CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s052

Trade Name:	KEYTRUDA
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp & Dohme Corp.
Approval Date:	June 10, 2019
Indication:	KEYTRUDA is a programmed death receptor-1 (PD-1)-blocking antibody indicated: Melanoma • for the treatment of patients with unresectable or metastatic melanoma. • for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. Non-Small Cell Lung Cancer (NSCLC) • in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC. • as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is: o stage III where patients are not candidates for surgical resection or definitive chemoradiation, or o metastatic. • as a single agent for the treatment of patients with metastatic

NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

Head and Neck Squamous Cell Cancer (HNSCC)

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

Classical Hodgkins Lymphoma (cHL)

- for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.[1]

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.[1]
- Limitations of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urotherial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[1]
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Microsatellite Instability-High Cancer

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

Gastric Cancer

- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two ro more prior lines of therapy including fluropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1]

Cervical Cancer

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

Hepatocellular Carcinoma (HCC)

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

Merkel Cell Carcinoma (MCC)

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

Renal Cell Carcinoma(RCC)

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s052

APPROVAL LETTER

BLA 125514/S-52

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Merck Sharp & Dohme Corp.
Attention: Seema Betigeri, Ph.D.
Director, Global Regulatory Affairs
126 E. Lincoln Ave., P.O. Box 2000
RY34-B293
Rahway, NJ 07065

Dear Dr. Betigeri:

Please refer to your supplemental biologics license application (sBLA), dated December 10, 2018, received December 10, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for KEYTRUDA (pembrolizumab) for injection, for intravenous use, 50 mg and for KEYTRUDA (pembrolizumab) injection, for intravenous use, 100 mg/4mL.

This Prior Approval supplemental biologics application provides for modifications of the approved indication for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy approved on August 5, 2016, under the provisions of 21 CFR 601.41, to remove the following language (italicized) that *This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.*

This supplement also provides for the following new indications:

- KEYTRUDA, in combination with platinum and fluorouracil (FU), for the first line treatment of patients with metastatic or with unresectable, recurrent HNSCC.

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

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling text for the Prescribing Information, and Medication Guide and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART E FULFILLED

We approved BLA 125514/S-9 under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills the following post marketing requirement (PMR) made under 21 CFR 601.41:

PMR #3100-1 Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of pembrolizumab over available therapy as determined by an improvement in overall survival in patients with metastatic squamous cell carcinoma of the head and neck.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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

You are no longer required to report on this requirement.

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 the necessary studies are impossible or highly impracticable as head and neck squamous cell carcinoma does not occur in children.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3625-1 Submit the clinical report and datasets for the final analysis of overall survival (OS) in the intent-to-treat (ITT) population (all patients regardless of tumor PD-L1 status) for the comparison of pembrolizumab as a single agent to the control arm in study KEYNOTE-048, “A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma”, to inform labeling.

In addition, provide updated results for OS in the ITT population for the comparison of pembrolizumab and chemotherapy to the control arm in the KEYNOTE-048 study based upon the protocol-specified timing for the final analysis of OS for this comparison to better characterize survival differences at late time points to inform labeling.

The timetable you submitted on May 30, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: July 2019

Submit 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 entered into each study/trial. All submissions, including supplements, relating to these

postmarketing commitments should be prominently labeled “Postmarketing Commitment Final Report” or “Postmarketing Commitment Correspondence.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

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

[3] When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

If you have any questions, please call Sharon Sickafuse, Senior Regulatory Health Project Manager, at 301-796-2320 or email sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
- Prescribing Information
- Medication Guide

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

/s/

PATRICIA KEEGAN
06/10/2019 04:02:03 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s052

LABELING

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

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

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

Indications and Usage (1)	06/2019
Dosage and Administration (2)	06/2019
Warnings and Precautions (5)	06/2019

----------INDICATIONS AND USAGE----------

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

Melanoma

- for the treatment of patients with unresectable or metastatic melanoma. (1.1)
- for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. (1.1)

Non-Small Cell Lung Cancer (NSCLC)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.2)
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC. (1.2)
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic. (1.2, 2.1)
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. (1.2, 2.1)

Head and Neck Squamous Cell Cancer (HNSCC)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC. (1.3)
- as a single agent for the first line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test. (1.3, 2.1)
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. (1.3)

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.[1] (1.4)

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.[1] (1.5)
- Limitations of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[1] (1.6, 2.1)
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.6)

Microsatellite Instability-High Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
  - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options,[1] or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1] (1.7)
- Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established. (1.7)

Gastric Cancer

- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1] (1.8, 2.1)

Cervical Cancer

- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.[1] (1.9, 2.1)

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC who have been previously treated with sorafenib.[1] (1.10)

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1] (1.11)

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of patients with advanced RCC. (1.12)

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

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

- Melanoma: 200 mg every 3 weeks. (2.2)
- NSCLC: 200 mg every 3 weeks. (2.3)
- HNSCC: 200 mg every 3 weeks. (2.4)
- cHL or PMBCL: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.5, 2.6)
- Urothelial Carcinoma: 200 mg every 3 weeks. (2.7)
- MSI-H Cancer: 200 mg every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.8)
- Gastric Cancer: 200 mg every 3 weeks. (2.9)
- Cervical Cancer: 200 mg every 3 weeks. (2.10)
- HCC: 200 mg every 3 weeks. (2.11)
- MCC: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.12)
- RCC: 200 mg every 3 weeks with axitinib 5 mg orally twice daily. (2.13)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

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

- For injection: 50 mg lyophilized powder in single-dose vial for reconstitution (3)
- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-dose vial (3)

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

None. (4)

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

- Immune-mediated pneumonitis: Withhold for moderate, and permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated hepatitis (KEYTRUDA) and hepatotoxicity (KEYTRUDA in combination with axitinib): Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA, axitinib, or KEYTRUDA and axitin b. Consider corticosteroid therapy. (2.14, 5.3)
- Immune-mediated endocrinopathies (5.4):
  - Hypophysitis: Withhold for moderate and withhold or permanently discontinue for severe or life-threatening hypophysitis.
  - Thyroid disorders: Monitor for changes in thyroid function. Withhold or permanently discontinue for severe or life-threatening hyperthyroidism.
  - Type 1 diabetes mellitus: Monitor for hyperglycemia. Withhold KEYTRUDA in cases of severe hyperglycemia.
- Immune-mediated nephritis: Monitor for changes in renal function. Withhold for moderate, and permanently discontinue for severe or life-threatening nephritis. (5.5)
- Immune-mediated skin adverse reactions including, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): Withhold for severe and permanently discontinue for life-threatening skin reactions. (5.6)
- Other immune-mediated adverse reactions: In organ transplant recipients, consider the benefit of treatment with KEYTRUDA versus the risk of possible organ rejection. (5.7)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.8)
- Complications of allogeneic HSCT (5.9):
  - Allogeneic HSCT after treatment with KEYTRUDA: Monitor for hepatic veno-occlusive disease, grade 3-4 acute GVHD including hyperacute GVHD, steroid-requiring febrile syndrome, and other immune-mediated adverse reactions. Transplant-related mortality has occurred.
  - Allogeneic HSCT prior to treatment with KEYTRUDA: In patients with a history of allogeneic HSCT, consider the benefit of treatment with KEYTRUDA versus the risk of GVHD.
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking ant body in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.10)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective method of contraception. (5.11, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (reported in ≥20% of patients) were:

- KEYTRUDA as a single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. (6.1)
- KEYTRUDA in combination with chemotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, and stomatitis. (6.1)
- KEYTRUDA in combination with axitin b: diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

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

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

1.2 Non-Small Cell Lung Cancer

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test *[see Dosage and Administration (2.1)],* with no EGFR or ALK genomic tumor aberrations, and is:

- stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
- metastatic.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

1.3 Head and Neck Squamous Cell Cancer

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

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

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

1.4 Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.4)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.5 Primary Mediastinal Large B-Cell Lymphoma

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

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.5)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

1.6 Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14.6)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

1.7 Microsatellite Instability-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.7)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

1.8 Gastric Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.8)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.9 Cervical Cancer

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

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.9)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.10 Hepatocellular Carcinoma

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

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.10)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.11 Merkel Cell Carcinoma

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

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

1.12 Renal Cell Carcinoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, or Cervical Cancer

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

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.2)]*.
- metastatic NSCLC *[see Clinical Studies (14.2)].*
- first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.3)]*.
- metastatic urothelial carcinoma *[see Clinical Studies (14.6)]*.
- metastatic gastric cancer *[see Clinical Studies (14.8)]*. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.
- recurrent or metastatic cervical cancer *[see Clinical Studies (14.9)]*.

Information on FDA-approved tests for the detection of PD-L1 expression for these indications is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage for Melanoma

The recommended dose of KEYTRUDA in patients with unresectable or metastatic melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease recurrence, unacceptable toxicity, or for up to 12 months in patients without disease recurrence.

2.3 Recommended Dosage for NSCLC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

2.4 Recommended Dosage for HNSCC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

2.5 Recommended Dosage for cHL

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.6 Recommended Dosage for PMBCL

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.7 Recommended Dosage for Urothelial Carcinoma

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.8 Recommended Dosage for MSI-H Cancer

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.9 Recommended Dosage for Gastric Cancer

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

2.10 Recommended Dosage for Cervical Cancer

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

2.11 Recommended Dosage for HCC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

2.12 Recommended Dosage for MCC

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

2.13 Recommended Dosage for RCC

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with 5 mg axitinib orally twice daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months in patients without disease progression. When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer. See also the Prescribing Information for recommended axitinib dosing information.

2.14 Dose Modifications

No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage adverse reactions as described in Table 1.

Table 1: Recommended Dose Modifications for Adverse Reactions

[see Warnings and Precautions (5.1-5.9)]

Adverse Reaction	Severity*	Dose Modification for KEYTRUDA
Immune-mediated pneumonitis	Grade 2	Withhold†
	Grades 3 or 4 or recurrent Grade 2	Permanently discontinue
Immune-mediated colitis	Grades 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Immune-mediated hepatitis in patients with HCC	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 5 times upper limit of normal (ULN) if baseline less than 2 times ULN; AST or ALT greater than 3 times baseline if baseline greater than or equal to 2 times ULN Total bilirubin greater than 2.0 mg/dL if baseline less than 1.5 mg/dL; or Total bilirubin greater than 3.0 mg/dL, regardless of baseline levels	Withhold‡
	ALT or AST greater than 10 times ULN; or Child-Pugh score greater than or equal to 9 points; Gastrointestinal bleeding suggestive of portal hypertension; or New onset of clinically detectable ascites; or encephalopathy	Permanently discontinue
Immune-mediated hepatitis in patients without HCC For liver enzyme elevations in RCC patients treated with combination therapy, see dosing guidelines following this table.	AST or ALT greater than 3 but no more than 5 times the ULN or total bilirubin greater than 1.5 but no more than 3 times the ULN	Withhold†
	In patients without liver metastases, AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN In patients with liver metastasis and Grade 2 AST or ALT at baseline, with an increase in AST or ALT of 50% or more relative to baseline that persists for at least 1 week	Permanently discontinue
Immune-mediated endocrinopathies	Grades 3 or 4	Withhold until clinically stable
Immune-mediated nephritis	Grade 2	Withhold†
	Grades 3 or 4	Permanently discontinue

Adverse Reaction	Severity*	Dose Modification for KEYTRUDA
Immune-mediated skin adverse reactions	Grade 3 or suspected Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
Other immune-mediated adverse reactions	Grades 2 or 3 based on the severity and type of reaction	Withhold†
	Grade 3 based on the severity and type of reaction or Grade 4	Permanently discontinue
Recurrent immune-mediated adverse reactions	Recurrent Grade 2 pneumonitis Recurrent Grades 3 or 4	Permanently discontinue
Inability to taper corticosteroid	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks after last dose of KEYTRUDA	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathy)	Grades 2 or 3 adverse reactions lasting 12 weeks or longer after last dose of KEYTRUDA	Permanently discontinue
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4)
† Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper.
‡ Resume in HCC patients when AST or ALT and total bilirubin recover to Grades 0-1 or to baseline.

In patients with RCC being treated with KEYTRUDA in combination with axitinib:

- If ALT or AST ≥3 times ULN but <10 times ULN without concurrent total bilirubin ≥2 times ULN, withhold both KEYTRUDA and axitinib until these adverse reactions recover to Grades 0-1. Consider corticosteroid therapy. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib Prescribing Information.
- If ALT or AST ≥10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN, permanently discontinue both KEYTRUDA and axitinib and consider corticosteroid therapy.

2.15 Preparation and Administration

Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Reconstituted and Diluted Solutions

The product does not contain a preservative.
Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Discard after 6 hours at room temperature or after 24 hours under refrigeration.

Do not freeze.

Administration

- Administer diluted solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg white to off-white lyophilized powder in a single-dose vial for reconstitution
- Injection: 100 mg/4 mL (25 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.14) and Adverse Reactions (6.1)].*

In clinical studies enrolling 2799 patients with various cancers who received KEYTRUDA as a single agent, pneumonitis occurred in 94 (3.4%) patients, including Grade 1 (0.8%), Grade 2 (1.3%), Grade 3 (0.9%), Grade 4 (0.3%), and Grade 5 (0.1%) pneumonitis. The median time to onset was 3.3 months (range: 2 days to 19.3 months), and the median duration was 1.5 months (range: 1 day to 17.2+ months). Sixty-three (67%) of the 94 patients received systemic corticosteroids, with 50 of the 63 receiving high-dose corticosteroids for a median duration of 8 days (range: 1 day to 10.1 months) followed by a corticosteroid taper. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation (2.9%). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 (59%) of the 94 patients.

In clinical studies enrolling 790 patients with NSCLC who received KEYTRUDA as a single agent as first-line therapy for advanced disease, pneumonitis occurred in 65 (8.2%) patients, including Grades 3-4 in 3.2% of patients. Forty-eight of the 65 patients received high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days). Pneumonitis occurred in 17% of patients with a history of prior thoracic radiation and 7.7% of patients who did not receive prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 29 (3.7%) patients. Pneumonitis resolved in 51% of the patients.

In KEYNOTE-048 enrolling 300 patients with HNSCC who received KEYTRUDA as a single agent pneumonitis occurred in 18 (6%) patients, including Grade 3 (1.3%), Grade 4 (0%), and Grade 5 (0.3%). Eight of the 18 patients received high-dose corticosteroids for a median duration of 14 days (range: 1 to 77 days). Pneumonitis led to discontinuation of KEYTRUDA in 2 (0.7%) patients. Pneumonitis resolved in 12 (66%) of the patients. Pneumonitis occurred in 15 (5.4%) patients of 276 patients with HNSCC receiving KEYTRUDA in combination with platinum and FU as first-line therapy for advanced disease, including Grade 3 (1.1%), Grade 4 (0%), and Grade 5 (0.4%) pneumonitis. Four of the 15 patients received high-dose corticosteroids for a median duration of 16 days (range: 2 to 32 days). Pneumonitis led to discontinuation of KEYTRUDA in 5 (1.8%) patients. Pneumonitis resolved in 12 (80%) of the patients.

5.2 Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis *[see Dosage and Administration (2.14) and Adverse Reactions (6.1)].*

Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.4%), Grade 3 (1.1%), and Grade 4 (<0.1%) colitis. The median time to onset was 3.5 months (range: 10 days to 16.2 months), and the median duration was 1.3 months (range: 1 day to 8.7+ months). Thirty-three (69%) of the 48 patients received systemic corticosteroids, with 27 of the 33 requiring high-dose corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 (85%) of the 48 patients.

5.3 Immune-Mediated Hepatitis (KEYTRUDA) and Hepatotoxicity (KEYTRUDA in Combination with Axitinib)

Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA *[see Dosage and Administration (2.14) and Adverse Reactions (6.1)].*

Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.4%), and Grade 4 (<0.1%) hepatitis. The median time to onset was 1.3 months (range: 8 days to 21.4 months), and the median duration was 1.8 months (range: 8 days to 20.9+ months). Thirteen (68%) of the 19 patients received systemic corticosteroids, with 12 of the 13 receiving high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 (79%) of the 19 patients.

Hepatotoxicity in Combination with Axitinib

KEYTRUDA in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib and consider administering corticosteroids as needed *[see Dosage and Administration (2.14)]*.

With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. The median time to onset of increased ALT was 2.3 months (range: 7 days to 19.8 months). Sixty-one percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (3%) or axitinib (31%) administered as a single agent or with both (50%), 55% had no recurrence of ALT >3 times ULN.

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

KEYTRUDA can cause hypophysitis. Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis and withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.14) and Adverse Reactions (6.1)].*

Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), Grade 3 (0.3%), and Grade 4 (<0.1%) hypophysitis. The median time to onset was 3.7 months (range: 1 day to 11.9 months), and the median duration was 4.7 months (range: 8+ days to 12.7+ months). Sixteen (94%) of the 17 patients received systemic corticosteroids, with 6 of the 16 receiving high-dose corticosteroids. Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 (41%) of the 17 patients.

Thyroid Disorders

KEYTRUDA can cause thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism *[see Dosage and Administration (2.14) and Adverse Reactions (6.1)].*

Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and Grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months), and the median duration was 2.1 months (range: 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 (74%) of the 96 patients.

Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and Grade 3 (0.1%) hypothyroidism. The median time to onset was 3.5 months (range: 1 day to 18.9 months), and the median duration was not reached (range: 2 days to 27.7+ months). Hypothyroidism led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Hypothyroidism resolved in 48 (20%) of the 237 patients. The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC (16%) receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism.

Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. The median time of onset was 1.2 months (range: 0.5 to 3.5 months).

Type 1 Diabetes mellitus

KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia *[see Dosage and Administration (2.14) and Adverse Reactions (6.1)]*.

5.5 Immune-Mediated Nephritis and Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis *[see Dosage and Administration (2.14) and Adverse Reactions (6.1)].*

Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis. The median time to onset was 5.1 months (range: 12 days to 12.8 months), and the median duration was 3.3 months (range: 12 days to 8.9+ months). Eight (89%) of

the 9 patients received systemic corticosteroids, with 7 of the 8 receiving high-dose corticosteroids for a median duration of 15 days (range: 3 days to 4.0 months) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 (56%) of the 9 patients. Nephritis occurred in 1.7% of 405 patients receiving KEYTRUDA in combination with pemetrexed and platinum in the KEYNOTE-189 study, including Grade 3 (1%) and Grade 4 (0.5%) nephritis. The median time to onset was 3.2 months (range: 16 days to 11.1 months) and the duration ranged from 1.6 to 16.8+ months. Six (86%) of the 7 patients received systemic corticosteroids, with all 6 receiving high-dose corticosteroids for a median duration of 3 days (range: 1 to 17 days) followed by a corticosteroid taper. Nephritis led to discontinuation of KEYTRUDA in 5 (1.2%) patients. Nephritis resolved in 2 (29%) of the 7 patients.

5.6 Immune-Mediated Skin Adverse Reactions

Immune-mediated rashes, including SJS, TEN (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA *[see Dosage and Administration (2.14)].*

5.7 Other Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving KEYTRUDA. While immune-mediated adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, they may occur after discontinuation of treatment.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction *[see Dosage and Administration (2.14) and Adverse Reactions (6.1)].*

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients treated with KEYTRUDA: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other trials, including cHL, and post-marketing use.

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA versus the risk of possible organ rejection in these patients.

5.8 Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.14)]*.

5.9 Complications of Allogeneic HSCT

Allogeneic HSCT after treatment with KEYTRUDA

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA. Of 23 patients with

cHL who proceeded to allogeneic HSCT after treatment with KEYTRUDA on any trial, 6 patients (26%) developed graft-versus-host-disease (GVHD), one of which was fatal, and 2 patients (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning, one of which was fatal. Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

Allogeneic HSCT prior to treatment with KEYTRUDA

In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with KEYTRUDA. Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with KEYTRUDA. Consider the benefit of treatment with KEYTRUDA versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

5.10 Increased Mortality in Patients with Multiple Myeloma when KEYTRUDA is Added to a Thalidomide Analogue and Dexamethasone

In two randomized trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled trials.

5.11 Embryo-Fetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling.

- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)]*.
- Immune-mediated colitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated hepatitis (KEYTRUDA) and hepatotoxicity (KEYTRUDA in combination with axitinib) *[see Warnings and Precautions (5.3)]*.
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.4)]*.
- Immune-mediated nephritis and renal dysfunction *[see Warnings and Precautions (5.5)]*.
- Immune-mediated skin adverse reactions *[see Warnings and Precautions (5.6)]*.
- Other immune-mediated adverse reactions *[see Warnings and Precautions (5.7)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.8)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to KEYTRUDA as a single agent in 2799 patients in three randomized, open-label, active-controlled trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001), which enrolled 655 patients with melanoma and 550 patients with NSCLC. In addition to the 2799 patients, certain subsections in the WARNINGS AND PRECAUTIONS describe adverse reactions observed with exposure to KEYTRUDA as a single agent in two randomized, open-label, active-controlled clinical trials (KEYNOTE-042 and KEYNOTE-024), which

enrolled 790 patients with NSCLC; in a non-randomized, open-label, multi-cohort trial (KEYNOTE-012), a non-randomized, open-label, single-cohort trial (KEYNOTE-055), and two randomized, open-label, active-controlled trials (KEYNOTE-040 and KEYNOTE-048 single agent arms), which enrolled 909 patients with HNSCC; in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087), which enrolled 241 patients with cHL; in combination with chemotherapy in a randomized, active-controlled trial (KEYNOTE-189), which enrolled 405 patients with nonsquamous NSCLC, in a randomized, open-label, active-controlled trial (KEYNOTE-048 combination arm), which enrolled 276 patients with HNSCC; in combination with axitinib in a randomized, active-controlled trial (KEYNOTE 426), which enrolled 429 patients with RCC; and in post-marketing use. Across all trials, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among the 2799 patients, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

The data described in this section were obtained in nine randomized, controlled trials (KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-042, KEYNOTE-045, KEYNOTE-048, KEYNOTE-189, KEYNOTE-407, and KEYNOTE 426) and eight non-randomized, open-label trials (KEYNOTE-012, KEYNOTE-087, KEYNOTE-170, KEYNOTE-052, KEYNOTE-059, KEYNOTE-158, KEYNOTE-224, and KEYNOTE-017). The data described in this section also included a single randomized, double-blind, placebo-controlled trial (KEYNOTE-054) in which KEYTRUDA was administered for the adjuvant treatment of 509 patients with melanoma with involvement of lymph node(s) following complete surgical resection. In these trials, KEYTRUDA was administered at 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks.

Melanoma

Ipilimumab-Naive Melanoma

The safety of KEYTRUDA for the treatment of patients with unresectable or metastatic melanoma who had not received prior ipilimumab and who had received no more than one prior systemic therapy was investigated in KEYNOTE-006. KEYNOTE-006 was a multicenter, open-label, active-controlled trial where patients were randomized (1:1:1) and received KEYTRUDA 10 mg/kg every 2 weeks (n=278) or KEYTRUDA 10 mg/kg every 3 weeks (n=277) until disease progression or unacceptable toxicity or ipilimumab 3 mg/kg every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity (n=256) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA 10 mg/kg every 2 or 3 weeks, respectively, for ≥6 months. No patients in either arm received treatment for more than one year.

The study population characteristics were: median age of 62 years (range: 18 to 89); 60% male; 98% White; 32% had an elevated lactate dehydrogenase (LDH) value at baseline; 65% had M1c stage disease; 9% with history of brain metastasis; and approximately 36% had been previously treated with systemic therapy which included a BRAF inhibitor (15%), chemotherapy (13%), and immunotherapy (6%).

In KEYNOTE-006, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both KEYTRUDA arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). Tables 2 and 3 summarize selected adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-006.

Table 2: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-006

Adverse Reaction	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue	28	0.9	28	3.1
Skin and Subcutaneous Tissue				
Rash‡	24	0.2	23	1.2
Vitiligo§	13	0	2	0
Musculoskeletal and Connective Tissue				
Arthralgia	18	0.4	10	1.2
Back pain	12	0.9	7	0.8
Respiratory, Thoracic and Mediastinal				
Cough	17	0	7	0.4
Dyspnea	11	0.9	7	0.8
Metabolism and Nutrition				
Decreased appetite	16	0.5	14	0.8
Nervous System				
Headache	14	0.2	14	0.8

* Adverse reactions occurring at same or higher incidence than in the ipilimumab arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and exfoliative rash.
§ Includes skin hypopigmentation

Other clinically important adverse reactions occurring in ≥10% of patients receiving KEYTRUDA were diarrhea (26%), nausea (21%), and pruritus (17%).

Table 3: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-006

Laboratory Test†	KEYTRUDA 10 mg/kg every 2 or 3 weeks		Ipilimumab	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	45	4.2	45	3.8
Hypertriglyceridemia	43	2.6	31	1.1
Hyponatremia	28	4.6	26	7
Increased AST	27	2.6	25	2.5
Hypercholesterolemia	20	1.2	13	0
Hematology				
Anemia	35	3.8	33	4.0
Lymphopenia	33	7	25	6

* Laboratory abnormalities occurring at same or higher incidence than in ipilimumab arm
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: KEYTRUDA n=429 and ipilimumab n=183; hypercholesterolemia: KEYTRUDA n=484 and ipilimumab n=205.
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were increased hypoalbuminemia (27% all Grades; 2.4% Grades 3-4), increased ALT (23% all Grades; 3.1% Grades 3-4), and increased alkaline phosphatase (21% all Grades, 2% Grades 3-4).

Ipilimumab-Refractory Melanoma

The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was investigated in KEYNOTE-002. KEYNOTE-002 was a multicenter, partially blinded (KEYTRUDA dose), randomized (1:1:1), active-controlled trial in which 528 patients received KEYTRUDA 2 mg/kg (n=178) or 10 mg/kg

(n=179) every 3 weeks or investigator's choice of chemotherapy (n=171), consisting of dacarbazine (26%), temozolomide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 16.6 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 16.8 months). In the KEYTRUDA 2 mg/kg arm, 36% of patients were exposed to KEYTRUDA for ≥6 months and 4% were exposed for ≥12 months. In the KEYTRUDA 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA for ≥6 months and 6% of patients were exposed to KEYTRUDA for ≥12 months.

The study population characteristics were: median age of 62 years (range: 15 to 89); 61% male; 98% White; 41% with an elevated LDH value at baseline; 83% with M1c stage disease; 73% received two or more prior therapies for advanced or metastatic disease (100% received ipilimumab and 25% a BRAF inhibitor); and 15% with history of brain metastasis.

In KEYNOTE-002, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving KEYTRUDA; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). Tables 4 and 5 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-002.

Table 4: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-002

Adverse Reaction	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks n=357		Chemotherapy† n=171	
	All Grades‡ (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Skin and Subcutaneous Tissue				
Pruritus	28	0	8	0
Rash§	24	0.6	8	0
Gastrointestinal				
Constipation	22	0.3	20	2.3
Diarrhea	20	0.8	20	2.3
Abdominal pain	13	1.7	8	1.2
Respiratory, Thoracic and Mediastinal				
Cough	18	0	16	0
General				
Pyrexia	14	0.3	9	0.6
Asthenia	10	2.0	9	1.8
Musculoskeletal and Connective Tissue				
Arthralgia	14	0.6	10	1.2

* Adverse reactions occurring at same or higher incidence than in chemotherapy arm
† Chemotherapy: dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin
‡ Graded per NCI CTCAE v4.0
§ Includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (43%), nausea (22%), decreased appetite (20%), vomiting (13%), and peripheral neuropathy (1.7%).

Table 5: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-002

Laboratory Test†	KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks		Chemotherapy	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	49	6	44	6
Hypoalbuminemia	37	1.9	33	0.6
Hyponatremia	37	7	24	3.8
Hypertriglyceridemia	33	0	32	0.9
Increased alkaline phosphatase	26	3.1	18	1.9
Increased AST	24	2.2	16	0.6
Decreased bicarbonate	22	0.4	13	0
Hypocalcemia	21	0.3	18	1.9
Increased ALT	21	1.8	16	0.6

* Laboratory abnormalities occurring at same or higher incidence than in chemotherapy arm.

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 320 to 325 patients) and chemotherapy (range: 154 to 161 patients); hypertriglyceridemia: KEYTRUDA n=247 and chemotherapy n=116; decreased bicarbonate: KEYTRUDA n=263 and chemotherapy n=123.

‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were anemia (44% all Grades; 10% Grades 3-4) and lymphopenia (40% all Grades; 9% Grades 3-4).

Adjuvant Treatment of Resected Melanoma

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-054, a randomized (1:1) double-blind trial in which 1019 patients with completely resected stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma received 200 mg of KEYTRUDA by intravenous infusion every 3 weeks (n=509) or placebo (n=502) for up to one year *[see Clinical Studies (14.1)]*. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Seventy-six percent of patients received KEYTRUDA for 6 months or longer.

The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had stage IIIA, 46% had stage IIIB, 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (≥4 positive lymph nodes).

Two patients treated with KEYTRUDA died from causes other than disease progression; causes of death were drug reaction with eosinophilia and systemic symptoms and autoimmune myositis with respiratory failure. Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. Adverse reactions leading to permanent discontinuation occurred in 14% of patients receiving KEYTRUDA; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 19% of patients; the most common (≥1%) were diarrhea (2.4%), pneumonitis (2%), increased ALT (1.4%), arthralgia (1.4%), increased AST (1.4%), dyspnea (1%), and fatigue (1%). Tables 6 and 7 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-054.

Table 6: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-054

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=509		Placebo n=502	
	All Grades† (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea	28	1.2	26	1.2
Nausea	17	0.2	15	0
Skin and Subcutaneous Tissue				
Pruritus	19	0	12	0
Rash	13	0.2	9	0
Musculoskeletal and Connective Tissue				
Arthralgia	16	1.2	14	0
Endocrine				
Hypothyroidism	15	0	2.8	0
Hyperthyroidism	10	0.2	1.2	0
Respiratory, Thoracic and Mediastinal				
Cough	14	0	11	0
General				
Asthenia	11	0.2	8	0
Influenza like illness	11	0	8	0
Investigations				
Weight loss	11	0	8	0

* Adverse reactions occurring at same or higher incidence than in placebo arm
† Graded per NCI CTCAE v4.03

Table 7: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-054

Laboratory Test†	KEYTRUDA 200 mg every 3 weeks		Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Increased ALT	27	2.4	16	0.2
Increased AST	24	1.8	15	0.4
Hematology				
Lymphopenia	24	1	16	1.2

* Laboratory abnormalities occurring at same or higher incidence than placebo.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range:503 to 507 patients) and placebo (range: 492 to 498 patients).
‡ Graded per NCI CTCAE v4.03

NSCLC

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

The safety of KEYTRUDA in combination with pemetrexed and investigator's choice of platinum (either carboplatin or cisplatin) was investigated in KEYNOTE-189, a multicenter, double-blind, randomized (2:1), active-controlled trial in patients with previously untreated, metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations *[see Clinical Studies (14.2)]*. A total of 607 patients received KEYTRUDA 200 mg, pemetrexed and platinum every 3 weeks for 4 cycles followed by KEYTRUDA and pemetrexed (n=405) or placebo, pemetrexed, and platinum every 3 weeks for 4 cycles followed by placebo and pemetrexed (n=202). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 7.2 months (range: 1 day to 20.1 months). Sixty percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months. Seventy-two percent of patients received carboplatin.

The study population characteristics were: median age of 64 years (range: 34 to 84), 49% age 65 or older; 59% male; 94% White and 3% Asian; and 18% with history of brain metastases at baseline.

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 53% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (13%), asthenia/fatigue (7%), anemia (7%), thrombocytopenia (5%), diarrhea (4%), pneumonia (4%), increased blood creatinine (3%), dyspnea (2%), febrile neutropenia (2%), upper respiratory tract infection (2%), increased ALT (2%), and pyrexia (2%). Tables 8 and 9 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-189.

Table 8: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE-189

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=405		Placebo Pemetrexed Platinum Chemotherapy n=202	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	56	3.5	52	3.5
Constipation	35	1.0	32	0.5
Diarrhea	31	5	21	3.0
Vomiting	24	3.7	23	3.0
General				
Fatigue†	56	12	58	6
Pyrexia	20	0.2	15	0
Metabolism and Nutrition				
Decreased appetite	28	1.5	30	0.5
Skin and Subcutaneous Tissue				
Rash‡	25	2.0	17	2.5
Respiratory, Thoracic and Mediastinal				
Cough	21	0	28	0
Dyspnea	21	3.7	26	5

* Graded per NCI CTCAE v4.03

† Includes asthenia and fatigue

‡ Includes genital rash, rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

Table 9: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-189

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy		Placebo Pemetrexed Platinum Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Anemia	85	17	81	18
Lymphopenia	64	22	64	25
Neutropenia	48	20	41	19
Thrombocytopenia	30	12	29	8
Chemistry				
Hyperglycemia	63	9	60	7
Increased ALT	47	3.8	42	2.6
Increased AST	47	2.8	40	1.0
Hypoalbuminemia	39	2.8	39	1.1
Increased creatinine	37	4.2	25	1.0
Hyponatremia	32	7	23	6
Hypophosphatemia	30	10	28	14
Increased alkaline phosphatase	26	1.8	29	2.1
Hypocalcemia	24	2.8	17	0.5
Hyperkalemia	24	2.8	19	3.1
Hypokalemia	21	5	20	5

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/pemetrexed/platinum chemotherapy (range: 381 to 401 patients) and placebo/pemetrexed/platinum chemotherapy (range: 184 to 197 patients).

† Graded per NCI CTCAE v4.03

First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy

The safety of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or paclitaxel protein-bound was investigated in KEYNOTE-407, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in 558 patients with previously untreated, metastatic squamous NSCLC *[see Clinical Studies (14.2)]*. Safety data are available for the first 203 patients who received KEYTRUDA and chemotherapy (n=101) or placebo and chemotherapy (n=102). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA was 7 months (range: 1 day to 12 months). Sixty-one percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months. A total of 139 of 203 patients (68%) received paclitaxel and 64 patients (32%) received paclitaxel protein-bound in combination with carboplatin.

The study population characteristics were: median age of 65 years (range: 40 to 83), 52% age 65 or older; 78% male; 83% White; and 9% with history of brain metastases.

KEYTRUDA was discontinued for adverse reactions in 15% of patients, with no single type of adverse reaction accounting for the majority. Adverse reactions leading to interruption of KEYTRUDA occurred in 43% of patients; the most common (≥2%) were thrombocytopenia (20%), neutropenia (11%), anemia (6%), asthenia (2%), and diarrhea (2%). The most frequent (≥2%) serious adverse reactions were febrile neutropenia (6%), pneumonia (6%), and urinary tract infection (3%).

The adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs. 36%) and peripheral neuropathy (31% vs. 25%) were observed in the KEYTRUDA and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.

Previously Untreated NSCLC

The safety of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, open-label, randomized (1:1), active-controlled trial in 1251 patients with PD-L1 expressing, previously untreated stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC *[see Clinical Studies (14.2)].* Patients received KEYTRUDA 200 mg every 3 weeks (n=636) or investigator's choice of chemotherapy (n=615), consisting of pemetrexed and carboplatin followed by optional pemetrexed (n=312) or paclitaxel and carboplatin followed by optional pemetrexed (n=303) every 3 weeks. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA was 5.6 months (range: 1 day to 27.3 months). Forty-eight percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA 200 mg for ≥6 months.

The study population characteristics were: median age of 63 years (range: 25 to 90), 45% age 65 or older; 71% male; and 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Eighty-seven percent had metastatic disease (stage IV), 13% had stage III disease (2% stage IIIA and 11% stage IIIB), and 5% had treated brain metastases at baseline.

KEYTRUDA was discontinued for adverse reactions in 19% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3.0%), death due to unknown cause (1.6%), and pneumonia (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 33% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were pneumonitis (3.1%), pneumonia (3.0%), hypothyroidism (2.2%), and increased ALT (2.0%). The most frequent (≥2%) serious adverse reactions were pneumonia (7%), pneumonitis (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%).

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

Table 10: Adverse Reactions Occurring in ≥10% of Patients in KEYNOTE-042

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=636		Chemotherapy n=615	
	All Grades* (%)	Grades 3-5 (%)	All Grades (%)	Grades 3-5 (%)
General				
Fatigue†	25	3.1	33	3.9
Pyrexia	10	0.3	8	0
Metabolism and Nutrition				
Decreased appetite	17	1.7	21	1.5
Respiratory, Thoracic and Mediastinal				
Dyspnea	17	2.0	11	0.8
Cough	16	0.2	11	0.3
Skin and Subcutaneous Tissue				
Rash‡	15	1.3	8	0.2
Gastrointestinal				
Constipation	12	0	21	0.2
Diarrhea	12	0.8	12	0.5
Nausea	12	0.5	32	1.1
Endocrine				
Hypothyroidism	12	0.2	1.5	0
Infections				
Pneumonia	12	7	9	6
Investigations				
Weight loss	10	0.9	7	0.2

* Graded per NCI CTCAE v4.03
† Includes fatigue and asthenia
‡ Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

Table 11: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients in KEYNOTE-042

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	52	4.7	51	5
Increased ALT	33	4.8	34	2.9
Hypoalbuminemia	33	2.2	29	1.0
Increased AST	31	3.6	32	1.7
Hyponatremia	31	9	32	8
Increased alkaline phosphatase	29	2.3	29	0.3
Hypocalcemia	25	2.5	19	0.7
Hyperkalemia	23	3.0	20	2.2
Increased prothrombin INR	21	2.0	15	2.9
Hematology				
Anemia	43	4.4	79	19
Lymphopenia	30	7	41	13

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 598 to 610 patients) and chemotherapy (range: 588 to 597 patients); increased prothrombin INR: KEYTRUDA n=203 and chemotherapy n=173.

† Graded per NCI CTCAE v4.03

Previously Treated NSCLC

The safety of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, open-label, randomized (1:1:1), active-controlled trial, in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy and, if positive for EGFR or ALK genetic aberrations, appropriate therapy for these aberrations *[see Clinical Studies (14.2)]*. A total of 991 patients received KEYTRUDA 2 mg/kg (n=339) or 10 mg/kg (n=343) every 3 weeks or docetaxel (n=309) at 75 mg/m^2 every 3 weeks. Patients with autoimmune disease, medical conditions that required systemic corticosteroids or other immunosuppressive medication, or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

The median duration of exposure to KEYTRUDA 2 mg/kg every 3 weeks was 3.5 months (range: 1 day to 22.4 months) and to KEYTRUDA 10 mg/kg every 3 weeks was 3.5 months (range 1 day to 20.8 months). The data described below reflect exposure to KEYTRUDA 2 mg/kg in 31% of patients exposed to KEYTRUDA for ≥6 months. In the KEYTRUDA 10 mg/kg arm, 34% of patients were exposed to KEYTRUDA for ≥6 months.

The study population characteristics were: median age of 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; and 8% with advanced localized disease, 91% with metastatic disease, and 15% with history of brain metastases. Twenty-nine percent received two or more prior systemic treatments for advanced or metastatic disease.

In KEYNOTE-010, the adverse reaction profile was similar for the 2 mg/kg and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=682). Treatment was discontinued for adverse reactions in 8% of patients receiving KEYTRUDA. The most common adverse events resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.8%). Adverse reactions leading to interruption of KEYTRUDA occurred in 23% of patients; the most common (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%). Tables 12 and 13 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-010.

Table 12: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-010

Adverse Reaction	KEYTRUDA 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m^2 every 3 weeks n=309	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Metabolism and Nutrition				
Decreased appetite	25	1.5	23	2.6
Respiratory, Thoracic and Mediastinal				
Dyspnea	23	3.7	20	2.6
Cough	19	0.6	14	0
Gastrointestinal				
Nausea	20	1.3	18	0.6
Constipation	15	0.6	12	0.6
Vomiting	13	0.9	10	0.6
Skin and Subcutaneous Tissue				
Rash‡	17	0.4	8	0
Pruritus	11	0	3	0.3
Musculoskeletal and Connective Tissue				
Arthralgia	11	1.0	9	0.3
Back pain	11	1.5	8	0.3

* Adverse reactions occurring at same or higher incidence than in docetaxel arm
† Graded per NCI CTCAE v4.0
‡ Includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA were fatigue (25%), diarrhea (14%), asthenia (11%) and pyrexia (11%).

Table 13: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving KEYTRUDA in KEYNOTE-010

Laboratory Test†	KEYTRUDA 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Chemistry				
Hyponatremia	32	8	27	2.9
Increased alkaline phosphatase	28	3.0	16	0.7
Increased AST	26	1.6	12	0.7
Increased ALT	22	2.7	9	0.4

* Laboratory abnormalities occurring at same or higher incidence than in docetaxel arm.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 631 to 638 patients) and docetaxel (range: 274 to 277 patients).
‡ Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥20% of patients receiving KEYTRUDA were hyperglycemia (44% all Grades; 4.1% Grades 3-4), anemia (37% all Grades; 3.8% Grades 3-4), hypertriglyceridemia (36% all Grades; 1.8% Grades 3-4), lymphopenia (35% all Grades; 9% Grades 3-4), hypoalbuminemia (34% all Grades; 1.6% Grades 3-4), and hypercholesterolemia (20% all Grades; 0.7% Grades 3-4).

HNSCC

First-line treatment of metastatic or unresectable, recurrent HNSCC

The safety of KEYTRUDA, as a single agent and in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, was investigated in KEYNOTE-048, a multicenter, open-label, randomized (1:1:1), active-controlled trial in patients with previously untreated, recurrent or metastatic HNSCC *[see Clinical Studies (14.3)]*. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. A total of 576 patients received KEYTRUDA 200 mg every 3 weeks either as a single agent (n=300) or in combination with platinum and FU (n=276) every 3 weeks for 6 cycles followed by KEYTRUDA, compared to 287 patients

who received cetuximab weekly in combination with platinum and FU every 3 weeks for 6 cycles followed by cetuximab.

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

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

KEYTRUDA was discontinued for adverse reactions in 16% of patients in the combination arm. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 45% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (14%), thrombocytopenia (10%), anemia (6%), pneumonia (4.7%), and febrile neutropenia (2.9%).

Tables 14 and 15 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-048.

Table 14: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-048

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

* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

‡ Includes diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis

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

¶ Includes cough, productive cough

Includes dyspnea, exertional dyspnea

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

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

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

Table 15: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-048

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		KEYTRUDA 200 mg every 3 weeks Platinum FU		Cetuximab Platinum FU	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology						
Lymphopenia	54	25	69	35	74	45
Anemia	52	7	89	28	78	19
Thrombocytopenia	12	3.8	73	18	76	18
Neutropenia	7	1.4	67	35	71	42
Chemistry						
Hyperglycemia	47	3.8	55	6	66	4.7
Hyponatremia	46	17	56	20	59	20
Hypoalbuminemia	44	3.2	47	4.0	49	1.1
Increased AST	28	3.1	24	2.0	37	3.6
Increased ALT	25	2.1	22	1.6	38	1.8
Increased alkaline phosphatase	25	2.1	27	1.2	33	1.1
Hypercalcemia	22	4.6	16	4.3	13	2.6
Hypocalcemia	22	1.1	32	4	58	7
Hyperkalemia	21	2.8	27	4.3	29	4.3
Hypophosphatemia	20	5	35	12	48	19
Hypokalemia	19	5	34	12	47	15
Increased creatinine	18	1.1	36	2.3	27	2.2
Hypomagnesemia	16	0.4	42	1.7	76	6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/chemotherapy (range: 235 to 266 patients), KEYTRUDA (range: 241 to 288 patients), cetuximab/chemotherapy (range: 249 to 282 patients).

† Graded per NCI CTCAE v4.0

Previously treated recurrent or metastatic HNSCC

Among the 192 patients with HNSCC enrolled in KEYNOTE-012 *[see Clinical Studies (14.3)]*, the median duration of exposure to KEYTRUDA was 3.3 months (range: 1 day to 27.9 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for KEYNOTE-012.

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

KEYTRUDA was discontinued due to adverse reactions in 17% of patients. Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); therefore, summary safety results are provided in a pooled analysis. The most common adverse reactions (occurring in ≥20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism *[see Warnings and Precautions (5.4)]*.

cHL

Among the 210 patients with cHL enrolled in KEYNOTE-087 *[see Clinical Studies (14.4)]*, the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). KEYTRUDA was discontinued due to adverse reactions in 5% of patients, and treatment was interrupted due to adverse reactions in 26%. Fifteen percent (15%) of patients had an adverse reaction requiring systemic

corticosteroid therapy. Serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, pyrexia, dyspnea, graft versus host disease and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock. Tables 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-087.

Table 16: Adverse Reactions in ≥10% of Patients with cHL in KEYNOTE-087

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=210	
	All Grades* (%)	Grade 3 (%)
General		
Fatigue[†]	26	1.0
Pyrexia	24	1.0
Respiratory, Thoracic and Mediastinal		
Cough[‡]	24	0.5
Dyspnea[§]	11	1.0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[¶]	21	1.0
Arthralgia	10	0.5
Gastrointestinal		
Diarrhea[#]	20	1.4
Vomiting	15	0
Nausea	13	0
Skin and Subcutaneous Tissue		
Rash[Þ]	20	0.5
Pruritus	11	0
Endocrine		
Hypothyroidism	14	0.5
Infections		
Upper respiratory tract infection	13	0
Nervous System		
Headache	11	0.5
Peripheral neuropathy[β]	10	0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes cough, productive cough
§ Includes dyspnea, dyspnea exertional, wheezing
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
# Includes diarrhea, gastroenteritis, colitis, enterocolitis
Þ Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, dermatitis acneiform, dermatitis contact, rash erythematous, rash macular, rash papular, rash pruritic, seborrhoeic dermatitis, dermatitis psoriasiform
β Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

Other clinically important adverse reactions that occurred in less than 10% of patients on KEYNOTE-087 included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), and myelitis and myocarditis (0.5% each).

Table 17: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of cHL Patients Receiving KEYTRUDA in KEYNOTE-087

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Chemistry		
Hypertransaminasemia‡	34	2
Increased alkaline phosphatase	17	0
Increased creatinine	15	0.5
Hematology		
Anemia	30	6
Thrombocytopenia	27	4
Neutropenia	24	7

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

† Graded per NCI CTCAE v4.0

‡ Includes elevation of AST or ALT

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

PMBCL

Among the 53 patients with PMBCL treated in KEYNOTE-170 *[see Clinical Studies (14.5)],* the median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 22.8 months).

KEYTRUDA was discontinued due to adverse reactions in 8% of patients, and treatment was interrupted due to adverse reactions in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 26% of patients, and included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment. Tables 18 and 19 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-170.

Table 18: Adverse Reactions in ≥10% of Patients with PMBCL in KEYNOTE-170

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

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

Other clinically important adverse reactions that occurred in less than 10% of patients in KEYNOTE-170 included hypothyroidism (8%), hyperthyroidism and pericarditis (4% each), and thyroiditis, pericardial effusion, pneumonitis, arthritis and acute kidney injury (2% each).

Table 19: Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of PMBCL Patients Receiving KEYTRUDA in KEYNOTE-170

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Hematology		
Anemia	47	0
Leukopenia	35	9
Lymphopenia	32	18
Neutropenia	30	11
Chemistry		
Hyperglycemia	38	4
Hypophosphatemia	29	10
Hypertransaminasemia‡	27	4
Hypoglycemia	19	0
Increased alkaline phosphatase	17	0
Increased creatinine	17	0
Hypocalcemia	15	4
Hypokalemia	15	4

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 44 to 48 patients)
† Graded per NCI CTCAE v4.0
‡ Includes elevation of AST or ALT

Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The safety of KEYTRUDA was investigated in KEYNOTE-052, a single-arm trial that enrolled 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible *[see Clinical Studies (14.6)]*. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression.

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

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

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

Table 20 summarizes adverse reactions in patients on KEYTRUDA in KEYNOTE-052.

Table 20: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

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

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

Previously Treated Urothelial Carcinoma

The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in KEYNOTE-045. KEYNOTE-045 was a multicenter, open-label, randomized (1:1), active-controlled trial in which 266 patients received KEYTRUDA 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) *[see Clinical Studies (14.6)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible.

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

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis. Tables 21 and 22 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-045.

Table 21: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

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

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

Table 22: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Hyperglycemia	52	8	60	7
Anemia	52	13	68	18
Lymphopenia	45	15	53	25
Hypoalbuminemia	43	1.7	50	3.8
Hyponatremia	37	9	47	13
Increased alkaline phosphatase	37	7	33	4.9
Increased creatinine	35	4.4	28	2.9
Hypophosphatemia	29	8	34	14
Increased AST	28	4.1	20	2.5
Hyperkalemia	28	0.8	27	6
Hypocalcemia	26	1.6	34	2.1

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 240 to 248 patients) and chemotherapy (range: 238 to 244 patients); phosphate decreased: KEYTRUDA n=232 and chemotherapy n=222.

† Graded per NCI CTCAE v4.0

Gastric Cancer

Among the 259 patients with gastric cancer enrolled in KEYNOTE-059 *[see Clinical Studies (14.8)]*, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 21.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression or with clinical evidence of ascites by physical exam were ineligible. Adverse reactions occurring in patients with gastric cancer were similar to those occurring in patients with melanoma or NSCLC.

Cervical Cancer

Among the 98 patients with cervical cancer enrolled in Cohort E of KEYNOTE-158 *[see Clinical Studies (14.9)]*, the median duration of exposure to KEYTRUDA was 2.9 months (range: 1 day to 22.1 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%). Tables 23 and 24 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-158.

Table 23: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158

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

* Graded per NCI CTCAE v4.0

† Includes asthenia, fatigue, lethargy, malaise

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

§ Includes edema peripheral, peripheral swelling

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

Includes colitis, diarrhea, gastroenteritis

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

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

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

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

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

Table 24: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with Cervical Cancer in KEYNOTE-158

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Hematology		
Anemia	54	24
Lymphopenia	47	9
Chemistry		
Hypoalbuminemia	44	5
Increased alkaline phosphatase	42	2.6
Hyponatremia	38	13
Hyperglycemia	38	1.3
Increased AST	34	3.9
Increased creatinine	32	5
Hypocalcemia	27	0
Increased ALT	21	3.9
Hypokalemia	20	6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 76 to 79 patients)

† Graded per NCI CTCAE v4.0

Other laboratory abnormalities occurring in ≥10% of patients receiving KEYTRUDA were hypophosphatemia (19% all Grades; 6% Grades 3-4), increased INR (19% all Grades; 0% Grades 3-4), hypercalcemia (14% all Grades; 2.6% Grades 3-4), platelet count decreased (14% all Grades; 1.3% Grades 3-4), activated partial thromboplastin time prolonged (14% all Grades; 0% Grades 3-4), hypoglycemia (13% all Grades; 1.3% Grades 3-4), white blood cell decreased (13% all Grades; 2.6% Grades 3-4), and hyperkalemia (13% all Grades; 1.3% Grades 3-4).

HCC

Among the 104 patients with HCC who received KEYTRUDA in KEYNOTE-224 *[see Clinical Studies (14.10)]*, the median duration of exposure to KEYTRUDA was 4.2 months (range: 1 day to 1.5 years). Adverse reactions occurring in patients with HCC were generally similar to those in patients with melanoma or NSCLC, with the exception of increased incidences of ascites (8% Grades 3-4) and immune-mediated hepatitis (2.9%). Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (20%), ALT (9%), and hyperbilirubinemia (10%).

MCC

Among the 50 patients with MCC enrolled in KEYNOTE-017 *[see Clinical Studies (14.11)]*, the median duration of exposure to KEYTRUDA was 6.6 months (range 1 day to 23.6 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MCC were similar to those occurring in patients with melanoma or NSCLC. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (11%) and hyperglycemia (19%).

RCC

The safety of KEYTRUDA in combination with axitinib was investigated in KEYNOTE-426 *[see Clinical Studies (14.12)]*. 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 years or older; 71% male; 80% White; and 80% Karnofsky Performance Status (KPS) of 90-100 and 20% KPS of 70-80.

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

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

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

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

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

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

Tables 25 and 26 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in at least 20% of patients treated with KEYTRUDA and axitinib in KEYNOTE-426.

Table 25: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

Adverse Reaction	KEYTRUDA and Axitinib n=429		Sunitinib n=425	
	All Grades* (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal				
Diarrhea†	56	11	45	5
Nausea	28	0.9	32	0.9
Constipation	21	0	15	0.2
General				
Fatigue/Asthenia	52	5	51	10
Vascular				
Hypertension‡	48	24	48	20
Hepatobiliary				
Hepatotoxicity§	39	20	25	4.9
Endocrine				
Hypothyroidism	35	0.2	32	0.2
Metabolism and Nutrition				
Decreased appetite	30	2.8	29	0.7
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysaesthesia syndrome	28	5	40	3.8
Stomatitis/Mucosal inflammation	27	1.6	41	4
Rash¶	25	1.4	21	0.7
Respiratory, Thoracic and Mediastinal				
Dysphonia	25	0.2	3.3	0
Cough	21	0.2	14	0.5

* Graded per NCI CTCAE v4.03

† Includes diarrhea, colitis, enterocolitis, gastroenteritis, enteritis, enterocolitis hemorrhagic

‡ Includes hypertension, blood pressure increased, hypertensive crisis, labile hypertension

§ Includes ALT increased, AST increased, autoimmune hepatitis, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis fulminant, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased

¶ Includes rash, butterfly rash, dermatitis, dermatitis acneform, dermatitis atopic, dermatitis bullous, dermatitis contact, exfoliative rash, genital rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, seborrhoeric dermatitis, skin discoloration, skin exfoliation, perineal rash

Table 26: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

Laboratory Test*	KEYTRUDA and Axitinib		Sunitinib	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	62	9	54	3.2
Increased ALT	60	20	44	5
Increased AST	57	13	56	5
Increased creatinine	43	4.3	40	2.4
Hyponatremia	35	8	29	8
Hyperkalemia	34	6	22	1.7
Hypoalbuminemia	32	0.5	34	1.7
Hypercalcemia	27	0.7	15	1.9
Hypophosphatemia	26	6	49	17
Increased alkaline phosphatase	26	1.7	30	2.7
Hypocalcemia‡	22	0.2	29	0.7
Blood bilirubin increased	22	2.1	21	1.9
Activated partial thromboplastin time prolonged§	22	1.2	14	0
Hematology				
Lymphopenia	33	11	46	8
Anemia	29	2.1	65	8
Thrombocytopenia	27	1.4	78	14

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/axitinib (range: 342 to 425 patients) and sunitin b (range: 345 to 422 patients).
† Graded per NCI CTCAE v4.03
‡ Corrected for albumin
§ Two patients with a Grade 3 elevated activated partial thromboplastin time prolonged (aPTT) were also reported as having an adverse reaction of hepatotoxicity.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to pembrolizumab in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks, 27 (2.1%) of 1289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies of whom six (0.5%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding antibody development.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. There are no available human data informing the risk of embryo-fetal toxicity. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue *(see Data)*. Human IgG4 (immunoglobulins) are known to cross

the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with KEYTRUDA to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects of the PD-1 pathway on reproduction demonstrated that a central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering KEYTRUDA during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 knockout mice. Based on its mechanism of action, fetal exposure to pembrolizumab may increase the risk of developing immune-mediated disorders or of altering the normal immune response.

8.2 Lactation

Risk Summary

There are no data on the presence of pembrolizumab in either animal or human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with KEYTRUDA and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating KEYTRUDA *[see Use in Specific Populations (8.1)].*

Contraception

KEYTRUDA can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for at least 4 months following the final dose.

8.4 Pediatric Use

The safety and effectiveness of KEYTRUDA have been established in pediatric patients with cHL, PMBCL, and MSI-H cancer. Use of KEYTRUDA in pediatric patients with cHL, PMBCL, and MSI-H cancers is supported by evidence from adequate and well-controlled studies of KEYTRUDA in adults with additional pharmacokinetic and safety data in pediatric patients *[see Adverse Reactions (6.1), Clinical Studies (14,4, 14.5, 14.7), Clinical Pharmacology (12.3)]*.

There is limited experience with KEYTRUDA in pediatric patients. In a trial (NCT02332668), 40 pediatric patients (16 children ages 2 years to less than 12 years and 24 adolescents ages 12 years to 18 years) with various cancers, including unapproved usages, were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range: 1-17 doses), with 34 patients (85%) receiving KEYTRUDA for 2 doses or more.

The safety profile in these pediatric patients was similar to that seen in adults; adverse reactions that occurred at a higher rate (≥15% difference) in pediatric patients when compared to adults <65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), increased transaminases (28%) and hyponatremia (18%).

The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The safety and effectiveness of KEYTRUDA in pediatric patients have not been established in the other approved indications *[see Indications and Usage (1)]*.

8.5 Geriatric Use

Of 3991 patients with melanoma, NSCLC, HNSCC, cHL or urothelial carcinoma who were treated with KEYTRUDA in clinical studies, 46% were 65 years and over and 16% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

11 DESCRIPTION

Pembrolizumab is a programmed death receptor-1 (PD 1)-blocking antibody. Pembrolizumab is a humanized monoclonal IgG4 kappa antibody with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in recombinant Chinese hamster ovary (CHO) cells.

KEYTRUDA (pembrolizumab) for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials for intravenous use. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

KEYTRUDA (pembrolizumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.2 Pharmacodynamics

Based on dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks in patients with melanoma or NSCLC.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2993 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks.

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Distribution

The geometric mean value (CV%) for volume of distribution at steady state is 6.0 L (20%).

Elimination

Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] at steady state than that after the first dose [252 mL/day (37%)]; this decrease in clearance with time is not considered clinically important. The terminal half-life ($t_{1/2}$) is 22 days (32%).

Specific Populations

The following factors had no clinically important effect on the CL of pembrolizumab: age (range: 15 to 94 years), sex, race (89% White), renal impairment (eGFR ≥ 15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or tumor burden. The impact of moderate or severe hepatic impairment on the pharmacokinetics of pembrolizumab is unknown.

Pediatric Patients: Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients (2 to 17 years) are comparable to those of adults at the same dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

14 CLINICAL STUDIES

14.1 Melanoma

Ipilimumab-Naive Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-006 (NCT01866319), a randomized (1:1:1), open-label, multicenter, active-controlled trial in 834 patients. Patients were randomized to receive KEYTRUDA at a dose of 10 mg/kg intravenously every 2 weeks or 10 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity. Patients with disease progression could receive additional doses of treatment unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Randomization was stratified by line of therapy (0 vs. 1), ECOG PS (0 vs. 1), and PD-L1 expression (≥1% of tumor cells [positive] vs. <1% of tumor cells [negative]) according to an investigational use only (IUO) assay. Key eligibility criteria were unresectable or metastatic melanoma; no prior ipilimumab; and no more than one prior systemic treatment for metastatic melanoma. Patients with BRAF V600E mutation-positive melanoma were not required to have received prior BRAF inhibitor therapy. Patients with autoimmune disease; a medical condition that required immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection, were ineligible. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by blinded independent central review [BICR] using Response Evaluation Criteria in Solid Tumors [RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target

lesions per organ]). Additional efficacy outcome measures were overall response rate (ORR) and duration of response (DoR).

The study population characteristics were: median age of 62 years (range: 18 to 89); 60% male; 98% White; 66% had no prior systemic therapy for metastatic disease; 69% ECOG PS of 0; 80% had PD-L1 positive melanoma, 18% had PD-L1 negative melanoma, and 2% had unknown PD-L1 status using the IUO assay; 65% had M1c stage disease; 68% with normal LDH; 36% with reported BRAF mutation-positive melanoma; and 9% with a history of brain metastases. Among patients with BRAF mutation-positive melanoma, 139 (46%) were previously treated with a BRAF inhibitor.

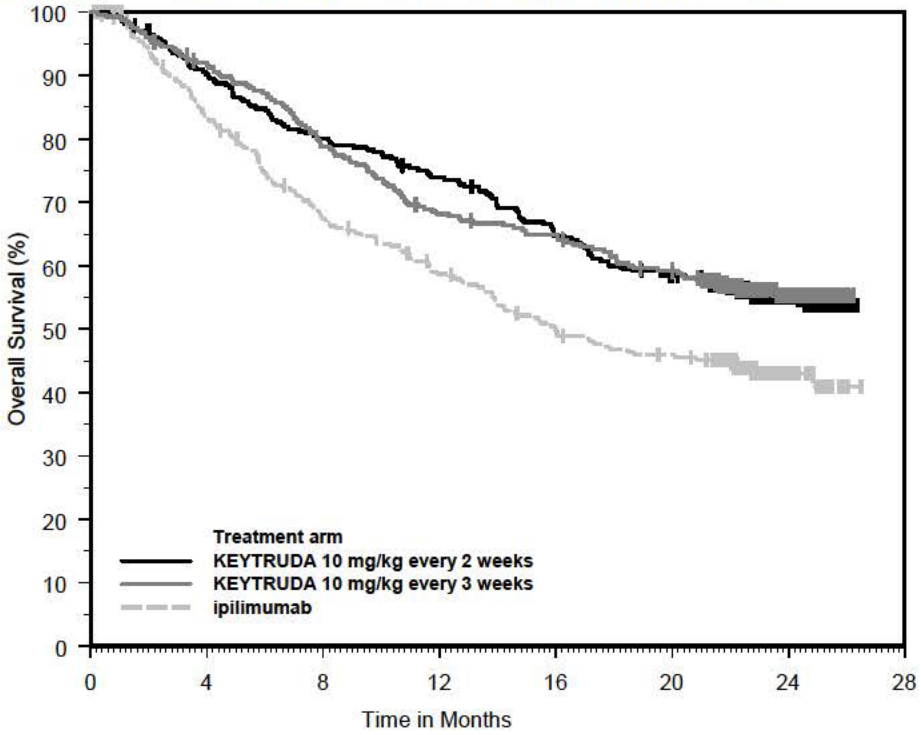
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to KEYTRUDA 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months. Efficacy results are summarized in Table 27 and Figure 1.

Table 27: Efficacy Results in KEYNOTE-006

Endpoint	**KEYTRUDA 10 mg/kg every 3 weeks n=277**	**KEYTRUDA 10 mg/kg every 2 weeks n=279**	**Ipilimumab 3 mg/kg every 3 weeks n=278**
OS			
Deaths (%)	92 (33%)	85 (30%)	112 (40%)
Hazard ratio* (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value (stratified log-rank)	0.004	<0.001	---
PFS by BICR			
Events (%)	157 (57%)	157 (56%)	188 (68%)
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Hazard ratio* (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Best overall response by BICR			
ORR (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response rate	6%	5%	1%
Partial response rate	27%	29%	10%

* Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model

Figure 1: Kaplan-Meier Curve for Overall Survival in KEYNOTE-006*



Number at Risk								
KEYTRUDA 10 mg/kg every 2 weeks:	279	249	221	202	176	156	44	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	251	215	184	174	156	43	0
ipilimumab:	278	213	170	145	122	110	28	0

**based on the final analysis with an additional follow-up of 9 months (total of 383 deaths as pre-specified in the protocol)*

Ipilimumab-Refractory Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-002 (NCT01704287), a multicenter, randomized (1:1:1), active-controlled trial in 540 patients randomized to receive one of two doses of KEYTRUDA in a blinded fashion or investigator's choice chemotherapy. The treatment arms consisted of KEYTRUDA 2 mg/kg or 10 mg/kg intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens: dacarbazine 1000 mg/m^2 intravenously every 3 weeks (26%), temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 mg/mL/min intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 mg/mL/min plus paclitaxel 175 mg/m^2 every 3 weeks (25%), paclitaxel 175 mg/m^2 intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 mg/mL/min intravenously every 3 weeks (8%). Randomization was stratified by ECOG PS (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. Patients received KEYTRUDA until unacceptable toxicity; disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumor status was performed at 12 weeks after randomization, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced progression of disease were offered KEYTRUDA. The major efficacy outcomes were PFS as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. Additional efficacy outcome measures were confirmed ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The study population characteristics were: median age was 62 years (range: 15 to 89), 43% age 65 or older; 61% male; 98% White; and 55% ECOG PS of 0 and 45% ECOG PS of 1. Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease.

The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm. There was no statistically significant difference between KEYTRUDA 2 mg/kg and chemotherapy or between KEYTRUDA 10 mg/kg and chemotherapy in the OS analysis in which 55% of the patients who had been randomized to receive chemotherapy had crossed over to receive KEYTRUDA. Among the 38 patients randomized to KEYTRUDA 2 mg/kg with an objective response, response durations ranged from 1.3+ to 11.5+ months. Among the 46 patients randomized to KEYTRUDA 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months. Efficacy results are summarized in Table 28.

Table 28: Efficacy Results in KEYNOTE-002

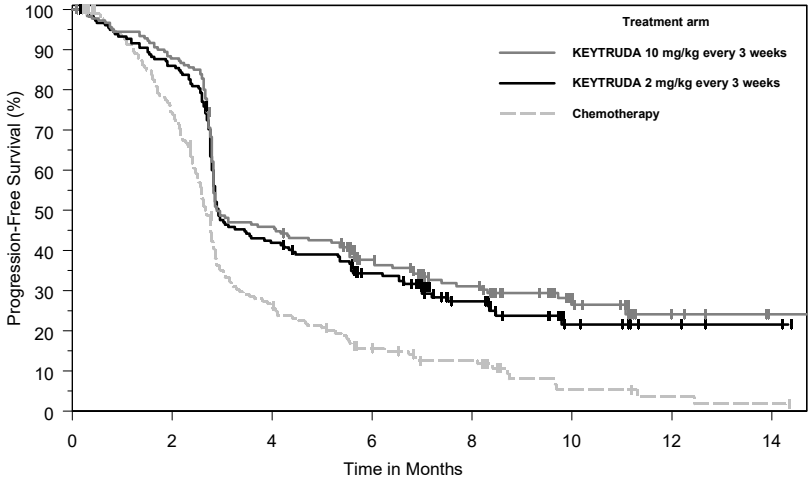
Endpoint	**KEYTRUDA 2 mg/kg every 3 weeks n=180**	**KEYTRUDA 10 mg/kg every 3 weeks n=181**	**Chemotherapy n=179**
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
p-Value (stratified log-rank)	<0.001	<0.001	---
Hazard ratio* (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
OS†			
Deaths (%)	123 (68%)	117 (65%)	128 (72%)
Hazard ratio* (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value (stratified log-rank)	0.117	0.011‡	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Objective Response Rate			
ORR (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response rate	2%	3%	0%
Partial response rate	19%	23%	4%

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

† With additional follow-up of 18 months after the PFS analysis

‡ Not statistically significant compared to multiplicity adjusted significance level of 0.01

Figure 2: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-002



Number at Risk								
KEYTRUDA 10 mg/kg:	181	158	82	55	39	15	5	1
KEYTRUDA 2 mg/kg:	180	153	74	53	26	9	4	2
Chemotherapy:	179	128	43	22	15	4	2	1

Adjuvant Treatment of Resected Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-054 (NCT02362594), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with completely resected stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma. Patients were randomized to KEYTRUDA 200 mg intravenously every three weeks or placebo for up to one year until disease recurrence or unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer 7th edition (AJCC) stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes) and geographic region (North America, European countries, Australia, and other countries as designated). Patients must have undergone lymph node dissection and, if indicated, radiotherapy within 13 weeks prior to starting treatment. The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1 positive tumors where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first two years, then every 6 months from year 3 to 5, and then annually.

The study population characteristics were: median age of 54 years (range: 19 to 88), 25% age 65 or older; 62% male; and 94% ECOG PS of 0 and 6% ECOG PS of 1. Sixteen percent had stage IIIA, 46% had stage IIIB, 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (≥4 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild-type; and 84% had PD-L1 positive melanoma with TPS ≥1% according to an IOU assay.

The trial demonstrated a statistically significant improvement in RFS for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 29 and Figure 3.

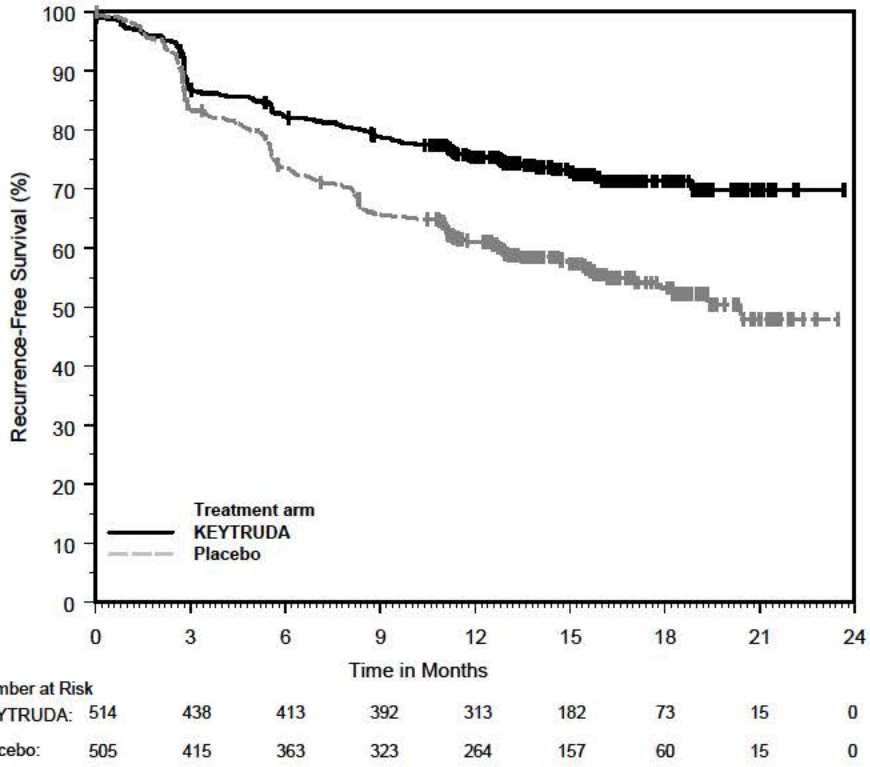
Table 29: Efficacy Results in KEYNOTE-054

Endpoint	KEYTRUDA 200 mg every 3 weeks n=514	Placebo n=505
RFS		
Number (%) of patients with event	135 (26%)	216 (43%)
Median in months (95% CI)	NR	20.4 (16.2, NR)
Hazard ratio*† (95% CI)	0.57 (0.46, 0.70)	
p-Value† (log-rank)	<0.001±	

* Based on the stratified Cox proportional hazard model
† Stratified by American Joint Committee on Cancer 7th edition (AJCC) stage
± p-Value is compared with 0.008 of the allocated alpha for this interim analysis.
NR = not reached

For patients with PD-L1 positive tumors, the HR was 0.54 (95% CI: 0.42, 0.69); p<0.001. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression.

Figure 3: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054



14.2 Non-Small Cell Lung Cancer

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

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189 (NCT02578680), a randomized, multicenter, double-blind, active-controlled trial conducted in 616 patients with metastatic nonsquamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking status (never vs. former/current), choice of platinum (cisplatin vs. carboplatin), and tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%). Patients were randomized (2:1) to one of the following treatment arms:

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

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

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

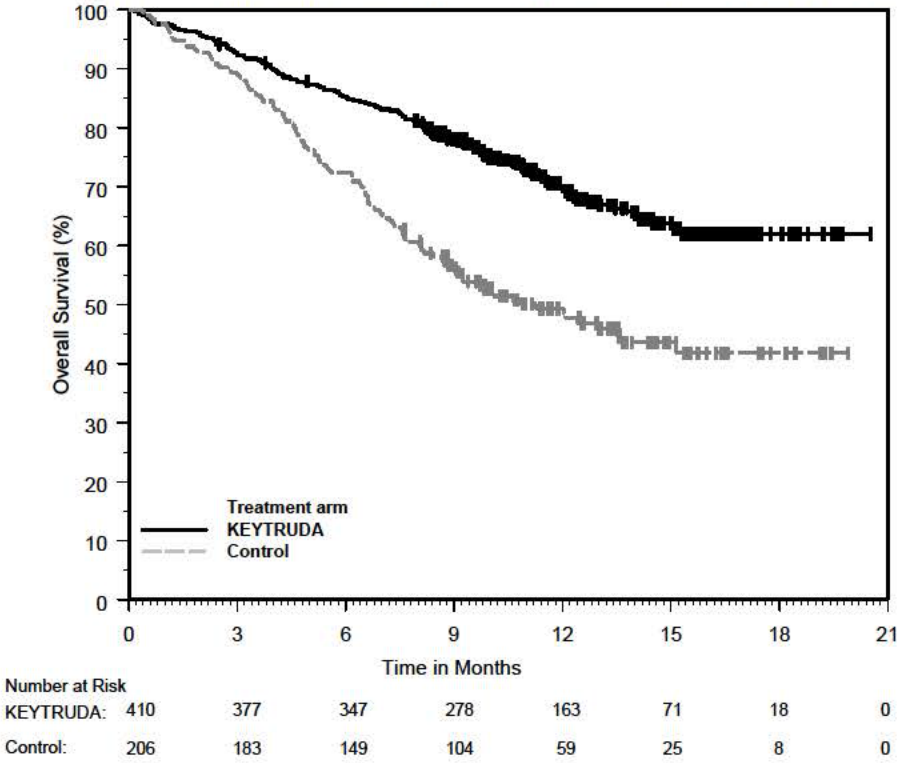
The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 30 and Figure 4 summarize the efficacy results for KEYNOTE-189.

Table 30: Efficacy Results in KEYNOTE-189

Endpoint	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=410	Placebo Pemetrexed Platinum Chemotherapy n=206
OS		
Number (%) of patients with event	127 (31%)	108 (52%)
Median in months (95% CI)	NR (NR, NR)	11.3 (8.7, 15.1)
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.0001	
PFS		
Number of patients with event (%)	244 (60%)	166 (81%)
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.0001	
Objective Response Rate		
ORR‡ (95% CI)	48% (43, 53)	19% (14, 25)
Complete response	0.5%	0.5%
Partial response	47%	18%
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test.
‡ Response: Best objective response as confirmed complete response or partial response
§ Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy and smoking status
NR = not reached

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



Number at Risk

KEYTRUDA:	410	377	347	278	163	71	18	0
Control:	206	183	149	104	59	25	8	0

First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy

The efficacy of KEYTRUDA in combination with carboplatin and investigator's choice of either paclitaxel or paclitaxel protein-bound was investigated in KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial conducted in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 status (TPS <1% [negative] vs. TPS ≥1%), choice of paclitaxel or paclitaxel protein-bound, and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Placebo and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo every 3 weeks.

Treatment with KEYTRUDA and chemotherapy or placebo and chemotherapy continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Patients randomized to the placebo and chemotherapy arm were offered KEYTRUDA as a single agent at the time of disease progression. Assessment of tumor status was performed every 6 weeks through Week 18,

every 9 weeks through Week 45 and every 12 weeks thereafter. The main efficacy outcome measures were PFS and ORR as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. An additional efficacy outcome measure was DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 65 years (range: 29 to 88), 55% age 65 or older; 81% male; 77% White; 71% ECOG PS of 1; and 8% with a history of brain metastases. Thirty-five percent had tumor PD-L1 expression TPS <1%; 19% were from the East Asian region; and 60% received paclitaxel.

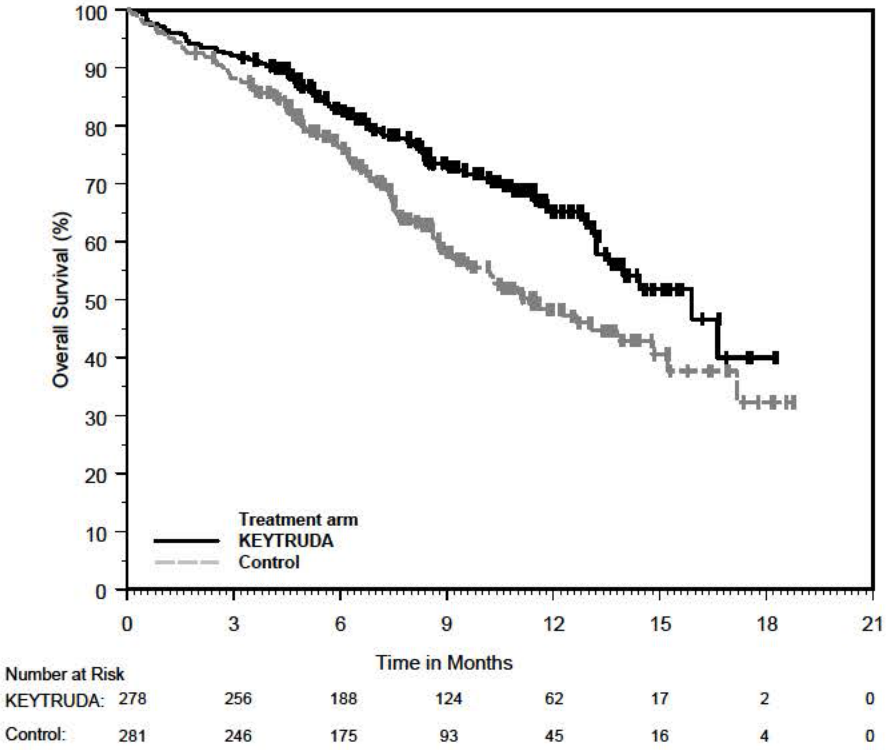
The trial demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy compared with patients randomized to placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy. Table 31 and Figure 5 summarize the efficacy results for KEYNOTE-407.

Table 31: Efficacy Results in KEYNOTE-407

Endpoint	**KEYTRUDA 200 mg every 3 weeks Carboplatin Paclitaxel/Paclitaxel protein-bound n=278**	**Placebo Carboplatin Paclitaxel/Paclitaxel protein-bound n=281**
OS		
Number of events (%)	85 (31%)	120 (43%)
Median in months (95% CI)	15.9 (13.2, NE)	11.3 (9.5, 14.8)
Hazard ratio* (95% CI)	0.64 (0.49, 0.85)	
p-Value†	0.0017	
PFS		
Number of events (%)	152 (55%)	197 (70%)
Median in months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.3, 5.7)
Hazard ratio* (95% CI)	0.56 (0.45, 0.70)	
p-Value†	<0.0001	
	n=101	**n=103**
Objective Response Rate‡		
ORR (95% CI)	58% (48, 68)	35% (26, 45)
Difference (95% CI)	23.6% (9.9, 36.4)	
p-Value§	0.0008	
Duration of Response‡		
Median duration of response in months (range)	7.2 (2.4, 12.4+)	4.9 (2.0, 12.4+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ ORR primary analysis and DOR analysis were conducted with the first 204 patients enrolled.
§ Based on a stratified Miettinen-Nurminen test
NE = not estimable

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



First-line treatment of metastatic NSCLC as a single agent

KEYNOTE-042

The efficacy of KEYTRUDA was investigated in KEYNOTE-042 (NCT02220894), a randomized, multicenter, open-label, active-controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumors expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. Randomization was stratified by ECOG PS (0 vs. 1), histology (squamous vs. nonsquamous), geographic region (East Asia vs. non-East Asia), and PD-L1 expression (TPS ≥50% vs. TPS 1 to 49%). Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of either of the following platinum-containing chemotherapy regimens:

- Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies.

Treatment with KEYTRUDA continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Treatment with KEYTRUDA could be reinitiated at the time of subsequent disease

progression and administered for up to 12 months. Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measure was OS in the subgroup of patients with TPS ≥50% NSCLC, the subgroup of patients with TPS ≥20% NSCLC, and the overall population with TPS ≥1% NSCLC. Additional efficacy outcome measures were PFS and ORR in the subgroup of patients with TPS ≥50% NSCLC, the subgroup of patients with TPS ≥20% NSCLC, and the overall population with TPS ≥1% NSCLC as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 63 years (range: 25 to 90), 45% age 65 or older; 71% male; and 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Sixty-nine percent had ECOG PS of 1; 39% with squamous and 61% with nonsquamous histology; 87% with M1 disease and 13% with Stage IIIA (2%) or Stage IIIB (11%) who were not candidates for surgical resection or definitive chemoradiation per investigator assessment; and 5% with treated brain metastases at baseline. Forty-seven percent of patients had TPS ≥50% NSCLC and 53% had TPS 1 to 49% NSCLC.

The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to KEYTRUDA as compared with chemotherapy. Table 32 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%.

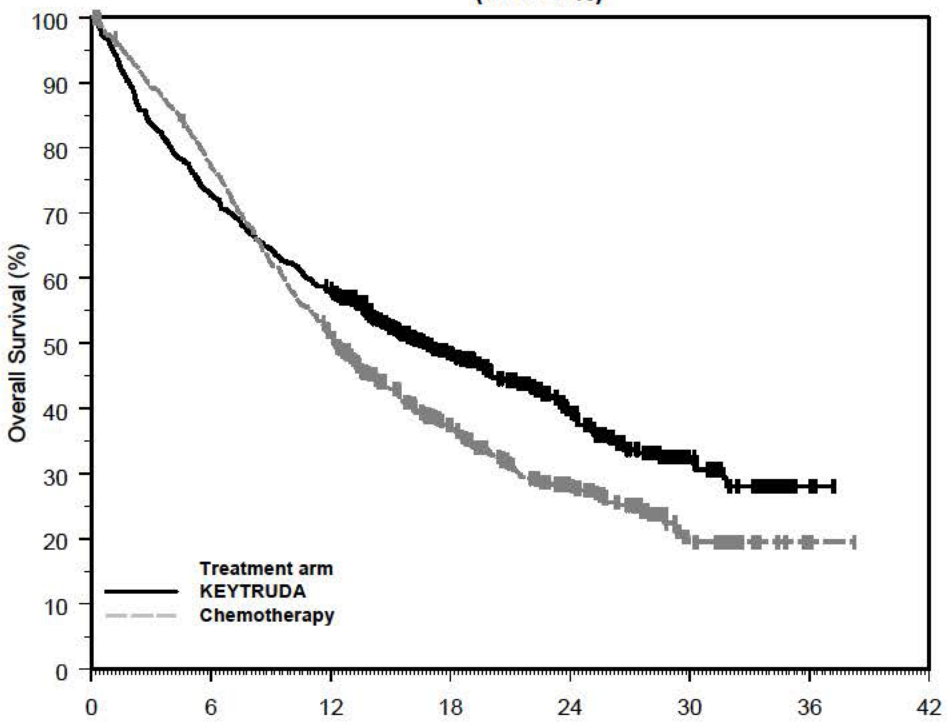
Table 32: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

	TPS ≥1%		**TPS ≥50%**	
Endpoint	**KEYTRUDA 200 mg every 3 weeks n=637**	**Chemotherapy n=637**	**KEYTRUDA 200 mg every 3 weeks n=299**	**Chemotherapy n=300**
OS				
Number of events (%)	371 (58%)	438 (69%)	157 (53%)	199 (66%)
Median in months (95% CI)	16.7 (13.9, 19.7)	12.1 (11.3, 13.3)	20.0 (15.4, 24.9)	12.2 (10.4, 14.2)
Hazard ratio* (95% CI)	0.81 (0.71, 0.93)		0.69 (0.56, 0.85)	
p-Value†	0.0036		0.0006	
PFS				
Number of events (%)	507 (80%)	506 (79%)	221 (74%)	233 (78%)
Median in months (95% CI)	5.4 (4.3, 6.2)	6.5 (6.3, 7.0)	7.1 (5.9, 9.0)	6.4 (6.1, 6.9)
Hazard ratio*,‡ (95% CI)	1.07 (0.94, 1.21)		0.81 (0.67, 0.99)	
p-Value†	-‡		NS§	
Objective Response Rate				
ORR‡ (95% CI)	27% (24, 31)	27% (23, 30)	39% (33.9, 45.3)	32% (26.8, 37.6)
Complete response rate	0.5%	0.5%	0.7%	0.3%
Partial response rate	27%	26%	39%	32%
Duration of Response				
% with duration ≥12 months¶	47%	16%	42%	17%
% with duration ≥18 months¶	26%	6%	25%	5%

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test; compared to a p-Value boundary of 0.0291
‡ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints
§ Not significant compared to a p-Value boundary of 0.0291
¶ Based on observed duration of response

The results of all efficacy outcome measures in the subgroup of patients with PD-L1 TPS ≥20% NSCLC were intermediate between the results of those with PD-L1 TPS ≥1% and those with PD-L1 TPS ≥50%. In a pre-specified exploratory subgroup analysis for patients with TPS 1-49% NSCLC, the median OS was 13.4 months (95% CI: 10.7, 18.2) for the pembrolizumab group and 12.1 months (95% CI: 11.0, 14.0) in the chemotherapy group, with an HR of 0.92 (95% CI: 0.77, 1.11).

Figure 6: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-042 (TPS ≥1%)



Number at Risk								
KEYTRUDA:	637	463	365	214	112	35	2	0
Chemotherapy:	637	485	316	166	88	24	1	0

KEYNOTE-024

The efficacy of KEYTRUDA was also investigated in KEYNOTE-024 (NCT02142738), a randomized, multicenter, open-label, active-controlled trial in 305 previously untreated patients with metastatic NSCLC. The study design was similar to that of KEYNOTE-042, except that only patients whose tumors had high PD-L1 expression (TPS of 50% or greater) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit were eligible. Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of any of the following platinum-containing chemotherapy regimens:

- Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m^2 on Days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for nonsquamous histologies).

Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression.

The main efficacy outcome measure was PFS as assessed by BICR review according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were OS and ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 65 years (range: 33 to 90), 54% age 65 or older; 61% male; 82% White and 15% Asian; 65% with ECOG PS of 1; 18% with squamous and 82% with nonsquamous histology and 9% with history of brain metastases. A total of 66 patients in the chemotherapy arm received KEYTRUDA at the time of disease progression.

The trial demonstrated a statistically significant improvement in both PFS and OS for patients randomized to KEYTRUDA as compared with chemotherapy. Table 33 and Figure 7 summarize the efficacy results for KEYNOTE-024.

Table 33: Efficacy Results in KEYNOTE-024

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=154**	**Chemotherapy n=151**
PFS		
Number (%) of patients with event	73 (47%)	116 (77%)
Median in months (95% CI)	10.3 (6.7, NR)	6.0 (4.2, 6.2)
Hazard ratio* (95% CI)	0.50 (0.37, 0.68)	
p-Value (stratified log-rank)	<0.001	
OS		
Number (%) of patients with event	44 (29%)	64 (42%)
Median in months (95% CI)†	30.0 (18.3, NR)	14.2 (9.8, 19.0)
Hazard ratio* (95% CI)	0.60 (0.41, 0.89)	
p-Value (stratified log-rank)	0.005‡	
Objective Response Rate		
ORR (95% CI)	45% (37, 53)	28% (21, 36)
Complete response rate	4%	1%
Partial response rate	41%	27%
p-Value (Miettinen-Nurminen)	0.001	
Median duration of response in months (range)	NR (1.9+, 14.5+)	6.3 (2.1+, 12.6+)

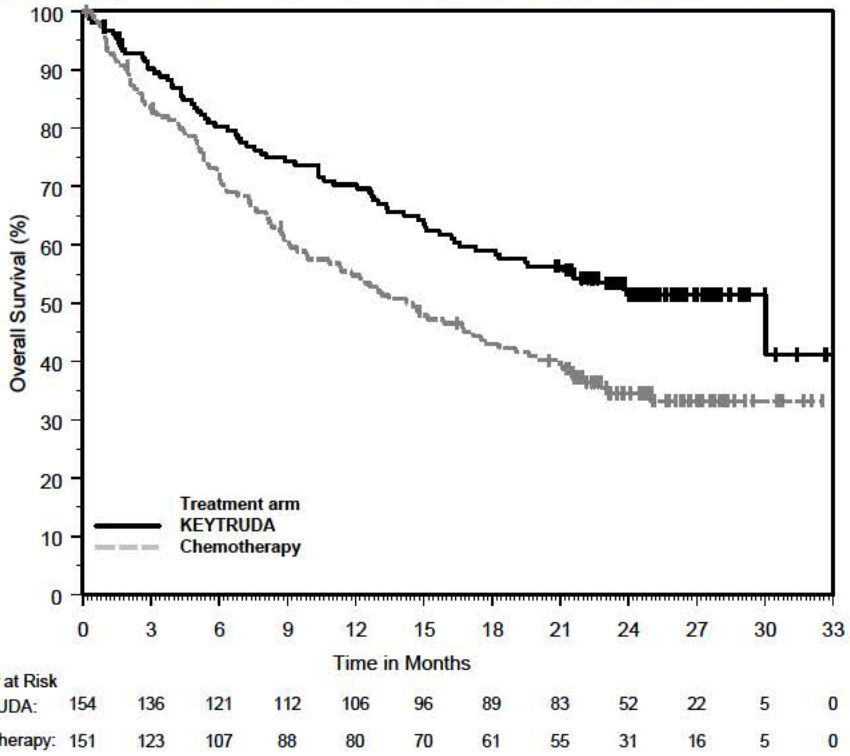
* Based on the stratified Cox proportional hazard model for the interim analysis

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

‡ p-Value is compared with 0.0118 of the allocated alpha for the interim analysis

NR = not reached

Figure 7: Kaplan-Meier Curve for Overall Survival in KEYNOTE-024*



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

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

Previously treated NSCLC

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

The study population characteristics were: median age 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG PS of 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic

aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease.

Tables 34 and 35 and Figure 8 summarize efficacy results in the subgroup with TPS ≥50% population and in all patients, respectively.

Table 34: Efficacy Results of the Subgroup of Patients with TPS ≥50% in KEYNOTE-010

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=139	KEYTRUDA 10 mg/kg every 3 weeks n=151	Docetaxel 75 mg/m^2 every 3 weeks n=152
OS			
Deaths (%)	58 (42%)	60 (40%)	86 (57%)
Median in months (95% CI)	14.9 (10.4, NR)	17.3 (11.8, NR)	8.2 (6.4, 10.7)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	89 (64%)	97 (64%)	118 (78%)
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
Objective Response Rate			
ORR† (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 16.8+)	NR (2.1+, 17.8+)	8.1 (2.1+, 8.8+)

* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† All responses were partial responses

NR = not reached

Table 35: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

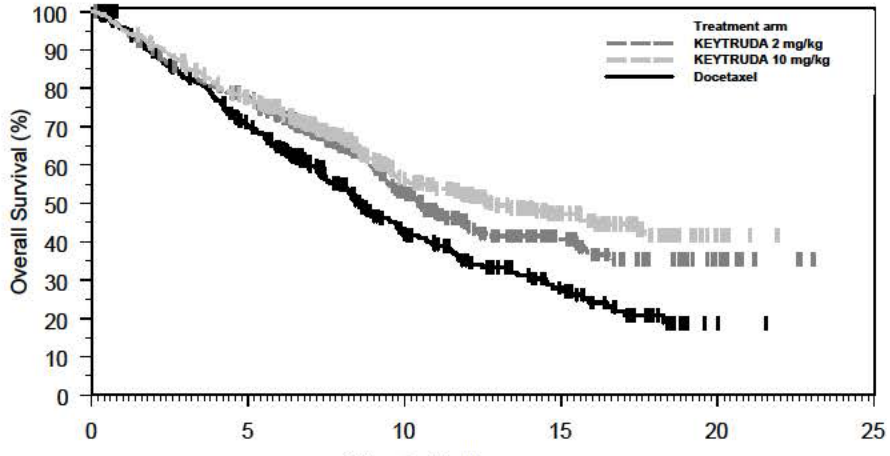
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
PFS			
Events (%)	266 (77%)	255 (74%)	257 (75%)
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value (stratified log-rank)	0.068	0.005	---
Objective Response Rate			
ORR† (95% CI)	18% (14, 23)	19% (15, 23)	9% (7, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 20.1+)	NR (2.1+, 17.8+)	6.2 (1.4+, 8.8+)

* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model

† All responses were partial responses

NR = not reached

Figure 8: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-010 (TPS ≥1%)



Number at Risk						
KEYTRUDA 2 mg/kg:	344	259	115	49	12	0
KEYTRUDA 10 mg/kg:	346	255	124	56	6	0
Docetaxel:	343	212	79	33	1	0

14.3 Head and Neck Squamous Cell Cancer

First-line treatment of metastatic or unresectable, recurrent HNSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS ≥50% or <50%) according to the PD-L1 IHC 22C3 pharmDx kit, HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs. 1). Patients were randomized 1:1:1 to one of the following treatment arms:

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

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

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)

sequentially tested in the subgroup of patients with CPS ≥20, the subgroup of patients with CPS ≥1, and the overall population.

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

The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA in combination with chemotherapy compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis in the overall population. The trial also demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 randomized to KEYTRUDA as a single agent compared to those randomized to cetuximab in combination with chemotherapy. At the time of the interim analysis, there was no significant difference in OS between the KEYTRUDA single agent arm and the control arm for the overall population. Table 36 and Figure 9 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

Table 36: Efficacy Results for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048

Endpoint	KEYTRUDA 200 mg every 3 weeks Platinum FU n=281	Cetuximab Platinum FU n=278
OS		
Number (%) of patients with event	197 (70%)	223 (80%)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
Hazard ratio* (95% CI)	0.77 (0.63, 0.93)	
p-Value†	0.0067	
PFS		
Number of patients with event (%)	244 (87%)	253 (91%)
Median in months (95% CI)	4.9 (4.7, 6.0)	5.1 (4.9, 6.0)
Hazard ratio* (95% CI)	0.92 (0.77, 1.10)	
p-Value†	0.3394	
Objective Response Rate		
ORR‡ (95% CI)	36% (30.0, 41.5)	36% (30.7, 42.3)
Complete response rate	6%	3%
Partial response rate	30%	33%
Duration of Response		
Median in months (range)	6.7 (1.6+, 30.4+)	4.3 (1.2+, 27.9+)

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response

In KEYNOTE-048, OS HRs for patients randomized to KEYTRUDA in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS ≥1 (HR 0.71, 95% CI: 0.57, 0.88), CPS ≥20 (HR 0.69, 95% CI:0.51, 0.94).

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

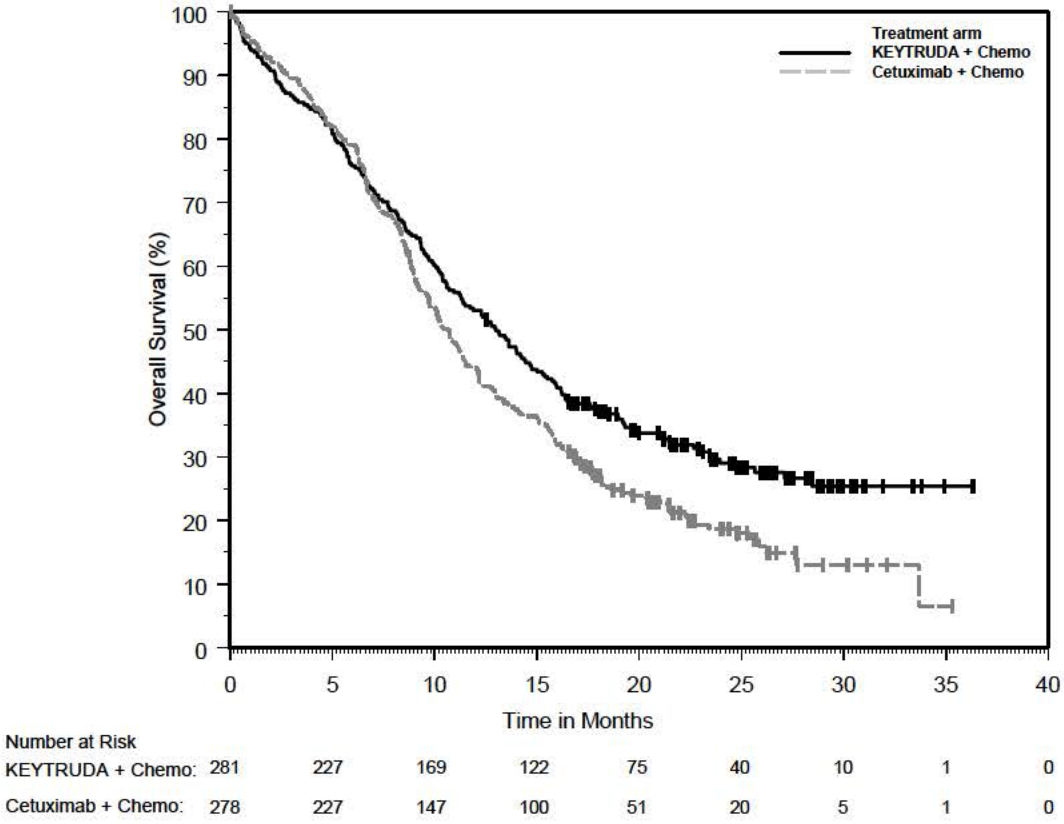


Table 37 summarizes efficacy results for KEYTRUDA as a single agent in the subgroup of patients with CPS ≥1 HNSCC and CPS ≥20 HNSCC. Figure 10 summarizes the OS results in the subgroup of patients with CPS ≥1 HNSCC.

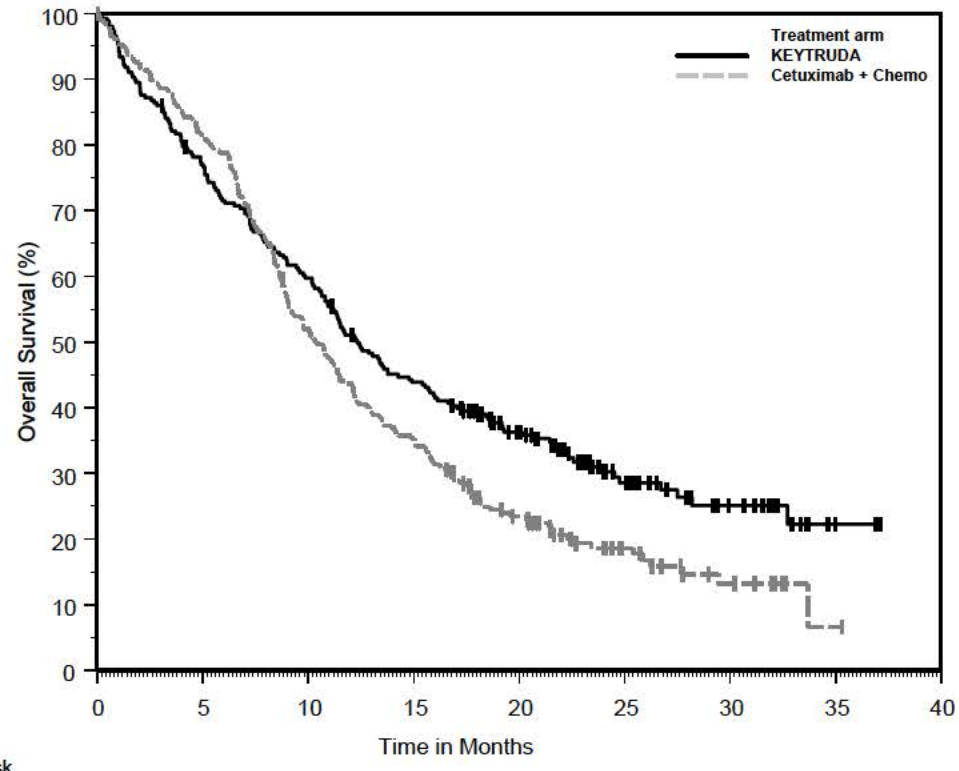
Table 37: Efficacy Results for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)

Endpoint	CPS ≥1		CPS ≥20	
	KEYTRUDA 200 mg every 3 weeks n=257	Cetuximab Platinum FU n=255	KEYTRUDA 200 mg every 3 weeks n=133	Cetuximab Platinum FU n=122
OS				
Number of events (%)	177 (69%)	206 (81%)	82 (62%)	95 (78%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0,11.5)	14.9 (11.6, 21.5)	10.7 (8.8, 12.8)
Hazard ratio* (95% CI)	0.78 (0.64, 0.96)		0.61 (0.45, 0.83)	
p-Value†	0.0171		0.0015	
PFS				
Number of events (%)	225 (88%)	231 (91%)	113 (85%)	111 (91%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 5.8)	3.4 (3.2, 3.8)	5.0 (4.8, 6.2)
Hazard ratio‡ (95% CI)	1.15(0.95, 1.38)		0.99 (0.75, 1.29)	
Objective Response Rate				
ORR‡ (95% CI)	19% (14.5, 24.4)	35% (29.1, 41.1)	23% (16.4, 31.4)	36% (27.6, 45.3)
Complete response rate	5%	3%	8%	3%
Partial response rate	14%	32%	16%	33%
Duration of Response				
Median in months (range)	20.9 (1.5+, 34.8+)	4.5 (1.2+, 28.6+)	20.9 (2.7, 34.8+)	4.2 (1.2+, 22.3+)

* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC, the median OS was 10.8 months (95% CI: 9.0, 12.6) for KEYTRUDA as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.90 (95% CI: 0.68, 1.18).

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



Number at Risk									
KEYTRUDA:	257	196	152	110	74	34	17	2	0
Cetuximab + Chemo:	255	207	131	89	47	21	9	1	0

Previously treated recurrent or metastatic HNSCC

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

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

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

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

14.4 Classical Hodgkin Lymphoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-087 (NCT02453594), a multicenter, non-randomized, open-label trial in 210 patients with relapsed or refractory cHL. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or > 5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months in patients who did not progress. Disease assessment was performed every 12 weeks. The major efficacy outcome measures (ORR, Complete Response Rate, and DoR) were assessed by BICR according to the 2007 revised International Working Group (IWG) criteria.

The study population characteristics were: median age of 35 years (range: 18 to 76), 9% age 65 or older; 54% male; 88% White; and 49% ECOG PS of 0 and 51% ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range: 1 to 12). Fifty-eight percent were refractory to the last prior therapy, including 35% with primary refractory disease and 14% whose disease was chemo-refractory to all prior regimens. Sixty-one percent of patients had undergone prior auto-HSCT, 83% had received prior brentuximab vedotin and 36% of patients had prior radiation therapy.

Efficacy results for KEYNOTE-087 are summarized in Table 38.

Table 38: Efficacy Results in KEYNOTE-087

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

* Median follow-up time of 9.4 months

† Based on patients (n=145) with a response by independent review

14.5 Primary Mediastinal Large B-Cell Lymphoma

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

The study population characteristics were: median age 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 39.

Table 39: Efficacy Results in KEYNOTE-170

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

* Median follow-up time of 9.7 months

† Based on patients (n=24) with a response by independent review

NR = not reached

14.6 Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-052 (NCT02335424), a multicenter, open-label, single-arm trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Tumor response assessments were performed at 9 weeks after the first dose, then every 6 weeks for the first year, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by independent radiology review, and DoR.

The study population characteristics were: median age of 74 years; 77% male; and 89% White. Eighty-seven percent had M1 disease, and 13% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 19% of patients had a primary tumor in the upper tract. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Reasons for cisplatin ineligibility included: 50% with baseline creatinine clearance of <60 mL/min, 32% with ECOG PS of 2, 9% with ECOG PS of 2 and baseline creatinine clearance of <60 mL/min, and 9% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

Among the 370 patients, 30% (n = 110) had tumors that expressed PD-L1 with a CPS ≥10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. The study population characteristics of these 110 patients were: median age 73 years, 68% male, and 87% White. Eighty-two percent had M1 disease, and 18% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 18% of patients had a primary tumor in the upper tract. Seventy-six percent of patients had visceral metastases, including 11% with liver metastases. Reasons for cisplatin ineligibility included: 45% with baseline creatinine clearance of <60 mL/min, 37% with ECOG PS of 2, 10% with ECOG PS of 2 and baseline creatinine clearance of <60 mL/min, and 8% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

The median follow-up time for 370 patients treated with KEYTRUDA was 7.8 months (range 0.1 to 20 months). Efficacy results are summarized in Table 40.

Table 40: Efficacy Results in KEYNOTE-052

Endpoint	KEYTRUDA 200 mg every 3 weeks		
	All Subjects n=370	**PD-L1 CPS <10 n=260***	**PD-L1 CPS ≥10 n=110**
Objective Response Rate			
ORR (95% CI)	29% (24, 34)	21% (16, 26)	47% (38, 57)
Complete response rate	7%	3%	15%
Partial response rate	22%	18%	32%
Duration of Response			
Median in months (range)	NR (1.4+, 17.8+)	NR (1.4+, 16.3+)	NR (1.4+, 17.8+)

* Includes 9 subjects with unknown PD-L1 status
\+ Denotes ongoing
NR = not reached

Previously Untreated Urothelial Carcinoma

KEYNOTE-361 (NCT02853305) is an ongoing, multicenter, randomized study in previously untreated patients with metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy. The study compares KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. The trial also enrolled a third arm of monotherapy with KEYTRUDA to compare to platinum-based chemotherapy alone. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and found that in patients classified as having low PD-L1 expression (CPS <10), those treated with KEYTRUDA monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The iDMC recommended to stop further accrual of patients with low PD-L1 expression in the monotherapy arm, however, no other changes were recommended, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm.

Previously Treated Urothelial Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-045 (NCT02256436), a multicenter, randomized (1:1), active-controlled trial in 542 patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients were randomized to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=90), docetaxel 75 mg/m^2 (n=92), or vinflunine 320 mg/m^2 (n=90). Treatment continued until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed at 9 weeks after randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

The study population characteristics were: median age 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 41 and Figure 11 summarize the efficacy results for KEYNOTE-045.

Table 41: Efficacy Results in KEYNOTE-045

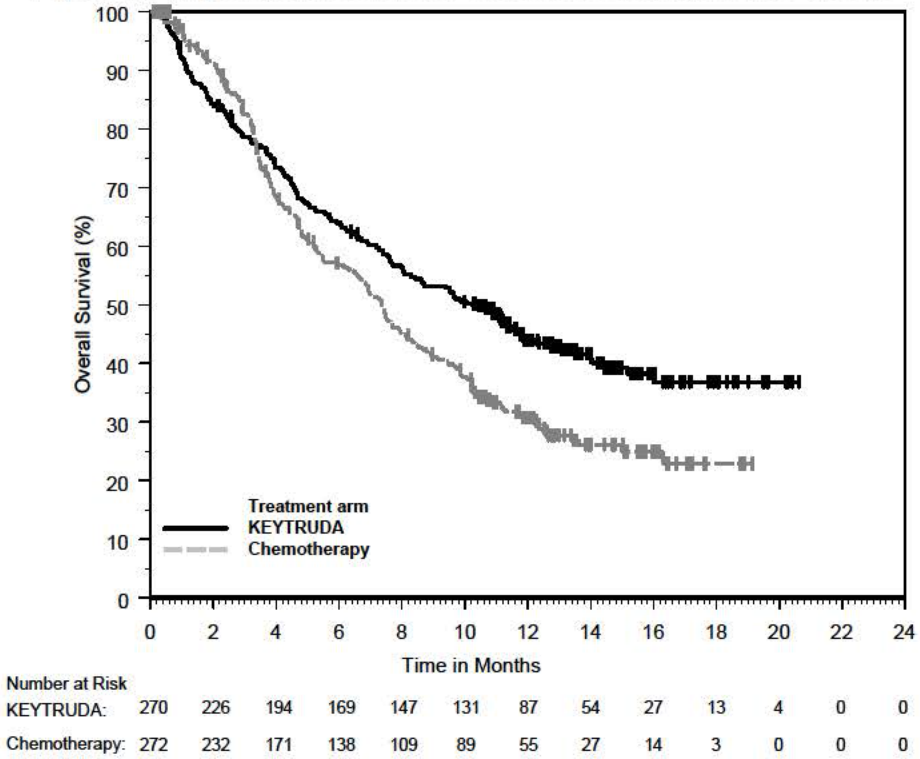
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
Hazard ratio* (95% CI)	0.98 (0.81, 1.19)	
p-Value (stratified log-rank)	0.833	
Objective Response Rate		
ORR (95% CI)	21% (16, 27)	11% (8, 16)
Complete response rate	7%	3%
Partial response rate	14%	8%
p-Value (Miettinen-Nurminen)	0.002	
Median duration of response in months (range)	NR (1.6+, 15.6+)	4.3 (1.4+, 15.4+)

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model

\+ Denotes ongoing

NR = not reached

Figure 11: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



14.7 Microsatellite Instability-High Cancer

The efficacy of KEYTRUDA was investigated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

Table 42: MSI-H Trials

Study	Design and Patient Population	Number of Patients	MSI-H/dMMR Testing	Dosage	Prior Therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

CRC = colorectal cancer
PCR = polymerase chain reaction
IHC = immunohistochemistry

A total of 149 patients with MSI-H or dMMR cancers were identified across the five trials. Among these 149 patients, the baseline characteristics were: median age 55 years, 36% age 65 or older; 56% male; 77% White, 19% Asian, 2% Black; and 36% ECOG PS of 0 and 64% ECOG PS of1. Ninety-eight percent of patients had metastatic disease and 2% had locally advanced, unresectable disease. The median number of prior therapies for metastatic or unresectable disease was two. Eighty-four percent of patients with metastatic CRC and 53% of patients with other solid tumors received two or more prior lines of therapy.

The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.

Efficacy results are summarized in Tables 43 and 44.

Table 43: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	KEYTRUDA 200 mg every 3 weeks n=149
Objective Response Rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4%
Partial response rate	32.2%
Duration of Response	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

NR = not reached

Table 44: Response by Tumor Type

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

14.8 Gastric Cancer

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

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

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

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

14.9 Cervical Cancer

The efficacy of KEYTRUDA was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort (Cohort E) in KEYNOTE-158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR, and DoR.

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

No responses were observed in patients whose tumors did not have PD-L1 expression (CPS <1). Efficacy results are summarized in Table 45 for patients with PD-L1 expression (CPS ≥1).

Table 45: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158

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

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

14.10 Hepatocellular Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-224 (NCT02702414), a single-arm, multicenter trial in 104 patients with HCC who had disease progression on or after sorafenib or were intolerant to sorafenib; had measurable disease; and Child-Pugh class A liver impairment. Patients with active autoimmune disease, greater than one etiology of hepatitis, a medical condition that required immunosuppression, or clinical evidence of ascites by physical exam were ineligible for the trial. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity, investigator-assessed confirmed disease progression (based on repeat scan at least 4 weeks from the initial scan

showing progression), or completion of 24 months of KEYTRUDA. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were ORR and DoR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

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

Efficacy results are summarized in Table 46.

Table 46: Efficacy Results in KEYNOTE-224

Endpoint	KEYTRUDA 200 mg every 3 weeks n=104
BICR-Assessed Objective Response Rate (RECIST v1.1)	
ORR (95% CI)*	17% (11, 26)
Complete response rate	1%
Partial response rate	16%
BICR-Assessed Response Duration	
% with duration ≥6 months	89%
% with duration ≥12 months	56%

* Based on patients (n=18) with a confirmed response by independent review

14.11 Merkel Cell Carcinoma

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

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

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

Efficacy results are summarized in Table 47.

Table 47: Efficacy Results in KEYNOTE-017

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=50
Objective Response Rate	
ORR (95% CI)	56% (41, 70)
Complete response rate (95% CI)	24% (13, 38)
Partial response rate (95% CI)	32% (20, 47)
Duration of Response	
Range in months*	5.9-34.5+
Patients with duration ≥6 months, n (%)	27 (96%)
Patients with duration ≥12 months, n (%)	15 (54%)

* The median duration of response was not reached.

14.12 Renal Cell Carcinoma

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

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

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

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

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

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR, as assessed by BICR. A statistically significant improvement in OS was demonstrated at the pre-specified interim analysis in patients randomized to KEYTRUDA in combination with axitinib compared with sunitinib. The trial also demonstrated statistically significant improvements in PFS and ORR. Table 48 and Figure 12 summarize the efficacy results for KEYNOTE-426. The median follow-up time was 12.8 months (range 0.1 to 22.0 months). Consistent results were observed across pre-specified subgroups, IMDC risk categories and PD-L1 tumor expression status.

Table 48: Efficacy Results in KEYNOTE-426

Endpoint	KEYTRUDA 200 mg every 3 weeks and Axitinib n=432	Sunitinib n=429
OS		
Number of patients with event (%)	59 (14%)	97 (23%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.53 (0.38, 0.74)	
p-Value†	<0.0001‡	
12-month OS rate	90% (86, 92)	78% (74, 82)
PFS		
Number of patients with event (%)	183 (42%)	212 (49%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.1 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.57, 0.84)	
p-Value†	0.0001§	
ORR		
Overall confirmed response rate (95% CI)	59% (54, 64)	36% (31, 40)
Complete response rate	6%	2%
Partial response rate	53%	34%
p-Value¶	<0.0001	

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

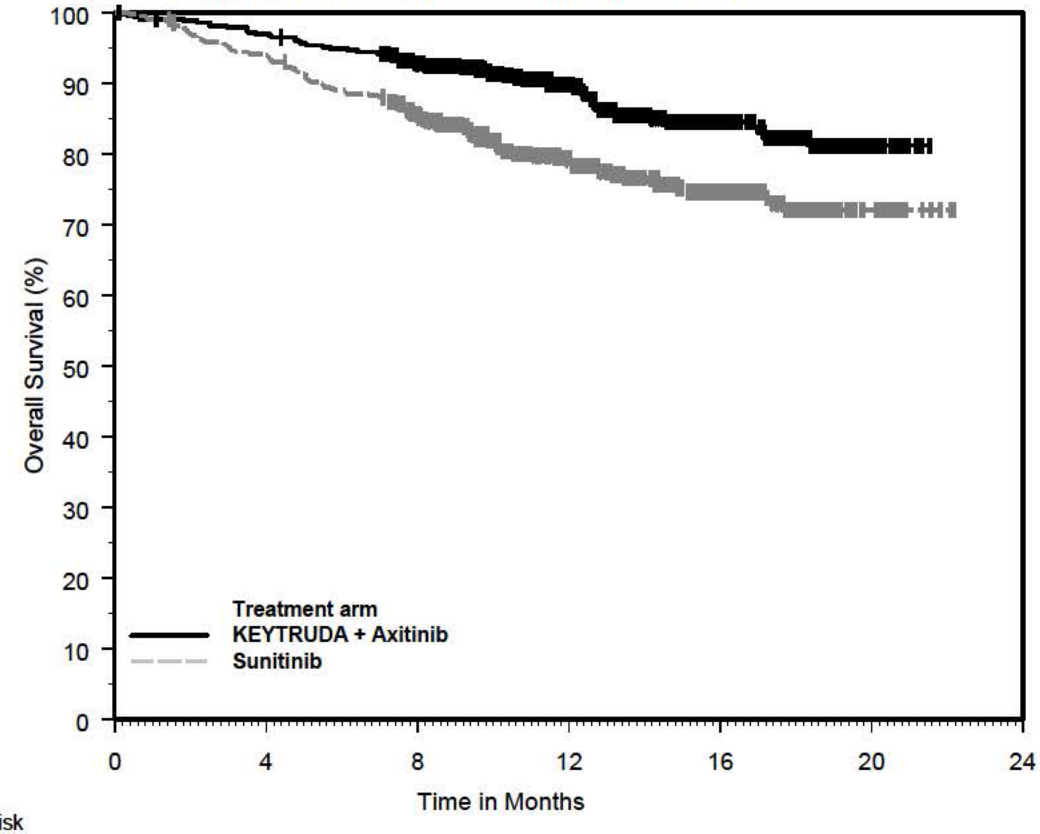
‡ p-Value (one-sided) is compared with the allocated alpha of 0.0001 for this interim analysis (with 39% of the planned number of events for final analysis).

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

¶ Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region

NR = not reached

Figure 12: Kaplan-Meier Curve for Overall Survival in KEYNOTE-426



Number at Risk							
KEYTRUDA + Axitin b:	432	417	378	256	136	18	0
Sunitinib:	429	401	341	211	110	20	0

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA for injection (white to off-white lyophilized powder):

Carton containing one 50 mg single-dose vial (NDC 0006-3029-02)
Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

KEYTRUDA injection (clear to slightly opalescent, colorless to slightly yellow solution):

Carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02)
Carton containing two 100 mg/4 mL (25 mg/mL), single-dose vials (NDC 0006-3026-04)
Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA. These reactions may include:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.

- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
- Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.
- Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.4)].*
- Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes *[see Warnings and Precautions (5.4)].*
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*.
- Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN *[see Warnings and Precautions (5.6)]*.
- Other immune-mediated adverse reactions:
  - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms *[see Warnings and Precautions (5.7)]*.
  - Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection *[see Warnings and Precautions (5.7)]*.

Infusion-Related Reactions

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.8)]*.

Complications of Allogeneic HSCT

- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.9)].*

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1, 8.3)].*
- Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for 4 months after the last dose *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1, 8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with KEYTRUDA and for 4 months after the final dose *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.3, 5.4, 5.5)]*.

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

U.S. License No. 0002

For KEYTRUDA for injection, at:
MSD International GmbH,
County Cork, Ireland

For KEYTRUDA injection, at:
MSD Ireland (Carlow)
County Carlow, Ireland

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

uspi-mk3475-iv-1906r027

MEDICATION GUIDE

KEYTRUDA® (key-true-duh)
(pembrolizumab)
for injection

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

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

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

Call or see your doctor right away if you develop any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Symptoms of pneumonitis may include:
- shortness of breath
- chest pain
- new or worse cough

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:
- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems, including hepatitis. Signs and symptoms of liver problems may include:
- yellowing of your skin or the whites of your eyes
- nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine
- bleeding or bruising more easily than normal

Hormone gland problems (especially the thyroid, pituitary, adrenal glands, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:
- rapid heart beat
- weight loss or weight gain
- increased sweating
- feeling more hungry or thirsty
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- muscle aches
- dizziness or fainting
- headaches that will not go away or unusual headache

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:
- change in the amount or color of your urine

Skin problems. Signs of skin problems may include:
- rash
- itching
- blisters, peeling or skin sores
- painful sores or ulcers in your mouth or in your nose, throat, or genital area

Problems in other organs. Signs and symptoms of these problems may include:
- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness
- low red blood cells (anemia)
- swollen lymph nodes, rash or tender lumps on skin, cough, shortness of breath, vision changes, or eye pain (sarcoidosis)

- confusion, fever, muscle weakness, balance problems, nausea, vomiting, stiff neck, memory problems, or seizures (encephalitis)
- shortness of breath, irregular heartbeat, feeling tired, or chest pain (myocarditis)

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

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

Rejection of a transplanted organ. People who have had an organ transplant may have an increased risk of organ transplant rejection. Your doctor should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.

Complications, including graft-versus-host-disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be severe and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with KEYTRUDA. Your doctor will monitor you for the following signs and symptoms: skin rash, liver inflammation, stomach-area (abdominal) pain, and diarrhea.

Getting medical treatment right away may help keep these problems from becoming more serious.
Your doctor will check you for these problems during treatment with KEYTRUDA. Your doctor may treat you with corticosteroid or hormone replacement medicines. Your doctor may also need to delay or completely stop treatment with KEYTRUDA, if you have severe side effects.

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat:

- a kind of skin cancer called melanoma. KEYTRUDA may be used:
  - when your melanoma has spread or cannot be removed by surgery (advanced melanoma), **or**
  - to help prevent melanoma from coming back after it and lymph nodes that contain cancer have been removed by surgery.
- a kind of lung cancer called non-small cell lung cancer (NSCLC).
  - KEYTRUDA may be used with the chemotherapy medicines pemetrexed and a platinum as your first treatment when your lung cancer:
    - has spread (advanced NSCLC), **and**
    - is a type called “nonsquamous”, **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
  - KEYTRUDA may be used with the chemotherapy medicines carboplatin and either paclitaxel or paclitaxel protein-bound as your first treatment when your lung cancer:
    - has spread (advanced NSCLC), **and**
    - is a type called “squamous”.
  - KEYTRUDA may be used alone as your first treatment when your lung cancer:
    - has not spread outside your chest (stage III) and you cannot have surgery or chemotherapy with radiation **or**
    - your NSCLC has spread to other areas of your body (advanced NSCLC), **and**
    - your tumor tests positive for “PD-L1”, **and**
    - does not have an abnormal “EGFR” or “ALK” gene.
  - KEYTRUDA may also be used alone when:
    - you have received chemotherapy that contains platinum to treat your advanced NSCLC, and it did not work or it is no longer working, **and**
    - your tumor tests positive for “PD-L1”, **and**
    - if your tumor has an abnormal “EGFR” or “ALK” gene, you have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.
- a kind of cancer called head and neck squamous cell cancer (HNSCC).
  - KEYTRUDA may be used with the chemotherapy medicines fluorouracil and a platinum as your first treatment when your head and neck cancer has spread or returned and cannot be removed by surgery.

- KEYTRUDA may be used alone as your first treatment when your head and neck cancer:
  - has spread or returned and cannot be removed by surgery, **and**
  - your tumor tests positive for "PD-L1".
- KEYTRUDA may be used alone when your head and neck cancer:
  - has spread or returned, **and**
  - you have received chemotherapy that contains platinum and it did not work or is no longer working.

- a kind of cancer called classical Hodgkin lymphoma (cHL) in adults and children when:
  - you have tried a treatment and it did not work **or**
  - your cHL has returned after you received 3 or more types of treatment.
- a kind of cancer called primary mediastinal B-cell lymphoma (PMBCL) in adults and children when:
  - you have tried a treatment and it did not work **or**
  - your PMBCL has returned after you received 2 or more types of treatment.
- a kind of bladder and urinary tract cancer called urothelial carcinoma. KEYTRUDA may be used when your bladder or urinary tract cancer:
  - has spread or cannot be removed by surgery (advanced urothelial cancer) **and**,
  - you are not able to receive chemotherapy that contains a medicine called cisplatin, and your tumor tests positive for "PD-L1", **or**
  - you are not able to receive a medicine called cisplatin or carboplatin, **or**
  - you have received chemotherapy that contains platinum, and it did not work or is no longer working.
- a kind of cancer that is shown by a laboratory test to be a microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumor. KEYTRUDA may be used in adults and children to treat:
  - cancer that has spread or cannot be removed by surgery (advanced cancer), **and**
  - has progressed following treatment, and you have no satisfactory treatment options, **or**
  - you have colon or rectal cancer, and you have received chemotherapy with fluoropyrimidine, oxaliplatin, and irinotecan but it did not work or is no longer working.

  It is not known if KEYTRUDA is safe and effective in children with MSI-H cancers of the brain or spinal cord (central nervous system cancers).
- a kind of stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma that tests positive for "PD-L1." KEYTRUDA may be used when your stomach cancer:
  - has returned or spread (advanced gastric cancer), **and**
  - you have received 2 or more types of chemotherapy including fluoropyrimidine and chemotherapy that contains platinum, and it did not work or is no longer working, **and**
  - if your tumor has an abnormal "HER2/neu" gene, you also received a HER2/neu-targeted medicine and it did not work or is no longer working.
- a kind of cancer called cervical cancer that tests positive for "PD-L1." KEYTRUDA may be used when your cervical cancer:
  - has returned, or has spread or cannot be removed by surgery (advanced cervical cancer), **and**
  - you have received chemotherapy, and it did not work or is no longer working.
- a kind of liver cancer called hepatocellular carcinoma, after you have received the medicine sorafenib.
- a kind of skin cancer called Merkel cell carcinoma (MCC) in adults and children. KEYTRUDA may be used to treat your skin cancer when it has spread or returned.
- a kind of kidney cancer called renal cell carcinoma (RCC). KEYTRUDA may be used with the medicine axitinib as your first treatment when your kidney cancer has spread or cannot be removed by surgery (advanced RCC).

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant, such as a kidney or liver
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have lung or breathing problems
- have liver problems
- have any other medical problems
- are pregnant or plan to become pregnant
  - KEYTRUDA can harm your unborn baby.

  Females who are able to become pregnant:
  - Your doctor will give you a pregnancy test before you start treatment with KEYTRUDA.
  - You should use an effective method of birth control during and for at least 4 months after the final dose of KEYTRUDA. Talk to your doctor about birth control methods that you can use during this time.
  - Tell your doctor right away if you think you may be pregnant or if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed.

- It is not known if KEYTRUDA passes into your breast milk.
- Do not breastfeed during treatment with KEYTRUDA and for 4 months after your final dose of KEYTRUDA.

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

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive KEYTRUDA?

- Your doctor will give you KEYTRUDA into your vein through an intravenous (IV) line over 30 minutes.
- KEYTRUDA is usually given every 3 weeks.
- Your doctor will decide how many treatments you need.
- Your doctor will do blood tests to check you for side effects.
- If you miss any appointments, call your doctor as soon as possible to reschedule your appointment.

What are the possible side effects of KEYTRUDA?

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

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

Common side effects of KEYTRUDA when given with certain chemotherapy medicines include: feeling tired or weak, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, trouble breathing, fever, hair loss, inflammation of the nerves that may cause pain, weakness, and paralysis in the arms and legs, swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina, and mouth sores.

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

In children, feeling tired, vomiting and stomach-area (abdominal) pain, and increased levels of liver enzymes and decreased levels of salt (sodium) in the blood are more common than in adults.

These are not all the possible side effects of KEYTRUDA. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you or that does not go away.

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

General information about the safe and effective use of KEYTRUDA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about KEYTRUDA, talk with your doctor. You can ask your doctor or nurse for information about KEYTRUDA that is written for healthcare professionals. For more information, go to www.keytruda.com.

What are the ingredients in KEYTRUDA?

Active ingredient: pembrolizumab

Inactive ingredients:

KEYTRUDA for injection: L-histidine, polysorbate 80, and sucrose. May contain hydrochloric acid/sodium hydroxide.

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

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

For KEYTRUDA for injection, at:
MSD International GmbH, County Cork, Ireland
For KEYTRUDA injection, at:
MSD Ireland (Carlow), County Carlow, Ireland
U.S. License No. 0002
For patent information: www.merck.com/product/patent/home.html

usmg-mk3475-iv-1906r024

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: June 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s052

MULTI-DISCIPLINE REVIEW

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

Application Type	sBLA
Application Number	125514/S-52
Priority or Standard	Priority
Submit Date	December 10, 2018
Received Date	December 10, 2018
PDUFA Goal Date	June 10, 2019
Division/Office	DOP2/OHOP
Review Completion Date	June 10, 2019
Established Name	Pembrolizumab
Trade Name	Keytruda
Pharmacologic Class	Programmed Death-Receptor-1 (PD-1) Blocking Antibody
Code name	MK-3475
Applicant	Merck Sharp & Dohme Corp.
Formulations	For injection, supplied in 50 mg single use vial; Injection, supplied in 100 mg/4 mL (25 mg/mL) single-use vial
Dosing Regimen	200 mg every 3 weeks until disease progression, unacceptable toxicity, or a maximum of 24 months, whichever is earlier
Applicant Proposed Indication	KEYTRUDA, as a single agent or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)	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.

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Regulatory Project Manager	Sharon Sickafuse
Clinical Reviewer	Shanti Marur
Clinical Team Leader	Erin Larkins
Statistical Reviewer	Pourab Roy
Statistical Team Leader	Pallavi Mishra-Kalyani
Cross-Disciplinary Team Leader	Erin Larkins
Associate Division Director (OB)	Yuan-Li Shen
Division Director (OHOP)	Patricia Keegan
Designated Signatory Authority	Patricia Keegan

Reviewers of Multi-Disciplinary Review and Evaluation

Additional Reviewers of Application

OPDP	Rachael Conklin
Patient Labeling	Sharon Mills

OPDP=Office of Prescription Drug Promotion

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
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
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Pembrolizumab is a humanized monoclonal antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2), releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Pembrolizumab is approved for the treatment of multiple solid tumors, including for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. This indication was approved under accelerated approval based on tumor response rate and durability of response.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The primary trial supporting this sBLA is KEYNOTE-048, a randomized, multicenter, three-arm, open-label, active-controlled trial comparing pembrolizumab as a single agent and pembrolizumab in combination with cisplatin or carboplatin and 5-fluorouracil (5-FU)] to cetuximab in combination with cisplatin or carboplatin and 5-FU (control arm) as first-line systemic therapy for 882 patients with metastatic head and neck squamous cell carcinoma (HNSCC) who had not received prior therapy for metastatic disease or with recurrent HNSCC who were not candidates for surgical resection or definitive chemoradiation. The co-primary endpoints for this study were overall survival (OS) and progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to a modified version of RECIST v1.1 (up to 10 total target lesions and up to 5 target lesions per organ), tested sequentially in the subgroup of patients with tumors with PD-L1 Combined Positive Score (CPS) ≥ 20 (CPS ≥20 HNSCC), the subgroup with CPS ≥1 HNSCC, and the overall population (intent-to treat [ITT]).

Pembrolizumab as a single agent
For the comparison of patients randomized to pembrolizumab as a single agent to patients randomized to cetuximab in combination with chemotherapy in KEYNOTE-048, efficacy results at the second interim analysis demonstrated a statistically significant improvement in OS for the CPS ≥20 and the CPS ≥1 subgroups of patients. The magnitude of the treatment effect was larger in the CPS ≥20 subgroup with a hazard ratio (HR) for OS of 0.61 (95% CI: 0.45, 0.83; p=0.0015) and a 4.2-month improvement in median OS (14.9 months and 10.7 months for those randomized to pembrolizumab and control, respectively) than in the CPS ≥1 subgroup. The HR for OS in the CPS ≥1 subgroup was 0.78 (95% CI: 0.64, 0.96; p= 0.0171), with a median OS 12.3 months and 10.3 months for those randomized to pembrolizumab and control, respectively. At the time of the interim analysis, there was no significant difference in OS

between the pembrolizumab as a single agent arm and the cetuximab plus chemotherapy arm for the ITT population. To further explore the potential impact of the level of PD-L1 expression on the observed treatment effect, exploratory analyses were conducted in the subgroup of patients with CPS 1-19 HNSCC. In this subgroup, the median OS was 10.8 months (95% CI: 9.0, 12.6) for pembrolizumab as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an OS HR of 0.90 (95% CI: 0.68, 1.18).

Pembrolizumab as a single agent did not demonstrate an improvement in PFS for the CPS ≥20 HNSCC subgroup (median PFS 3.4 months [95% CI 3.2, 3.8] vs 5.0 months [95% CI 4.8, 6.2] in the control arm, HR 0.99 [95% CI 0.75, 1.29]) or the CPS ≥1 HNSCC subgroup (median PFS 3.2 months [95% CI 2.2, 3.4] vs 5.0 months [95% CI 4.8, 5.8] in the control arm, HR 1.15 [95% CI 0.95, 1.38]). Given the sequential testing procedure, no other secondary endpoints could be tested for statistical significance. For the CPS ≥20 HNSCC subgroup, the point estimate for overall response rate (ORR) was lower in the pembrolizumab single agent arm compared to the control arm but the 95% CI overlapped (ORR 23% [95% CI 16, 31] vs 36% [95% CI 27, 45]. In the CPS ≥1 HNSCC subgroup, ORR was lower in the pembrolizumab single agent arm compared to the control arm (ORR 19% [95% CI 14, 24] vs 35% [95% CI 29, 41]. The median DOR was longer in the pembrolizumab as a single agent arm compared to the control arm in both the CPS ≥20 HNSCC subgroup (20.9 months [range 2.7 to 34.8+] vs 4.2 months [1.2+ to 22.3+]) and the CPS ≥1 HNSCC subgroup (20.9 months [range 1.5+ to 34.8+] vs 4.5 months [1.2+ to 28.6+]).

Pembrolizumab in combination with platinum and fluorouracil
For the comparison of patients randomized to pembrolizumab in combination with chemotherapy to patients randomized to cetuximab in combination with chemotherapy in KEYNOTE-048, efficacy results at the second interim analysis demonstrated a statistically significant improvement in OS for the ITT population, with an HR for OS of 0.77 (95% CI 0.63, 0.93; p=0.0067) and median OS of 13.0 months and 10.7 months for those randomized to pembrolizumab plus chemotherapy and control, respectively. Similar results were observed in the prespecified interim analyses of OS in the subgroups of patients with CPS ≥20 HNSCC (HR 0.69 [95% CI 0.51, 0.94]) and CPS ≥1 HNSCC (HR 0.71 [95% CI 0.57, 0.88]). In an exploratory analysis OS in the subgroup of patients with CPS <1 HNSCC, the HR was 1.07 (95% CI 0.66, 1.74), corresponding to a median OS of 11.3 months in the pembrolizumab plus chemotherapy arm and 10.7 months in the control arm.

There were no significant differences between PFS and ORR between the pembrolizumab plus chemotherapy arm and the control arm, with median PFS 4.9 months (95% CI 4.7, 6.0) in the pembrolizumab plus chemotherapy arm and 5.1 months (95% CI 4.9, 6.0) in the control arm and ORR 36% in both arms. The median DOR was 6.7 months (range 1.6+ to 30.4+) in the pembrolizumab plus chemotherapy arm compared to 4.3 months (range 1.2+ to 27.9+) in the control arm.

The submitted evidence meets the statutory evidentiary standard for regular approval. The results of KEYNOTE-048 demonstrate a statistically significant and clinically meaningful (2.0 -

month difference in estimated median OS) improvement in OS for patients with CPS ≥1 HNSCC receiving pembrolizumab as a single agent compared to cetuximab in combination with chemotherapy as first-line treatment for recurrent/metastatic HNSCC. These results are supported by demonstration of a longer median duration of response in the pembrolizumab arm compared to the cetuximab plus chemotherapy arm. The results of KEYNOTE-048 also demonstrate a statistically significant and clinically meaningful (2.3-month difference in estimated median OS) improvement in OS for all patients, regardless of PD-L1 status, receiving pembrolizumab in combination with platinum and 5-FU compared to cetuximab in combination with platinum and 5-FU as first-line treatment for recurrent/metastatic HNSCC. These results are supported by demonstration of a modest improvement in median duration of response in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm.

1.3. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Summary and Assessment

Pembrolizumab is a humanized monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2; it is approved for the treatment of multiple solid tumors, including head and neck squamous cell carcinoma (HNSCC). Pembrolizumab is approved as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response.

Metastatic HNSCC is a life-threatening condition with poor survival. The combination of cetuximab with cisplatin or carboplatin and 5-fluorourcil (5-FU) is a standard of care option for the first-line treatment of patients with metastatic HNSCC. A median overall survival (OS) of approximately 10 to 11 months has been reported with platinum-based combination regimens, with a median OS of 10.1 months reported for cetuximab in combination with cisplatin or carboplatin and 5-FU.

This application is primarily supported by a randomized, multicenter, three-arm, open-label, active-controlled trial, KEYNOTE-048, comparing pembrolizumab as a single agent and pembrolizumab in combination with cisplatin or carboplatin and 5-FU to cetuximab in combination with cisplatin or carboplatin and 5-FU (control) as first-line systemic therapy for 882 patients with metastatic HNSCC who had not received prior therapy for metastatic disease or with recurrent HNSCC who were not candidates for surgical resection or definitive chemoradiation. The co-primary endpoints for this study were overall survival (OS) and progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to modified RECIST v1.1, tested sequentially in the subgroup of patients with tumors with PD-L1 Combined Positive Score (CPS) ≥ 20 (CPS ≥20 HNSCC), the subgroup with CPS ≥1 HNSCC, and the overall population (intent-to treat [ITT]).

For the comparison of patients randomized to pembrolizumab as a single agent to patients randomized to cetuximab in combination with chemotherapy in KEYNOTE-048, efficacy results at the second interim analysis demonstrated a statistically significant improvement in OS for the CPS ≥20 and the CPS ≥1 subgroups of patients. The magnitude of the treatment effect was larger in the CPS ≥20 subgroup with a hazard ratio (HR) for OS of 0.61 (95% CI: 0.45, 0.83, p=0.0015) and a 4.2-month improvement in median OS (14.9 months and 10.7 months for those randomized to pembrolizumab and control, respectively). The HR for OS in the CPS ≥1 subgroup was 0.78 (95% CI: 0.64, 0.96, p= 0.0171, with a median OS 12.3 months and 10.3 months for those randomized to pembrolizumab and control, respectively. At the time of the interim analysis, there was no significant difference in OS between the pembrolizumab as a single agent arm and the cetuximab plus chemotherapy arm for the ITT population. To further explore the potential impact of the level of PD-L1 expression on the observed treatment effect, exploratory analyses were conducted in the subgroup of patients with CPS 1-19 HNSCC. In this subgroup, the median OS was 10.8 months (95% CI: 9.0, 12.6) for pembrolizumab as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an OS HR of 0.90 (95% CI: 0.68, 1.18).

Pembrolizumab as a single agent did not demonstrate an improvement in PFS for the CPS ≥20 HNSCC subgroup (median PFS 3.4 months [95% CI 3.2, 3.8] vs 5.0 months [95% CI 4.8, 6.2] in the control arm, HR 0.99 [95% CI 0.75, 1.29]) or the CPS ≥1 HNSCC subgroup (median PFS 3.2 months [95% CI 2.2, 3.4] vs 5.0 months [95% CI 4.8, 5.8] in the control arm, HR 1.15 [95% CI 0.95, 1.38]). Given the sequential testing procedure, no other secondary endpoints could be tested for statistical significance. For the CPS ≥20 HNSCC subgroup, the point estimate for overall response rate (ORR) was lower in the pembrolizumab single agent arm compared to the control arm but the 95% CI overlapped (ORR 23% [95% CI 16, 31] vs 36% [95% CI 27, 45]. In the CPS ≥1 HNSCC subgroup, ORR was lower in the pembrolizumab single agent arm compared to the control arm (ORR 19% [95% CI 14, 24] vs 35% [95% CI 29, 41]. The median DOR was longer in the pembrolizumab as a single agent arm compared to the control arm in both the CPS ≥20 HNSCC subgroup (20.9 months [range 2.7 to 34.8+] vs 4.2 months [1.2+ to 22.3+]) and the CPS ≥1 HNSCC subgroup (20.9 months [range 1.5+ to 34.8+] vs 4.5 months [1.2+ to 28.6+]).

For the comparison of patients randomized to pembrolizumab in combination with chemotherapy to patients randomized to cetuximab in combination with chemotherapy in KEYNOTE-048, efficacy results at the second interim analysis demonstrated a statistically significant improvement in OS for the ITT population, with an HR for OS of 0.77 (95% CI 0.63, 0.93, p=0.0067) and median OS of 13.0 months and 10.7 months for those randomized to pembrolizumab plus chemotherapy and control, respectively. Similar results were observed in the prespecified interim analyses of OS in the subgroups of patients with CPS ≥20 HNSCC (HR 0.69 [95% CI 0.51, 0.94]) and CPS ≥1 HNSCC (HR 0.71 [95% CI 0.57, 0.88]). In an exploratory analysis OS in the subgroup of patients with CPS <1 HNSCC, the HR was 1.07 (95% CI 0.66, 1.74), corresponding to a median OS of 11.3 months in the pembrolizumab plus chemotherapy arm and 10.7 months in the control arm.

There were no significant differences in PFS and ORR between the pembrolizumab plus chemotherapy arm and the control arm, with median PFS 4.9 months (95% CI 4.7, 6.0) in the pembrolizumab plus chemotherapy arm and 5.1 months (95% CI 4.9, 6.0) in the control arm and ORR 36% in both arms. The median DOR was 6.7 months (range 1.6+ to 30.4+) in the pembrolizumab plus chemotherapy arm compared to 4.3 months (range 1.2+ to 27.9+) in the control arm.

The observed safety profile of pembrolizumab is acceptable when assessed in the context of the treatment of a life-threatening disease. The most common adverse reactions in the pembrolizumab single agent arm were fatigue/asthenia, constipation, rash, cough, hypothyroidism, nausea, diarrhea, decreased appetite, weight loss, dyspnea, pyrexia, pneumonia, headache and pruritis. The most common adverse reactions in pembrolizumab plus chemotherapy patients were nausea, fatigue, constipation, vomiting, mucosal inflammation, diarrhea, decreased appetite, stomatitis, cough, pneumonia, rash, weight loss, hypothyroidism, peripheral sensory neuropathy, myalgia, dyspnea, neck pain, insomnia, and dizziness. There was a lower incidence of SAEs (40% vs 59% vs 49%), Grade 3-4 AEs (54% vs 85% vs 84%) and AEs leading to discontinuation of any study drug (12% vs 31% vs 27%) in patients treated with pembrolizumab as a single agent compared to patients treated with

pembrolizumab plus chemotherapy and the control arm. The incidence of deaths due to an AE in the pembrolizumab-containing arms (8 and 12%) of KEYNOTE-048 were similar to that observed in pooled safety data from 609 patients with R/M HNSCC who received pembrolizumab as single agent (the HNSCC monotherapy dataset, 8.9%) but higher than in the pembrolizumab single agent Reference Safety Database (RSD)" (3.9%). This suggests that underlying malignancy, co-morbid conditions and other confounding factors might have all contributed to the increased number of deaths due to AEs in the pembrolizumab arms of KEYNOTE-048 relative to the pembrolizumab single agent RSD.

The overall safety profile of pembrolizumab reported in KEYNOTE-048 was consistent with the known safety profile based on the pembrolizumab single agent RSD, except for a higher incidence of pneumonitis in KEYNOTE-048. The incidence of pneumonitis was 6% in the pembrolizumab single agent arm and 5% in the pembrolizumab plus chemotherapy arm of KEYNOTE-048, compared to an incidence of 4% in the HNSCC pembrolizumab monotherapy dataset and 3.4% in the pembrolizumab single agent RSD. In KEYNOTE-048, pembrolizumab was administered as first line treatment in the R/M setting and prior therapies such as relatively recent radiation therapy/chemoradiation may have contributed to the increased incidence of pneumonitis. The increased incidence of pneumonitis observed in KEYNOTE-048 will be included in the KEYTRUDA Prescribing Information. Significant and serious adverse reactions, including pneumonitis and other immune-mediated adverse reactions, are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in 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 safe use.

The results of KEYNOTE-048 demonstrate a statistically significant and clinically meaningful (2.0-month difference in estimated median OS) improvement in OS for patients with CPS ≥1 HNSCC receiving pembrolizumab as a single agent compared to cetuximab in combination with chemotherapy as first-line treatment for recurrent/metastatic HNSCC. These results are supported by demonstration of a longer median duration of response in the pembrolizumab arm compared to the cetuximab plus chemotherapy arm. The magnitude of the treatment effect on OS was larger in the CPS ≥20 subgroup than in the CPS ≥1 subgroup. To provide transparency and inform prescribers, results of the exploratory analysis of OS in the CPS 1-19% subgroup will be included in product labeling.

The results of KEYNOTE-048 also demonstrate a statistically significant and clinically meaningful (2.3-month difference in estimated median OS) improvement in OS for all patients, regardless of PD-L1 status, receiving pembrolizumab in combination with chemotherapy compared to cetuximab in combination with chemotherapy as first-line treatment for recurrent/metastatic HNSCC. Similar results were demonstrated in the prespecified interim analyses of OS in the subgroups of patients with CPS ≥20 HNSCC (HR 0.69 [95% CI 0.51, 0.94]) and CPS ≥1 HNSCC. The results in the ITT population are supported by demonstration of a modest improvement in median duration of response in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm.

In the opinion of the reviewers, the submitted evidence meets the statutory evidentiary standard for regular approval and provides substantial evidence of the effectiveness of pembrolizumab in combination with platinum and 5-FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC and of pembrolizumab as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥1). The reviewers recommend granting regular approval of pembrolizumab for the following indications:

- "Pembrolizumab, 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)."
- "Pembrolizumab, 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."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HNSCC accounts for 3.2% of all new cancers (51,000 new HNSCC cases) and 2.2% of all cancer deaths (10,000 deaths) annually in the United States. • Despite intensive multimodality treatment, loco-regional recurrences develop in 30% to 40% of patients and distant metastases in 20% to 30%. • The prognosis for recurrent/metastatic HNSCC is dismal with a median overall survival of 10-13 months.	Metastatic HNSCC is a life-threatening condition with poor survival.
Current Treatment Options	• Cetuximab with cisplatin or carboplatin and 5-FU is a standard of care option for the first-line treatment of patients with metastatic HNSCC.	Median OS of approximately 10-11 months has been reported with platinum-based combination regimens, with a median OS of 10.1 months reported for cetuximab in combination with cisplatin or carboplatin and 5-FU.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• This application is primarily supported by a randomized, multicenter, three-arm, open-label, active-controlled trial, KEYNOTE-048, comparing pembrolizumab as a single agent and pembrolizumab in combination with cisplatin or carboplatin and 5-FU to cetuximab in combination with cisplatin or carboplatin and 5-FU (control arm) as first-line systemic therapy for 882 patients with metastatic HNSCC who had not received prior therapy for metastatic disease or with recurrent HNSCC who were not candidates for surgical resection or definitive chemoradiation. The co-primary endpoints for this study were overall survival (OS) and progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to RECIST v1.1, tested sequentially in the subgroup of patients with tumors with PD-L1 Combined Positive Score (CPS) ≥ 20 (CPS ≥20 HNSCC), the subgroup with CPS ≥1 HNSCC, and the overall population (intent-to treat [ITT]). • For the comparison of patients randomized to pembrolizumab as a single agent to patients randomized to cetuximab in combination with chemotherapy in KEYNOTE-048, efficacy results at the second interim analysis demonstrated a statistically significant improvement in OS for the CPS ≥20 (HR 0.61 [95% CI 0.45, 0.83], median OS 14.9 months vs 10.7 months) and the CPS ≥1 (HR 0.78 [95% CI 0.64, 0.96], median OS 12.3 months vs 10.3 months) subgroups of patients. • At the time of the interim analysis, there was no significant difference in OS between the pembrolizumab as a single agent arm and the control arm for the ITT population. • In an exploratory analysis of OS in the subgroup of patients with CPS 1-19 HNSCC, OS HR was 0.90 (95% CI: 0.68, 1.18), with median OS 10.8 months vs 10.1 months.	The submitted evidence meets the statutory evidentiary standard for regular approval and provides substantial evidence of the effectiveness of pembrolizumab in combination with platinum and 5-FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC and of pembrolizumab as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥1). The results of KEYNOTE-048 demonstrate a statistically significant and clinically meaningful (2.0-month difference in estimated median OS) improvement in OS for patients with CPS ≥1 HNSCC for pembrolizumab as a single agent compared to cetuximab in combination with chemotherapy as first-line treatment for recurrent/metastatic HNSCC, supported by demonstration of a longer median duration of response in the pembrolizumab arm compared to the cetuximab plus chemotherapy arm. The magnitude of the treatment effect on OS was larger in the CPS ≥20 subgroup than in the CPS ≥1 subgroup. To provide transparency and inform prescribers, results of the exploratory analysis of OS in the CPS 1-19% subgroup will

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Pembrolizumab as a single agent did not demonstrate an improvement in PFS for the CPS ≥20 HNSCC subgroup (HR 0.99 [95% CI 0.75, 1.29], median PFS 3.4 months vs 5.0 months) or the CPS ≥1 HNSCC subgroup (HR 1.15 [95% CI 0.95, 1.38], median PFS 3.2 months vs 5.0 months). • For the CPS ≥20 HNSCC subgroup, the point estimate for overall response rate (ORR) was lower in the pembrolizumab single agent arm compared to the control arm (23% vs 36%). In the CPS ≥1 HNSCC subgroup, ORR was lower in the pembrolizumab single agent arm compared to the control arm (ORR 19% vs 35%). • The median DOR was longer in the pembrolizumab as a single agent arm compared to the control arm in both the CPS ≥20 HNSCC subgroup (20.9 months [range 2.7 to 34.8+] vs 4.2 months [1.2+ to 22.3+]) and the CPS ≥1 HNSCC subgroup (20.9 months [range 1.5+ to 34.8+] vs 4.5 months [1.2+ to 28.6+]). • For the comparison of patients randomized to pembrolizumab in combination with chemotherapy to patients randomized to cetuximab in combination with chemotherapy in KEYNOTE-048, efficacy results at the second interim analysis demonstrated a statistically significant improvement in OS for the ITT population (HR 0.77 [95% CI 0.63, 0.93], median OS 13.0 months vs 10.7 months). • Similar results were observed in the prespecified interim analyses of OS in the subgroups of patients with CPS ≥20 HNSCC (HR 0.69 [95% CI 0.51, 0.94]) and CPS ≥1 HNSCC (HR 0.71 [95% CI 0.57, 0.88]). • In an exploratory analysis OS in the subgroup of patients with CPS <1 HNSCC, the HR was 1.07 (95% CI 0.66, 1.74), corresponding to a median OS of 11.3 months in the pembrolizumab plus chemotherapy arm and 10.7 months in the control arm.	be included in product labeling. The results of KEYNOTE-048 also demonstrate a statistically significant and clinically meaningful (2.3-month difference in estimated median OS) improvement in OS for all patients, regardless of PD-L1 status, for pembrolizumab in combination with chemotherapy compared to cetuximab in combination with chemotherapy as first-line treatment for recurrent/metastatic HNSCC, supported by demonstration of a modest improvement in median duration of response in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm. Similar results were observed in the prespecified interim analyses of OS in the subgroups of patients with CPS ≥20 HNSCC (HR 0.69 [95% CI 0.51, 0.94]) and CPS ≥1 HNSCC. In an exploratory analysis OS in the subgroup of patients with CPS <1 HNSCC, the HR was 1.07 (95% CI 0.66, 1.74), corresponding to a median OS of 11.3 months in the pembrolizumab plus chemotherapy arm and 10.7 months in the control arm.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• PFS and ORR were similar for the pembrolizumab plus chemotherapy arm and the control arm (median PFS 4.9 months vs 5.1 months) and ORR (36% in both arms). The median DOR was 6.7 months (range 1.6+ to 30.4+) in the pembrolizumab plus chemotherapy arm compared to 4.3 months (range 1.2+ to 27.9+) in the control arm.	
Risk and Risk Management	• In KEYNOTE-048, the most common adverse reactions in the pembrolizumab single agent arm were fatigue/asthenia, constipation, rash, cough, hypothyroidism, nausea, diarrhea, decreased appetite, weight loss, dyspnea, pyrexia, pneumonia, headache and pruritis. • The most common adverse reactions in pembrolizumab plus chemotherapy patients were nausea, fatigue, constipation, vomiting, mucosal inflammation, diarrhea, decreased appetite, stomatitis, cough, pneumonia, rash, weight loss, hypothyroidism, peripheral sensory neuropathy, myalgia, dyspnea, neck pain, insomnia, and dizziness. • There was a lower incidence of SAEs (40% vs 59% vs 49%), Grade 3-4 AEs (54% vs 85% vs 84%) and AEs leading to discontinuation of any study drug (12% vs 31% vs 27%) in patients treated with pembrolizumab as a single agent compared to patients treated with pembrolizumab plus chemotherapy and control. • The incidence of deaths due to an AE in the pembrolizumab-containing arms (8 and 12%) of KEYNOTE-048 were similar to pooled safety data from 609 patients with R/M HNSCC who received pembrolizumab as single agent (the HNSCC monotherapy dataset, 8.9%) but higher than in the Pembrolizumab Single Agent Reference Safety Database (RSD) (3.9%). • The overall safety profile of pembrolizumab reported in KEYNOTE-048 was consistent with the known safety profile based on the	The observed safety profile of pembrolizumab is acceptable when assessed in the context of the treatment of a life-threatening disease. The finding of an incidence of deaths due to AE in the pembrolizumab-containing arms of KEYNOTE-048 higher than in the RSD but similar to the HNSCC monotherapy dataset suggests that underlying malignancy, co-morbid conditions and other confounding factors might have all contributed to the increased number of deaths due to AEs in the pembrolizumab arms of KEYNOTE-048 relative to the pembrolizumab single agent RSD. The higher incidence of pneumonitis observed in the pembrolizumab-containing arms of KEYNOTE-048 compared to the pembrolizumab single agent RSD may be due to the fact that in KEYNOTE-048 pembrolizumab was administered as first-line treatment in the R/M setting and prior therapies such as relatively recent radiation

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pembrolizumab single agent RSD, except for a higher incidence of pneumonitis. The incidence of pneumonitis was 6% in the pembrolizumab single agent arm and 5% in the pembrolizumab plus chemotherapy arm of KEYNOTE-048, compared to an incidence of 4% in the HNSCC pembrolizumab monotherapy dataset and 3.4% in the pembrolizumab single agent RSD.	therapy/chemoradiation may have contributed to the increased incidence of pneumonitis. The increased incidence of pneumonitis observed in KEYNOTE-048 will be included in the KEYTRUDA Prescribing Information. Significant and serious adverse reactions, including pneumonitis and other immune-mediated adverse reactions, are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in 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 safe use.

1.4. Patient Experience Data

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

□	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable

	x	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			x	Patient reported outcome (PRO)	Section 8.1.2, Study Results, "Efficacy Results – Secondary or exploratory COA (PRO) endpoints"
			□	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.				

Erin Larkins, M.D.
Cross-Disciplinary Team Leader

2 Therapeutic Context

- Analysis of Condition

Head and neck cancers are an anatomically heterogenous group of cancers that arise from the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx and spread to the regional cervical lymph nodes. The majority of head and neck cancers (90%) are squamous cell carcinomas, arising from the epithelium of the mucosal lining of the upper aerodigestive tract. Worldwide, HNSCC ranks as the ninth most common cancer with an estimated 650,000 new cases and 330,000 deaths per annum, with two-thirds of these cases occurring outside of United States[1]. In the United States, HNSCC accounts for 3.2% of all new cancers (approximately 53,000 new cases) and 2.2% of all cancer deaths (10,800 deaths), annually[2]. Over the past two decades a steady increase in human papilloma virus (HPV)-related oropharynx squamous cell carcinoma (OPSCC) has been observed[3]. Patients with HPV-positive OPSCC are typically middle-aged, nonsmoking white men and the prognosis is substantially better than that for patients with HPV-negative tobacco-related cancers treated similarly.[3]

At initial diagnosis, over 40% of patients with HNSCC present with locally advanced disease and 10% present with metastatic disease[4]. Treatment options for Stage I to Stage IVB HNSCC (AJCC 7th edition TNM staging) include surgery, radiation or chemoradiation. Despite intensive multimodality treatment, locoregional recurrences develop in 30% to 40% of patients, and distant metastases develop in 20% to 30%[4]. The prognosis for recurrent/metastatic HNSCC is dismal with a median overall survival of 10-13 months.[4]

2.2. Analysis of Current Treatment Options

Systemic treatment options for patients with unresectable, locally recurrent or metastatic HNSCC (R/M HNSCC) depend on the patient's overall performance status and comorbidities. For patients with good performance status, the current standard of care for first-line treatment is platinum-based combination chemotherapy and cetuximab[5]. The EXTREME trial demonstrated the addition of cetuximab to platinum plus 5-FU improved median OS from 7.4 months to 10.1 months. Patients with poor performance status or comorbidities are generally treated with single-agent chemotherapy or best supportive care.

In patients with R/M HNSCC who experience disease progression on first-line therapy, the objective responses to second-line cytotoxic chemotherapy are in the range of 10-16%, and prognosis is generally poor. The most widely used agents, as single agent or in combination, include platinum compounds (cisplatin, carboplatin), taxanes (docetaxel, paclitaxel), methotrexate, 5-FU, and single agent cetuximab.[6-12] In 2016, the United States Food and Drug Administration (FDA) granted accelerated approval for pembrolizumab for the treatment of

patients with R/M HNSCC who have progressed on prior platinum therapy based on tumor response rate and durability of response (ORR 16%, with 82% of responders having DOR ≥6 months) [7]. Later that same year, nivolumab, another anti-PD-1 antibody, received regular approval from the FDA for the same indication based upon an improvement in OS compared to investigator's choice (cetuximab, methotrexate, or docetaxel) of second-line therapy (median OS 7.5 months for nivolumab arm vs 5.1 months for control arm).[8]

Table 1: Agents Approved for First-Line Recurrent or Metastatic HNSCC

APPROVAL DATE	INDICATION	STUDIES AND APPROVAL ENDPOINTS
Nov 2011	CETUXIMAB [5, 11] In combination with platinum-based therapy and 5-fluorouracil for the first-line treatment of recurrent or metastatic HNSCC.	cisplatin/carboplatin plus 5FU plus cetuximab vs cisplatin/carboplatin plus 5FU • Median OS: 10.1 vs 7.4 months HR 0.80 (95% CI 0.64, 0.99) p=0.034 • Median PFS: 5.5 vs 3.3 months HR 0.57 (95% CI, 0.46, 0.72) p<0.0001 • ORR: 35.6% vs 19.5% p=0.0001 • Median DOR: 5.6 vs 4.7 months

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pembrolizumab (KEYTRUDA®) is approved in the U.S. for the following indications:

Melanoma

- Treatment of patients with unresectable or metastatic melanoma. Approval for the melanoma indication was granted on September 4, 2014 (accelerated approval, BLA 125514/0 with conversion to regular approval on December 18, 2015, BLA 125514/S-04 and S-06).
- Adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection (regular approval on February 15, 2019, BLA 125514/S-40).

NSCLC

- In combination with pemetrexed and platinum chemotherapy, for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations (accelerated approval on May 10, 2017, BLA 125514/S-16 with conversion to regular approval on August 20, 2018, BLA 125514/S-35).
- In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, for the first-line treatment of patients with metastatic squamous NSCLC (regular approval on October 30, 2018, BLA 125514/S-41).
- As a single agent, for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC, and whose tumors express PD L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. Regular approval as a single agent for first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (TPS ≥50%) as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations on October 24, 2016, BLA 125514/S-12; the cut-point for first-line treatment was expanded to PD-L1 TPS ≥1% in the population described in the current indication on April 11, 2019, BLA 125514/S-47).
- Treatment of patients with metastatic NSCLC whose tumors express PD-L1 TPS ≥1% as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab (accelerated approval on October 2, 2015, for the PD-L1 TPS ≥50% population (BLA 125504/S-05) and regular approval on October 24, 2016, with cut-point expanded to PD-L1 TPS ≥1%, BLA 125514/S-08).

Head and Neck Squamous Cell Cancer

- Treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy (accelerated approval on August 5, 2016, BLA 125514/S-09).

Classical Hodgkin Lymphoma

- Treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma, or those who have relapsed after three or more prior lines of therapy (accelerated approval on March 14, 2017, BLA 125514/S-15).

Primary Mediastinal Large B-Cell Lymphoma

- 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 (accelerated approval on June 13, 2018, BLA 125514/S-30).

Urothelial Carcinoma

- Treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy (accelerated approval granted on May 18, 2017, BLA 125514/S-17). On June 19, 2018, the indication was revised to limit the use to patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 Combined Proportion Score (CPS) ≥10 as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status (BLA 125514/S-43 and S-46).
- Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (regular approval on May 18, 2017, BLA 125514/S-18)

Microsatellite Instability-High Cancer

- Treatment of adult and pediatric patients with:
  - Unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have not satisfactory alternative treatment options, or
  - Metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (accelerated approval on May 23, 2017, BLA 125514/S-14).

Gastric Cancer

- Treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 CPS ≥1 as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2*neu*-targeted therapy (accelerated approval on September 22, 2017, BLA 125514/S-24).

Cervical Cancer

- 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 (accelerated approval on June 12, 2018, BLA 125514/S-34).

Hepatocellular Carcinoma (HCC)

- Treatment of patients with HCC who have been previously treated with sorafenib (accelerated approval on November 9, 2018, BLA 125514/S-42).

Merkel Cell Carcinoma (MCC)

- Treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (accelerated approval on December 19, 2018, BLA 125514/S-45).

Renal Cell Carcinoma (RCC)

- In combination with axitinib, for the first-line treatment of patients with advanced RCC (regular approval on April 19, 2019, BLA 125514/S-54).

3.2. Summary of Presubmission/Submission Regulatory Activity

DATE	MILESTONE
7/30/2014	Initial IND 122325 for HNSCC was submitted containing the protocol for the KEYNOTE-055 study, entitled: "A Phase II Clinical Trial of Single Agent Pembrolizumab (MK-3475) in Subjects With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC) Who Have Failed Platinum and Cetuximab".
8/8/2014	Merck submitted an initial Pediatric Study Plan for HNSCC including a request for waiver from the requirements of PREA.
12/22/2014	Protocol for the KEYNOTE-048 study entitled "A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma" was submitted to IND 122325.
8/13/2015 to 10/2/2015	Notification on August 13, 2015 (SDN 0449), informing FDA of a pause in enrollment to the pembrolizumab and chemotherapy combination arm in KEYNOTE-048 based on Data Monitoring Committee (DMC) request. The DMC reviewed data on 3 patients (out of 14 patients enrolled as of July 24, 2015) enrolled on the pembrolizumab plus chemotherapy arm that died on study. Two of these deaths were due to disease progression and one death was due to pneumonia and severe neutropenia. Notification to FDA that this temporary halt to enrollment was removed as of October 2, 2015 (SDN 471) per DMC recommendation.
2/11/2016	FDA agreement letter on agreed iPSP for pembrolizumab for the treatment of recurrent or metastatic HNSCC issued.
8/5/2016	KEYTRUDA® received accelerated approval for the treatment of patients with R/M HNSCC with disease progression on or after platinum-containing chemotherapy based on KEYNOTE-012 with supporting data from KEYNOTE-055.
2/28/2018	Supplemental BLA filing (b) (4) for the treatment of patients with R/M HNSCC with disease progression on or after platinum-containing chemotherapy based on the results of- KEYNOTE-040 (A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Control in Patients with Recurrent or Metastatic Head and Neck Cancer).

DATE	MILESTONE
8/6/2018	Merck proposal to fulfill PMR 3100-1 with results of KEYNOTE-048. Merck requested FDA's consideration for the submission of results of study KEYNOTE-048 instead of KEYNOTE-040 to fulfill post-marketing requirement 3100-1 for the Accelerated Approval received on August 5, 2016 for sBLA S-09 (KEYNOTE-012) for the treatment of patients with R/M HNSCC with disease progression on or after platinum containing chemotherapy. Merck also informed FDA of plan to file an sBLA based on the results of KEYNOTE-048 by December 2018.
8/28/2018	Withdrawal of sBLA (b) (4) for KEYNOTE-040 by Merck.
8/29/2018	FDA acknowledged Merck's withdrawal of sBLA (b) (4) (KEYNOTE-040).
10/10/2018	FDA preliminary comments for Type B pre-sBLA meeting for October 17, 2018, to discuss the content and format of an sBLA based on KEYNOTE-048.
12/18/2018	sBLA based on the results of KEYNOTE-048 submitted with two proposed indications.

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

4.1. Office of Scientific Investigations (OSI)

Clinical site inspection was not requested for BLA 125514/S-52, given the non-subjective nature of the primary endpoint (OS) and supportive results from prior clinical studies in metastatic HNSCC.

The pivotal study supporting this application is KEYNOTE-048, a randomized, active-controlled, open-label, multi-national study. The primary efficacy parameters of the study are OS and PFS, as assessed by blinded independent central review (BICR). The trial randomized a total of 882 across 200 centers in 37 countries.

CDER's Clinical Investigator Site Selection Tool (CISST) version 2.5.10 was used to rank sites according to risk to patient safety and data integrity. A review of major safety and efficacy parameters using dataset aae.xpt, the incidence and causes of serious adverse events (SAEs), Grade 3 to 5 AEs and deaths at the 5 highest enrolling sites (> 5 patients) did not reveal unexpected findings that would impact the overall study results or the risk-benefit assessment of the trial. Two of the 5 sites had been inspected by FDA previously. (b) (4) was the contract research organizations (CRO) that was responsible for IRC assessments and (b) (4) inspected by FDA in March 2018 for BLA 125514 S-034 and no action were indicated. Therefore, clinical site or CRO inspections were not deemed necessary for this efficacy supplement.

Reviewer Comment: During review of the application, Merck notified FDA that an error had been noted at (b) (4) *in their algorithmic program for calculating tumor status. Merck provided corrected data for affected patients with minimal effects on the results. This is discussed in the clinical section of this review.*

Merck conducted directed audits of 12 investigators during the period November 21, 2016, to October 12, 2017. Merck had a comprehensive audit program to assess the quality of contracted contract research organizations (CROs), laboratories, central facilities and any other type of vendor supporting the clinical development programs. Merck conducted a process, vendor and technology audit on a facility (b) (4) located in (b) (4) that was the contracted CRO on (b) (4)

4.2. Product Quality

No new CMC information was provided in the supplement S-52 application. Refer to CDER's Quality Review for the original BLA submission.

4.3. Clinical Microbiology

No clinical microbiology data were submitted in the supplement S-52 application.

4.4. Devices and Companion Diagnostic Issues

On January 18, 2018, Dako North America, Inc submitted a supplemental premarket application (sPMA, P150013/S014) for the PD-L1 IHC 22C3 pharmDx companion diagnostic device with a proposal to include data from KEYNOTE-048 in the device labeling and to expand the intended use to include identification of HNSCC patients for treatment with KEYTRUDA. The PD-L1 IHC 22C3 pharmDx companion diagnostic device is currently approved as a companion diagnostic identifying patients with NSCLC, gastric and gastro-esophageal junction, cervical, and urothelial cancer for treatment with KEYTRUDA. The following information regarding the sPMA was provided to CDER by the CDRH review team (Division of Molecular Genetics and Pathology, Office of In Vitro Diagnostics and Radiological Health).

The PD-L1 IHC 22C3 pharmDx device is a qualitative immunohistochemical (IHC) assay using monoclonal mouse anti-PD-L1, clone 22C3, intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) tumor tissue. The submission for sPMA P150012/S014 included analytical validation of the PD-L1 IHC in the HNSCC indication establishing the performance characteristics for the device and referenced the sBLA application and KEYNOTE-048 to support the clinical validation of the device as a companion diagnostic (CDx) for selecting HNSCC patients eligible for treatment with KEYTRUDA®. Of note the sPMA application was limited to reviewing the clinical validity of the PD-L1 IHC 22C3 in selecting patients with HNSCC eligible for KEYTRUDA as a single agent and reviewed data from the control arm and the KEYTRUDA as a single agent arm of KEYNOTE-048 and did not assess outcomes in the KEYTRUDA and chemotherapy arm.

Combined Positive Score (CPS) is defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. Analytical validation for the CDx test was performed at two clinical cutoffs of CPS $\geq$1 and CPS $\geq$20. Analytical validation of the CPS $\geq$1 cutoff for HNSCC tumor specimens met prespecified acceptance criteria, and the assay performance was appropriately characterized for use at this clinical cutoff. However, analytical validation for the CPS $\geq$20 cutoff did not pass pre-specified acceptance criteria and, therefore, the test was considered not validated for use at this clinical cutoff.

For the clinical validation of the PD-L1 IHC 22C3 test, the final test was used to test tumor specimens from patients enrolled in KEYNOTE-048 for purposes of stratification, which was based on the Tumor Proportion Score (TPS) $\geq$50% cutoff. Based on protocol revisions, the tumor specimens were retrospectively assessed for dichotomous PD-L1 status based on CPS $\geq$1 and CPS $\geq$20 cutoffs in two additional independent reads by a qualified pathologist. The underlying

continuous CPS score was recorded for the tumor specimens with each round of PD-L1 scoring. However, large variability in the assessment of the continuous score (30% discordance for specimens with CPS scores >1-19) indicated that the reader variability was high and that the assay was not adequately validated to assess the underlying continuous scores.

The MDUFA date for this sPMA is July 17, 2019. CDRH plans to take action concurrently with CDER on the action date for BLA125514/S-0452 and will be recommending approval of the sPMA with addition of the following intended use for HNSCC at the CPS ≥1 cutoff:

> *PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying head and neck squamous cell carcinoma patients for treatment with KEYTRUDA® (pembrolizumab).*

5 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology data were submitted in the supplement S-52 application.

6 Clinical Pharmacology

6.1. Executive Summary:

No clinical pharmacology data were submitted in the supplement S-52 application.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The primary evidence to support the efficacy and safety of pembrolizumab as a single agent and in combination with platinum plus 5-FU is based on results from 882 patients enrolled on KEYNOTE-048, an ongoing, randomized, multicenter, active-controlled, open-label clinical trial in patients with R/M HNSCC considered incurable by local therapies (Table 2).

The study has three treatment arms:

- Pembrolizumab plus chemotherapy (platinum plus 5-FU) (n=281)
- Pembrolizumab single agent (n=301)
- Control (cetuximab plus platinum plus 5-FU, commonly referred to as the EXTREME regimen) (n=278)

Efficacy data in this submission are based on the second interim analysis (IA2) of KEYNOTE-048 with a data cutoff date of June 13, 2018, 38 months after study start and 17 months after the last participant was enrolled.

The primary safety review for pembrolizumab in the indicated first-line R/M HNSCC population focused on data submitted from KEYNOTE-048, and the results were compared with pooled safety data for patients with previously treated R/M HNSCC who received pembrolizumab as a single agent in three clinical trials, KEYNOTE-040, KEYNOTE-012 Cohorts B and B2, and KEYNOTE-055 (referred to hereafter as the HNSCC safety dataset). Enrollment is complete in all four studies.

Table 2: Clinical Trials to Support Efficacy and Safety of Pembrolizumab in R/M HNSCC

Study ID/Title	Trial Design	Population	Regimen/ schedule/ route	Study Endpoints	Patients Enrolled
CLINICAL TRIALS TO SUPPORT EFFICACY AND SAFETY					
KEYNOTE-048 "A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma"	Randomized (1:1:1), active controlled parallel-group, multi-site, open-label	Males/females Age: 18 and older Metastatic HNSCC who have not previously received systemic therapy for metastatic disease.	Pembrolizumab monotherapy Pembrolizumab 200 mg Q3W Pembrolizumab + Chemotherapy Pembrolizumab 200 mg Q3W + platinum (cisplatin 100 mg/m^2 Q3W or carboplatin AUC 5 mg/mL/min Q3W) + 5-FU 1000 mg/m^2/day 4 days Q3W Control Cetuximab (400mg/m^2 load then 250 mg/m^2 QW) + platinum (cisplatin 100mg/m^2 Q3W or carboplatin AUC 5 mg/mL/min Q3W) + 5FU 1000 mg/m^2/day 4 days Q3W	Primary: PFS and OS in ITT, CPS $\geq$1, CPS $\geq$20 Secondary: ORR, DOR	IA2 = 882 Pembrolizumab N=301 Pembrolizumab + chemotherapy N=281 Chemotherapy N=278

Study ID/Title	Trial Design	Population	Regimen/ schedule/ route	Study Endpoints	Patients Enrolled
CLINICAL TRIALS TO SUPPORT SAFETY					
KN-040 A Phase III Randomized Trial of MK-3475 (Pembrolizumab) Versus Control in Subjects With Recurrent or Metastatic Head and Neck Cancer	Randomized, multicenter, active-controlled, open-label clinical study	Males/females Age: 18 and older R/M HNSCC whose disease had progressed on or after prior platinum-containing chemotherapy (which was administered up to 6 months following definitive/adjuvant therapy or as either 1L or 2L therapy for R/M disease).	Pembrolizumab monotherapy Pembrolizumab 200 mg Q3W Investigator Choice Standard Monotherapy with methotrexate 40 mg/m^2 to 60 mg/m^2 QW, docetaxel 75 mg/m^2 Q3W, or cetuximab 400 mg/m^2 loading dose followed by 250 mg/m^2 QW	Primary: OS Secondary: PFS, ORR	Pembrolizumab N=246 IC Standard N=235
KN-055 A Phase II Clinical Trial of Single Agent Pembrolizumab (MK-3475) in Subjects With Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC) Who Have Failed Platinum and Cetuximab	Phase 2, nonrandomized, multicenter, single-cohort, open label	Males/females Age: 18 and older R/M HNSCC whose disease has progressed on or after prior platinum-containing chemotherapy and cetuximab therapy	Pembrolizumab monotherapy Pembrolizumab 200 mg Q3W	Primary: Safety Secondary: ORR	Pembrolizumab N=172
KN-012 A Phase Ib Multi-Cohort Study of MK-3475 in Subjects With Advanced Solid Tumors	Phase 1b, nonrandomized, multicenter, open-label, multi-cohort	Males/females Age: 18 and older Advanced solid tumors, including R/M HNSCC	Cohort B (N=60): Pembrolizumab 10 mg/kg Q2W. • Cohort B2 (N=132): Pembrolizumab 200 mg Q3W	Primary: Safety Secondary: ORR	Cohort B N=60 Cohort B2 N=132

7.2. Review Strategy

The efficacy review was focused on data submitted from IA2 for the 882 patients randomized to one of the three arms (pembrolizumab as a single agent, pembrolizumab plus chemotherapy, and control) in KEYNOTE-048. The median duration of follow-up was 13.0 months (range: 0.1-36.6) in the pembrolizumab plus chemotherapy arm, 11.7 months (range: 0.2-37.3) in the pembrolizumab arm, and 10.7 months (range: 0.1-35.3) in the control arm.

During the review period, the following issue was identified:

- The pre-specified statistical plan per amendment 5 included a hierarchical non-inferiority testing of OS of each pembrolizumab arm compared to the control arm in the overall population after the tests for OS in subgroups CPS $\geq$20, CPS $\geq$10 and CPS $\geq$1 and before the superiority test in the overall population. This modification in amendment 5 was not discussed with FDA and was not agreed upon with Merck. A teleconference was held on March 21, 2019 and Merck was informed that the changes made to protocol amendment 5 were not agreed upon by FDA, and that it was unlikely that the results of the non-inferiority analysis for the comparison of pembrolizumab as a single agent to standard therapy would be considered adequate to support an indication for pembrolizumab as a single agent in all comers based on the non-inferiority margin chosen, which is not acceptable to FDA.

The primary safety profile review for pembrolizumab in the indicated R/M HNSCC population was focused on data submitted from KEYNOTE-048, and the results were compared to data outputs provided by Merck from the HNSCC safety dataset described above in Section 7.1. Safety analyses included all patients who received at least one dose of study medication for each study or cohort as of the data cutoff dates shown below:

Study or Cohort and Data Cutoff Date
KEYNOTE-048: 13-JUN-2018
KEYNOTE-040: 15-MAY-2017
KEYNOTE-012: 26-APR-2016
KEYNOTE-055: 22-APR-2016

To assess the reliability and quality of the data, the clinical reviewer conducted random cross-validation of datasets with CRF forms for KEYNOTE-048. Datasets, clinical study reports, case report forms, case narratives, Data Monitoring Committee reports, and all supportive analyses submitted by the applicant for KEYNOTE-048 were reviewed.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. KEYNOTE-048

Trial Design

KEYNOTE-048 is an ongoing, randomized, multicenter, active-controlled, open-label clinical trial in patients with R/M HNSCC considered incurable by local therapies. Randomization is stratified by HPV status (positive versus negative), ECOG PS (0 versus 1), and tumor PD-L1 expression (TPS ≥50% versus <50%). TPS is defined by the percentage of neoplastic cells expressing PD-L1 at any intensity (weak, moderate, or strong), and only takes into account the expression of PD-L1 on neoplastic cells. The sample size of patients considered to have tumors "strongly positive" for PD-L1 (TPS ≥50%) was projected to be approximately 200 patients across the three arms. However, the protocol may be amended to increase the sample size "to ensure that at least 100 strongly positive PD-L1 subjects are enrolled in each of the pembrolizumab and control arms if the prevalence of the strongly positive PD-L1 subgroup is lower than expected based on emerging data."

The study has three arms:

Experimental:

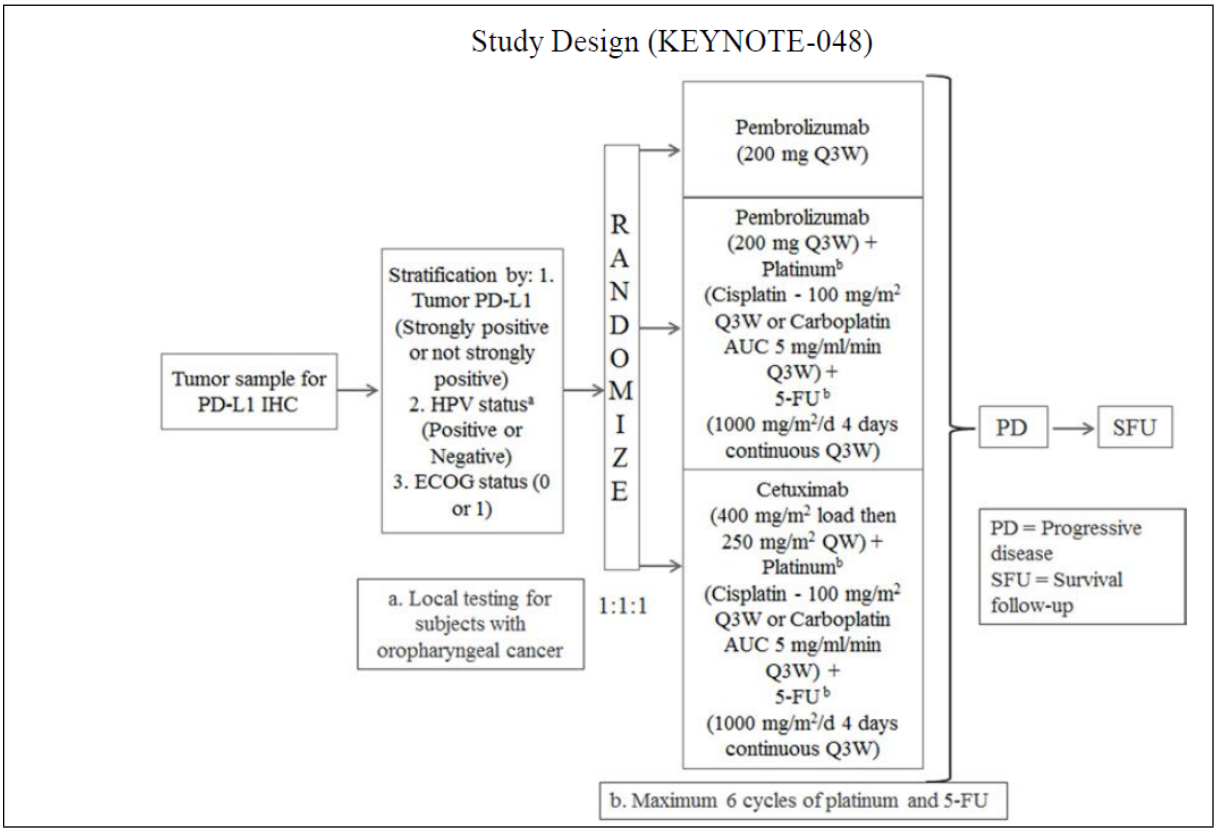
- Pembrolizumab 200 mg IV every 3 weeks (Q3W), platinum (cisplatin 100 mg/m^2 IV Q3W or carboplatin AUC 5 mg/mL/min IV Q3W) and 5FU 1000 mg/m^2/day IV continuously for 4 days Q3W for 6 cycles followed by pembrolizumab 200 mg IV Q3W until disease progression or a maximum of 35 doses of pembrolizumab
  OR
- Pembrolizumab 200 mg IV Q3W until disease progression or a maximum of 35 doses of pembrolizumab

Control:

- Cetuximab (400 mg/m^2 loading dose then 250 mg/m2 IV QW), platinum (cisplatin 100 mg/m^2 IV Q3W or carboplatin AUC 5 mg/mL/min IV Q3W) and 5FU 1000 mg/m^2/day continuously for 4 days Q3W for 6 cycles followed by cetuximab 250 mg/m^2 IV QW until disease progression

Patients are evaluated radiographically for tumor status at Weeks 6, 12, and 18 and then every 9 weeks for the first 48 weeks and every 12 weeks thereafter. The study schema is presented in Figure 1.

Figure 1: KEYNOTE-048 Study Schema



Eligibility Criteria:

Key Inclusion Criteria:

1. Histologically or cytologically-confirmed R/M HNSCC that is considered incurable by local therapies.
   - Patients may not have had prior systemic therapy administered in the recurrent or metastatic setting. Systemic therapy which was completed more than 6 months prior to signing consent if given as part of multimodal treatment for locally advanced disease was allowed.
   - The eligible primary tumor locations were oropharynx, oral cavity, hypopharynx, and larynx.
   - Patients with primary tumor site of nasopharynx (any histology) were not allowed.

2. Age ≥18 years.
3. Measurable disease based on RECIST 1.1 as determined by the site. Tumor lesions situated in a previously irradiated area were considered measurable if progression has been demonstrated in such lesions.
4. Performance status of 0 or 1 on the ECOG Performance Scale.
5. Demonstrated adequate organ function on labs performed within 10 days of treatment initiation.
6. Had results from local testing of HPV positivity for oropharyngeal cancer defined as p16 IHC testing using CINtec® p16 Histology assay and a 70% cutoff point. Note: HPV stratification in this trial was performed using local testing of HPV status only in patients with oropharynx cancer.
7. Provided tissue for PD-L1 biomarker analysis from a core or excisional biopsy (fine needle aspirate is not adequate). Repeat samples were required if adequate tissue was not provided. The diagnostic sample for patients with a new diagnosis of metastatic HNSCC was acceptable. If obtained for a patient with recurrent disease for locally advanced disease, then it must have been obtained after completion of the previous initial management with no other treatment from the time of biopsy until the start of study treatment.
   Note: Patients for whom newly obtained samples could not be obtained (e.g., inaccessible or patient safety concern), were allowed to submit an archived specimen only upon agreement from the Sponsor. Newly obtained tissue was required to be obtained up to 90 days prior to treatment initiation.
8. Female patients of childbearing potential with a negative blood pregnancy test within 72 hours prior to receiving the first dose of study medication.
9. Female patients of childbearing potential willing to use 2 methods of birth control or be surgically sterile or abstain from heterosexual activity for the course of the study through 180 days after the last dose of study medication. Patients of childbearing potential were those who have not been surgically sterilized or have not been free from menses for >1 year. Note: Abstinence was acceptable if this is the established and preferred method of contraception for the patient.
10. Male patients were expected to agree to use an adequate method of contraception starting with the first dose of study therapy through 180 days after the last dose of study therapy.

Key Exclusion Criteria:

1. Disease suitable for local therapy administered with curative intent.
2. Progressive disease within six months of completion of curatively intended treatment for locoregionally advanced HNSCC.
3. Participating and receiving study therapy or have participated in a study of an investigational agent and received study therapy, or used an investigational device, any of which occurred within 4 weeks of the first dose of treatment. Participation in the follow-up phase (receiving no study treatment) of a prior study is allowed.
4. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use

of physiologic doses of corticosteroids was allowed if approved after consultation with the Sponsor.

5. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or *in situ* cervical cancer with no evidence of that disease recurrence for 5 years since initiation of that therapy. Note: The time requirement for no evidence of disease for 5 years did not apply to the tumor for which the patient was enrolled in the trial.
6. Known active central nervous system metastases and/or carcinomatous meningitis. Note: Patients with previously treated brain metastases were allowed to participate provided they were stable (without evidence of progression by imaging (using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), had no evidence of new or enlarging brain metastases, and were not using steroids for at least 7 days prior to trial treatment. Carcinomatous meningitis was excluded regardless of clinical stability.
7. Active autoimmune disease that required systemic treatment in 2 years prior to study enrollment (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) were not considered a form of systemic treatment.
8. Evidence of active, non-infectious pneumonitis.
9. Active infection requiring systemic therapy.
10. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or are not in the best interest of the patient to participate, in the opinion of the treating investigator.
11. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 180 days after the last dose of trial treatment.
13. Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or if the patient has previously participated in Merck MK-3475 clinical trials.
14. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
15. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Received a live vaccine within 30 days of planned start of study therapy.
17. Immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) was given allowing exception to this criterion for a specific patient.

Study Endpoints

The primary endpoints were PFS per RECIST 1.1 assessed by BICR and OS in three analysis populations: all patients, patients with CPS ≥1 HNSCC, and patients with CPS ≥20 HNSCC.

PFS was defined as the time from randomization to the first documented disease progression per RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, based on BICR or death due to any cause, whichever occurs first. Patients without a documented progression event at the time of the analysis were censored at the date of the last known disease assessment.

OS was defined as the time from randomization to death due to any cause. Patients without documented death at the time of the analysis were censored at the date of the last known contact.

Major secondary endpoints were ORR and DOR. ORR was defined as the proportion of patients who have a confirmed complete response (CR) or partial response (PR). DOR was defined as the time from first documented evidence of CR or PR until disease progression or death. DOR for patients who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment. Both ORR and DOR were based on confirmed assessments by BICR per RECIST 1.1.

Reviewer Comment: Although RECIST 1.1 states that a maximum of 5 target lesions and 2 target lesions per organ should be assessed, the modified RECIST criteria used in KEYNOTE-048 by Merck permitted up to a maximum of 10 target lesions and 5 target lesions per organ for assessment of tumors. A similar approach has been taken throughout Merck's development program for pembrolizumab.

Additionally, patient reported outcome (PRO) endpoints were included as exploratory endpoints. Global health status/quality of life assessment was based on the global health status/quality of life scales of the QLQ-C30 (items 29 and 30); pain was based on the pain multi-item scales of the EORTC QLQ-H&N35 (items 31-34); and time to deterioration in swallowing was based on the swallowing multi-item scales of the EORTC QLQ-H&N35 (items 35-38).

Statistical Analysis Plan

The co-primary endpoints of PFS and OS were tested using a stratified log-rank test in the 14 primary hypotheses shown in

Figure 2. The hazard ratios (HR) and corresponding 95% confidence intervals (CI) were estimated by stratified Cox models with Efron's method for handling ties. For the CPS ≥20 HNSCC subpopulation analyses, only HPV status and ECOG were used as stratification factors in the models due to the small numbers of patients in other cells.

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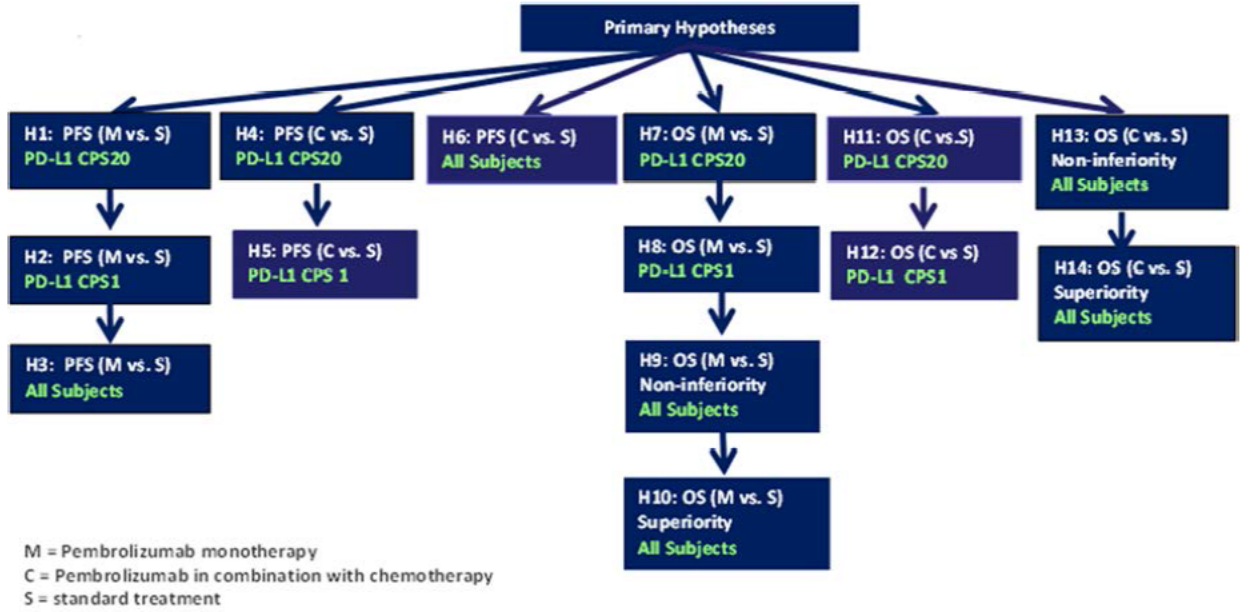
Figure 2: Primary Hypotheses Testing Plan



Source: Protocol MK-3475-048-10 page 22

A statistical plan for testing of multiple endpoints is proposed to control the overall one-sided type I error rate at 2.5%. The initial alpha allocations are shown in Table 3.

Table 3: Initial Alpha Allocation of Each Hypothesis (One-Sided)

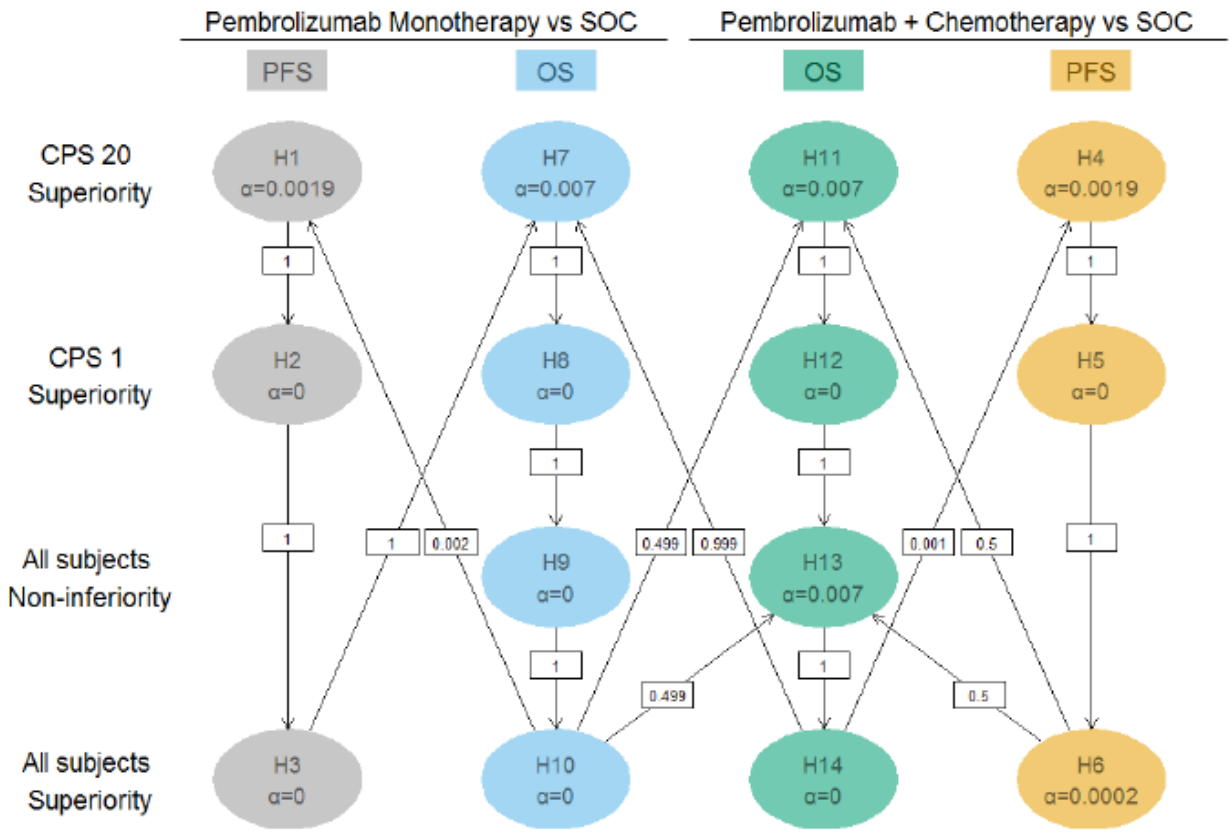
Hypothesis	H1	H4	H6	H7	H11	H13
Alpha (One-sided)	0.19%	0.19%	0.02%	0.7%	0.7%	0.7%

For the PFS hypotheses of pembrolizumab as a single agent vs. the control arm, a fixed sequential testing is applied in the order of PFS superiority in patients with CPS ≥20 HNSCC (H1), in patients with CPS ≥1 HNSCC (H2), and then in all patients (H3). Similarly, fixed sequential testing will be applied to H4 and H5, comparing pembrolizumab in combination with chemotherapy vs. the control arm in patients with CPS ≥20 HNSCC and patients with CPS ≥1 HNSCC, respectively. If the hypothesis test H5 is statistically significant, the corresponding alpha will be fully allocated to the PFS superiority hypothesis comparing pembrolizumab in combination with chemotherapy vs. the control arm for all patients (H6). If either of the PFS hypotheses in all patients (H3 and H6) is statistically significant, the corresponding alpha will be distributed to the OS hypotheses for the corresponding experimental treatment, using the graphical approach of Maurer and Bretz (2013).

Similarly, H7 through H10 comparing OS for pembrolizumab as a single agent to the control arm in patients with CPS ≥20 HNSCC, patients with CPS ≥1 HNSCC, and all patients (both non-inferiority and superiority) were to be tested sequentially. If H10 (the test of OS superiority in

all patients for pembrolizumab single agent versus the control arm) is statistically significant, then the corresponding alpha was to be reallocated and distributed equally to H11 and H13, if not already significant, with a very small fraction (0.002) reallocated to H1. If H14, the hypothesis test of OS superiority comparing pembrolizumab in combination with chemotherapy to the control arm in all patients is statistically significant, the corresponding alpha was to be reallocated to H7, if not already significant, with a very small fraction (0.001) reallocated to H4. A graphical depiction of the alpha re-allocation strategy is provided in Figure 3.

Figure 3: Multiplicity Strategy Diagram



Source: Protocol MK-3475-048-10 page 120; Note: The alphas reported in this graph are one-sided

Two interim efficacy analyses were planned and the Hwang-Shih-DeCani alpha-spending function with different gamma parameter values were used to calculate the group sequential efficacy boundaries for each PFS and OS hypothesis. Results from the first two interim analyses were reviewed by an external data monitoring committee.

Reviewer Comment: FDA did not agree to the non-inferiority hypothesis tests or proposed non-inferiority margins comparing overall survival in patients randomized to pembrolizumab as a single agent to the control arm in the ITT population (H9) or comparing patients randomized to pembrolizumab in combination with chemotherapy to the control arm in the ITT population

(H13). The results of these analyses tests are not considered substantial evidence of effectiveness for either treatment regimen in the patient population of KEYNOTE-048; therefore, the results of hypothesis tests H9 and H13 will not be presented in this review.

Sample Size

PFS analyses were planned at interim analyses 1 (IA1) and 2 (IA2). The sample size calculation assumes an enrollment time of 21 months with a yearly drop-out rate of 5%, the median PFS in the control arm is 6 months, and the HRs are 0.58 for patients with CPS ≥20 HNSCC, 0.59 for patients with CPS ≥1 HNSCC and 0.6 for all patients. Additionally, it was expected that there will be at least 9 months follow-up at IA1 and 17 months follow-up at IA2. The estimated efficacy boundaries, with one-sided p-values, are given in Table 4.

Table 4: PFS Efficacy Boundaries

Hypothesis	Population	Interim Analysis 1				Interim Analysis 2 (Final for PFS)			
		Expected number of events	Efficacy Boundary Values			Expected number of events	Efficacy Boundary Values		
			Z-statistic	p-value	Approx. observed HR		Z-statistic	p-value	Approx. observed HR
H1	CPS ≥20	211	3.0357	0.0012	0.66	237	2.9755	0.0015	0.68
H2	CPS ≥1	337	3.0357	0.0012	0.72	378	2.9755	0.0015	0.74
H3	ITT pop.	423	3.0357	0.0012	0.74	474	2.9755	0.0015	0.76
H4	CPS ≥20	211	3.0357	0.0012	0.66	237	2.9755	0.0015	0.68
H5	CPS ≥1	337	3.0357	0.0012	0.72	378	2.9755	0.0015	0.74
H6	ITT pop.	423	3.7190	0.0001	0.70	474	3.6331	0.0002	0.72

OS analyses were planned at IA1, IA2, and the final analysis. The final analysis was expected to occur about 44 months after the start of the study. The OS sample size calculation assumes an enrollment time of 21 months with a yearly drop-out rate of 2%, the median OS in the control arm is 10 months, and the HRs are 0.6 for patients with CPS ≥20 HNSCC, 0.65 for patients with CPS ≥1 HNSCC, and 0.7 for all patients. Additionally, it was expected that there will be at least 9 months of follow-up at IA 1, 17 months of follow-up at IA 2, and 23 months of follow-up for the final analysis. The estimated efficacy boundaries, with one-sided p-values, are given in Table 5.

Table 5: OS Efficacy Boundaries

Hypothesis	Population	Interim Analysis 1			Interim Analysis 2			Final Analysis		
		Exp # of events	p-value	Approx. observed HR	Exp # of events	p-value	Approx. observed HR	Exp # of events	p-value	Approx. observed HR
H7	CPS ≥20	171	0.0027	0.65	205	0.0041	0.69	≥222	0.0052	0.71
H8	CPS ≥1	278	0.0028	0.79	332	0.0041	0.75	≥359	0.0052	0.76
H9*	ITT	352	0.0028	0.89	421	0.0041	0.93	≥455	0.0052	0.94
H10	ITT	352	0.0028	0.74	421	0.0041	0.77	≥455	0.0052	0.79
H11	CPS ≥20	171	0.0027	0.65	205	0.0041	0.69	≥222	0.0052	0.71
H12	CPS ≥1	278	0.0028	0.79	332	0.0041	0.75	≥359	0.0052	0.76
H13*	ITT	352	0.0028	0.89	421	0.0041	0.93	≥455	0.0052	0.94
H14	ITT	352	0.0028	0.74	421	0.0041	0.77	≥455	0.0052	0.79

* NI test with a margin of 1.2

Protocol Amendments

Table 6: Protocol Amendments

IND 122325 –Protocol Amendment History	
12/22/2014	KEYNOTE-048, Original Protocol
7/2/2015	KEYNOTE-048, Amendment 01: • Sample size increased from 750 to 780 based on prevalence of strongly positive PD-L1 expression seen in data from the HNSCC cohorts in KEYNOTE-012. • Added PFS hypothesis for pembrolizumab in combination with chemotherapy vs. the control arm in patients with strongly positive PD-L1 expression. • Added objectives and hypotheses for PFS and OS in patients with any positive PD-L1 expression.
8/11/2016	KEYNOTE-048, Amendment 05: • OS was changed from a secondary objective to a primary objective, and biomarker population was updated to include CPS ≥20 HNSCC, CPS ≥10 HNSCC, and CPS ≥1 HNSCC. • Added non-inferiority hypotheses H9 (OS for pembrolizumab as a single agent is non-inferior to the control arm) and H11 (OS for pembrolizumab in combination with chemotherapy is non-inferior to the control arm) to statistical analysis plan • Sample size increased from 780 to 825 due to these changes.

IND 122325 –Protocol Amendment History	
3/22/2017	KEYNOTE-048, Amendment 07: • Analyses for CPS ≥10 HNSCC were removed from the statistical analysis plan; leaving CPS ≥20 HNSCC and CPS ≥1 HNSCC as selected populations for hypothesis testing.
8/30/2017	KEYNOTE-048, Amendment 08: • Increased follow-up time at the interim and final analyses by 3 months based on data from published immuno-oncology trials, which indicate a longer follow-up period may be required to achieve data maturity.
1/25/2018	KEYNOTE-048, Amendment 09: • Updated dose modifications for pembrolizumab, including the addition of guidelines for the management of myocarditis based upon health authority feedback. • Added hypotheses for PFS and OS superiority in biomarker positive subpopulation for comparison of pembrolizumab in combination with chemotherapy vs. the control arm. • Increased follow-up period by 3 months for second interim analysis and final analysis based on recent literature, which showed prolongation of median OS compared with the median OS in the EXTREME paper published in 2008. • DOR moved to an exploratory endpoint. • Addition of language to enable survival follow-up activities throughout the study at timepoints specified by the Sponsor
1/11/2019	KEYNOTE-048, Amendment 10 Updated power and sample size calculations based on the expected number of events, rather than the required events

8.1.2. Study Results

Compliance with Good Clinical Practices

The submission contains a statement indicating that all studies were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human patients that were in place at the time the studies were performed.

Financial Disclosure

- Merck submitted Certification of Financial Interests and Arrangement of Clinical Investigators (Form 3465) for KEYNOTE-048 with a list of all investigators and sub-investigators who provided information that they had no financial conflicts of interest as defined in 21 CFR54.2 (a,b,c,f).

- The financial disclosure information submitted for KEYNOTE-048 is summarized in Tables 7 and 8.
- One (b) (6) at clinical site (b) (6) had a spouse with equity interest. Clinical site (b) (6) enrolled a total of (b) (6) patients ((b) (6) patients to the pembrolizumab arm and (b) (6) patients to the pembrolizumab plus chemotherapy arm). All of these patients were enrolled by (b) (6) , who had no significant financial interest or arrangements with Merck to disclose. This site had (b) (6) who had no significant financial interest or arrangements with Merck to disclose
- Financial disclosure information for KEYNOTE-012, KEYNOTE-040, and KEYNOTE-055 were not re-submitted as Merck provided the financial disclosure components for all clinical investigators involved with these protocols in BLA 125514/S-(b) (4) submitted on February 28, 2018.

Table 7: Summary of Investigators by Category for the Covered Clinical Study

Description	Sub-Total (if applicable)	Total
Grand Total Number of All Investigators/Sub-Investigators		1445
Total Number of Investigators/ Sub-Investigators Certified Regarding the Absence of Financial Interests and/or Arrangements		1441
Total Number of Investigators/ Sub-Investigators Not Certified	• Investigator Did Not Return Requested Information n= 3 • Reason: Did not return form with requested information. Multiple due diligence attempts made.	3
Total Number of Investigators/ Sub-Investigators Who Hold Financial Interests and/or Arrangements Requiring Disclosure	• Compensation n= 0 • Equity Interest n= 1 • Proprietary or Financial Interests n= 0 • Significant Payments of Other Sorts n= 0	1

Table 8: All Clinical investigators/sub-investigators who hold financial interest and/or arrangements requiring disclosure

Site	Investigator/Sub-investigator	Role	Financial Interest or Arrangements
(b) (6) (b) (6) *patients enrolled at this site by investigator* (b) (6)	(b) (6)	Sub-investigator	Equity Interest: $1,800,000.00 Merck Common Stock $1,800,000.00 estimated value owned by a trust for which my (b) (6) is an administrator and trustee as reported by investigator on 05-26-2015. These values have been reduced by stock sales at market prices and the value of Merck stock is approximately $900,000.00. No control over the funds nor the stock as reported by investigator on 10-19-2017.

Data Quality and Integrity

The submission contains all the required components of the eCTD. Merck's categorization of data and coding methods was deemed appropriate. The overall quality and integrity of the application was acceptable. The reviewers were able to perform the review using the data submitted.

On May 14, 2019, Merck notified the FDA of imaging measurement discrepancies that were identified and remediated. Nineteen measurement discrepancies (incidence of 0.085%) were identified across 17 timepoints for 16 patients. After remediation, four patients (incidence of 0.018%) were found to have a change in visit response, of which only one patient in the pembrolizumab as a single agent arm had a change in time of progression.

Reviewer Comment: The impact of the imaging measurement discrepancies on the analysis of PFS was negligible, and there were no differences in the observed estimates of ORR and DOR. The results of the corrected data after remediation are presented in this review.

Patient Disposition

Based on external DMC recommendation, KEYNOTE-048 had an enrollment pause for the pembrolizumab in combination with chemotherapy arm on August 13, 2015, after 20 patients were randomized to the arm. Enrollment to this arm was reopened on October 2, 2015, after the DMC completed their safety review. To account for this pause in the comparison to the control arm, the protocol was amended to exclude data from all patients randomized to the

control arm during the pause from the efficacy analyses comparing the pembrolizumab in combination with chemotherapy arm with the control arm. Thus, comparisons were made between 281 patients in the pembrolizumab combination therapy with only 278 (out of the 300) patients enrolled to the control arm.

Of 882 total patients, 601 were randomized to either the pembrolizumab as a single agent arm (n=301) or the control arm (n=300) (Table 9). Among the randomized patients to pembrolizumab arm, one patient died prior to initiating treatment. On the control arm, 6 patients died, 6 patients withdrew from study prior to initiating treatment; and for 1 patient the reason the patient never received treatment was not provided. The median duration of follow-up for all randomized patients was 11.7 months (range: 0.2, 37.3) in the pembrolizumab arm and 10.7 months (range: 0.1, 35.3) in the control arm.

Fewer patients in the pembrolizumab arm compared with the control arm [Table 9]:

- discontinued the trial (71.8% versus 81.7%),
- discontinued study medication (89.3% versus 96.5%),
- discontinued from the trial due to death (67.4% versus 75.7%).

Discontinuations from study treatment due to progressive disease were similar between the two arms.

In KEYNOTE-048, of 882 total patients, excluding patients randomized during the pause in enrollment to the pembrolizumab plus chemotherapy arm, 559 were randomized to either the pembrolizumab plus chemotherapy arm (n=281) or the control arm (n=278). Among the randomized patients to pembrolizumab plus chemotherapy arm, 3 patients died, 1 patient withdrew from study prior to initiating treatment, and for 1 patient the reason the patient never received treatment was not provided. The median duration of follow-up for all randomized patients was 13.0 months (range: 0.1, 36.6) in the pembrolizumab plus chemotherapy arm and 10.7 months (range: 0.1, 35.3) in the control arm.

Fewer patients in the pembrolizumab plus chemotherapy arm compared with the control arm [Table 9]:

- discontinued the trial (71.2% versus 82.0%),
- discontinued study medication (90.2% versus 97.0 %),
- discontinued study medication due to progressive disease (PD, 56.9% versus 64.7%),
- discontinued the trial due to death (66.9% versus 76.3%).

Table 9: Patient Disposition KEYNOTE-048

Status	Pembrolizumab	Cetuximab + Chemotherapy	Pembrolizumab + Chemotherapy	Cetuximab + Chemotherapy
Total Randomized (n)	301	300	281	278
Total started treatment(n)	300	287	276	277
Discontinued Trial (%)	72	82	71	82
Discontinued Study Drug (%)	89	96	90	97
Due to PD (%)	62	65	57	65
Due to AE (%)	11	15	16	16
Death (%)	67	76	67	76
Lost to Follow-up (%)	0.3	0.3	0.3	0.3
Withdrawal (%)	4	5.7	4	5
Ongoing (%)	28	18	6	18

Protocol Violations/Deviations

Overall, there were 371 instances of protocol deviations reported in the 303 patients enrolled in the three arms (Tables 10 and 11).

Table 10: Protocol Deviations Categories

Deviation Category	Total
Inclusion/Exclusion Criteria	63
Informed Consent Form	117
Prohibited Medications	1
Safety Reporting	104
Study intervention	45
Trial Procedures	41
Total	371

- *Source BLA125514/S-52: SAS dataset dv.xpt*

Table 11: Protocol Violation or Deviation Terms

Protocol Deviation Term	Total
Antineoplastic agent given while on treatment	1
Baseline imaging scans not done within protocol defined window	17
Dose variation >10% in C1 for SOC medications	26
Events of Clinical Interest (ECIs) specifically potential DILI and overdose or other protocol-specific defined ECIs requiring regulatory reporting not reported within 24 hours of learning of event.	30
Female participants of childbearing potential who did not have a negative urine or serum pregnancy test performed and reviewed within 72 hours prior to receiving the first dose of trial medication.	5
Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7	12
Has an active infection requiring systemic therapy	2
Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable	1
Imaging assessment not completed for a scheduled time point per protocol.	23
Imaging assessment with missing anatomy that resulted in a scheduled time point being Not Evaluable.	3
Overdose of standard of care medications greater than or equal to 20% over the prescribed dose.	2
Participant progressed within 6 months of completing curatively-intended prior systemic treatment	15
Participant was randomized with incorrect stratification factors in IVRS (ECOG PS and/or HPV positivity)	21
Participants entered into the trial who did not have measurable disease per RECIST 1.1 at baseline. (Note: Lesions situated in a previously irradiated area are considered measurable if progression	1
Participant's HNSCC is neither recurrent nor metastatic	10
Participants who received incorrect study treatment and/or were administered improperly stored study treatment.	22
Participants with no documented initial consent to enter the trial.	1
Participants with Serious adverse events (SAEs) that were not reported within 24 hours of learning of event.	76
Participants without updated consent per the Informed Consent implementation plan following a significant safety change to the Risk Language/Informed Consent (following site/regional approval of the protocol and ICF)	116
Primary tumor location is not oropharynx, oral cavity, hypopharynx, or larynx	1
Prior systemic therapy was completed less than 6 months prior to signing the consent form	2

- *Source BLA125514/S-52: SAS dataset dv.xpt*

The most common categories of protocol deviation were study reporting (serious AEs were not reported within 24 hours of learning of event), re-consenting and maintaining updated

informed consent forms, and study intervention (received chemotherapy doses or pembrolizumab doses that were either more or less than those specified in the protocol).

Reviewer Comment: The proportions of deviations were similar between the treatment arms and the deviations, with the following exceptions that affected a small number of patients (i.e., receiving concurrent anti-neoplastic therapy on study (n=1); participants who received incorrect study treatment and/or were administered improperly stored study treatment (n=20); participant's HNSCC is neither recurrent nor metastatic(n=10); primary tumor location is not oropharynx, oral cavity, hypopharynx, or larynx (n=1); prior systemic therapy was completed less than 6 months prior to signing the consent form (n=2)), are unlikely to impact the study results on overall survival.

Table of Demographic Characteristics

In the overall study population (n=882), demographic and baseline disease characteristics included: median age of 61 years (range: 20 to 94); 36% age 65 years or older; 83% male; 73% White, 20% Asian and 2.4% Black; 61% had ECOG PS of 1; and 79% were former/current smokers. Twenty-two percent of patients' tumors were HPV-positive, 23% had PD-L1 TPS ≥50%, and 95% had Stage IV disease (Stage IVA 19%, Stage IVB 6%, and Stage IVC 70%). Eighty-five percent of patients' tumors had PD-L1 expression of CPS ≥1 and 43% had CPS ≥20.

Table 12 and Table 13 summarize the demographic and baseline disease characteristics of the primary efficacy analysis populations for the comparison of the pembrolizumab arm to the standard therapy arm and the comparison of the pembrolizumab in combination with chemotherapy arm to the standard therapy arm. Overall, the patients' demographic and baseline disease characteristics were similar across all three arms for all the factors identified below.

Table 12: Demographic and Clinical Characteristics of the Primary Efficacy Analysis Population (Pembrolizumab vs.Control Cetuximab Plus Chemotherapy)

Baseline Demographic and Clinical Characteristics	Treatment Group		Total (N=601) %
	Pembrolizumab (N=301) %	Cetuximab + Chemotherapy (N=300) %	
Sex			
Male	83	87	85
Female	17	13	15
Age			
Mean years (SD)	61 (9.4)	61(10)	61 (9.7)
Median (years)	62	61	61
Min, max (years)	22,94	24,84	22,94
Age Group			
< 65 years	63	65	64
≥ 65 years	37	35	36
Race			
White	73	75	74
Black or African American	1.3	2	1.7
Asian	19	18	19
American Indian or Alaska Native	1.7	2	1.8
Multi-Racial	4	3	3.5
Missing	1	0.3	0.7
Ethnicity			
Hispanic or Latino	15	15	15
Not Hispanic or Latino	77	77	77
Region			
North America	25	21	23
Rest of the World	46	44	45
EU	29	35	32
Smoking Status			
Never Smoker	21	21	21
Current Smoker	18	14	16
Prior Smoker	62	64	63
ECOG			
0-1	100	100	100
HPV Status			
Positive	21	22	22
Negative	79	78	78
PD-L1 CPS			
CPS <1	15	15	15
CPS ≥1	85	85	85

Baseline Demographic and Clinical Characteristics	Treatment Group		Total (N=601) %
	Pembrolizumab (N=301) %	Cetuximab + Chemotherapy (N=300) %	
CPS <20	55.5	58	57
CPS ≥1-19	41	44	43
CPS ≥20	44	41	42
Disease Status			
Metastatic	72	68	70
Recurrent	27	31	29
Primary Tumor Location			
Oral cavity	27	30	29
Larynx	25	20	22.5
Hypopharynx	13	13	13
Oropharynx	37.5	38	38

[1] Database Cutoff Date: 13 Jun 2018.

Table 13: Demographic and Clinical Characteristics of the Primary Efficacy Analysis Population (Pembrolizumab Plus Chemotherapy vs.Control Cetuximab Plus Chemotherapy)

Baseline Demographic and Clinical Characteristics	Treatment Group		Total (N=559) %
	Pembrolizumab + Chemotherapy (N=281) %	Cetuximab + Chemotherapy (N=278) %	
Sex			
Male	80	87	83
Female	20	13	17
Age			
Mean years (SD)	60.7 (9.8)	60.9 (10)	60.8 (10)
Median (years)	61	61	61
Min, max (years)	20,85	24,84	20,85
Age Group			
< 65 years	64	65	65
≥ 65 years	36	35	35
Race			
White	72	74.5	73
Black or African American	4	2.2	3
Asian	21	18	19.5
American Indian or Alaska Native	1	2	1.6
Multi-Racial	1.4	3	2.3
Missing	0	0.4	0.2

Baseline Demographic and Clinical Characteristics	Treatment Group		Total (N=559) %
	Pembrolizumab + Chemotherapy (N=281) %	Cetuximab + Chemotherapy (N=278) %	
Ethnicity			
Hispanic or Latino	16	16	16
Not Hispanic or Latino	76	76	76
Region			
North America	21	21	21
Rest of the World	31	34	33
EU	47	45	46
Smoking Status			
Never Smoker	20	22	21
Current Smoker	20	13	16.5
Prior Smoker	60	64	62
ECOG			
0-1	100	100	100
HPV Status			
Positive	21	22	22
Negative	79	78	78
PD-L1 CPS			
CPS <1	14	15.5	15
CPS ≥1	86	84.5	85
CPS ≥1-19	41	45	43
CPS <20	55	59	57
CPS ≥20	45	40	42
Disease Status			
Metastatic	71.5	67	69
Recurrent	27	32	29
Primary Tumor Location			
Oral cavity	29	30	30
Larynx	16	20	18
Hypopharynx	16	13	14
Oropharynx	40	38.5	40

[1] Database Cutoff Date: 13 Jun 2018.

Reviewer Comment: The high proportion of white male patients, oropharynx as primary site, HPV negative disease, and prior or current smokers in KEYNOTE-048 is reflects that generally observed in the R/M HNSCC population. Demographic and baseline characteristics for the pembrolizumab as a single agent arm were similar to those for patients in the HNSCC reference safety dataset for pembrolizumab as a single agent provided by Merck., except for a higher proportion of Asian (19% vs 8%) and Hispanic/Latino patients (15% vs 6%) in KEYNOTE-048 compared to the HNSCC reference safety dataset.

Efficacy Results – Primary Endpoint

The results presented in this review are from IA2 with a data cutoff of June 13, 2018. As defined in the protocol, this is the final PFS analysis and the second interim analysis for OS.

Pembrolizumab as a Single Agent

PFS
The results of the analysis of PFS for patients randomized to the pembrolizumab as a single agent arm compared to those randomized to control are presented in Table 14. The hypotheses are presented in the order in which they were tested. There was no significant improvement in PFS when comparing pembrolizumab to control in any of the pre-specified analysis populations. The Kaplan-Meier plots for the CPS ≥20 HNSCC and CPS ≥1 HNSCC subgroups are shown in Figure 4 and Figure 5.

Table 14: PFS Results for Pembrolizumab as a Single Agent

	Pembrolizumab	Control
H1: PFS for PD-L1 CPS **≥20;** boundary: 0.0032 (two-sided)		
# Events (%)	113 (85%)	111 (91%)
Median in months (95% CI)	3.4 (3.2, 3.8)	5.0 (4.8, 6.2)
HR (95% CI)	0.99 (0.75, 1.29)	
P-value	0.944	
H2: PFS for PD-L1 CPS **≥1;** no alpha remaining for testing		
# Events (%)	225 (88%)	231 (91%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 5.8)
HR (95% CI)	1.15 (0.95, 1.38)	
H3: PFS for all patients; no alpha remaining for testing		
# Events (%)	269 (90%)	270 (90%)
Median in months (95% CI)	2.3 (2.2, 3.3)	5.2 (4.9, 6.0)
HR (95% CI)	1.32 (1.11, 1.57)	

Reviewer Comment: Prior to remediation of the imaging measurement discrepancies, the results comparing the pembrolizumab as a single therapy arm to control were very similar to the post-remediation results provided in Table 14. The pre-remediation results of the pembrolizumab as a single agent arm differed in the following ways:

- *CPS ≥20 subgroup: Number of PFS events (%): 114 (86%)*
- *CPS ≥1 subgroup: Number of PFS events (%): 226 (88%); HR (95% CI): 1.16 (0.96, 1.39)*

- *All patients: Number of PFS events (%): 270 (99%); HR (95% CI): 1.34 (1.13, 1.59)*

Figure 4: Kaplan-Meier Plot of PFS for Patients with CPS **≥20** HNSCC: Pembrolizumab as a Single Agent vs. Control

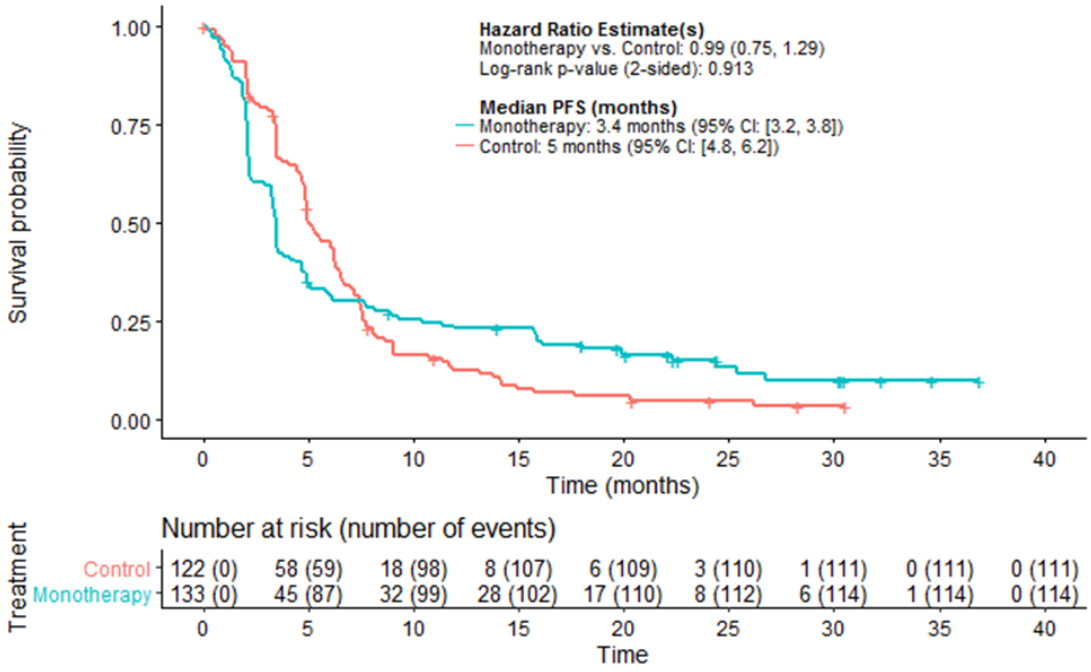


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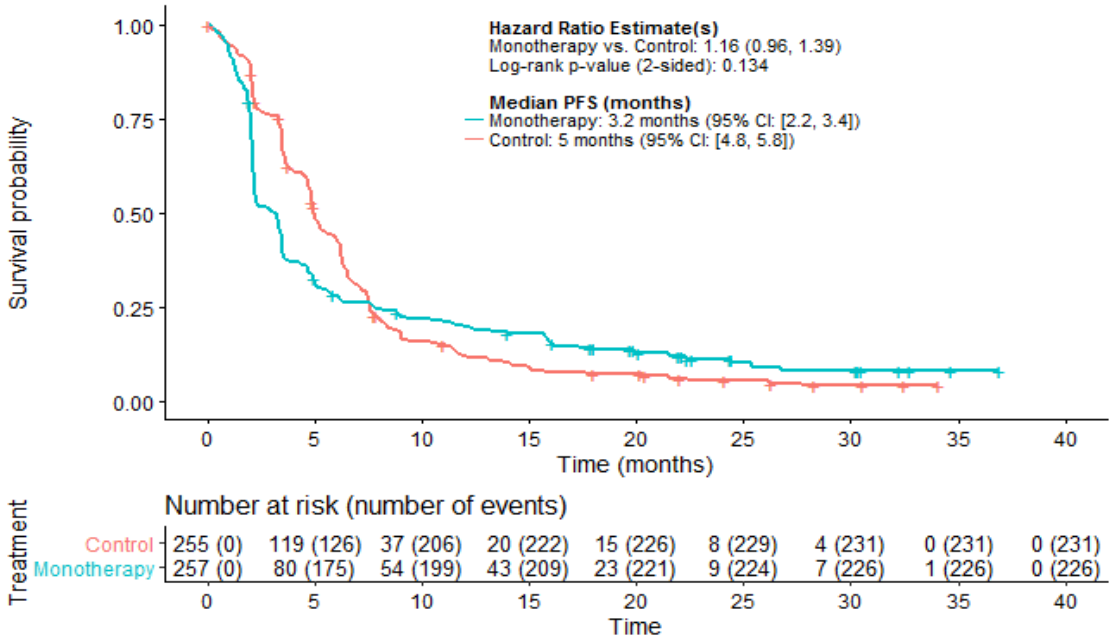
Figure 5: Kaplan-Meier Plot of PFS for Patients with CPS **≥1** HNSCC: Pembrolizumab as a Single Agent vs. Control



Overall Survival

The results of the analysis of OS for patients randomized to the pembrolizumab as a single agent arm compared to those randomized to control are presented in Table 15. The hypotheses are presented in the order in which they were tested. There was a statistically significant improvement in OS in the pembrolizumab arm compared to the control arm for the subgroups of patients with CPS ≥20 HNSCC and CPS ≥1 HNSCC. However, there was no demonstrated improvement in OS when comparing the control arm with the pembrolizumab arm for the ITT population. The Kaplan-Meier plots for the CPS ≥20 HNSCC and CPS ≥1 HNSCC subgroups are shown in Figure 6 and Figure 7.

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Table 15: OS Results for Pembrolizumab as a Single Agent

Parameters	Pembrolizumab	Control
H7: OS for PD-L1 CPS **≥20;** boundary: 0.0048 (two-sided)		
# Events (%)	82 (62%)	95 (78%)
Median in months (95% CI)	14.9 (11.6, 21.5)	10.7 (8.8, 12.8)
HR (95% CI)	0.61 (0.45,0.83)	
P-value	0.0015	
H8: OS for PD-L1 CPS **≥1;** boundary: 0.0218 (two-sided, from H7 and H14)		
# Events (%)	177 (69%)	206 (81%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)
HR (95% CI)	0.78 (0.64, 0.96)	
P-value	0.0171	
H10: OS for all patients; boundary: 0.0234 (two-sided, from H8 and H9)		
# Events (%)	213 (71%)	240 (80%)
Median in months (95% CI)	11.6 (10.5, 13.6)	10.7 (9.3, 11.7)
HR (95% CI)	0.85 (0.71, 1.03)	
P-value	0.0913	

Figure 6: Kaplan-Meier Plot of OS for Patients with CPS **≥20** HNSCC: Pembrolizumab As a Single Agent vs. Control

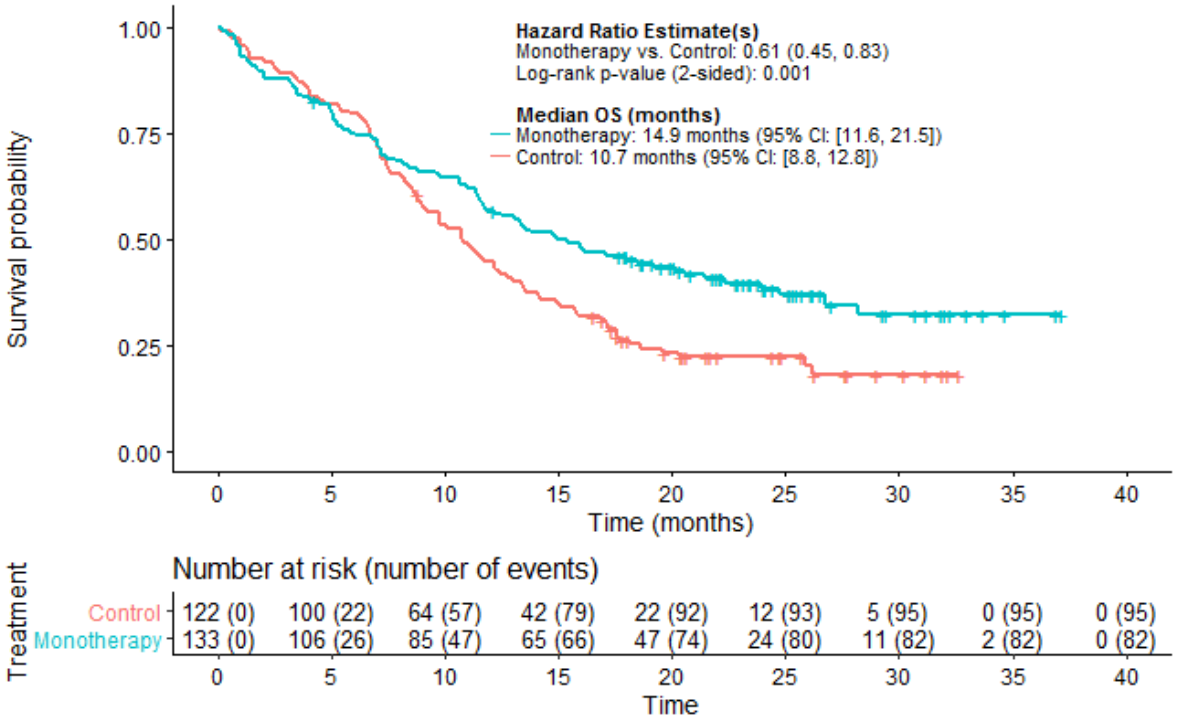
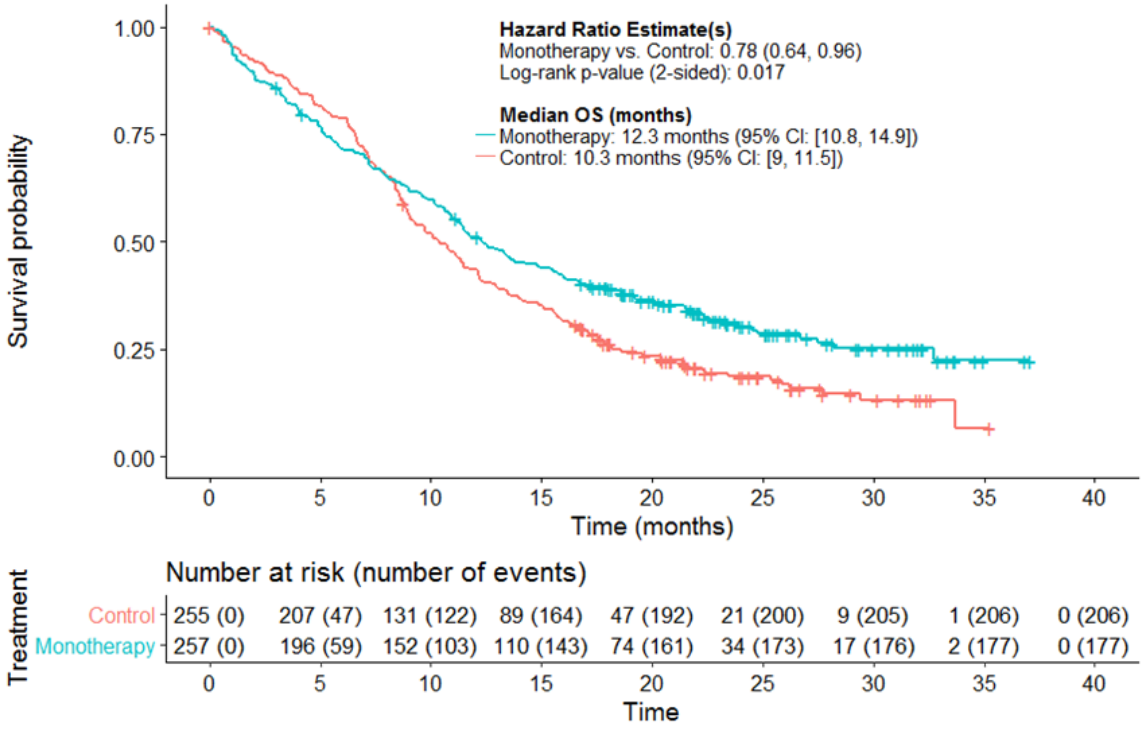


Figure 7: Kaplan-Meier Plot of OS for Patients with CPS **≥1** HNSCC: Pembrolizumab Monotherapy vs. Control



Upon visual inspection, the Kaplan-Meier plots for OS comparing pembrolizumab as a single agent to control in the subgroups of patients with CPS ≥20 HNSCC and CPS ≥1 HNSCC exhibit non-proportional hazards. Formal testing of the proportional hazards assumption indicates that the assumption is violated for OS comparing pembrolizumab monotherapy to control these two subgroups (p-values of 0.0125 and 0.0156 for CPS ≥20 HNSCC and CPS ≥1 HNSCC respectively).

As an alternative data presentation in the presence of non-proportional hazards, landmark OS rates for each arm at 6, 12, and 24 months are presented in Table 16.

Table 16: Kaplan-Meier Estimated Survival Rates for Pembrolizumab Monotherapy Compared to Control

		Survival Rate (95% CI)	
		Pembrolizumab Monotherapy	Control
CPS **≥1** HNSCC subpopulation	6-month rate	71% (65,77)	79% (73,83)
	12-month rate	51% (45,57)	44% (37,50)
	24-month rate	30% (24,36)	19% (14,24)
CPS **≥20** HNSCC subpopulation	6-month rate	75% (67,82)	79% (71,86)
	12-month rate	57% (48,65)	45% (36,53)
	24-month rate	38% (30,47)	22% (15,30)

Pembrolizumab in Combination with Chemotherapy

PFS

The results of the analysis of PFS for patients randomized to the pembrolizumab in combination with chemotherapy arm compared to those randomized to control are presented in Table 17. The hypotheses are presented in the order in which they were tested. There was no demonstrated improvement in PFS when comparing pembrolizumab in combination with chemotherapy to control in any of the pre-specified analysis populations. The Kaplan-Meier plot for the ITT population is shown in Figure 8.

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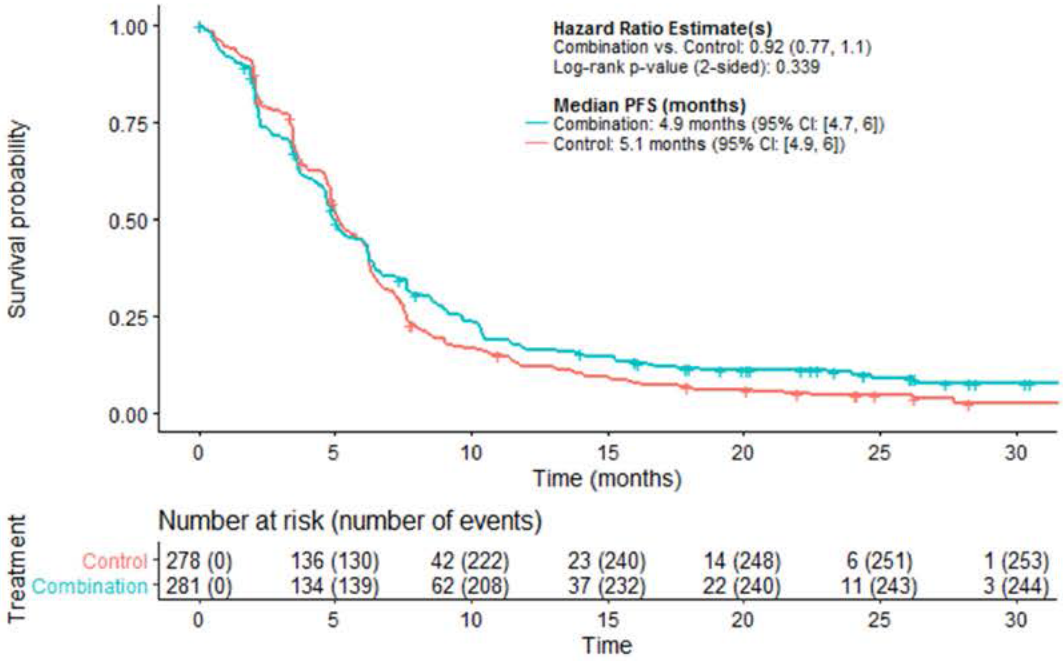
Table 17: PFS Results for Pembrolizumab plus Chemotherapy

Parameters	Pembrolizumab plus Chemotherapy	Control
H4: PFS for PD-L1 CPS ≥20; boundary: 0.0034 (two-sided)		
# Events (%)	102 (81%)	101 (92%)
Median in months (95% CI)	5.8 (4.7, 7.6)	5.2 (4.8, 6.2)
HR (95% CI)	0.73 (0.55, 0.97)	
P-value	0.0324	
H5: PFS for PD-L1 CPS ≥1; no alpha remaining		
# Events (%)	206 (85%)	215 (91%)
Median in months (95% CI)	5.0 (4.7, 6.2)	5.0 (4.8, 5.8)
HR (95% CI)	0.82 (0.67, 1.00)	
H6: PFS for all patients; boundary: 0.0004 (two-sided)		
# Events (%)	244 (87%)	253 (91%)
Median in months (95% CI)	4.9 (4.7, 6.0)	5.1 (4.9, 6.0)
HR (95% CI)	0.92 (0.77, 1.10)	
P-value	0.3394	

Figure 8: Kaplan-Meier Plot of PFS for the ITT Population: Pembrolizumab in Combination with Chemotherapy vs. Control



OS

The results of the analysis of OS for patients randomized to the pembrolizumab in combination with chemotherapy arm compared to those randomized to control are presented in Table 18. The hypotheses are presented in the order in which they were tested. There was a statistically significant improvement in OS when comparing pembrolizumab in combination with chemotherapy to control in the ITT population. These results are also demonstrated in the Kaplan-Meier plot in Figure 9.

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Table 18: OS Results for Pembrolizumab plus Chemotherapy

Parameters	Pembrolizumab plus Chemotherapy	Control
H11: OS for PD-L1 CPS **≥20;** boundary: 0.0036 (two-sided)		
# Events (%)	79 (63%)	85 (77%)
Median in months (95% CI)	14.7 (10.3, 19.3)	11.0 (9.2, 13.0)
HR (95% CI)	0.69 (0.51, 0.94)	
P-value	0.0197	
H12: OS for PD-L1 CPS **≥1;** no alpha remaining		
# Events (%)	164 (68%)	190 (81%)
Median in months (95% CI)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)
HR (95% CI)	0.71 (0.57, 0.88)	
H14: OS for All Patients boundary: 0.0082 (two-sided)		
# Events (%)	197 (70%)	223 (80%)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
HR (95% CI)	0.77 (0.63, 0.93)	
P-value	0.0067	

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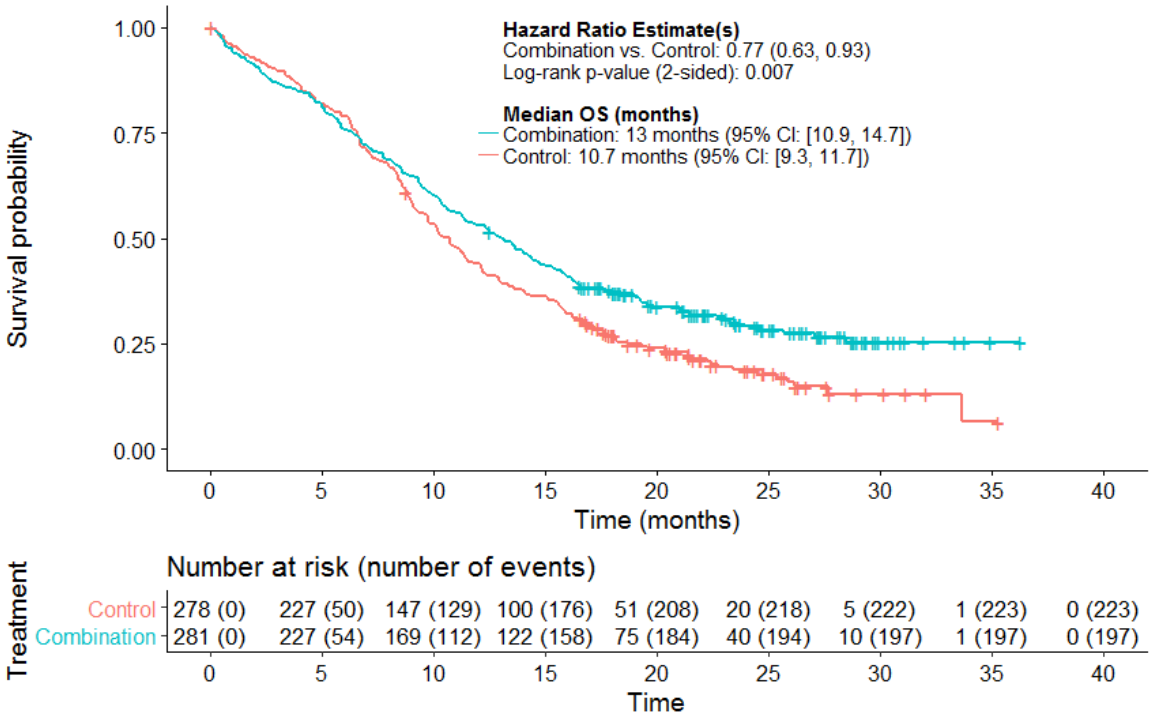
Figure 9: Kaplan-Meier Plot of OS for the ITT Population: Combination vs. Control



Upon visual inspection, the Kaplan-Meier plot for OS comparing pembrolizumab in combination with chemotherapy to control in the overall population exhibits non-proportional hazards. Formal testing of the proportional hazards assumption indicates that the assumption is violated for OS comparing pembrolizumab in combination with chemotherapy to control (p-value = 0.0385).

As an alternative data presentation in the presence of non-proportional hazards, landmark OS rates for each arm at 6, 12, and 24 months are presented in Table 19.

Table 19: Kaplan-Meier Estimated Survival Rates for Pembrolizumab in Combination with Chemotherapy compared to Control

		Survival Rate (95% CI)	
		Pembrolizumab in Combination with Chemotherapy	Control
CPS **≥1** HNSCC subpopulation	6-month rate	75.8% (70.4,80.4)	79.1% (73.8,83.4)
	12-month rate	53.0% (47.0,58.7)	43.9% (38.0,49.7)
	24-month rate	29.0% (23.5,34.7)	18.7% (13.9,24.0)

Subgroup Analyses

Results of exploratory analyses of OS in the subgroups of patients with CPS <1 HNSCC and CPS 1-19 HNSCC are presented in this section.

Table 20: Exploratory OS Analyses for Pembrolizumab as a Single Agent Compared with Control in the CPS < 1 and CPS 1-19 Subgroups

	CPS < 1		CPS 1-19	
	Pembrolizumab	Control	Pembrolizumab	Control
# Events (Total)	36 (44)	34 (45)	95 (124)	111 (133)
Median in months (95% CI)	7.9 (4.7, 13.6)	11.3 (9.1, 15.9)	10.8 (9.0, 12.6)	10.1 (8.7, 12.1)
HR (95% CI)	1.37 (0.86, 2.20)		0.90 (0.68, 1.18)	

Table 21: Exploratory OS Analyses for Pembrolizumab in Combination with Chemotherapy Compared with Control in the CPS <1 and CPS 1-19 Subgroups

	CPS < 1		CPS 1-19	
	Pembrolizumab + Chemotherapy	Control	Pembrolizumab + Chemotherapy	Control
# Events (Total)	33 (39)	33 (43)	85 (116)	105 (125)
Median in months (95% CI)	11.3 (9.5,14)	10.7 (8.5,15.9)	12.7 (9.4,15.3)	9.9 (8.6,11.5)
HR (95% CI)	1.07 (0.66, 1.74)		0.75 (0.57, 1.01)	

Reviewer Comment: The results for these complementary subgroup analyses are considered exploratory, since the study was not designed to have adequate power for the log-rank tests conducted in these subgroups. This is further demonstrated by the comparatively small sample sizes and wider confidence intervals in both Table 20 and Table 21.

Interaction Tests

Interaction tests were performed to determine whether there was any modification of the treatment effect on OS by PD-L1 status as determined by CPS. A Cox proportional hazards model was fit with variables for treatment, an indicator for PD-L1 CPS <1, and the interaction of these two variables. The p-value of the interaction term for this model was estimated and compared to a threshold of 0.05 to identify a statistically significant interaction.

The p-value of the interaction coefficient for monotherapy is 0.027 (two-sided), indicating a significant modification of treatment effect by CPS ≥1 HNSCC subgroups. The model estimates a hazard ratio of 0.43 [95% CI: 0.23, 0.81] in the CPS ≥1 HNSCC subgroup patients who received monotherapy compared to the CPS ≥1 HNSCC subgroup patients who received control. In the model for pembrolizumab in combination with chemotherapy, the p-value of the interaction was not statistically significant.

Posterior Predictive Probability

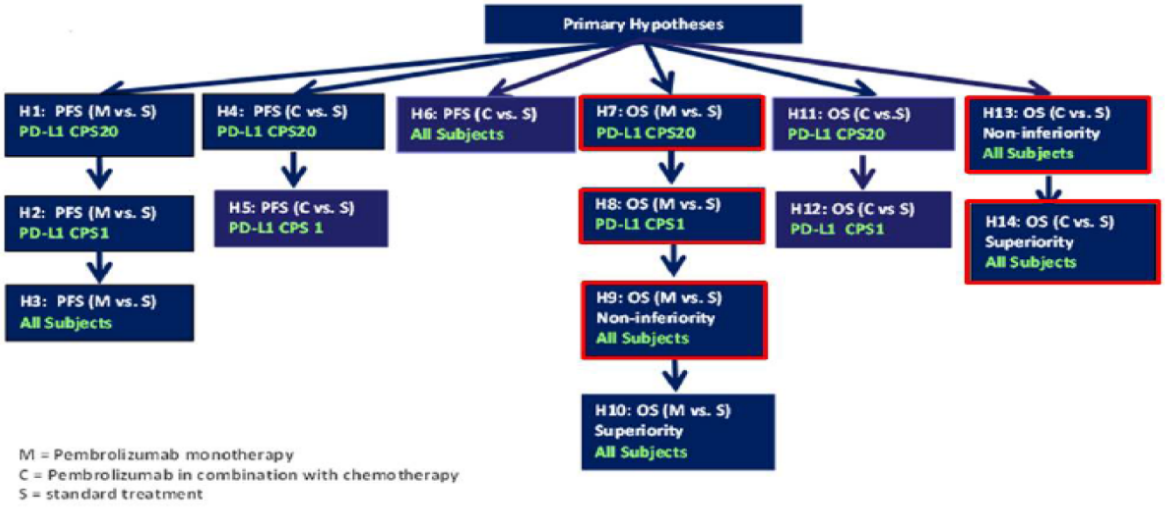
Bayesian posterior predictive probabilities were determined for the three comparisons in which statistically significant results were observed. The censored observations were simulated for 12 more months using an exponential model. The process was repeated 50 times and estimated p-values were calculated. The numbers provide supportive information for the efficacy results obtained in the pre-specified analyses. Results are show in Table 22.

Table 22: Posterior Predictive Model P-value Distribution

Test population	Median p-value	Minimum p-value	Maximum p-value
Comparing pembrolizumab as a single agent to control in the CPS ≥1 HNSCC subpopulation	0.0154	0.0023	0.0896
Comparing pembrolizumab as a single agent to control in the CPS ≥20 HNSCC subpopulation	0.0092	0.0012	0.0862
Comparing pembrolizumab combination therapy to control in the ITT population	0.0062	0.0013	0.0419

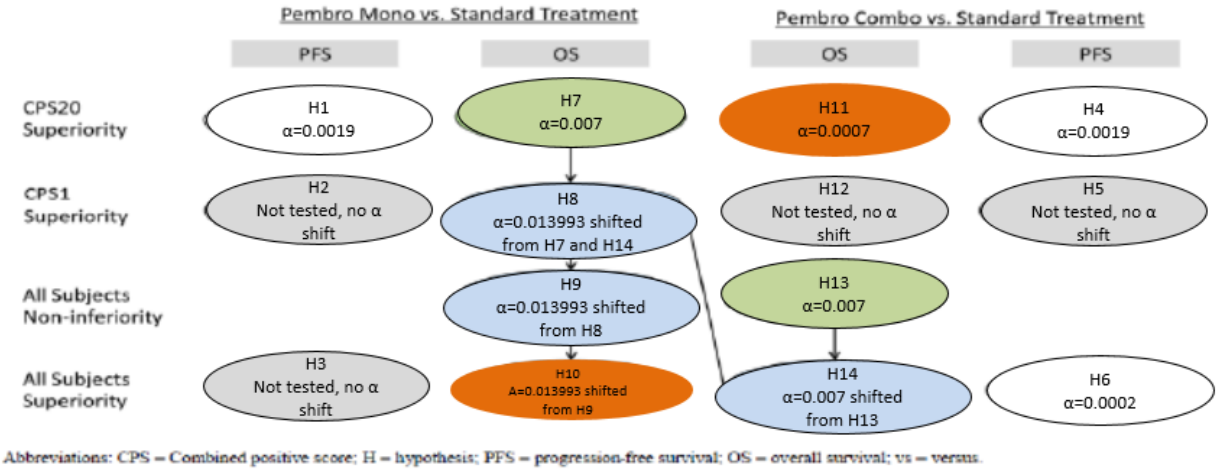
The significant hypotheses after the second interim analysis are marked in red in Figure 10 and the alpha allocation after the second interim analysis is shown in Figure 11. None of the PFS tests were successful, either due to the test not achieving the pre-specified significance thresholds (H1, H4 and H6) or not having any alpha remaining for a formal test (H2, H3 and H5). The final analysis for OS has not been conducted for H10 (pembrolizumab as a single agent vs control in ITT) and H11 (pembrolizumab and chemotherapy vs control in CPS ≥20 HNSCC), and Merck has one more opportunity to test H10 and H11. H12 (pembrolizumab and chemotherapy vs. control in CPS ≥1 HNSCC) can also be tested for significance if H11 is successful.

Figure 10: Significant Hypotheses after Interim Analysis 2



Source: Figure 2 on page 4 of Type B Preliminary Meeting Comments held on October 17, 2018

Figure 11: Alpha Reallocation after Interim Analysis 2*



Abbreviations: CPS = Combined positive score; H = hypothesis; PFS = progression-free survival; OS = overall survival; vs = versus.

*Note: The alphas reported in this graph are one-sided

Efficacy Results – Secondary and other relevant endpoints

Table 23 presents the analysis of confirmed ORR per BIRC assessment. Since the PFS results were not significant in any population, ORR was not formally tested.

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Table 23: ORR and DOR Comparison between the Treatment and Control Groups

	ITT Population		CPS **≥1** HNSCC Subpopulation		CPS **≥20** HNSCC Subpopulation	
	Treatment	Control	Treatment	Control	Treatment	Control
Comparison of Pembrolizumab as a Single Agent with Control						
No of Patients	n = 301	n = 300	n = 257	n = 255	n = 133	n = 122
Overall Response Rate (95% CI[1])	17% (13, 22)	36% (31, 42)	19% (15, 24)	35% (29, 41)	23% (17, 32)	36% (28, 45)
CR/PR	5%/12%	3%/33%	5%/14%	3%/32%	8%/16%	3%/33%
Median DOR[2] (range)	20.9 (1.5+, 34.8+)	4.5 (1.2+, 30.6+)	20.9 (1.5+, 34.8+)	4.5 (1.2+, 28.6+)	20.9 (2.7+, 34.8+)	4.2 (1.2+, 22.3+)
Comparison of Pembrolizumab plus Chemotherapy with Control						
No of Patients	n = 281	n = 278	n = 242	n = 235	n = 126	n = 110
Overall Response Rate (95% CI[1])	36% (30, 41)	36% (31, 42)	36% (30, 43)	36% (30, 42)	43% (34, 52)	38% (29, 48)
CR/PR	6%/30%	3%/33%	7%/30%	3%/33%	10%/33%	4%/35%
Median DOR[2] (range)	6.7 (1.6+, 30.4+)	4.3 (1.2+, 27.9+)	6.7 (1.6+, 30.4+)	4.3 (1.2+, 27.9+)	7.1 (2.1+, 30.4+)	4.2 (1.2+, 22.3+)

[1] Estimated using Clopper-Pearson Method
[2] Kaplan-Meier Estimates

Dose/Dose Response

Not applicable for this supplement. All patients received pembrolizumab 200 mg IV Q3W.

Durability of Response

Duration of response is included in "Efficacy Results – Secondary and other relevant endpoints" section.

Persistence of Effect

Duration of response is included in "Efficacy Results – Secondary and other relevant endpoints" section.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient reported outcomes (PROs) were collected at pre-specified timepoints during the study. The analysis population for PRO endpoints was the full analysis set (FAS), which included all patients who had at least one available PRO assessment and received at least one dose of study drug.

EORTC QLQ-C30 is a cancer-specific health-related quality of life instrument, which contains 30

items and measures 5 functional dimensions (physical, role, emotional, cognitive and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale. EORTC QLQ-C30 was administered at the beginning of every cycle (± 3 days) for the first four cycles and then every two cycles after that.

Additional PROs included EORTC QLQ-H&N35 and EuroQol EQ-5D; the results of these instruments were generally similar to those of the EORTC QLQ-C30. Table 24 and Table 25 provide the completion rates of EORTC QLC-C30 in the pembrolizumab as a single agent and pembrolizumab in combination with chemotherapy arms compared to the control arm, respectively. The completion rates were similar in each of the treatment arms and the control arm. Similar results were also observed for the CPS ≥1 HNSCC and CPS ≥20 HNSCC subpopulations.

Table 24: Completion Rate of EORTC QLQ-C30 in the FAS Population - Pembrolizumab as a Single Agent vs. Control

Treatment Visit	Pembrolizumab as a Single Agent		Control	
	Expected # of Completed Questionnaires	Actual # of Completed Questionnaires (%)	Expected # of Completed Questionnaires	Actual # of Completed Questionnaires (%)
Baseline	294	280 (95.2)	280	262 (93.6)
Week 3	277	263 (94.9)	262	241 (92.0)
Week 6	260	239 (91.9)	237	219 (92.4)
Week 9	244	225 (92.2)	241	217 (90.0)
Week 15	207	191 (92.3)	230	183 (79.6)
Week 21	154	145 (94.2)	182	151 (83.0)
Week 27	122	105 (86.1)	145	122 (84.1)
Week 33	98	82 (83.7)	96	76 (79.2)
Week 39	79	69 (87.3)	62	49 (79.0)
Week 45	67	64 (95.5)	42	32 (76.2)
Week 51	56	42 (75.0)	31	27 (87.1)

Table 25: Completion Rate of EORTC QLQ-C30 in the FAS Population - Pembrolizumab Combination vs. Control

Treatment Visit	Pembrolizumab in Combination with Chemotherapy		Control	
	Expected # of Completed Questionnaires	Actual # of Completed Questionnaires (%)	Expected # of Completed Questionnaires	Actual # of Completed Questionnaires (%)
Baseline	270	255 (94.4)	260	244 (93.8)
Week 3	241	223 (92.5)	242	222 (91.7)
Week 6	219	206 (94.1)	217	202 (93.1)
Week 9	224	210 (93.8)	222	201 (90.5)
Week 15	211	173 (82.0)	213	168 (78.9)
Week 21	185	153 (82.7)	169	140 (82.8)
Week 27	162	131 (80.9)	136	113 (83.1)
Week 33	124	105 (84.7)	88	69 (78.4)
Week 39	96	84 (87.5)	55	45 (81.8)
Week 45	79	61 (77.2)	35	27 (77.1)
Week 51	65	53 (81.5)	25	21 (84.0)

The analysis method specified for change from baseline for the QLQ-C30 was a constrained longitudinal analysis (cLDA) model, which would estimate the mean score change from baseline and the corresponding 95% confidence interval via least squares.

Table 26 and Table 27 present the analysis of QLQ-C30 score at week 15 in the pembrolizumab as a single agent arm and the pembrolizumab in combination with chemotherapy arm compared to the control arm, respectively.

Table 26: Analysis of Change from Baseline of EORTC QLQ-C30 at Week 15 - Monotherapy vs. Control

Treatment	Baseline		Week 15		Change from Baseline	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)
All Patients						
Pembrolizumab as a Single Agent	280	61.3 (21.59)	191	64.7 (20.55)	294	0.85(-1.90,3.59)
Control	262	59.7 (21.47)	182	62.6 (18.80)	279	0.60(-2.19,3.40)
Diff in LS Means (95% CI)					0.24 (-3.34,3.82)	
p-value					0.893	
PD-L1 CPS **≥1** Population						
Pembrolizumab as a Single Agent	243	60.8 (21.35)	166	64.5 (20.90)	252	0.99 (-1.95,3.94)
Control	225	59.4 (21.78)	155	64.3 (18.33)	237	2.20 (-0.82,5.23)
Diff in LS Means (95% CI)					-1.21 (-5.07,2.65)	
p-value					0.538	
PD-L1 CPS **≥20** Population						
Pembrolizumab as a Single Agent	122	61.5 (20.73)	93	63.7 (20.03)	129	1.94(-1.96,5.84)
Control	108	60.3 (21.96)	75	63.9 (19.34)	112	0.93 (-3.28,5.14)
Diff in LS Means (95% CI)					1.00 (-4.25,6.26)	
p-value					0.707	

Table 27: Analysis of Change from Baseline of EORTC QLQ-C30 at Week 15 – Pembrolizumab Plus Chemotherapy vs. Control

Treatment	Baseline		Week 15		Change from Baseline	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)
All Patients						
Pembrolizumab plus Chemotherapy	255	62.2 (21.18)	173	64.6 (21.10)	268	1.17 (-1.79,4.12)
Control	244	60.0 (21.86)	167	63.3 (18.73)	259	0.77 (-2.22,3.76)
Diff in LS Means (95% CI)					0.40 (-3.46,4.26)	
p-value					0.839	

Treatment	Baseline		Week 15		Change from Baseline	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)
PD-L1 CPS **≥1** Population						
Pembrolizumab plus Chemotherapy	219	62.0 (20.60)	149	64.1 (20.99)	229	1.10 (-2.11, 4.30)
Control	209	60.1 (22.16)	142	65.0 (18.20)	219	2.30 (-0.97, 5.57)
Diff in LS Means (95% CI)					-1.20 (-5.38, 2.98)	
p-value					0.572	
PD-L1 CPS **≥20** Population						
Pembrolizumab plus Chemotherapy	115	62.0 (20.48)	82	64.1 (19.93)	118	1.57 (-2.69, 5.84)
Control	98	61.2 (22.29)	67	65.3 (18.78)	101	0.52 (-3.06, 6.10)
Diff in LS Means (95% CI)					1.05 (-5.64 ,5.74)	
p-value					0.985	

Figure 12 and Figure 13 show the mean QLQ-C30 score change from baseline for patients, comparing monotherapy to control and combination therapy to control, respectively.

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Figure 12: Mean Change of QLQ-C30 Score from Baseline – Pembrolizumab as a Single Agent vs. Control

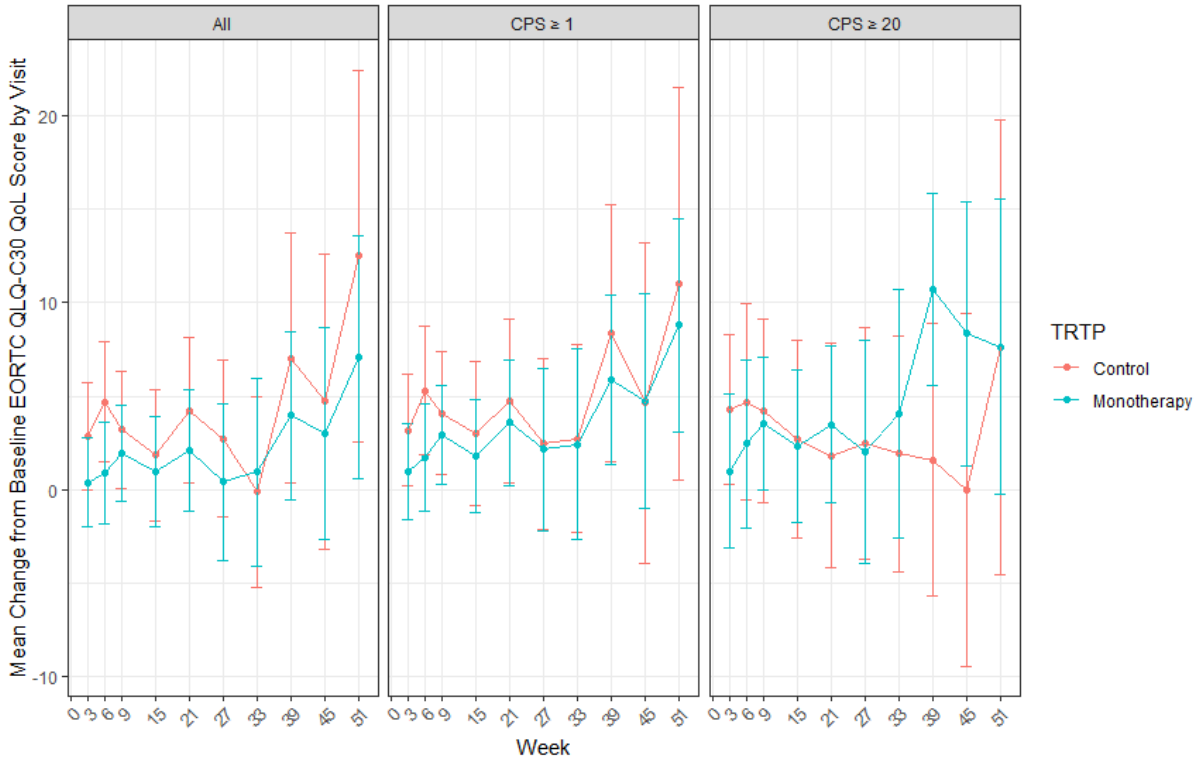

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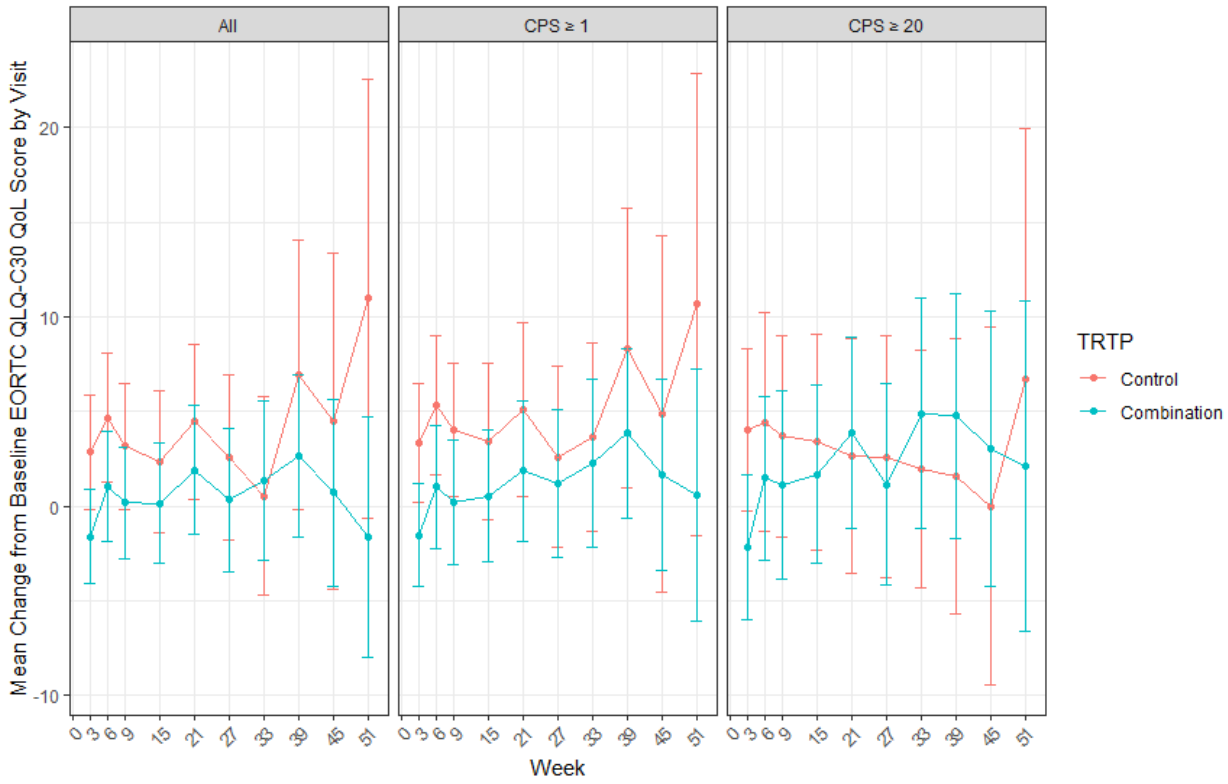
Figure 13: Mean Change of EORTC QLQ-C30 Score from Baseline – Pembrolizumab plus Chemotherapy vs. Control



Reviewer Comment: The results of the PRO exploratory endpoints, including EORTC QLQ-C30, indicate no statistically significant differences between the pembrolizumab as a single agent or pembrolizumab in combination with chemotherapy and the control arm.

8.1.3. Integrated Review of Effectiveness

No integrated assessment of effectiveness was conducted for this sBLA. KEYNOTE-048 was the only study submitted to support the proposed indication.

8.1.4. Assessment of Efficacy Across Trials

KEYNOTE-048 is the only study submitted to support the efficacy of pembrolizumab in the first-line treatment of patients with R/M HNSCC.

8.2. Review of Safety

The review of safety was focused on data submitted for patients randomized in KEYNOTE-048 who received at least one dose of study drug. The data cutoff for KEYNOTE-048 was June 13,

2018.

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8.2.1. Safety Review Approach

The review of safety included analysis of the submitted study report, datasets, line listings, case narratives, and case report forms (CRFs) from KEYNOTE-048. The review tools used included JMP and Excel programs.

The overall incidence and severity of AEs were compared to the safety data provided by Merck in the summary of clinical safety (SCS) from: a) pooled safety data from 609 patients with R/M HNSCC who received pembrolizumab as single agent in KEYNOTE-040, KEYNOTE-012 and KEYNOTE-055 and b) the Pembrolizumab Single Agent Reference Safety Database (RSD), consisting of data from 2799 patients treated with pembrolizumab as a single agent, including patients with advanced melanoma (KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006) and patients with NSCLC (KEYNOTE-001 and KEYNOTE-010).

Pooling of safety data from KEYNOTE-048 with other safety data was not conducted by the reviewers for this application. The reviewer referred to Merck's SCS for pooled safety data analyses.

8.2.2. Review of the Safety Database

Overall Exposure

In KEYNOTE-048, 300 of the 301 patients randomized to the single agent pembrolizumab arm received at least one 200 mg dose of pembrolizumab; one patient died prior to initiating treatment. On the pembrolizumab plus chemotherapy arm 276 of the 281 randomized to that arm received at least one 200 mg dose of pembrolizumab and carboplatin or cisplatin and fluorouracil; three patients died and one patient withdrew from study prior to initiating treatment. On the control arm, 287 of the 300 patients randomized to that arm received at least one dose of cetuximab, cisplatin or carboplatin, and 5-FU. Among 13 patients who were randomized and did not start planned treatment, 6 patients died, 6 patients withdrew from study, and in one patient the reason for lack of data is not specified.

Treatment exposure per treatment arm in the safety population is summarized in Table 28.

Table 28: KEYNOTE-042 Summary of Treatment Exposure

	Pembrolizumab N = 300 (%)	Pembrolizumab + Chemotherapy N = 276 (%)	Cetuximab + Chemotherapy N = 287 (%)
Treatment Duration (Months)			
Median (Min - Max)	3.5 (1 day to 24.2 months)	5.8 (3 days to 24.2 months)	5.0 (1 day-35 months)
Number of Cycles			
Median (Min - Max)	6 (1 to 40)	8 (1 to 35)	7 (1 to 48)
Duration of Exposure			
Treated	100%	100%	100%
≥ 3 months (%)	55	71	72
≥ 6 months (%)	35	47	37
≥ 12 months (%)	17	18	8

Source ADaM dataset: adexsum.xpt and SDTM dataset: ex.xpt

Relevant characteristics of the safety population:

The safety population from KEYNOTE-048 is comprised of 863 patients with advanced or metastatic HNSCC, who had not previously received systemic therapy for metastatic disease. The safety population included 300 patients who received pembrolizumab, 276 patients who received pembrolizumab in combination with chemotherapy and 287 patients who received chemotherapy in combination with cetuximab.

The characteristics of the safety population of the 576 pembrolizumab-treated patients in KEYNOTE-048 is consistent with the epidemiology and natural history of patients with metastatic HNSCC: the median age was 62 years (range 25 to 89), with 36% of the patients 65 years or older; 84% of the patients were male; 73% were White and 20% were Asian , 39% had ECOG performance status (PS) 0 and 61% had ECOG PS 1.

Refer to Tables 12 and 13 for the patient demographics and baseline disease characteristics of the ITT population.

Adequacy of the safety database:

Overall, the safety database submitted by Merck comprising of 576 patients who received pembrolizumab either as a single agent or in combination with platinum and 5-FU chemotherapy, with a median exposure of 3.5 and 6 months, respectively, was sufficient to identify AEs occurring at an incidence of approximately ≥ 0.5%.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The application contains all the agreed upon components of the electronic Common Technical Document. The submission was well organized and allowed for clinical review.

Categorization of Adverse Events

Categorization of AEs in KEYNOTE-048 is consistent with pembrolizumab's clinical development program. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. AE severity was graded according to The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3

AEs were collected from the first dose of study drug to up to 30 days after the last dose of study drug. Serious AEs (SAEs) and adverse-events of special interest (AEOSIs), as defined by Merck in the pembrolizumab clinical development program, were collected for up to 90 days after the last dose of study treatment or 30 days if the patient started a non-study anticancer treatment, whichever was earlier.

AEOSI are defined in accordance with pembrolizumab's clinical development program i.e., as immune-related AEs (irAEs) based on Merck's predefined list of preferred AE terms that are potentially associated with an immune etiology (Table 40). This list was developed by Merck and includes AEOSI terms identified using MedDRA, Version 20.1 preferred terms, which have been based on ongoing monitoring of the pembrolizumab safety profile during the development program.

All AEOSIs are included in the analysis regardless of investigator-assessed causality and generally include all AE grades. Merck states that in order to capture all informative data, the list of terms is intentionally broad; consequently, some reported terms may not have an obvious immune mechanism. The list of terms is updated periodically by Merck based on emerging pembrolizumab safety data.

Routine Clinical Tests

Routine clinical tests included complete blood count with differential, comprehensive chemistry panel, creatinine clearance calculation, urinalysis, coagulation parameters (PT/INR and

aPTT/PTT), and thyroid function tests (T3 or FT3, FT4 and TSH) performed within 28 days of initiation of randomization, at regular pre-specified intervals during trial and when medically necessary. Vital signs were assessed at baseline and pre- and post-pembrolizumab and chemotherapy infusion

8.2.4. Safety Results

An overview of AEs observed in KEYNOTE-048 is shown in Table 29.

Table 29: Overview of Adverse Events in KEYNOTE-048

Adverse Event	Pembrolizumab N = 300 %	Pembrolizumab + Chemotherapy N = 276 %	Cetuximab + Chemotherapy N = 287 %
Any AE*^	98	98	100
Grade 3 to 5 AE	54	85	84
Any SAE	40	59	49
Any deaths due to AE	8	12	9
Drug Related deaths	1	4	3
AE Leading to treatment discontinuation	12	31[#]	27[#]
AE Leading to treatment interruption	31	63[#]	63[#]

Source: ADaM dataset: adae.xpt., SDTM dataset: ae.xpt.
**Includes non-serious AEs up to 30 days after last study drug and SAEs up to 90 days of last study drug*
^Excludes MedDRA PTs "Neoplasm progression", "Malignant neoplasm progression", "Disease Progression"
[#] Discontinuation and interruption of any drug in the combination

In KEYNOTE-048, comparing the pembrolizumab single agent arm to cetuximab in combination with chemotherapy, there was a lower incidence of SAEs (40% vs 49%), Grade 3-5 AEs (54% vs 84%), AEs resulting in discontinuation of study drug (21% vs 29%) and AEs leading to treatment interruption (31% vs 63%).

Comparing the pembrolizumab in combination with chemotherapy arm to the cetuximab in combination with chemotherapy arm (control arm), there was a higher incidence of SAEs (59% vs 49%), death due to an AE (12% vs 9%), and discontinuation of study drug due to an AE (36% vs 29%) in patients in the pembrolizumab in combination with chemotherapy arm. The incidence of Grade 3-5 AEs was similar in the pembrolizumab plus chemotherapy arm and the cetuximab plus chemotherapy arm (85% vs 84%).

Reviewer Comment: The pembrolizumab single agent arm had a more favorable safety profile compared to the chemotherapy containing arms. This is not unexpected given the platinum-based chemotherapy backbone in the combination treatment arms. The AE profile for the

pembrolizumab as a single agent arm was similar to that based on the HNSCC pembrolizumab monotherapy RSD. The AE summary profile for the pembrolizumab in combination with chemotherapy arm revealed a higher incidence of AEs in all categories compared to the HNSCC pembrolizumab monotherapy dataset provided in the Merck's SCS. This reflects the increased toxicity anticipated with the addition of chemotherapy to pembrolizumab. The incidence of SAEs was higher in the pembrolizumab in combination with chemotherapy arm compared to the cetuximab in combination with chemotherapy arm; see Table 33 for details regarding SAEs.

Deaths

At the time of the data cutoff date, more patients in the cetuximab plus chemotherapy arm had died compared to the pembrolizumab plus chemotherapy arm and the pembrolizumab single agent arm (80% vs 70% vs 71%). Death attributed to an AE occurred in 8% of patients in the pembrolizumab arm, 12% in the pembrolizumab plus chemotherapy arm and 9% in the cetuximab and chemotherapy arm (Table 29). Case report forms and narratives of all patients who experienced an AE leading to death were reviewed. Causes of death per MedDRA PT occurring in more than two patients in any treatment arm are listed in Table 30.

Table 30: AEs Leading to Death.

Preferred Term	Pembrolizumab N = 300 %	Pembrolizumab + Chemotherapy N = 276 %	Cetuximab + Chemotherapy N = 287 %
Deaths due to an AE*	8.3	11.6	9.4
Infections**	3.0	4.3	4.9
Septic Shock	0.3	1.8	0.7
Pneumonia	0.7	0.8	2.0
Death	0.7	0.8	0.7
Multiorgan dysfunction	0.7	0.8	0
Myocardial Infarction	0.7	0.8	0.7
Cardiac Arrest	0	0.8	0
Pulmonary Embolism	0.3	0.4	0.7
Tumor hemorrhage	0.3	0.4	1.0
Pneumonitis	0.3	0.4	0
Hypoxia	0	0	0.3

Source ADaM dataset: adae.xpt. and SDTM dataset: ae.xpt.
* Exclude MedDRA preferred terms: "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression"
** Includes MedDRA preferred terms: Acinetobacter infection, bronchitis, infection, lung infection pseudomonal, nosocomial infection, osteomyelitis, pneumonia, pseudomonal sepsis, sepsis, septic shock, soft tissue infection, stoma site infection.

Infection was the most common cause of death in all treatment arms, with incidence ranging from 3 to 4.5% across the arms. The only other causes of death with incidence ≥1% were pneumonia (2%) and tumor hemorrhage (1%) in the cetuximab plus chemotherapy arm and septic shock (2%) in the pembrolizumab plus chemotherapy arm. A total of four (<1%) patients

across the two pembrolizumab arms died while on study of unknown causes, compared to two patients (<1%) in the cetuximab plus chemotherapy arm. Brief narratives for the patients who died of known causes are presented in Table 31.

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Table 31: Patient Narratives for AEs Leading to Death In Patients Who Received Pembrolizumab as Single Agent or in Combination with Chemotherapy in KEYNOTE-048

Patient ID	AE leading to death (MedDRA PT)	Summary	Causal Attribution (FDA)
(b) (6)	Pneumonia	60 yo white male with T4N2M1 oral cavity SCC was hospitalized with fever, shortness of breathing and hypotension on D15 of pembrolizumab plus chemotherapy, was diagnosed with aspiration pneumonia / sepsis. On D16 developed aphasia and right hemiparesis, CT scan revealed left parietal infarct. On D17 patient died due to pneumonia.	Causal association of sepsis and stroke to pembrolizumab cannot be completely ruled out.
(b) (6)	Embolic Stroke	60 yo white male with T0N3M1 oral cavity SCC treated on pembrolizumab plus chemotherapy arm was hospitalized on D379 for Grade 2 compression fracture in thoracic spine and diffuse metastatic disease along the spine. On D383 a brain MRI revealed numerous small foci of acute infarction. On D387 patient died due to embolic stroke. Cause of death was reported as not known.	Causal association of embolic stroke to pembrolizumab cannot be completely ruled out.
(b) (6)	Bronchitis	66 yo white male with HPV positive T4N2M0 recurrent disease of oropharynx SCC treated on pembrolizumab plus chemotherapy arm was hospitalized on D26 for SOB, confusion, elevated WBC count of 17.1. On D28 patient deteriorated and died due to bronchitis per Sponsor.	Causal association with pembrolizumab cannot be completely ruled out. Patient had received radiation one month prior to study start and had dysphagia at screening.
(b) (6)	Carotid artery Perforation	65 yo white female with T4N0M0 recurrent disease of oral cavity SCC treated on pembrolizumab plus chemotherapy arm was hospitalized on D46 with acute onset bleeding from orocutaneous fistula, followed by massive bleeding due to tumor invading the carotid artery. Patient died the same day from severe blood loss and shock. During the study patient had developed Grade 3 mucosal inflammation.	Death attributed to tumor invading carotid artery. Causal association to pembrolizumab, chemotherapy that could have caused mucosal inflammation cannot be ruled out.

Patient ID	AE leading to death (MedDRA PT)	Summary	Causal Attribution (FDA)
(b) (6)	MI	69 yo white male with TxNxM1 disease of oropharynx SCC treated on pembrolizumab plus chemotherapy arm was hospitalized on D308 for possible MI. Patient declined aggressive medical management and was transferred to hospice. Patient died on D312. Last treatment was on D296 with pembrolizumab.	Causal association to pembrolizumab cannot be completely ruled out due to temporal association.
(b) (6)	Pulmonary Embolism	69 yo white male with T3N0M0 disease of oropharynx SCC treated on pembrolizumab plus chemotherapy arm on D23. On D25 patient had a cardiac arrest and due to sudden onset, PE was suspected. Resuscitation was unsuccessful.	Causal association to pembrolizumab cannot be completely ruled out due to temporal association.
(b) (6)	Hemoptysis	63 yo Asian male with T3N0M0 disease of oropharynx SCC treated on pembrolizumab plus chemotherapy arm received cycle 1 D1-4 and on D4 experienced Grade 2 hemoptysis and was treated with tranexamic acid. Platelets and PT, PTT, INR were normal. On D5 had a tracheostomy for airway protection. ENT noted an ulcerative tumor at the right posterior pharyngeal wall. On D6 patient had massive hemoptysis and patient was placed on ventilator. Despite medical intervention patient died.	Hemoptysis likely multifactorial. Causal association to pembrolizumab cannot be completed ruled out due to temporal association.
(b) (6)	Sepsis	40 yo Asian female with T4N2M0 disease of oropharynx SCC treated on pembrolizumab plus chemotherapy arm received cycle 1 D1-4. On D30 patient was admitted for dyspnea, fever, and CXR revealed pneumonia. Patient was not neutropenic. Patient was treated with appropriate antibiotics. On D36 gastrostomy wound culture was positive for multiple organisms. On D37 patient died of acute respiratory failure due to sepsis secondary to pneumonia.	Causal association to study pembrolizumab cannot be ruled out due to temporal association.

Patient ID	AE leading to death (MedDRA PT)	Summary	Causal Attribution (FDA)
(b) (6)	Septic Shock	53 yo Asian male with T3N2M1 disease of oral cavity SCC treated on pembrolizumab arm received cycle 1and Cycle 2. On D41 patient was admitted for abdominal pain and general weakness. Blood culture was positive for *C. tropicalis* and had a positive urine culture. On D42 scans confirmed progression of disease. On D43 patient was noted to have Grade 4 septic shock. On D52 patient condition deteriorated further and died.	Causal association to study pembrolizumab cannot be ruled out due to temporal association.
(b) (6)	Pulmonary Sepsis	63 yo male with T4N1M1 disease of larynx with lung mets treated on pembrolizumab arm received 2 cycles of treatment. On D30 patient presented with weakness, hypotension and decreased urine output. On D34, PEG tube was placed. On D35 patient was diagnosed with pneumonia/sepsis and treated accordingly. On D41 patient was started on pressors. On D43 patient died.	Causal association to study pembrolizumab cannot be ruled out due to temporal association.
(b) (6)	Pneumonitis	59 yo female with TXN0M1 disease of oral cavity with lung mets treated on pembrolizumab arm received 1 cycles of treatment. On D10 patient experienced Grade 2 dyspnea, treated with steroids and resolved D16. On D22 presented with increasing SOB, hypoxia and CXR showed patchy consolidation. CT chest revealed new ground-glass infiltrate/solid nodules. Patient required high dose steroids, supportive care and non-invasive ventilation. D24 worsening interstitial infiltrates in both lungs. On D26 patient died due to Grade 5 pneumonitis.	Pneumonitis is definitely related to pembrolizumab.
(b) (6)	Aspiration	71 yo female with T4N2M1 disease of oral cavity with metastases was treated on pembrolizumab arm and received 2 cycles of treatment. Last treatment was on D22. On D29 patient was found unconscious at home. On admission was intubated for respiratory failure, noted to have elevated WBC, and was comatose. On D30 patient died due to aspiration.	Cause of death is unclear and causal association to study pembrolizumab cannot be ruled out due to temporal association.

Patient ID	AE leading to death (MedDRA PT)	Summary	Causal Attribution (FDA)
(b) (6)	Death	69 yo female with T4N2M1 disease of oral cavity with metastases treated on pembrolizumab arm received 2 cycles of treatment. After first dose of pembrolizumab patient had skin necrosis in area of defect in right cheek requiring wound care. On D27, 4 days after Cycle 2, patient experienced mild dyspnea and later died at home.	Cause of death is unclear and causal association to study pembrolizumab cannot be ruled out due to temporal association.
(b) (6)	Pneumonia	64 yo male hospitalized with T3N0M1 disease of larynx with metastases treated on pembrolizumab arm received 1 cycles of treatment. On D6 patient experienced dysphagia, and PEG tube was placed. On D9 patient was admitted for altered consciousness, tachypnea, respiratory distress, and right basal pneumonia. Patient continued to rapidly decline requiring ventilator assistance. CXR on D14-17 revealed interstitial infiltrates. On D17 patient had a cardiorespiratory arrest resulting in death.	Cause of death is unclear, per Sponsor cause of death is pneumonia. However, causal association to study pembrolizumab cannot be ruled out due to temporal association

Reviewer Comment: The proportion of patients who died due to an AE was higher in the pembrolizumab plus chemotherapy arm (12%) compared to the pembrolizumab single agent arm or the control arm (8% and 9%). Death due to an unknown cause/sudden death was similar in the three arms. The incidence of deaths due to infections were slightly higher in the chemotherapy-containing arms compared to the pembrolizumab single agent arm.

The proportion of patients who died due to an AE and death due to unknown cause in KEYNOTE-048 was compared to pembrolizumab's safety data base. The incidence of death due to an AE was higher in both pembrolizumab arms in KEYNOTE-048 compared to the pembrolizumab single agent RSD and the pembrolizumab cumulative dataset. Deaths due to unknown cause in pembrolizumab-treated patients were similar in KEYNOTE-048 when compared to the pembrolizumab single agent RSD and the pembrolizumab cumulative dataset. Results are presented in Table 30.

Table 32 Comparison of Death due to AE between KN-048 and Pembrolizumab Safety Data Sets

	KEYNOTE-048 Pembrolizumab Arm N=300	KEYNOTE-048 Pembrolizumab-Chemotherapy Arm N=276	HNSCC Safety Dataset N=609	Pembrolizumab Monotherapy RSD* N=2799	Pembrolizumab Cumulative Data Set N=5246
Deaths due to an AE	25 (8.3)	32 (11.6)	54 (8.9)	110 (3.9)	38 (0.7)
Death due to unknown cause^ (NOS)	2 (0.6)	2 (0.7)	NA	17 (0.6)	40 (0.7)

** RSD = pembrolizumab monotherapy Reference Safety Database*
^ Includes: death and sudden death

Reviewer Comment: The underlying malignancy, co-morbid conditions and other confounding factors might have all contributed to the increased number of deaths due to AEs in the pembrolizumab arms. The incidence was similar compared to the control arm in KEYNOTE-048 and the pembrolizumab HNSCC monotherapy dataset. Infections, sepsis and pneumonia were the most common causes of death in the pembrolizumab arms in KEYNOTE-048 and similar in frequency compared to the cetuximab plus chemotherapy arm, suggesting this may be related to underlying disease and patient characteristics. With the lack of additional information (e.g., autopsy reports), a causal association to pembrolizumab cannot be completely ruled out. FDA will continue to closely monitor all adverse event reports associated with pembrolizumab in ongoing trials and in the post-marketing setting.

Serious Adverse Events

In KEYNOTE-048, an SAE is defined as an AE that resulted in death, was life-threatening, resulted in persistent or significant disability/incapacity, resulted in prolonged hospitalization, resulted in a congenital anomaly/birth defect, development of a new cancer or was associated with an overdose. Data on SAEs was collected up to 90 days after the last dose of study drug. SAEs occurred at a higher frequency in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm and pembrolizumab single agent arm (59% vs 49% vs 40%).

The most common SAEs in the pembrolizumab plus chemotherapy arm were in the system organ class (SOC) categories of infections and infestations (22.4%), blood and lymphatic system disorders (14.5%), respiratory, thoracic and mediastinal disorders (13%) and gastrointestinal disorders (10%). The most common SAEs in the cetuximab plus chemotherapy arm were in the SOC categories of infections and infestations (17%), blood and lymphatic system disorders (10%) and gastrointestinal disorders (12%). The most common SAEs in the pembrolizumab

single agent arm were in the SOC categories of infections and infestations (16%) and respiratory, thoracic and mediastinal disorders (12%). SAEs occurring in >1% of patients in any treatment arm in KEYNOTE-048 are listed in Table 33.

Table 33: Serious AEs occurring in ≥1% of Patients in Any Treatment Arm

MedDRA SOC/ PT	Pembrolizumab N = 300 (%)	Pembrolizumab + Chemotherapy N = 276 (%)	Cetuximab + Chemotherapy N = 287 (%)
Patients with at least one serious AE	121 (40)	162 (59)	141 (49)
Blood and lymphatic system disorders	3 (1)	40 (14.5)	28 (10)
Anemia	1 (0.3)	14 (5)	9 (3)
Febrile neutropenia	0 (0)	16 (6)	14 (5)
Neutropenia	0 (0)	7 (2.5)	5 (1.7)
Infections and infestations	49 (16)	62 (22)	48 (17)
Pneumonia*	20 (7)	31 (11)	24 (8)
Sepsis**	7 (2)	11 (4)	6 (2)
Gastrointestinal disorders	20 (7)	34 (12)	28(10)
Nausea	0	6 (2)	8 (3)
Vomiting	0	5 (2)	5(1.7)
Dysphagia	5 (1.7)	2 (0.7)	2 (0.7)
Respiratory, thoracic & mediastinal dis.	36 (12)	36 (13)	26 (9)
Dyspnea	7 (2)	4 (1.4)	4 (1.4)
Aspiration Pneumonia	6 (2)	8 (3)	3 (1)
Pneumonitis***	4 (1.3)	5 (1.8)	2 (0.7)
Hemorrhage****	2 (0.7)	4 (1.4)	2 (0.7)
Pulmonary Embolism	2 (0.7)	4 (1.4)	6 (2)
Cardiac disorders	6 (2)	10 (4)	9 (3)
Myocardial infarction/ischemia^	3 (1)	7 (2.5)	4 (1.4)
General disorders & adm. site cond.	14 (5)	21 (8)	14 (5)
Death/Sudden death	2 (0.7)	3 (1.1)	2 (0.7)
Tumor hemorrhage	9 (3)	6 (2.2)	5 (1.7)
Metabolism and nutrition disorders	12 (4)	30 (11)	19 (7)
Hypercalcemia	5 (1.7)	3 (1.1)	2 (0.7)

**Includes: pneumonia, pneumonia bacterial, pneumonia Klebsiella, mycoplasma pneumonia, staphylococcal pneumonia, respiratory tract infection, pulmonary sepsis, atypical pneumonia, lower respiratory tract infection, lung infection, lung abscess, lung infection pseudomonal.*
***Includes: sepsis, septic shock, urosepsis, wound sepsis*
**** Includes: pneumonitis and interstitial lung disease*
*****Includes: Hemoptysis, epistaxis, pharyngeal hemorrhage, respiratory tract hemorrhage*
^Includes: Myocardial infarction, myocardial ischemia, autoimmune myocarditis, cardiac arrest

SAEs that occurred at a ≥ 1% higher frequency in the pembrolizumab plus chemotherapy arm and/or the control arm compared to the pembrolizumab single agent arm were febrile neutropenia, anemia, thrombocytopenia, nausea and pulmonary embolism. SAEs that occurred at similar frequency between arms were pneumonia, pneumonitis, and sudden death or death

NOS. SAEs occurring at a ≥ 1% higher frequency in the pembrolizumab single agent arm compared to the control arm were tumor hemorrhage and hypercalcemia.

Reviewer Comments:
In comparison to the pembrolizumab monotherapy HNSCC dataset the incidence of SAEs was lower in the pembrolizumab single agent arm treatment arm (46% vs 40%). In KN-048 pembrolizumab was administered in the first line setting and may have been better tolerated compared to the second line and beyond patients included in the pembrolizumab monotherapy HNSCC dataset.

In comparison to the pembrolizumab monotherapy HNSCC dataset, the incidence of SAEs was higher in the pembrolizumab plus chemotherapy treatment arm (46% vs 59%); this is not unexpected with addition of chemotherapy.

Dropouts and/or Discontinuations Due to Adverse Effects

AEs leading to treatment discontinuation of pembrolizumab or any drug in the combination arms are listed in Table 34. AEs leading to discontinuation of pembrolizumab were 12% (n=36) in the pembrolizumab single agent arm and 16% (n=43) in the pembrolizumab plus chemotherapy arm. The most common AEs in the pembrolizumab single agent arm leading to discontinuation of pembrolizumab were sepsis (1.7%) and pneumonia (1.3%). The most common AEs in the pembrolizumab plus chemotherapy arm leading to discontinuation of pembrolizumab were pneumonia (3.6%), pneumonitis (1.8%), and septic shock (1.4%).

Table 34: AEs Leading to Treatment Discontinuation of Any Protocol-specified Drug in ≥ 1% of Patients

Treatment Discontinuation due to an AE	Pembrolizumab N = 300 (%)	Pembrolizumab + Chemotherapy N = 276 (%)	Cetuximab + Chemotherapy N = 287 (%)
No. of Patients with ≥ 1 AE	36 (12)	85 (31)	78 (27)
Sepsis*	6 (2)	6 (2.2)	4 (1.4)
Pneumonia**	4 (1.2)	10 (3.6)	5 (1.8)
Renal disorders***	1 (0.3)	11 (4)	6 (2)
Pneumonitis****	2 (0.6)	5 (1.8)	2 (0.7)
Mucosal Inflammation****	1 (0.3)	6 (2.2)	3 (1)
Neutropenia^	0 (0)	6 (2.2)	4 (1.4)
Hearing disorders^^	0 (0)	5 (1.8)	7 (2.4)
Anemia	0 (0)	2 (0.7)	4 (1.4)
Infusion Reaction	0 (0)	1 (0.4)	10 (3)

**Includes: sepsis, septic shock, urosepsis, wound sepsis, MODS*
*** pneumonia, pneumonia bacterial, pneumonia Klebsiella, mycoplasma pneumonia, staphylococcal pneumonia, respiratory tract infection, pulmonary sepsis, atypical pneumonia, lower respiratory tract infection, lung infection, lung abscess, lung infection pseudomonal.*
****Includes: acute kidney injury, creatinine increase, tubulointerstitial nephritis, renal failure acute, renal injury, renal function disorder.*
***** Includes: pneumonitis and interstitial lung disease*
****** Includes: mucosal inflammation, stomatitis*
^ Includes: neutropnia, febrile neutropenia
^^ Includes: tinnitus, hypoacusis, deafness.

The incidence of AEs leading to discontinuation of any protocol-specified drug in the regimen was similar between the pembrolizumab plus chemotherapy arm and cetuximab plus chemotherapy arm (31% vs 27%). Pembrolizumab was discontinued due to an AE in 16% of patients in the pembrolizumab plus chemotherapy arm and in 12% of patients in the pembrolizumab single agent arm. The most common (≥1%) AEs leading to discontinuation of pembrolizumab in the pembrolizumab plus chemotherapy arm were pneumonia (2.5%), pneumonitis (1.8%) and septic shock (1.4%). The most common AEs (≥1%) leading to discontinuation in the pembrolizumab single agent arm were sepsis (1.7%) and pneumonia (1.3%). In the cetuximab plus chemotherapy arm, infusion-related reaction (3%) was the most common AE leading to discontinuation of study drug.

The incidence of AEs leading to interruption of any protocol-specified drug in the regimen was similar between the pembrolizumab plus chemotherapy arm and cetuximab plus chemotherapy arm (63% vs 63%). The most common (≥ 2%) AEs leading to interruption of any drug in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm were neutropenia (19% vs 18%), thrombocytopenia (12% vs 7%), anemia (9% vs 6%), pneumonia (6.5% vs 4%), acute kidney injury (5% vs <1%), mucosal inflammation (5% vs 4.5%), and fatigue (5% vs 6%).

AEs leading to interruption of pembrolizumab were 31% in the pembrolizumab single agent arm and 45% in the pembrolizumab plus chemotherapy arm. The most common (≥ 2%) AEs in the pembrolizumab single agent arm leading to interruption of pembrolizumab were pneumonia (2.3%), pneumonitis (2.3%), and hyponatremia (2.0%). The most common (≥ 2%) AEs in the pembrolizumab plus chemotherapy arm leading to interruption of pembrolizumab were neutropenia (14%), thrombocytopenia (10%), anemia (6%), pneumonia (4.7%) and febrile neutropenia (2.9%).

In the pembrolizumab single agent arm compared to the cetuximab plus chemotherapy arm, anemia (5% vs 6%), pneumonia (3% vs 4%), pneumonitis (2.3% vs 0%) and hyponatremia (2% vs 0.7%) were the most common AEs leading to interruption of treatment.

A higher proportion of patients in the cetuximab plus chemotherapy arm had diarrhea (3% vs 1.4%), nausea (3% vs 0.4%), rash (3.1% vs 0.4%), infusion-related reaction (3.5% vs 0.4%), and dermatitis acneiform events resulting in study drug interruption compared with the pembrolizumab plus chemotherapy arm.

Reviewer Comments:
In comparison to the pembrolizumab monotherapy HNSCC dataset, the incidence of AEs leading to discontinuation of treatment was higher (36% vs 14%) in the pembrolizumab plus chemotherapy arm of KEYNOTE-048, as was the incidence of treatment interruption due to AEs (54% vs 10%); this is not unexpected with addition of chemotherapy.

In comparison to the pembrolizumab monotherapy HNSCC dataset, the incidence of AEs leading to interruption of treatment was higher in the pembrolizumab single agent arm of KEYNOTE-048 (18% in KEYNOTE-048 vs 10%). The incidence of AEs leading to interruption of pembrolizumab in the single agent pembrolizumab arm of KEYNOTE-048 compared to the pembrolizumab monotherapy HNSCC dataset was slightly higher (31% in KEYNOTE-048 vs 26%).

Significant Common Adverse Events

AE severity was graded using NCI-CTCAE version 4.03. AEs (all Grades and Grades 3-5) occurring in more than 5% of patients by MedDRA SOC and PT in either treatment arm are listed in Table 35 comparing the pembrolizumab single agent arm to the cetuximab plus chemotherapy arm.

Table 35: Adverse Events Occurring in **≥5%** of Patients in either Treatment Arm: Pembrolizumab Single Agent vs Cetuximab plus Chemotherapy

MedDRA SOC and PT	Pembrolizumab N=300 %		Cetuximab+Chemotherapy N=287 %	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Patients with AEs	97	52	100	80
Cardiac Disorders				
Arrythmias**	4.0	0.6	7	0.6
Endocrine Disorders				
Hypothyroidism	18	0	6	0
Gastrointestinal Disorders				
Constipation	20	0.3	33	1.4
Diarrhea***	16	0.7	35	3.1
Nausea	17	0	51	6
Stomatitis	3.3	0	28	3.5
Vomiting	11	0.3	28	2.8
Dysphagia	8	2.3	10	2.1
General Disorders & Admin. Site				
Fatigue^	33	4.0	48	8
Mucosal Inflammation	4.3	1.3	28	5
Pyrexia	13	0.7	12	0
Infections and infestations				
Pneumonia^^	12	7	13	6
Upper respiratory tract infection	6	0.4	5	0.3
Injury, Poisoning & Procedures				
Infusion related reaction	0.3	0	6	1.0
Investigations				
Weight decreased	15	2.0	21	1.4
Metabolism and Nutrition Disorders				
Decreased appetite	15	1.0	30	3.5
Musculoskeletal & Connective Tissue				
Neck pain	6	0.7	7	0.7
Athralgia	5	0	3.0	0
Musculoskeletal pain^^^	5	0	7	0
Myalgia^^^^	12	1.0	11	0.3
Neoplasms, benign, malign. unspecified				
Tumor hemorrhage^^^^^	6	2.3	6	0.7
Nervous System Disorders				
Dizziness	4.7	0.3	13	0.3
Headache	12	0.3	8	0.3
Peripheral sensory neuropathy#	1.0	0	7	1
Dysguesia	3.0	0	7	0
Psychiatric disorders				
Insomnia	7	0.7	8	0
Anxiety/Agitation	6	0.3	6	0

MedDRA SOC and PT	Pembrolizumab N=300 %		Cetuximab+Chemotherapy N=287 %	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Respiratory, Thoracic and Mediastinal				
Cough[##]	18	0.3	15	0
Dyspnea[###]	14	2.0	8	1.0
Hemoptysis	5	0.3	3.1	0.3
Pneumonitis	6	1.3	1.0	0.6
Skin and Subc. Tissue Disorders				
Alopecia	0.3	0	5	0
Pruritus	11	0	10	0.3
Rash [####]	20	2.3	70	8
Vascular Disorder				
Thrombosis[#####]	5	1.7	9	3.0

[*]*Includes: acute myocardial infarction, myocardial infarction, myocardial ischemia, acute coronary syndrome, cardiac arrest, cardiovascular insufficiency, coronary artery stenosis*
[**] *Includes: arrhythmia, atrial fibrillation, bradycardia, palpitations, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, ventricular arrhythmia*
[***] *Includes: diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis*
**** *Includes: ALT increase, AST increase, autoimmune hepatitis, bilirubin increase, GGT increase, hepatic failure, hepatotoxicity, hyperbilirubinemia, hypertransaminasaemia*
[^] *Includes: asthenia, fatigue*
[^^] *Includes: pneumonia, bacterial pneumonia, staphylococcal pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal*
[^^^] *musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain*
[^^^^] *Includes: back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia*
[^^^^^]*Includes: tumor hemorrhage included arterial hemorrhage, arterial perforation, arterial rupture, carotid artery perforation, hemorrhage tumor necrosis, laryngeal hemorrhage, lip hemorrhage, mouth hemorrhage, tonsillar hemorrhage, pharyngeal hemorrhage, soft tissue hemorrhage, tongue hemorrhage, tracheal hemorrhage, tumor hemorrhage, venous hemorrhage, wound hematoma, and wound hemorrhage.*
[#]*Includes: peripheral sensory neuropathy, peripheral neuropathy, hypoaesthesia, dysaesthesia*
[##] *Includes: cough, productive cough*
[###]*Includes dyspnea, exertional dyspnea*
[####]*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: all thrombosis and embolism and pulmonary embolism*

Among patients treated with pembrolizumab as a single agent (Table 35), the most common AEs occurring in ≥ 10% of patients were fatigue/asthenia, constipation, rash, hypothyroidism, cough, nausea, decrease appetite, diarrhea, weight decrease, dyspnea, pneumonia, myalgia, pyrexia, headache, vomiting, and pruritis.

MedDRA Preferred Term AEs (all grades) that occurred at a ≥ 5% higher incidence in the pembrolizumab single agent arm compared to the cetuximab plus chemotherapy arm were pneumonitis (6% vs 1.0%), hypothyroidism (18% vs 6%), and dyspnea (14% vs 8%).

Among the AEs listed in Table35, there were no Grade 3-4 AEs that occurred at a ≥ 2% higher frequency in the pembrolizumab single agent arm compared to the cetuximab plus chemotherapy arm.

Reviewer Comments: The overall incidence of Grade 3 and 4 AEs was lower in the pembrolizumab single agent arm compared to the cetuximab plus chemotherapy arm (80% vs 52%). The incidence of hypothyroidism (18% vs 15.1%) and dyspnea (14% vs 16%) were similar between the pembrolizumab single agent arm in KEYNOTE-048 and the HNSCC pembrolizumabRSD.

AEs (all grades and Grades 3-5) occurring in more than 5% of patients by MedDRA SOC and PT in either treatment arm are listed in Table 36 comparing pembrolizumab plus chemotherapy to cetuximab plus chemotherapy.

Table 36: Adverse Events Occurring in **≥5%** of Patients in either Treatment Arm (Pembrolizumab plus Chemotherapy vs Cetuximab plus Chemotherapy)

MedDRA System Organ Class and Preferred Term	Pembrolizumab + Chemotherapy N=276 %		Cetuximab + Chemotherapy N=287 %	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Patients with AEs	97	84	100	80
Cardiac Disorders				
Arrythmias **	3.0	0.3	7	0.6
Endocrine Disorders				
Hyperthyroidism	5	0	1.0	0
Hypothyroidism	15	0	6	0
Gastrointestinal Disorders				
Constipation	37	0	33	1.4
Diarrhea***	29	3.3	35	3.1
Nausea	51	6	51	6
Stomatitis	26	8	28	3.5
Vomiting	32	3.6	28	2.8
Dysphagia	12	2.9	10	2.1
General Disorders & Admin. Site				
Fatigue^	49	11	48	8
Mucosal Inflammation	31	10	28	5
Pyrexia	16	0.7	12	0

MedDRA System Organ Class and Preferred Term	Pembrolizumab + Chemotherapy N=276 %		Cetuximab + Chemotherapy N=287 %	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Infections and infestations				
Pneumonia^^	19	11	13	6
Upper respiratory tract infection	4.0	0.3	5	0.3
Injury, Poisoning & Procedures				
Infusion related reaction	1.0	0.3	6	1.0
Investigations				
Weight decreased	16	2.9	21	1.4
Metabolism and Nutrition Disorders				
Decreased appetite	29	4.7	30	3.5
Musculoskeletal & Connective				
Neck Pain	10	1.1	7	0.7
Athralgia	5	0	3.0	0
Musculoskeletal pain^^^	8	0.3	7	0
Myalgia^^^^	13	0.4	11	0.3
Neoplasms, benign, malign.				
Tumor hemorrhage^^^^^	9	2.8	6	2.0
Nervous System Disorders				
Dizziness	10	0.4	13	0.3
Headache	11	0.7	8	0.3
Peripheral sensory neuropathy#	14	1.1	7	1.0
Dysguesia	7	0	7	0
Psychiatric disorders				
Insomnia	10	0	8	0
Anxiety/Agitation	5	0	6	0
Respiratory, Thoracic and				
Cough##	22	0	15	0
Dyspnea###	10	1.8	8	1.0
Hemoptysis	7	0.7	3.1	0.3
Pneumonitis	5	1.0	1.0	0.6
Aspiration/Aspiration pneumonia	5	3.3	2.0	1.0
Skin and Subc. Tissue Disorders				
Alopecia	5	0	5	0
Pruritus	8	0	10	0.3
Rash ####	20	2.3	70	8
Vascular Disorder				
Thrombosis#####	8	3.0	9	3.0

**Includes: acute myocardial infarction, myocardial infarction, myocardial ischemia, acute coronary syndrome, cardiac arrest, cardiovascular insufficiency, coronary artery stenosis*
*** Includes: arrhythmia, atrial fibrillation, bradycardia, palpitations, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, ventricular arrhythmia*
**** Includes: diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis*

***** Includes: ALT increase, AST increase, autoimmune hepatitis, bilirubin increase, GGT increase, hepatic failure, hepatotoxicity, hyperbilirubinemia, hypertransaminasaemia*
^ Includes: asthenia, fatigue
^^ Includes: pneumonia, bacterial pneumonia, staphylococcal pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal
^^^ musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain
^^^^ Includes: back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia
^^^^^Includes: tumor hemorrhage included arterial hemorrhage, arterial perforation, arterial rupture, carotid artery perforation, hemorrhage tumor necrosis, laryngeal hemorrhage, lip hemorrhage, mouth hemorrhage, tonsillar hemorrhage, pharyngeal hemorrhage, soft tissue hemorrhage, tongue hemorrhage, tracheal hemorrhage, tumor hemorrhage, venous hemorrhage, wound hematoma, and wound hemorrhage.
#Includes: peripheral sensory neuropathy, peripheral neuropathy, hypoaesthesia, dysaesthesia
Includes: cough, productive cough
###Includes dyspnea, exertional dyspnea
####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: all thrombosis, embolism and pulmonary embolism

Among patients treated with pembrolizumab plus chemotherapy, the most common AEs occurring in ≥ 10% of patients (Table 34) were nausea, fatigue/asthenia, constipation, vomiting, mucosal inflammation, decrease appetite, diarrhea, stomatitis, cough, pneumonia, rash, pyrexia, weight loss, hypothyroidism, peripheral neuropathy, myalgia, dysphagia, headache, dyspnea, dizziness, neck pain, and insomnia.

MedDRA Preferred Term AEs (all grades) that occurred at a ≥ 5% higher incidence in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm were pneumonia (19% vs 12%), cough (22% vs 15%), peripheral neuropathy (14% vs 7%), and hypothyroidism (15% vs 6%).

Of the AEs listed in Table 36, Grade 3-4 AE that occurred at a ≥ 2% higher frequency in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm were stomatitis (8% vs 3.5%), mucosal inflammation (10% vs 5%), and pneumonia (12% vs 7%).

Reviewer Comment: The overall incidence of Grade 3 and 4 AEs was similar in the pembrolizumab plus chemotherapy arm and the cetuximab plus chemotherapy arm (84% vs 80%).

The incidence of bleeding from tumor site (tumor hemorrhage) in the pembrolizumab plus chemotherapy arm (9%) of KEYNOTE-048 was higher than in the cetuximab plus chemotherapy arm (6%), but comparable to the HSNCC safety dataset for pembrolizumab (7.4%). See Section 8.2.5, Analysis of Submission-Specific Safety Issues for additional details.

Laboratory Findings

In KEYNOTE-048, laboratory tests to assess serum chemistry (sodium, potassium chloride, BUN, serum creatinine, glucose, magnesium, phosphorus, calcium), liver function (ALT, AST, Alk phosphatase and bilirubin), and complete blood count (CBC) were obtained at screening (day 1 to 28), at every cycle during the trial, and when medically necessary.

Laboratory alterations from baseline through the study, graded per NCI CTCAE v. 4.03, were analyzed and the findings are summarized in the following tables (Tables 37-39).

Table 37: Hematologic* Abnormalities Worsened from Baseline

Laboratory Abnormalities	Pembrolizumab * %			Pembrolizumab + Chemotherapy * %			Cetuximab + Chemotherapy* %		
	N^	All Grades	Grade 3-4	N^	All Grades	Grade 3-4	N^	All Grades	Grade 3-4
Lymphopenia	288	54	25	266	69	35	282	74	45
Anemia	288	52	7	266	89	28	282	78	19
Thrombocytopenia	288	12	3.8	266	73	18	282	76	18
Neutropenia	288	7	1.4	266	67	35	282	71	42
Prolonged aPTT	96	9	1.1	90	22	1.1	113	17	1.8

* *Occurring in ≥ 20 patients in any treatment arm*
^ *Number of patients with at least one baseline and ^ post-baseline laboratory measurement is used as the denominator in percentage calculation.*
Source ADaM dataset: adlbgrd.xpt. and SDTM dataset: lb.xpt.

Reviewer Comment: As expected given the use of chemotherapy in the combination arms, the incidence of cytopenias was higher in the pembrolizumab plus chemotherapy arm and the cetuximab plus chemotherapy arms compared to the pembrolizumab single agent arm. The incidence of Grade 3-4 anemia was higher in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm. The incidence of anemia (52% vs 46%) and neutropenia (7% vs 10%) were similar in the pembrolizumab as a single agent arm in KEYNOTE-048 and the HNSCC pembrolizumab dataset.

Renal and Electrolyte Assessment

Renal function and serum electrolyte changes from baseline in KEYNOTE-048 are summarized in Table 38.

Table 38: Selected* Renal and Electrolyte Abnormalities Worsened from Baseline

Laboratory Abnormalities	Pembrolizumab * %			Pembrolizumab + Chemotherapy * %			Cetuximab + Chemotherapy* %		
	N^	All Grades	Grade 3-4	N^	All Grades	Grade 3-4	N^	All Grades	Grade 3-4
Hyponatremia	288	46	17	263	56	20	281	59	20
Hypocalcemia	287	22	1.1	263	32	4	278	58	7
Hypercalcemia	287	22	4.6	263	16	4.3	278	13	2.6
Hyperkalemia	287	21	2.8	265	27	4.3	281	29	4.3
Hypophosphatemia	287	20	5	264	35	12	279	48	19
Hypokalemia	288	19	5	265	34	12	281	47	15
Increased creatinine	288	18	1.1	264	36	2.3	278	27	2.2
Hypomagnesemia	241	16	0.4	235	42	1.7	249	76	6

* *Occurring in ≥ 20 patients in any treatment arm*
^ Number of patients with at least one baseline and ^ post-baseline laboratory measurement is used as the denominator in percentage calculation.
Source ADaM dataset: adlbgrd.xpt. and SDTM dataset: lb.xpt.

Reviewer Comment: The rate of hypercalcemia in the pembrolizumab single agent arm in KEYNOTE-048 was higher compared to the combination arms (22% vs 16% vs 13%). HNSCC is known to be associated with hypercalcemia. The rate of increased creatinine was higher in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm (36% vs 27%); however, Grade 3-4 increased creatinine was similar between these arms. Other electrolyte abnormalities, specifically hypokalemia, hypomagnesemia, hypocalcemia, and hypophosphatemia, were higher in the cetuximab plus chemotherapy compared to the pembrolizumab-containing arms. This is anticipated with the addition of cetuximab to platinum-based chemotherapy.

Liver Function Tests Assessment

Liver function test changes from baseline in KN-048 are summarized in Table 39.

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Table 39: Selected* Liver Function Test Abnormalities Worsened from Baseline

Laboratory Abnormalities	Pembrolizumab * N (%)			Pembrolizumab + Chemotherapy * N (%)			Cetuximab + Chemotherapy* N (%)		
	N^	All Grades	Grade 3-4	N^	All Grades	Grade 3-4	N^	All Grades	Grade 3-4
Increased ALT	289	25	2.1	263	22	1.6	279	38	1.8
Hypoalbuminemia	289	44	3.2	262	47	4.0	280	49	1.1
Increased ALP	289	25	2.1	264	27	1.2	279	33	1.1
Increased AST	289	28	3.1	264	24	2.0	279	37	3.6
Increased bilirubin	290	7	0.3	264	11	0.8	279	17	1.8

ALT:Alanine aminotransferase; ALP : Alkaline phosphatase: AST: Aspartate aminotransferase
** Occurring in ≥ 20 patients in any treatment arm*
^ Number of patients with at least one baseline and ^ post-baseline laboratory measurement is used as the denominator in percentage calculation.
Source ADaM dataset: adlbgrd.xpt and SDTM dataset: lb.xpt.
[#] Included here as additional laboratory abnormality.

Reviewer Comment: The incidence of all grade AST, ALT, and bilirubin elevation was higher in the cetuximab plus chemotherapy arm compared to the pembrolizumab single agent arm and pembrolizumab plus chemotherapy arm; the incidence of Grade 3 to 4 elevations was low in all arms.

Vital Signs

Vital signs (temperature, pulse, respiratory rate, weight and blood pressure) were collected at screening, prior to the administration of each dose of study treatment and during the follow-up period. Merck evaluated the mean change in each vital sign from baseline over time for patients enrolled in KEYNOTE-048. Based on Merck's analyses, no clinically meaningful changes from baseline were noted in the safety population.

Electrocardiograms (ECGs)

Electrocardiograms (12-lead ECGs) were performed at baseline in all patients and throughout the study as clinically warranted. Abnormalities in ECGs were reported as AEs. AEs with potential ECG abnormalities were captured as arrhythmias and are listed in the footnotes of Table 35 and Table 36.

QT
There is no dedicated QTc study submitted in this supplement. A QTc sub-study was submitted in the original BLA and reviewed by CDER's QT-IRT team

Immunogenicity

No immunogenicity study was included in this submission.

8.2.5. Analysis of Submission-Specific Safety Issues

Immune-mediated adverse events (imAE) are known toxicities of checkpoint inhibitor class products, including pembrolizumab. Please refer to section 8.2.3 for a detailed description of AEOSI definition as per Merck.

Immune-Related Adverse Event/Adverse Events of Special Interest

Table 40 summarizes the AEOSI Preferred terms used based on MEdDRA Version 21.0.

Table 40: AEOSI Preferred Terms based on MedDRA Version 21.0

AEOSI	Preferred Terms
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug induced liver injury
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus
Severe Skin Reactions Including Stevens- Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption;

AEOSI	Preferred Terms
or If Grade 3 or higher	Erythema, Erythema multiforme, Rash, Rash erythematous, Rash generalised, Rash maculopapular, Rash pruritic, Rash pustular, Pruritus, Pruritus generalised, Pruritus genital
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated necrotising myopathy, Rhabdomyolysis, Myopathy, Dermatomyositis
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia

Table 41 summarizes the incidence of AEOSI observed in KEYNOTE-048 by NCI CTCAE v 4.03 toxicity grades.

Table 41: AEOSI incidence in KN-048

AEOSI	Pembrolizumab N=300 (%)		Pembrolizumab + Chemotherapy N=276 (%)		Cetuximab + Chemotherapy N=287 (%)	
	All Grades	Grades 3-5	All Grades	Grades 3-5	All Grades	Grades 3-5
Patients with ≥ 1 AEOSI	91 (30)	20 (7)	71 (26)	13 (5)	68 (24)	30 (10.5)
Endocrinopathies						
Hypothyroidism	54 (18)	0	42 (15)	0	18 (6)	0
Hyperthyroidism	8 (3)	0	13 (5)	0	3 (1)	0
Thyroiditis	0	0	1(0.4)	0	0	0
Adrenal insufficiency	1 (0.3)	1 (0.3)	0	0	0	0
Hypophysitis	1 (0.3)	1 (0.3)	2 (0.8)	1 (0.3)	0	0
AEOSI by Organ system or tissue						

Pneumonitis	18 (6)	5 (1.6)	15 (5)	4 (1.4)	3 (1)	2 (0.7)
Hepatitis	2 (0.7)	2 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Colitis	3 (1)	0	7 (2.5)	2 (0.8)	2 (0.7)	2 (0.7)
Nephritis	2 (0.7)	1 (0.3)	2 (0.8)	0	1 (0.3)	0
Myocarditis	0 (0)	0	1 (0.3)	1 (0.3)	0	0
Pancreatitis	2 (0.7)	0	1	1 (0.3)	0	0
Severe skin reactions	8 (2.7)	6 (2.0)	2 (0.8)	2 (0.7)	20 (7)	19 (6.6)
Infusion-related reaction	3 (1.3)	1 (0.3)	5 (2.2)	1 (0.4)	21 (9.4)	5 (1.7)
Uveitis	1 (0.3)	0	0	0	0	0

AEOSI were reported in 30% of patients in the pembrolizumab arm, 26% in the pembrolizumab plus chemotherapy arm and 24% in the cetuximab plus chemotherapy arm. The most common immune-related AEs were hypothyroidism (18%), pneumonitis (6%) and hyperthyroidism (3%) with pembrolizumab single agent. The most common immune-related AEs were hypothyroidism (15%), pneumonitis (5%) and hyperthyroidism (5%) with pembrolizumab in combination with chemotherapy. Immune-related AEs were severe (Grade 3 to 5) in 7% of patients in the pembrolizumab arm and 5% in the pembrolizumab plus chemotherapy arm. The most common (>1%) Grade 3 or 4 AEOSI was pneumonitis (1.7%) and severe skin reaction (2.0%) with pembrolizumab single agent and pneumonitis (1.4%) with pembrolizumab plus chemotherapy. Grade 3 severe skin reactions in patients treated with pembrolizumab single agent included rash, generalized rash, maculopapular rash, exfoliative dermatitis, erythema multiforme, and skin necrosis. Fatal pneumonitis occurred in one patient who received pembrolizumab as a single agent and one patient who received pembrolizumab plus chemotherapy.

Reviewer Comments: Case narratives and CRFs of all events coded as AEOSI were reviewed in detail. The clinical course, severity and outcome of the events observed in KEYNOTE-048 are consistent with the events currently described in the KEYTRUDA label except for pneumonitis which occurred at a higher incidence in the pembrolizumab single agent arm (6%) and pembrolizumab combination arm (5%) compared to the HNSCC pembrolizumab monotherapy dataset (4%) and the pembrolizumab single agent RSD (3%) (Table 42). In KEYNOTE-048, pembrolizumab was administered as first line treatment in the R/M setting and prior therapies such as relatively recent radiation therapy/chemoradiation may have contributed to the increased incidence.

Table 42: Specific AEOSI Incidence Compared to HNSCC Safety Data Set and RSD

AEOSI	Pembro N=300 n (%)	Pembro + Chemo N=276 n (%)	Cetux + Chemo N=287 n (%)	HNSCC Safety Dataset for Pembro N=609 n (%)	Reference Safety Dataset for Pembro N=2799 n (%)
Pneumonitis	18 (6)	15 (5)	3 (1)	23 (4)	94 (3)
Severe skin reactions	8 (2.7)	3 (1.2)	20 (7)	9 (1.5)	38 (1.4)
Infusion-related reaction	4 (1.3)	6 (2.2)	27 (9.4)	11 (9.4)	70 (2.5)

Bleeding from Tumor Site and Airway Obstruction

AEs specific to HNSCC are bleeding from tumor site and airway obstruction. Table 43 compares the rate of bleeding from tumor site and airway obstruction between the three arms in KEYNOTE-048 and the HNSCC safety dataset.

Table 43: AES specific to HNSCC

Preferred Term	Pembrolizumab N=300	Pembrolizumab + Chemotherapy N=276	Cetuximab + Chemotherapy N=287	HNSCC Safety Dataset N=609
Tumor hemorrhage*	19 (6.3)	24 (8.7)	16 (5.6)	45 (7.4)
Airway obstruction **	3 (1)	2 (0.7)	1 (0.3)	13 (2.1)

** The PTs for tumor hemorrhage included arterial hemorrhage, arterial perforation, arterial rupture, carotid artery perforation, hemorrhage tumor necrosis, laryngeal hemorrhage, lip hemorrhage, mouth hemorrhage, tonsillar hemorrhage, pharyngeal hemorrhage, soft tissue hemorrhage, tongue hemorrhage, tracheal hemorrhage, tumor hemorrhage, venous hemorrhage, wound hematoma, and wound hemorrhage.*
*** The PTs for airway obstruction included epiglottic edema, laryngeal obstruction, laryngeal edema, laryngeal stenosis, laryngeal tracheal edema, oropharyngeal swelling, palatal edema, pharyngeal edema, stridor, swollen tongue, tongue edema, tongue swelling, tracheal edema, and wheezing.*

Reviewer comment: The incidence of bleeding from tumor site was higher in the pembrolizumab plus chemotherapy arm compared to the cetuximab plus chemotherapy arm and the pembrolizumab single agent arm. However, the incidence in the pembrolizumab plus chemotherapy arm was similar to the incidence in the HNSCC safety dataset. The incidence of airway obstruction was similar across the three arms of KEYNOTE-048 and lower than the HNSCC safety dataset; the higher incidence in the HNSCC safety dataset may be related to the inclusion of patients with HNSCC receiving second or later line treatment for recurrent/metastatic disease. FDA will continue to closely monitor all adverse event reports associated with pembrolizumab, including tumor hemorrhage in patients with HNSCC, in ongoing trials and in the post-marketing setting.

Case narratives for fatal events with tumor hemorrhage are outlined in Table 44.

Table 44: Narratives for Grade 5 Tumor Hemorrhage

Adverse Event	Narrative
Carotid artery perforation Malignant neoplasm progression	65 yo female received treatment with pembrolizumab plus chemotherapy. Last treatment was on D40. Patient was noted to have tumor encasing the great vessels in the neck. On D46 was noted to have a fatal event of carotid artery perforation and cause of death was reported as malignant neoplasm progression.
Tumor hemorrhage	85 yo female received treatment with pembrolizumab plus chemotherapy. Last treatment was on D22. On D38 patient experienced a fatal event of tumor hemorrhage.
Tumor hemorrhage	68 yo male received treatment with pembrolizumab single agent. Last treatment was on D64. On D69 patient experienced a fatal event of tumor hemorrhage.
Tumor hemorrhage	45 yo female received treatment with pembrolizumab single agent. Last treatment was on D1. On D5 patient experienced a fatal event of tumor hemorrhage.

Reviewer Comment: The fatal events described are not unexpected in patients with HNSCC.

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

Patient Reported Outcome (PRO) questionnaires (Electronic (e) EQ-5D, eEORTC QLQ-C30, and eEORTC QLQ-LC13) were administered at pre-specified time points during the study.

8.2.7. Safety Analyses by Demographic Subgroups

Age

In the KEYNOTE-048 safety population, 315 (36.5%) of the patients were age 65 years or older. Table 45 presents an overview of the incidence of AEs by age <65 years and ≥65 years of age.

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Table 45: Overview of Adverse Events by Age

	Pembrolizumab N=300 (%)		Pembrolizumab + Chemotherapy N=276 (%)		Cetuximab + Chemotherapy N=287 (%)	
	<65	≥65	<65	≥65	<65	≥65
N	189	111	176	100	183	104
N with any AE*	156 (83)	94 (85)	153 (87)	89 (89)	174 (95)	97 (93)
Grade 3-5 AEs*	86 (46)	59 (53)	134 (76)	76 (76)	150 (82)	82 (79)
Serious AE*	69 (37)	35 (32)	92 (53)	55 (55)	92 (50)	51 (49)
Died due to a drug-related AE*	13 (7)	11 (10)	16 (9)	16 (16)	15 (8)	12 (11.5)
Discontinued due to an AE*	36 (19)	14 (13)	47 (27)	38 (38)	45 (25)	32 (31)

Source: BLA125514/S-52: ISS ADaM-adsl.xpt; adae.xpt
*Excludes PTs malignant neoplasm progression, neoplasm progression, disease progression

Reviewer comment: In all treatment arms, the overall incidence of adverse events and serious AEs were similar between patients who were <65 years old and those who were 65 or older. Grade 3-5 AEs were ≥5% higher in patients 65 years and older compared to patients <65 years old in the pembrolizumab single agent arm. The proportion of patients with fatal events due to AEs was ≥5% higher in patients 65 years and older compared to patients <65 years old in the pembrolizumab plus chemotherapy arm. In the pembrolizumab single agent arm, the proportion of patients who discontinued treatment due to an AE was ≥5% higher in patients <65 years compared to patients ≥65 years old, while in the chemotherapy-containing treatment arms, the proportion of patients who discontinued treatment due to an AE was ≥5% higher in patients 65 years and older.

Gender

In the KEYNOTE-048 safety population, approximately 83% of the patients were male. Table 46 summarizes the incidence of AEs by gender.

Table 46: Overview of Adverse Events by Gender

	Pembrolizumab N=300 (%)		Pembrolizumab + Chemotherapy N=276		Cetuximab + Chemotherapy N=287 (%)	
	Male	Female	Male	Female	Male	Female
N	249	51	220	56	249	38
N with any AE*	214 (86)	36 (71)	193 (88)	51 (91)	235 (94)	35 (92)
Grade 3-5 AEs*	122 (49)	23 (45)	164 (75)	46 (82)	198 (80)	33 (87)
Serious AE*	97 (39)	17 (33)	111 (50)	36 (64)	121 (49)	19 (50)
Died due to a drug-related AE*	19 (8)	6 (12)	25 (11)	6 (11)	22 (9)	6 (16)
Discontinued due to an AE*	30 (12)	6 (12)	67 (30)	12 (21)	66 (27)	11 (29)

Source: BLA 125514/S-52: ISS ADaM-adsl.xpt; adae.xpt
*Excludes PTs malignant neoplasm progression, neoplasm progression, disease progression

Reviewer comment: Due to the small number of female patients, no conclusions can be reached regarding potential differences.

8.2.8. Specific Safety Studies/Clinical Trials

8.2.9. No specific safety studies or clinical trials were included in this application. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No carcinogenicity studies were conducted.

Human Reproduction and Pregnancy

No reproductive toxicity studies were conducted

Pediatrics and Assessment of Effects on Growth

Not applicable for this supplement. Merck was granted a waiver from the requirement to conduct pediatric studies under PREA based on the low incidence of HNSCC in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdoses were reported with pembrolizumab in KEYNOTE-048, according to Merck. Based on pembrolizumab's mode of administration and pharmacological properties, there are no concerns regarding the potential for abuse, withdrawal, or rebound with pembrolizumab.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Pembrolizumab was first granted marketing authorization in the United States on September 4, 2014, for the treatment of patients with unresectable or metastatic melanoma. The current approved indications for pembrolizumab in the United States are listed in section 3.1.

Based on the pembrolizumab Periodic Safety Update Report (PSUR) covering the period of September 4, 2017 to March 3, 2018, pembrolizumab has been registered and approved in 86 countries. Cumulatively, there were approximately (b) (4) patients exposed to marketed pembrolizumab and 25,519 subjects have been treated in the pembrolizumab development program, of which approximately 18,793 patients have participated in Merck-sponsored clinical trials.

Since the initial approval, pembrolizumab labeling has been revised to include additional immune-mediated adverse events identified in ongoing clinical trials with pembrolizumab. These include potential risks of hypophysitis, nephritis, uveitis, type 1 diabetes mellitus, severe skin reactions, myositis, pancreatitis, Guillain-Barré Syndrome, fatal pneumonitis, myocarditis, Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), encephalitis, and sarcoidosis.

In addition, the following information has been added to the "Warnings and Precautions" section of the Keytruda label:

- Increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab for hematologic malignancies (March 14, 2017).
- Increased mortality in patients with multiple myeloma when pembrolizumab is added to a thalidomide analogue and dexamethasone (November 29, 2017).

Pembrolizumab has not been withdrawn from investigational use for reasons related to safety or efficacy in any country.

Expectations on Safety in the Postmarket Setting

Pembrolizumab has been marketed in the U.S. since 2014 and the safety profile of pembrolizumab, as well as the safety profiles of cisplatin and carboplatin with 5-FU, is well-established. FDA will continue to monitor pembrolizumab safety in the post-marketing setting.

8.2.11. Integrated Assessment of Safety

Pooling of safety data was not conducted by the reviewer in this application.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

KEYNOTE-048 demonstrated a statistically significant improvement in OS in the CPS ≥1 HNSCC and CPS ≥20 HNSCC subpopulations for the pembrolizumab as a single agent arm compared to the control arm. The study also demonstrated a statistically significant improvement in OS in the ITT population for the pembrolizumab plus chemotherapy arm compared to the control arm. Neither the single agent arm nor the combination arm demonstrated superior PFS results compared to the standard of care.

There were crossings of the curves of each experimental arm with the control arm in the Kaplan-Meier plots for OS, indicating that the proportional hazards assumption was inappropriate. Formal tests of the proportional hazards assumption indicated that the assumption was not valid in any of the OS models. Therefore, as an alternative way to present the data, landmark analyses were included in this review.

Interaction tests revealed that there was a modification of treatment effect by CPS score on OS in the pembrolizumab as a single agent arm compared to the control arm. The treatment effect in the CPS ≥1 HNSCC subpopulation was significantly different than that for the CPS <1 HNSCC population comparison, per the interaction test, corresponding to an observed improvement in the hazard ratio for the CPS ≥1 HNSCC subpopulation compared to CPS <1 HNSCC.

8.4. Conclusions and Recommendations

This application relies primarily on the results of KEYNOTE-048, a randomized, multicenter, three-arm, open-label, active-controlled trial comparing pembrolizumab single agent and pembrolizumab in combination with cisplatin or carboplatin and fluorouracil to an acceptable control arm (cetuximab, cisplatin or carboplatin, and fluorouracil (EXTREME regimen)) as first-line systemic therapy in 882 patients with recurrent HNSCC who were not candidates for surgical resection or definitive chemoradiation or with metastatic HNSCC who had not received prior systemic therapy for metastatic disease. The co-primary endpoints for this study were OS and PFS for comparisons of each pembrolizumab-containing arm to the control arm sequentially tested in the subgroup of patients with PD-L1 CPS ≥20 HNSCC, the subgroup of patients with PD-L1 CPS ≥1 HNSCC and the ITT population.

Key efficacy results with 70% mature data at the second interim analysis demonstrated a statistically significant and clinically meaningful improvement in OS in the PD-L1 CPS ≥1 HNSCC subgroup treated with pembrolizumab as a single agent compared with control with an HR for OS of 0.78, (95% CI: 0.64, 0.96, p= 0.0171). The estimated median OS is 12.3 months for the pembrolizumab arm and 10.3 months for the control arm. In the PD-L1 CPS ≥20 HNSCC subgroup, pembrolizumab as a single agent demonstrated a statistically significant improvement in OS compared with control with a HR for OS of 0.61 (95% CI: 0.45, 0.83, p= 0.0015), with an estimated median OS of 14.9 months for the pembrolizumab arm and 10.7 months in the control arm. In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC, the median OS was 10.8 months (95% CI: 9.0, 12.6) for the pembrolizumab as a single agent arm and 10.1 months (95% CI: 8.7, 12.1) for the cetuximab in combination with chemotherapy arm, with an HR of 0.90 (95% CI: 0.68, 1.18). At the time of the interim analysis, there was no significant difference in OS between the pembrolizumab as a single agent arm and the cetuximab plus chemotherapy arm for the ITT population.

Pembrolizumab as a single agent did not demonstrate an improvement in PFS for the PD-L1 CPS ≥1 HNSCC population. In fact, the results indicate an inferior result for pembrolizumab as a single agent compared to cetuximab plus chemotherapy for PFS (median PFS 3.2 months vs 5.0 months in the control arm, HR 1.15 [95% CI 0.95, 1.38]) and the ORR was also lower in the pembrolizumab arm (19% [95% CI 14.5, 24.4 in the control arm). The median DOR was longer in the pembrolizumab single agent arm (20.9 months [range 1.5+ to 34.8+]) compared to the control arm (4.5 months [range 1.2+ to 30.6+]) in the PD-L1 CPS ≥1 HNSCC population.

Comparing the pembrolizumab plus chemotherapy arm to the cetuximab plus chemotherapy arm, key efficacy results with 70% mature data revealed a statistically significant and clinically meaningful benefit in OS with pembrolizumab plus chemotherapy compared with control with a HR 0.77 (95% CI 0.63, 0.93, p = 0.0067). The estimated median OS is 13.0 months for the pembrolizumab arm and 10.7 months for the control arm. Results in the pre-specified interim analyses of OS similar results were observed in the two subgroups of CPS ≥20 (HR 0.69; 95% CI: 0.51, 0.94) and CPS ≥1 (HR 0.71; 95% CI: 0.57, 0.88). There was no significant differences between arms for PFS and ORR in the ITT population; the results were numerically similar for PFS and ORR between the pembrolizumab plus chemotherapy arm and the control arm, with median PFS 4.9 months (95% CI 4.7, 6.0) in the pembrolizumab plus chemotherapy arm and 5.1 months (95% CI 4.9, 6.0) in the control arm and ORR 36% in both arms. The median DOR was 6.7 months (range 1.6+ to 30.4+) in the pembrolizumab plus chemotherapy arm compared to 4.3 months (range 1.2+ to 27.9+) in the control arm.

In KEYNOTE-048, the most common adverse reactions in the pembrolizumab single agent arm were fatigue/asthenia, constipation, rash, cough, hypothyroidism, nausea, diarrhea, decreased appetite, weight loss, dyspnea, pyrexia, pneumonia, headache and pruritis. The most common adverse reactions in pembrolizumab plus chemotherapy patients were nausea, fatigue, constipation, vomiting, mucosal inflammation, diarrhea, decreased appetite, stomatitis, cough,

pneumonia, rash, weight loss, hypothyroidism, peripheral sensory neuropathy, myalgia, dyspnea, neck pain, insomnia, and dizziness. There was a lower incidence of SAEs (40% vs 59% vs 49%), Grade 3-4 AEs (54% vs 85% vs 84%) and AEs leading to discontinuation of any study drug (12% vs 31% vs 27%) in patients treated with pembrolizumab as a single agent compared to patients treated with pembrolizumab plus chemotherapy and control. The incidence of deaths due to an AE in the pembrolizumab-containing arms (8 and12%) of KEYNOTE-048 were similar to the HNSCC monotherapy dataset (8.9%) but higher than in the pembrolizumab single agent RSD (3.9%). This suggests that underlying malignancy, co-morbid conditions and other confounding factors might have all contributed to the increased number of deaths due to AEs in the pembrolizumab arms of KEYNOTE-048 relative to the pembrolizumab single agent RSD.

The overall safety profile of pembrolizumab reported in KEYNOTE-048 was consistent with the known safety profile based on the pembrolizumab single agent RSD, except for a higher incidence of pneumonitis. The incidence of pneumonitis was 6% in the pembrolizumab single agent arm and 5% in the pembrolizumab plus chemotherapy arm of KEYNOTE-048, compared to an incidence of 4% in the HNSCC pembrolizumab monotherapy dataset and 3.4% in the pembrolizumab single agent RSD. In KEYNOTE-048, pembrolizumab was administered as first line treatment in the R/M setting and prior therapies such as relatively recent radiation therapy/chemoradiation may have contributed to the increased incidence of pneumonitis.

In the opinion of the reviewers, the submitted evidence meets the statutory evidentiary standard for regular approval and provides substantial evidence of the effectiveness of pembrolizumab as single agent in patients with PD-L1 CPS $\geq$1 HNSCC and in combination with platinum/5FU in all comers for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC. The treatment effect on OS is statistically robust and clinically meaningful and is consistent with a significant improvement in the treatment of patients with recurrent/metastatic HNSCC, which has been associated with an expected median survival of 10-11 months following treatment with standard first-line cetuximab and platinum-containing regimens. This benefit is supported by evidence of positive treatment effects on durability of response. The clinical benefits outweigh the risks of pembrolizumab, when administered a single agent or in combination with platinum and 5-FU. These risks are considered acceptable for the treatment of patients with metastatic HNSCC in the proposed indication in the context of the poor prognosis and magnitude of improvement in survival observed.

The review team recommends regular approval of pembrolizumab for the following indications:

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

Pourab Roy, Ph.D.

Primary Statistical Reviewer

Pallavi Mishra-Kalyani, Ph.D.

Statistical Team Leader

Shanthi Marur, M.D.

Primary Clinical Reviewer

Erin Larkins, M.D.

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The Division did not refer this efficacy supplement to an advisory committee because the application did not raise significant public health questions regarding the role of pembrolizumab for the proposed indication. Pembrolizumab is a marketed biologic approved for the treatment of several solid tumor and hematologic malignancies. The safety profiles of pembrolizumab, cisplatin, carboplatin, 5-FU chemotherapies are well established in patients with advanced malignancies. The demonstrated benefit-risk profile for pembrolizumab as single agent and in combination with platinum/5-FU is favorable based on the improvement in survival in the populations of patients with previously untreated recurrent/metastatic HNSCC.

10 Pediatrics

According to the World Health Organization, GLOBOCAN 2018[1], the estimated HNSCC cancer incidence in the pediatric population age 0 to 15 is 0.0 in the United States and worldwide.

The OCE PeRC concurred with granting a waiver from the requirements of the Pediatric Research Equity Act (PREA) to conduct studies with pembrolizumab in pediatric patients for any age group for the treatment of HNSCC in pediatric population because it would be highly impractical or impossible given the small number of pediatric patients with this disease.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

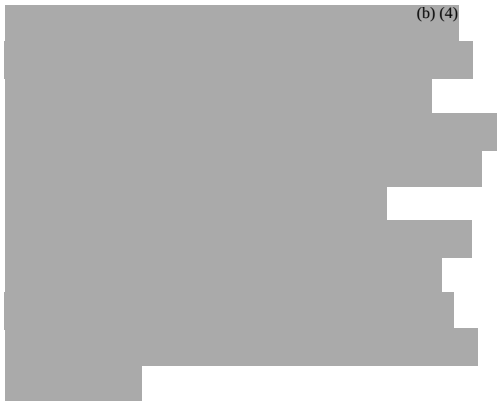
Labeling negotiations on Merck's proposed Prescribing Information for BLA125514/S-52 are ongoing at the time of this review. Table 47 provides a high-level summary of significant proposed labeling changes.

Table 47: Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (high level changes and not direct quotations)		
Section	Proposed Labeling by Merck	Revisions during Labeling Negotiations
Indication and Usage	KEYTRUDA, as a single agent or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).	Two separate indications: 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. Modification made to the recently added NSCLC indication at Merck's request for

		clarity. Revised first line to state KEYTRUDA is indicated in NSCLC expressing TPS ≥1% as determined by an FDA-approved test and is stage III where patients are not candidates for surgical resection or definitive chemoradiation or are metastatic.
Dosage and Administration Dosage Modification for Adverse Events	No changes.	In Section 2.1, under "Select patients for treatment with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression" added first-line treatment of metastatic or unresectable, recurrent HNSCC.
Dosage forms and Strengths	No changes	-
Contraindications	No changes	-
Warnings and Precautions	Updated the incidence of new or worsening hypothyroidism in patients with HNSCC receiving KEYTRUDA (b) (4) [redacted]	Given similar incidences of new or worsening hypothyroidism in patients with HNSCC receiving KEYTRUDA as a single agent or in combination with platinum and 5-FU, presented pooled data for this population. Given the higher incidence of pneumonitis observed in pembrolizumab-treated patients in KEYNOTE-048 compared to the pooled data for patients treated with pembrolizumab as a single agent, added information on the

		incidence of pneumonitis in each pembrolizumab-containing arm of KN-048.
Adverse Reactions	Added safety results from KEYNOTE-048. (b) (4)	(b) (4)
Use in Specific Populations	No changes	
Description	No changes	
Pharmacodynamics	No changes	
Pharmacokinetics	No changes	
Nonclinical Toxicology	No changes	
Clinical Studies	Added subsection for efficacy results from KEYNOTE-048 including: • Table with non-inferiority results and Kaplan-Meier curve for OS in the ITT population for the comparison of pembrolizumab as a single agent to control. • (b) (4) • Table with efficacy results and Kaplan-Meier curve for OS in the ITT population for the comparison of pembrolizumab in combination with platinum and 5-FU to control. (b) (4)	For the comparison of pembrolizumab as a single agent to control, modified to instead include table presenting efficacy results in the subgroups of patients with CPS ≥1 and CPS ≥20 and Kaplan-Meier curve for OS in the CPS ≥1 population. Added text under the table pembrolizumab as a single agent table with the results of the exploratory analysis of OS in the subgroup of patients with CPS 1-19 HNSCC. Added text under the pembrolizumab in combination with platinum and 5-FU to communicate the similar

	 	OS HRs observed in the subgroups of patients with CPS ≥20 HNSCC and CPS ≥1 HNSCC relative to the ITT population.  

12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team does not recommend that risk evaluation and mitigation strategies (REMS) be required to ensure safe and effective use of pembrolizumab for the new indications given the well-established safety profile of pembrolizumab and of cisplatin, carboplatin, and 5-FU chemotherapy, the lack of new safety signals with pembrolizumab in this population, the modest increase in known serious adverse reactions (i.e., immune-mediated pneumonitis), and the experience of the medical oncology community in managing immune-mediated adverse reactions, based on use of pembrolizumab and other marketed products of the same class. Recommendations for safe and effective use of pembrolizumab, including monitoring for immune-mediated adverse events, are included in the product labeling and the Medication Guide for KEYTRUDA.

13 Postmarketing Requirements and Commitment

The following Postmarketing Commitment (PMC) was recommended and agreed upon with Merck:

> Submit the clinical report and datasets for the final analysis of overall survival (OS) in the intent-to-treat (ITT) population (all patients regardless of tumor PD-L1 status) for the comparison of pembrolizumab as a single agent to the control arm in the KEYNOTE-048 study, "A phase 3 clinical trial of pembrolizumab (MK-3475) in first line treatment of recurrent/metastatic head and neck squamous cell carcinoma", to inform labeling.
>
> In addition, provide updated results for OS in the ITT population for the comparison of pembrolizumab and chemotherapy to the control arm in the KEYNOTE-048 study based upon the protocol-specified timing for the final analysis of OS for this comparison to better characterize survival differences at late time points to inform labeling.
>
> Final report submission: July 2019

Rationale for PMC:
Merck submitted the results from a pre-specified interim analysis of efficacy (IA2) for 883 patients enrolled on KEYNOTE-48 to support a regular approval.

The approval of pembrolizumab as a single agent for the first-line treatment of patients with R/M HNSCC is limited to patients with tumors expressing PD-L1 CPS ≥1. Pembrolizumab as a single agent did not demonstrate OS benefit over chemotherapy plus cetuximab at IA2; per protocol, a final analysis comparing OS between these two arms will be conducted and the results and will provide important information regarding the treatment effect of pembrolizumab as a single agent in the ITT population.

The results of the KEYNOTE-048 demonstrated a statistically significant improvement in OS in the ITT population for pembrolizumab and chemotherapy compared to the control arm at the time of IA2. The clinical report and datasets for the follow-up analyses of OS for the comparison of these two arms based upon the protocol-specified timing for the final analysis of OS will better characterize survival differences at late time points to inform labeling.

APPEARS THIS WAY ON ORIGINAL

14 Associate Division Director (OB)

Yuan-Li Shen, Ph.D.

15 Division Director (Clinical)

I concur with the findings of the clinical and statistical review teams that Merck has provided substantial evidence of effectiveness, based on a statistically significant improvement in overall survival, for pembrolizumab, in combination with a platinum and fluorouracil, in all patients, regardless of PD-L1 expression, receiving first-line treatment of metastatic or recurrent, locally advanced HNSCC and for pembrolizumab, as a single agent, in patients receiving first-line treatment of metastatic or recurrent, locally advanced, PD-L1 expressing (CPS ≥1%) HNSCC. The results are based on an adequate and well-controlled study in which the risks of pembrolizumab, alone or in combination with chemotherapy, was similar to that previously described in prior approvals, except for a higher incidence of immune-mediated adverse reactions (primarily endocrinopathies), a slightly higher incidence of immune-mediated pneumonitis (both arms) and in the early deaths (pembrolizumab combination arm). In general, toxicity of pembrolizumab alone is less severe than in chemotherapy-containing regimens; the toxicity of pembrolizumab plus a platinum-flourouracil regimen is similar to that of control arm, which is accepted treatment regimen for this population in the U.S., offering the potential for a lower incidence of serious cutaneous toxicity and infusion-related reactions. Given these findings, I concur that the risk:benefit assessment is favorable and that REMS are not required to ensure safe use.

The major review issues with this application were: (1) the general lack of improvement in tumor-related endpoints and no evidence of differences in common health-related PRO measures and (2) the apparent differential treatment effects based on intensity of PD-L1 tumor expression. With regard to the former, despite these effects on survival, there were no significant or numerical improvements in PFS or ORR for pembrolizumab, with chemotherapy or as a single agent, as compared with cetuximab and chemotherapy. While the effects on PFS and ORR appeared similar to those in the control arm for those randomized to pembrolizumab and chemotherapy, it appeared to be inferior at early timepoints (for PFS) and at all timepoints (for ORR) among those receiving pembrolizumab as a single agent as compared to the control. The PFS were appeared inferior for pembrolizumab as a single agent for approximately the first 8 months (corresponding to 40% of the events), with the curves crossing at that point and an apparent benefit of approximately 10% absolute differenced in PFS in those surviving for at least 12 months. Similarly, the ORR was numerically inferior, although when observed, was more durable that with cetuximab/chemotherapy.

With regard to the second review issue, the role of PD-L1 tumor expression remains unclear and this trial was not designed to elucidate the role based on the sequential analysis approach that incorporated patients with lower/no PD-L1 tumor expression into those with higher expression levels rather than evaluating these as distinct subgroups. In KEYNOTE-048, there are signals based on exploratory analyses indicating that PD-L1 tumor expression is important in predicting outcomes on survival in HNSCC. In patients receiving pembrolizumab as a single agent and in those receiving pembrolizumab and chemotherapy, the treatment effects on OS

were somewhat larger than in those with PD-L1-expressing HNSCC than in those without PD-L1-expressing tumors. Unfortunately, the trial was not designed to address the question of efficacy in PD-L1 non-expressing HNSCC, which represented only 15% of the patients enrolled in the trial. Based on the observed trends of larger effects on survival correlating with increasing expression of PD-L1, FDA reviewers conducted formal interaction tests to assess the relationship between OS and PD-L1 tumor expression. The p-value of the interaction coefficient for pembrolizumab as a single agent is 0.027 (two-sided), indicating a significant modification of treatment effect by CPS-positive HNSCC subgroups, whereas in the model for pembrolizumab in combination with chemotherapy, the p-value of the interaction was not statistically significant. Given the totality of the data, FDA restricted approval of pembrolizumab as a single agent to patients with CPS ≥1, based on the interaction and the suggestion of inferior survival [HR 1.37 (95% CI: 0.86, 2.20)], corresponding to median survival of 7.9 and 11.3 months, in the pembrolizumab and chemotherapy arms, respectively, in the subgroup of patients with CPS <1 HNSCC who received pembrolizumab as a single agent. In contrast, there was no evidence of an interaction with PD-L1 expression for the pembrolizumab and chemotherapy arm and the survival curves comparing results in the subgroup of patients with CPS <1 HNSCC appeared superimposable, with an OS HR of 1.07 (95% CI: 0.66, 1.74), corresponding to median survival times of 11.3 and 10.7 months in the pembrolizumab/chemotherapy and cetuximab/chemotherapy arms, respectively.

A post-marketing commitment was agreed-upon to provide mature survival data from KEYNOTE-048 to allow continued assessment of long-term effects. Future studies of pembrolizumab in HNSCC should assess for baseline PD-L1 expression and assess outcomes in subgroups based on the intensity of PD-L1 tumor expression.

Patricia Keegan, M.D.

16 Office Director (or designated signatory authority)

Not applicable.

APPEARS THIS WAY
ON ORIGINAL

17 Appendices

17.1. References

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17.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): KEYNOTE-048

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1445		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsors: 1 (See table below) Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☒	No ☐ (Request information

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

PEMBROLIZUMAB- P048V01MK3475 Financial Disclosure
1.3.4 Financial Disclosure HEAD AND NECK SQUAMOUS CELL CARCINOMA

Table 4	Table of All Clinical Investigators/Sub-Investigators Not Certified *Due Diligence Completed*		
Product/Protocol/Site	Investigator/ Sub-Investigator	Role	Reason
	(b) (6)		Did not return form with requested information. Multiple due diligence attempts made: 6-17-16; 07-28-2016
			Did not return form with requested information. Multiple due diligence attempts made: 06-17-16; 07-28-2016
			Did not return form with requested information. Multiple due diligence attempts made: 12-02-2018; 12-03-2018

Table 5	Table of All Clinical Investigators/Sub-Investigators Who Hold Financial Interests and/or Arrangements Requiring Disclosure		
Product/Protocol/Site	Investigator/ Sub-Investigator	Role	Financial Interests and/or Arrangements
	(b) (6)		Equity Interest: $1,800,000.00 Merck Common Stock 1,800,000.00 estimated value owned by a trust for which my (b) (6) is an administrator and trustee as reported by investigator on 05-26-2015. These values have been reduced by stock sales at market prices and the value of Merck stock is approximately $900,000.00. No control over the funds nor the stock as reported by investigator on 10-19-2017.

17.3. Additional Clinical Outcome Assessment Analyses

COA analyses are presented in the subsection "Efficacy Results – Secondary or exploratory COA (PRO) endpoints" under Section 8.1.2, Study Results.

[1]

[2] 21st Century Cures (Section 3001) states: "Following the approval of an application that was submitted under section 505(b) of this Act or section 351(a) of the Public Health Service Act at least 180 days after the date of enactment of the 21st Century Cures Act, the Secretary shall make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of such application."
[3] See http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm for more information.
[4] Refer to MAPP 6010.2 Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments
[5] The 2007 Food and Drug Administration Amendments Act (FDAAA) regulations updated Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) so that pediatric study and clinical trial information can be easily posted and found by the public on the FDA Web site. The Division of Pediatric and Maternal Health in the Office of Drug Evaluation IV must collect specific information about the inclusion of children in clinical trials for this Web posting from this section of your review.
[6] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126
[7] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
[8] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073139.pdf
[9] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf
[10] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf
[11] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf
[12] https://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf
[14] See Draft Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness Non-Inferiority Clinical Trials at https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf
[15] See Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, https://www.fda.gov/downloads/drugs/guidances/ucm073122.pdf
[16] See: Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions
[17] The organizational structure, section and subsection headings in Attachment B: Clinical Safety Review of an NDA or BLA may not correlate exactly with the clinical review template.
[18] CSC Clinical Reviewer Portal
[19] You may find Guidance for Industry: Premarket Risk Assessment useful when evaluating the quantity of the safety database (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126958.pdf)
[20] As discussed in ICH E-1 Guideline for Industry: The extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073083.pdf
[21] Adverse event refers to any untoward medical event associated with the use of a drug in humans, whether or not it is considered drug related.
[22] http://www.meddra.org/sites/default/files/guidance/file/9491-1710_termselptc_r4.8_sep2014.pdf

[24] Significant adverse event refers to the definition in the ICH guideline for industry E3 Structure and Content of Clinical Study Reports that includes: Marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events.
[25] For purposes of prescription drug labeling, *an adverse reaction* (21 CFR 201.57(c)(7)) is defined as an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and ECG. This

definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. For the purposes of good review practice (GRP), the term *adverse event (*or *adverse experience)* refers to any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related.

[26] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf

[27] Refer to E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf)

[28] Refer to MAPP 6010.2 Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments

[29] https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm120877.pdf.

[30] See Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf)

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/s/

SHARON K SICKAFUSE
06/10/2019 03:13:11 PM

POURAB ROY
06/10/2019 03:14:39 PM

PALLAVI S MISHRA-KALYANI
06/10/2019 03:16:23 PM

YUAN L SHEN
06/10/2019 03:17:27 PM

SHANTHI N MARUR
06/10/2019 03:18:12 PM

ERIN A LARKINS
06/10/2019 03:26:36 PM

PATRICIA KEEGAN
06/10/2019 03:34:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s052

CLINICAL REVIEW(S)

DOP2 CLINICAL REVIEW: sBLA 125514/S-52

Application Type	sBLA
Application Number	125514/S-52
Priority or Standard	Priority
Submit Date	December 10, 2018
Received Date	December 10, 2018
PDUFA Goal Date	June 10, 2019
Division/Office	DOP2/OHOP
Review Completion Date	May 17, 2019
Established Name	Pembrolizumab
Trade Name	Keytruda
Pharmacologic Class	Programmed Death-Receptor-1 (PD-1) Blocking Antibody
Code name	MK-3475
Applicant	Merck Sharp & Dohme Corp.
Formulations	50 mg lyophilized powder; 100 mg/4 mL (25 mg/mL) solution
Dosing Regimen	200 mg every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression
Applicant Proposed Indication	KEYTRUDA as a single agent or in combination with platinum and 5-FU chemotherapy as first-line treatment of patients with recurrent or metastatic HNSCC.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication)	KEYTRUDA as a single agent for the first line treatment of patients with metastatic or recurrent, unresectable HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1%] as determined by an FDA-approved test. KEYTRUDA in combination with platinum and FU for the first line treatment of patients with metastatic or recurrent, unresectable HNSCC.

Merck submitted Supplement 52 to BLA 125514 for pembroluzimab (KEYTRUDA) for the treatment of patients with metastatic head and neck squamous cell carcinoma(HNSCC) to fulfill the following PMR:

3100-1: Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of pembrolizumab over available therapy as determined by an improvement in overall survival in patients with metastatic squamous cell carcinoma of the head and neck.

The clinical review is complete and has been added to the Multidisciplinary Review and Evaluation of BLA 125514 /S52 which will be uploaded to DARRTS when it is finalized. Refer to the Multidisciplinary Review and Evaluation under BLA 125514 /S52 for additional details. There are no outstanding issues from a clinical perspective that would prevent approval of this application.

From a clinical standpoint the following indications are supported by the application.

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

- KEYTRUDA in combination with platinum and FU for the first line treatment of patients with metastatic or recurrent, unresectable HNSCC.

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/s/

SHANTHI N MARUR
05/17/2019 03:59:57 PM

ERIN A LARKINS
05/17/2019 04:07:08 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s052

PRODUCT QUALITY REVIEW(S)

Memorandum of Review:

Submission Tracking Number (STN):	BLA 125514/SUPPL-52
Subject:	Efficacy supplement
Primary Reviewer:	Shadia Zaman, Ph.D., DBRR1/OBP/OPQ/CDER
Secondary Reviewer:	Jennifer Swisher, Ph.D., TL, DBRR1/OBP/OPQ/CDER
RBPM:	Andrew Shiber
Consults:	None
Applicant:	Merck Sharp & Dohme Corp
Product:	Pembrolizumab
Indication:	Recurrent or metastatic head and neck squamous cell carcinoma

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

- **Future Inspection Items: None**

- **Executive Summary:** This memo is for efficacy supplement 52 for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy. A categorical exclusion from environmental assessment per 21 CFR 25.31(c) was claimed and is acceptable.

- **Review:**

Reviewer comments are in italicized text.

1.12.14 Environmental Analysis

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

Reviewer comment: *This is acceptable.*

Shadia Zaman

Digitally signed by Shadia Zaman
Date: 5/28/2019 11:23:19AM
GUID: 583dce940076eea0edb730e401622d6d

Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 5/28/2019 11:34:19AM
GUID: 508da6d7000262dc015dcdc5f6541612

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s052

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - MEMO

NDA/BLA #:	BLA 125514 – S52
Drug Name:	KEYTRUDA ® (pembrolizumab)
Indication(s):	First-line treatment of patients with recurrent/metastatic head and neck squamous cell carcinoma
Applicant:	Merck Sharp and Dohme Corp.
Date(s):	Submitted: 12/10/2018
	Review Completion: 05/17/2019
	PDUFA goal: 06/10/2019
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Pourab Roy
Concurring Reviewers:	Pallavi Mishra-Kalyani, Statistical Team Leader
	Yuan Li Shen, Supervisory Associate Director
Medical Division:	Office of Hematology and Oncology Products, Division of Oncology Products 2
Clinical Team:	Shanthi Marur, Clinical Reviewer
	Erin Larkins, Clinical Review Team Leader
	Patricia Keegan, Division Director
Project Manager:	Sharon Sickafuse
Keywords:	Randomized trial, Overall survival

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

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/s/

POURAB ROY
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PALLAVI S MISHRA-KALYANI
05/17/2019 02:34:54 PM

YUAN L SHEN
05/20/2019 10:55:18 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s052

OTHER REVIEW(S)

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

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

Memorandum

Date: 6/6/19

Sharon Sickafuse, Senior Regulatory Health Project Manager, DOP2

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, Team Leader, OPDP

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

BLA: 125514/Supplement 52

In response to DOP2's consult request dated December 31, 2018, OPDP has reviewed the proposed product labeling (PI) for BLA 125514 KEYTRUDA (pembrolizumab) for injection, for intravenous use; KEYTRUDA (pembrolizumab) injection, for intravenous use (Keytruda) S-52. This supplement adds an indication for head and neck squamous cell carcinoma.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide emailed to OPDP on May 16, 2019, and are provided below.

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

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

PI

OPDP does not have any comments on the PI at this time.

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

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/s/

RACHAEL E CONKLIN
06/06/2019 10:19:26 AM

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

PATIENT LABELING REVIEW

Date:	May 21, 2019
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	KEYTRUDA (pembrolizumab) for injection, for intravenous use KEYTRUDA (pembrolizumab) injection, for intravenous use
Application Type/Number:	BLA 125514
Supplement Number:	S-052
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On December 10, 2018, Merck Sharp & Dohme Corp. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved Biologics License Application (BLA) 125514/S-052 for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection. With this supplement, the Applicant proposes to add a new indication for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection as a single agent or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy for the first-line treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on December 31, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection.

2 MATERIAL REVIEWED

- Draft KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection MG received on December 10, 2018 and revised on April 25, 2019, and received by DMPP and OPDP on May 16, 2019.
- Draft KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection Prescribing Information (PI) received on December 10, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 16, 2019.
- Approved KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection labeling dated April 19, 2019.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHARON R MILLS
05/21/2019 10:49:35 AM

RACHAEL E CONKLIN
05/21/2019 10:53:50 AM

LASHAWN M GRIFFITHS
05/21/2019 01:46:16 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s052

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 122325

MEETING PRELIMINARY COMMENTS

Merck Sharp & Dohme Corp.
Attention: Margaret McCann, D.V.M., Ph.D.
Executive Director, Global Regulator Affairs
126 E. Lincoln Ave., P.O. Box 2000
RY34-B293
Rahway, NJ 07076

Dear Dr. McCann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pembrolizumab.

We also refer to your July 27, 2018, correspondence, received July 27, 2018, requesting a meeting to discuss the content and format of an sBLA for (b) (4) based on the results of study KEYNOTE-048, "A Phase 3 Clinical Trial of Pembrolizumab in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma."

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call me at (301) 796-2320 or email sharon.sickafuse@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: pre-sBLA

Meeting Date: October 17, 2018

Application Number: IND 122325
Product Name: Pembrolizumab
Indication: (b) (4)

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

INTRODUCTION

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 17, 2018, between Merck and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

On July 27, 2018, Merck submitted a meeting request (SDN 614) to discuss the content and format of a proposed sBLA for (b) (4) based on the results of study KEYNOTE-

048, "A Phase 3 Clinical Trial of Pembrolizumab in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma." The meeting package was submitted on September 17, 2018 as SDN 620.

Regulatory

Pembrolizumab was granted accelerated approval for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy on August 5, 2016, under the provisions of 21 CFR 610.41. As a condition of approval, Merck is required to fulfill the following post-marketing requirement:

> PMR #3100-1: Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of pembrolizumab over available therapy as determined by an improvement in overall survival in patients with metastatic squamous cell carcinoma of the head and neck.

Merck intends for the results from study KEYNOTE-048 to fulfill this requirement.

Clinical and Statistical

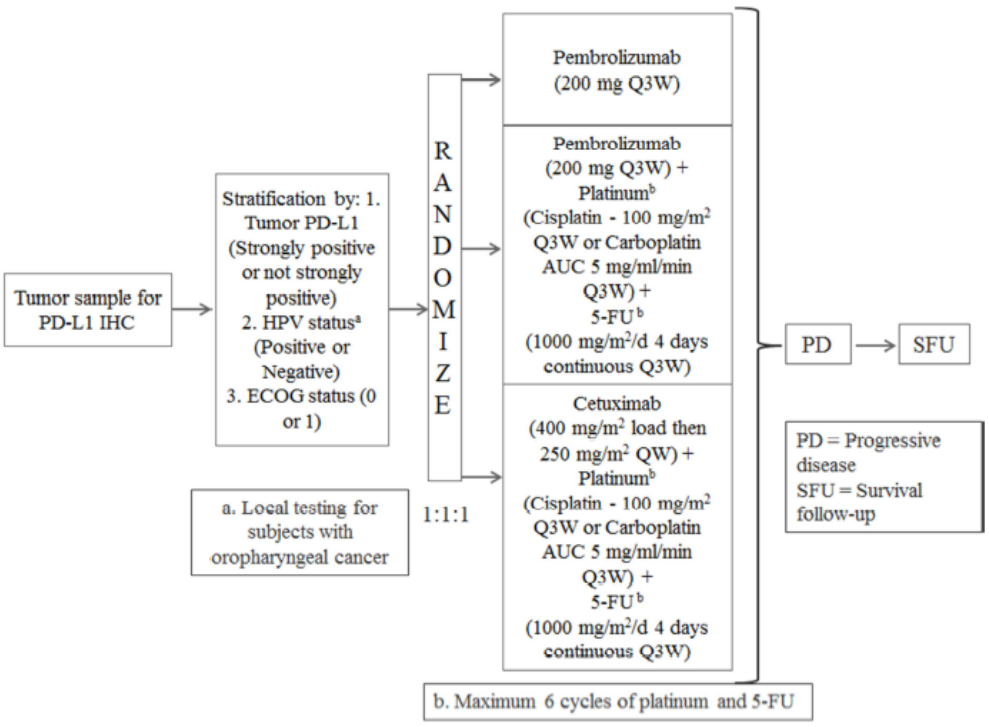
With this submission, Merck states KEYNOTE-048 will form the primary basis of the proposed sBLA submission based on the efficacy and safety data from the second interim analysis. Prior HNSCC trials of pembrolizumab in recurrent/metastatic HNSCC (KEYNOTE-040, KEYNOTE-012, and KEYNOTE-055) are proposed for including in this sBLA as supportive evidence.

KEYNOTE-048 is an ongoing randomized, multicenter, active-controlled, open label clinical trial to examine the efficacy and safety of pembrolizumab as a single agent and pembrolizumab in combination with chemotherapy (platinum plus 5-FU) versus standard treatment (cetuximab plus chemotherapy) as first-line treatment in patients with relapsed/metastatic HNSCC. Participants were randomized 1:1:1 to receive treatment with pembrolizumab 200 mg every 3 weeks (Q3W), pembrolizumab plus chemotherapy, or cetuximab plus chemotherapy (Figure 1). Randomization was stratified by ECOG performance score (0 versus 1), HPV status (positive versus negative), and PD-L1 status [strongly positive versus not strongly positive, where strongly positive is defined as Tumor Proportion Score (TPS) ≥50%]. Planned enrollment was approximately 825 patients; the prevalence of the PD-L1 positive sub-population based on Combined Positive Score (CPS) was projected to be 50% for PD-L1 CPS ≥20 and 80% for PD-L1 CPS≥1.

Imaging assessment is at 9 weeks following start of treatment then every 6 weeks for the first year and every 9 weeks thereafter. The primary endpoints of the study are overall survival (OS) and progression-free survival (PFS) using RECIST 1.1 by central radiology review. The secondary endpoints include overall response rate (ORR), patient reported outcomes and safety endpoints.

Figure 1

KEYNOTE-048 Trial Diagram



Abbreviation: 5-FU=5-fluorouracil; AUC=area under the curve; ECOG= Eastern Cooperative Oncology Group; HPV=human papilloma virus; IHC=immunohistochemistry; PD-L1=programmed cell death ligand 1; QW=weekly; Q3W=every 3 weeks.

The focus of this application will address hypotheses H7, H8, H9, and H14, defined below:

Hypothesis (H7): Pembrolizumab monotherapy prolongs OS in in the first line treatment of recurrent/metastatic HNSCC subjects with PD-L1 CPS $\geq$20 compared to standard treatment.

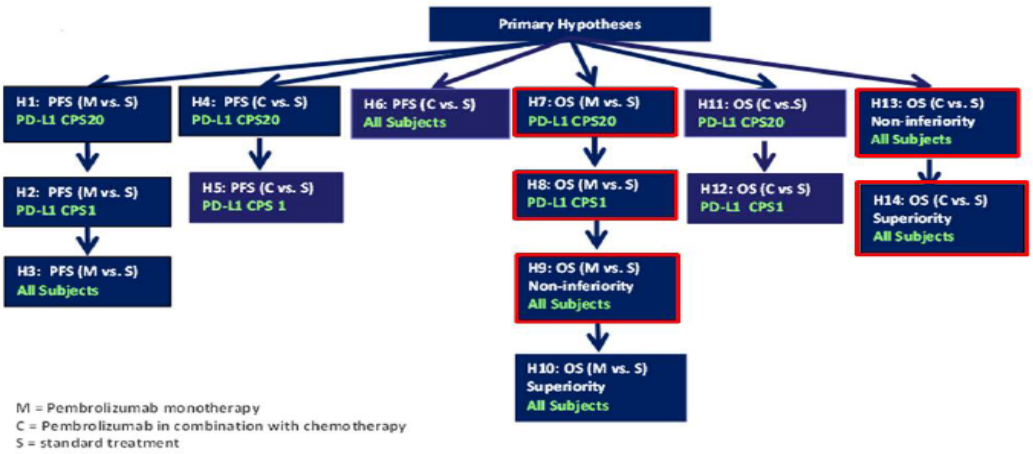
Hypothesis (H8): Pembrolizumab monotherapy prolongs OS in the first line treatment of recurrent/metastatic HNSCC subjects with PD-L1 CPS $\geq$1 compared to standard treatment.

Hypothesis (H9): Pembrolizumab monotherapy is non-inferior to standard treatment in terms of OS in all first line relapsed/metastatic HNSCC subjects.

Hypothesis (H14): Pembrolizumab in combination with chemotherapy prolongs OS in the first line treatment of recurrent/metastatic HNSCC subjects compared to standard treatment.

Figure 2

Primary Hypotheses Schematic



(Except for H9 and H13, all the other hypotheses were tested for superiority); boxes outlined in red denote hypotheses that are statistically significant at IA2).
Abbreviations: CPS=Combined positive score; PD-L1=Programmed cell death 1 ligand; PFS=progression-free survival; OS=overall survival; vs=versus.

The primary superiority hypotheses were evaluated by comparing pembrolizumab (as a single agent and in combination with chemotherapy) to standard treatment, for PFS and OS in all patients and in the subpopulation of patients with positive PD-L1 expression (PD-L1 CPS ≥20 and CPS ≥1), using a stratified log-rank test. Hazard ratios were estimated using a stratified Cox regression model, while subgroup/supportive analyses did not use stratified analyses. Event rates over time were estimated within each treatment group using the KM method. A summary of PFS and OS analyses, the required number of events for endpoints of interest, and purpose of analysis at each interim and final analysis is illustrated in the table below.

Summary of PFS and OS Analysis Strategies

PFS and OS Analyses	Key Endpoints	Timing of Analysis	Required Number of Events at the Time of Analysis	Primary Purpose of Analysis
Interim analysis 1	• PFS • OS	30 months from trial start	• ~423 PFS events between pembrolizumab plus chemotherapy and standard treatment in all participants	• Demonstrate PFS and OS superiority
Interim analysis 2	• OS	38 months from trial start	• ~421 deaths between pembrolizumab plus chemotherapy and standard treatment in all participants	• Demonstrate PFS (if not significant at IA1) and OS superiority
Final analysis	• OS	~44 months from trial start	• ≥222 deaths between one experimental treatment and standard treatment in PD-L1 CPS ≥20 • ≥359 deaths between one experimental treatment and standard treatment in PD-L1 CPS ≥1 • ≥455 deaths between one experimental treatment and standard treatment in all participants	• Demonstrate OS superiority

For the interim analyses, the actual timing is determined by the minimum follow-up; and for the final analysis, the actual timing is determined by both the required event numbers and minimum follow-up.
The table only lists the timing and the required event numbers of the hypotheses that drive the analysis. The event numbers of other hypotheses are provided in Section 8.2.9.2 of the protocol.
Abbreviations: CPS=Combined positive score; IA1=interim analysis 1; PD-L1=Programmed cell death 1 ligand; PFS=progression-free survival; OS=overall survival.

The overall type I error rate is strongly controlled at 2.5% (one-sided) with allocation of alpha towards H1 and H4 (0.0019), H7 (0.007), and H11 (0.007). The multiplicity strategy for the trial is depicted in the figure below. Hypotheses that are statistically significant at IA2 are outlined in red. A group-sequential approach was used to allocate alpha between the interim and final analyses. There was reallocation of alpha after IA2 to allow alpha for H9 and H14 as illustrated in figures below.

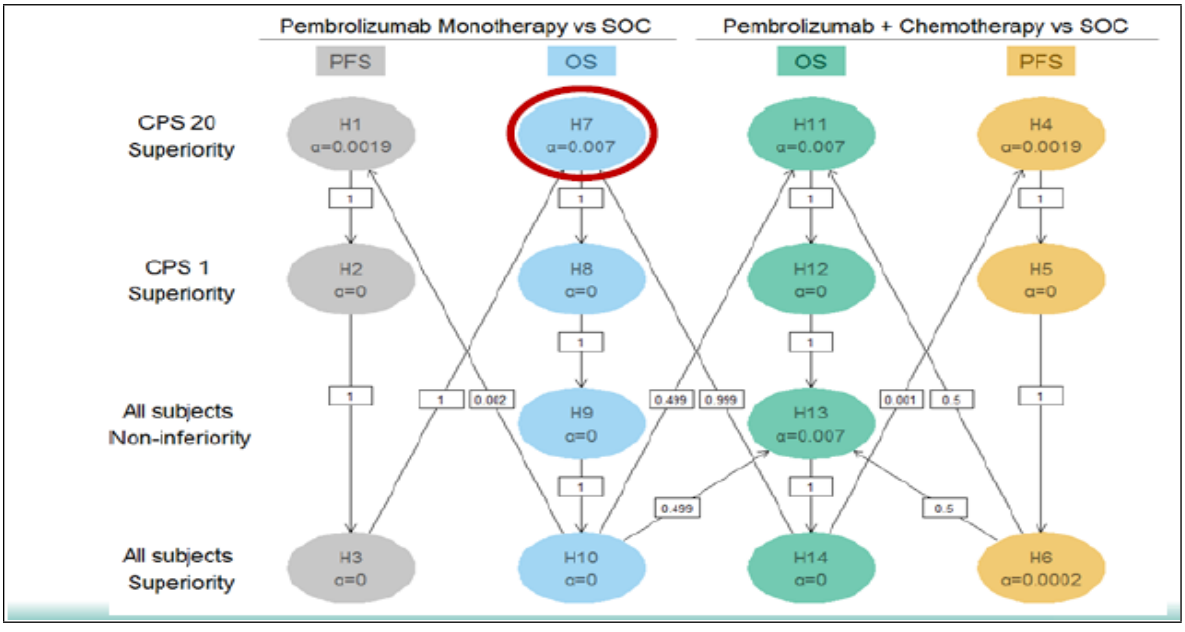
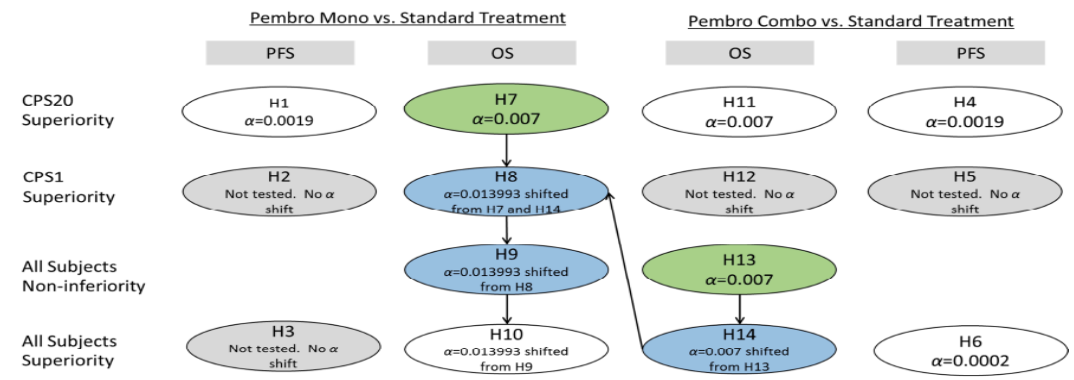


Figure 4

Alpha Reallocation Strategy at KEYNOTE-048 IA2



Abbreviations: CPS = Combined positive score; H = hypothesis; PFS = progression-free survival; OS = overall survival; vs = versus.

RESULTS from Interim Analysis 2 (IA2):

Overall, a total of 882 participants were enrolled in KEYNOTE-048, 301 to the pembrolizumab monotherapy arm, 300 to the standard treatment arm and 281 to the pembrolizumab plus chemotherapy arm. Enrollment in the pembrolizumab plus chemotherapy arm was paused early in the trial to evaluate 3 deaths noted among the first 14 patients enrolled. Merck states as a result of the enrollment pause, randomization between the pembrolizumab plus chemotherapy versus standard treatment was not simultaneous between August 13, 2015, and October 2, 2015. Per Merck, according to the intent-to-treat (ITT) principle, the 22 participants randomized to the standard treatment arm during the enrollment pause were excluded from the efficacy analysis population of pembrolizumab plus chemotherapy versus standard treatment comparisons. The first and last participants were randomized on April 20, 2015, and January 17, 2017, respectively. The Last Participant Last Visit date prior to IA2 was June 13, 2018, and the database lock date for IA2 was June 29, 2018.

Baseline demographics were generally balanced across the three arms, with a median age of 62 and a majority of patients being male, white, and never or ex-smokers. The majority had ECOG PS of 0-1, HPV negative tumors and metastatic disease. Eighty-five percent of patients had tumors with CPS >1 and 50% had tumors with CPS >20.

At IA2, among the hypothesis that were tested, H7, H8, and H14 have demonstrated superiority of an experimental arm over the control arm and H9 and H13 have demonstrated non-inferiority of an experimental arm compared to the control arm with alpha that was originally allocated or later re-allocated from other previously tested hypotheses (Table 4 below).

Table 4

Overall Alpha Level, Nominal p-value and p-value at Boundary for Each Hypothesis at IA2

Hypothesis	Population	Test	Overall alpha	Nominal p-value	p-value boundary	Outcome
H1: PFS (M vs. S)	CPS ≥20	Superiority	0.0019	0.45625	0.0016	Not yet successful
H2: PFS (M vs. S)	CPS ≥1	Superiority	NA	0.93303	NA	Not tested
H3: PFS (M vs. S)	All participants	Superiority	NA	0.99951	NA	Not tested
H4: PFS (C vs. S)	CPS ≥20	Superiority	0.0019	0.01622	0.0017	Not yet successful
H5: PFS (C vs. S)	CPS ≥1	Superiority	NA	0.02286	NA	Not tested
H6: PFS (C vs. S)	All participants	Superiority	0.0002	0.16971	0.0002	Not tested
H7: OS (M vs. S)	**CPS ≥20**	**Superiority**	**0.007**	**0.00074**	**0.0024**	**Successful with initial alpha allocation**
H8: OS (M vs. S)	**CPS ≥1**	**Superiority**	**0.013993†**	**0.00855**	**0.0109**	**Successful with alpha shifted from H7 and H14**
H9: OS (M vs. S)	**All participants**	**Non-inferiority**	**0.013993†**	**0.0001399**	**0.0117**	**Successful with alpha shifted from H8**
H10: OS (M vs. S)	All participants	Superiority	0.013993†	0.04563	0.0117	Not yet successful
H11: OS (C vs. S)	CPS ≥20	Superiority	0.007	0.00984	0.0018	Not yet successful
H12: OS (C vs. S)	CPS ≥1	Superiority	NA	0.00072	NA	Not tested
H13: OS (C vs. S)	**All participants**	**Non-inferiority**	**0.007**	**0.0000040**	**0.0041**	**Successful with initial alpha allocation**
H14: OS (C vs. S)	**All participants**	**Superiority**	**0.007†**	**0.00335**	**0.0041**	**Successful with alpha shifted from H13**

Abbreviations: C = pembrolizumab plus chemotherapy; CPS = Combined positive score; H = hypothesis; M = pembrolizumab monotherapy; NA = not applicable; PFS = progression-free survival; OS = overall survival; S = standard treatment; vs = versus.
NA = Not applicable, no alpha allocated to the hypothesis due to multiplicity strategy.
† Alpha shifted from other hypotheses due to a positive outcome at IA2.

IA2 results comparing pembrolizumab plus chemotherapy versus standard treatment:

The median duration of follow up in KEYNOTE-048 at the database cutoff date was 13.0 months (range: 0.1, 36.6) and 10.7 months (range: 0.1, 35.3) in the pembrolizumab plus chemotherapy and standard treatment groups, respectively.

The pembrolizumab plus chemotherapy and standard treatment arms were generally balanced for all baseline characteristics. The prevalence of participants whose tumors expressed PD-L1 CPS ≥1 and PD-L1 CPS ≥20 was 85.3% and 42.2%, respectively in the pembrolizumab plus chemotherapy and standard treatment arms combined.

As of IA2, fewer participants in the pembrolizumab plus chemotherapy group compared with the standard treatment group had discontinued the trial (71.2% versus 82.0%), had discontinued study medication (90.2% versus 97.0 %), had discontinued study medication due to progressive disease (56.9% versus 64.7%) and had died (66.9% versus 76.3%).

Safety data revealed the frequency of drug-related and Grade 3 to 5 adverse events (AEs) were similar in both treatment groups. The most common Grade 3 to 5 AEs were neutropenia and anemia. The pembrolizumab plus chemotherapy group experienced a higher frequency of drug related serious adverse events (SAEs) (37.0%) compared to standard treatment (25.4%). The most frequently reported SAEs in the pembrolizumab plus chemotherapy group were febrile neutropenia (5.8%), pneumonia (5.4%) and anemia (5.1%), compared with the standard treatment group where pneumonia (6.3%) and febrile neutropenia (4.9%) were the most

frequently reported SAEs. The rate of deaths due to AEs and the incidence of AEs leading to discontinuation of all drugs were comparable in the pembrolizumab plus chemotherapy group and standard treatment group (11.6% versus 9.4% and 30.8% versus 27.2%).

Key efficacy results (Table 5) with 70% mature data revealed, a statistically significant and clinically meaningful benefit in OS compared with standard treatment (EXTREME) (OS HR 0.77 [0.63, 0.93], p = 0.00335). Pembrolizumab plus chemotherapy demonstrated an ORR of 35.6% (30, 41.5) compared with the ORR for standard treatment of 36.3% (30.7, 41.5), and a similar median time to response, for all participants, as well as for participants with PD-L1 CPS ≥1 or PD-L1 CPS ≥20.

The median duration of response (DOR) was longer in pembrolizumab plus chemotherapy responders 6.7 (1.6+ -30.4+) compared with standard treatment responders 4.3 (1.2-27.9), and more pembrolizumab plus chemotherapy responders (53.5%, n=49) had an estimated response duration ≥6 months (KM estimation) than standard treatment responders (36.8% n=28) for all participants.

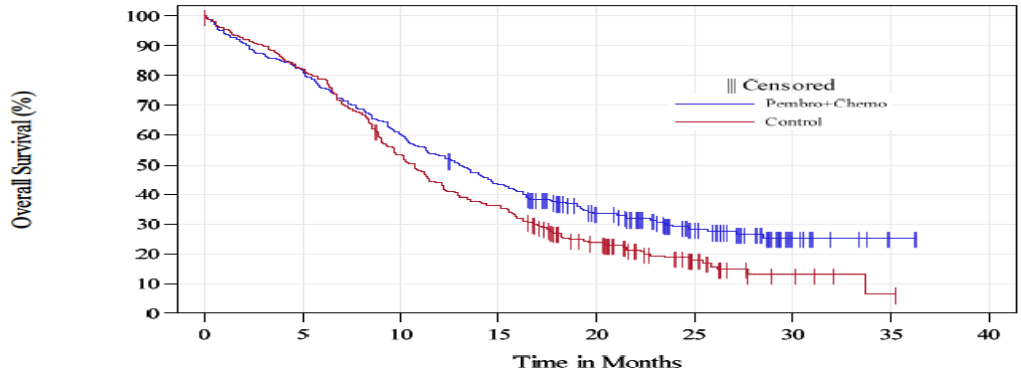
Table 5

Key Efficacy Results
Pembrolizumab Plus Chemotherapy versus Standard Treatment
ITT, CPS ≥1/CPS ≥20 Population Findings
KEYNOTE-048

	ITT (All Participants)		PD-L1 CPS ≥1		PD-L1 CPS ≥20	
	Pembrolizumab Plus Chemotherapy N=281	Std Treatment N=278	Pembrolizumab Plus Chemotherapy N=242	Std Treatment N=235	Pembrolizumab Plus Chemotherapy N=126	Std Treatment N=110
OS						
Number of events (%)	197 (70.1)	223 (80.2)	164 (67.8)	190 (80.9)	79 (62.7)	85 (77.3)
Median in month (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)	14.7 (10.3, 19.3)	11.0 (9.2, 13.0)
HR (95% CI)	0.77 (0.63, 0.93)		0.71 (0.57, 0.88)		0.69 (0.51, 0.94)	
P-value (superiority statistic)	0.00335		0.00072		0.00984	
OS rate at 12 months (95% CI)	53.0 (47.0, 58.7)	43.9 (38.0, 49.7)	55.0 (48.5, 61.0)	43.5 (37.0, 49.7)	57.1 (48.0, 65.2)	46.1 (36.6, 55.1)
OS rate at 18 months (95% CI)	37.6 (31.9, 43.2)	27.0 (21.9, 32.4)	39.1 (32.9, 45.2)	26.4 (20.9, 32.3)	43.5 (34.7, 51.9)	27.2 (19.2, 35.9)
PFS (BICR per RECIST 1.1)						
Number of events (%)	244 (86.8)	253 (91.0)	206 (85.1)	215 (91.5)	102 (81.0)	101 (91.8)
Median in months (95% CI)	4.9 (4.7, 6.0)	5.1 (4.9, 6.0)	5.0 (4.7, 6.2)	5.0 (4.8, 5.8)	5.8 (4.7, 7.6)	5.2 (4.8, 6.2)
HR (95% CI)[b]	0.92 (0.77, 1.10)		0.82 (0.67, 1.00)		0.73 (0.55, 0.97)	
P-value	0.16971		0.02286		0.01622	
PFS rate at 6 months (95% CI)	44.6 (38.6, 50.3)	44.1 (38.1, 50.0)	44.7 (38.3, 51.0)	42.4 (35.9, 48.7)	49.4 (40.3, 57.9)	45.3 (35.7, 54.5)
PFS rate at 9 months (95% CI)	26.6 (21.5, 32.0)	19.3 (14.8, 24.3)	27.6 (22.0, 33.5)	17.9 (13.1, 23.2)	35.3 (26.9, 43.8)	19.1 (12.2, 27.2)
PFS rate at 12 months (95% CI)	16.7 (12.5, 21.4)	12.1 (8.5, 16.4)	19.2 (14.4, 24.5)	10.7 (7.0, 15.3)	23.5 (16.4, 31.4)	10.8 (5.7, 17.8)
ORR (BICR per RECIST 1.1)						
% (95% CI)	35.6 (30.0, 41.5)	36.3 (30.7, 42.3)	36.4 (30.3, 42.8)	35.7 (29.6, 42.2)	42.9 (34.1, 52.0)	38.2 (29.1,47.9)
Difference (95% CI)	-0.8 (-8.7, 7.2)		0.5 (-8.2, 9.1)		5.0 (-7.5, 17.4)	
P-value[e]	0.5740		0.4586		0.2161	
DOR (Confirmed CR or PR, BICR per RECIST 1.1)						
Median in months (range)	6.7 (1.6+ - 30.4+)	4.3 (1.2+ -	6.7 (1.6+ - 30.4+)	4.3 (1.2+ - 27.9+)	7.1 (2.1+ - 30.4+)	4.2 (1.2+ - 22.3+)

Figure 5

Kaplan-Meier Estimates of Overall Survival
(Pembro Combo vs Control)
(ITT Population)



At Risk

Pembro+Chemo	281	227	169	122	75	40	10	1	0
Control	278	227	147	100	51	20	5	1	0

Source: [P048V01MK3475: adam-adtte]

IA2 results comparing pembrolizumab monotherapy versus standard treatment:

The median duration of follow up in KEYNOTE-048 at the database cutoff date was 11.7 months (range: 0.2, 37.3), and 10.7 months (range: 0.1, 35.3) in the pembrolizumab monotherapy and standard treatment arms, respectively.

The pembrolizumab monotherapy and standard treatment arms were generally balanced for all baseline characteristics. The prevalence of participants whose tumors expressed PD-L1 CPS ≥1 and PD-L1 CPS ≥20 was 85.2% and 42.4%, respectively in all participants in the pembrolizumab monotherapy and standard treatment arms combined.

As of IA2, fewer participants overall in the pembrolizumab monotherapy group compared with the standard treatment group had discontinued the trial (71.8% versus 81.7%), had discontinued study medication (89.3% versus 96.5%) and had died (67.4% versus 75.7%).

Safety data revealed that the frequencies of drug-related AEs (58.3% versus 96.9%), Grade 3 to 5 AEs (54.0% versus 83.6%), SAEs (40.3% versus 49.1%) and AEs with fatal outcome (8.3% versus 9.4%) were all lower in the pembrolizumab monotherapy group compared to the standard treatment group. Discontinuations due to an AE were 12.0% in the pembrolizumab monotherapy group compared with 27.2% in the standard treatment group. The most frequently reported Grade 3 to 5 AEs (≥5%) in the pembrolizumab monotherapy group were hyponatremia (5.7%) and pneumonia (5.3%) vs 6.3% and 6.6% in the standard treatment group. The most frequently reported Grade 3 to 5 AEs in the standard treatment group were neutropenia (21.6%), anemia (16.4%), and neutrophil count decrease (12.9%). The most common AEOSIs in the pembrolizumab monotherapy group were hypothyroidism and pneumonitis.

Key efficacy results (Table 6 and Figures 14,15, and 16) with 70% mature data revealed that OS was non-inferior (HR 0.85 [0.71, 1.03], p = 0.0001399) in the pembrolizumab monotherapy group compared with the standard treatment group in the ITT population. In the CPS ≥1 subgroup, pembrolizumab monotherapy demonstrated a statistically significant improvement in OS compared with standard treatment. (HR for OS was 0.78, [95% CI: 0.64, 0.96], p= 0.00855). In the CPS ≥20 subgroup, pembrolizumab monotherapy demonstrated a statistically significant improvement in OS compared with standard treatment (HR for OS of 0.61 [95% CI: 0.45, 0.83], p=of 0.00074).

Pembrolizumab monotherapy did not demonstrate improvement in ORR 16.9 % (12.9, 21.7) (n=51) compared with standard treatment 36.0% (30.6,41.7) (n=108). Pembrolizumab monotherapy demonstrated a similar median time to response, for all participants, as well as for participants with PD-L1 CPS ≥1 or PD-L1 CPS ≥20 (Table 6).

The median DOR was longer in pembrolizumab monotherapy responders with 20.9 months (1.5+ - 34.8+) compared to 4.5 months (1.2+ - 30.6+) with standard treatment responders. Comparing the pembrolizumab monotherapy and standard treatment arms, 36/51 and 32/108 responders had an estimated response duration ≥6 months (KM estimation) in the ITT population.

Table 6

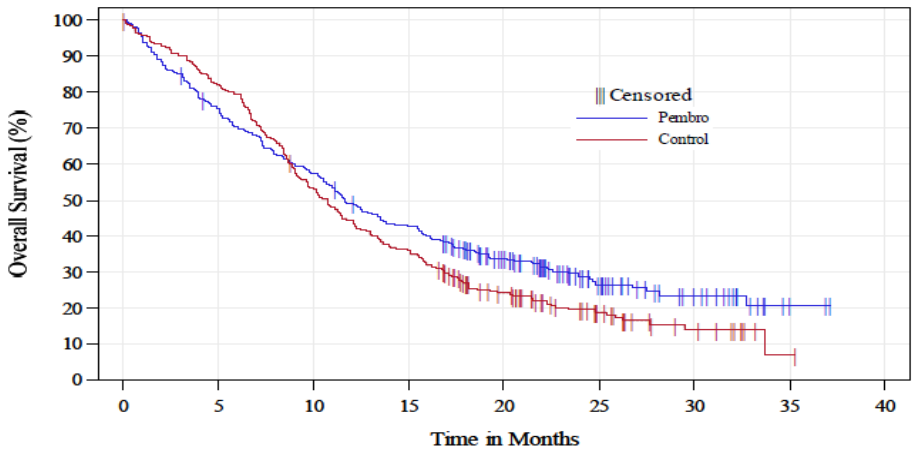
Key Efficacy Results
Pembrolizumab Monotherapy versus Standard Treatment
ITT, CPS ≥1/CPS ≥20 Population Findings
KEYNOTE-048

	ITT (All Participants)		PD-L1 CPS ≥1		PD-L1 CPS ≥20	
	Pembrolizumab Monotherapy N=301	**Std Treatment N=300**	**Pembrolizumab Monotherapy N=257**	**Std Treatment N=255**	**Pembrolizumab Monotherapy N=133**	**Std Treatment N=122**
OS						
Number of events (%)	213 (70.8)	240 (80.0)	177 (68.9)	206(80.8)	82 (61.7)	95 (77.9)
Median in month (95% CI)	11.6 (10.5, 13.6)	10.7 (9.3, 11.7)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)	14.9 (11.6, 21.5)	10.7 (8.8, 12.8)
HR (95% CI)	0.85 (0.71, 1.03)		0.78 (0.64, 0.96)		0.61 (0.45, 0.83)	
P-value (superiority statistic)	0.04563		0.00855		0.00074	
OS rate at 12 months (95% CI)	49.2 (43.4, 54.7)	44.4 ((38.7, 49.9)	51.0 (44.7, 57.0)	43.6 (37.4, 49.6)	56.9 (48.0, 64.8)	44.9 (35.9, 53.4)
OS rate at 18 months (95% CI)	36.6 (31.1, 42.1)	27.0 (22.1, 32.2)	39.5 (33.4, 45.4)	26.3 (21.0, 31.9)	46.1 (37.5, 54.4)	26.2 (18.7, 34.4)
PFS (BICR per RECIST 1.1)						
Number of events (%)	270 (89.7)	270 (90.0)	226 (87.9)	231 (90.6)	114 (85.7)	111 (91.0)
Median in months (95% CI)	2.3 (2.2, 3.3)	5.2 (4.9, 6.0)	3.2 (2.2, 3.4)	5.0 (4.8, 5.8)	3.4 (3.2, 3.8)	5.0 (4.8, 6.2)
HR (95% CI)b	1.34 (1.13, 1.59)		1.16 (0.96, 1.39)		0.99 (0.75, 1.29)	
P-value	0.99951		0.93303		0.45625	
PFS rate at 6 months (95% CI)	25.3 (20.5, 30.3)	44.9 (39.1, 50.6)	28.1 (22.7, 33.7)	43.0 (36.8, 49.1)	32.3 (24.5, 40.3)	45.0 (35.8, 53.7)
PFS rate at 9 months (95% CI)	19.1 (14.9, 23.8)	20.2 (15.8, 25.1)	22.5 (17.5, 27.8)	18.5 (13.8, 23.6)	26.1 (18.9, 33.8)	19.8 (13.1, 27.5)
PFS rate at 12 months (95% CI)	16.7 (12.7, 21.2)	13.7 (10.0, 18.0)	19.6 (15.0, 24.7)	11.9 (8.2, 16.4)	22.9 (16.2, 30.4)	12.4 (7.1, 19.2)
ORR (BICR per RECIST 1.1)						
% (95% CI)	16.9 (12.9,21.7)	36.0 (30.6,41.7)	19.1 (14.5,24.4)	34.9 (29.1,41.1)	23.3 (16.4,31.4)	36.1 (27.6,45.3)
Difference (95% CI)	-19.0 (-25.8,-12.1)		-15.9 (-23.4,-8.3)		-12.8 (-23.8,-1.5)	
P-value	1.0000		1.0000		0.9869	
DOR (Confirmed CR or PR, BICR per RECIST 1.1)						
Median in months (range)	20.9 (1.5+ - 34.8+)	4.5 (1.2+ - 30.6+)	20.9 (1.5+ - 34.8+)	4.5 (1.2+ - 28.6+)	20.9 (2.7 - 34.8+)	4.2 (1.2+ - 22.3+)
Median time to response (range)	2.1 (1.5-9.1)	2.1 (1.3-6.2)	2.1 (1.5-9.1)	2.1 (1.3-6.2)	2.1 (1.5-9.1)	2.1 (1.9-6.0)
Number (Kaplan-Meier %) With Extended Response Duration (≥6 months)	36 (75.7)	32 (38.8)	36 (78.9)	24 (36.0)	24 (83.5)	12 (34.8)

Abbreviations: BICR=Blinded independent central review; CI=Confidence interval; CPS=Combined positive score; CR=Complete response; DOR=Duration of response; HR=Hazard ratio; ITT=Intention to treat; NR=Not reached; ORR=Objective response rate; OS=Overall survival; PD-L1=Programmed cell death ligand 1; PFS=Progression-free survival; PR=Partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors Version 1.1; Std=Standard.
Database cutoff date: 29-JUN-2018

Figure 14

Kaplan-Meier Estimates of Overall Survival
(Pembro Mono vs Control)
(ITT Population)



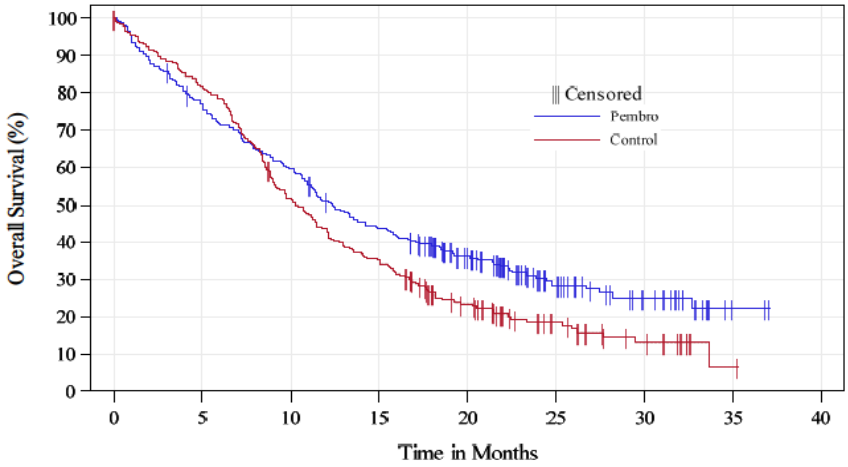
At Risk

Pembro	301	225	172	125	81	37	18	2	0
Control	300	245	158	107	57	26	10	1	0

Source: [P048V01MK3475: adam-adtte]

Figure 15

Kaplan-Meier Estimates of Overall Survival
(Pembro Mono vs Control)
(ITT Population) (CPS>=1)



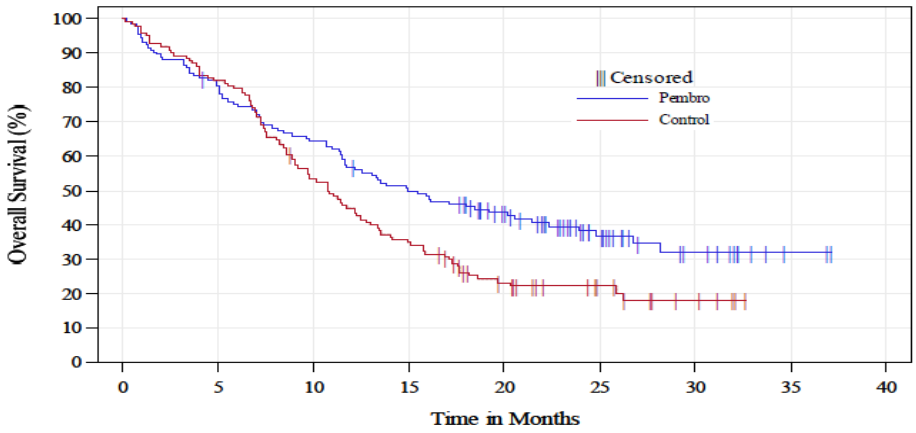
At Risk

Pembro	257	196	152	110	74	34	17	2	0
Control	255	207	131	89	47	21	9	1	0

Source: [P048V01MK3475: adam-adtte]

Figure 16

Kaplan-Meier Estimates of Overall Survival
(Pembro Mono vs Control)
(ITT Population) (CPS>=20)



At Risk

Pembro	133	106	85	65	47	24	11	2	0
Control	122	100	64	42	22	12	5	0	0

Source: [P048V01MK3475: adam-adtte]

SPONSOR QUESTIONS AND FDA RESPONSES

1. *Data from KEYNOTE-048 IA2 demonstrate that, in the population of all participants, OS for pembrolizumab plus chemotherapy (platinum plus 5-FU) is superior to standard treatment (the EXTREME regimen, cetuximab plus platinum plus 5-FU) as 1L treatment for R/M HNSCC, with a manageable tolerability profile.*

   Data from KEYNOTE-048 IA2 also demonstrate that in participants with PD-L1 CPS ≥1 and CPS ≥20, OS for pembrolizumab monotherapy is superior to standard treatment as 1L treatment of R/M HNSCC. In the population of all participants, overall survival for pembrolizumab monotherapy is non-inferior to standard treatment, with a substantially improved tolerability profile.

   Does the Agency agree that the data from this analysis are sufficient to enable an evaluation of a sBLA for pembrolizumab plus chemotherapy and pembrolizumab monotherapy for approval for the following proposed indications?

   - *KEYTRUDA, in combination with 5-FU and platinum chemotherapy, is indicated for the 1L treatment of patients with R/M HNSCC.*
   - *KEYTRUDA, as a single agent, is indicated for the 1L treatment of patients with R/M HNSCC.*

   FDA Response:
   FDA agrees there is sufficient data to support the filing of an sBLA for the proposed indications provided that the sBLA also addresses FDA's requests for additional information in the responses to Questions 3, 6, and 7 and in FDA's additional comments 9 and 10. A final decision regarding indications will be made after a detailed and comprehensive review of OS in the subgroups (CPS <1, CPS ≥1, CPS < 20, CPS ≥20) comparing the pembrolizumab monotherapy arm and the pembrolizumab with chemotherapy arm to the standard chemotherapy arm.

2. *Does the agency agree the data from KEYNOTE-048 IA2, supported by data from the final analysis of KEYNOTE-040, could meet the requirements to serve as the confirmatory trial(s) for the accelerated approval of KEYNOTE-012 and KEYNOTE-055 for the treatment of patients with R/M HNSCC with disease progression on or after platinum-containing chemotherapy?*

   FDA Response:
   FDA agrees that the results in the pembrolizumab with chemotherapy arm meet the criteria identified in the PMR.

3. *Data from KEYNOTE-048 IA2 will form the basis of this sBLA. The CSRs from KEYNOTE-040, KEYNOTE-012, and KEYNOTE-055 will be included as supportive data in the KEYNOTE-048 application. The summary modules (2.5, 2.7.3, 2.7.4) will reflect data from KEYNOTE-048; supporting data from KEYNOTE-040, KEYNOTE-012, and KEYNOTE-055 will be included in module 2.7.3. The Sponsor* (b) (4)

(b) (4)

Modules 2.7.1 and 2.7.2 will be cross-referenced from previous submissions to the BLA.

Does the Agency concur (b) (4) *would be acceptable to support review of the sBLA?*

FDA Response:

(b) (4)

4. *The Sponsor is targeting submission of this sBLA in November 2018 and the database cutoff date for KEYNOTE-048 IA2 is 13-JUN-2018, when all the participants had been followed for at least 17 months. The median follow-up duration (months, range) for each treatment group in the trial is:*

Pembrolizumab monotherapy:	*11.7 (0.2, 37.3).*
Pembrolizumab plus chemotherapy:	*13.0 (0.1, 36.6).*
Standard treatment:	*10.7 (0.1, 35.3).*

The duration of follow-up included within the sBLA is considered sufficient to assess the safety of pembrolizumab monotherapy and pembrolizumab plus chemotherapy in the population of patients with R/M HNSCC. All participants in the pembrolizumab plus chemotherapy group completed chemotherapy (maximum of 6 cycles) before the sBLA database lock date, and, therefore, all participants in that group are now in the pembrolizumab or cetuximab maintenance phase. The pembrolizumab monotherapy safety profile in the population under study is well established. Based on available data in KEYNOTE-048, the safety profile for pembrolizumab plus chemotherapy is generally consistent with that of pembrolizumab alone in addition to chemotherapy alone as assessed in prior studies of HNSCC, and the safety profile for pembrolizumab monotherapy is consistent with pembrolizumab monotherapy in the reference safety dataset. For these reasons, the Sponsor does not consider that a SUR would provide meaningful information to support an evaluation of the risk/benefit profile of pembrolizumab for the proposed indication.

Does the Agency agree that submission of a SUR 120 days after submission of the sBLA is not required?

FDA Response:
FDA agrees that an SUR is not required unless Merck identifies new serious and unexpected suspected adverse events that should be included in product labeling during review of this supplement.

5. The Sponsor proposes the following approach for the ISS: data will be presented side by side in the same table with 5 columns (pembrolizumab plus chemotherapy) and 4 columns (pembrolizumab monotherapy). Two sets of tables will be included in the sBLA.

Pembrolizumab plus Chemotherapy

a. KEYNOTE-048 Pembrolizumab plus Chemotherapy Dataset.
b. KEYNOTE-048 Standard Treatment Dataset.
c. Previous Pooled HNSCC Dataset (KEYNOTE-040 plus KEYNOTE-012, and KEYNOTE-055).
d. Reference Safety Dataset: Pooled safety data from KEYNOTE-001 (lung and melanoma), KEYNOTE-002 (melanoma), KEYNOTE-006 (melanoma), and KEYNOTE-010 (lung) studies.
e. Pembrolizumab Monotherapy Cumulative Running Safety Dataset: Pooled safety data for pembrolizumab monotherapy from the KEYNOTE-048 monotherapy group, KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010 integrated with safety data from any KEYTRUDA trial that has been submitted to any agency at least 6 weeks prior to the database lock of KEYNOTE-048.

Pembrolizumab Monotherapy

a. KEYNOTE-048 Monotherapy Dataset.
b. Previous Pooled HNSCC Dataset as above.
c. Reference Safety Dataset: as above.
d. Pembrolizumab Monotherapy Cumulative Running Safety Dataset: as above.

Does the Agency agree with the proposed approach for presenting safety data for pembrolizumab to support the sBLA?

FDA Response:

Rather the presentation as above, FDA requests one table with the following 5 columns:

a. KEYNOTE-048 Monotherapy Dataset.
b. KEYNOTE-048 Pembrolizumab plus Chemotherapy Dataset.
c. KEYNOTE-048 Standard Treatment Dataset.
d. Previous Pooled HNSCC Dataset (KEYNOTE-040 plus KEYNOTE-012, and KEYNOTE-055).
e. Reference Safety Dataset: Pooled safety data from KEYNOTE-001 (lung and melanoma), KEYNOTE-002 (melanoma), KEYNOTE-006 (melanoma), and KEYNOTE-010 (lung) studies.

6. We are continually evaluating ways to simplify and improve our regulatory submissions. One consideration is to eliminate narratives for Grade 1 AEOSIs in CSRs that are submitted in KEYTRUDA sBLAs. The Sponsor proposes not including patient narratives for Grade 1 AEOSIs in the KEYNOTE-048 sBLA and in future CSRs submitted in KEYTRUDA sBLAs.

Does FDA agree with the approach to the provision of narratives in the CSR for KEYNOTE-048 and for future CSRs for KEYTRUDA?

FDA Response:
For the proposed sBLA, FDA would like to review the grade 1 AEOSI that are of particular interest in HNSCC to include, but not limited to, hypothyroidism, facial edema, bleeding from the tumor site, and airway obstruction with dyspnea.

Provide a definition for suspected treatment-emergent hypothyroidism and a description of planned analyses characterizing the risks of hypothyroidism. Provide a separate single data set for hypothyroidism that includes, but may not be limited to, adverse event grade, laboratory abnormalities (including baselines), concomitant medication and adverse event symptomology.

DOP2 is unable to comment on the acceptability of the proposed approach for future CSRs for KEYTRUDA, which should be discussed on a case by case basis with the appropriate clinical review division.

7. *KEYN0TE-048 is a pivotal trial with N=882 participants who were enrolled and randomized to treatment with pembrolizumab monotherapy, pembrolizumab plus chemotherapy, or standard treatment. The CSR of KEYN0TE-048 will be included in the sBLA along with the Study Data Tabulation and Analysis Package for KEYN0TE-048. The Analysis Package for the ISS will also be included in the sBLA.*

Does the Agency agree with the contents of the proposed electronic submission package?

FDA Response:
The proposed contents of the electronic submission package appear acceptable. Please include the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro programs, please provide all necessary macro programs in the sBLA submission. Additionally, please provide SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert.

8. Does the Agency agree that providing site-level datasets for KEYNOTE-048 with no financial disclosure information will satisfy OSI requirements?

FDA Response:
FDA agrees.

ADDITIONAL FDA COMMENTS

9. In the proposed sBLA, provide the following information as an addendum to the CSR:

- A summary analysis and efficacy data (OS, PFS, ORR) to support the treatment effect in the relevant subgroup of patients with CPS <1, CPS≥1, CPS <20, and CPS ≥20.
- A summary analysis regarding subsequent second line therapy (choice of drug administered and date of initiation) upon progression for all patients.
- PFS 2 in the control and experimental arms for all patients who initiated second line therapy.
- Summary analyses of the proportion of patients within each arm with progression of disease in <30 days versus 30-60 days versus >60 days from randomization.
- Summary analyses of the proportion of patients within each arm who died <30 days versus 30-60 days versus >60 days from randomization.

10. Please include in the text portion of the Summary of Clinical Efficacy, a section to include the risk/benefit assessment and efficacy evaluation based on data from study KN-048 and supporting data from studies KN-040, KN-055, and KN-012 with a hyperlink to the CSR and datasets for studies KN-040, KN-055, and KN-012.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines 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. 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 conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

FDA acknowledges receipt of Merck's Agreed Initial Pediatric Study Plan submitted on January 13, 2016, and also refers to our February 11, 2016, letter confirming FDA's agreement. This fulfills Merck's requirements at this stage of development to reach an Agreed Initial Pediatric Study Plan with the Agency as required by FDASIA for products that would trigger PREA at the time of BLA submission, as the provisions of FDARA are not fully implemented.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products;
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential;
- Regulations and related guidance documents;
- A sample tool illustrating the format for Highlights and Contents; and,
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module

1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

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

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

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

/s/

SHARON K SICKAFUSE
10/10/2018