT and cisplatin. The incidence of AEs leading to any study treatment discontinuation was 24.4% in the pembrolizumab group and 14.3% in the SoC group [Table 28]. After adjustment for exposure, the rates were similar.

Discontinuation of study drug due to AEs in the pembrolizumab group did not suggest any new safety concerns.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. In the neoadjuvant phase, permanent discontinuation of pembrolizumab due to an adverse event occurred in 2.8% of patients (n=10)

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who received pembrolizumab as neoadjuvant treatment. The adverse event which resulted in permanent discontinuation of neoadjuvant pembrolizumab in more than one patient was arthralgia (n=2). In the adjuvant phase, permanent discontinuation of adjuvant pembrolizumab due to an adverse event occurred in 17% of patients. The most frequent ($\geq 1\%$) adverse events that led to permanent discontinuation of adjuvant pembrolizumab were pneumonitis, colitis, immune-mediated hepatitis and death not otherwise specified.

Additionally, of the 361 patients who received pembrolizumab as neoadjuvant treatment, 11% (n=38) did not receive surgery. Surgical cancellation on the pembrolizumab arm was due to disease progression in 4% (n=15), patient decision in 3% (n=10), adverse events in 1.4% (n=5), physician's decision in 1.1% (n=4), unresectable tumor in 0.6% (n=2), loss of follow-up in 0.3% (n=1), and use of non-study anti-cancer therapy in 0.3% (n=1).

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data:

Table 32: Applicant – Participants With Adverse Events Resulting in Any Treatment Interruption (Sorted by Decreasing Incidence) (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	113	(31.3)	53	(16.8)
with no adverse events	248	(68.7)	262	(83.2)
Neutrophil count decreased	11	(3.0)	24	(7.6)
Stomatitis	10	(2.8)	5	(1.6)
White blood cell count decreased	7	(1.9)	12	(3.8)
Aspartate aminotransferase increased	5	(1.4)	0	(0.0)
COVID-19	5	(1.4)	0	(0.0)
Radiation skin injury	5	(1.4)	3	(1.0)
Vomiting	5	(1.4)	0	(0.0)
Cellulitis	4	(1.1)	0	(0.0)
Nausea	4	(1.1)	1	(0.3)
Rash	4	(1.1)	0	(0.0)
Blood creatinine increased	0	(0.0)	3	(1.0)
Every participant is counted a single time for each applicable row and column.				
Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included.				
MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded.				
Database Cutoff Date: 25JUL2024.				

Source: [P689V01MK3475: adam-adsl; adae]

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

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The Applicant's Position: The types of AEs and incidence of participants with AEs and drug-related AEs leading to interruption of any study drug in the pembrolizumab group were generally consistent with the established safety profile of pembrolizumab and the individual safety profiles of RT and cisplatin. Overall, the incidence of AEs resulting in any study treatment interruption in the pembrolizumab group and SoC group was 31.3% and 16.8%, respectively [Table 29]. The most frequently reported AEs (incidence $\geq 3\%$) resulting in interruption of any study drug were: neutrophil count decreased (3.0%) in the pembrolizumab group and neutrophil count decreased (7.6%) and white blood cell count decreased (3.8%) in the SoC group.

There were no specific trends in interruption of study drug due to AEs in the pembrolizumab group that suggest any new safety concerns.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. However, as described above, given the difficulty in accurately assigning attribution of adverse events to study therapy, FDA did not complete an independent review of drug-related AEs.

Significant Adverse Events

Data:

Table 33: Applicant – Adverse Event Summary AEOSI Overall (APaT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	158	(43.8)	34	(10.8)
with no adverse event	203	(56.2)	281	(89.2)
with drug-related ^a adverse events	128	(35.5)	13	(4.1)
with toxicity grade 3-5 adverse events	36	(10.0)	2	(0.6)
with toxicity grade 3-5 drug-related adverse events	34	(9.4)	0	(0.0)
with serious adverse events	29	(8.0)	1	(0.3)
with serious drug-related adverse events	27	(7.5)	0	(0.0)
who died	1	(0.3)	0	(0.0)
who died due to a drug-related adverse event	1	(0.3)	0	(0.0)
discontinued drug due to an adverse event	28	(7.8)	0	(0.0)
discontinued drug due to a drug-related adverse event	28	(7.8)	0	(0.0)
discontinued drug due to a serious adverse event	17	(4.7)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	17	(4.7)	0	(0.0)
^a Determined by the investigator to be related to the drug. Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0. Grades are based on NCI CTCAE version 4.03.				

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Source: [P689V01MK3475: adam-adsl; adae]

Table 34: Applicant – Participants With Adverse Events of Special Interest (AEOSI) (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	158	(43.8)	34	(10.8)
with no adverse events	203	(56.2)	281	(89.2)
Adrenal Insufficiency	7	(1.9)	0	(0.0)
Colitis	9	(2.5)	1	(0.3)
Gastritis	5	(1.4)	1	(0.3)
Hepatitis	8	(2.2)	1	(0.3)
Hyperthyroidism	32	(8.9)	10	(3.2)
Hypoparathyroidism	1	(0.3)	1	(0.3)
Hypophysitis	2	(0.6)	1	(0.3)
Hypothyroidism	89	(24.7)	17	(5.4)
Infusion Reactions	4	(1.1)	2	(0.6)
Myocarditis	1	(0.3)	0	(0.0)
Myositis	1	(0.3)	0	(0.0)
Nephritis	3	(0.8)	0	(0.0)
Pancreatitis	5	(1.4)	0	(0.0)
Pneumonitis	20	(5.5)	0	(0.0)
Severe Skin Reactions	10	(2.8)	2	(0.6)
Thyroiditis	2	(0.6)	1	(0.3)
Uveitis	1	(0.3)	0	(0.0)
Every participant is counted a single time for each applicable row and column.				
Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included.				
MedDRA Version: 27.0				
Database Cutoff Date: 25JUL2024.				

Source: [P689V01MK3475: adam-adsl; adae]

The Applicant's Position: The incidence of AEOSI was 43.8% and 10.8% in the pembrolizumab group and SoC group, respectively, with drug-related AEOSI also having a higher incidence in the pembrolizumab group (35.5% vs 4.1%) [Table 33]. The higher incidence of drug-related AEOSIs in the pembrolizumab group was driven by hypothyroidism [Table 31]. One participant died due to a drug-related AEOSI (pneumonitis) in the pembrolizumab group.

The overall incidence of participants who discontinued any drug due to an AEOSI was 7.8% in the pembrolizumab group and 0.0% in the SoC group. Most AEOSI were manageable with

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supportive care, dose interruption, systemic corticosteroids, and/or hormone replacement therapy.

In the pembrolizumab group, no new indication-specific, immune-mediated AEs causally associated with pembrolizumab were identified with the addition of RT ± cisplatin.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. However, given the difficulty in accurately assigning attribution of adverse events to study therapy, FDA did not complete an independent review of drug-related AEs.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 1735: Applicant – Adverse Event Summary (APaT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	348	(96.4)	305	(96.8)
with no adverse event	13	(3.6)	10	(3.2)
with drug-related ^a adverse events	294	(81.4)	258	(81.9)
with toxicity grade 3-5 adverse events	275	(76.2)	233	(74.0)
with toxicity grade 3-5 drug-related adverse events	161	(44.6)	135	(42.9)
with serious adverse events	179	(49.6)	116	(36.8)
with serious drug-related adverse events	69	(19.1)	33	(10.5)
who died	25	(6.9)	24	(7.6)
who died due to a drug-related adverse event	4	(1.1)	1	(0.3)
discontinued drug due to an adverse event	88	(24.4)	45	(14.3)
discontinued drug due to a drug-related adverse event	64	(17.7)	39	(12.4)
discontinued drug due to a serious adverse event	47	(13.0)	11	(3.5)
discontinued drug due to a serious drug-related adverse event	27	(7.5)	8	(2.5)
^a Determined by the investigator to be related to the drug. Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded. Grades are based on NCI CTCAE version 4.03. Database Cutoff Date: 25JUL2024.				

Source: [P689V01MK3475: adam-adsl; adae]

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Table 36: Applicant – Participants With Adverse Events (Sorted by Decreasing Incidence)
 (Incidence $\geq$ 10% in One or More Treatment Groups) (APaT Population)

	Pembrolizumab		SoC	
	n	(%)	n	(%)
Participants in population	361		315	
with one or more adverse events	348	(96.4)	305	(96.8)
with no adverse events	13	(3.6)	10	(3.2)
Stomatitis	150	(41.6)	172	(54.6)
Radiation skin injury	144	(39.9)	151	(47.9)
Weight decreased	129	(35.7)	86	(27.3)
Anaemia	123	(34.1)	105	(33.3)
Dysphagia	105	(29.1)	100	(31.7)
Constipation	97	(26.9)	70	(22.2)
Hypothyroidism	89	(24.7)	17	(5.4)
Nausea	88	(24.4)	87	(27.6)
Fatigue	85	(23.5)	52	(16.5)
Dry mouth	81	(22.4)	81	(25.7)
Diarrhoea	78	(21.6)	33	(10.5)
Lymphocyte count decreased	65	(18.0)	48	(15.2)
Insomnia	64	(17.7)	25	(7.9)
Vomiting	59	(16.3)	32	(10.2)
Dysgeusia	55	(15.2)	60	(19.0)
Alanine aminotransferase increased	53	(14.7)	29	(9.2)
Hypokalaemia	52	(14.4)	40	(12.7)
Hyponatraemia	49	(13.6)	25	(7.9)
Oral pain	48	(13.3)	28	(8.9)
Decreased appetite	47	(13.0)	42	(13.3)
Pyrexia	45	(12.5)	17	(5.4)
Neutrophil count decreased	44	(12.2)	61	(19.4)
Aspartate aminotransferase increased	43	(11.9)	23	(7.3)
White blood cell count decreased	43	(11.9)	55	(17.5)
Rash	41	(11.4)	5	(1.6)
Asthenia	39	(10.8)	39	(12.4)
Pruritus	38	(10.5)	6	(1.9)
Oral candidiasis	37	(10.2)	19	(6.0)
Procedural pain	30	(8.3)	32	(10.2)
Every participant is counted a single time for each applicable row and column. A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. Non-serious AEs up to 30 days and serious AEs up to 90 days of last administration of the entire study treatment, including protocol-specified surgery, are included. MedDRA Version: 27.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the study treatment are excluded. Database Cutoff Date: 25JUL2024.				

Source: [P689V01MK3475: adam-adsl; adae]

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The Applicant's Position:

The incidences and types of AEs, including drug-related AEs, AEs leading to death, and Grade 3 to 5 AEs in the pembrolizumab group were similar to the SoC group (<10% difference in incidence) [Table 32]. The incidences of SAEs and AEs leading to treatment discontinuation were higher in the pembrolizumab group compared with the SoC group ($\geq 10\%$ difference in incidence). After adjusting for exposure (median duration on therapy [pembrolizumab group: 9.1 months; SoC group: 2.9 months], most event rates were lower in the pembrolizumab group compared with the SoC.

The most frequently reported (incidence $\geq 25\%$ in either treatment group) AEs are known risks of RT or cisplatin [Table 33]. AEs (incidence $\geq 10\%$) with a higher risk difference for the pembrolizumab group (where the lower bound of the 95% CI for the treatment difference was $>0\%$) were hypothyroidism (24.7% vs 5.4%), diarrhea (21.6% vs 10.5%), rash (11.4% vs 1.6%), insomnia (17.7% vs 7.9%), pruritus (10.5% vs 1.9%), weight decreased (35.7% vs 27.3%), pyrexia (12.5% vs 5.4%), fatigue (23.5% vs 16.5%), vomiting (16.3% vs 10.2%), hyponatremia (13.6% vs 7.9%), ALT increased (14.7% vs 9.2%), AST increased (11.9% vs 7.3%), and oral candidiasis (10.2% vs 6.0%). These AEs are known risks of either pembrolizumab monotherapy, RT, or cisplatin.

After adjusting for exposure, the AE event rates were generally similar between the pembrolizumab and SoC groups.

In the high-risk category, the incidence of SAEs was higher in the pembrolizumab group compared with the SoC group. In the low-risk category, SAEs, drug-related SAEs, drug-related Grade 3 to 5, discontinuation due to an AE, discontinuation due to a drug-related AE, and discontinuation due to an SAE were higher in the pembrolizumab group compared with the SoC group. The incidences of AEs by toxicity grade were generally similar in the high- and low-risk category except for Grade 2 hypothyroidism, which was higher in the pembrolizumab group compared with the SoC group in the high-risk and low-risk participants.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. However, given the difficulty in accurately assigning attribution of adverse events to study therapy, FDA did not complete an independent review of drug-related AEs.

Laboratory Findings

The Applicant's Position: No new safety concerns based on laboratory abnormalities were reported in KEYNOTE-689. The most frequently reported (incidence >0) laboratory abnormalities in the pembrolizumab group were generally similar compared with the SoC group; most laboratory abnormalities were Grade 1 or Grade 2 in both groups.

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The mean changes in laboratory values from baseline over time in the 2 groups (pembrolizumab and SoC) were consistent with the known safety profiles of pembrolizumab and cisplatin and RT.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that laboratory findings were generally consistent with the known toxicities of the components of the regimen. The most frequent laboratory abnormalities from KEYNOTE-689 are presented below in Table 37.

Table 37: FDA - Select Laboratory Abnormalities ($\geq 20\%$) that Worsened from Baseline in Patients with HNSCC Who Received Pembrolizumab in KEYNOTE689

Laboratory Test*	Pembrolizumab Neoadjuvant then adjuvant beginning with radiation with or without cisplatin		Radiation with or without cisplatin	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Lymphopenia	76	50	86	55
Anemia	75	12	74	12
Neutropenia	32	13	35	19
Thrombocytopenia	22	1.7	29	1.9
Chemistry				
Hyperglycemia	57	6	47	2.7
Hyponatremia	47	16	36	11
Increased ALT	42	6	37	2.0
Hypoalbuminemia	40	1.4	38	1.0
Increased AST	38	4.8	23	2.0
Hypomagnesemia	34	1.2	22	1.3
Hypokalemia	29	7	20	7
Hyperkalemia	29	3.4	24	2.3
Increased alkaline phosphatase	27	2.5	19	0.0
Hypocalcemia	27	2.6	26	3.3
Hypophosphatemia	23	6	15	7
Increased creatinine	22	2.0	27	2.9
Hypercalcemia	21	2.0	14	1.3

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Vital Signs

The Applicant's Position: In KEYNOTE-689, clinically meaningful abnormalities in vital signs were reported as AEs [Table 3] [Table 4] [Table 5] [Table 6]; There were no clinically meaningful findings in vital sign measurements over time between the treatment groups.

The FDA's Assessment:

FDA agrees with the Applicant's position. There was no clear effect on vital signs in the safety population during the study period.

Electrocardiograms (ECGs)

The Applicant's Position: No new information is provided in the current submission.

The FDA's Assessment:

FDA agrees with the Applicant's position. There was no clear effect on EKGs in the safety population during the study period

QT

The Applicant's Position: No new information is provided in the current submission.

The FDA's Assessment:

FDA agrees with the Applicant's position. Pembrolizumab is a large molecule and is not expected to inhibit human ether-a-go-go related gene channel function or prolong the QTcF interval.

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: There are no new safety issues specific to this submission.

The FDA's Assessment:

Not applicable.

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

The Applicant's Position: Results from the patient-reported outcomes analyses are in Section 8.1.2. (Study Results).

The FDA's Assessment:

Refer to Section 8.1.2 of the Assessment Aid for more information on clinical outcome assessments in KEYNOTE-689.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position: The safety findings in KEYNOTE-689 based on age, race, geographic region, and ECOG performance status were generally consistent with the established safety profile of pembrolizumab monotherapy and the known safety profile of the individual RT and cisplatin components.

The FDA's Assessment:

FDA generally agrees with the Applicant's position; however, we note a higher frequency of Grade 3 to 4 TEAEs in women compared to men (90% vs 71%) (Table 30). Although these data may represent a chance finding and should be interpreted with caution, these results are consistent with prior reports of higher rates of TEAEs in female versus male patients with HNSCC receiving radiation therapy (Meyer, et al. 2012). Representative Grade 3 to 4 TEAEs that were more common in women than men in KEYNOTE-689 included: anemia (20% vs 9%), skin infection (5.2% vs 0.7%), and general physical health deterioration (3.9% vs 0.0%).

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 this submission.

The FDA's Assessment:

Not applicable.

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Human Reproduction and Pregnancy

The Applicant's Position: No new information is provided in this submission.

The FDA's Assessment:
Not applicable.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position: No new information is provided in this submission.

The FDA's Assessment:
Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position: There were no reports of overdose in KEYNOTE-689. Potential for drug abuse or dependence is not expected for an anti-PD-1 monoclonal antibody, and no reports of drug abuse with pembrolizumab have occurred. No withdrawal or rebound effects are expected with an anti-PD-1 monoclonal antibody, and none have been observed in pembrolizumab clinical studies to date.

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

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position: The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2023 through 03-SEP-2024, specifically Appendix 20.3 (Numbers of Adverse Drug Reactions by Preferred Term from Postauthorization Sources). There are no records of any pembrolizumab registration being revoked or withdrawn for safety reasons in any country.

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

Expectations on Safety in the Postmarket Setting

The Applicant's Position: The Company Safety database contains all data from postmarket sources, including health care providers, consumers, and scientific literature as well as competent

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authorities worldwide. The Sponsor closely monitors postmarket safety data associated with pembrolizumab on a continuing basis.

There are no specific safety concerns associated with subpopulations not adequately represented in the safety database. No difference in pembrolizumab administration in the postmarket setting is expected relative to KEYNOTE-689. There are no specific safety concerns not already included in pembrolizumab labeling expected from off-label use.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position: Pembrolizumab, as neoadjuvant therapy and continued as adjuvant therapy in combination with RT, with or without cisplatin followed by pembrolizumab monotherapy, has a manageable safety profile that is generally consistent with the established safety profile of pembrolizumab monotherapy, and the individual safety profiles of RT and cisplatin. No new safety concerns for pembrolizumab were identified. AEOSI in the pembrolizumab group were generally consistent with the established safety profile of pembrolizumab monotherapy in type and severity, and no new indication-specific, immune-mediated AEs causally associated with pembrolizumab were identified when pembrolizumab was added to RT ± cisplatin.

The FDA's Assessment:

In general, FDA agrees with the Applicant's position. The addition of single-agent pembrolizumab to SoC therapy compared to SoC therapy alone in the ITT population did not appear to compromise surgical resectability, post-surgical morbidity and mortality, or ability to receive adjuvant radiation therapy. However, in an exploratory subgroup analysis of patients with PD-L1 positive hypopharyngeal primary tumors (n=51), patients on the pembrolizumab arm had lower rates of complete (R0) surgical resection compared to patients on the SoC arm (74% vs 87%).

Overall safety outcomes in terms of TEAEs that led to death, SAEs, and Grade 3 to 4 TEAEs were associated with slightly higher rates in the pembrolizumab arm compared to the SoC arm. However, no new safety signals were identified and the safety profile was generally consistent with the known toxicities of the components of the study therapy. No updates were made to the current Warnings and Precautions section of the USPI for pembrolizumab (Section 5).

The incidence and severity of immune-related adverse events (irAEs) in the pembrolizumab arm were also consistent with the known toxicity profile of pembrolizumab as described in the approved product labeling for pembrolizumab. Due to the lack of data to demonstrate the contribution of the radiation and adjuvant post-radiation phases of treatment to the overall safety

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and efficacy of the treatment regimen, FDA specifically analyzed the risk profile, including irAEs, of the adjuvant phase of treatment with pembrolizumab. Although the observed safety profile was generally consistent with the known safety profile of pembrolizumab monotherapy, unresolved and long-term sequelae of irAEs were observed.

A significant review issue for this application was an inability to assess the contribution of all phases of this perioperative regimen, with the most concern focused on the uncertainty around the need for pembrolizumab in combination with radiation (with or without cisplatin) followed by an additional 12 cycles as a single agent in the adjuvant phase of therapy. The safety analysis was particularly important for this application given that the risk of overtreatment is proportional to the severity of the toxicities observed in the adjuvant phase. However, adverse event analyses and PRO data supported that single agent pembrolizumab was relatively well tolerated in the adjuvant phase. The review team assessed that the potential benefits of the perioperative pembrolizumab-based regimen outweighed the uncertainty around the contribution of phase of treatment. Importantly, studies of future perioperative regimens for HNSCC including pembrolizumab or other add-on drugs should be designed to improve the ability to demonstrate the contribution of pembrolizumab in the neoadjuvant and adjuvant phases of therapy.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The Applicant submitted data and results from EFS, OS, and mPR across 3 populations: PD-L1 CPS ≥ 10 , PD-L1 CPS ≥ 1 , and all patients, for the comparison of perioperative pembrolizumab in combination with SoC therapy versus SoC in patients with Stage III-IVA resectable LA HNSCC. According to the multiple testing hierarchy, EFS was to be tested in patients with tumor PD-L1 CPS ≥ 10 first, followed by PD-L1 CPS ≥ 1 , and finally in the ITT population. At IA1, EFS crossed the boundary for statistical significance in the PD-L1 CPS ≥ 10 [HR = 0.66, 95% CI (0.49, 0.88), $p=0.00217$], PD-L1 CPS ≥ 1 [HR = 0.70 95% CI (0.55, 0.89), $p=0.0124$], and ITT populations [HR = 0.73, 95% CI (0.58, 0.92), $p=0.00411$]. At the time of the IA1 cutoff, OS did not cross the boundary in the PD-L1 CPS ≥ 10 population, and statistical testing was stopped. mPR was statistically significant with an mPR rate difference of 13.7% (95% CI: 9.7, 18.7, $p < 0.00001$) in the PD-L1 CPS ≥ 10 population, 9.8% (95% CI: 7.0, 13.3, $p < 0.00001$) in the PD-L1 CPS ≥ 1 population, and 9.3% (95% CI: 6.7, 12.8, $p < 0.00001$) in the ITT population.

Although mPR was analyzed with appropriate Type-1 error control this endpoint has not been validated as an early endpoint likely to predict clinical benefit in resectable HNSCC. It is uncertain whether improvements in mPR translate into improvements in long-term outcomes of EFS and OS in the perioperative treatment setting. There is insufficient evidence to support the

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use of this endpoint in the regulatory setting. Patients in the standard of care arm did not receive treatment in the neoadjuvant period of the trial, and therefore did not have an opportunity to achieve mPR. Accordingly, there were no patients with mPR in the SoC arm. Additionally, mPR reflects the benefit of neoadjuvant treatment only, and does not predict the benefit of the overall perioperative treatment including the adjuvant phase of therapy.

As mentioned in Section 8.1.2 of the Assessment Aid, the small sample size of the PD-L1 negative subgroup (n=27) does not properly allow for a definitive assessment of benefit/risk. In this small subgroup, the EFS HR was 2.57 (95% CI: 0.50, 13.36) and the OS HR was of 1.73 (95% CI: 0.32, 9.54), suggesting a potential lack of benefit in patients treated with pembrolizumab. Because of the small number of patients and events in the two arms and the wide confidence interval, this result should be interpreted with caution in the context of the known mechanism of action of pembrolizumab and other available information as discussed in Section 8.1.2 Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) of the Assessment Aid.

Another important subgroup finding in a small subgroup was in patients with primary hypopharyngeal tumors. For patients with PD-L1 positive (CPS ≥ 1) hypopharyngeal tumors, the EFS hazard ratio was 2.28 (95% CI: 0.79, 6.56) and the OS hazard ratio was 2.03 (0.62, 6.60), suggesting a detriment in patients treated with pembrolizumab. In contrast, treatment with pembrolizumab was favored for patients with PD-L1 positive HNSCC with all other primary tumor sites: for laryngeal tumors, the EFS HR was 0.62 (95% CI: 0.36, 1.06) and the OS HR was 0.65 (95% CI: 0.38, 1.14); for oral cavity tumors, the EFS HR was 0.71 (95% CI: 0.53, 0.95) and the OS HR was 0.74 (95% CI: 0.54, 1.02); and for oropharyngeal tumors, the EFS HR was 0.32 (95% CI: 0.15, 0.68) and the OS HR was 0.38 (95% CI: 0.15, 0.93) (see [Table 16](#)). The hypopharyngeal subgroup is notably small, and the wide confidence intervals around the hazard ratio indicate that results should be interpreted with caution; nevertheless, the EFS result for this subgroup raises questions about the benefit of treatment with pembrolizumab for patients with primary hypopharyngeal tumors.

Overall, the primary analysis results of KEYNOTE-689 provide statistically persuasive evidence of improvement in EFS for patients with resectable, PD-L1 positive (CPS ≥ 1) LA HNSCC when treated with perioperative pembrolizumab. Results from secondary endpoints also support the effectiveness of this perioperative pembrolizumab-based treatment for these patients.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The primary trial supporting this sBLA is KEYNOTE-689, a multicenter, global, open-label, randomized trial in patients with resectable Stage III to IVA HNSCC, per the AJCC 8th edition staging system. A total of 714 patients were randomized 1:1 to receive either:

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- Neoadjuvant pembrolizumab 200 mg Q3W for 2 cycles prior to surgical resection; followed by 3 cycles of adjuvant pembrolizumab 200 mg Q3W in combination with RT) with or without 3 cycles of cisplatin 100 mg/m² Q3W; followed by pembrolizumab 200 mg Q3W as a single agent for up to 12 cycles.
- No neoadjuvant treatment prior to surgery; followed by adjuvant RT with or without 3 cycles of concurrent cisplatin 100 mg/m² Q3W (SoC Arm).

On both treatment arms, patients received cisplatin with adjuvant RT if high-risk pathological features (i.e., positive margins <1 mm or extranodal extension) were present at surgery.

The primary endpoint of KEYNOTE-689 was EFS as assessed by BICR analyzed hierarchically in patients with tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , then the ITT population. Major pathological response by BIPR and OS were key secondary endpoints.

The study met its primary EFS endpoint, meeting the pre-specified boundary for significance in the tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT populations, with EFS hazard ratios (HR) of 0.66 (95% CI: 0.49, 0.88; $p=0.00217$), 0.70 (95% CI: 0.55, 0.89; $p=0.00140$), and 0.73 (95% CI: 0.58, 0.92; $p=0.00411$), respectively.

However, in an exploratory subgroup analysis of patients with PD-L1 CPS <1 ($n=27$), the EFS HR was 2.57 (95% CI: 0.50, 13.36). An exploratory analysis of OS for patients in this PD-L1 negative subgroup also showed a trend toward potential detriment with pembrolizumab with an OS HR of 1.73 (95% CI: 0.32, 9.54). The small sample size makes it difficult to draw definitive conclusions regarding the benefit:risk profile of perioperative pembrolizumab for patients with PD-L1 negative, LA HNSCC. However, this trend in a potential detriment is consistent with prior findings with pembrolizumab monotherapy for patients with PD-L1 negative recurrent or metastatic HNSCC, both in the first-line treatment setting (i.e., in the KEYNOTE-048 trial) and the refractory treatment setting (i.e., in KEYNOTE-040). The mechanism of action of pembrolizumab also provides scientific rationale that the efficacy of pembrolizumab monotherapy may be limited in patients with PD-L1 negative tumors. Taken together, the FDA review team recommends that the current indication is limited to patients with PD-L1 positive (CPS ≥ 1) tumors.

For patients with PD-L1 positive (CPS ≥ 1) HNSCC, there was a statistically significant and clinically meaningful 30% reduction in risk of an EFS event in the pembrolizumab arm vs the SoC arm with a HR of 0.70 (95% CI: 0.55, 0.89; one-sided p -value of 0.00140, compared with the pre-specified one-sided boundary of 0.0124). In patients with PD-L1 positive (CPS ≥ 1) HNSCC, the median EFS was 59.7 months (CI 95%: 37.9, NR) in the pembrolizumab arm and 29.6 months (CI 95%: 19.5, 41.9) in the SoC arm, corresponding to a 30.1-month improvement in median EFS.

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The observed improvement in EFS appeared to be driven by fewer events of distant disease progression compared to events of local recurrence. Among patients in the PD-L1 CPS ≥ 1 population, disease progression accounted for 37% of EFS events on the pembrolizumab arm compared to 47% of EFS events on the SoC arm, with the largest difference in EFS events being related to distant progression (7% vs 15% for pembrolizumab and SoC, respectively). In the PD-L1 CPS ≥ 1 subgroup, the pembrolizumab arm also had a higher rate of R0 surgical resections at 91% compared to 85% R0 resections for the SoC arm.

At the first mPR interim analysis (IA1), the study also met the pre-specified boundary for statistical significance of this secondary endpoint in patients with tumor PD-L1 CPS ≥ 10 , then CPS ≥ 1 , and then in the ITT population with differences in mPR rates of 13.7% (95% CI: 9.7, 18.7; $p < 0.00001$), 9.8% (95% CI: 7.0, 13.3; $p < 0.00001$), and 9.3% (95% CI: 6.7, 12.8; $p < 0.00001$), favoring the pembrolizumab arm. As expected, no major pathological responses were observed in patients on the SoC control arm as they did not receive any neoadjuvant therapy. While this secondary endpoint was statistically significant, mPR is not a validated endpoint and the clinical meaningfulness of mPR has not been established for patients with resectable HNSCC.

At IA1, the key secondary endpoint of OS in patients with tumor PD-L1 CPS ≥ 10 had not reached statistical significance, although there was a numerical difference in OS favoring the pembrolizumab arm. The median OS was not reached (NR) (95% CI: NR, NR) in the pembrolizumab arm and was 61.8 months (95% CI: 49.2, NR) in the SoC arm, corresponding to a HR of 0.72 (95% CI: 0.52, 0.98). Because the hierarchical testing strategy requires OS to reach statistical significance in the patients with PD-L1 CPS ≥ 10 before proceeding with testing OS in other populations, OS was not tested in patients with PD-L1 CPS ≥ 1 or in the ITT population. However, in a descriptive analysis of OS in patients with PD-L1 CPS ≥ 1 , the OS HR estimate was 0.72 (95% CI: 0.56, 0.94), favoring pembrolizumab over SoC. This descriptive analysis suggests a potential trend in improved OS with the pembrolizumab-based regimen for patients with PD-L1 positive (CPS ≥ 1) LA HNSCC. Overall survival will be tested again at interim analysis 2 (IA2), when approximately 187 patients with PD-L1 CPS ≥ 10 have had OS events (93% information fraction of the final OS analysis).

The EFS treatment effect was largely preserved across subgroups of patients with PD-L1 positive (CPS ≥ 1) tumors, except for patients with primary tumors originating from the hypopharynx. In exploratory subgroup analyses by primary tumor site in patients with CPS ≥ 1 , the EFS HR for patients with hypopharyngeal tumors ($n=51$) was 2.28 (95% CI: 0.79, 6.56) favoring the SoC arm. For patients with PD-L1 positive disease for all other primary tumor sites, EFS results favored the pembrolizumab arm over the SoC arm. Specifically, for patients with PD-L1 positive oral cavity ($n=415$), oropharyngeal ($n=71$), and laryngeal ($n=144$) primary tumor sites, the EFS HRs were 0.71 (95% CI: 0.53, 0.95), 0.32 (95% CI: 0.15, 0.68), and 0.62 (95% CI: 0.36, 1.06), respectively. In addition, the rate of complete (R0) surgical resections, a predictor of HNSCC overall survival, was lower in the pembrolizumab arm compared to the SoC arm for

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patients with PD-L1 positive (CPS ≥ 1) hypopharyngeal tumors, at 74% vs 87%, respectively. For all other primary tumor subsites, the R0 resection rate was higher in the pembrolizumab arm compared to the SoC arm at 91% vs 85%, respectively.

Given a potential detriment with pembrolizumab for patients with PD-L1 positive, hypopharyngeal tumors, the EFS and R0 resection results for this subgroup of patients in KEYNOTE-689 are included in Section 14 of the USPI for pembrolizumab. We acknowledge this potential detriment for perioperative pembrolizumab for patients with PD-L1 positive, hypopharyngeal tumors was observed in a small subgroup of only 51 patients and therefore this exploratory analysis should be interpreted with caution. Therefore, the FDA review team recommends approval of the KEYNOTE-689 perioperative pembrolizumab regimen for the entire PD-L1 positive population, without a limitation of use for patients with hypopharyngeal cancer.

The observed safety profile of pembrolizumab is considered acceptable in the context of a life-threatening disease. The primary safety population was of 361 patients who received at least one dose of therapy in the pembrolizumab arm and 351 patients in the SoC arm. In the neoadjuvant phase, rates of surgical cancellation were similar (11% vs 12%) for patients on the pembrolizumab arm compared to the SoC arm. No new safety signals were identified in the pembrolizumab arm, and the observed safety profile including immune-related adverse events were generally consistent with that described for pembrolizumab as a single agent in current product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure the safe use of perioperative pembrolizumab for HNSCC.

A major limitation of the design of KEYNOTE-689 is the inability of this two-arm trial to isolate the contribution of effect of the neoadjuvant, adjuvant radiation, and adjuvant post-radiation phases to the overall regimen, raising the concern for overtreatment. The inability to isolate the contribution of treatment phase in perioperative immunotherapy-based regimens for NSCLC, another solid tumor, was the subject of an Oncologic Drugs Advisory Committee (ODAC) meeting on July 25, 2024. Although the perioperative regimen with durvalumab, another anti-PD-(L)1 antibody, evaluated for NSCLC in the AEGEAN trial was unable to isolate the effect of each phase of therapy, the ODAC members generally agreed that an additional trial prior to approval was not necessary. Since KEYNOTE-689 was initiated in 2017 prior to this ODAC, FDA will similarly not require an additional trial prior to approval of perioperative pembrolizumab for resectable HNSCC, despite the uncertainty surrounding the need for the adjuvant phase of treatment. Based on additional discussions at the July 25, 2024, ODAC, future perioperative trials in solid tumors including resectable HNSCC should be designed to improve the ability to demonstrate the contribution of each phase of therapy. Based on the available data, the FDA clinical review team does not consider that the lack of demonstration of clinical benefit of each phase of treatment significantly alters the overall benefit-risk evaluation of the regimen

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given the safety profile of pembrolizumab in the adjuvant setting.

The results from KEYNOTE-689 meet the statutory evidentiary standard for traditional approval and provide substantial evidence of effectiveness of pembrolizumab for adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test, as neoadjuvant treatment, continued as adjuvant treatment in combination with RT with or without cisplatin, and then as a single agent. The magnitude of the EFS treatment effect, with a HR of 0.70 (95% CI: 0.55, 0.89; $p=0.00140$) and corresponding to 30.1-month improvement in median EFS, is statistically significant and clinically meaningful, and represents a major improvement for the treatment of patients with resectable, LA HNSCC. These results are also supported by a trend towards improved OS with pembrolizumab. Overall, data from KEYNOTE-689 support a favorable benefit:risk assessment for perioperative pembrolizumab for patients with resectable, LA HNSCC. Therefore, the FDA review team recommends traditional approval for the following indication:

KEYTRUDA for the treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.

8.4.1. Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (*enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response*):

KEYTRUDA for the treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1], as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.

2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)

- 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

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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

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The FDA’s Assessment:

FDA did not refer this supplemental application to an advisory committee or seek input from other external consultants because no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

10 Pediatrics

The Applicant’s Position: KEYNOTE-689 did not enroll pediatric participants. The Applicant has submitted a PREA waiver.

The FDA’s Assessment:

FDA agrees with the Applicant’s position.

11 Labeling Recommendations

Data:

Table 38: Applicant – Summary of Significant Proposed Labeling Changes

Section	Applicant’s Proposed Labeling	FDA’s Proposed Labeling
PRESCRIBING INFORMATION: HIGHLIGHTS OF PRESCRIBING INFORMATION	Update proposed indication to align to section 1 and update Adverse Reactions section to align with the safety date presented in section 6.1 for KEYNOTE-689	HIGHLIGHTS was revised for consistency with the Full Prescribing Information.
INDICATIONS AND USAGE	Added indication for patients with LA HNSCC	New indication added. FDA specified “adult” patients and [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test. <i>1.4 Head and Neck Squamous Cell Cancer</i> <i>KEYTRUDA is indicated for the treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined</i>

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

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		<i>by an FDA-approved test [see Dosage and Administration (2.1)], as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without platinum-containing chemotherapy and then as a single agent.</i>
DOSAGE AND ADMINISTRATION	Added dosing information for patients with LA HNSCC	FDA added patient selection criteria to Section 2 and revised the dosage instructions for clarity.
ADVERSE REACTIONS	Update to include safety details and safety information from KEYNOTE-689	FDA revised the Applicant's proposed text to include safety data by neoadjuvant and adjuvant phases of the study.
CLINICAL STUDIES	Added study description and efficacy results for KEYNOTE-689	New subsection: <i>14.4 Head and Neck Squamous Cell Cancer</i> <i>Neoadjuvant and Adjuvant Treatment of Locally Advanced HNSCC for Tumors Expressing PD-L1 (CPS$\geq$ 1).</i> FDA specified the companion diagnostic: PD-L1 IHC 22C3 pharmDx kit. FDA (b) (4) (b) (4) FDA added the number of R0 resections by tumor location.
MEDICATION GUIDE: What is KEYTRUDA®?	Update to include information based on KEYNOTE-689	The Medication Guide was revised for consistency with the USPI. Please see reviews by the Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP).

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The Applicant's Position: [Table 34] summarizes the significant proposed labeling changes.

The FDA's Assessment: The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. Table 34 summarizes key changes.

APPEARS THIS WAY ON ORIGINAL

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12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

There were no significant safety concerns identified during the review of this supplement requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy to ensure safe use of perioperative pembrolizumab for patients with resectable LA HNSCC as in the proposed indication.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following Post-Marketing Commitments were issued and agreed upon with the Applicant:

PMC 1 (Clinical)

PMC Rationale:

Traditional approval was granted for perioperative single agent pembrolizumab as neoadjuvant and adjuvant therapy added to standard of care (SoC) surgery and postoperative radiation or chemoradiation for patients with resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC). Approval was based on a clinically meaningful improvement in event-free survival (EFS) demonstrated in the KEYNOTE-689 trial. The current overall survival (OS) data from the KEYNOTE-689 trial are immature. The results of the final OS analysis will better characterize the benefits and risks of perioperative pembrolizumab for patients with resectable LA HNSCC and may potentially inform updated labeling.

PMC Language:

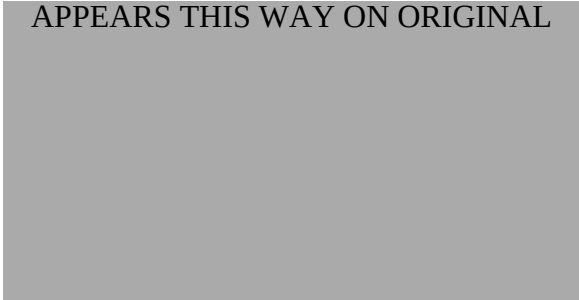
Complete clinical trial, KEYNOTE-689 (NCT03765918), titled, "Study of Pembrolizumab Given Prior to Surgery and in Combination With Radiotherapy Given Post-surgery for Advanced Head and Neck Squamous Cell Carcinoma (MK-3475-689)" to provide long-term efficacy data. Provide the final overall survival (OS) analysis once the required number of events for OS, as prespecified in the statistical analysis plan, have occurred in the intention-to-treat population.

Trial Completion:	11/2026
Final Report Submission:	05/2027

Submit the final OS analysis and datasets with the final report submission.

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14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

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X

18 Office Director (or designated signatory authority)

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

X

19 Appendices

19.1. References

The Applicant’s References:

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19.2. Financial Disclosure

The Applicant's Position: Disclosure of financial interests of the investigators who conducted KEYNOTE-689 is described in this submission, including statements of due diligence (FDA

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{Insert Product Trade and Generic Name}

forms 3454) in cases where the Applicant was unable to obtain a signed form from the investigator.

The FDA's Assessment:

FDA reviewed the financial disclosures for all study investigators. Of the 1,970 investigators and sub-investigators participating in KEYNOTE-689, seven investigators (0.36%) reported significant financial disclosures and together accounted for screening of 23 patients (3.2%) and enrollment of 14 patients (2.0%) on KEYNOTE-689.

- One sub-investigator affiliated with study site (b) (6) (located in the US) disclosed receiving stock equity in MSD exceeding \$50,000.00. Site (b) (6) screened and randomized (b) (6) patients.
- One sub-investigator affiliated with study site (b) (6) (located in the US) disclosed a \$150,000.00 grant to fund research to (b) (6). Site (b) (6) screened (b) (6) and randomized (b) (6) patient(s).

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- One principal investigator affiliated with study site (b) (6) was reported by the Applicant to have received \$56,039.37 for speaker fees and honoraria. Site (b) (6) screened (b) (6) and randomized (b) (6) patients.
- One sub-investigator affiliated with study site (b) (6) (located in the US) received a research grant paid to (b) (6) for clinical trial in the amount of \$735,142.97. Site (b) (6) screened (b) (6) and randomized (b) (6) patients.
- One sub-investigator affiliated with study site (b) (6) received \$999,738.00 for an investigator initiated trial. Site (b) (6) screened and randomized (b) (6) patient.
- One sub-investigator affiliated with study site (b) (6) received \$36,000.00 as speaker bureau/fees. Site (b) (6) screened (b) (6) patient and randomized (b) (6).
- One sub-investigator affiliated with study site (b) (6) disclosed that (b) (6) received restricted stock units based on (b) (6).

Six sub-investigators did not disclose financial interest and/or arrangements with MSD, did not respond to due diligent attempts by MSD, and internal financial information for them was not provided by MSD. Together, these 6 sub-investigators accounted for screening of 58 patients (8.1%) and enrollment of 42 patients (5.9%) on KEYNOTE-689.

Based on the above, it is the opinion of the FDA clinical review team that the submitted financial disclosures in KEYNOTE-689 are very unlikely to have impacted the randomization of patients, treatment effect, or safety outcomes observed in any meaningful way.

Covered Clinical Study (Name and/or Number):* KEYNOTE-689

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>1,970</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>1</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>7</u>		
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: <u>0</u> Significant payments of other sorts: <u>5</u>		

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 {Insert Product Trade and Generic Name}

Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>2</u> Sponsor of covered study: <u>Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA</u>		
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) <u>9</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position: No new data are being submitted.

The FDA's Assessment: Not applicable

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The Applicant's Position: No new data are being submitted.

The FDA's Assessment: Not applicable

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment: Not applicable

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Yun Oh, MD	CDER/ OND/OOD/DOII	Sections: All	Select one: ☒ Authored ☐ Approved
	Signature: Yun W. Oh -S Digitally signed by Yun W. Oh -S Date: 2025.06.10 08:58:38 -04'00'			
Supervisory Associate Director (Acting)	Paz Vellanki, MD, PhD	CDER/ OND/OOD/DOII	Sections: All	Select one: ☒ Approved
	Signature: See signature in DARRTS.			
Clinical Team Leader	Justin Malinou, MD	CDER/OND/OOD/DOII	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature: See signature in DARRTS.			
Cross-Disciplinary Team Leader (CDTL)	Justin Malinou, MD	CDER/OND/OOD/DOII	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature: See signature in DARRTS.			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Biostatistical Reviewer	Michelle Marcovitz, PhD	CDER/OTS/OB/DBV	Sections: 1, 8.1, 8.3	Select one: ☒ Authored ☐ Approved
				Signature: MICHELLE S. MARCOVITZ -S Digitally signed by MICHELLE S. MARCOVITZ -S Date: 2025.06.09 16:27:26 -04'00'
Biostatistical Team Lead	Flora Mulkey, MS	CDER/OTS/OB/DBV	Sections: 1, 8.1, 8.3	Select one: ☐ Authored ☒ Approved
				Signature: Flora M. Mulkey -S Digitally signed by Flora M. Mulkey -S Date: 2025.06.09 12:10:26 -04'00'
Supervisory Mathematical Statistician	Anup Amatya, PhD	CDER/OTS/OB/DBV	Sections: 1, 8.1, 8.3	Select one: ☐ Authored ☒ Approved
				Signature: ANUP K. AMATYA -S Digitally signed by ANUP K. AMATYA -S Date: 2025.06.09 13:18:55 -04'00'
Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OND/OOD/DOII	Sections: 11	Select one: ☒ Authored ☐ Approved
				Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2025.06.10 08:42:36 -04'00'

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/

JUSTIN N MALINOU
06/12/2025 03:32:20 PM

PAZ J VELLANKI
06/12/2025 03:41:06 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125514Orig1s180

OTHER REVIEW(S)

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

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

Memorandum

Date: May 29, 2025

To: Ashley Lane, MS, Senior Regulatory Health Project Manager
Division of Oncology 2 (DO2)

From: Andrew Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP
Barbara Scepura, MS, CRNP, Associate Director for Labeling, DO2

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

BLA: 125514/S-180

Background:

In response to DO2's consult request dated January 21, 2025, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide (MG) for supplement 180 for KEYTRUDA® (pembrolizumab) injection, for intravenous use. This supplement proposes a new indication for use of KEYTRUDA for the treatment of patients with resectable locally advanced head and neck squamous cell cancer, as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT), with or without platinum-containing chemotherapy, and then as a single agent.

PI/MG:

OPDP's review of the proposed PI is based on the draft labeling sent by electronic mail to OPDP on May 27, 2025, accessed via SharePoint on May 27, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed MG, and comments were sent under separate cover.

Thank you for your consult. If you have any questions, please contact Andrew Nguyen at 240-402-0512 or andrew.nguyen@fda.hhs.gov.

174 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
05/29/2025 09:56:48 AM

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

PATIENT LABELING REVIEW

Date: May 29, 2025

To: Ashley Lane, MS
Senior Regulatory Health Project Manager
Division of Oncology II (DO2)

Through: Barbara Fuller, MSN, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Laurie Buonaccorsi, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Andrew Nguyen, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): KEYTRUDA (pembrolizumab)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 125514

Supplement Number: S-180

Applicant: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.

1 INTRODUCTION

On December 23, 2024, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved Biologics License Application (BLA) 125514/S-180 for KEYTRUDA (pembrolizumab) injection. With this submission, the Applicant proposes KEYTRUDA (pembrolizumab) injection for the treatment of patients with resectable locally advanced head and neck squamous cell cancer as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy with or without platinum-containing chemotherapy, and then as a single agent.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on January 21, 2025, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for KEYTRUDA (pembrolizumab) injection.

2 MATERIAL REVIEWED

- Draft KEYTRUDA (pembrolizumab) injection MG received on December 23, 2024, and received by DMPP and OPDP on May 22, 2025.
- Draft KEYTRUDA (pembrolizumab) injection PI received on December 23, 2024, revised throughout the review cycle, and received by DMPP and OPDP on May 22, 2025.
- Approved KEYTRUDA (pembrolizumab) injection MG dated January 28, 2025 and PI April 21, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

LAURIE J BUONACCORSI
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ANDREW D NGUYEN
05/29/2025 09:10:23 AM

BARBARA A FULLER
05/29/2025 09:21:43 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 10, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 125514/S-180
Product Name, Dosage Form, and Strength:	Keytruda (pembrolizumab) injection, 100 mg/4 mL (25 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
FDA Received Date:	December 23, 2024
TTT ID #:	2025-12676
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted an Efficacy Supplement for Keytruda (pembrolizumab) injection to propose an additional indication:

For the treatment of patients with resectable Locally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC) as neoadjuvant treatment, then continued as adjuvant treatment in combination with radiotherapy (RT) with or without platinum-containing chemotherapy and then as a single agent.

Subsequently, the Division of Oncology 2 (DO2) requested that we review the proposed Keytruda Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

Our evaluation of the proposed Keytruda Prescribing Information (PI) and Medication Guide (MG) did not identify areas of vulnerability that may lead to medication errors. We note that there are no changes to Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information. We have no recommendations at this time.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Keytruda received on December 23, 2024 from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Table 2. Relevant Product Information for Keytruda	
Initial Approval Date	September 4, 2014
Proper Name	pembrolizumab
Indication	Melanoma Non-Small Cell Lung Cancer Malignant Pleural Mesothelioma Head and Neck Squamous Cell Cancer (HNSCC) Classical Hodgkin Lymphoma Primary Mediastinal Large B-Cell Lymphoma Urothelial Cancer Microsatellite Instability-High or Mismatch Repair Deficient Cancer Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer Gastric Cancer Esophageal Cancer Cervical Cancer Hepatocellular Carcinoma Biliary Tract Cancer Merkel Cell Carcinoma Renal Cell Carcinoma Endometrial Carcinoma Tumor Mutational Burden-High Cancer Cutaneous Squamous Cell Carcinoma Triple-Negative Breast Cancer
Dosage Form	injection
Strength	100 mg/4 mL (25 mg/mL)
Route of Administration	Intravenous

Table 2. Relevant Product Information for Keytruda			
Dose and Frequency	See Keytruda PI ^a for dosing information.		
	<u>Proposed addition:</u>		
	Indication	Recommended Dosage of KEYTRUDA	Duration/Timing of Treatment
	Adult patients with locally advanced HNSCC	200 mg every 3 weeks* or 400 mg every 6 weeks*	(b) (4)
		(b) (4)	

^a Keytruda [Prescribing Information]. DailyMed. U.S. National Library of Medicine. Jan 2025. [Cited 2025 MAR 06]. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9333c79b-d487-4538-a9f0-71b91a02b287>.

Table 2. Relevant Product Information for Keytruda	
How Supplied	Carton containing one 100 mg/4 mL single dose vial Carton containing two 100 mg/4 mL single dose vials
Storage	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.
Container Closure	Single dose vial

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Keytruda labels and labeling submitted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc..

- Prescribing Information received on December 23, 2024, available from <\\CDSESUB1\EVSPROD\bla125514\6568\m1\us\01-wrm-uspi-mk3475-iv-hn689v01.docx>
- Medication Guide received on December 23, 2024, available from <\\CDSESUB1\EVSPROD\bla125514\6568\m1\us\01-wrm-usmg-mk3475-iv-hn689v01.docx>

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On March 6, 2025, we searched for previous DMEPA reviews relevant to this current review using the terms, 125514. Our search identified 1 previous review(s)^c since the date of our last search on August 19, 2024, and we considered our previous recommendations to see if they are applicable for this current review.

^c Stewart, J. Label and Labeling Review for Keytruda (BLA 125514/S-161). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 AUG 26. OSE RCM No.: 2024-8931.

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/s/

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Clinical Inspection Summary

Date	May 23, 2025
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Kassa Ayalew, MD, MPH, Division Director, DCCE, OSI
To	Yun Oh, Medical Officer Justin Malinou, Medical Team Leader Paz Vellanki, Supervisory Associate Director Division of Oncology 2 (DO2), Office of Oncology Products
BLA #	BLA 125514 S180
Applicant	Merck Sharp & Dohme Corp.
Drug	Pembrolizumab
NME (Yes/No)	No
Therapeutic Classification	Programmed death receptor-1 (PD-1)-blocking antibody
Proposed Indication(s)	Treatment of patients with resectable locally advanced head and neck squamous cell cancer (HNSCC) as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without platinum-containing chemotherapy and then as a single agent.
Consultation Request Date	February 3, 2025
Summary Goal Date	May 29, 2025
Action Goal Date	June 12, 2025
PDUFA Date	June 23, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study MK-3475-689 were submitted to the Agency in support of supplemental Biologics License Application (sBLA) 125514 S-180 for pembrolizumab given prior to surgery and in combination with radiotherapy given post-surgery for advanced head and neck squamous cell cancer (HNSCC). Two clinical investigators, Drs. Irene Brana Garcia (Site # 1200), and Anupama Nehra (Site # 2053), as well as the Sponsor, Merck Sharp & Dohme Corp. (thereafter Merck) and the imaging Contract Research Organization (CRO), (b) (4) were inspected.

Inspections of Drs. Brana Garcia, Nehra, the Sponsor, Merck, and the imaging CRO, (b) (4) did not find significant concerns regarding the study conduct, data discrepancies or integrity, Good Clinical Practice (GCP), or regulatory compliance. Based on these inspections, Study MK-3475-689 appears to have been conducted adequately, and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

Of note, the inspection results of Dr. Brana Garcia, are based on a summary provided by the FDA field investigator and are therefore preliminary. If significantly new or different information is contained in the final FDA Establishment Inspection Report, an addendum to this clinical inspection summary will be filed.

II. BACKGROUND

Merck Sharp & Dohme LLC submitted BLA125514 S-180 seeking approval for pembrolizumab to treat resectable locally advanced HNSCC as neoadjuvant and adjuvant treatment combined with radiotherapy (RT), with or without platinum-containing chemotherapy, and then as a single agent. The primary evidence supporting this indication is based on data from Study MK-3475-689.

Pembrolizumab is currently approved for various adult solid tumors and hematologic malignancies, including first-line treatment of advanced HNSCC, alone or combined with platinum and 5FU chemotherapy, for first-line and previously treated, advanced metastatic, unresectable, recurrent HNSCC.

MK-3475-689 is a phase III, randomized, multicenter, open-label, active-control trial in subjects with resectable locally advanced (Stage III-IVA) HNSCC. Eligible subjects were randomized 1:1 to either:

- Arm A: Neoadjuvant pembrolizumab before surgical resection, followed by pembrolizumab with radiation plus cisplatin or radiation alone, then pembrolizumab alone
- Arm B: Surgery followed by cisplatin or radiation alone

Randomization was stratified by primary tumor site, tumor stage, and PD-L1 status.

Treatment with pembrolizumab continued until disease progression (as defined by RECISTv1.1 and assessed by BICR), completion of treatment (17 cycles), disease progression precluding definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection, or unacceptable toxicity.

The primary efficacy endpoint was event-free survival (EFS) by BICR. Key secondary endpoints were major pathological response (mPR) rate and overall survival (OS).

Informed consent was required before any study-related procedure. Screening procedures, including tumor assessment, medical history, physical examination, laboratory tests, and imaging, were performed within 28 days of treatment initiation.

Tumor imaging was performed at screening, prior to surgery, and at regular intervals

during the adjuvant phase. After Year 5, participants entered Survival Follow-up every 12 weeks until death, withdrawal of consent, or study end.

At the data cut-off date (July 25, 2024), the ongoing study had randomized 714 subjects (263 in the pembrolizumab arm, 351 in the control arm) across 192 sites in 24 countries, including 98 subjects at 39 US sites.

III. RESULTS (by site)

1. Dr. Irene Brana Garcia (Site # 1200)

Passeig De La Vall
Dhebron 119-129
Barcelona, SPAIN

Inspection dates: May 5 – 9, 2025

Dr. Garcia was inspected as a BIMO review-based inspection for Study MK-3475-689. This was the first inspection for this investigator.

At the time of the data cut-off date, the site had screened 16 subjects and randomized 15 in Study MK-3475-689, of whom 10 subjects completed study treatment and are in the follow-up phase, 5 subjects had died.

Source records for all 15 subjects randomized at the site were reviewed. Records reviewed included, but were not limited to informed consent forms, eligibility criteria, and adverse event reporting. No significant discrepancies were found when source data were compared with the data submitted to the BLA.

The inspection also verified that radiology studies to assess the primary efficacy endpoint were performed according to protocol-specified time points and all scans were submitted for central review.

Based on the preliminary results provided by the FDA field investigator, data generated by Dr. Garcia appear to be acceptable in support of the BLA.

2. Dr. Anupama Nehra (Site # 2053)

205 South Orange Ave
A-1115, Newark
New Jersey, 07101

Inspection dates: March 17 – 21 and 24, 2025

Dr. Nehra was inspected as a BIMO review-based inspection for Study MK-3475-689.

This was the first FDA inspection for this investigator.

At the time of the inspection, the site had screened 9 subjects and enrolled 7 subjects. Of these, 2 were in the follow-up phase, 4 subjects had died, and 1 subject was withdrawn due to non-compliance.

Source records for all 7 enrolled subjects were reviewed and compared with the data listings submitted to the BLA. Records reviewed included but were not limited to, informed consent forms, eligibility criteria, radiation therapy, adherence to protocol, concomitant medications, protocol deviation logs, investigational product handling accountability records, and adverse event reporting. No significant or impactful discrepancies were found when source data were compared with the data submitted to the BLA.

The inspection verified that imaging scans to evaluate the primary efficacy endpoint were performed as specified in the protocol and all scans were submitted for central review, consistent with the data submitted to the BLA. No significant discrepancies regarding the primary endpoint data were observed.

Additional records reviewed during the inspection included but were not limited to, staff training information, CR/sponsor monitoring activities documents, electronic records, and IRB approvals and communications. The inspection observed some poor record-keeping practices which appear non-critical to the safety or efficacy of the drug or subject safety during the trial. Dr. Nehra acknowledged the deficiencies in her April 5, 2025, response. She implemented a CAPA, where applicable, and her response is adequate.

Despite this, and based on the inspection, the data generated at Dr. Nehra's site appear acceptable in support of the proposed indication in the BLA.

3. Merck Sharp & Dohme Corp.

2025 E. Scott Ave
Rahway, New Jersey 07065

Inspection dates: March 13 – 27, 2025.

This inspection assessed Merck's oversight responsibilities for Study MK-3475-689. Merck was last inspected in October 2021.

Documents reviewed included, but were not limited to site training, safety monitoring, control of investigational product, and financial disclosure. Other records reviewed were assessments of qualifications and training documentation for CRAs who served as clinical site monitors, Independent Data Monitoring Committee records, vendor contracts, protocol deviations, written procedures, and safety data. Monitoring files for four clinical sites (Sites # 1200, 2053, 0901, and 0554) were reviewed in depth for compliance. Issues with record keeping and delays in completing source document

reviews by monitors were observed in sites # 1200 and 2053; however, these findings did not impact subject safety or data reliability.

The inspection did not observe issues related to safety or adverse event reporting for the MK-3475-689 study.

Based on the inspection results, Merck's overall oversight of the study and monitoring of the clinical investigators appear adequate.

4.

(b) (4)
(b) (4)

Inspection dates: (b) (4)

(b) (4) was inspected as a directed BIMO review-based inspection for Study MK-3475-689. The firm was last inspected in (b) (4) without significant findings.

This inspection reviewed (b) (4) responsibilities in performing an independent central imaging review for Study MK-3475-689. Documents reviewed included, but were not limited to, (b) (4) adherence to the imaging review charter, the process for selecting readers, training records, blinding procedures, and financial disclosure statements. No issues were observed.

Imaging scans were verified for disease non-progression/progression for 14 subjects. Source data were compared to the efficacy line listing submitted to the NDA. No discrepancies were observed. The ID of the subjects whose tumor measures were reviewed are as follows:

Subject ID
(b) (6)

Additional documents reviewed included, but were not limited to, Imaging Charters and Master Service Agreements for (b) (4) and for Study MK-3475-689, the Quality Assurance System, SOPs related to data backup, data storage, record retention, and staff training related to the studies. The review found the processes adequate.

Based on the results of the inspection, the imaging review data generated by (b) (4) appears acceptable in support of the proposed indication in the BLA.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H. signing for Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigation

CC:

Review Division /Project Manager/Ashley Lane
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125514Orig1s180

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 122325

MEETING MINUTES

Merck Sharp & Dohme LLC
Attention: Steven S. Mundt, M. S.
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000
Rahway, NJ 07065

Dear Steven Mundt:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KEYTRUDA® (pembrolizumab, MK-3475).

We also refer to the video conference between representatives of your firm and the FDA on November 25, 2024. The purpose of the meeting was to discuss acceptability of the efficacy and safety results from the interim analysis 1 results of the KEYNOTE-689 trial to support evaluation of a supplemental Biological License Application (sBLA) to add pembrolizumab in combination with standard of care (SoC) therapy as a new indication for locally advanced head and neck squamous cell carcinoma (HNSCC) to the US Prescribing Information (USPI) for KEYTRUDA.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

¹ 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>.

If you have any questions, call me at 240-402-4558 or email opeyemi.udoka@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Opeyemi Udoka DPT, CSM
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic
Diseases for Division of Oncology 2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-sBLA
Meeting Date and Time: November 25, 2024, 1:00PM – 2:00PM EST
Meeting Location: Video Conference
Application Number: IND 122325
Product Name: KEYTRUDA® (pembrolizumab, MK-3475)
Indication: treatment of patients with resectable locoregionally advanced head and neck squamous cell carcinoma (HNSCC) as neoadjuvant treatment, then continued as adjuvant treatment in combination with radiation therapy with or without cisplatin chemotherapy, followed by KEYTRUDA as a single agent.
Sponsor Name: Merck Sharp & Dohme LLC
Regulatory Pathway: 351(a) of the Public Health Service Act for biologics
Meeting Chair: Justin Malinou
Meeting Recorder: Opeyemi Udoka

FDA ATTENDEES

Erin Larkins, M.D., Acting Division Director, Division of Oncology 2 (DO2)
Justin Malinou, M.D., Acting Cross Disciplinary Team Leader, DO2
Yun Oh, M.D., Clinical Reviewer, DO2
Xiaoxue Li, Ph.D., Acting Biostatistics Team Leader, Division of Biometrics V (DBV)
Somak Chatterjee, Ph.D., Biostatistics Reviewer, DBV
Opeyemi Udoka, D.P.T., Senior Regulatory Health Project Manager, Division of Regulatory Operations for Oncologic Diseases (DRO-OD)

SPONSOR ATTENDEES

Gregory Lubiniecki, M.D. Vice President, Clinical Research
Burak Gumuscu, M.D., Ph.D. Dist. Scientist, Clinical Research
Behzad Bidadi, M.D. Sr. Principal Scientist, Clinical Research
Kimberly Benjamin, M.D. Sr. Principal Scientist, Clinical Research
Christine Gause, Ph.D. Vice President, Biostatistics
Anran Wang, Ph.D. Prin. Scientist, Biostatistics
Cole Manschot, Ph.D. Sr. Scientist, Biostatistics
Sabrina Girty, Ph.D. Dist. Scientist, Global Regulatory Affairs
Steven Mundt, M.S. Sr. Principal Scientist, Regulatory Affairs
Keith St. Amand, M.D. Assoc. Vice President, Clinical Safety and Risk Management

BACKGROUND

On September 26, 2024, Merck, Sharp and Dohme LLC (Merck) submitted a meeting request to discuss acceptability of the efficacy and safety results from interim analysis 1 (IA1) of the KEYNOT-689 trial to support evaluation of a supplemental Biological License Application (sBLA) to add pembrolizumab in combination with standard of care (SoC) therapy as a new indication for locally advanced HNSCC to the US Prescribing Information (USPI) for KEYTRUDA. The meeting was granted as a Type B pre-sBLA meeting on October 7, 2024. The meeting package was received on October 24, 2024.

Regulatory History

On July 17, 2017, a Type B/End-of-Phase meeting was held to discuss the design of KEYNOTE-689. At that time, FDA indicated that the proposed trial design would not be able to isolate the benefit of neoadjuvant pembrolizumab from post-surgical adjuvant pembrolizumab.

On June 25, 2018, a Type C meeting was held to discuss central pathological assessment for determination of risk categorization during the adjuvant phase. FDA acknowledged the challenges associated with central review and timely initiation of adjuvant treatment within 6 weeks of surgery, and therefore did not object to randomization based on local pathology assessment of the presence of high-risk features.

On October 3, 2024, an informal teleconference was held to discuss the Top-Line results from IA1 of KEYNOTE-689. FDA agreed that Merck could submit a request for a pre-sBLA meeting based on IA1 data. Additionally, FDA indicated specific information should be included in the meeting background package, including subgroup analyses (e.g., based on PD-L1 combined positive score [CPS] <1, CPS 1-9, and CPS ≥10), and rationale to support the contribution of the neoadjuvant and adjuvant phases of the investigational regimen.

Clinical

Merck proposes to submit a supplemental marketing application for pembrolizumab for the treatment of patients with resectable, locoregionally advanced HNSCC as neoadjuvant treatment, then continued as adjuvant treatment in combination with standard of care radiation therapy (RT) with or without cisplatin chemotherapy, followed by continuation of pembrolizumab as a single agent.

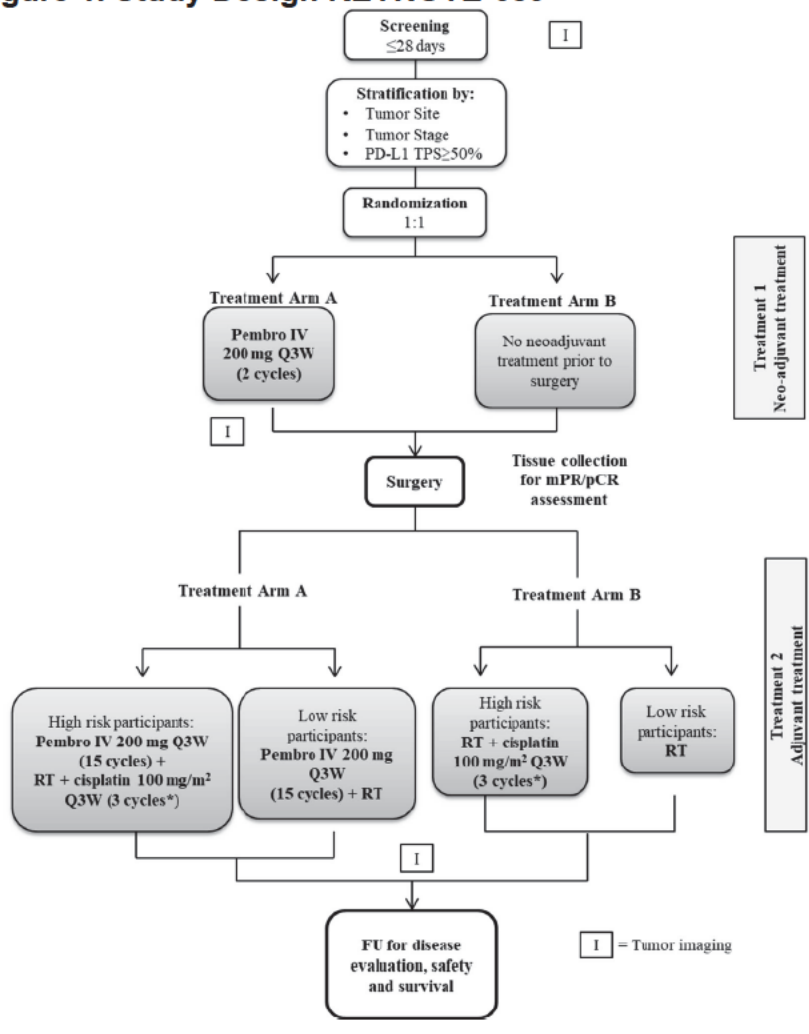
Study KEYNOTE-689

KEYNOTE-689 is a randomized, active-controlled, multi-site, open label study of neoadjuvant pembrolizumab followed by surgery and adjuvant pembrolizumab in combination with standard of care (SoC) RT with or without concurrent cisplatin, with subsequent pembrolizumab monotherapy to complete up to 17 cycles; versus SoC

U.S. Food and Drug Administration
Silver Spring, MD 20993
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surgery followed by RT with or without concurrent cisplatin in patients with treatment-naïve Stage III-IVA resectable HNSCC. The KEYNOTE-689 study design is shown below.

Figure 1. Study Design KEYNOTE-689

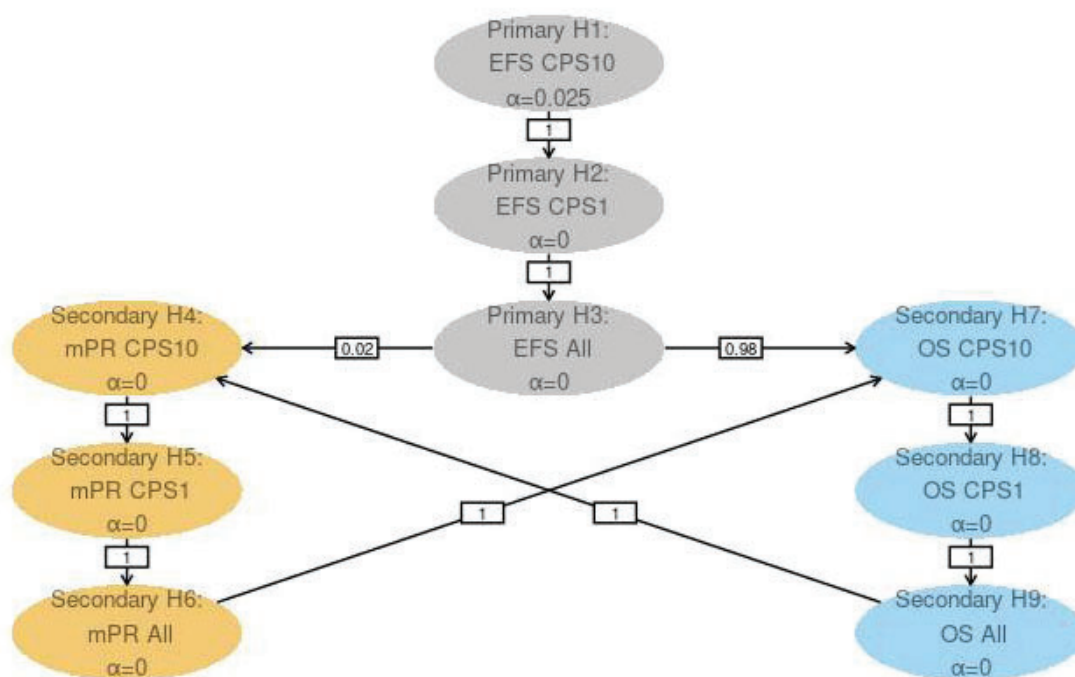


Source: Meeting background package page 17

A total of 714 patients were to be randomized 1:1 to the pembrolizumab or SoC groups. In the pembrolizumab group, patients received neoadjuvant therapy with 2 cycles of pembrolizumab followed by surgical resection and adjuvant therapy with 3 cycles of pembrolizumab plus SoC RT with or without cisplatin, followed by 12 cycles of pembrolizumab monotherapy. In the SoC group, no neoadjuvant therapy was received prior to surgical resection and adjuvant therapy was only with SoC RT with or without cisplatin. For adjuvant treatment in both arms, patients considered high-risk for recurrence (i.e., surgical specimen revealed positive margins [<1 mm] or extranodal extension) received cisplatin concurrently with RT; patients without these high-risk features did not receive cisplatin concurrently with RT.

Patients were stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor stage (III vs. IVA), and tumor PD-L1 status (TPS $\geq 50\%$ vs. TPS $< 50\%$). The primary endpoint is event-free survival (EFS) as assessed by blinded-independent central review (BICR) per RECIST 1.1 and key secondary endpoints are overall survival (OS) and major pathologic response (mPR) by blinded independent pathologic review (BIPR) after surgery in patients with PD-L1 CPS ≥ 10 and patients with CPS ≥ 1 . EFS in the CPS ≥ 10 subgroup was to be tested first, followed by EFS in the CPS ≥ 1 subgroup, and then in the ITT population in a hierarchical order. If all of the EFS hypotheses were rejected, alpha was to be allocated separately (i.e., split) for testing mPR and OS. In that case, mPR in the CPS ≥ 10 subgroup was to be tested first, followed by mPR in the CPS ≥ 1 subgroup, and then in the ITT population in a hierarchical order. Similarly, OS in the CPS ≥ 10 subgroup will be tested first, followed by OS in the CPS ≥ 1 subgroup, and in the ITT population, also in a hierarchical order.

Figure 2: Multiplicity Graph for Type I Error Control



Source: Meeting background package, protocol/amendment: 689-09, page 167

The planned sample size of 714 patients will result in approximately 462 patients whose tumors express PD-L1 CPS ≥ 10 and approximately 680 patients whose tumors express PD-L1 CPS ≥ 1 . For testing EFS in patients whose tumors express PD-L1 CPS ≥ 10 , a 0.025 one-sided alpha level was allocated to compare the pembrolizumab group to the SoC group, which would provide ~94.9% power to detect an EFS HR of 0.62. For testing OS in patients whose tumors express PD-L1 CPS ≥ 10 , a 0.0245 one-sided alpha level was allocated to compare the pembrolizumab group to the SoC group, which would provide ~84.9% power to detect an OS HR of 0.65.

U.S. Food and Drug Administration

Silver Spring, MD 20993

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Two interim analyses are planned (IA1 and IA2). This meeting package includes results from interim analysis 1 (IA1), which was planned to be performed when ~ 207 EFS events occurred in patients whose tumors PD-L1 with CPS ≥ 10 and ~ 6 months after the last patient had been randomized, or 9 months after the last patient was randomized regardless of number of EFS events, whichever occurred first. IA1 was performed ~9 months after the last patient was randomized and there were 192 EFS events in the CPS ≥ 10 population as of the data cutoff date (DCO) of July 25, 2024. IA2 will be performed after ~187 deaths in patients with CPS ≥ 10 have been observed and ~22 months after the last patient was randomized. The final analysis (FA) of OS will occur when 201 deaths have been observed.

Study KEYNOTE-689 Results

At the DCO date of July 25, 2024 for IA1, statistically significant improvements in EFS by BICR and mPR by BIPR were observed in the pembrolizumab group compared with the SoC group in the CPS ≥ 10 , CPS ≥ 1 , and intention-to-treat (ITT) populations. OS was not statistically significant in patients with CPS ≥ 10 at IA1. Per the multiplicity strategy prespecified in the statistical analysis plan (SAP), OS was not formally tested for the CPS ≥ 1 and ITT patient groups. Merck proposes to submit a marketing application based on the results of IA1. A summary of the EFS, mPR, and OS results at IA1 are presented in Tables 1 and 2 below.

Table 1. Summary of Efficacy Results for EFS at IA1

Patient population Number of patients per group	Number of events observed (Information Fraction)	Event-Free Survival, pembrolizumab group vs SoC group, Median in months (95% CI)	Observed HR (95% CI) Observed p-value
CPS ≥ 10 Pembrolizumab, n=234 SoC, n=231	192 (83%)	59.7 (41.1, NR) vs. 26.9 (18.3, 51.5)	0.66 (0.49, 0.88) 0.00217
CPS ≥ 1 Pembrolizumab, n=347 SoC, n=335	284 (80%)	59.7 (37.9, NR) vs. 29.6 (19.5, 41.9)	0.70 (0.55, 0.89) 0.00140
ITT Pembrolizumab, n=363 SoC, n=351	295 (80%)	51.8 (37.5, NR) vs. 30.4 (21.8, 50.1)	0.73 (0.58, 0.92) 0.00411

NR=Not Reached

Table 3. Summary of Efficacy Results for mPR at IA1

Pembrolizumab vs. SoC	mPR Rate (%) (95% CI)	Difference in % vs SoC
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CPS ≥10 Pembrolizumab, n=234 SoC, n=231	13.7 (9.7, 18.7) 0 (0.0, 1.6)	13.7
CPS ≥1 Pembrolizumab, n=347 SoC, n=335	9.8 (6.9, 13.4) 0 (0.0, 1.1)	9.8
ITT Pembrolizumab, n=363 SoC, n=351	9.4 (6.6, 12.8) 0 (0.0, 1.0)	9.3

Pathologic complete response (pCR) was not included in the multiplicity testing strategy, but the pembrolizumab arm demonstrated higher pCR rates than the SoC arm at a CPS ≥10 (4.3% versus 0%), CPS ≥1 (3.2% versus 0%), and ITT populations 3.0% versus 0%), respectively.

Table 2. Summary of Efficacy Results for OS at IA1

Patient population Number of patients per group	Number of events observed (Information Fraction)	Overall Survival, pembrolizumab group vs SoC group, Median in months (95% CI)	Observed HR (95% CI) Observed p-value
CPS ≥10 Pembrolizumab, n=234 SoC, n=231	162 (81%)	NR (NR, NR) vs. 61.8 (49.2, NR)	0.72 (0.52, 0.98) 0.01793
CPS ≥1 Pembrolizumab, n=347 SoC, n=335	234 (76%)	NR (NR, NR) vs. 61.8 (49.2, NR)	0.72 (0.56, 0.94) 0.00666
ITT Pembrolizumab, n=363 SoC, n=351	244 (75%)	NR (61.9, NR) vs. 61.8 (50.1, NR)	0.76 (0.59, 0.98) 0.01529

NR=Not Reached

As of July 25, 2024, the median duration of exposure to study treatment was 9.1 months in the pembrolizumab group and 2.9 months in the SoC group. A summary of safety results is provided in the table below.

Table 2. Summary of Safety Results at IA1

Adverse event type	Pembrolizumab group (n=361)	SoC group (n=315)
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Any adverse event (AE), %	96	97
Fatal AEs, %	7	8
Grade 3-5 AEs, %	76	74
SAEs, %	50	37
AEs leading to drug discontinuation, %	24	14

The most common AEs (occurring in $\geq 25\%$) in the pembrolizumab group and the SoC groups were stomatitis (42% vs 55%), decreased weight (36% vs 27%), anemia (34% vs 33%), and dysphagia (29% vs 32%). There was a higher incidence of hypothyroidism (25% vs 5%), diarrhea (22% vs 11%) and rash (11% vs 2.6%) in the pembrolizumab group compared to the SoC group.

KEYNOTE-689 Enrollment Status and Project ORBIS

As of July 25, 2024, 714 patients were enrolled on KEYNOTE-689. Approximately 16% were enrolled in North America, 40% were enrolled in Europe and 44% were enrolled in the rest of the world. Merck is requesting participation in Project ORBIS and to include the regulatory agencies from Australia, Brazil, Canada, Israel, Singapore, and the United Kingdom.

Proposed content and format for the BLA

Merck's proposal for the content and format of the BLA submission package is as follows:

- Module 2.5 will include a clinical overview of efficacy, safety and benefit/risk analysis.
- Module 2.7.3 will include the summary of clinical efficacy; however Merck will only provide a cover page as the integrated summary of efficacy since only 1 study (KEYNOTE-689) is intended to support the efficacy for this BLA filing. This module will also include analyses for CPS < 1 and CPS 1-9 populations for EFS, OS, and mPR and the Assessment Aid.
- Justification for Contribution of Phase for the neoadjuvant and adjuvant portions of the trial will be provided in Modules 2.7.3 and/or 2.5.
- Module 2.7.4 will include the summary of clinical safety and the narrative portion of the integrated summary of safety (ISS).
- Module 5.2 will include an appendix describing the rationale for the Applicability of Foreign Data to the US Population and US Medical Practice.
- Module 5.3.5.3 will include the ISS. In the ISS and the summary of clinical safety (SCS), data will be organized into tables to include 4 columns: the pembrolizumab arm of KEYNOTE-689 (n=361), the SoC arm of KEYNOTE-689 (n=315), pooled safety data from patients with HNSCC treated with pembrolizumab monotherapy (n=909) and pooled reference safety data for pembrolizumab monotherapy (n=2799).

FDA sent Preliminary Comments to Merck on November 20, 2024. On November 22, 2024, Merck provided responses and requested to further discuss Question 2 and FDA Additional Comment 12.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the efficacy and safety data from Interim Analysis 1 (IA1) from KN689 in this patient population are sufficient to support evaluation of an sBLA for pembrolizumab for the treatment of patients with resectable locoregionally advanced HNSCC as neoadjuvant treatment, then continued as adjuvant treatment in combination with radiation with or without cisplatin chemotherapy, followed by pembrolizumab monotherapy.

FDA Response: The efficacy and safety data from Interim Analysis 1 of Study KEYNOTE-689 appear acceptable to support the filing of a marketing application. A final determination regarding filing of the sBLA will be made after review of the contents of the submitted application. Whether the efficacy and safety results indicate a favorable benefit/risk profile and support approval of the sBLA in the proposed patient population will be determined during review of the marketing application.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's comment. No further discussion is required.

Discussion during the 11/25/2024 meeting: No discussion occurred.

2. The Sponsor is planning to submit a dossier consisting of the KEYNOTE-689 CSR as the pivotal study. Additionally, Merck is planning to provide Modules 2.2, 2.5, 2.7.3, 2.7.4, 5.2, an ISS (Module 5.3.5.3), and an Assessment Aid. Since the submission is based on a single pivotal study (KEYNOTE-689), no ISE will be included except for a reference page to that effect. Modules 2.7.1 and 2.7.2 in the existing lifecycle are considered current and will be referenced in the planned sBLA submission. Module 5.2 will be included to support Applicability of Foreign Data in review of the application.

Does the Agency agree that a dossier with these components would be acceptable to support evaluation of the sBLA?

FDA Response: The proposed components for a dossier are generally acceptable with one exception. An Integrated Summary of Efficacy (ISE) is required in applications submitted to the FDA in accordance with 21 CFR 314.50(d)(5)(v) and an ISE should be included for this sBLA. In the sBLA, please include an ISE that provides topline data from any other clinical trials, including descriptive investigator-initiated trials exploring pembrolizumab as part of

adjuvant and/or neoadjuvant therapy for locally advanced HNSCC, particularly for resectable disease. The ISE may also include data from trials of pembrolizumab for locally advanced HNSCC treated with definitive radiation or chemoradiation. These data may be helpful in our overall benefit:risk assessment as well as our assessment of the inclusion of both the neoadjuvant and adjuvant components of the investigational therapy, particularly as KEYNOTE-689 does not isolate the contribution of effect of these treatment components.

We also request these additional data and exploratory descriptive analyses:

- a. Data on time intervals between all treatment phases. For each patient and averaged for each treatment arm, please provide time intervals for:
 - Randomization to surgery or neoadjuvant pembrolizumab
 - Neoadjuvant pembrolizumab to surgery
 - Surgery to RT with or without cisplatin
 - RT with or without cisplatin to adjuvant pembrolizumab
- b. For both treatment arms, provide mPR and EFS results by N stage, T stage, primary tumor site, and HPV status for oropharyngeal tumors.
- c. For patients receiving chemoradiation therapy, provide the average number of cycles received and average total exposure of cisplatin for each treatment arm.
- d. For all patients, provide information on these baseline characteristics for each treatment arm:
 - Status of surgical margins and definition of clear margins
 - Classification of surgical resection as R0, R1, or R2
- e. Please provide PRO-CTCAE results in a stacked bar chart form within or as an appendix to the assessment aid.

We may request additional reports and analyses during our review of the sBLA.

Please also see FDA Additional Comments 8 to 12.

Please provide PRO-CTCAE results in a stacked bar chart form within or as an appendix to the assessment aid.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's comment and would like to discuss the Sponsor's plan for the ISE as summarized below.

The Sponsor will prepare and provide an ISE as requested which incorporates KN689, as well as descriptive summaries of the following trials evaluating pembrolizumab in combination with definitive treatment for patients with either resectable LA HNSCC or unresected LA HNSCC that have completed the primary efficacy analysis. The Sponsor would like to clarify that investigator-initiated trials supported through the Merck Investigator Studies program which

evaluate pembrolizumab will be based on the available published data because the Sponsor does not have direct access to these data. Table 1 includes a summary of clinical trials the Sponsor plans to include in the ISE evaluating perioperative pembrolizumab for patients with resectable LA HNSCC. Table 2 includes a summary of clinical trials the Sponsor plans to include in the ISE evaluating pembrolizumab in combination with CRT or RT for patients with unresected LA HNSCC not amenable to primary surgery.

Table 1. Summary of studies evaluating perioperative pembrolizumab for patients with resectable LA HNSCC

NCT #/Study name	Study Type	Experimental Arm Treatment	Control Arm Treatment	Sample Size	Primary Endpoint	Study Status
NCT02296684 ^{1,2}	Single-Arm Multi-Cohort Phase II	Group 1: 1 dose of NA pembro, HRPF present: POACRT followed by adj pembro X6 doses Q3W, HRPF absent: POART or Obs Group 2: 2 doses of NA pembro, POART or POACRT or obs (no Adj pembro administered)	N/A	Group 1: 36 Group 2: 31	Co-primary: 1-year Relapse rate for pts with HRPF, pTR-2 rate	Primary Efficacy Analysis Completed
NCT02641093 ³	Single-Arm Phase II	1 dose of NA Pembro, HRPF present: Adj PembroX6 doses Q3W + POACRT HRPF absent: Adj PembroX6 doses Q3W + POART	N/A	96	1-yr DFS	Primary Efficacy Analysis Completed

Legend: Pembro: Pembrolizumab, NA: Neoadjuvant, Adj: Adjuvant, POART: Post-operative adjuvant radiotherapy, POACRT: Post-operative adjuvant chemoradiotherapy, Obs: Observation, HRPF: High risk pathologic features (i.e. extranodal extension and/or positive margins), pTR-2: Pathologic tumor response $\geq 50\%$, pts: participants

Table 2. Summary of studies evaluating pembrolizumab for patients with unresected LA HNSCC not amenable to primary surgery

NCT #/Study Name	Study Type	Experimental Arm	Control Arm	Sample Size	Primary Endpoint	Study Status
NCT03040999 ^{4,5} KEYNOTE-412	Randomized double-blinded placebo-controlled Phase III	Chemoradiotherapy with high dose cisplatin 100 mg/m ² q3W and pembro X3 doses Q3W given concurrently and pembro X14 doses Q3W given as maintenance	Chemoradiotherapy with high dose cisplatin 100 mg/m ² q3W and placebo X3 doses Q3W given concurrently and placebo X14 doses Q3W given as maintenance	Total: 804, Pembro arm: 402, Placebo arm: 402	EFS	Completed
NCT02707588 ⁶ PembroRad	Open-label randomized Phase II	Pembro-RT arm: RT+ 3 doses pembro Q3W (Note- patients were platinum ineligible)	Cetux+ RT arm: RT + weekly cetux	Total: 133 Cetux-RT: 66, Pembro-RT: 67	LRC Rate 15 months post RT	Completed

Legend: Pembro: Pembrolizumab, Cetux: Cetuximab, W: Weekly, EFS: Event-free survival, LRC: Locoregional control, PFS: Progression-free survival

In addition to the assessment of contribution of the treatment components to be provided in the ISE, the Sponsor has also conducted additional post-hoc exploratory analyses of EFS data from KEYNOTE-689 to assess the contribution of pembrolizumab in the neoadjuvant and adjuvant phases. These additional KEYNOTE-689 analyses will be included in Module 2.7.3. and suggest that participants may benefit from both pembrolizumab as neoadjuvant treatment and then continued as adjuvant treatment in combination with SoC RT $\pm$ cisplatin compared with purely neoadjuvant or adjuvant treatment.

FDA comments 2a-e: Request for additional data and exploratory descriptive analyses for KN689:

The Sponsor will provide the additional data and exploratory descriptive analyses requested by FDA in bullets a-d in the appropriate modules of the sBLA dossier.

Data from the PRO-CTCAE assessment were not collected as a part of this study; hence the Sponsor cannot include this analysis in the Assessment Aid.

No further discussion is required for Agency comments in Question 2 a-e.

Discussion during the 11/25/2024 meeting: FDA stated that Merck's proposal for the ISE appears acceptable.

3. The safety analysis included in Module 2.7.4 and the ISS for this sBLA will consist of a 4-column table format to facilitate review. The 4 columns in the table will contain:

- Column A: KN-689 pembrolizumab arm*
 - Column B: KN-689 SoC arm*
 - Column C: pembrolizumab HNSCC monotherapy pool
 - Column D: US pembrolizumab monotherapy RSD
- * comparisons based on the combined safety analysis group, ie, neoadjuvant/surgery phase + adjuvant phase*

Does the Agency agree with this approach to presenting the safety data in the Module 2.7.4 and ISS?

FDA Response: While your proposal for a 4-column table is generally acceptable, we request that you provide additional safety data in the ISS. Please additionally provide topline data and a summary of results from any other clinical trials, including descriptive investigator-initiated trials exploring pembrolizumab as part of adjuvant and/or neoadjuvant therapy for locally advanced HNSCC to help facilitate our overall benefit:risk assessment.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's comment. The Sponsor will provide, as requested, additional descriptive safety summaries in the ISS which will consist of available safety results from those studies identified for inclusion in the ISE.

No further discussion is required.

Discussion during the 11/25/2024 meeting: FDA stated that Merck's proposal for the ISS appears acceptable.

4. A Study Data Standardization Plan (SDSP) in support of the development program and Registration of pembrolizumab as perioperative treatment for patients with LA HNSCC as described in Question 1 will be included in Module 1.20 of the eCTD.

Is the Agency in agreement with the SDSP?

FDA Response: Yes, the study data standardization plan (SDSP) appears acceptable. Please refer to page 4 of the FDA Study Data Technical Conformance Guide: <https://www.fda.gov/media/153632/download>.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's comment. No further discussion is required.

Discussion during the 11/25/2024 meeting: No discussion occurred.

5. Does the Agency agree with the Sponsor's plan to submit a 90-day Safety Update Report?

FDA Response: Yes, this appears acceptable.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's comment. No further discussion is required.

Discussion during the 11/25/2024 meeting: No discussion occurred.

6. The Sponsor proposes to provide narratives in the CSR for all participants who were enrolled and treated in KEYNOTE-689 and who had any of the following events as of the data cutoff date:
1. Deaths not related to PD
 2. Drug Related SAEs
 3. AE leading to permanent treatment discontinuation
 4. AEOSI (Grade 2 and above, for hypothyroidism Grade 3 and above)

Does the Agency agree with the Sponsor's approach to the provision of narratives in the IA CSR and for future CSR(s) for the KEYNOTE-689 study?

FDA Response: In general, this appears acceptable; however we request additional narratives and CRF's for the following adverse events, regardless of the investigator's or sponsor's causality assessment:

- All deaths on study or within 90 days of the last dose of study treatment. Please flag the narratives for fatal adverse events which are not attributed to disease progression.
- All serious adverse events (SAE) occurring during treatment or within 90 days of the last dose of study treatment.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's comment and will provide the additional narratives requested. No further discussion is required.

Discussion during the 11/25/2024 meeting: No discussion occurred.

7. Based on the results from KEYNOTE-689 and the existing unmet medical need in the target population, Merck would like to request participation in Project ORBIS to allow simultaneous review or sharing of FDA review document with other health authorities.

Does the Agency agree to participation in Project ORBIS based on the IA1 results of KEYNOTE-689?

FDA Response: Yes, we agree that this sBLA may be reviewed under Project ORBIS. Please send in your global submission plan (template available on the Project Orbis website at: <https://www.fda.gov/media/178535/download?attachment>). Once we have your plan, we will reach out to the ORBIS partners to confirm their participation.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's comment and will provide the global submission plan based on the FDA template in Module 1.11.3 of the CTD. No further discussion is required.

Discussion during the 11/25/2024 meeting: No discussion occurred.

Additional FDA Comments:

Clinical and Biostatistics

8. Provide a summary of enrollment by country for patients on KEYNOTE-689, including the number of US patients enrolled.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's additional comment. The enrollment by country will be included in Module 5.2. No further discussion is required.

Discussion during the 11/25/2024 meeting: No discussion occurred.

9. We will calculate the alpha boundaries for subsequent OS interim efficacy analysis based on the observed information fraction.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's additional comment. No further discussion is required.

Discussion during the 11/25/2024 meeting: No discussion occurred.

10. Whether the EFS results based on the censoring rules of the primary analysis or the sensitivity analysis would be more appropriate for the label will be a review issue.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's additional comment. No further discussion is required.

Discussion during the 11/25/2024 meeting: No discussion occurred.

11. Provide an anticipated timeline for the protocol-specified primary analyses of OS comparing the pembrolizumab group to the SoC group.

Merck's 11/22/24 email response: The prespecified timing of Interim Analysis 2 (IA2) for OS will occur when ~187 deaths in the CS $\geq$ 10 population have been observed and ~22 months after the last participant randomized (Section 3.7.1 in sSAP). If the events accrue slower than expected, the analysis can be delayed up to 3 months. The Sponsor anticipates the IA2 data cut-off will occur as early as 25-AUG-2025, but no later than 25-NOV-2025. It is expected the topline results will be available between November 2025 and February 2026.

No further discussion is required.

Discussion during the 11/25/2024 meeting: No discussion occurred.

12. KEYNOTE-689 did not evaluate the contribution of the neoadjuvant and adjuvant phases of therapy with pembrolizumab for patients with resectable HNSCC and there is concern for potential overtreatment, particularly in the adjuvant phase. An assessment of the effect of each phase of therapy is necessary to better characterize the relative contribution of these phases to the overall outcomes with the perioperative regimen.

Provide an integrated analysis of completed, ongoing, and planned trials of perioperative pembrolizumab for patients with resectable HNSCC to evaluate the contribution of phase of pembrolizumab when given as neoadjuvant treatment, as adjuvant treatment concurrent with standard of care adjuvant radiation with or without platinum chemotherapy, and as single agent adjuvant treatment after other treatments are completed. This analysis should include data from the KEYNOTE-412 and GORTEC 2015-01 trials and any updated data from the KEYCHAIN trial. This analysis should also include an evaluation of safety, including immune mediated adverse reactions that occur during each phase of treatment.

Include also, as proposed in the Type B pre-sBLA Meeting Package, the unstratified subgroup analysis of EFS in patients who have and have not achieved a pathologic response to explore the contribution of neoadjuvant pembrolizumab to treatment efficacy. Provide any additional analyses from KEYNOTE-689 that provide justification for each phase of pembrolizumab therapy.

Merck's 11/22/24 email response: The Sponsor acknowledges FDA's additional comment.

As requested, the Sponsor will provide descriptive summaries consisting of the studies referenced in Question 2 in order to evaluate the contribution of phase of pembrolizumab when given as neoadjuvant treatment, as adjuvant treatment

concurrent with standard of care adjuvant radiation with or without platinum chemotherapy, and as single agent adjuvant treatment after other treatments are completed. The Sponsor would like to clarify that the only data currently available for the KEYCHAIN trial are the results of the lead-in phase published and presented in 2019⁷. The ADRISK trial is an ongoing randomized open-label phase II comparing adjuvant pembrolizumab plus post-operative chemoradiotherapy with cisplatin versus post-operative chemoradiotherapy with cisplatin for patients with resectable LA HNSCC who have undergone surgery and are found to have intermediate or high-risk pathologic features. This trial evaluates adjuvant only pembrolizumab but cannot be included in this analysis at this time because the trial is ongoing and the primary analysis has not been completed. As stated in the response to Question 2, the Sponsor does not have direct access to the patient-level data for this or other investigator-initiated trials evaluating pembrolizumab.

Therefore, this descriptive summary will not include the ADRISK and KEYCHAIN trials. The analysis will include the following:

- Trials evaluating pembrolizumab as perioperative treatment for patients with resectable LA HNSCC (NCT02296684, and NCT02641093).
- Trials evaluating pembrolizumab for patients with unresected LA HNSCC (i.e. not amenable to primary surgery) requiring definitive CRT or RT (NCT03040999, and NCT02707588).

In addition, the Sponsor has conducted post-hoc exploratory analyses of EFS data from KEYNOTE-689 to assess the contribution of pembrolizumab in the neoadjuvant and adjuvant phases. These additional KEYNOTE-689 analyses will be included in Module 2.7.3.

Discussion during the 11/25/2024 meeting: FDA acknowledged Merck's response. FDA stated that the proposed information, including Merck's post-hoc exploratory analyses from KN-689, will be considered during the sBLA review. FDA stated that all of the data will be considered in the context of the KN-689 study results and the overall risk-benefit assessment for the proposed indication. FDA stated that if the ADRISK trial results were to become available during the sBLA review, Merck should submit topline results to the sBLA.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for

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the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

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FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.⁴

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁵

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <http://www.fda.gov/ectd>

⁵ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR⁶: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid⁷

SPLIT REAL TIME APPLICATION REVIEW (STAR) PILOT PROGRAM

The FDA is conducting a pilot program, the Split Real Time Application Review (STAR). STAR is a pilot review process allowing earlier patient access to therapies that address an unmet medical need via interactive engagement with the application so that review and analysis of data may commence prior to full supplemental new drug application (sNDA)/supplemental biologics license application (sBLA) submission. An applicant can communicate interest in participating in this pilot program to the FDA review division by submitting a STAR Entry Request if the applicant believes a proposed efficacy supplement fulfills the conditions outlined in the eligibility criteria. Those applicants who do not wish to participate in the pilot program will follow the usual submission process

⁶ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

⁷ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

with no impact on review timelines. More information on this pilot program, including eligibility criteria and timelines, can be found at the FDA website for STAR.⁸

⁸ <https://www.fda.gov/drugs/development-resources/split-real-time-application-review-star>
U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

ISSUES REQUIRING FURTHER DISCUSSION

Please refer to meeting minutes.

ACTION ITEMS

Please refer to meeting minutes

ATTACHMENTS AND HANDOUTS

KN689 IAI Type B pre-sBLA Response to prelim comments.pdf

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ORIGINAL



Background:

Reference is made to protocol KEYNOTE-689 (KN689) “A Phase III, Randomized, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant Therapy and in Combination With Standard of Care as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)”. KN689 was initially submitted to IND 122325 by Merck Sharp & Dohme LLC (Merck) on September 6, 2017 (Seq. No. 0563).

A Type B pre-sBLA Meeting Request was submitted to IND 122325 on September 26, 2024 (Seq. No. 0837) for a meeting to discuss acceptability of the efficacy and safety results from KN689 IA1 to support evaluation of an sBLA to add pembrolizumab in combination with SoC as a new perioperative indication for LA HNSCC to the USPI for KEYTRUDA.

Further reference is made to the informal meeting on October 3, 2024 between Merck and the FDA to discuss the initial KN689 top-line results for IA1 at which the Agency agreed with Merck’s plan to conduct a pre-sBLA meeting and submit a dossier based on the data.

Final references are made to the October 7, 2024 formal Meeting Request Granted letter (Reference ID: 5458840) in which the request for a Type B pre-sBLA virtual face-to-face video conference was granted for November 25, 2024 from 1:30PM – 2:30PM ET, and to the October 23, 2024 submission to IND 122325 of background materials in support of the meeting (Seq. No. 0841).

FDA’s Meeting Correspondence dated November 20, 2024 (Reference ID: 5482815) provided the Agency’s Preliminary Meeting Comments to the questions included in the background materials. Based on FDA’s preliminary responses, the Sponsor would like to move forward with the meeting. The Sponsor is providing responses to the Agency feedback below with discussion sought on FDA’s comments for Question 2, as well as FDA additional comment 12.

It is noted that the original timing indicated in the Meeting Request Granted letter and the FDA Preliminary Meeting Comments for the meeting from 1:30 - 2:30PM 25-Nov-2024 is incorrect. The actual meeting time is 1:00 - 2:00 PM on 25-Nov-2024. It is expected this will be reflected in the final meeting minutes.

APPEARS THIS WAY ON
ORIGINAL

QUESTION 1:

Does the Agency agree that the efficacy and safety data from Interim Analysis 1 (IA1) from KN689 in this patient population are sufficient to support evaluation of an sBLA for pembrolizumab for the treatment of patients with resectable locoregionally advanced HNSCC as neoadjuvant treatment, then continued as adjuvant treatment in combination with radiation with or without cisplatin chemotherapy, followed by pembrolizumab monotherapy.

FDA RESPONSE TO QUESTION 1:

The efficacy and safety data from Interim Analysis 1 of Study KEYNOTE-689 appear acceptable to support the filing of a marketing application. A final determination regarding filing of the sBLA will be made after review of the contents of the submitted application. Whether the efficacy and safety results indicate a favorable benefit/risk profile and support approval of the sBLA in the proposed patient population will be determined during review of the marketing application.

COMPANY RESPONSE 1:

The Sponsor acknowledges FDA's comment. No further discussion is required.

QUESTION 2:

The Sponsor is planning to submit a dossier consisting of the KEYNOTE-689 CSR as the pivotal study. Additionally, Merck is planning to provide Modules 2.2, 2.5, 2.7.3, 2.7.4, 5.2, an ISS (Module 5.3.5.3), and an Assessment Aid. Since the submission is based on a single pivotal study (KEYNOTE-689), no ISE will be included except for a reference page to that effect. Modules 2.7.1 and 2.7.2 in the existing lifecycle are considered current and will be referenced in the planned sBLA submission. Module 5.2 will be included to support Applicability of Foreign Data in review of the application.

Does the Agency agree that a dossier with these components would be acceptable to support evaluation of the sBLA?

FDA RESPONSE TO QUESTION 2:

The proposed components for a dossier are generally acceptable with one exception. An Integrated Summary of Efficacy (ISE) is required in applications submitted to the FDA in accordance with 21 CFR 314.50(d)(5)(v) and an ISE should be included for this sBLA. In the sBLA, please include an ISE that provides topline data from any other clinical trials, including descriptive investigator-initiated trials exploring pembrolizumab as part of adjuvant and/or neoadjuvant therapy for locally advanced HNSCC, particularly for resectable disease. The ISE may also include data from trials of pembrolizumab for locally advanced HNSCC treated with definitive radiation or chemoradiation. These data may be helpful in our overall benefit:risk assessment as well as our assessment of the inclusion of both the neoadjuvant and adjuvant components of the investigational therapy, particularly as KEYNOTE-689 does not isolate the contribution of effect of these treatment components.

We also request these additional data and exploratory descriptive analyses:

- a. Data on time intervals between all treatment phases. For each patient and averaged for each treatment arm, please provide time intervals for:
 - o Randomization to surgery or neoadjuvant pembrolizumab
 - o Neoadjuvant pembrolizumab to surgery
 - o Surgery to RT with or without cisplatin
 - o RT with or without cisplatin to adjuvant pembrolizumab
- b. For both treatment arms, provide mPR and EFS results by N stage, T stage, primary tumor site, and HPV status for oropharyngeal tumors.
- c. For patients receiving chemoradiation therapy, provide the average number of cycles received and average total exposure of cisplatin for each treatment arm.
- d. For all patients, provide information on these baseline characteristics for each treatment arm:
 - o Status of surgical margins and definition of clear margins
 - o Classification of surgical resection as R0, R1, or R2

e. Please provide PRO-CTCAE results in a stacked bar chart form within or as an appendix to the assessment aid.

COMPANY RESPONSE 2:

The Sponsor acknowledges FDA's comment and would like to discuss the Sponsor's plan for the ISE as summarized below.

The Sponsor will prepare and provide an ISE as requested which incorporates KN689, as well as descriptive summaries of the following trials evaluating pembrolizumab in combination with definitive treatment for patients with either resectable LA HNSCC or unresected LA HNSCC that have completed the primary efficacy analysis. The Sponsor would like to clarify that investigator-initiated trials supported through the Merck Investigator Studies program which evaluate pembrolizumab will be based on the available published data because the Sponsor does not have direct access to these data. Table 1 includes a summary of clinical trials the Sponsor plans to include in the ISE evaluating perioperative pembrolizumab for patients with resectable LA HNSCC. Table 2 includes a summary of clinical trials the Sponsor plans to include in the ISE evaluating pembrolizumab in combination with CRT or RT for patients with unresected LA HNSCC not amenable to primary surgery.

Table 1. Summary of studies evaluating perioperative pembrolizumab for patients with resectable LA HNSCC

NCT #/Study name	Study Type	Experimental Arm Treatment	Control Arm Treatment	Sample Size	Primary Endpoint	Study Status
NCT02296684 ^{1,2}	Single-Arm Multi-Cohort Phase II	Group 1: 1 dose of NA pembro, HRPf present: POACRT followed by adj pembro X6 doses Q3W, HRPf absent: POART or Obs Group 2: 2 doses of NA pembro, POART or POACRT or obs (no Adj pembro administered)	N/A	Group 1: 36 Group 2: 31	Co-primary: 1-year Relapse rate for pts with HRPf, pTR-2 rate	Primary Efficacy Analysis Completed
NCT02641093 ³	Single-Arm Phase II	1 dose of NA Pembro, HRPf present: Adj PembroX6 doses Q3W + POACRT HRPf absent: Adj PembroX6 doses Q3W + POART	N/A	96	1-yr DFS	Primary Efficacy Analysis Completed

Legend: Pembro: Pembrolizumab, NA: Neoadjuvant, Adj: Adjuvant, POART: Post-operative adjuvant radiotherapy, POACRT: Post-operative adjuvant chemoradiotherapy, Obs: Observation, HRPf: High risk pathologic features (i.e. extranodal extension and/or positive margins), pTR-2: Pathologic tumor response $\geq 50\%$, pts: participants

¹ <https://pmc.ncbi.nlm.nih.gov/articles/PMC7547532/>

² https://ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.6008

³ <https://pmc.ncbi.nlm.nih.gov/articles/PMC8976828/>

Table 2. Summary of studies evaluating pembrolizumab for patients with unresected LA HNSCC not amenable to primary surgery

NCT #/Study Name	Study Type	Experimental Arm	Control Arm	Sample Size	Primary Endpoint	Study Status
NCT03040999 ^{4,5} KEYNOTE-412	Randomized double-blinded placebo-controlled Phase III	Chemoradiotherapy with high dose cisplatin 100 mg/m ² q3W and pembro X3 doses Q3W given concurrently and pembro X14 doses Q3W given as maintenance	Chemoradiotherapy with high dose cisplatin 100 mg/m ² q3W and placebo X3 doses Q3W given concurrently and placebo X14 doses Q3W given as maintenance	Total: 804, Pembro arm: 402, Placebo arm: 402	EFS	Completed
NCT02707588 ⁶ PembroRad	Open-label randomized Phase II	Pembro-RT arm: RT+ 3 doses pembro Q3W (Note- patients were platinum ineligible)	Cetux+ RT arm: RT + weekly cetux	Total: 133 Cetux-RT: 66, Pembro-RT: 67	LRC Rate 15 months post RT	Completed

Legend: Pembro: Pembrolizumab, Cetux: Cetuximab, W: Weekly, EFS: Event-free survival, LRC: Locoregional control, PFS: Progression-free survival

In addition to the assessment of contribution of the treatment components to be provided in the ISE, the Sponsor has also conducted additional post-hoc exploratory analyses of EFS data from KEYNOTE-689 to assess the contribution of pembrolizumab in the neoadjuvant and adjuvant phases. These additional KEYNOTE-689 analyses will be included in Module 2.7.3. and suggest that participants may benefit from both pembrolizumab as neoadjuvant treatment and then continued as adjuvant treatment in combination with SoC RT ± cisplatin compared with purely neoadjuvant or adjuvant treatment.

FDA comments 2a-e: Request for additional data and exploratory descriptive analyses for KN689:

The Sponsor will provide the additional data and exploratory descriptive analyses requested by FDA in bullets a-d in the appropriate modules of the sBLA dossier.

Data from the PRO-CTCAE assessment were not collected as a part of this study; hence the Sponsor cannot include this analysis in the Assessment Aid.

No further discussion is required for Agency comments in Question 2 a-e.

⁴ <https://pubmed.ncbi.nlm.nih.gov/38561010/>

08QFDY ⁵ <https://clinicaltrials.gov/study/NCT03040999?term=NCT03040999&rank=1&tab=results>

⁶ <https://pubmed.ncbi.nlm.nih.gov/36522816/>

QUESTION 3:

The safety analysis included in Module 2.7.4 and the ISS for this sBLA will consist of a 4-column table format to facilitate review. The 4 columns in the table will contain:

- Column A: KN-689 pembrolizumab arm*
- Column B: KN-689 SoC arm*
- Column C: pembrolizumab HNSCC monotherapy pool
- Column D: US pembrolizumab monotherapy RSD

** comparisons based on the combined safety analysis group, ie, neoadjuvant/surgery phase + adjuvant phase*

Does the Agency agree with this approach to presenting the safety data in the Module 2.7.4 and ISS?

FDA RESPONSE TO QUESTION 3:

While your proposal for a 4-column table is generally acceptable, we request that you provide additional safety data in the ISS. Please additionally provide topline data and a summary of results from any other clinical trials, including descriptive investigator-initiated trials exploring pembrolizumab as part of adjuvant and/or neoadjuvant therapy for locally advanced HNSCC to help facilitate our overall benefit:risk assessment.

COMPANY RESPONSE 3:

The Sponsor acknowledges FDA's comment. The Sponsor will provide, as requested, additional descriptive safety summaries in the ISS which will consist of available safety results from those studies identified for inclusion in the ISE.

No further discussion is required.

QUESTION 4:

A Study Data Standardization Plan (SDSP) in support of the development program and registration of pembrolizumab as perioperative treatment for patients with LA HNSCC as described in Question 1 will be included in Module 1.20 of the eCTD.

Is the Agency in agreement with the SDSP?

FDA RESPONSE TO QUESTION 4:

Yes, the study data standardization plan (SDSP) appears acceptable. Please refer to page 4 of the FDA Study Data Technical Conformance Guide:

<https://www.fda.gov/media/153632/download>.

COMPANY RESPONSE 4:

The Sponsor acknowledges FDA's comment. No further discussion is required.

APPEARS THIS WAY ON
ORIGINAL

QUESTION 5:

Does the Agency agree with the Sponsor's plan to submit a 90-day Safety Update Report?

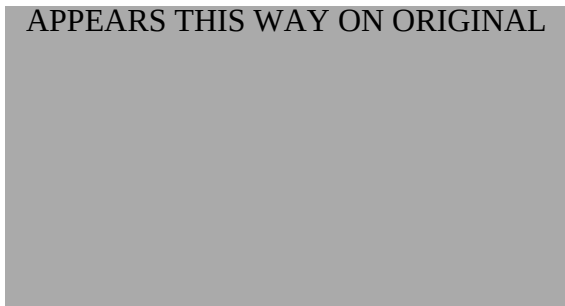
FDA RESPONSE TO QUESTION 5:

Yes, this appears acceptable.

COMPANY RESPONSE 5:

The Sponsor acknowledges FDA's comment. No further discussion is required.

APPEARS THIS WAY ON ORIGINAL



QUESTION 6:

The Sponsor proposes to provide narratives in the CSR for all participants who were enrolled and treated in KEYNOTE-689 and who had any of the following events as of the data cutoff date:

1. Deaths not related to PD
2. Drug Related SAEs
3. AE leading to permanent treatment discontinuation
4. AEOSI (Grade 2 and above, for hypothyroidism Grade 3 and above)

Does the Agency agree with the Sponsor's approach to the provision of narratives in the IA CSR and for future CSR(s) for the KEYNOTE-689 study?

FDA RESPONSE TO QUESTION 6:

In general, this appears acceptable; however, we request additional narratives and CRF's for the following adverse events, regardless of the investigator's or sponsor's causality assessment:

- o All deaths on study or within 90 days of the last dose of study treatment. Please flag the narratives for fatal adverse events which are not attributed to disease progression.
- o All serious adverse events (SAE) occurring during treatment or within 90 days of the last dose of study treatment.

COMPANY RESPONSE 6:

The Sponsor acknowledges FDA's comment and will provide the additional narratives requested.

No further discussion is required.

APPEARS THIS WAY ON
ORIGINAL

QUESTION 7:

Based on the results from KEYNOTE-689 and the existing unmet medical need in the target population, Merck would like to request participation in Project ORBIS to allow simultaneous review or sharing of FDA review document with other health authorities.

Does the Agency agree to participation in Project ORBIS based on the IA1 results of KEYNOTE-689?

FDA RESPONSE TO QUESTION 7:

Yes, we agree that this sBLA may be reviewed under Project ORBIS. Please send in your global submission plan (template available on the Project Orbis website at:

<https://www.fda.gov/media/178535/download?attachment>).

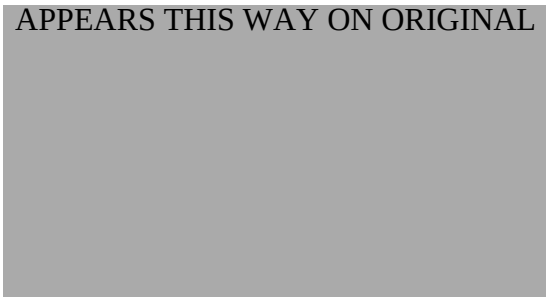
Once we have your plan, we will reach out to the ORBIS partners to confirm their participation.

COMPANY RESPONSE 7:

The Sponsor acknowledges FDA's comment and will provide the global submission plan based on the FDA template in Module 1.11.3 of the CTD.

No further discussion is required.

APPEARS THIS WAY ON ORIGINAL



ADDITIONAL FDA QUESTIONS/COMMENTS: CLINICAL AND BIOSTATISTICS

FDA ADDITIONAL COMMENT 8:

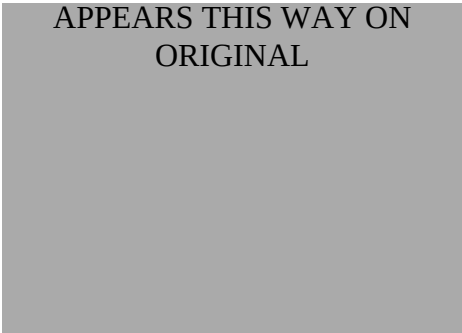
Provide a summary of enrollment by country for patients on KEYNOTE-689, including the number of US patients enrolled.

COMPANY RESPONSE TO FDA ADDITIONAL COMMENT 8:

The Sponsor acknowledges FDA's additional comment. The enrollment by country will be included in Module 5.2.

No further discussion is required.

APPEARS THIS WAY ON
ORIGINAL



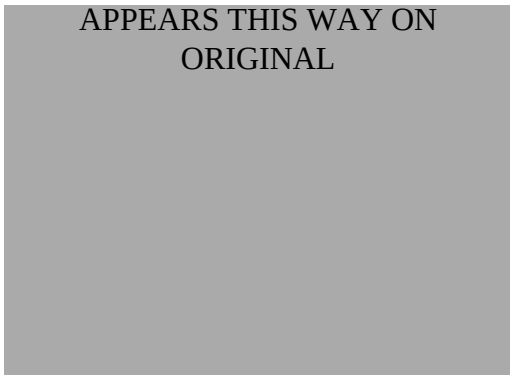
FDA ADDITIONAL COMMENT 9:

We will calculate the alpha boundaries for subsequent OS interim efficacy analysis based on the observed information fraction.

COMPANY RESPONSE TO FDA ADDITIONAL COMMENT 9:

The Sponsor acknowledges FDA's additional comment. No further discussion is required.

APPEARS THIS WAY ON
ORIGINAL



FDA ADDITIONAL COMMENT 10:

Whether the EFS results based on the censoring rules of the primary analysis or the sensitivity analysis would be more appropriate for the label will be a review issue.

COMPANY RESPONSE TO FDA ADDITIONAL COMMENT 10:

The Sponsor acknowledges FDA's additional comment. No further discussion is required.

APPEARS THIS WAY ON
ORIGINAL

FDA ADDITIONAL COMMENT 11:

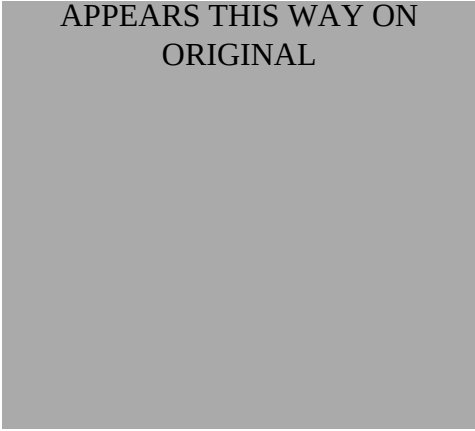
Provide an anticipated timeline for the protocol-specified primary analyses of OS comparing the pembrolizumab group to the SoC group.

COMPANY RESPONSE TO FDA ADDITIONAL COMMENT 11:

The prespecified timing of Interim Analysis 2 (IA2) for OS will occur when ~187 deaths in the CPS $\geq$ 10 population have been observed and ~22 months after the last participant randomized (Section 3.7.1 in sSAP). If the events accrue slower than expected, the analysis can be delayed up to 3 months. The Sponsor anticipates the IA2 data cut-off will occur as early as 25-AUG-2025, but no later than 25-NOV-2025. It is expected the topline results will be available between November 2025 and February 2026.

No further discussion is required.

APPEARS THIS WAY ON
ORIGINAL



FDA ADDITIONAL COMMENT 12:

KEYNOTE-689 did not evaluate the contribution of the neoadjuvant and adjuvant phases of therapy with pembrolizumab for patients with resectable HNSCC and there is concern for potential overtreatment, particularly in the adjuvant phase. An assessment of the effect of each phase of therapy is necessary to better characterize the relative contribution of these phases to the overall outcomes with the perioperative regimen.

Provide an integrated analysis of completed, ongoing, and planned trials of perioperative pembrolizumab for patients with resectable HNSCC to evaluate the contribution of phase of pembrolizumab when given as neoadjuvant treatment, as adjuvant treatment concurrent with standard of care adjuvant radiation with or without platinum chemotherapy, and as single agent adjuvant treatment after other treatments are completed. This analysis should include data from the KEYNOTE-412 and GORTEC 2015-01 trials and any updated data from the KEYCHAIN trial. This analysis should also include an evaluation of safety, including immune mediated adverse reactions that occur during each phase of treatment.

Include also, as proposed in the Type B pre-sBLA Meeting Package, the unstratified subgroup analysis of EFS in patients who have and have not achieved a pathologic response to explore the contribution of neoadjuvant pembrolizumab to treatment efficacy. Provide any additional analyses from KEYNOTE-689 that provide justification for each phase of pembrolizumab therapy.

COMPANY RESPONSE TO FDA ADDITIONAL COMMENT 12:

The Sponsor acknowledges FDA's additional comment.

As requested, the Sponsor will provide descriptive summaries consisting of the studies referenced in Question 2 in order to evaluate the contribution of phase of pembrolizumab when given as neoadjuvant treatment, as adjuvant treatment concurrent with standard of care adjuvant radiation with or without platinum chemotherapy, and as single agent adjuvant treatment after other treatments are completed. The Sponsor would like to clarify that the only data currently available for the KEYCHAIN trial are the results of the lead-in phase published and presented in 2019⁷. The ADRISK trial is an ongoing randomized open-label phase II comparing adjuvant pembrolizumab plus post-operative chemoradiotherapy with cisplatin versus post-operative chemoradiotherapy with cisplatin for patients with resectable LA HNSCC who have undergone surgery and are found to have intermediate or high-risk pathologic features. This trial evaluates adjuvant only pembrolizumab but cannot be included in this analysis at this time because the trial is ongoing and the primary analysis has not been completed. As stated in the response to Question 2, the Sponsor does not have direct access to the patient-level data for this or other investigator-initiated trials evaluating pembrolizumab. Therefore, this descriptive summary will not include the ADRISK and KEYCHAIN trials. The analysis will include the following:

- Trials evaluating pembrolizumab as perioperative treatment for patients with resectable LA HNSCC (NCT02296684, and NCT02641093).

- Trials evaluating pembrolizumab for patients with unresected LA HNSCC (i.e. not amenable to primary surgery) requiring definitive CRT or RT (NCT03040999, and NCT02707588).

In addition, the Sponsor has conducted post-hoc exploratory analyses of EFS data from KEYNOTE-689 to assess the contribution of pembrolizumab in the neoadjuvant and adjuvant phases. These additional KEYNOTE-689 analyses will be included in Module 2.7.3.

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/

OPEYEMI O UDOKA
12/23/2024 01:12:27 PM