CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s047

Trade Name:	Keytruda
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp & Dohme
Approval Date:	April 11, 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 stage III NSCLC, who are not candidates for surgical resection of 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.
- 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)

- for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

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.

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

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

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS)≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
- 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, or
    - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

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.

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 (CPS≥1) as determined by an FDA-approved test.

Hepatocellular Carcinoma (HCC)

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

Merkel Cell Carcinoma (MCC)

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

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

125514Orig1s047

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s047

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125514/S-47

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING COMMITMENT

Merck Sharp & Dohme Corp.
Attention: Cheryl Czachorowski
Director, Global Regulatory Affairs
126 E. Lincoln. Ave.
RY34-B292
Rahway, NJ 07065

Dear Ms. Czachorowski:

Please refer to your Supplemental Biologics License Application (sBLA), dated July 11, 2018, received July 11, 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.

We acknowledge receipt of your major amendment dated November 30, 2018, which extended the goal date by three months.

We also refer to our approval letter dated April 11, 2019, which contained the following error: incorrect version of Medication Guide attached.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain April 11, 2019, the date of the original approval letter.

This Prior Approval supplemental biologics application adds a new indication for KEYTRUDA, as a single agent, for the first-line treatment of patients with stage III non-small cell lung cancer (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.

APPROVAL & LABELING

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

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, 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 titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable because non-small cell lung cancer does not occur in children.

FULFILLMENT OF POSTMARKETING COMMITMENT

Approval of this supplement fulfills the following postmarketing commitment listed in the October 24, 2016, approval letter for BLA 125514/S-12:

3127-2 Submit the final report and efficacy datasets for Keynote-042, entitled: "A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer."

You are no longer required to report on this commitment.

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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, 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
04/11/2019 12:00:00 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s047

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)	04/2019
Dosage and Administration (2)	04/2019
Warnings and Precautions (5)	04/2019

----------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 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. (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)

- for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.[1] (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 elig ble 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 (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)

[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)

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: Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue. (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, and peripheral neuropathy. (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: 04/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Melanoma

KEYTRUDA® (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 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 *[see Dosage and Administration (2.1)]*.

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 is indicated 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 is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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 [Combined Positive Score (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 [Combined Positive Score (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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for NSCLC, 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, or metastatic NSCLC *[see Clinical Studies (14.2)]*.
- 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.

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 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	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
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

Adverse Reaction	Severity*	Dose Modification for KEYTRUDA
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.

2.14 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 (2.13) 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.

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 (2.13) 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 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 (2.13) 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.

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 (2.13) 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 (2.13) 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 patients with HNSCC occurring in 28 (15%) of 192 patients receiving KEYTRUDA, including Grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of 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 (2.13) 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 (2.13) 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 (2.13)].*

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 (2.13) 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 (2.13)]*.

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 *[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), which enrolled 192 patients with HNSCC; and in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087), which enrolled 241 patients with cHL; or in combination with chemotherapy in a randomized, active-controlled trial (KEYNOTE-189), which enrolled 405 patients with nonsquamous NSCLC; 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 seven randomized, controlled trials (KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-042, KEYNOTE-045, KEYNOTE-189, and KEYNOTE-407) 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 years), 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 years), 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 evaluated 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; 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 the 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 years 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 years or older; 71% male; 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Eighty-seven percent had metastatic disease (stage IV), 13% with stage III disease (2% stage IIIA and 11% stage IIIB); and 5% with 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 years or older, 61% male, 72% white and 21% Asian, 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

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 median age of patients was 60 years (range: 20 to 84), 35% were age 65 years or older, 83% were male, 77% were White, 15% were Asian, and 5% were 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 14 and 15 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-087.

Table 14: 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 15: 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 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-170.

Table 16: 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[β]	11	4
Nervous System		
Headache	11	0

* Graded per NCI CTCAE v4.0

† Includes arthralgia, back pain, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, bone pain, neck pain, non-cardiac chest pain

‡ Includes nasopharyngitis, pharyngitis, rhinorrhea, rhinitis, sinusitis, upper respiratory tract infection

§ Includes fatigue, asthenia

¶ Includes allergic cough, cough, productive cough

Includes diarrhea, gastroenteritis

Þ Includes abdominal pain, abdominal pain upper

β Includes atrial fibrillation, sinus tachycardia, supraventricular tachycardia, tachycardia

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 17: 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 18 summarizes adverse reactions in patients on KEYTRUDA in KEYNOTE-052.

Table 18: 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 19 and 20 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-045.

Table 19: 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 20: 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 21 and 22 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-158.

Table 21: 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 22: 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%).

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 every 2 weeks or 10 mg/kg every 3 weeks intravenously until disease progression or unacceptable toxicity or to ipilimumab 3 mg/kg every 3 weeks intravenously 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 response duration.

The study population characteristics were: median age of 62 years (range: 18 to 89 years), 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.

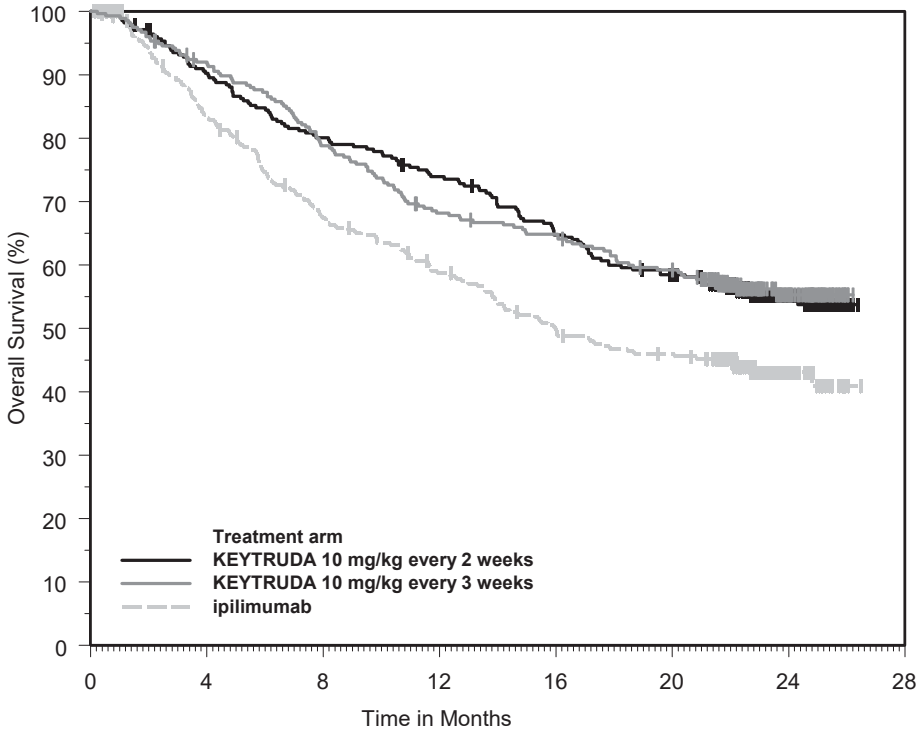
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients 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 23 and Figure 1.

Table 23: 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 intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 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 intravenously every 3 weeks (8%). Randomization was stratified by ECOG performance status (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 progression-free survival (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 overall survival (OS). Additional efficacy outcome measures were confirmed overall response rate (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 duration of response.

The study population characteristics were: median age was 62 years (range: 15 to 89 years), with 43% age 65 or older; 61% male; 98% White; and ECOG performance score was 0 (55%) and 1 (45%). 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 24.

Table 24: Efficacy Results in KEYNOTE-002

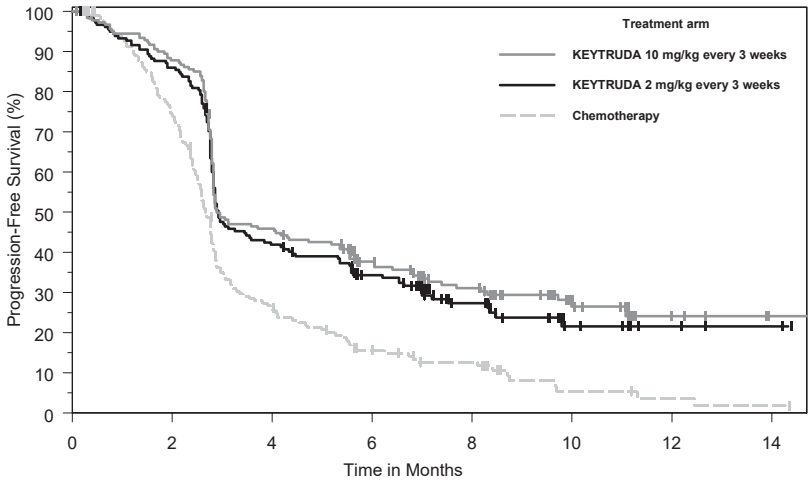
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 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 evaluated 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 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; 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 tumor proportion score (TPS ≥1%) according to an investigational use only 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 25 and Figure 3.

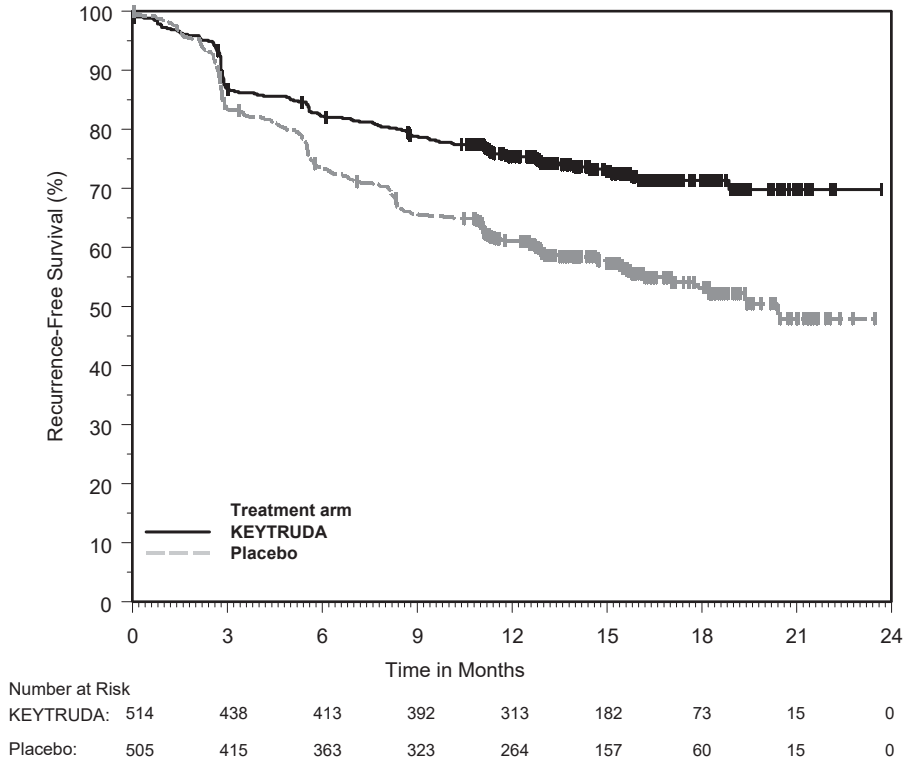
Table 25: Efficacy Results in KEYNOTE-054

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 duration of response, as assessed by the 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 performance status 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.

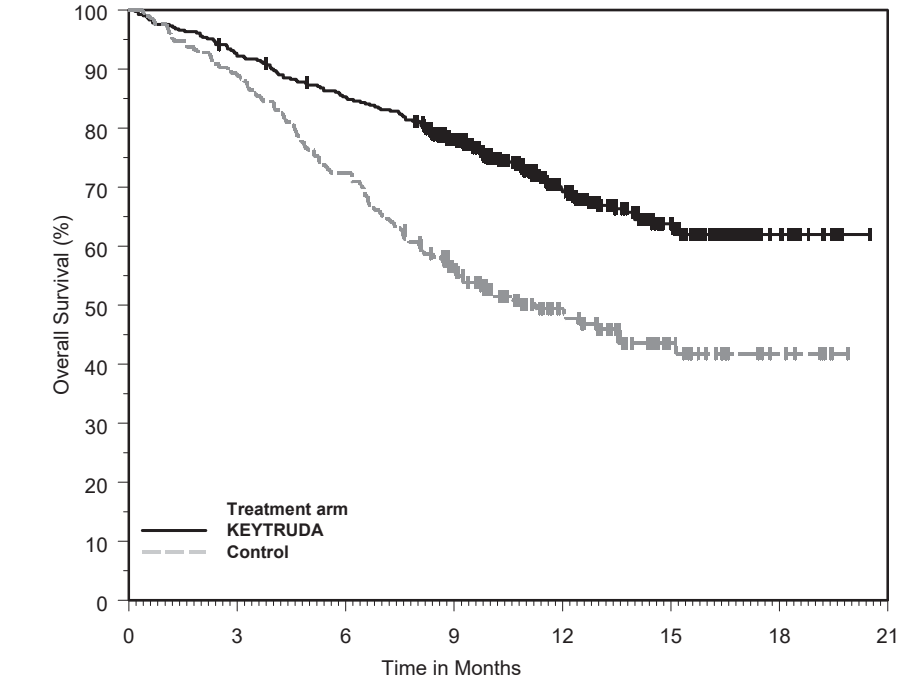
The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 26 and Figure 4 summarize the efficacy results for KEYNOTE-189.

Table 26: Efficacy Results in KEYNOTE-189

Endpoint	KEYTRUDA 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 performance status 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.

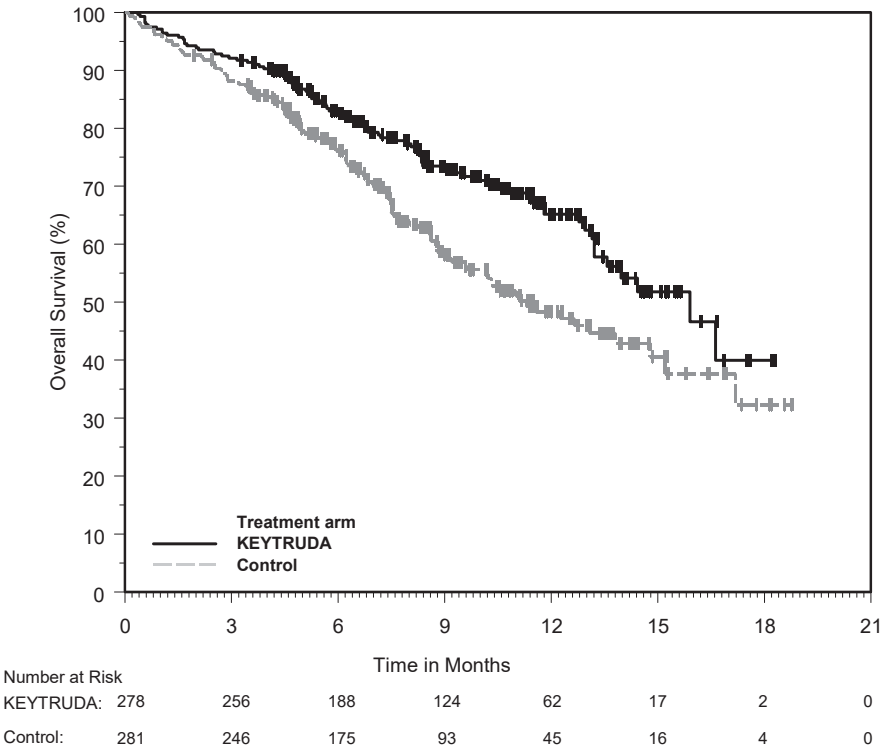
The trial demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy compared with patients randomized to placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy. Table 27 and Figure 5 summarize the efficacy results for KEYNOTE-407.

Table 27: Efficacy Results in KEYNOTE-407

Endpoint	KEYTRUDA 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 metastatic NSCLC, 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. 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 performance status (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 a 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.

The study population characteristics were: median age of 63 years (range: 25 to 90), 45% age 65 or older; 71% male; 64% White, 30% Asian, and 2% Black. Nineteen percent were Hispanic or Latino. Sixty-nine percent had ECOG performance status 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 28 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%.

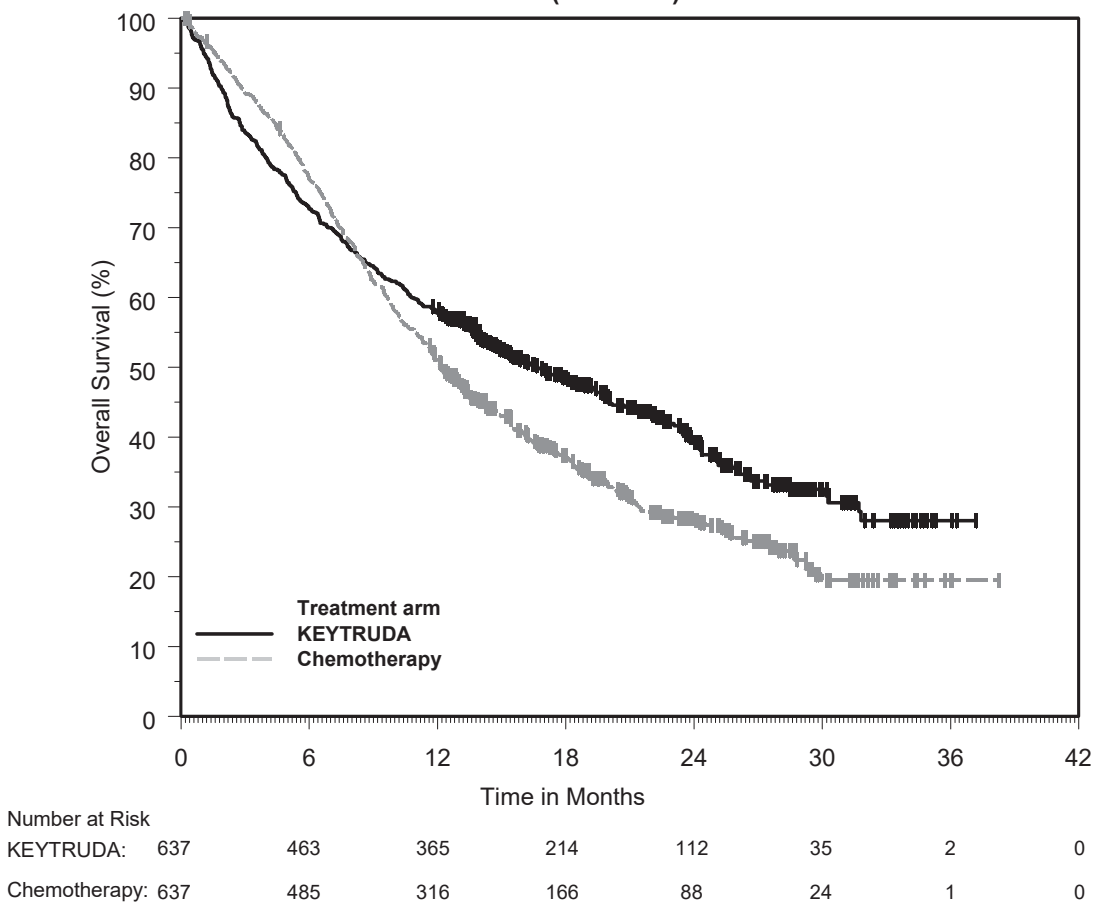
Table 28: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

	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%)



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 a blinded independent central radiologists' (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 the 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 performance status 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 29 and Figure 7 summarize the efficacy results for KEYNOTE-024.

Table 29: 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+)

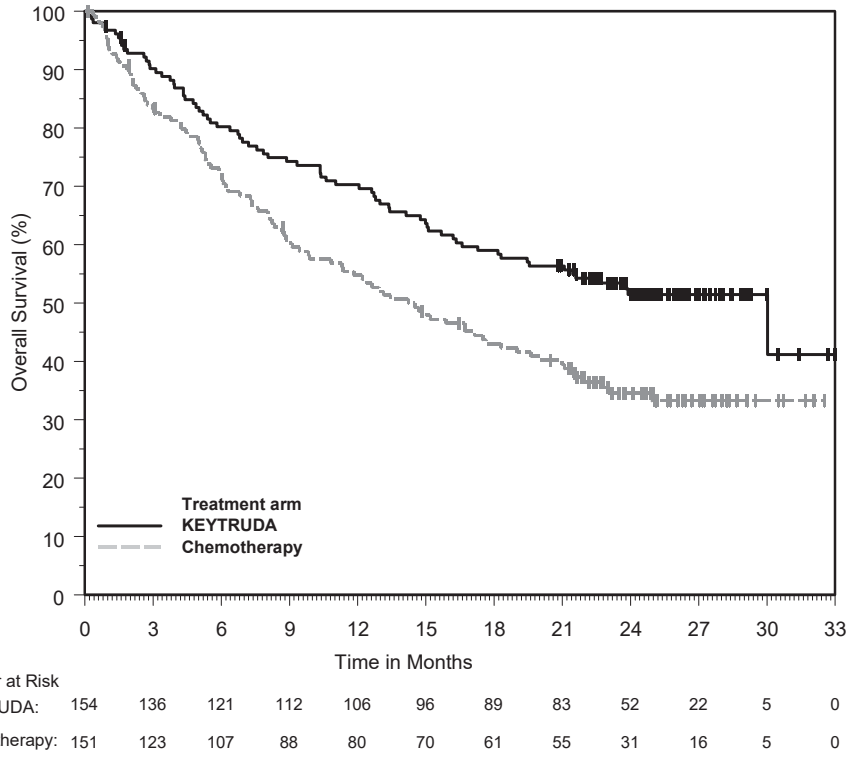
* Based on the stratified Cox proportional hazard model for the interim analysis

† 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 performance scale (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 the 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 performance status 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 30 and 31 and Figure 8 summarize efficacy results in the subgroup with TPS ≥50% population and in all patients, respectively.

Table 30: 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 31: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

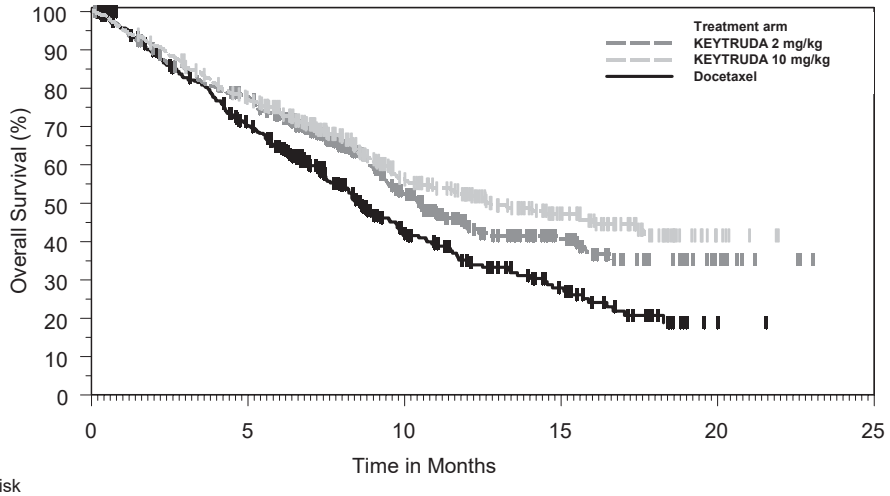
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)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

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 blinded independent central review, and duration of response.

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 duration of response had not been reached (range: 2.4+ to 27.7+ months), with 23 patients having responses of 6 months or longer. The ORR and duration of response 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, CRR, and duration of response) were assessed by blinded independent central review 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; 49% had an ECOG performance status (PS) of 0 and 51% had an 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 32.

Table 32: 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	22%
Partial response	47%
Response Duration	
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. The 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 blinded independent central review according to the 2007 revised IWG criteria. The efficacy outcome measures were overall response rate (ORR) and duration of response.

The study population characteristics were: median age 33 years (range: 20 to 61 years), 43% male; 92% White; 43% had an ECOG performance status (PS) of 0 and 57% had an 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 33.

Table 33: 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	11%
Partial response	34%
Response Duration	
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 duration of response.

The study population characteristics were: median age was 74 years, 77% were male, and 89% were 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 performance status of 2, 9% with ECOG 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 combined positive score (CPS) of ≥ 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 performance status of 2, 10% with ECOG 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 34.

Table 34: 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 duration of response.

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% with ECOG status of 0 and 56% with ECOG performance status 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 35 and Figure 9 summarize the efficacy results for KEYNOTE-045.

Table 35: Efficacy Results in KEYNOTE-045

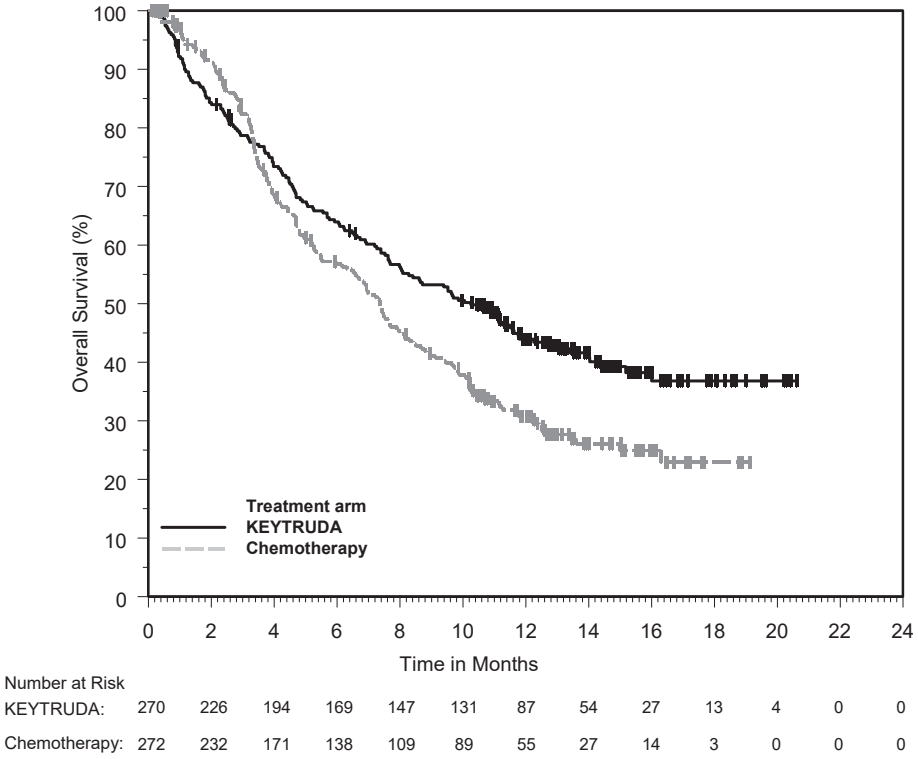
	KEYTRUDA 200 mg every 3 weeks n=270	**Chemotherapy n=272**
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	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 9: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



Number at Risk													
KEYTRUDA:	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy:	272	232	171	138	109	89	55	27	14	3	0	0	0

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 blinded independent central radiologists' (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, and duration of response.

Table 36: 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 ECOG PS 0 (36%) or 1 (64%). 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 37 and 38.

Table 37: Efficacy Results for Patients with MSI-H/dMMR Cancer

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

NR = not reached

Table 38: 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 blinded independent central review, and duration of response.

Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a combined positive score (CPS) of ≥ 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, 11% Asian; and ECOG PS of 0 (43%) and 1 (57%). 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 duration of response 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 duration of response 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 blinded independent central review, and duration of response.

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 PD-L1 IHC 22C3 pharmDx Kit. The baseline characteristics of these 77 patients were: median age was 45 years (range: 27 to 75 years); 81% were White, 14% Asian, 3% Black; ECOG PS was 0 (32%) or 1 (68%); 92% had squamous cell carcinoma, 6% adenocarcinoma, and 1% adenosquamous histology; 95% had M1 disease and 5% had recurrent disease; 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 39 for patients with PD-L1 expression (CPS ≥1).

Table 39: 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%
Response duration	
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 duration of response 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 blinded independent central review committee (BICR).

The study population characteristics were: median age 68 years (67% age 65 or older); 83% male; 81% White; 14% Asian; ECOG PS of 0 (61%) or 1 (39%). 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 40.

Table 40: 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%

* Modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ

† 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 duration of response as assessed by BICR per RECIST v1.1.

The study population characteristics were: median age was 71 years (range: 46 to 91 years), with 80% age 65 or older; 68% male; 90% White; and ECOG performance score was 0 (48%) and 1 (52%). 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 41.

Table 41: 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 (CR) rate (95% CI)	24% (13, 38)
Partial response (PR) 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

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)

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

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 (hepatitis). Signs and symptoms of hepatitis 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
- feeling less hungry than usual
- 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) that:

- has returned or spread **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.

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, and inflammation of the nerves that may cause pain, weakness, and paralysis in the arms and legs.

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-1904r022

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

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
04/11/2019 12:00:00 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s047

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	sBLA
Application Number	125514/S-47
Priority or Standard	Priority
Submit Date	7-11-2018
Received Date	7-11-2018
Major Amendment Date	11-30-2018
PDUFA Goal Date	1-11-2019 (original) 4-11-2019 (Revised due to Major Amendment)
Division/Office	DOP2/OHOP
Review Completion Date	April 11, 2019
Established Name	Pembrolizumab
Trade Name	Keytruda
Pharmacologic Class	Programmed death-receptor-1 (PD-1) blocking antibody
Applicant	Merck Sharp & Dohme Corp.
Formulations	For Injection: 50 mg lyophilized powder in single-dose vial Injection: 100 mg/4 mL (25 mg/mL) solution in single-dose vial
Dosing Regimen	200 mg over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression
Applicant Proposed Indication	KEYTRUDA is a program death receptor-1 (PD-1)-blocking antibody indicated for first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD L1 [Tumor Proportion Score (TPS) $\geq$ 1%], as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations
Recommendation on Regulatory Action	Regular approval
Recommended Indication	KEYTRUDA is a program death receptor-1 (PD-1)-blocking antibody indicated 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.

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Reviewers of Multi-Disciplinary Review and Evaluation

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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 antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with programmed death ligand-1 (PD-L1) and 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 the following non-small cell lung cancer (NSCLC) indications:

- In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
- As a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
- 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. Conclusions on the Substantial Evidence of Effectiveness

The primary trial supporting this sBLA is KEYNOTE-042, a randomized, multicenter, open-label, active-controlled trial comparing pembrolizumab as a single agent to platinum-based chemotherapy (carboplatin with either pemetrexed or paclitaxel) as first-line systemic therapy for 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC, whose tumors expressed PD-L1 (TPS ≥1%). The co-primary endpoints for this study were overall survival (OS) in the subgroup of patients with tumor TPS ≥50%, the subgroup with tumor TPS ≥20% and the intent-to-treat (ITT) population (TPS ≥1%).

Efficacy results at the second interim analysis of KEYNOTE-042 demonstrated a statistically significant improvement in OS for the TPS ≥50% and TPS ≥20% subgroups and for the ITT population (TPS ≥1%), which were tested hierarchically in that order. The magnitude of the treatment effect was largest in the TPS ≥50% subgroup, with an OS hazard ratio (HR) of 0.69 (95% confidence interval [CI] 0.56, 0.85, p-value 0.0006) and a 7.8-month improvement in median OS (20.0 months and 12.2 months for those randomized to pembrolizumab and

chemotherapy, respectively). The HR for OS in the ITT population (TPS ≥1%) was 0.81 (95% CI: 0.71, 0.93, p-value 0.0036), with a median OS of 16.7 months and 12.1 months for those randomized to pembrolizumab and chemotherapy, respectively. The results, for the OS analysis in the TPS ≥20% subgroup, were intermediate between the results in the TPS ≥50% subgroup and the ITT population (HR 0.77 [95% CI 0.64, 0.92]; median OS 17.7 months and 13.0 months for those randomized to pembrolizumab and chemotherapy, respectively).

In the TPS≥ 50% subgroup, the estimated median PFS was higher (7.1 months compared to 6.4 months) for those randomized to pembrolizumab and chemotherapy, respectively; this difference was not clinically meaningful nor statistically significant (HR 0.81 [95% CI 0.67, 0.99], two-sided p-value 0.034 compared to a boundary of 0.0291). Given the sequential testing procedure, no other secondary endpoints could be tested for statistical significance. The estimated median PFS times were lower in patients randomized to pembrolizumab compared to those randomized to chemotherapy in the TPS ≥20% subgroup (6.2 vs 6.6 months, HR 0.94 [95% CI 0.80, 1.11]) and in the ITT population (5.4 vs 6.5 months, HR 1.07 [95% CI 0.94, 1.21]); the point estimate for the hazard ratio favored those randomized to chemotherapy only for the ITT population. The ORR was higher in those randomized to pembrolizumab compared to those randomized to chemotherapy for the TPS ≥50% subgroup (39% vs 32%) and for TPS ≥20% subgroup (33% vs 29%) but was same in both arms for the ITT population (27%). The results of KEYNOTE-042 demonstrated a higher proportion of patients with durable (≥ 12 months) responses for those randomized to pembrolizumab as compared to chemotherapy in all of the efficacy analysis populations. In the ITT population (TPS ≥1%), the proportion of responders with duration of response (DOR) ≥12 months was 47% for those randomized to pembrolizumab vs 16% for those randomized to chemotherapy and the proportion of responders with DOR ≥18 months was 26% vs 6%, for those randomized to pembrolizumab and chemotherapy, respectively. The proportion of pembrolizumab-treated patients with DOR ≥12 months and ≥18 months was similar across the efficacy analysis populations (for TPS ≥50% / TPS ≥20% / ITT populations, the proportions of responders with DOR ≥12 months were 42% / 45% / 47% and the proportions of responders with DOR ≥18 months 25% / 25% / 26%).

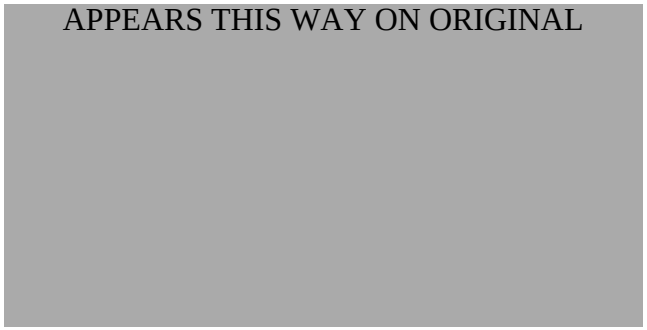
To further explore the potential impact of the level of PD-L1 tumor expression on the observed treatment effect, exploratory analyses were conducted in the subgroup of patients with PD-L1 TPS 1-49%, a predefined stratification factor for randomization in KEYNOTE-042. In this subgroup, the OS HR was 0.92 (95% CI 0.77, 1.11), with an estimated median OS of 13.4 months (95% CI 10.7, 18.2) for those randomized to pembrolizumab and 12.1 months (95% CI 11.0, 14.0) for those randomized to chemotherapy. The PFS HR was 1.32 (95% CI 1.11, 1.56) and the ORR was 17% vs 22% for those randomized to pembrolizumab and chemotherapy, respectively. The results of exploratory analyses in the TPS 1-49% subgroup raise uncertainty regarding the benefit of pembrolizumab in the TPS 1-49% subgroup and suggest the results in the ITT population (TPS ≥1%) may be driven by the treatment effect in the TPS ≥50% subgroup. The interpretation of these results, however, is complicated by the exploratory nature of these analyses and the observation of non-proportional hazard rates, and lack of a statistically significant test for interaction between PD-L1 expression (1-49% vs ≥ 50%) and survival

outcomes. For these reasons, it is not possible to draw definitive conclusions based upon the results of these exploratory analyses. The comparator in KEYNOTE-042 is an active control and there does not appear to be a detrimental effect on overall survival in the subpopulation of patients with NSCLC TPS 1-49% who were randomized to pembrolizumab as compared to chemotherapy.

Exploratory efficacy analyses were conducted in the subgroup of patients with stage III disease treated in KEYNOTE-042 (n=160) to investigate the merit of including patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, in the proposed indication. Overall, the efficacy findings of OS, PFS and ORR in patients with stage III disease with PD-L1 TPS ≥ 1% were similar to those observed in patients with metastatic disease.

The results of KEYNOTE-042 demonstrate a statistically significant and clinically meaningful (4.6-month difference in estimated median OS) improvement in OS for patients receiving single agent pembrolizumab compared to patients receiving carboplatin-based chemotherapy as first-line treatment for advanced, PD-L1-expressing (TPS ≥ 1%) NSCLC. These results are supported by demonstration of a higher proportion of patients with durable (≥ 12 months) responses in the pembrolizumab arm compared to the chemotherapy arm. The submitted evidence meets the statutory evidentiary standard for regular approval.

1.3. Benefit-Risk Assessment



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 non-small cell lung cancer (NSCLC). Pembrolizumab is approved as a single agent for the treatment of patients with metastatic NSCLC as first-line therapy for patients whose tumors have high PD-L1 expression (TPS ≥50%) or following progression on or after platinum-based chemotherapy for patients whose tumors express PD-L1 (TPS ≥1%) and is approved as first line therapy in combination with platinum-based chemotherapy for the treatment of patients with NSCLC, regardless of tumor PD-L1 expression.

Metastatic NSCLC is a life-threatening condition with poor survival. Platinum-based combination chemotherapy with or without pembrolizumab (regardless of histology) or atezolizumab and bevacizumab (non-squamous NSCLC) is a standard of care option for the first-line treatment of patients with metastatic NSCLC. While pembrolizumab is approved as a single agent for the first-line treatment of patients with metastatic NSCLC, this indication is limited to patients whose tumors have high PD-L1 expression (TPS ≥50%). At the time the study supporting this sBLA was being initiated, platinum-based combination chemotherapy, without an anti-PD-(L)1 antibody, was the most appropriate comparator for first-line treatment of NSCLC. Median OS of approximately 8 to 11 months has been reported with such platinum-based combination regimens.

This application is primarily supported by a randomized, multicenter, open-label, active-controlled trial, KEYNOTE-042, comparing pembrolizumab to platinum-based chemotherapy (carboplatin with either pemetrexed or paclitaxel) as first-line systemic therapy for 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC, whose tumors expressed PD-L1 (TPS ≥1%). The co-primary endpoints for this study were overall survival (OS) in the subgroups of patients with tumor TPS ≥50% or TPS ≥20% and in the intent-to-treat (ITT) population (TPS ≥1%).

Efficacy results at the second interim analysis of KEYNOTE-042 demonstrated a statistically significant improvement in OS for the TPS ≥50% and TPS ≥20% subgroups and for the ITT population (TPS ≥1%), which were tested hierarchically in that order. For the ITT population (TPS ≥1%), which is the most relevant analysis population for the proposed indication, the hazard ratio (HR) for OS was 0.81 (95% CI 0.71, 0.93; p-value 0.0036), with a median OS of 16.7 months in the pembrolizumab arm vs 12.1 months in the chemotherapy arm. The magnitude of the treatment effect on OS favoring pembrolizumab was largest in the TPS ≥50% subgroup (HR 0.69 [95% CI 0.56, 0.85; p-value 0.0006], median OS 20.0 vs 12.2 months), and results for the TPS ≥20% subgroup (HR 0.77 [95% CI 0.64, 0.92]; median OS 17.7 vs 13.0 months) were intermediate between the results in the TPS ≥50% subgroup and the ITT population.

In the TPS≥ 50% subgroup, the estimated median PFS was marginally higher in the pembrolizumab arm compared to the chemotherapy arm (7.1 vs 6.4 months), but this difference was not statistically significant (HR 0.81 [95% CI 0.67, 0.99], two-sided p-value 0.034 compared to a

boundary of 0.0291). Given the sequential testing procedure, no other secondary endpoints could be tested for statistical significance. The estimated median PFS was lower in those randomized to pembrolizumab compared to those randomized to chemotherapy in the TPS ≥20% subgroup (6.2 vs 6.6 months, HR 0.94 [95% CI 0.80, 1.11) and the ITT population (5.4 vs 6.5 months, HR 1.07 [95% CI 0.94, 1.21]). ORR was slightly higher in the pembrolizumab arm compared to the chemotherapy arm for the TPS ≥50% subgroup (39% vs 32%) and TPS ≥20% subgroup (33% vs 29%) but was same between arms for the ITT population (27%). There was an increased proportion of durable responses in the pembrolizumab arm vs the chemotherapy arm in all of the primary efficacy analysis populations. In the ITT population (TPS ≥1%), the proportion of responders with duration of response (DOR) ≥12 months was 47% in the pembrolizumab arm vs 16% in the chemotherapy arm and the proportion of responders with DOR ≥18 months was 26% in the pembrolizumab arm vs 6% in the chemotherapy arm. The proportions of pembrolizumab-treated patients with DOR ≥12 months and ≥18 months were similar across all three efficacy analysis populations.

To further explore the potential impact of level of PD-L1 expression on the observed treatment effect, exploratory analyses were conducted in the subgroup of patients with PD-L1 TPS 1-49%, a predefined subgroup and stratification factor in KEYNOTE-042. In this subgroup, the OS HR was 0.92 (95% CI 0.77, 1.11), with an estimated median OS of 13.4 months (95% CI 10.7, 18.2) in the pembrolizumab arm and 12.1 months (95% CI 11.0, 14.0) in the chemotherapy arm. The PFS HR was 1.32 (95% CI 1.11, 1.56), while ORR was 17% in the pembrolizumab arm vs 22% in the chemotherapy arm.

The observed safety profile of pembrolizumab is acceptable when assessed in the context of the treatment of a life-threatening disease. In KEYNOTE-042, the most common adverse reactions in pembrolizumab-treated patients were fatigue, decreased appetite, dyspnea, cough, rash, constipation, diarrhea, nausea, hypothyroidism, pneumonia, pruritis, and weight loss. There was a slightly higher incidence of serious AEs (41% vs 30%), AEs leading to death (11% vs 8%) and AEs leading to study drug discontinuation (19% vs 15%) in patients treated with pembrolizumab compared to patients treated with platinum-based chemotherapy, while the incidence of grade 3-5 AEs was slightly lower in the pembrolizumab arm compared to the chemotherapy arm (50% vs 57%). An increased number of deaths due to unknown cause or sudden death was also reported in the pembrolizumab arm (11 patients [1.8%] vs 5 patients [0.8%]). Although underlying malignancy, co-morbid conditions and other confounding factors might have all contributed to the increased number of deaths due to AEs, with the lack of additional information (e.g., autopsy reports), a causal association to pembrolizumab cannot be completely ruled out. However, given the extensive safety data available for pembrolizumab in patients with solid tumors and specifically in patients with NSCLC, the 11% incidence of death due to AE, including a 1.8% incidence of death due to unknown cause/sudden death, in KEYNOTE-042 does not raise particular concerns, since this is an isolated finding in one study in a patient population in whom pembrolizumab has been extensively studied and the results of KEYNOTE-042 demonstrate an improvement in OS for pembrolizumab vs chemotherapy. The incidence of adverse reactions of death leading to treatment discontinuation of pembrolizumab observed in KEYNOTE-042 will be included in the KEYTRUDA Prescribing Information.

The overall safety profile of pembrolizumab reported in KEYNOTE-042 was, in general, consistent with the known safety profile based on the pembrolizumab monotherapy Reference Safety Database, with the exception of immune-related pneumonitis, which was reported at a higher frequency in KEYNOTE-042 (8.3% versus 3.4%). A higher incidence of pneumonitis was also noted in KEYNOTE-024 (7.8%), another study of pembrolizumab as a single agent in patients with NSCLC, relative to the pembrolizumab monotherapy Reference Safety Database. The higher incidence of pneumonitis observed in these two clinical trials of pembrolizumab administered as a single agent in patients with previously untreated NSCLC compared to the pembrolizumab monotherapy RSD may be due to the differences in population, as patients with NSCLC have characteristics (e.g. smoking history) and underlying comorbid conditions (COPD, cardiovascular disease) that might predispose the population to drug-induced pulmonary toxicity. The increased incidence of pneumonitis observed in KEYNOTE-042 and KEYNOTE-024 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-042 demonstrate a statistically significant and clinically meaningful (4.6-month difference in estimated median OS) improvement in OS for pembrolizumab compared to chemotherapy in patients with advanced NSCLC whose tumors express PD-L1 (TPS ≥1%). The results of exploratory analyses in the TPS 1-49% subgroup raise uncertainty regarding the benefit of pembrolizumab in the TPS 1-49% subgroup and suggest the results in the ITT population (TPS ≥1%) may be driven by the treatment effect in the TPS ≥50% subgroup. The interpretation of these results, however, is complicated by the exploratory nature of these analyses and the observation of non-proportional hazard rates; therefore, it is not possible to draw definitive conclusions based upon the results of these exploratory analyses. The comparator in KEYNOTE-042 is an active control, and there does not appear to be a detrimental effect on overall survival in the subpopulation of patients with NSCLC TPS 1-49%.

In the opinion of the reviewers, based upon the results of analyses in the overall study population (TPS ≥1%), the submitted evidence meets the statutory evidentiary standard for regular approval and provides substantial evidence of the effectiveness of pembrolizumab for the first-line treatment of patients with advanced NSCLC whose tumors express PD-L1 (TPS ≥1%). The results of KEYNOTE-042 demonstrate a statistically significant and clinically meaningful (4.6-month difference in estimated median OS) improvement in OS for pembrolizumab compared to chemotherapy in patients with advanced NSCLC whose tumors express PD-L1 (TPS ≥1%), supported by demonstration of an increased proportion of durable responses in the pembrolizumab arm compared to the chemotherapy arm. Results of the exploratory analysis of OS in the TPS 1-49% subgroup will be included in product labeling to provide transparency and inform prescribers. The risks associated with pembrolizumab treatment are considered acceptable in the proposed indication in the context of the poor prognosis and the magnitude of improvement in survival observed. The reviewers recommend granting regular approval of pembrolizumab for the following indication:

"Pembrolizumab is indicated 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 core (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer death in the U.S., with 80% to 85% of all lung cancers cases classified as NSCLC. • 85% of cases of NSCLC are diagnosed at later stages and for patients with distant metastasis the 5-year survival rate is <5%.	Metastatic NSCLC is a life-threatening condition with poor survival.
Current Treatment Options	• Platinum-based combination chemotherapy, with/ without pembrolizumab (regardless of histology) or with/without atezolizumab and bevacizumab (non-squamous NSCLC) are generally recognized standard of care options for the first-line treatment of patients with metastatic NSCLC. • Pembrolizumab is approved as a single agent for the first-line treatment of patients with metastatic NSCLC, but this indication is limited to patients whose tumors have high PD-L1 expression (TPS≥50%).	At the time that KEYNOTE-042 (the study supporting this sBLA) was being initiated, platinum-based combination chemotherapy without an anti-PD-(L)1 antibody, was the most appropriate comparator for first-line treatment of NSCLC. Median OS of approximately 8 to 11 months has been reported with such platinum-based combination regimens.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• This application is primarily supported by a randomized, multicenter, open-label, active-controlled trial, KEYNOTE-042, comparing pembrolizumab to platinum-based chemotherapy (carboplatin with either pemetrexed or paclitaxel) as first-line systemic therapy in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC, whose tumors expressed PD-L1 (TPS ≥1%). The co-primary endpoints for this study were overall survival (OS) in the subgroup of patients with tumor TPS ≥50%, the subgroup with tumor TPS ≥20% and the intent-to-treat (ITT) population (TPS ≥1%). • Efficacy results at the second interim analysis of KEYNOTE-042 demonstrated a statistically significant improvement in OS for the TPS ≥50% and TPS ≥20% subgroups and the ITT population (TPS ≥1%), which were tested hierarchically in that order. • For the ITT population (TPS ≥1%), which is the most relevant analysis population for the proposed indication, the hazard ratio (HR) for OS was 0.81 (95% CI 0.71, 0.93), with a median OS of 16.7 months in the pembrolizumab arm vs 12.1 months in the chemotherapy arm. • The magnitude of the treatment effect on OS favoring pembrolizumab was largest in the TPS ≥50% subgroup (HR 0.69 [95% CI 0.56, 0.85], median OS 20.0 vs 12.2 months), and results for the TPS ≥20% subgroup (HR 0.77 [95% CI 0.64, 0.92]; median OS 17.7 vs 13.0 months) were intermediate between the results in the TPS ≥50% subgroup and the ITT population. • In the TPS≥ 50% subgroup, the estimated median PFS was higher in the pembrolizumab arm compared to the chemotherapy arm (7.1 vs 6.4 months), but this difference was not clinically meaningful nor statistically significant (HR 0.81 [95% CI 0.67, 0.99], p-value 0.034	The submitted evidence meets the statutory evidentiary standard for regular approval and provides substantial evidence of the effectiveness of pembrolizumab for the first-line treatment of patients with advanced NSCLC whose tumors express PD-L1 (TPS ≥1%). The results of KEYNOTE-042 demonstrate a statistically significant and clinically meaningful (4.6-month difference in estimated median OS) improvement in OS for pembrolizumab compared to chemotherapy in patients with advanced NSCLC whose tumors express PD-L1 (TPS ≥1%), supported by demonstration of an increased proportion of durable responses in the pembrolizumab arm compared to the chemotherapy arm. The results of exploratory analyses in the TPS 1-49% subgroup raise uncertainty regarding the benefit of pembrolizumab in the TPS 1-49% subgroup and suggest the results in the ITT population (TPS ≥1%) may be driven by the treatment effect in the TPS ≥50% subgroup. The interpretation of these results, however, is complicated by the exploratory nature of these analyses, the lack of a significant test for interaction between PD-L1 expression and survival, and the observation of non-proportional hazard rates. Therefore, it is not

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	compared to a boundary of 0.0291). Given the sequential testing procedure, no other secondary endpoints could be tested for statistical significance. The estimated median PFS was lower in the pembrolizumab arm compared to the chemotherapy arm in the TPS ≥20% subgroup and the ITT population (5.4 vs 6.5 months, HR 1.07 [95% CI 0.94, 1.21]). • ORR was higher in the pembrolizumab arm compared to the chemotherapy arm for the TPS ≥50% and TPS ≥20% subgroups but was the same between arms for the ITT population (27%). • There was an increased proportion of durable responses in the pembrolizumab arm vs the chemotherapy arm in all of the primary efficacy analysis populations. In the ITT population (TPS ≥1%), the proportion of responders with duration of response (DOR) ≥12 months was 47% in the pembrolizumab arm vs 16% in the chemotherapy arm and the proportion of responders with DOR ≥18 months was 26% in the pembrolizumab arm vs 6% in the chemotherapy arm. The proportion of pembrolizumab-treated patients with DOR ≥12 months and ≥18 months was similar across the primary efficacy analysis populations. • Exploratory analyses were conducted in the subgroup of patients with PD-L1 TPS 1-49%, a predefined subgroup and stratification factor in KEYNOTE-042. In this subgroup, the OS HR was 0.92 (95% CI 0.77, 1.11), with an estimated median OS of 13.4 months (95% CI 10.7, 18.2) in the pembrolizumab arm and 12.1 months (95% CI 11.0, 14.0) in the chemotherapy arm. The PFS HR was 1.32 (95% CI 1.11, 1.56), while ORR was 17% in the pembrolizumab arm vs 22% in the chemotherapy arm.	possible to draw definitive conclusions based upon the results of these exploratory analyses. The comparator in KEYNOTE-042 is an active control, and there does not appear to be a detrimental effect on overall survival in the subpopulation of patients with NSCLC TPS 1-49%. Results of the exploratory analysis of OS in the TPS 1-49% subgroup will be included in product labeling to provide transparency and inform prescribers.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• In KEYNOTE-042, the most common adverse reactions in pembrolizumab-treated patients were fatigue, decreased appetite, dyspnea, cough, rash, constipation, diarrhea, nausea, hypothyroidism, pneumonia, pruritis, and weight loss. • There was a slightly higher incidence of serious AEs (41% vs 30%), AEs leading to death (11% vs 8%) and AEs leading to study drug discontinuation (19% vs 15%) in patients treated with pembrolizumab compared to patients treated with platinum-based chemotherapy, while the incidence of grade 3-5 AEs was slightly lower in the pembrolizumab arm compared to the chemotherapy arm (50% vs 57%). • An increased number of deaths due to unknown cause or sudden death was also reported in the pembrolizumab arm (11 patients [1.8%] vs 5 patients [0.8%]). • The overall safety profile of pembrolizumab reported in KEYNOTE-042 was, in general, consistent with the known safety profile based on the pembrolizumab monotherapy Reference Safety Database, with the exception of immune-related pneumonitis, which was reported at a higher frequency in KEYNOTE-042 (8.3% versus 3.4%). A higher incidence of pneumonitis was also noted in KEYNOTE-024 (7.8%), another study of pembrolizumab as a single agent in patients with NSCLC, relative to the pembrolizumab monotherapy Reference Safety Database.	The observed safety profile of pembrolizumab is acceptable when assessed in the context of the treatment of a life-threatening disease. Given the extensive safety data available for pembrolizumab in patients with solid tumors and specifically in patients with NSCLC, the 11% incidence of death due to AE, including a 1.8% incidence of death due to unknown cause/sudden death, in KEYNOTE-042 does not raise particular concerns, since this is an isolated finding in one study in a patient population in whom pembrolizumab has been extensively studied and the results of KEYNOTE-042 demonstrate an improvement in OS for pembrolizumab vs chemotherapy. The incidence of adverse reactions of death leading to treatment discontinuation of pembrolizumab observed in KEYNOTE-042 will be included in the KEYTRUDA Prescribing Information. The higher incidence of pneumonitis observed in the two clinical trials of pembrolizumab administered as a single agent in patients with previously untreated NSCLC compared to the pembrolizumab monotherapy RSD may be due to the differences in population, as patients with NSCLC have characteristics (e.g. smoking

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	APPEARS THIS WAY ON ORIGINAL	history) and underlying comorbid conditions (COPD, cardiovascular disease) that might predispose the population to drug-induced pulmonary toxicity. The increased incidence of pneumonitis observed in KEYNOTE-042 and KEYNOTE-024 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 was not submitted as part of this application.

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

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

	□	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			□	Patient reported outcome (PRO)	
			□	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

2.1.1. Analysis of Condition

Lung cancer is the leading cause of cancer and cancer-related mortality worldwide[1] and the leading cause of cancer-related deaths in the US[2]. NSCLC accounts for approximately 85% of all lung cancer cases. Of the patients with NSCLC, tumor histology is approximately 50% adenocarcinoma, 15% squamous, and 5% neuroendocrine, with the remaining classified as "not otherwise specified" histology[3].

The majority of patients present with locally advanced or metastatic disease which is incurable with currently available therapeutic options. Approximately 17.6% of all lung cancers present with clinical stage IIIB, and 40% present with stage IV disease. The anticipated 5-year survival for patients with clinical stage IIIB NSCLC is approximately 26% and is less than 5% for patients who present with clinical stage IV disease[4].

The current standard of care for patients with locally advanced, stage III, resectable disease is complete surgical resection followed by sequential or concurrent chemotherapy and radiation therapy, which has been shown to provide survival benefit in randomized controlled studies [5-9]. Durvalumab, a PD-L1 blocking antibody received marketing approval for the treatment of patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum -based chemotherapy and radiation therapy based on a statistically significant and clinically meaningful improvement in PFS at a pre-specified interim analysis for patients randomized to the durvalumab arm as compared with the placebo arm [HR 0.52 (95% CI 0.42, 0.65), p value < 0.0001]. OS data were not mature at the time of the interim PFS analysis[10].

Current available treatment options for the first-line treatment of patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation or metastatic squamous NSCLC and non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations include cytotoxic chemotherapy with cisplatin or carboplatin-based doublets and immunotherapy[5-6].

Several randomized controlled trials have demonstrated that adding a second or third drug improved tumor response and survival over single agent chemotherapy[11]. Platinum administered in combination with vinorelbine, paclitaxel, docetaxel, or gemcitabine yields similar improvements in survival[12, 13] In historic front-line platinum-based chemotherapy trials, the ORR ranged from 25% to 35%, time to progression ranged from 4 to 6 months, and median OS ranged from 8 to 10 months[12-14]. Both carboplatin/paclitaxel and carboplatin/albumin-

bound paclitaxel are acceptable initial cytotoxic therapy options for patients with squamous cell lung cancer.[15-17]

Pembrolizumab is currently approved for fist-line treatment of patients with metastatic NSCLC as a single agent for patients whose tumors have PD-L1 TPS ≥ 50% or in combination with chemotherapy regardless of PD-L1 expression.[18]

FDA approved pembrolizumab as a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression, regardless of histology, in October 2016 (BLA125514/S12). The approval was based on a statistically significant and clinically meaningful improvement in OS for patients randomized to the pembrolizumab arm compared to the chemotherapy arm [HR 0.60 (95% CI 0.41, 0.89), p value 0.005]. The indication is limited to patients with tumors with high PD-L1 expression (tumor proportion score [TPS] ≥ 50%).

FDA granted approval for pembrolizumab, in combination with pemetrexed and platinum chemotherapy, for use as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations, in May 2017 (accelerated approval, BLA125514/S16), with conversion to regular approval in September 2018 (BLA125514/S35 regular approval). Regular approval was based on an improvement in OS over investigator's choice of platinum-based chemotherapy [HR 0.49 (0.38, 0.64), p <0.0001].

In October 2018, approval was also granted for pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, for use in first-line treatment of patients with metastatic squamous NSCLC based on an improvement in OS over chemotherapy [(HR 0.64 (0.49, 0.85), P-value 0.0017] (BLA125514/S41).

Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (PC) received regular approval in March 2019 for the first-line treatment of patients with metastatic non-squamous NSCLC. The approval was based on a statistical improvement in OS over bevacizumab and PC [HR 0.78 (95% CI 90.64, 0.96), p-value 0.016].[18]

Necitumumab[20], an EGFR antagonist monoclonal antibody, received approval for use in combination with gemcitabine and cisplatin as first-line treatment of patients with metastatic squamous cell lung cancer in November 2015 (BLA125547). The approval was based on demonstration of a statistically significant improvement in OS (HR 0.84 (0.74, 0.96)] p=0.01). The median OS was 11.5 months in the necitumumab containing arm compared to 8.9 months in the chemotherapy arm.

Treatment options for patients with squamous NSCLC or non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations who progress after first-line therapy include single agent docetaxel[21], ramucirumab in combination with docetaxel[22] and check-point inhibitors nivolumab[23] or atezolizumab[19] and pembrolizumab[18] for patients whose tumors express PD-L1

(TPS ≥ 1%) NSCLC. Currently, there is no clinical data to support the use of ramucirumab, nivolumab or atezolizumab as a single-agent in the first-line setting for NSCLC.

2.2. Analysis of Current Treatment Options

The following table lists the products currently approved by the FDA for the first-line treatment of patients with advanced or metastatic NSCLC, along with indication and the efficacy data supporting approval.

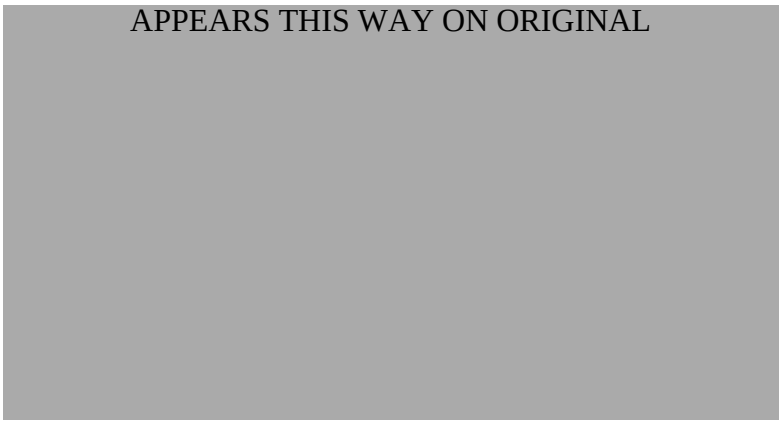


Table 1 Agents Approved for First-Line Advanced or Metastatic NSCLC

FOR FIRST-LINE TREATMENT		
FDA Approval Date	Product Indication	Studies and Approval Endpoints
JUN-1998	PACLITAXEL[24] In combination with cisplatin, for the first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation therapy	Paclitaxel + cisplatin vs etoposide • Median OS (mOS): 10.0 vs 7.4 months p=0.08 • Median TTP (mTTP): 4.9 vs 2.7 months p=0.004 • ORR: 35% vs 12% p<0.001
AUG-1998	GEMCITABINE[25] In combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced Stage IIIA or IIIB, or metastatic (Stage IV) NSCLC	1. Gemcitabine + cisplatin vs cisplatin • mOS: 9.0 (8.2-11.0) vs 7.6 (6.6-8.8) months p=0.008 • mTTP: 5.2 (4.2-5.7) vs 3.7 (3.0-4.3) months p=0.009 • ORR: 26% vs 10%; p<0.001 2. Gemcitabine + cisplatin vs etoposide + cisplatin • mOS: 8.7 vs 7.0 months p=0.18 • mTTP: 5.0 vs 4.1 months p=0.015 • ORR: 33% vs 14% p=0.01
DEC -1994 OCT- 2001	VINORELBINE[26] In combination with cisplatin or as single agent, for the first-line treatment of ambulatory patients with unresectable, advanced NSCLC	1. Vinorelbine + cisplatin vs cisplatin • mOS: 7.8 (6.9-9.6) vs 6.2 (5.4-7.7) months p=0.01 • ORR: 19% vs 8%; p< 0.001 2. Vinorelbine + cisplatin vs vindesine + cisplatin • Median OS: 9.2 (7.4-11.1) vs 7.4 (6.1-9.1) m, p=0.087 • ORR: 28% (22-35) vs 19% (14-25) p=0.03 3. Vinorelbine vs. 5-FU • mOS 30 wks vs. 22 wks; p =0.06 • ORR 11.1% vs. 3.5%
NOV- 2002	DOCETAXEL[27] In combination with cisplatin, unresectable, locally advanced or metastatic untreated NSCLC	Docetaxel + cisplatin vs vinorelbine + cisplatin • m OS: 10.9 vs 10.0 months; HR: 0.88 (0.74-1.06) p=0.122* • mTTP: 21.4 (19.3-24.6) vs 22.1 (18.1-25.6) weeks; p=NS^ • ORR: 31.6% (26.5-36.8) vs 24.4% (19.8- 29.2) p=NS

FOR FIRST-LINE TREATMENT		
FDA Approval Date	Product Indication	Studies and Approval Endpoints
OCT-2012	NAB-PACLITAXEL (505b2 pathway)[28] In combination with carboplatin, for the first-line treatment of locally advanced or metastatic NSCLC, in patients who are not candidates for curative surgery or radiation	Nab-paclitaxel + carboplatin vs paclitaxel + carboplatin • ORR: 33% (28.6-36.7) vs 25% (21.2- 28.5) p=0.005 • m DoR: 6.9 (5.6-8.0) vs 6.0 (5.6-7.1) months
APPROVAL DATE	INDICATION (AS A SINGLE AGENT)	STUDIES AND APPROVAL ENDPOINTS
OCT-2017	PEMBROLIZUMAB [18] As a single agent for first-line metastatic NSCLC whose tumors have high PD-L1 expression (TPS ≥50%), with no *EGFR* or *ALK* genomic tumor aberrations	Pembrolizumab vs. platinum doublet • mPFS = 10.3 vs. 6.0m [HR 0.5 (0.37, 0.68)] p<0.001 • mOS = 30.0 vs. 14.2 [HR 0.60 (0.41, 0.89)] p=0.005[#] • ORR = 45% (95% CI 37, 53) vs. 28% (95% CI 21, 36) p=0.001
APPROVAL DATE	INDICATION (IN COMBINATION WITH PLATINUM DOUBLET)	STUDIES AND APPROVAL ENDPOINTS
NOV-2015	NECITUMUMAB[20] In combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous non-small cell lung cancer	Necitumumab + gemcitabine/cisplatin vs. gemcitabine/cisplatin • OS = 11.5 vs. 9.9m [HR 0.84 (0.74, 0.96)] p=0.01 • PFS= 5.7m vs. 5.5m [HR 0.85 (0.74, 0.98)] p=0.02
MAY-2017 (AA) SEP-2018 (RA)	PEMBROLIZUMAB [18] in combination with pemetrexed and platinum chemotherapy for use as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations	Pembrolizumab + platinum/pemetrexed vs. platinum/pemetrexed • OS = NR[+] vs. 11.3 m HR 0.49 (0.38, 0.64), p <0.0001 • PFS= 8.8m vs. 4.9m [HR= 0.52 (0.43, 0.64), p<0.0001] • ORR 48% (43, 53) vs 19% (14, 25)
OCT- 2018	PEMBROLIZUMAB [18] in combination with carboplatin and either paclitaxel or nab-paclitaxel, for use in first-line treatment of patients with metastatic squamous NSCLC	Pembrolizumab + carboplatin/paclitaxel or nab-paclitaxel vs. carboplatin/paclitaxel or nab-paclitaxel • OS = 15.9m vs. 11.3m HR 0.64 (0.49, 0.85), p= 0.0017 • PFS = 6.4m vs. 4.8m [HR 0.56 (0.45, 0.70)] p <0.0001 • ORR 58% (48, 68) vs.35% (26, 45), p=0.0008

FOR FIRST-LINE TREATMENT		
FDA Approval Date	Product Indication	Studies and Approval Endpoints
MAR-2019	ATEZOLIZUMAB[18] In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGR or ALK genomic tumor aberrations	Atezolizumab + bevacizumab + paclitaxel/carboplatin (PC) vs. bevacizumab + PC vs. atezolizumab+ PC Atezolizumab + BPC vs. BPC • OS = 19.2 vs. 14.7 HR 0.78 (0.64, 0.96), p=0.016 • PFS 8.5m vs. 7.0m HR 0.71 (0.59, 0.85) p=0.0002 • ORR 55% (49, 60) vs. 42% (37, 48) Atezolizumab+ PC vs. BPC • OS=19.4 m vs. 14.7 HR 0.84 (0.72, 1.08), p=0.204 • PFS 6.7 vs. 7.0 m HR 0.94 (0.79, 1.13) p=0.522 • ORR 43% (38, 49) vs. 42% (37, 48)

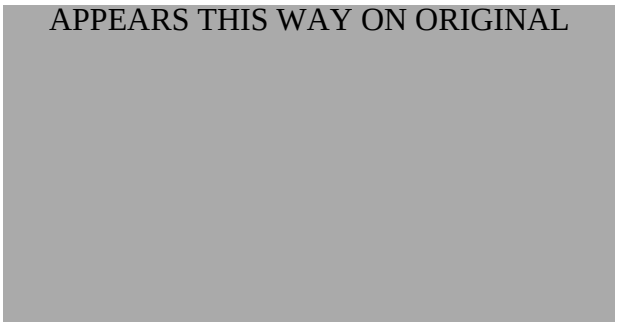
** The results of a further statistical analysis showed that at least (the lower bound of the 95% confidence interval) 62% of the known survival effect of vinorelbine when added to cisplatin (about a 2-month increase in median survival; Wozniak et al. JCO, 1998) was maintained (Taxotere PI).*

 # P-value is compared with 0.0118 of the allocated alpha for the interim analysis

^ NS= not significant

+ NR= not reached

3 Regulatory Background



3.1. U.S. Regulatory Actions and Marketing History

Pembrolizumab (KEYTRUDA®) is approved in the U.S. for the following indications[17]:

Melanoma

- For the treatment of patients with unresectable or metastatic melanoma. Approval for the melanoma indication was granted on September 4, 2014 (BLA125504/0 accelerated approval) and December 18, 2015 (BLA125504/S-04 and S-06 conversion to regular approval).
- For the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection (regular approval on February 15, 2019, BLA125514/S-40).

Non-Small Cell Lung Cancer

- 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 pembrolizumab. Accelerated approval was granted on October 2, 2015, for the TPS ≥50% population (BLA125504/S-05) and on October 24, 2016, regular approval was granted, with cut-point expanded to TPS ≥1% (BLA125504/S-08).
- For the 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 (regular approval granted on October 24, 2016, BLA125504/S-12).
- For treatment, in combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer, with no EGFR or ALK genomic tumor aberrations (accelerated approval granted on May 10, 2017, BLA125504/S-16; regular approval granted on August 20, 2018, BLA125514/S-35).
- For treatment, in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of patients with metastatic squamous, non-small cell lung cancer (regular approval granted on October 30, 2018, BLA125514/S-41).

Head and Neck Squamous Cell Cancer

- For the 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 was granted on August 5, 2016, BLA125504/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 was granted on March 14, 2017, BLA125504/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 (AA granted 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, BLA125514/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 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 (sBLA 125514/S43 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 granted on May 18, 2017, BLA125514/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 granted 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 [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 (accelerated approval granted on September 22, 2017, BLA 125514/S-24).

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 (CPS ≥ 1) as determined by an FDA-approved test (accelerated approval granted on June 12, 2018, BLA 125514/S-34).

Hepatocellular Carcinoma

- For the treatment of patients with HCC who have been previously treated with sorafenib (accelerated approval granted on November 9, 2018, BLA125514/S-42).

Merkel Cell Carcinoma (MCC)

- For the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (accelerated approval granted on December 19, 2018, BLA125514/S-45).

3.2. Summary of Presubmission/Submission Regulatory Activity

The pre-submission regulatory activity for pembrolizumab pertaining to supplements S-12 and S-47 are summarized below:

Table 2 Pre-Submission Regulatory Activity Related to Submission

DATE	MILESTONE
DEC-09-2010	New IND 110080 submitted for Protocol 001, the first-in-human (FIH) study with pembrolizumab, entitled: "Phase I Safety Study of MK-3475 in Patients with Solid Tumors"
APR-21-2016	The protocol for KEYNOTE-042 study was submitted to IND 116833. The study is a randomized, open-label study of pembrolizumab versus platinum-based chemotherapy in previously untreated patients with PD-L1 positive advanced or metastatic NSCLC. The study was ongoing outside the U.S. at the time of submission. Merck stated that the if results of the study are positive, Merck may submit an sBLA to expand the USPI to include patients with previously-untreated advanced or metastatic NSCLC whose tumors express PD-L1 with a TPS of ≥1%. The co-primary endpoints of the trial were OS in patients with TPS ≥50%, and in the ITT population (TPS ≥1%)
OCT-24-2016	Regular approval granted for pembrolizumab as a single agent for first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (TPS ≥ 50%) based on the results of KEYNOTE-024 (BLA125514/S-12). As a condition of approval, Merck agreed to fulfill the following post-marketing commitment: PMC # 3127-2: Submit the final report and efficacy datasets for Keynote-042, entitled: "A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer"
MAR-06-2017	FDA provided written comments to a Type C meeting request regarding

	Merck's proposal to revise the KEYNOTE-042 protocol to introduce a new cutpoint for PD-L1 (TPS ≥ 20%) and revise the co-primary endpoints of the trial to OS in patients with TPS ≥50%, in the ITT population (TPS ≥1%) and in the subgroup with TPS ≥ 20% FDA expressed concerns regarding Merck's proposal to evaluate efficacy of pembrolizumab in the subgroup with TPS ≥ 20% based on the PD-L1 expression scores already collected and stated that since randomization was not stratified based on TPS score ≥ or < 20% imbalances may exist between the treatment arms. FDA recommended that Merck provide sensitivity analyses to evaluate any potential imbalances between arms and stated that determination of the ability of the data to support a labeling claim for the subgroup with TPS ≥ 20% will be made at the time of review of the application. FDA recommended that the O'Brien-Fleming method be used for determining the efficacy boundaries for the interim analyses. Merck also informed FDA of their plan to revise the protocol to enroll additional Chinese patients to support a registration in China. Merck stated that the protocol revision will be implemented only in China and would extend the study beyond the planned study population for global analysis of safety and efficacy. FDA did not object to the plan to enroll additional Chinese patients and extend the study but requested that Merck, at the time of the sBLA submission, submit a proposal for a PMC to submit the final efficacy and safety results of the China extension study.
APR-25-2017	The KEYNOTE-042 protocol was revised to add the TPS≥ 20 cutpoint and revise the co-primary endpoints of the trial to OS in patients with TPS ≥50%, in the ITT population (TPS ≥1%) and in the subgroup with TPS ≥ 20%
DEC-05-2017 – DED-07-2017	Merck submitted a proposal to revise the statistical analysis plan (SAP) for KEYNOTE-042 to introduce a new interim analysis (IA2) and add a final analysis (FA). Merck stated that the change was necessary in order to preserve the data maturity originally planned for the final analysis since the rate of event accrual in KEYNOTE-042 was faster than expected FDA provided comments on December 7, 2017 and recommended that the final analysis be based on the pre-specified number of events. FDA stated that if Merck modified the design as proposed, Merck should be aware that FDA will evaluate the final results considering the difference between the pre-specified number of events and the actual observed number of events at the time of the final analysis. FDA stated that if there is a substantial difference between the observed number of events and the pre-specified number of events, the appropriate adjustments to the analysis will be a review issue. FDA also stated that in general, FDA recommends that the O'Brien Fleming method be used to adjust alpha for the interim analyses. However, since Merck needs to preserve the alpha already spent for the first interim analysis, the Hwang-Shih-Decani

	spending function was acceptable
JAN-12-2018	The KEYNOTE-042 protocol was revised to incorporate the changes to the SAP as proposed in the December 5, 2017 submission and to provided updates on guidelines for immune-related adverse events associated with pembrolizumab.
APR-09-2018	Merck informed the FDA of the results of the second interim analysis (IA2) performed after 1245 randomized patients were followed for 12.8 months. The OS was statistically significant for all three TPS cut-points. PFS had not reached statistical significance for any of the three cut-points. Merck proposed to submit an sBLA. FDA advised Merck to request a type B pre-sBLA meeting.
JUL-02-2018	Type B Written Response Only pre-sBLA meeting. The FDA agreed that the OS results of KEYNOTE-042 from IA2 can potentially permit a substantive review of an sBLA to support a labeling expansion for pembrolizumab to include patients with previously untreated, locally advanced or metastatic NSCLC whose tumor express PD-L1 with a TPS ≥ 1% with no EGFR or ALK genomic tumor aberrations. FDA recommended that the sBLA describe the treatment effects for OS across subgroups, including the exploratory analysis of the subgroup of patients with TPS ≥ 1% and < 50% and TPS ≥ 20% and < 50%. The sBLA should contain a discussion on why clinical benefit has been demonstrated in the absence of statistically significant effects on secondary endpoints. FDA agreed with the format and content of the sBLA proposed by Merck.
JUL-11-2018	sBLA submitted with request for Priority Review Designation
OCT-31-2018	FDA requested an updated survival analysis in the ITT population (TPS≥ 1%) and datasets with an additional 6 months of follow-up beyond the cutoff date of February 26, 2018. Merck was also asked to provide an updated survival analysis with an additional 6 months of follow-up beyond the cutoff date of February 26, 2018, and subset analyses presented as forest plots, in the subgroup of patients whose tumors have PD-L1 expression TPS 1-49%.
NOV-30-2018	Merck submitted the requested information and corresponding datasets.
DEC-16-2018	FDA issued an Efficacy Supplement Major Amendment letter, which extended the user fee goal date to April 11, 2019.

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 BLA125514/S-47 given the non-subjective nature of the primary endpoint (OS) and supportive results from prior clinical studies in metastatic NSCLC.

The pivotal study supporting this application is KEYNOTE-042, a randomized, open label, active-controlled, international study of pembrolizumab for patients with previously untreated, PD-L1 TPS ≥ 1, advanced or metastatic NSCLC. The study randomized 1274 patients across 196 investigational sites in 32 countries. The primary efficacy parameter is OS. Key secondary efficacy parameters are PFS and ORR. The study was monitored by an external Data Monitoring Committee. Data from a pre-specified interim analysis (IA2) was being submitted to support the application.

Using CDER's Clinical Investigator Site Selection Tool (CISST) version 2.5.10., sites have been ranked according to risk to patient safety and data integrity. A review of the primary efficacy parameter and major safety parameters (incidence and causes of death, serious adverse events, grade 3 -5 adverse events) and selected case narratives of the 10 clinical sites ranked as having the highest risk (i.e., sites 0377, 0238, 0271, 0185, 0034, 0012, 0190, 0288, 0211, and 0212) did not reveal unexpected findings that would impact on the overall findings of the trial. Therefore, clinical site inspections are not deemed to be necessary for this supplement.

4.2. Product Quality

No new CMC information was provided in the supplement S-47 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-47 application.

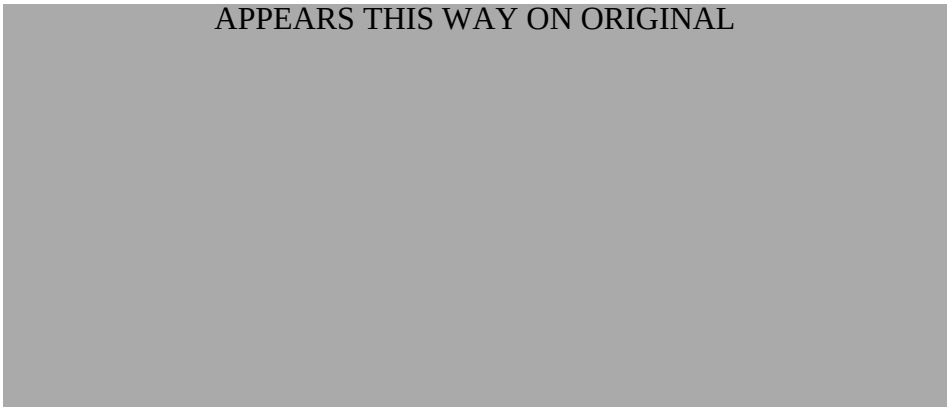
4.4. Devices and Companion Diagnostic Issues

On August 8, 2018, Dako North America, Inc submitted an sPMA (P150013/S012) for the PD-L1 IHC 22C3 pharmDx companion diagnostic device with a proposal to include data from KEYNOTE-042 in the device labeling. The PD-L1 IHC 22C3 pharmDx companion diagnostic device is currently approved as a companion diagnostic "for TPS 50% and TPS 1% for identifying NSCLC patients for treatment with KEYTRUDA".

sPMA # P150013/S012 is under review by the Division of Molecular Genetics and Pathology, OIR, CDRH. The MDUFA date for this sPMA is June 8, 2019. CDRH plans to take action concurrently with CDER on BLA125514/S-047 action date.

5 Nonclinical Pharmacology/Toxicology

No clinical pharmacology/toxicology data were submitted in the supplement S-47 application.



Clinical Pharmacology

No clinical pharmacology data were submitted in the supplement S-47 application.

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

One study was included in the sBLA submission to support a labeling expansion for pembrolizumab to include patients with previously untreated, locally advanced or metastatic NSCLC whose tumor express PD-L1 with a TPS ≥1% with no *EGFR* or *ALK* genomic tumor aberrations and to fulfill Postmarketing Commitment 3127-2 under BLA125514/S-012.

Table 3 Clinical Study to Support Efficacy and Safety of the Pembrolizumab

Study ID/Title	Trial Design	Population	Regimen/ schedule/ route	Study Endpoints	Patients Randomized	Countries
3475-042 Phase III Study of Efficacy and Safety Of Pembrolizumab (MK- 3475) Compared With Platinum Based Chemotherapy in Treatment-Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer	Multicenter, international randomized, open-label, active-controlled, parallel group	Males/females patients, at least 18 years of age with NSCLC who did not have an EGFR sensitizing mutation and were ALK translocation negative, whose tumors demonstrated PDL-1 expression, who have not received systemic anti-cancer therapy for their advanced or metastatic NSCLC.	Pembrolizumab Arm Pembrolizumab 200 mg IV Q3W until 35 cycles Chemotherapy Arm Carboplatin AUC 5 or 6 + paclitaxel 200 mg/m^2 IV Q3W x 4-6 cycles, followed by optional pemetrexed 500 mg/m^2 IV Q3W (non-squamous histologies only) until progression OR Carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 Q3W for 4-6 cycles, followed by optional pemetrexed 500 mg/m^2 IV Q3W until progression (non-squamous histologies only)	Primary OS Secondary: PFS and ORR	Pembrolizumab 637 subjects Chemotherapy 637 subjects	Argentina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Estonia, Guatemala, Hongkong, Hungary, Japan, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russia, South Africa, South Korea, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, Vietnam.

6.2. Review Strategy

The key data submitted to support this sBLA are the efficacy and safety results of Interim Analysis 2 (IA2) from 1274 patients randomized in KEYNOTE-042, with the data cut-off date of February 26, 2018. On October 31, 2018, following an initial review of the S-47 submission, FDA requested additional efficacy and safety data to support the labeling expansion proposal for pembrolizumab to include patients with previously untreated, locally advanced or metastatic NSCLC whose tumor express PD-L1 with a TPS ≥1% with no *EGFR* or *ALK* genomic tumor aberrations

During the review, concern was raised by the clinical reviewer that there was no clear evidence of benefit observed in the pre-defined subgroup of patients with tumors with TPS 1-49%. The review team also noted that there were no clinically meaningful differences in PFS or ORR between the pembrolizumab and the control arm in the ITT population (TPS ≥1%) that support the treatment effects observed on OS (improvement in OS) with pembrolizumab. FDA requested the following additional information and datasets in order to further assess outcomes in the ITT population and the subgroup of patients with TPS 1-49%:

1. Provide an updated survival analysis in the ITT population (TPS ≥1%) and corresponding datasets with an additional 6 months of follow-up beyond cutoff date of February 26, 2018 and provide an updated survival analysis with an additional 6 months of follow-up beyond cutoff date of February 26, 2018 and subset analyses presented as forest plots in the subgroup of patients whose tumors have PD-L1 expression TPS 1-49%.
2. Provide side-by-side comparison of the baseline demographic and prognostic characteristics for patients in the KEYNOTE-024 trial and the subpopulation of patients in KEYNOTE-042 with TPS≥50%.
3. Resubmit data from the KEYNOTE-010 study for efficacy endpoints. Provide subgroup analyses of OS, PFS and ORR in the following populations: ITT, TPS 1-49% subgroup and TPS ≥ 50% subgroup.
4. Provide a side-by- side comparison of the baseline demographic and prognostic characteristics for patients in KEYNOTE-042 and KEYNOTE-010 with TPS ≥ 1-49 %.
5. Provide an integrated risk: benefit assessment and thorough discussion for the differences observed in efficacy results between KN-042, KN-024, and KN-010 for the following populations/subgroups based on TPS expression: 1) TPS ≥ 1%, 2) TPS 1-49% and 3) TPS ≥ 50%.
6. In addition, for KEYNOTE-042 provide a side-by-side comparison for the TPS≥1%, 1-49%, and ≥50% populations for: patient disposition, baseline demographics, baseline prognostic disease characteristics, and median drug exposure.
7. For KEYNOTE-042 submit tables for subjects with AEs by MedDRA SOC and PT, by treatment arm for Grade 3-5 AEs, SAEs, AEs resulting in death, AEs resulting in treatment discontinuation and interruption.
8. Provide a dataset containing the protocol deviations by investigational site.

Merck submitted the requested information and datasets on November 20, 2018. On December 16, 2018, a major amendment was issued which extended the user fee goal date to April 11, 2019.

To assess the reliability and quality of the data, the clinical reviewer conducted random cross validation of datasets with CRF forms. Data sets, clinical study reports, case report forms, case narratives, Data Monitoring Committee reports, and all supportive analyses submitted by the Merck at the time of the initial review and the November 30, 2018 amendment.

The primary efficacy analysis was performed based on the results from IA2 that was pre-specified to be performed after 38 months of follow-up since the first patient's randomization date. Efficacy analyses were performed for the primary and secondary endpoints of OS, PFS and ORR in each of the analysis populations defined based on tumor PD-L1 status of TPS ≥ 1%, TPS ≥ 20%, TPS ≥ 50% that consisted of 1254, 818 and 599 patients, respectively. Efficacy was also assessed in the pre-defined subgroup (used for stratification) of patients with tumors with TPS 1-49%, given Merck's proposal to expand labeling to include this population. An additional 6 months of follow-up data was also assessed for OS in TPS ≥ 1%, TPS ≥ 20%, TPS ≥ 50%, and TPS 1-49%.

The review of safety was focused on data submitted for the 1251 patients enrolled in KEYNOTE-042 who received at least one dose of study treatment (636 in the pembrolizumab arm and 615 in the chemotherapy arm). Safety data from KEYNOTE-042 was compared to the data from KEYNOTE-024, which enrolled a similar population of patients with previously untreated metastatic NSCLC, as well as the pembrolizumab monotherapy Reference Safety Database and Merck's pembrolizumab Cumulative Running Safety Dataset.

7 Statistical and Clinical and Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. KEYNOTE-042 (P042V01MK3475)

Protocol Title: "A Randomized, Open Label, Phase III Study of Overall Survival comparing Pembrolizumab (MK-3475) versus Platinum based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042)"

Trial Design

KEYNOTE-042 is an open-label, randomized, international, active-controlled study comparing the safety and efficacy of pembrolizumab with platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic, PD-L1 positive (TPS ≥ 1%) NSCLC with no EGFR or ALK genomic tumor aberrations. Randomization is stratified by ECOG performance status (0 vs. 1), histology (squamous vs. non-squamous), geographic region (east Asia vs. non-East Asia), and tumor PD-L1 expression (TPS ≥ 50% vs. TPS 1-49%). Eligible patients were randomly assigned in a 1:1 ratio to two treatment arms:

Experimental

- Pembrolizumab 200 mg IV every 3 weeks until progression or a maximum of 35 doses

Control

- Carboplatin AUC 5 or 6 IV and paclitaxel 200 mg/m^2 IV on Day 1 of each 21-day cycle for 4 to 6 cycles, followed by optional pemetrexed 500 mg/m^2 IV every 3 weeks (non-squamous histologies only) until progression

OR

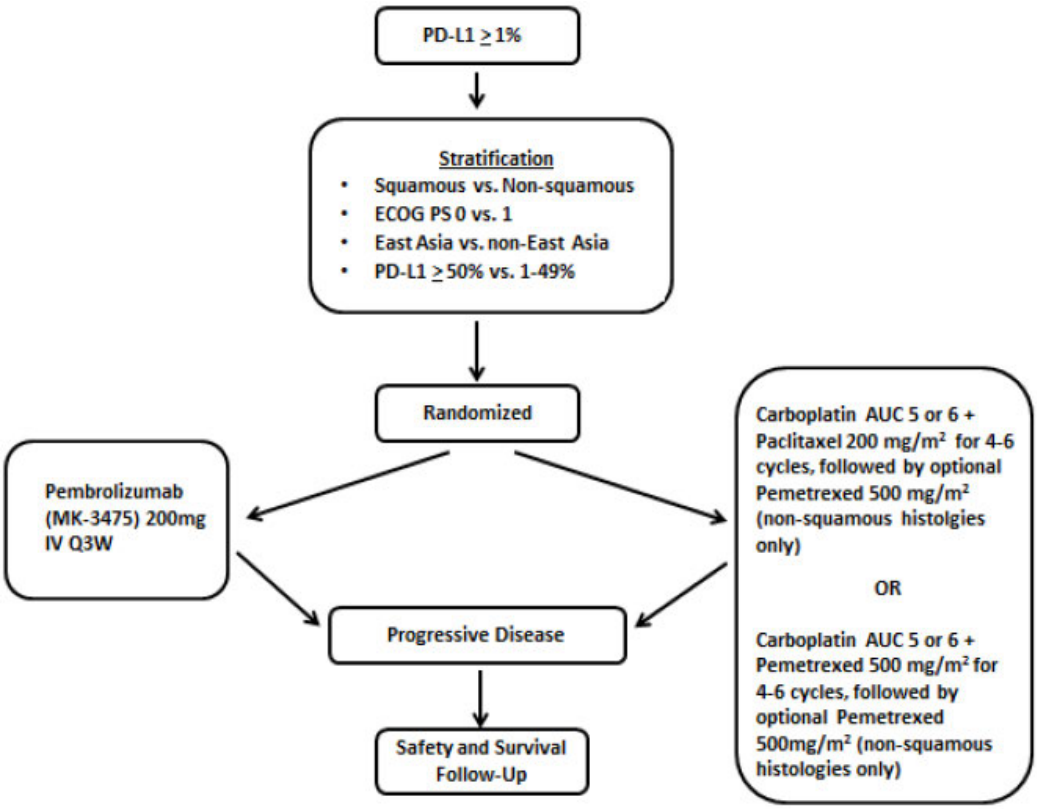
- Carboplatin AUC 5 or 6 IV and pemetrexed 500 mg/m^2 on Day 1 of each 21-day cycle for 4-6 cycles, followed by optional pemetrexed 500 mg/m^2 IV every 3 weeks (non-squamous histologies only) until progression

The choice of paclitaxel or pemetrexed was determined by the investigator prior to randomization. Only patients with non-squamous histology may receive pemetrexed. Treatment with pembrolizumab is 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 35 treatments. Patients who experience RECIST-defined disease progression are eligible to continue pembrolizumab if the patient is clinically stable and deriving clinical benefit as determined by the investigator. Pembrolizumab-treated subjects, who achieve a confirmed CR or who stop trial treatment after 35 administrations of study medication for reasons other than disease progression or intolerability, may consider stopping trial treatment. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 17 additional cycles.

Patients are to be evaluated radiographically for tumor status every 9 weeks and followed by telephone contacts every 2 months during the survival follow-up phase of the study. All imaging obtained on study are to be submitted for central independent radiologist review.

The study schema is shown in the following figure.

Figure 1 KEYNOTE-042 Study Schema



Source: MK-3475-042-06 protocol, Trial Diagram

Study Endpoints

Co-primary efficacy endpoints

- Overall survival (OS) in TPS ≥ 50%, TPS ≥ 20%, and TPS ≥ 1%.
  OS is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the analysis will be censored at the date of the last known contact.

Key Secondary Endpoint

- Progression-free survival (PFS) in TPS ≥ 50%, TPS ≥ 20%, and TPS ≥ 1%.

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent radiologists' assessment or death due to any cause, whichever occurs first. Censoring rules for PFS in different scenarios are defined as below.

Scenario	Censoring Rule; Date
No Event (i.e., No disease progression and no death); No subsequent anticancer treatment	Censored; Date of last disease assessment
No event; Subsequent anticancer treatment initiated	Censored; Date of last disease assessment before new anticancer treatment
PD or death documented after ≤1 missed disease assessment	Progressed; Date of documented PD or death
PD or death documented after ≥2 missed disease assessments	Progressed; Date of documented PD or death

- Overall response rate (ORR) in TPS ≥ 50%, TPS ≥ 20%, and TPS ≥ 1%.
  ORR is defined as the proportion of the subjects in the analysis population who have a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 based on blinded independent radiologists' assessment.

  ORR was further characterized by duration of response (DoR), 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.

Other secondary endpoints

- Safety and tolerability in patients with NSCLC TPS≥ 1%.

Reviewer's comment: RECIST v1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ was used to characterize PFS and ORR.

Statistical Analysis Plan

The primary analysis populations were the intent-to-treat (ITT) population and in subgroups with NSCLC TPS ≥ 50% or NSCLC TPS ≥ 20%.

Primary Analysis methods

- OS: A stratified log-rank test was used to test for the difference between treatment arms. The hazard ratio and the corresponding 95% confidence intervals were estimated

using stratified cox model with Efron's tie handling method. Kaplan-Meier method will be used to estimate the medians and the survival curves.

- PFS: PFS is analyzed using the same analysis methods used for OS.
- ORR: A stratified Miettinen and Nurminen method with weights proportional to the stratum size was used.

Interim Analyses

Two interim analyses were planned in this study. A data monitoring committee was appointed to overlook the data and perform the overall benefit-risk assessment. The first interim analysis was event driven and the second interim and final analyses were based on calendar time.

1. Interim Analysis 1 (IA-1): This interim analysis was planned to be performed after observing at least 250 deaths in the NSCLC TPS ≥50% and at least 6 months of minimum follow-up for last randomized patient. All the efficacy endpoints were planned to be tested sequentially at this interim analysis.
2. Interim Analysis 2 (IA-2): This interim analysis was to be performed after about 38 months after first patient randomized. By this time, approximately 340 deaths were projected to occur in the patients with NSCLC TPS ≥50%.
3. Final analysis (FA): The final analysis was to be performed about 45 months after the first patient randomized. At this time, approximately 398 deaths are projected to occur in patients with TPS ≥50%.

Multiplicity

The overall type I error is strongly controlled at 2.5% (one-sided) for multiple endpoints and for the two interim looks.

Multiple endpoints: The hypotheses for efficacy endpoints are tested sequentially in the following order, at a significance level obtained after adjusting for two interim looks, provided the hypotheses preceding any given hypothesis is significant.

- OS in TPS ≥ 50%
- OS in TPS ≥ 20%
- OS in TPS ≥ 1%
- PFS in TPS ≥ 50%
- PFS in TPS ≥ 20%
- PFS in TPS ≥ 1%
- ORR in TPS ≥ 50%
- ORR in TPS ≥ 20%
- ORR in TPS ≥ 1%

Interim looks: Before amendment #6, the study was designed to have only one interim analysis. Therefore, using the Lan-DeMets alpha spending function with O'Brien-Fleming boundary method and based on the 293 observed deaths, the alpha level spent for the first interim analysis was 0.01576 (one-sided).

During amendment #6, an additional interim analysis (IA-2) to occur about 38 months after trial start was added to the statistical analysis plan and the alpha spending function used to calculate the stopping boundaries for IA-2 and final analysis was changed to Hwang-Shih-DeCani alpha spending function with the gamma parameter -0.9023. Under this revised alpha allocation plan, the alpha actually spent at IA1 will be kept intact and the re-allocation will only be applied to the remaining unspent alpha.

Table 4 below provides the stopping boundaries based on the pre-specified number of deaths and calendar time for the two interim and final analyses. The actual stopping boundaries will be calculated based on the observed number of deaths at each analysis timepoint and will be presented in the study results section of this review.

Table 4: Decision rules for primary OS hypotheses at pre-specified interim and final analyses

Analysis	Targeted Number of Events/Targeted Study Time	Cumulative Alpha	Efficacy Bars in Subjects with TPS≥50%[1]	Efficacy Bars in Subjects with TPS≥20% (if OS positive in TPS≥50%)[1]	Efficacy Bars in Subjects with TPS≥1% (if OS positive in both TPS≥50% and TPS≥20%)[1]
IA1	• At least 250 deaths observed in two arms in the subjects with TPS≥50% AND at least 6 month after last subject is enrolled (~32 months after study start) • At IA1, 293 deaths were observed in the subjects with TPS≥50%	• 1.576%	• (One-sided) p-value for OS < 1.576%, i.e., observed HR < ~0.78 (~3.7-month improvement)	• (One-sided) p-value for OS < 1.576%, i.e., observed HR < ~0.81 (~3.1-month improvement)	• (One-sided) p-value for OS < 1.576%, i.e., an observed HR < ~0.85 (2.3-month improvement)
IA2	• About 38 months after study start[2]	• 1.94%	• (One-sided) p-value for OS < 1.233%, i.e., observed HR < ~0.78 (3.6-month improvement)	• (One-sided) p-value for OS < 1.197%, i.e., observed HR < ~0.81 (3.0-month improvement)	• (One-sided) p-value for OS < 1.228%, i.e., observed HR < ~0.85 (2.3-month improvement)
FA	• About 45 months after study start[2]	• 2.5%	• (One-sided) p-value for OS < 1.521%, i.e., observed HR < ~0.80 (3.2-month improvement)	• (One-sided) p-value for OS < 1.497%, i.e., observed HR < ~0.83 (2.6-month improvement)	• (One-sided) p-value for OS < 1.556%, i.e., observed HR < ~0.87 (2.0-month improvement)

[1] Nominal alpha and boundaries will be re-calculated if the actual number of events at analyses is altered from the expected. In this hypothetical scenario, the numbers of death at IA2 and final are assumed to be the same as the projected, i.e., 340 and 398 in the subjects with TPS≥50%, 474 and 557 in the subjects with TPS≥20%, and 780 and 900 in the subjects with TPS≥1%. The actual boundaries will need to be recalculated based on the observed number of deaths.
[2] Study start is defined as the date when the first subject was randomized.

Source: Table-11 from protocol amendment-7

Sample Size

The sample size for this study is driven by OS hypothesis in the TPS ≥ 50% and TPS ≥ 1% analysis populations. A total of 530 patients in the TPS ≥ 50% and 1240 in TPS ≥ 1% were planned to be randomized based on the following assumptions:

- Median OS of 13 months in the control arm,
- A piece-wise hazard ratio of 0.65 in the subjects with TPS ≥ 50%,
- An enrollment period of approximately 26 months and a minimum follow-up time of 19 months,

- A drop-out rate of 0.003 per month for OS.

In the TPS ≥ 50% group, assuming a piece-wise OS hazard ratio (HR) of 0.65, a total of 398 deaths were needed to show a statistically significant difference in OS between the treatment and control arm based on 0.025 (one-sided) level stratified log-rank test. With 398 deaths, the study has approximately 99% power. Approximately 530 patients were to be randomized and followed for a minimum of 19 months to observe 398 deaths. However, the final analysis for OS is based on calendar time and will occur about 45 months after the start of the study, irrespective of the actual number of deaths equal to 398.

In the TPS ≥ 20% and TPS ≥ 1% groups, the expected number of deaths at the final analysis is projected to be 557 and 900 respectively. With 557 deaths, the study has approximately 98% power to detect a piecewise OS hazard ratio of 0.8 before month 6 and 0.64 after month 6 at alpha=2.5% (one-sided) in the subjects with TPS ≥ 20%. With 900 deaths, the study has approximately 91% power to detect a piecewise OS hazard ratio of 0.92 by month 6 and 0.73 after month 6 at alpha=2.5% (one-sided) in the subjects with TPS ≥ 1%.

Subgroup Analyses
Pre-specified exploratory subgroup analyses of OS in ITT population (TPS ≥ 1%) were conducted in the subgroups described below.

- Age category (< 65, ≥ 65)
- Gender (Male, Female)
- Race (white, Asian)
- Region (Asia, Non-East Asia)
- Smoking status (Current, Former vs Never)
- ECOG performance status at baseline (o vs 1)
- Histology (squamous vs Non-Squamous)
- Choice of chemotherapy (Paclitaxel and Carboplatin vs Pemetrexed and Carboplatin)
- Disease stage (Advance vs Metastatic)
- History of brain metastases (Yes vs No)

Protocol Amendments

The KEYNOTE-042 protocol underwent three global and four country-specific amendments. Key revisions are summarized below:

- Initial protocol (June 18, 2014)
- Country-specific amendment # 1 (August 28, 2014): Benefit and Risk section added to the protocol to comply with regulatory requirements by the MPA in Sweden.
- Global amendment # 2 (December 21, 2015):
    - Primary objective of the study updated to a co-primary endpoint of overall

survival in PD-L1 strongly positive subpopulation and the overall PD-L1 positive population; update was based on new efficacy data from KEYNOTE-010
- Additional changes to update and clarify inclusion/exclusion criteria, assessment schedule, end-of the study, update safety and efficacy data

- Global amendment # 3 (April 12, 2017)
  - Added intermediate TPS ≥ 20% to the primary, secondary, and exploratory objectives hypotheses and analyses with step-down to TPS ≥ 1%.
  - Updates to the Statistical Analysis Plan due to update in endpoints with inclusion of TPS≥ 20%
  - ORR elevated to secondary objective as follows: Evaluation of ORR by RECIST 1.1 by central independent radiologists' review in subjects with TPS≥50%, ≥ 20%, and ≥ 1% NSCLC treated with pembrolizumab compared to SOC chemotherapy.
  - Number of interim analyses changed from two to one; timing and number of events for analysis updated.
  - Multiplicity adjustment exponential spending function changed to O'Brien-Fleming per FDA's feedback
  - Interim analysis boundaries updated according to O'Brien-Fleming per FDA's feedback
  - Baseline characteristics to be summarized by treatment group in patients with TPS≥ 50%, TPS≥20%, and TPS≥ 1%, respectively, to evaluate possible imbalance, per FDA's feedback.
- Country-specific amendment # 4 (December 21, 2016): to extend the enrollment period beyond the global study in China to achieve required exposure and number of events to investigate efficacy and safety of pembrolizumab as first-line treatment in Chinese patients with NSCLC.
- Country-specific amendment # 5 (June 1, 2017): to revise the SAP to update the number of events and timing of analysis for Global Study and China Extension. Patients from China randomized after completion of enrollment in the global study will not be included in the analyses of the global study.
- Global amendment # 6 (January 9, 2018):
  - SAP changed to add an additional interim analysis, based on calendar time to occur about 38 months after trial start, in order to maintain sufficient minimal follow-up duration and desired trial power in patients with TPS≥ 1%
  - Changed the alpha spending to be based on the calendar time of analysis. Updated trial powers based on the revised alpha allocation and analysis timing
  - PFS hypotheses will be tested at both interim analyses and final analysis.
  - PK and anti-pembrolizumab antibodies are removed from the trial flow chart since sufficient data has allowed adequate characterization of the clinical pharmacology of pembrolizumab
  - The pembrolizumab dose modification guidelines are expanded to cover supportive care, monitoring and follow-up. Risk of myocarditis was added.
- Country-specific amendment # 7 (January 9, 2018): same changes as amendment # 6.

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. This reviewer was able to perform the review using the data submitted.

7.1.2. Study Results

KEYNOTE-042

First Patient: November 21, 2014
Study Status: Ongoing
Data Cutoff date: February 26, 2018
Investigational sites: 196 investigational sites in 32 countries ex-US

Compliance with Good Clinical Practices

The submission contains a statement indicating that KEYNOTE-042 was conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the study was performed.

Financial Disclosure

Merck submitted Certification of Financial Interests and Arrangement of Clinical Investigators (Form 3465) for KEYNOTE-042 with a list of 1476 investigators and sub-investigators who provided information that they had no financial conflicts of interest as defined in 21 CFR54.2(1)(b).

Merck reported that one investigator (b) (6) clinical site (b) (6) (b) (6) of a Merck Employee (b) (6) Financial disclosure was not available for one investigator, (b) (6) (site (b) (6)), despite due diligence attempts made by Merck. The investigator reportedly left the site.

The financial disclosure information submitted for the KEYNOTE-042 trial is summarized in Appendix, Section 18.2 of this document.

Study Population
The Intent-to-Treat (ITT) population consists of 1274 patients with NSCLC with tumor PD-L1 expression TPS ≥ 1% (637 randomized to the pembrolizumab arm and 637 randomized to the chemotherapy arm). Of the 1274 patients, 818 (64.2%) had tumor with PD-L1 TPS ≥ 20% and 599 (47%) had PD-L1 TPS ≥ 50%. More than half of the patients (52.9%) had PD-L1 TPS 1-49%. The safety population consists of 1251 patients who received at least one dose of study drug. A

total of 23 patients who were randomized did not receive study treatment (one patient in the pembrolizumab arm and 22 patients in the chemotherapy arm).

Table 5 KEYNOTE-042 Study Population

Study Population	Total N (%)	Pembrolizumab N	Chemotherapy N
ITT	1274 (100)	637	637
TPS ≥ 1%	1274 (100)	637	637
TPS ≥ 20%	818 (64.2)	413	405
TPS 1-49%	675 (52.9)	338	337
TPS ≥ 50%	599 (47.0)	299	300
Safety Population	1251 (98.2)	636	615
Randomized but did not receive study drug	23 (1.8)	1	22

Source: BLA125514/S047, aDAM, adsl.xpt

KEYNOTE-042 was conducted entirely outside the U.S. A total of 1274 patients were randomized in 32 countries across Eastern Europe, including Russia and Ukraine (37%), East Asia (29%), Latin America (21%) and others, including Canada, Turkey and South Africa (13%). A list of the countries and number of patients enrolled in each country is provided in Table 6. The following countries enrolled more that 5% of the ITT population: Brazil (8.9%), Turkey (8.6%), Japan (7.3%), China (7.2%), and Ukraine, Poland and Russia (7.1% each).

Table 6 KEYNOTE-042 Patient Enrollment by Country

Country	Pembrolizumab N=637 (%)	Chemotherapy N=637 (%)	Total 1274 (100%)
Brazil	56 (4.4)	57 (4.5)	113 (8.9)
Turkey	62 (4.9)	47 (4.9)	109 (8.6)
Japan	47 (3.7)	46 (3.6)	93 (7.3)
China	44 (3.5)	48(3.8)	92 (7.2)
Ukraine	45 (3.5)	46 (3.6)	91 (7.1)
Poland	48 (3.8)	42 (3.3)	90 (7.1)
Russian Federation	39 (3.1)	51 (4.0)	90 (7.1)
Thailand	23 (1.8)	29 (2.3)	52 (4.1)
Latvia	28 (2.2)	21 (1.7)	49 (3.8)
Chile	13 (1.0)	29 (2.3)	41 (3.3)
Argentina	22 (1.7)	18 (1.4)	40 (3.1)
Czech Republic	18 (1.4)	22 (1.7)	40 (3.1)
Korea, Republic of	21 (1.7)	18 (1.4)	39 (3.1)
Malaysia	14 (1.1)	21 (1.7)	35(2.8)
South Africa	11 (0.9)	23 (1.8)	34 (2.7)
Mexico	17 (1.3)	15 (1.2)	32 (2.5)
Lithuania	15 (1.2)	15 (1.2)	30 (2.5)
Romania	16 (1.3)	10 (0.8)	26(2.4)
Canada	10 (0.8)	15 (1.2)	25 (2.0)
Peru	14 (1.1)	9 (0.7)	23(1.9)
Philippines	13 (1.0)	9 (0.7)	22 (1.7)
Taiwan	14 (1.1)	8 (0.6)	22 (1.7)
Switzerland	9 (0.7)	7 (0.6)	16 (1.3)
Hong Kong	7 (0.6)	6 (0.5)	13 (1.0)
Estonia	6 (0.5)	6 (0.5)	12 (0.9)
Portugal	4 (0.3)	8 (0.6)	12 (0.9)
Guatemala	8 (0.6)	3 (0.2)	11 (0.9)
Colombia	6 (0.5)	2 (0.2)	8 (0.6)
Sweden	3 (0.2)	4 (0.3)	7 (0.6)
Hungary	2 (0.2)	1 (0.1)	3 (0.2)
Bulgaria	1 (0.1)	1 (0.1)	2 (0.2)
Viet Nam	2 (0.2)	0	2 (0.2)

In KEYNOTE-042, none of the 1274 patients were enrolled at an investigational site in the US. Merck was asked to provide justification for extrapolation of the data from foreign sites to the US considering the regulations as described in the 21 CFR 312.120, 21 CFR 314.106 and FDA guidance, titled International Conference on Harmonization E5 Guidance on Ethnic Factors in the Acceptability of Foreign Clinical data.

Merck provided reference literature indicating that disease characteristics and the natural history of NSCLC are generally similar across the global population and that the KEYNOTE-042

study population was similar to other NSCLC trials involving the US population. Merck states that the approach to the diagnosis, staging and management is similar across the US and the regions in which KEYNOTE-042 was conducted. Clinical pharmacology information was provided to support the assertion that pembrolizumab PK is similar across tumor types, race and region.

Reviewer's comment: Merck's justification for extrapolation of the KEYNOTE-042 data to the US population was reviewed and considered to be acceptable to support extrapolation.

Patient Disposition

KEYNOTE-042 patient disposition at the time of the data cutoff date (by PD-L1 TPS cutpoint) is summarized in Table 7. At the time of the data cutoff, in the overall (TPS ≥ 1%) population, more patients in the chemotherapy arm had discontinued from the study compared to the pembrolizumab arm (71.3% versus 58.4%). The most common reason for discontinuation from study was death (57.8% in the chemotherapy arm and 39.5% in the pembrolizumab arm). More patients in the pembrolizumab arm discontinued study due to an AE (18.5% versus 11.0%).

Table 7 KEYNOTE-042 Patient Disposition by PDL-1 TPS ≥ 1%, TPS 1-49% and TPS ≥ 50%*

	TPS ≥ 1%		TPS 1-49%		TPS ≥50%	
Study Population	Pembrolizumab N =637	Chemotherapy N = 637	Pembrolizumab N =338	Chemotherapy N = 337	Pembrolizumab N =299	Chemotherapy N = 300
Study Status						
Status not recorded	265 (42)	183 (29)	123 (36)	89 (26)	142 (48)	94 (31)
Discontinued from Study	372 (58)	454 (71)	215 (64)	248 (74)	157 (53)	206 (69)
- Due to an AE	118 (19)	70 (11)	74 (22)	37 (11)	44 (15)	33 (11)
- Died	252 (40)	368 (58)	140 (41)	202 (60)	112 (38)	166 (55)
- Withdraw by patient/guardian	2 (0.3)	14 (2)	1 (0.3)	8 (2.4)	1 (0.3)	6 (2.0)
- Lost to follow-up	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Study drug status						
Status not recorded	87 (14)	30 (4.9)	33 (10)	10 (3.0)	54 (18)	20 (7.0)
Completed	42 (7)	160 (26)	15 (4.4)	88 (27)	27 (9)	72 (25)
Discontinued	507 (80)	425 (69)	290 (86)	231 (70)	217 (73)	194 (68)
- Due to an AE	127 (20)	92 (15)	66 (20)	47 (14)	61 (21)	45 (16)
- Disease progression	366 (58)	300 (49)	217 (64)	167 (51)	149 (50)	133 (47)
- Patient's request	12 (2)	21 (3)	7 (2.1)	11 (3.3)	5 (1.7)	10 (3.5)
- Physician's decision	2 (0.3)	11 (2)	0 (0.0	6 (1.8)	2 (0.7)	5 (1.7)
- Protocol violation	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Source: BLA125514/S047, ADaM, adsl.xpt and adapted Merck's table 26, Response to FDA Comments submitted on November 30, 2018

** Data cutoff date: February 26, 2018*

Protocol Violations/Deviations

Overall, 224 instances of protocol deviation were reported during the conduct of KEYNOTE-042 study at the time of IA2: 120 deviations in the 637 patients enrolled in the pembrolizumab arm and 104 deviations in the 637 patients in the chemotherapy arm.

The most common protocol deviations were in the consent form category (60% of all deviations), including patients without updated consent following a significant safety change to the risk language following document site/regional approval and in the safety reporting category (36% of all reported deviations), and in the safety reporting category (30%), including safety events not reported per the timelines outlined in the protocol.

Table 8 Protocol Deviation Categories per Treatment Arm

	Pembrolizumab Arm	Chemotherapy Arm	
Number of protocol deviations	N=120	N=104	Total = 224
Deviation Category			
- Informed Consent Form	73 (60)	62 (60)	135 (60)
- Safety Reporting	35 (30)	37 (36)	92 (36)
- Inclusion/Exclusion	5 (4)	1 (1)	6 (5)
- Trial Procedures	4 (3)	1 (1)	5 (4)
- Discontinuation Criteria	3 (3)	-	3 (2)
- Study intervention	-	3 (3)	3 (1)

Source: BLA125514/S-47: ADaM dataset addv.xpt

In KEYNOTE-042, "important" deviations are pre-defined as any protocol deviation that may significantly impact the quality or integrity of key study data or that may significantly affect a patient's safety, well-being or patient's rights. The following important deviations were identified during the review:

Pembrolizumab Arm:

- *Patient ID* (b) (6) *experienced a grade 3 drug-related ALT increase between Cycles 6 and 7, should have been permanently discontinued but received pembrolizumab at the visit Cycle 7.*
- *Patient ID* (b) (6) *experienced a Grade 3 liver enzyme elevation, should have been permanently discontinued but was administered pembrolizumab at the visit Cycle 5.*
- *Patient ID* (b) (6) *was inadvertently treated for Cycle 13 following a drug-related grade 3 ALT increase. The site was re-trained.*
- *Patient ID* (b) (6) *had a history of rheumatoid arthritis (RA) that was not active and no systemic treatment was administered or required at the time of screening. Patient had previously received methotrexate and methylprednisolone for the RA.*

- *Patient ID* (b) (6) *had a history of RA for 5 years, patients was being treated with methotrexate. History of RA was not reported at the time of enrollment.*
- *Patient ID* (b) (6) *was identified as having EGFR status "could not be determined", and not negative as per protocol eligibility.*
- *Patient ID* (b) (6) *had a serum creatinine level greater than 1.5 x ULN and creatinine clearance level not greater than 50mL/min.*
- *Patient ID* (b) (6) *- screening Lab was not taken.*

Chemotherapy Arm

- *Patient ID* (b) (6) *received one dose of docetaxel prior to study entry.*
- *Patient ID* (b) (6) *: the wrong NSCLC histology was entered into IVRS leading to patient being mis-stratified and leading to a patient with squamous tumor histology being assigned to pemetrexed maintenance chemotherapy*
- *Patient ID* (b) (6) *: patient received incorrect study treatment: site prescribed pemetrexed maintenance for a patient with squamous cell cancer.*
- *Patient ID* (b) (6) *: patient received three infusions of SOC (paclitaxel, carboplatin and pemetrexed) in same day due to investigator mistake.*

Based on the information provided by Merck, once deviations were identified, the trial monitor discussed the finding with the study team and the site staff were re-trained on the matter.

Reviewer's Comment: The proportions of deviations were, in general, similar between the treatment arms, and the deviations identified in the review are unlikely to impact on KEYNOTE-042's efficacy results.

Table of Demographic Characteristics

Table 9 and Table 10 below summarizes the demographics and baseline disease characteristics of the ITT population. Overall, the patients' demographic and baseline disease characteristics were similar between the treatment arms for all the factors identified below.

Table 9 Demographics and Baseline Characteristics in ITT (TPS≥ 1%)

	Pembrolizumab N=637 (100%)	Chemotherapy N=637 (100%)	Total
Sex			
Male	450 (70.6%)	452 (71%)	902 (70.8%)
Female	187 (29.4%)	185 (29%)	372 (29.2%)
Age			
Mean years (SD)	62.5 (9.9)	63.1(9.4)	62.8 (9.7)
Median (years)	63	63	63
Min, max (years)	25, 89	31,90	25, 90
Age Group			
< 65 years	359 (56.4%)	348 (54.6%)	707 (55.5%)
≥ 65 years	278 (43.6%)	289 (45.4%)	567 (44.5%)
Race			
White	398 (62.5%)	412 (64.7%)	810 (63.6%)
Black or African American	10 (1.6%)	13 (2%)	23 (1.8%)
Asian	189 (29.7%)	187 (29.4%)	376 (29.5%)
American Indian or Alaska Native	10 (1.6%)	5 (0.8%)	15 (1.2%)
Other	30 (4.7%)	20 (3.2%)	50 (3.92%)
Ethnicity			
Hispanic or Latino	120 (18.8%)	123 (19.3%)	243 (19.1%)
Not Hispanic or Latino	512 (80.4%)	507 (79.6%)	1019 (80%)
Not Reported	5 (0.8%)	7 (1.1%)	12 (0.9%)
Region			
East Asia	185 (29%)	185 (29%)	370 (29%)
Europe	149 (23.4%)	137 (21.5%)	286 (22.4%)
Latin America	136 (21.4%)	133 (20.9%)	269 (21.1%)
Other	167 (26.2%)	182 (28.6%)	349 (27.4%)

Reviewer's Comment: In KEYNOTE-042, patients enrolled in Ukraine (N=91, 7.1%) and Russian Federation (N=90, 7.1%) were included in the regional category of "Other" by Merck. The "Europe" (denoted as EU in the submission) region, includes six countries from eastern Europe (Poland, Latvia, Czech Republic, Lithuania, Romania, and Estonia) plus Switzerland. In the opinion of the reviewer, Ukraine and Russian Federation should be included in the (Eastern) Europe regional category; thus, an exploratory subgroup analysis of OS in PD-L1 TPS ≥1% was conducted with the "Europe + Ukraine + Russian Federation" population. Result is shown in the Additional Efficacy Considerations subsection of this review.

Table 10 Baseline Disease Characteristics

		Pembrolizumab N=637 (100%)	Chemotherapy N=637 (100%)	Total
Tumor Stage	Stage IV	561 (88.1%)	553 (86.8%)	1114 (87.4%)
	Stage IIIA	13 (2%)	10 (1.6%)	23 (1.8%)
	Stage IIIB	63 (9.9%)	74 (11.6%)	137 (10.8%)
PDL-1	TPS ≥ 1%	637 (100%)	637 (100%)	1274 (100%)
	TPS 1-49%	338 (53.1%)	337 (52.9%)	675 (52.9%)
	TPS ≥ 20%	413 (64.8%)	405 (63.6%)	818 (64.2%)
	TPS >= 50%	299 (46.9%)	300 (47.1%)	599 (47%)
Histology	Non-Squamous	394 (61.9%)	388 (60.9%)	782 (61.4%)
	Squamous	243 (38.1%)	249 (39.1%)	492 (38.6%)
ECOG PS	0	198 (31.1%)	192 (30.1%)	390 (30.6%)
	1	439 (68.9%)	445 (69.9%)	884 (69.4%)
Smoking History	Current Smoker	125 (19.6%)	146 (22.9%)	271 (21.3%)
	Former Smoker	370 (58.1%)	351 (55.1%)	721 (56.6%)
	Never Smoker	142 (22.3%)	140 (22%)	282 (22.1%)
Brain Metastasis	No	602 (94.5%)	602 (94.5%)	1204 (94.5%)
	Yes	35 (5.5%)	35 (5.5%)	70 (5.5%)
Choice of Chemotherapy	Paclitaxel	325 (51%)	313(49.1%)	638 (50.1%)
	Pemetrexed	312 (49%)	324 (50.9%)	636 (49.9%)

Subgroup of Patients with Stage III Disease

Data from the patients with stage III disease enrolled in KEYNOTE-042 is submitted to support the inclusion of the "locally advanced" population in the proposed indication of "pembrolizumab for first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD L1 TPS $\geq$ 1%".

In KEYNOTE-042, 160 patients (12.6 %) had stage III disease at the time of enrollment (23 with stage IIIA, 137 with stage IIIB). Patient demographics and disease characteristics of the patients with stage III and IV (metastatic) disease enrolled in KEYNOTE-042 are summarized in Table 11.

Overall, the stage III population was comparable to the stage IV population in KEYNOTE-042 , with the following notable differences: 1) Latin American countries enrolled lower number of patients with stage III disease compared with other regions (15% versus 28% in Eastern Europe, vs. 31% in East Asia); 2) more patients with stage III disease had squamous cell histology compared to stage IV population (65% vs. 35%); and 3) in the pembrolizumab arm, 45% of the patients with stage III disease had TPS 1-19% and 36% with TPS ≥50%. The percentage of patients with low TPS expression (1-49%) was higher in the stage III disease subgroup when compared to the stage IV population (65% for stage III disease versus 52% for stage IV disease).

Table 11 Demographics and baseline characteristics by treatment arm for Stage III and Stage IV patients in TPS ≥ 1%, and TPS ≥ 50%

	TPS>=1%				TPS>=50%			
	Stage III disease N=160 (%)		Stage IV disease N=1114 (%)		Stage III disease N=160 (%)		Stage IV disease N=1114 (%)	
	Pembro N= 76	Chemo N=84	Pembro N=561	Control N=553	Pembro N=27	Control N=35	Pembro N=272	Control N=265
Demographics								
Sex								
Female	20 (26)	19 (23)	167 (30)	166(30)	7 (26)	7 (20)	87 (32)	83 (31)
Male	56 (74)	65 (77)	394 (70)	387(70)	20 (74)	28 (80)	185 (68)	182(69)
Age (years)								
Mean	64	63	62	63	64	64	62	63
Std Dev	8.09	8.52	10.11	9.53	7.52	7.27	9.99	9.84
Median	64	63	63	64	66	63	63	64
Range	41 - 87	49 - 85	25 - 89	31 - 90	41 - 76	49 - 77	25 - 89	36 - 90
Age Group 2								
< 65	41 (54)	49 (58)	318 (57)	299(54)	12 (44)	21 (60)	155 (57)	140(53)
65 - 74	29 (38)	26 (31)	184 (33)	199(36)	14 (52)	11 (31)	92 (34)	106(40)
75 - 84	5 (7)	8 (10)	54 (10)	49 (9)	1 (4)	3 (9)	21 (8)	14 (5)
>= 85	1 (1)	1 (1)	5 (1)	6 (1)	0 (0)	0 (0)	4 (1)	5 (2)
Region								
Latin Am	14 (18)	10 (12)	122 (22)	123(22)	4 (15)	5 (14)	49 (18)	58 (22)
EU	20 (26)	25 (30)	129 (23)	112(20)	5 (19)	13 (37)	66 (24)	53 (20)
East Asia	20 (26)	30 (36)	165 (29)	155(28)	8 (30)	13 (37)	84 (31)	81 (31)
Other	22 (29)	19 (23)	145 (26)	163(29)	10 (37)	4 (11)	73 (27)	73 (28)
ECOG								
0	26 (34)	29 (35)	172 (31)	163(29)	11 (41)	14 (40)	85 (31)	77 (29)
1	50 (66)	55 (65)	389 (69)	390(71)	16 (59)	21 (60)	187 (69)	188(71)
PD-L1 TPS								
TPS 1-19%	34 (45)	33 (39)	190 (34)	199(36)				
TPS 20-49%	15 (20)	16 (19)	99 (18)	89 (16)				
TPS ≥50%	27 (36)	35 (42)	272 (48)	265(48)				
Disease characteristics								
Histology								
Squamous	47 (62)	57 (68)	196 (35)	192(35)	17 (63)	22 (63)	90 (33)	92 (35)
Non-squamous	29 (38)	27 (32)	365 (65)	361(65)	10 (37)	13 (37)	182 (67)	173(65)
Brain Metastases								
Yes	0 (0)	0 (0)	35 (6)	35 (6)	0 (0)	0 (0)	19 (7)	15 (6)
No	76 (100)	84(100)	526 (94)	518(94)	27 (100)	35(100)	253 (93)	250(94)

Stage III Patient Selection

In the KEYNOTE-042 protocol, exclusion criterion # 6 states *"Subject's NSCLC can be treated with curative intent with either surgical resection and/or chemo-radiation*". During the application review, FDA noted that the reason why patients were deemed ineligible for treatment with curative intent was not captured in the Case Report Form. FDA requested that the information, as documented in the medical record, for each of the 160 patients with stage III disease be submitted for review. Merck retrospectively collected the data from the investigational sites and submitted the information to the sBLA on October 10, 2018, under SND 2192.

A tabular listing of all 160 patients with stage III disease and reasons why patients were considered not eligible for definitive treatment was reviewed and this information is summarized in Table 12.

Table 12 Reasons Patients with Stage III NSCLC were Not Eligible for Surgery and/or Chemoradiation (per Investigator)

Reason Not Eligible for Surgery and/or Chemoradiation	Patients with stage III NSCLC N=160 (100%)
Tumor location/site	96 (60)
Unresectable tumor	24 (15)
High risk for definitive therapy due to patient's medical condition	17 (11)
Initial Stage upgraded from III to IV	11 (7)
Patient refused treatment with definitive therapy	6 (4)
Miscellaneous reasons	6 (4)

The majority of the patients were deemed by the site investigator to be ineligible for definitive treatment due to tumor location (60%), either due to high volume disease, satellite node or secondary pulmonary nodules; 25% of the stage III patients were considered to have tumors that were "unresectable"; and 11% were not eligible for definitive therapy due to co-morbid conditions such as poor respiratory function or cardiovascular disease. Eleven patients had disease initially coded as stage III upgraded to stage IV following enrollment.

Reviewer's comment: The current standard of care for patients with stage III, resectable disease, is complete surgical resection followed by adjuvant treatment with chemoradiation. For patients who are deemed medically inoperable, the current standard of care in the U.S., is definitive chemoradiation therapy, followed by durvalumab[10]. In KEYNOTE-042, it is unclear if a proportion of patients deemed ineligible for definite treatment by the site investigator due to "tumor location/site" or "unresectable tumor" might have benefited from definitive chemoradiation therapy.

It is noted that 7% (N=11) of the patients with stage III disease had disease stage upgraded to stage IV following enrollment; given that stage was not a stratification variable for randomization and the small number of patients (0.9% of the ITT population), lack of accurate initial staging is not anticipated to have affected the final study results.

Refer to the Additional Efficacy Considerations subsection below for results of the exploratory efficacy analysis of patients with stage III disease and further discussion.

Efficacy Results – Primary Endpoint

The efficacy analysis results based on the second interim analysis, with a database lock date of February 26, 2018, are reported in this section. The second interim analysis was prespecified to occur about 38 months after the first patient randomization date (Date: November 21, 2014). By this time, approximately 340 deaths were projected to occur in the patients with NSCLC TPS ≥50%. This review includes the data from this pre-specified interim analysis based on 356 observed number of deaths in TPS ≥ 50% and all p-values are compared against a stopping boundary of 0.0291.

Primary OS Analysis:
The interim results demonstrated a statistically significant improvement in OS for the TPS ≥ 50% and TPS ≥ 20% subgroups and for the ITT population (TPS ≥ 1%), which were tested hierarchically in that order. The primary OS analysis results are summarized in Table 13.

Table 13: OS Results in TPS ≥ 50%, TPS ≥ 20%, and TPS ≥ 1%

	TPS ≥ 50%		TPS ≥ 20%		TPS ≥ 1%	
	Pembro N=299	Chemo N=300	Pembro N=413	Chemo N=405	Pembro N=637	Chemo N=637
Deaths (%)	157(52.5)	199(66.3)	230(55.7)	266(65.7)	371(58.2)	438(68.8)
Median in mos (95% CI)	20.0 (15.4,24.9)	12.2 (10.4,14.2)	17.7 (15.3,22.1)	13.0 (11.6,15.3)	16.7 (13.9,19.7)	12.1 (11.3,13.3)
Adjusted HR[a] (95% CI)	0.69 (0.56,0.85)		0.77 (0.64,0.92)		0.81 (0.71,0.93)	
p-value[b]	0.0006		0.004		0.0036	
OS Rate at 12 mos (95% CI)	63.5 (57.8, 68.7)	50.7 (44.9, 56.2)	61.3 (56.4, 65.8)	53.2 (48.1, 57.9)	57.8 (53.8,61.5)	50.7 (46.7, 54.5)
OS Rate at 18 mos (95% CI)	51.8 (45.7, 57.6)	37.8 (32.1, 43.5)	49.6 (44.4, 54.5)	38.9 (33.9, 43.9)	48.3 (44.2,52.2)	37.4 (33.5, 41.4)
OS Rate at 24 mos (95% CI)	44.7 (38.2, 50.9)	30.1 (24.3, 36.0)	40.5 (35.0, 45.9)	29.6 (24.6, 34.7)	39.3 (34.9,43.6)	28.0 (24.2, 32.0)

[a] Hazard ratio calculated using cox proportional hazards model with treatment group as a single covariate and stratified by histology, ECOG status, region and PD-L1 status
[b] Based on stratified log-rank test; compared with stopping boundary value of 0.0291, tested hierarchically in order: TPS ≥ 50%, TPS ≥ 20%, TPS ≥ 1%.

The Kaplan-Meier plots of OS for the TPS ≥ 50% and TPS ≥ 20% subgroups and the ITT population (TPS ≥ 1%) are provided in Figure 2, Figure 3, and Figure 4.

Figure 2: Kaplan-Meier Plot of OS in TPS ≥ 50%

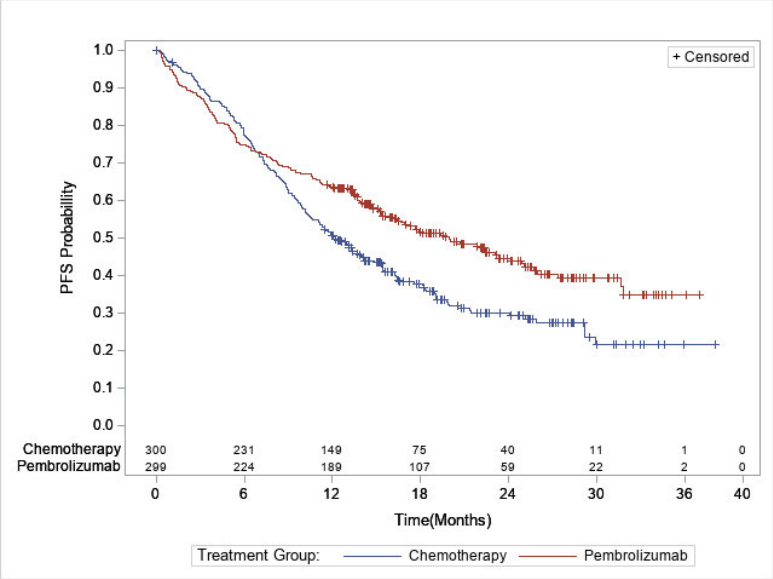


Figure 3: Kaplan-Meier Plot of OS in TPS ≥ 20%

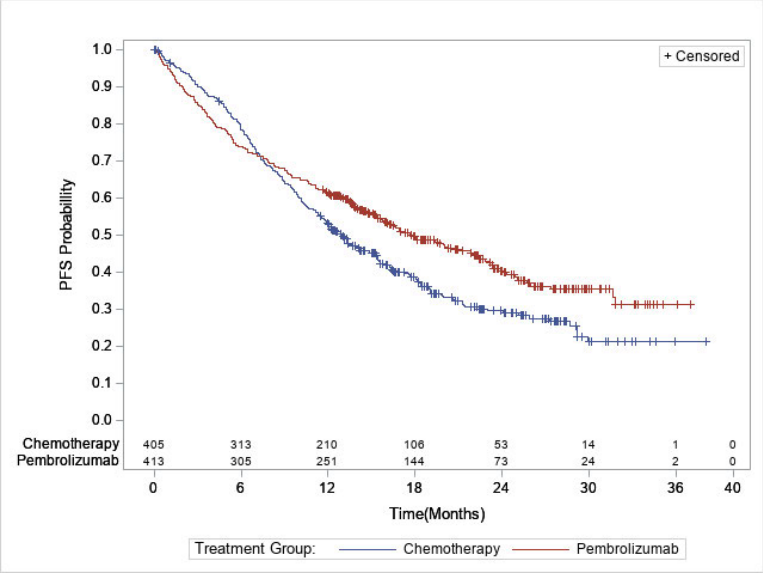
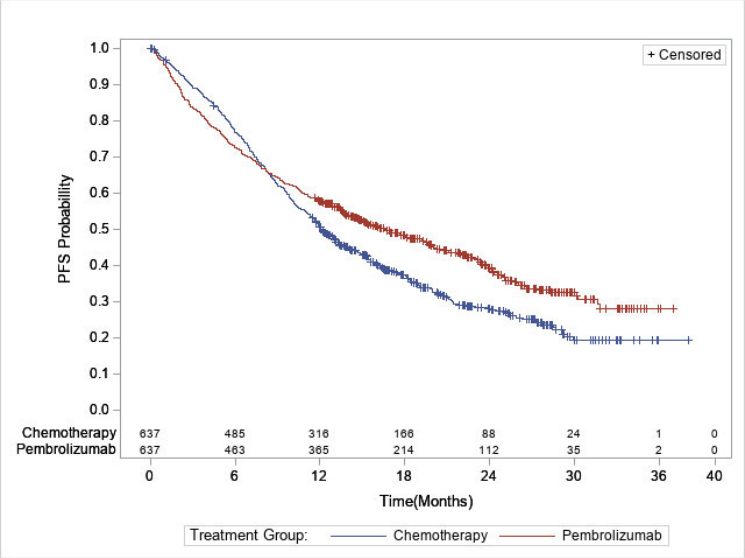


Figure 4: Kaplan-Meier Plot of OS in TPS ≥ 1%



Reviewer's Comment: Of note, in this trial it was observed that the Kaplan-Meier curves of OS for pembrolizumab and chemotherapy arms crossed each other, violating the proportional hazards assumption, a scenario observed recently in many of the immunotherapy trials; as a result, the hazard ratios and estimates of medians reported to summarize the treatment benefit are not optimal summary measures to describe treatment benefit. Consequently, we report other exploratory measures of the treatment effect, that do not rely on this assumption.

In addition to the survival rates presented previously, Table 14 *below shows the estimated restricted mean survival time (RMST) during the first 12, 24 and 36 months and the corresponding 95% CI.*

The average survival during the first 36 months in patients with TPS ≥ 1% who received pembrolizumab was 2.3 months longer than the average survival for patients in the chemotherapy arm. Similarly, in the TPS ≥ 20% and TPS ≥ 50% subgroups, the average survival for those randomized to pembrolizumab as compared to those randomized to chemotherapy was increased by 2.6 and 3.6 months, respectively, during the first 36 months. All of these differences indicate a smaller treatment effect (i.e., smaller in magnitude) than that suggested by the difference in KM-estimated median survival between arms, which were 4.6, 4.7, and 7.8 months in the TPS ≥1%, TPS ≥20% and TPS ≥50% populations, respectively.

Table 14: RMST analysis for TPS ≥ 50%, TPS ≥ 20%, and TPS ≥ 1%

Estimate (95% CI)	TPS ≥ 50%		TPS ≥ 20%		TPS ≥ 1%	
	Pembro N=299	Chemo N=300	Pembro N=413	Chemo N=405	Pembro N=637	Chemo N=637
Over 12 months	9.3 (8.9,9.8)	9.2 (8.8,9.6)	9.2 (8.8,9.6)	9.3 (9,9.7)	9 (8.7,9.3)	9.2 (8.9,9.5)
Over 24 months	15.7 (14.7,16.8)	13.7 (12.8,14.7)	15.3 (14.4,16.2)	14 (13.1,14.8)	14.8 (14.1,15.5)	13.6 (13,14.3)
Over 36 months	20.3 (18.7,22)	16.7 (15.2,18.2)	19.4 (18,20.8)	16.8 (15.5,18.1)	18.6 (17.5,19.7)	16.3 (15.3,17.3)

Subgroup analyses of OS:
OS in TPS≥ 1% were examined in subgroups as presented in Table 15.

All exploratory subgroup efficacy analyses were performed using the primary analysis data of OS in TPS≥ 1% and only the subgroups with sufficient sample sizes are presented in this review. All results presented in this section should be considered exploratory. There were no pre-specified hypotheses and power analyses for these subgroups nor pre-specified multiplicity adjustment.

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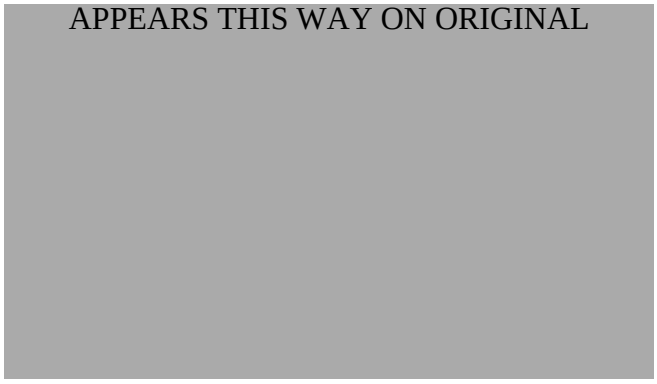


Table 15: Subgroup analysis of OS in **TPS≥** 1%

Subgroup	# Events/N Pembro	# Events/N Chemo	Hazard Ratio (95% CI)
Overall	371/637	438/637	0.81 (0.71, 0.93)
Age Category			
< 65	203/359	241/348	0.81 (0.67, 0.99)
>= 65	168/278	197/289	0.82 (0.66, 1.01)
Gender			
Female	107/187	118/185	0.9 (0.69, 1.18)
Male	264/450	320/452	0.8 (0.68, 0.94)
Race			
White	252/398	303/412	0.83 (0.7, 0.99)
Asian	93/189	107/187	0.79 (0.6, 1.05)
American Indian Or Alaska Native	7/10	5/5	0.14 (0.01, 1.42)
Black Or African American	5/10	12/13	0.83 (0.19, 3.52)
Multiple	14/30	11/19	1.01 (0.43, 2.39)
Region			
Non-East Asia	281/452	332/452	0.82 (0.7, 0.96)
East Asia	90/185	106/185	0.79 (0.6, 1.05)
Smoking			
Current	74/125	101/146	0.96 (0.7, 1.31)
Former	215/370	256/351	0.71 (0.59, 0.86)
Never	82/142	81/140	1.02 (0.74, 1.4)
Baseline ECOG			
0	96/198	119/192	0.77 (0.58, 1.01)
1	275/439	319/445	0.83 (0.71, 0.98)
Histology			
Non-Squamous	218/394	248/388	0.86 (0.71, 1.03)
Squamous	153/243	190/249	0.75 (0.6, 0.93)
Choice of Chemo			
Paclitaxel and Carboplatin	202/325	236/313	0.74 (0.61, 0.9)
Pemetrexed and Carboplatin	169/312	202/324	0.87 (0.71, 1.07)
Disease Stage			
Advanced	42/76	56/84	0.8 (0.52, 1.22)
Metastatic	329/561	382/553	0.83 (0.71, 0.96)
History of Brain Metastases			
No	355/602	415/602	0.82 (0.71, 0.95)
Yes	16/35	23/35	0.8 (0.4, 1.6)

Reviewer's comments: There are no outliers among the subgroup analyses in the table above, and subgroup results are supportive of the overall results. Confidence intervals for the HRs may be wide due to the relatively small sample sizes for each subgroup.

Updated OS results:

FDA requested that Merck submit updated OS information with an additional 6 months of survival follow-up in order to further assess the benefit observed in the ITT population and to support an exploratory analysis of efficacy in the subgroup of patients with NSCLC TPS 1-49%.

An information request (IR) was sent to the Merck on October 31, 2018 requesting this information.

Merck responded to the IR on November 2, 2018, clarifying that the updated OS results and the corresponding analysis datasets would be submitted on November 30, 2018. This reviewer has performed a quality data check of the dataset submission and confirmed Merck's updated results.

The updated OS analysis results in PD-L1 TPS ≥ 1% and TPS ≥ 50%, based on a database cutoff date of September 4, 2018, are provided in Table 16. Based on the updated analysis results, the significance of the OS results in patients with NSCLC PD-L1 TPS ≥ 1% was consistent with that of the OS results from IA-2. Additionally, updated OS results in TPS ≥ 50% and TPS≥ 20% were also analyzed to augment the primary analysis results.

Table 16: Updated OS analysis results in **TPS≥** 1%, **TPS≥** 20% and TPS **≥** 50%

	TPS≥ 1%		TPS≥ 20%		TPS≥ 50%	
	Pembro (N=637)	Chemo (N=637)	Pembro N=413	Chemo N=405	Pembro (N=299)	Chemo (N=300)
Deaths (%)	422 (66.2)	481 (75.5)	261	296	180 (60.2)	220 (73.3)
Median in mons (95% CI)	16.4 (14.0, 19.7)	12.1 (11.3, 13.3)	18 (15.4, 21.9)	13 (11.6, 15.3)	20 (15.9, 24.2)	12.2 (10.4, 14.6)
Adjusted HR (95% CI)	0.82 (0.71, 0.93)		0.77 (0.65, 0.91)		0.71 (0.58, 0.86)	

Source: FDA Reviewer's analysis
Database cutoff date: September 4, 2018.

Reviewer's Comment: Merck considered the updated analysis results based on cutoff date of September 4, 2018 as the final OS analysis. This corresponds to a 6.2 months additional follow-up period since the cutoff date for IA-2. However, the final OS analysis was pre-specified to occur about 45 months after first patient randomized date, which corresponds to 7 months of additional follow-up since IA-2.

The Kaplan-Meier plot of OS in TPS ≥ 1%, ≥ 50% and ≥ 20% subgroups are provided in Figure 5 Figure 6 and Figure 7.

Figure 5: Updated OS curves in TPS ≥ 1%

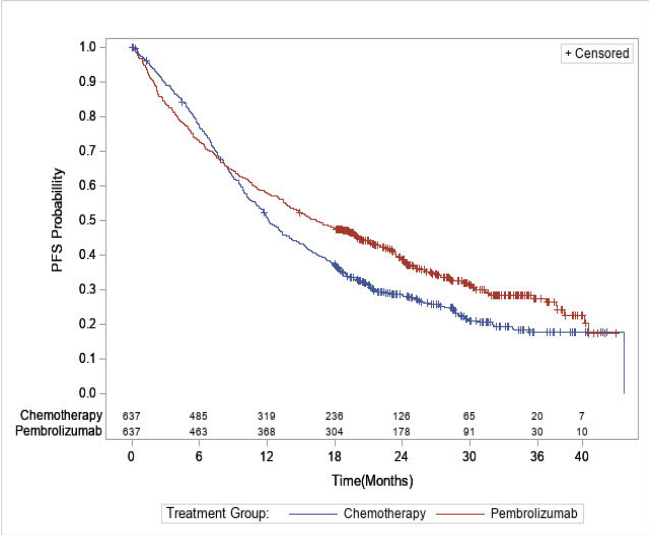


Figure 6:Updated OS curves in TPS ≥ 50%

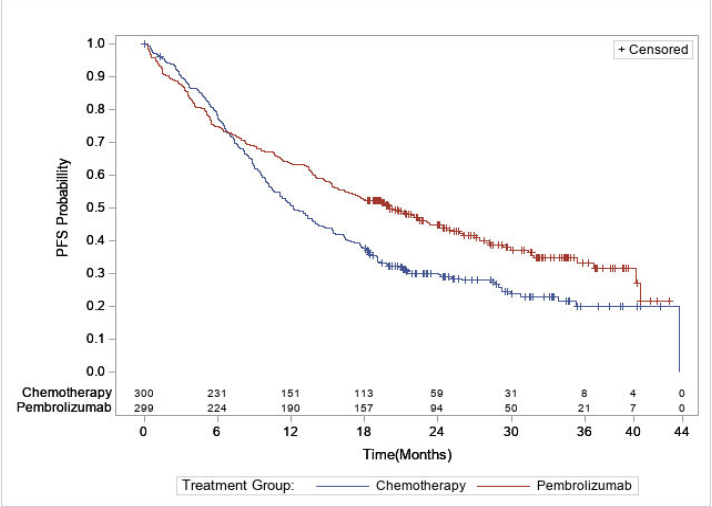
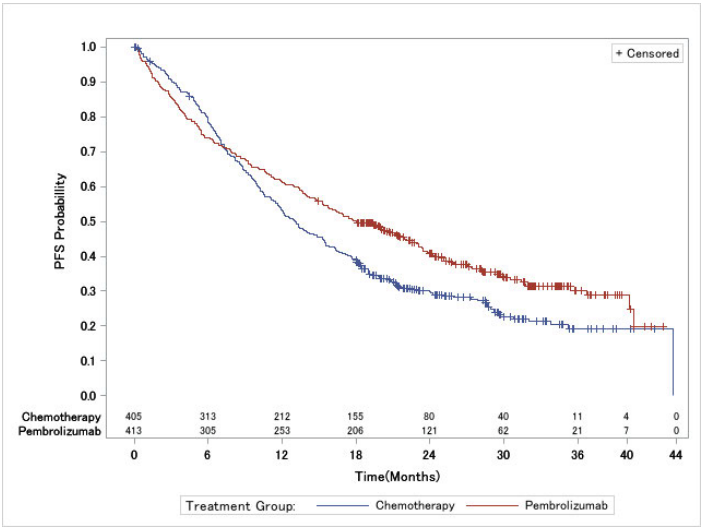


Figure 7:Updated OS curves in TPS ≥ 20%



Efficacy Results – Secondary and other relevant endpoints

The analysis results for the secondary endpoints of PFS and ORR, along with DoR are presented in Table 17.

The analysis of PFS in the NSCLC TPS≥ 50% subgroup did not demonstrate a statistically significant difference between treatment arms with a stratified log-rank test p-value of 0.034, compared against the p-value boundary of 0.0291. As a result, based on the hierarchical testing methodology defined in Section 7.1.1: Statistical Analysis Plan – Multiplicity, PFS in TPS ≥ 20% and TPS ≥ 1% and ORR in all three TPS analysis populations were not formally tested and are summarized descriptively.

Table 17: PFS, ORR and DoR analysis results

	TPS ≥ 50%		TPS ≥ 20%		TPS ≥ 1%	
	Pembro N=299	Chemo N=300	Pembro N=413	Chemo N=405	Pembro N=637	Chemo N=637
PFS						
Events (%)	221(73.9)	233(77.7)	317(76.8)	314 (77.5)	507 (79.6)	506 (79.4)
Median in mos (95% CI)	7.1 (5.9,9.0)	6.4 (6.1,6.9)	6.2 (5.1, 7.8)	6.6 (6.2, 7.3)	5.4 (4.3, 6.2)	6.5 (6.3, 7.0)
Adjusted HR (95% CI)	0.81(0.67,0.99)		0.94 (0.80, 1.11)		1.07 (0.94, 1.21)	
p-value	0.034*					
ORR						
# Responses	118	96	138	117	174	169
% Responses (95% CI)	39.5 (33.9,45.3)	32.0 (26.8,37.6)	33.4 (28.9,38.2)	28.9 (24.5,33.6)	27.3 (23.9,31.0)	26.5 (23.1,30.1)
CR	2 (0.7%)	1 (0.3%)	2 (0.5%)	1 (0.2%)	3 (0.5%)	3 (0.5%)
PR	116 (38.8%)	95 (31.7%)	136 (32.9%)	116 (28.6%)	171 (26.8%)	166 (26.1%)
DoR						
Median in mos	20.2	10.8	20.2	8.3	20.2	8.3
Range	2.1+, 31.2+	1.8+, 24.9+	2.1+, 31.2+	1.8+, 24.9+	2.1+, 31.2+	1.8+, 28.1
DoR ≥ 12 mos, n/ #responders (%)	50/118 (42.4%)	16/96 (16.7%)	62/138 (44.9%)	21/117 (17.9%)	81/174 (46.6%)	27/169 (16%)
DoR ≥ 18 mos, n/ #responders (%)	29/118 (24.6%)	5/96 (5.2%)	35/138 (25.4%)	6/117 (5.1%)	45/174 (25.9%)	10/169 (5.9%)

*The two-sided p-value of PFS hypothesis in TPS≥ 50% is not significant as compared to the boundary value of 0.0291; therefore, the subsequent hypotheses were not evaluated for statistical significance in accordance with the prespecified sequential testing procedure for the secondary endpoints.
CR=Complete Response, PR=Partial Response

The Kaplan-Meier plots of PFS for TPS ≥ 50%, TPS ≥ 20%, and TPS ≥1% are provided in Figure 8, Figure 9, and Figure 10 respectively.

Figure 8: Kaplan-Meier Plot of PFS in TPS ≥ 50%

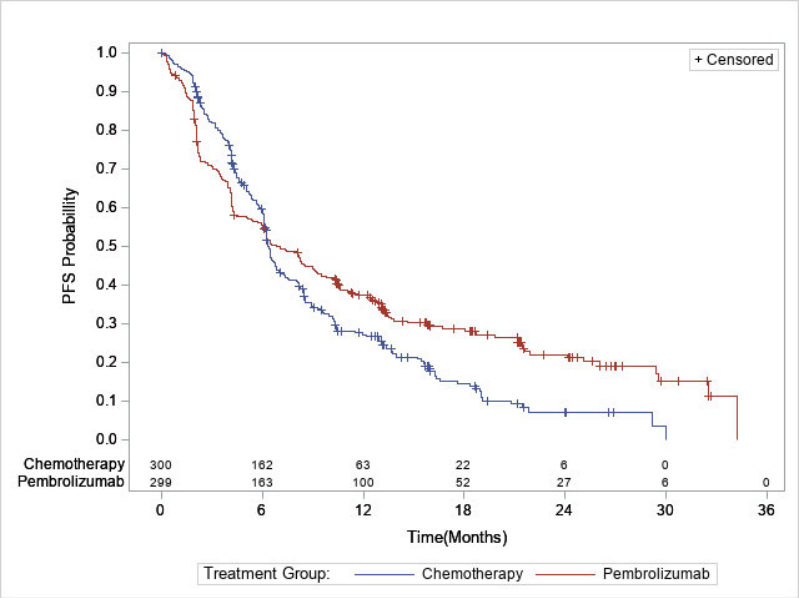


Figure 9: Kaplan-Meier Plot of PFS in TPS ≥ 20%

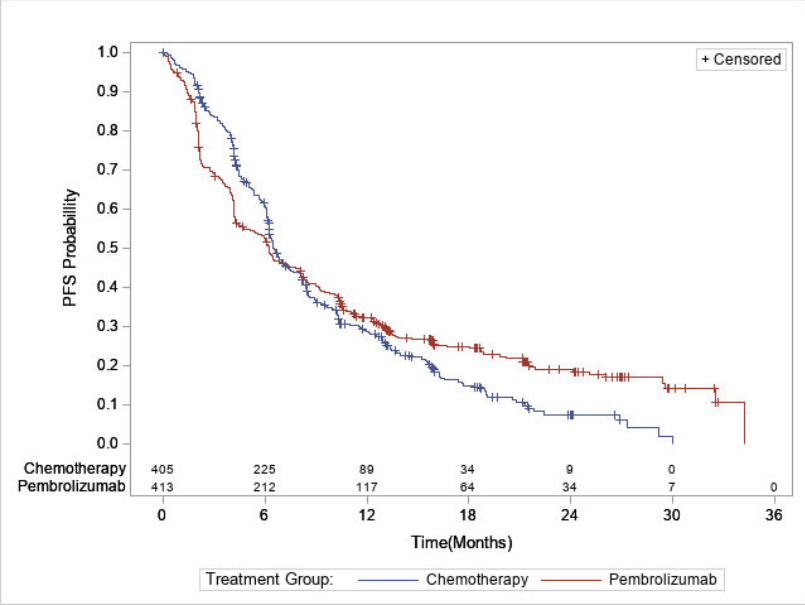
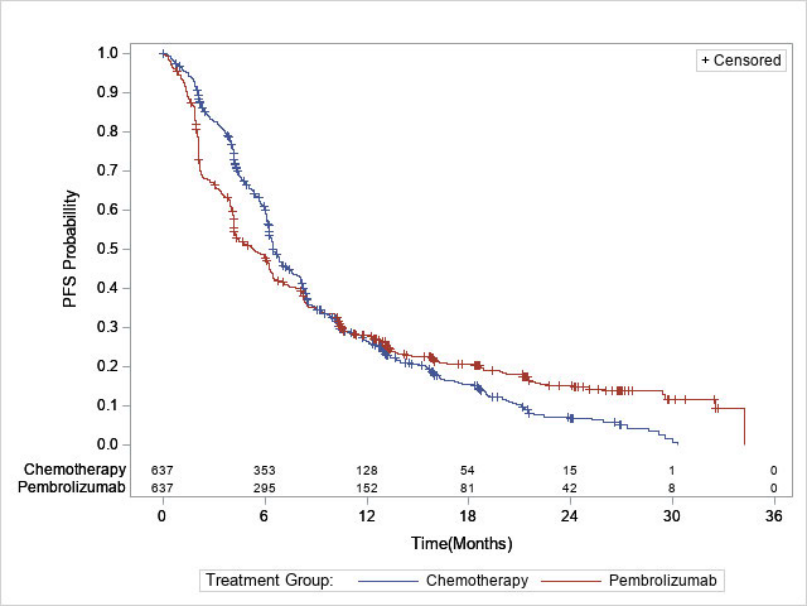


Figure 10: Kaplan-Meier Plot of PFS in TPS ≥ 1%



Reviewer's Comment: Of note, in this trial it was observed that the Kaplan-Meier curves of PFS for pembrolizumab and chemotherapy arms crossed each other, violating the proportional hazards assumption, a scenario observed in many trials evaluating the efficacy of anti-PD-L1 and anti-PD-1 antibodies. As a result, the hazard ratios and estimated medians reported to summarize the treatment effect may not provide the best characterization of the treatment effects. However, no alternative has been identified and generally accepted as a better measure of characterizing these treatment effects.

Dose/Dose Response

A single flat dose of pembrolizumab (200 mg) administered IV every 3 weeks was studied in KEYNOTE-042. Exposure-response analyses were not conducted given the extensive experience with pembrolizumab that indicate the exposure-response is relatively flat over doses ranging from 2 mg/kg every 3 weeks to 10 mg/kg every 2 weeks in multiple primary cancers, including NSCLC.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Patient Reported Outcome (PRO) questionnaires were not planned or administered in KEYNOTE-042.

Exploratory efficacy analysis in PD-L1 TPS 1-49% subgroup (Database cutoff date of February 26, 2018)

FDA conducted exploratory analyses of OS, PFS and ORR in the pre-specified stratum of patients with PDL-1 TPS 1-49%, a population of interest given the proposed expansion of the indication for first-line pembrolizumab as a single agent to include patients with NSCLC TPS ≥1% up to 49%, are presented in Table 18.

Table 18: OS, PFS and ORR analysis results in PD-L1 TPS 1-49% subgroup.

	TPS 1-49%	
	Pembrolizumab N=338	Chemotherapy N=337
OS		
Deaths (%)	214 (63.3)	239 (70.9)
Median in mons (95% CI)	13.4 (10.7, 18.2)	12.1 (11.0, 14.0)
Adjusted HR (95% CI)	0.92 (0.77, 1.11)	
PFS		
Events (%)	286 (84.7)	273 (81.1)
Median in mons (95% CI)	4.2 (4.1, 5.2)	6.8 (6.3, 8.1)
Adjusted HR (95% CI)	1.32 (1.11, 1.56)	
ORR		
# Responses	56	73
ORR (95% CI)	16.6 (12.8, 21)	21.7 (17.4, 26.5)
ORR Difference (95% CI)	-5.1 (-11,0.8)	
Complete Responses	1 (0.3%)	2 (0.6%)
Partial Responses	55 (16.3%)	71 (21.1%)

Database cutoff date: February 26, 2018.

Reviewer's comment: Note that these results should be considered exploratory. No conclusion can be drawn regarding efficacy in this subgroup.

Exploratory Subgroup Analysis in PD-L1 TPS 1-49% subgroup (Updated OS analysis with cutoff date of September 4, 2018)

The OS analysis results with an additional 6 months of follow-up since IA-2 in PD-L1 TPS≥ 1% and TPS 1-49% were requested by FDA. The updated OS results in patients with PD-L1 TPS≥ 1% were presented in Section-7.1.2: Efficacy Results – Primary Endpoint. In this section we present the results of exploratory analyses in the PD-L1 TPS 1-49% subgroup.

Based on a database cutoff date of September 4, 2018, updated OS analysis results in the PD-L1 TPS 1-49% subgroup are provided in Table 19.

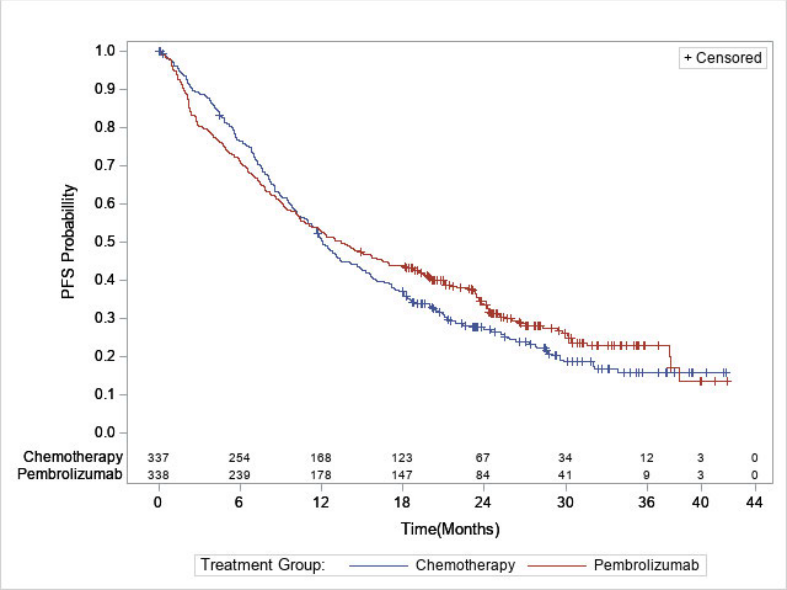
Table 19: Updated OS analysis results in TPS 1-49%.

	TPS 1-49%	
	Pembro (N=338)	Chemo (N=337)
Deaths (%)	242 (71.6)	261 (77.4)
Median in mons	13.4	12.1
(95% CI)	(10.7, 16.9)	(11.0, 14.0)
Adjusted HR (95% CI)	0.91 (0.77, 1.09)	

Database cutoff date: September 4, 2018.

The Kaplan-Meier plot of OS in the TPS ≥ 1-49% subgroup is provided in Figure 11.

Figure 11:Updated OS curves in TPS 1-49%



Reviewer's comment: These results are considered exploratory and no conclusions can be made based on these results. The pattern of crossing survival curves was also observed in TPS ≥ 50% subgroup, although the curves crossed at an earlier timepoint (approximately 6 months) and the separation of the curves is greater for the TPS ≥50% subgroup after the curves cross. An exploratory analysis was conducted by including an interaction term for TPS in the Cox proportional hazards model. The interaction test for treatment by TPS subgroup based on 50% cutoff was not significant at a 5% significance level (p-value=0.0702).

7.1.3. Assessment of Efficacy Across Trials

In the subgroup of patients with PDL-1 TPS 1-49%, a stratification factor for randomization in KEYNOTE-042, an improvement in OS could not be evaluated as there was no pre-specified hypothesis for evaluation of efficacy endpoints in this subgroup. To further evaluate the association between levels of PDL-1 expression by TPS in NSCLC and the treatment effect of pembrolizumab, we examined the OS, PFS and ORR results previously reported in the KEYNOTE-024 and KEYNOTE-010 studies (refer to section 3.1) to assess for consistency of treatment effects in patients with TPS ≥50% NSCLC.

Efficacy Across KEYNOTE-042 and KEYNOTE-024 (Previously Untreated NSCLC, TPS **≥** 50%)

The approval of pembrolizumab for first-line treatment of patients with metastatic strongly expressing PDL-1 (TPS ≥ 50%) NSCLC was granted on October 24, 2016 (BLA125514/S12). Approval was based on data from KEYNOTE-024, a multicenter, global, randomized, open-label, active-controlled study of pembrolizumab versus platinum-based chemotherapy in 305 previously untreated patients with metastatic TPS ≥50% NSCLC with no *EGFR* or *ALK* genomic tumor aberrations. Randomization was stratified by ECOG PS (0 versus 1), histology (squamous versus non-squamous), and geographic region of the enrolling site (East Asia versus non-East Asia). Patients randomized to the chemotherapy arm who experienced disease progression and who met all crossover criteria had the opportunity to receive pembrolizumab at the time of progression. The primary efficacy endpoint was PFS as assessed by a BICR according to RECIST 1.1. Key secondary efficacy endpoints were OS and ORR.

The overall study design of KEYNOTE-024 was, in general, similar to KEYNOTE-042 with the following notable differences: 1) KEYNOTE-024 enrolled only patients with PDL-1 TPS ≥50% while KEYNOTE-042 enrolled patients with TPS ≥ 1%; 2) KEYNOTE-024 enrolled only patients with metastatic (stage IV) disease; 3) in KEYNOTE-024, patients randomized to the chemotherapy arm were allowed to receive pembrolizumab at the time of disease progression; and 4) in KEYNOTE-024 13% of the ITT population were from an US investigational site, while KEYNOTE-042 was conducted entirely ex-US.

In KEYNOTE-042, 47% (599 of 1274) of patients had tumors that expressed PDL-1 TPS ≥ 50% compared to 100% (305 of 305) of patients in KEYNOTE-024. Table 20 compares the patient demographics and selected baseline characteristics from the KEYNOTE-042 PDL-1 TPS ≥ 50% subgroup and patients in KEYNOTE-024. In general, there were more male patients (70% vs. 62%), more patients with squamous cell histology (37% vs 18%), and more patients from East Asian countries (31% vs. 14%) in KEYNOTE-042 compared to KEYNOTE-024. In KEYNOTE-024, 44% of the patients enrolled in the chemotherapy arm received pembrolizumab upon disease progression. The impact of these differences on the final efficacy results are unclear.

Table 20 Comparison of Demographics and Selected Baseline Characteristics between KEYNOTE-042 and KEYNOTE-024

	KEYNOTE-042 TPS ≥ 50% N= 599		KEYNOTE-024 TPS ≥ 50% N=305	
	Pembrolizumab % (N=299)	Chemotherapy % (N=300)	Pembrolizumab % (N=154)	Chemotherapy % (N=151)
Sex (male)	69	70	60	63
Age (median, range years)	63 (25 to 89)	64 (31 to 90)	65 (33 to 90)	66 (38 to 95)
ECOG PS 0/1	30/68	30/70	35/64	35/65
Brain metastasis	6.4	5.0	11.7	6.6
Histology (squamous cell)	36	38	19	17
Region East Asia/non-East Asia	31/69	31/69	14/86	13/87
Crossover to pembrolizumab	-	0	-	44

Source: BLA125514/S-047 Summary of Clinical Efficacy and BLA125514/S-12 Clinical and Statistical Review

Efficacy results from KEYNOTE-042 and KEYNOTE-024 are summarized in Table 21. Overall, the median OS, median PFS and observed ORR in the control (chemotherapy) arms of both studies were similar.

A statistically significant difference in OS, favoring those randomized to pembrolizumab was demonstrated in both KEYNOTE-024 [HR 0.60 (95% CI 0.41, 0.89)] and the subgroup of patients with TPS ≥ 50% in KEYNOTE-042 [HR 0.69 (95% CI: 0.56, 0.85)]. The estimated median OS was 30.0 months in the KEYNOTE-024 pembrolizumab arm and 20.0 months in the KEYNOTE-042 pembrolizumab arm TPS ≥50% subgroup.

Statistically significant differences in PFS and ORR, favoring the pembrolizumab arm, were demonstrated in KEYNOTE-024 . In KEYNOTE-024, the PFS HR was 0.50 (95% CI 0.37, 0.68; p-value < 0.001), with an estimated median PFS of 10.3 months in the pembrolizumab arm compared to 6.0 months in the chemotherapy arm. The ORR was 44.8% versus 27.8%, favoring the pembrolizumab arm. In contrast, there was no statistically significant difference in PFS for the TPS ≥ 50% subgroup based on the allocated alpha for this analysis (p=0.291, two-sided) in KEYNOTE_042. The estimated median PFS was 7.1 months in the pembrolizumab arm and 6.4 months in the chemotherapy arm. In the TPS ≥ 50% subgroup, ORR was higher in the pembrolizumab arm (39.5% versus 32.0%); the p-value was not evaluated for statistical significance of ORR due to lack of alpha for testing under the sequential testing procedure. In both the KEYNOTE-042 and KEYNOTE-024 studies, the prolonged durations (≥ 12 months) of responses in some of the responding patients were clinically meaningful. The median duration of response at the time of the original data cutoff was 20.2 months in the TPS ≥ 50% subgroup in KEYNOTE-042 while the median was not reached at the time of the data cut-off date for the responders in the pembrolizumab arm of KEYNOTE-024.

Table 21 KEYNOTE-042 subgroup with TPS **≥50%** and KEYNOTE-024 Efficacy Results (per FDA)

	KEYNOTE-042 Subgroup TPS ≥ 50% N= 599		KEYNOTE-024 TPS ≥ 50% (ITT) N=305	
Endpoint	Pembrolizumab N=299	Chemotherapy N=300	Pembrolizumab N= 154	Chemotherapy N=151
OS				
HR[4] (95% CI) p-value[1]	0.69 (0.56, 0.85) 0.0006[2]		0.60 (0.41, 0.89) 0.005[3]	
Median months 95% CI	20.0 (15.4, 24.9)	12.2 (10.4, 14.2)	30.0 (18.3, n/r)	14.2 (9.8, 19.0)
PFS				
HR[4] (95% CI) p-value[1]	0.81 (0.67, 0.99) 0.034[2]		0.50 (0.37, 0.68) <0.001	
Median month (95% CI)	7.1 (5.9, 9.0)	6.4 (6.1, 6.9)	10.3 (6.7, n/r)	6.0 (4.2, 6.2)
ORR				
ORR % 95% CI	39.5% (33.9, 45.3)	32% (26.8, 37.6)	44.8% (36.8, 53.0)	27.8% (20.8, 35.7)
DoR (median, range)	20.2 (2.1+- 31.2+)	10.8 (1.8+, 24.9+)	N/R (1.9+ - 14.5)	6.3 (2.1+-12.6+)

Source: BLA125514/S-047 Summary of Clinical Efficacy and BLA125514/S-12 Clinical and Statistical Review

[1] Stratified log-rank

[2] Two-sided p-value based on a stratified log-rank test and compared to the boundary value of 0.0291

[3] P-value is compared with 0.0118 of the allocated α for this interim analysis

[4]Based on the stratified Cox proportional hazard model

Reviewer's Comment: The results from the subgroup of patients with PDL-1 TPS ≥ 50% in KEYNOTE-042 confirms the OS benefit of pembrolizumab previously observed in the KEYNOTE-024 study when compared to standard of care platinum-based chemotherapy. Whether the numerical differences in OS, PFS and ORR between the pembrolizumab arms in the two trials are due to the minor differences in population and/or differences in study conduct or due to chance is unclear.

Efficacy Across Trials by PDL-1 Expression (KEYNOTE-010 and KEYNOTE-042)

To further evaluate the association between PDL-1 expression and efficacy outcomes in patients with metastatic NSCLC, FDA requested resubmission of datasets from KEYNOTE-010 pertaining to efficacy endpoints and subgroup analyses of OS, PFS and ORR in the ITT population and in the subgroups of patients with TPS 1-49% and TPS ≥ 50%.

Regular approval for pembrolizumab for the treatment of patients with previously treated metastatic NSCLC whose tumors express PD-L1 TPS ≥1% was based on the data from KEYNOTE-010, a randomized, active-controlled trial of pembrolizumab (two arms, 2 mg/kg Q3W and 10 mg/kg Q3W) compared to docetaxel (BLA125514/S-08). The primary analysis for OS and PFS, the primary endpoints of the study, were performed in the PD-L1 TPS ≥50% subpopulation and in the TPS ≥1% (all randomized) population. Approval was based on a statistically significant

improvement in OS for the all randomized population with TPS ≥ 1%. The HR was 0.71 (95% CI: 0.58, 0.88; p<0.001) for the 2 mg/kg arm and HR 0.61 (95% CI: 0.49, 0.75; p<0.001) for the 10 mg/kg arm. In the TPS ≥ 1% population the ORR was 18% in the 2 mg/kg arm, 19% in the 10 mg/kg arm and 9% in the docetaxel arm. The OS for the subgroup of patients with PD-L1 TPS ≥50% was statistically significant, with a HR of 0.54 (95% CI: 0.38, 0.77; p<0.001) and HR 0.50 (95% CI: 0.36, 0.70; p<0.001) in the 2 mg/kg and 10 mg/kg arms, respectively. PFS was statistically improved in the 10 mg/kg arm for the overall population with TPS ≥ 1% and in the subgroup of patients with PD-L1 TPS ≥ 50% for both the pembrolizumab arms (2 mg/kg and 10 mg/kg). In the TPS ≥50% subpopulation, the ORR was 30% in the 2 mg/kg arm, 29% in the 10 mg/kg arm and 8% in the docetaxel arm.

Exploratory analyses were conducted by the FDA statistical reviewer at the time of the BLA 125514/S-08 review in the subgroup of patients with PD-L1 TPS 1-49% to assess whether the effect on OS was potentially being driven by results in the TPS ≥50% subgroup. In the subgroup of patients with TPS 1-49%, the HR for OS in the 2 mg/kg arm vs docetaxel was 0.79 (95% CI: 0.61, 1.04) and in the 10 mg/kg arm the HR was 0.71 (95% CI: 0.53, 0.94). The estimated median OS was 9.4 months (95% CI 8.7, 10.5) and 10.8 months (95% CI 8.9, 13.3) for the pembrolizumab 2mg/kg and 10mg/kg arms, respectively and 8.6 months (95% CI 7.8, 9.9) for the docetaxel arm. Based on the results in the ITT population, FDA granted approval for the entire population studied, encompassing the TPS 1-49% subpopulation.

KEYNOTE-010 efficacy results by TPS Expression, per Merck, are shown in the following table. Pembrolizumab results are based on pooled data from the 2 mg/kg and 10 mg/kg arms.

Table 22 KEYNOTE-010 efficacy results by TPS Expression (per Merck)

	TPS ≥ 1%		TPS 1-49%		TPS ≥ 50%	
	Pembro[1]	Docetaxel	Pembro[1]	Docetaxel	Pembro[1]	Docetaxel
	N=690	N=343	N=400	N=191	N=290	N=152
OS						
Events (%)	328 (47.5)	193 (56.3)	210 (52.5)	107 (56.0)	118 (40.7)	86 (56.6)
Median in mos (95% CI)	11.2 (10.0, 12.7)	8.5 (7.5, 9.8)	9.7 (9.0, 11.2)	8.6 (7.8, 9.9)	15.8 (11.8, NR)	8.2 (6.4, 10.7)
Adjusted HR[2] (95% CI)	0.67 (0.56, 0.80)		0.76 (0.60, 0.96)		0.53 (0.40, 0.70)	
PFS						
Events (%)	521 (75.5)	257 (74.9)	335 (83.8)	139 (72.8)	186 (64.1)	118 (77.6)
Median in mos (95% CI)	4.0 (3.1, 4.2)	3.9 (3.1, 4.1)	2.6 (2.1, 3.4)	3.9 (2.5, 4.3)	5.2 (4.2, 6.2)	4.1 (3.6, 4.3)
Adjusted HR[2] (95% CI)	0.85 (0.73, 0.98)		1.04 (0.85, 1.27)		0.59 (0.46, 0.74)	
ORR						
# Responses	126	32	40	20	86	12
ORR (95% CI)	18.3 (15.4, 21.3)	9.3 (6.5, 12.9)	10.0 (7.2, 13.4)	10.5 (6.5, 15.7)	29.7 (24.5,35.3)	7.9 (4.1, 13.4)
ORR Difference (95% CI)	8.9 (4.5,13.1)		-0.1 (-5.9,4.8)		22.9 (16.0,29.3)	

Source: Merck's Tables 11-19 in Response to IR document, dated November 30, 2018.

[1] Pooled from pembrolizumab 2 mg/kg and 10 mg/kg arms

[2] Hazard ratio stratified by ECOG (0 vs. 1), Geographic region (East Asian vs. non-East Asian) and PD-L1 status (strongly positive, weakly Positive, and unknown Positive)

Similar to KEYNOTE-042, KEYNOTE-010 enrolled patients with PD-L1 TPS ≥ 1%. Notable differences between the two trials are: 1) KEYNOTE-010 enrolled patients with previously treated metastatic NSCLC; 2) in KEYNOTE-010, the pembrolizumab dosage was either 2 mg/kg Q3W or 10 mg/kg Q2W; 3) in line with the study populations, the chemotherapy in the control arm was docetaxel in KEYNOTE-010 and platinum-based chemotherapy in KEYNOTE-042. The key differences between the KEYNOTE-010 and KEYNOTE-042 study populations are summarized in Table 23. In general, there were more male patients (71% vs. 61%), more patients with squamous cell lung cancer histology (39% vs 22%) and more patients from East Asian countries (29% vs. 19%) in KEYNOTE-042 compared to KEYNOTE-010. In KEYNOTE-010, 26% of patients were from an US investigational site, while all patients enrolled in KEYNOTE-042 were enrolled outside of the US. In KEYNOTE-010, 70% of patients had received at least one line of prior therapy for metastatic NSCLC and nearly 30% had received two or more lines of prior therapy. The proportion of the patients with PD-L1 TPS 1-49% and ≥ 50% were similar between the two studies.

Table 23 Comparison of Demographics and Selected Baseline Characteristics between KEYNOTE-042 and KEYNOTE-010 (ITT Population with TPS ≥ 1%)

	KEYNOTE-042 % (N= 1274)	KEYNOTE-010 % (N=1033)
Sex (male)	71	61
Age (median, range years)	63 years (25 -90)	63 years (20-88)
ECOG PS 0/1	31/69	34/66
Region East Asia/non-East Asia US/ex-US	 29/71 0/100	 19/79 26/74
Histology (squamous cell)	39	22
PDL-1 TPS ≥ 1% TPS 1-49% TPS ≥ 50%	 100 53 47	 100 57 43
Brain metastasis	5.5	15
Prior lines of treatment 0 1 2 ≥ 3	 100 0 0 0	 0 69 20 9

Source: BLA125514/S-47 KEYNOTE-042 and Clinical and Statistical Review of BLA125514/S-08
**Pooled from pembrolizumab 2 mg/kg and 10 mg/kg arms*

Table 24 summarizes KEYNOTE-042 efficacy results by TPS expression, per FDA analyses.

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Table 24 KEYNOTE-042 efficacy results by TPS expression (per FDA analyses)

	TPS ≥ 1%		TPS ≥ 1-49%		TPS ≥ 50%	
	Pembro N=637	Chemo N=637	Pembro N=338	Chemo N=337	Pembro N=299	Chemo N=300
OS						
Events (%)	371(58.2)	438(68.8)	214 (63.3)	239 (70.9)	157(52.5)	199(66.3)
Median in mos (95% CI)	16.7 (13.9,19.7)	12.1 (11.3,13.3)	13.4 (10.7, 18.2)	12.1 (11.0, 14.0)	20.0 (15.4, 24.9)	12.2 (10.4, 14.2)
Adjusted HR[1] (95% CI)	0.81 (0.71,0.93)		0.92 (0.77, 1.11)		0.69 (0.56, 0.85)	
p-value[2]	0.0036		.. [3]		0.0006	
PFS						
Events (%)	507 (79.6)	506 (79.4)	286 (84.7)	273 (81.1)	221(73.9)	233(77.7)
Median in mos (95% CI)	5.4 (4.3, 6.2)	6.5 (6.3, 7.0)	4.2 (4.1, 5.2)	6.8 (6.3, 8.1)	7.1 (5.9,9.0)	6.4 (6.1,6.9)
Adjusted HR[1] (95% CI)	1.07 (0.94, 1.21)		1.32 (1.11, 1.56)		0.81(0.67,0.99)	
p-value	. . [4]		. . [3]		0.034[5]	
ORR						
# Responses	174	169	56	73	118	96
ORR (95% CI)	27.3 (23.9,31.0)	26.5 (23.1,30.1)	16.6 (12.8, 21)	21.7 (17.4,26.5)	39.5 (33.9,45.3)	32.0 (26.8,37.6)
Median duration Range	20.2 (2.1+,31.2+)	8.3 (1.8+, 28.1)	17.4 (2.2, 28.5+)	8.2 (1.9+, 28.1)	20.2 (2.1+, 31.2+)	10.8 (1.8+,24.9+)

[1] Hazard ratio calculated using cox proportional hazards model with treatment group as a single covariate and stratified by histology, ECOG status, region and PD-L1 status
[2] Two-sided p-values based on stratified log-rank test; compared with stopping boundary value of 0.0291, tested hierarchically in order
[3] TPS ≥ 1-49% is an exploratory subgroup and OS hypothesis in this subgroup was not adjusted for multiplicity; therefore p-values are not reported for this subgroup.
[4] No alpha left for this analysis since testing of PFS in TPS ≥ 50% failed to cross boundary.
[5] Two-sided p-value of PFS hypothesis in TPS≥ 50% is not significant as compared to the boundary value of 0.0291; therefore, the subsequent hypotheses were not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints.

Reviewer's comment: A statistically significant improvement in OS in the overall population of patients with NSCLC with PD-L1 TPS ≥ 1% was observed in both KEYNOTE-042 and KEYNOTE-010. In both trials, a larger magnitude of treatment effect was observed in the subgroup of patients with NSCLC TPS ≥50% as compared to the subgroup with NSCLC TPS 1-49%. In KEYNOTE-010, results of the exploratory analysis of OS in the subgroup with TPS 1-49% [HR 0.79 (95% CI: 0.61, 1.04) in the 2 mg/kg arm, and HR 0.71 (95% CI: 0.53, 0.94) in 10 mg/kg arm)] indicates that the activity observed in the overall population with TPS ≥ 1% may not be driven by or largely attributable to the results in the TPS ≥ 50% subgroup. A similar conclusion cannot be drawn from the exploratory analysis results from the subgroup of patients with TPS 1-49% enrolled in KEYNOTE-042 [OS HR: 0.92 (0.77, 1.11)].

Additional Efficacy Considerations

Efficacy in the Subgroup of Patients with Stage III Disease

Data to support the inclusion of patients with "locally advanced" NSCLC in the proposed indication of *"pembrolizumab for first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD L1 TPS ≥ 1%"* consists of data from 160 patients (12.6%) with stage III disease (1.8% with stage IIIA and 10.8% with stage IIIB) enrolled in KEYNOTE-042 who were not candidates for surgical resection or definitive chemoradiation per investigator assessment. The patient demographics and baseline disease characteristics of patients in this subgroup and the reasons patients were not eligible for definite treatment, per investigator assessment, are summarized in Tables 11 and 12 earlier in this review.

Exploratory efficacy analyses were conducted to investigate the merit of including patients with stage III disease in the proposed indication. Results are shown in Tables 25 and 26.

Table 25 Exploratory OS and PFS Analysis in Patients with Stage III and Stage IV disease

		# Events/N		Median (months)		Stratified HR (95% CI)
	N	Pembro	Chemo	Pembro	Chemo	
OS						
TPS ≥ 1%						
Stage IIIA/B	160	42/76	56/84	23.79	13.34	0.79 (0.52, 1.22)
Stage IV	1114	329/561	382/553	15.8357	11.89	0.83 (0.71,0.96)
TPS ≥ 50%						
Stage IIIA/B	62	9/27	25/35	NR	13.34	0.29 (0.12, 0.69)
Stage IV	537	148/272	174/265	17.7084	11.99	0.75 (0.60, 0.94)
PFS						
TPS **≥1%**						
Stage IIIA/B	160	53/76	64/84	8.31	7	0.999 (0.67, 1.49)
Stage IV	1114	454/561	442/553	4.73	6.47	1.11 (0.97, 1.27)
TPS ≥ 50%						
Stage IIIA/B	62	13/27	28/35	13.01	7.29	0.53 (0.27, 1.06)
Stage IV	537	208/272	205/265	6.28	6.34	0.86 (0.70, 1.05)

Table 26 Exploratory ORR Analysis in Patients with Stage III and Stage IV Disease by TPS Expression

		Pembro		Chemo		ORR Diff. (95% CI)
	N	# Responders /N	ORR (95% CI)	# Responders /N	ORR (95% CI)	
TPS ≥ 1%						
Stage IIIA/B	160	26/76	34.21 (23.71, 45.99)	23/84	27.38 (18.21, 38.2)	6.83 (-7.48, 21.14)
Stage IV	1114	148/561	26.38 (22.78, 30.24)	146/553	26.4 (22.77, 30.29)	-0.02 (-5.2, 5.16)
TPS ≥ 50%						
Stage IIIA/B	62	17/27	62.96 (42.37, 80.6)	12/35	34.29 (19.13, 52.21)	28.68 (4.61, 52.74)
Stage IV	537	101/272	37.13 (31.37, 43.17)	84/265	31.7 (26.14, 37.67)	5.43 (-2.59, 13.46)

Reviewer's Comment:
Overall, the subgroup analyses suggest that pembrolizumab is effective in patients with stage III NSCLC with PD-L1 TPS ≥ 1% and TPS ≥ 50% based on subgroup analyses of OS, PFS and ORR the treatment effects in the stage III subgroup are and consistent with the treatment effects observed in patients with stage IV disease and the ITT population, despite a higher proportion of patients with NSCLC TPS 1-19% in the stage III subgroup compared to the subgroup with stage IV disease (45% versus 34%, Table 11).

The clinical reviewer acknowledges the exploratory nature of these findings; however, based on the available data, Merck's proposal to include the population of patients with "locally advanced" NSCLC in the indication is appropriate as this subgroup is relatively large (N=160) such that the subgroup analyses are likely to be reliable. The clinical reviewer recommends that the proposed indication statement be revised to reflect the population studied, i.e., "pembrolizumab for the first-line treatment of patients with metastatic NSCLC or stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation and whose tumors express PD L1 (TPS ≥ 1%)".

OS Analysis Based on Modified Country-Region Classification

Merck classified two countries – Ukraine and Russian Federation – into the "Others" category for region while considering the following to define region in the datasets – (Eastern) Europe, East Asia, Latin America and other. The review team believes that these two countries should be classified into the "(Eastern) Europe" region. The OS benefit by region in the TPS ≥ 1% population was reassessed based on this reclassification. The OS benefit was similar between these two classifications.

7.1.4. Integrated Assessment of Effectiveness

Pooling of data from different trials to assess effectiveness was not conducted for this sBLA. Refer to section 7.1.3 for Assessment of Effectiveness Across Trials.

7.2. Review of Safety

Safety Review Approach

The review of safety was focused on data submitted for 1251 patients randomized in KEYNOTE-042 who received at least one dose of study drug.

The review of safety included analysis of the submitted study report, datasets, line listings, case narratives, and case report forms (CRFs) from KEYNOTE-042. The review tools used included JMP and Excel programs.

The overall incidence and severity of AEs were compared to the safety data from: a) 154 patients enrolled in the pembrolizumab arm in KEYNOTE-024 (BLA125514/S-12), b) the pembrolizumab monotherapy Reference Safety Database (RSD), consisting of data from 2799 patients treated with pembrolizumab, including 1567 patients with advanced melanoma (KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006), and 1232 patients with NSCLC (KEYNOTE-001 and KEYNOTE-010) and c) the Cumulative Running Safety Dataset, consisting of data from 5246 patients who received at least one dose of pembrolizumab in the product's clinical development program for various hematologic and solid malignancies.

Pooling of safety data from KEYNOTE-042 with other safety data was not conducted for this application.

7.2.2. Review of the Safety Database

Overall Exposure

In KEYNOTE-042, a total of 636 patients received at least one 200 mg dose of pembrolizumab. Pembrolizumab 200 mg was administered as a 30-minute IV infusion Q3W. Treatment was to continue until 35 administrations were completed, disease progression, unacceptable toxicity, intercurrent illness that prevents further treatment, investigator or patient's decision to withdraw, pregnancy, noncompliance, or administrative reasons.

Patients randomized to the chemotherapy arm received carboplatin to AUC 5 or 6 IV and investigator's choice of either paclitaxel 200 mg/m^2 IV or pemetrexed 500 mg/m^2 on Day 1 of each 21-day cycle for 4 to 6 cycles, followed by optional pemetrexed 500 mg/m^2 IV every 3 weeks (non-squamous histologies only) until progression or other discontinuation criterion was met.

For patients randomized to receive chemotherapy who experience disease progression, no crossover to the pembrolizumab arm was allowed.

Treatment exposure per treatment arm in the ITT population (TPS ≥1%), TPS 1-49% and TPS ≥ 50% is summarized in the following table. The median duration of pembrolizumab exposure was 5.6 months (range 1 day to 27.3 months). The median number of pembrolizumab cycles administered was 9 (range 1 to 36). Among the 636 patients who received pembrolizumab, 65% received pembrolizumab for ≥3 months, 47.5% for ≥6 months and 29.4 % for ≥12 months.

The duration of exposure to pembrolizumab was longer in the TPS ≥ 50% subgroup when compared to TPS 1-49% (9.7 months versus 7.1 months).

Table 27 KEYNOTE-042 Summary of Treatment Exposure

	TPS ≥ 1%	
	Pembrolizumab N=636 (%)	Chemotherapy N=615 (%)
Treatment Duration (Months)		
Mean (SD)	8.3 (7.8)	5.1 (5.3)
Median (Min - Max)	5.6 (0.03 to 27.3)	3.5 (0.03 to 29.5)
Number of Cycles		
Mean (SD)	12.5 (10.9)	9.0 (7.3)
Median (Min - Max)	9 (1 to 36)	6 (1 to 42)
Duration of Exposure		
Treated	636	615
≥ 3 months	413 (65%)	408 (66)
≥ 6 months	302 (47.5)	143 (23.3)
≥ 12 months	187 (29.4)	65 (10.6)

Source ADaM dataset: adexsum.xpt and SDTM dataset: ex.xpt.

The type of chemotherapy administered in KEYNOTE-042 per tumor histology is summarized in the following table. All patients with squamous NSCLC histology received carboplatin in combination with paclitaxel, with two patients given maintenance therapy with pemetrexed, a protocol violation. The majority of patients (83%) with non-squamous cell NSCLC randomized to chemotherapy received carboplatin and pemetrexed. Among the 375 patients with non-squamous histology randomized to receive chemotherapy, 196 (52%) received pemetrexed as maintenance therapy.

Table 28 Pembrolizumab and Chemotherapy Received per Tumor Histology

Treatment	Safety Population N=1251	
	Non-Squamous N=769	Squamous N=482
Pembrolizumab	394	242
Chemotherapy	375	240
	n (%)	n (%)
- Paclitaxel/Carboplatin w Pemetrexed Maintenance	18 (4.8)	2 (0.8)
- Paclitaxel/Carboplatin w/o Pemetrexed Maintenance	45 (12)	238 (99)
- Pemetrexed/Carboplatin w Pemetrexed Maintenance	178 (47)	0 (0.0)
- Pemetrexed/Carboplatin w/o Pemetrexed Maintenance	134 (36)	0 (0.0)

Source ADaM dataset: ADaM dataset: adsl.xpt

Relevant characteristics of the safety population:

The safety population from KEYNOTE-042 is comprised of 1251 patients with advanced or metastatic NSCLC, who had not previously received systemic therapy for metastatic disease. A total of 636 patients received pembrolizumab and 615 patients received chemotherapy.

The characteristics of the safety population of pembrolizumab-treated patients in KEYNOTE-042 is consistent with the epidemiology and natural history of patients with metastatic NSCLC: the median age was 63 years (range 25 to 89), with 47% of the patients 65 years or older; 71% of the patients were male. The majority of patients were either former (56.6%) or current (21.3%) smokers; 63% were White and 30% were Asian; 88% had stage IV disease and 12% had stage III disease, while 6% had a history of brain metastases at baseline.

Refer to section 8.1.2, Tables 9 and 10 for the patient demographics and baseline disease characteristics of the ITT population.

Adequacy of the safety database

Overall, the safety database submitted by Merck, comprised of 636 pembrolizumab-treated patients with a median exposure of 5.6 months, was sufficient to identify AEs occurring at an incidence of approximately ≥ 0.5%.

7.2.3. 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 the KEYTRUDA-042 trial 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 (Appendix, Section 18.3). 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/placebo and chemotherapy infusion.

7.2.4. Safety Results

An overview of the AEs observed in KEYNOTE-042 is shown in Table 29. In KEYNOTE-042, there was a higher incidence of serious AE (41% vs. 30%), death due to an AE (11% vs. 8%) discontinuation of study drug due to an AE (19% vs. 15%) and serious AE (16% vs. 9%) in patients in the pembrolizumab arm when compared to the chemotherapy arm. The incidence of grade 3-5 AEs was also higher in the chemotherapy arm (57% vs. 50%).

Table 29 Overview of Adverse Events

	Pembrolizumab N=636 (%)	Chemotherapy N=615 (%)
No. of patients with one or more AE*^	610 (96)	606 (99)
Grade 3-5	318 (50)	351 (57)
Serious AEs	259 (41)	187 (30)
Patients died due to AE	70 (11)	46 (7.5)
Died due to a drug-related AE	13 (2.1)	14 (2.3)
Discontinued study drug(s) due to an AE	122 (19)	89 (15)
Discontinued study drug(s) due to a SAE	102 (16)	57 (9.0)

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"

Deaths

At the time of the data cutoff date, more patients in the chemotherapy arm had died compared to the pembrolizumab arm (69% vs. 58%). Death attributed to an AE occurred in 11% of patients in the pembrolizumab and 7.5% in the chemotherapy arm. 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 either treatment arm are listed in the following table.

Table 30 AEs Leading to Death occurring in ≥ 2 Patients in either Treatment Arm

MedDRA PT	Pembrolizumab N=636 (%)	Chemotherapy N=615 (%)
All deaths at the time of data cutoff^	371/637[&] (58.2)	438/637[&] (68.8)
Deaths due to an AE*	70 (11.0)	46 (7.5)
Death/sudden death	11 (1.8)	5 (0.8)
Pneumonia	8 (1.3)	7 (1.1)
Pulmonary embolism	6 (0.9)	5 (0.8)
Pulmonary hemorrhage	4 (0.6)	2 (0.3)
Respiratory failure	3 (0.5)	3 (0.5)
Cardiac arrest	2 (0.3)	0 (0.0)
Cardio-respiratory arrest	2 (0.3)	1 (0.2)
Gastric ulcer hemorrhage	2 (0.3)	0 (0.0)
Sepsis	2 (0.3)	0 (0.0)
Septic shock	2 (0.3)	1 (0.2)
Pulmonary sepsis	1 (0.2)	2 (0.3)
Pulmonary edema	0 (0.0)	2 (0.3)

^ Based on the ITT population (N=1274)

& include MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" *Source ADaM dataset: adae.xpt. and SDTM dataset: ae.xpt.*
* Exclude MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression"

Death due to an unknown cause/sudden death and pneumonia and pulmonary embolism were the most common causes of death in both treatment arms. A total of 11 (1.8%) patients in the pembrolizumab arm died while on study of unknown causes, compared to 5 patients (0.8%) in the chemotherapy arm. Brief narratives for the patients who died of unknown cause are presented in the following table.

Table 31 Summary Narrative of Adverse Events leading to Death in the Pembrolizumab Arm

	Patient ID	Cause of death MedDRA PT	Cycle/ Study date/ Days after last study drug	Summary
1	(b) (6)	Death	Post C1 Day 42 Day 18	58yo white female with stage IV, T3N2M1b with no significant co-morbid disease, died on study 18 days after one dose of pembrolizumab 200 mg. The patient was diagnosed with grade 1 hyperthyroidism on day 21. No other information available.
2	(b) (6)	Death	Post C11 Day 237 Day 19	69yo white female with stage IV adenoca and history of hypertension and Type 2 DM, died of unknown causes on study day 237, 19 days after the last dose of pembrolizumab. The patient experienced AEOSI with grade 2 hypothyroidism and grade 3 colitis, reportedly resolved prior to death
3	(b) (6)	Death	Post C3 Day 43 Day 0	66 yo white female diagnosed with stage IV adenoca of the lung and history of hypertension. The patient developed dyspnea, hypotension, asystole ≈ 2 hours after receiving the 3rd dose of pembrolizumab 200 mg. Cause of death was reported as unknown, secondary to lung cancer.
4	(b) (6)	Death	Post C5 Day 115 Day 30	70 yo white male with stage IV squamous NSCLC and history of MI, cardiac failure, LBBB with ventricular extrasystoles, developed fatigue (grade 2) on study day 105, became disabled and died, 30 days after the last dose of pembrolizumab. No other information is available.
5	(b) (6)	Death	Post C2 Day 24 Day 2	79yo black male with stage IV squamous cell NSCLC, history of hypertension, COPD and RBBB, died 2 days after receiving the 2nd dose of pembrolizumab; the patient reportly feel tired, sat down and died. Cause of death was reported as unknown.

6	(b) (6)	Death	Post C14 Day 290 Day 13	69yo Asian female with metastatic poorly differentiated NSCLC and history of hypertension, benign pituitary tumor died 13 days after receiving pembrolizumab cycle 14. The patient had an episode of Gr 3 dyspnea 6 days prior to death, reported as resolved. Cause of death was reported as unknown.
7	(b) (6)	Death	Post C11 Day 223 Day 11	72yo white male with stage IV squamous cell NSCLC and history of DM, HTN, and cerebral artery embolism died suddenly on study day 223, 11 days after the last dose of pembrolizumab. Cause of death was reported as sudden death NOS.
8	(b) (6)	Death	Post C7 Day 150 Day 3	75yo white male with stage IV adenoca NSCLC and history of DM, HTN, hyperlipidemia and hypercalcemia died suddenly at home on study day 3 days after receiving pembrolizumab C7. Cause of death was reported as unknown.
9	(b) (6)	Sudden Death	Post C2 Day 30 Day 7	56yo Asian female with stage IV adenoca of the lung and history of hypertension developed sudden onset of dyspnea followed by cardiac arrest 7 days after pembrolizumab C2. Pulmonary embolism was suspected but not confirmed. Cause of death was reported as sudden death.
10	(b) (6)	Death	Post C1 Day 7 Day 1	67yo white male with stage IV adenoca of the lung and history of myocardial infarction and cardiac failure, complained of not feeling well, collapsed and died on study day 7. Cause of death was unknown.
11	(b) (6)	Death	Post C11 Day 222 Day 12	79yo white male with stage IV squamous NSCLC and no pertinent co-morbid disease hospitalized with dehydration grade 3 gastroenteritis died suddenly while receiving treatment. Gastroenteritis was ongoing at the time of death. Cause of death was reported as unknown.

Reviewer's comment: The proportion of patients who died due to an AE was higher in the pembrolizumab arm compared to the chemotherapy arm (11.0% vs. 7.5%). Of the AEs leading to death, death due to an unknown cause/sudden death was numerically higher in the pembrolizumab arm compared to the chemotherapy arm (1.8% vs. 0.8%).

The proportion of patients who died due to an AE and death due to unknown cause in the KEYNOTE-042 study was compared to pembrolizumab's safety data base. The incidence of death due to an AE and due to unknown cause in pembrolizumab-treated patients was higher in KEYNOTE-042 when compared to pembrolizumab-treated patients enrolled in KEYNOTE-024, the pembrolizumab monotherapy RSD and the pembrolizumab cumulative dataset, as shown in the following table.

Table 32 Comparison of Incidence of Death due to an AE and Death due to an Unknown Cause Between KEYNOTE-042, KEYNOTE-024 and Pembrolizumab Safety Data Sets

	KEYNOTE-042 Pembrolizumab Arm N=636	KEYNOTE-024 Pembrolizumab Arm N=154	Pembrolizumab Monotherapy RSD* N=2799	Pembrolizumab Cumulative Data Set N=5246
Deaths due to an AE	70 (11.0)	10 (6.5)	111 (3.9)	38 (0.7)
Death due to unknown cause^ (NOS)	11 (1.8)	1 (0.6)	17 (0.6)	40 (0.7)

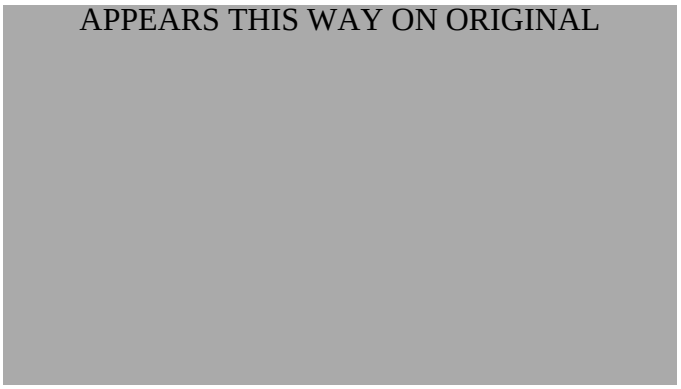
** RSD = pembrolizumab monotherapy Reference Safety Database*
^ Includes: death and sudden death

Reviewer's Comment: Although 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 arm relative to the chemotherapy arm in KEYNOTE-042 and relative to other available safety data for pembrolizumab, with the lack of additional information (e.g., autopsy reports), a causal association to pembrolizumab cannot be completely ruled out.

The reviewer recommends that the adverse reactions of death/sudden death leading to treatment discontinuation of pembrolizumab in KEYNOTE-042 (refer to section below) be included in the KEYTRUDA Prescribing Information. This captures the majority (10 of 11) of the adverse reactions reported as death due to unknown cause or sudden death. FDA will continue to closely monitor all adverse event reports associated with pembrolizumab in ongoing trials and in the postmarketing setting.

CDTL Comment: The finding of an increased incidence of death due to AE and death due to unknown cause/sudden death relative to the incidence observed in the pooled safety datasets for pembrolizumab are likely due to the factors cited above by the clinical reviewer (i.e., underlying malignancy and comorbid conditions). The increased incidence in KEYNOTE-042 relative to KEYNOTE-024 may be at least partially due to differences in standard of care and/or study conduct, given that KEYNOTE-042 was conducted entirely ex-U.S. Given the extensive safety data available for pembrolizumab in patients with solid tumors and specifically in patients with NSCLC, the 11% incidence of death due to AE, including a 1.8% incidence of death due to unknown cause/sudden death, in KEYNOTE-042 does not raise particular concerns, since this is an isolated finding in one study in a patient population in whom pembrolizumab has been extensively studied and the results of KEYNOTE-042 demonstrate an improvement in OS for pembrolizumab vs chemotherapy.

Serious Adverse Event



In KEYNOTE-042, 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 arm compared to the chemotherapy arm (41% vs. 30%). The most common SAEs in the pembrolizumab were in the SOC categories of respiratory, thoracic and mediastinal disorders (14.2%) and infections and infestations (12.1%). The most common SAEs in the chemotherapy arm were in the SOC categories of infections and infestations (10.4 %) and blood and lymphatic system disorders (6.8%).

SAEs that occurred at a ≥ 1% higher frequency in the pembrolizumab compared to the chemotherapy arm were: death/sudden death (1.8 % vs. 0.8%), pneumonitis (4.5% vs. 0.4%), pneumonia (8.1% vs. 6.3%), dyspnea (1.3 % vs. 0.3%), and pleural effusion (2.2% vs. 0.8%). SAEs occurring in ≥ 1% of patients in any treatment arm in KEYNOTE-042 are listed in Table 33.

Table 33 Serious AEs occurring in ≥ 1% of Patients in Any Treatment Arm

MedDRA SOC/ PT	Pembrolizumab N=636 (%)	Chemotherapy N=615 (%)
Patients with at least one serious AE	259 (41)	187 (30)
Blood and lymphatic system disorders	6 (0.9)	42 (6.8)
Anemia	1 (0.2)	17 (2.8)
Febrile neutropenia	0 (0.0)	15 (2.4)
Neutropenia	0 (0.0)	6 (1.0)
Cardiac disorders	27 (4.2)	10 (1.6)
Pericardial effusion	6 (0.9)	0 (0.0)
Endocrine disorders	8 (1.3)	0 (0.0)
Gastrointestinal disorders	29 (4.6)	11 (1.8)
General disorders & adm. site cond.	22 (3.5)	14 (2.3)
Death/Sudden death	11 (1.8)	5 (0.8)
Hepatobiliary disorders	9 (1.4)	1 (0.2)
Infections and infestations	77 (12.1)	64 (10.4)
Bronchitis	7 (1.1)	2 (0.3)
Pneumonia*	52 (8.1)	39 (6.3)
Injury, poisoning & procedural compl.	7 (1.1)	1 (0.2)
Investigations	8 (1.3)	7 (1.1)
Metabolism and nutrition disorders	12 (1.9)	16 (2.6)
Nervous system disorders	15 (2.4)	15 (2.4)
Renal and urinary disorders	7 (1.1)	5 (0.8)
Respiratory, thoracic & mediastinal dis.	90 (14.2)	41 (6.7)
Dyspnea	8 (1.3)	2 (0.3)
Hemoptysis	7 (1.1)	1 (0.2)
Pleural effusion	14 (2.2)	5 (0.8)
Pneumonitis^	29 (4.5)	2 (0.4)
Pulmonary embolism	15 (2.4)	11 (1.8)
Vascular disorders	7 (1.1)	9 (1.5)

**Includes: pneumonia, pneumonia bacterial, pneumonia Klebsiella, pneumocystis jirovecii pneumonia, lower respiratory tract infection, lung infection, lung abscess*
^ Includes: pneumonitis and interstitial lung disease

Dropouts and/or Discontinuations Due to Adverse AEs leading to treatment discontinuation are listed in Table 34. More patients in the pembrolizumab arm than in the chemotherapy arm discontinued study treatment due to an AE (19.2% vs. 14.5%) or a serious AE (16.0% vs. 9.3%). The most common AEs leading to discontinuation of pembrolizumab were pneumonitis (3.0%), death due to unknown cause/sudden death (1.6%) and pneumonia (1.4%). In the chemotherapy arm, pneumonia was the most common AE leading to discontinuation of chemotherapy (1.3%).

Table 34 AEs Leading to Treatment Discontinuation Occurring in ≥ 1 % of the Patients in the Pembrolizumab Arm

Treatment Discontinuation due to an AE	Pembrolizumab N=636 (%)	Chemotherapy N=615 (%)
No. of Patients with ≥ 1 AE	122 (19.2)	89 (14.5)
Pneumonitis^	19 (3.0)	0 (0.0)
Death*	10 (1.6)	4 (0.7)
Pneumonia	9 (1.4)	8 (1.3)
ALT increased	6 (0.9)	4 (0.7)
Pulmonary Embolism	6 (0.9)	4 (0.7)

^ *Includes: pneumonitis and interstitial lung disease*
* *Includes: death and sudden death*

The incidence of AEs leading to study drug interruption was similar between the pembrolizumab and chemotherapy arms (33.3% vs. 36.6%). The most common (≥ 2%) AEs leading to interruption of pembrolizumab were pneumonitis (3.1%), pneumonia (3.0%), hypothyroidism (2.2%), increased ALT (2.0%). In the chemotherapy arm, anemia (9.0%) was the most common AE leading to interruption of chemotherapy.

Significant Adverse Events

AE severity was graded using the NCI-CTCAE version 4.03. The incidence of Grade 3-5 AEs in KEYNOTE-042 are listed in Table 35.

The incidence of Grade 3-5 AEs was higher in the chemotherapy arm compared to the pembrolizumab arm (57% vs. 50%). The most common Grade 3-5 AEs in the pembrolizumab arm were in the SOC categories of respiratory, thoracic and mediastinal disorders (14%) and infections and infestations (12%). The most common Grade 3-5 AEs in the chemotherapy arm were in the SOC categories of blood and lymphatic system disorders (24%) and infections and infestations (12%).

The only Grade 3-5 AE that occurred at a ≥ 2% higher frequency in the pembrolizumab arm compared to the chemotherapy arm was pneumonitis (3.2% vs. 0.0%).

Treatment Emergent Adverse Events and Adverse Reactions

AEs (all grades and grade 3-5) occurring in more than 5% of patients by MedDRA SOC and PT in either treatment arm are listed in Table 35. The most common adverse reaction reported in both treatment arms was fatigue/asthenia (27% and 35%).

MedDRA Preferred Term AEs (all grades) that occurred at a ≥ 5% higher incidence in the pembrolizumab arm compared to the chemotherapy arm were: pneumonitis (7% vs. 0.2%), hyperthyroidism (6% vs. 0.7%), hypothyroidism (12% vs. 1.5%), cough (16% vs. 11%), dyspnea (17% vs. 11%), and pruritus (10% vs. 2.9%).

Among patients treated with pembrolizumab, the most common AEs occurring in ≥ 10% of patients were: fatigue/asthenia (25%), dyspnea (17%), decreased appetite (17%), cough (16%), rash (15%), hypothyroidism (12%), constipation (12%), diarrhea (12%), nausea (12%), pneumonia (12%), pyrexia (10%), and weight loss (10%).

Known chemotherapy related AEs of nausea and vomiting, alopecia and peripheral neuropathy were, as expected, observed at a higher frequency in the chemotherapy arm compared to the pembrolizumab arm: nausea (32% vs. 12%), vomiting (17% vs. 8%), peripheral and sensory neuropathy (16% vs. 1.4%) and alopecia (22% vs. 0.5%).

Table 35 Adverse Events Occurring in **≥5%** of Patients in either Treatment Arm

MedDRA SOC and PT	Pembrolizumab N=636 (%)		Chemotherapy N=615 (%)	
	All Grades	Grade 3-5	All Grades	Grade 3-5
Patients with AEs	610 (96)	318 (50)	606 (99)	351 (57)
Cardiac Disorders	50 (8)	28 (4.4)	41 (7)	13 (2.1)
Endocrine Disorders	106 (17)	8 (1.3)	17 (2.8)	0 (0)
Hyperthyroidism	39 (6)	1 (0.2)	4 (0.7)	0 (0)
Hypothyroidism	77 (12)	1 (0.2)	9 (1.5)	0 (0)
Eye Disorders	34 (6)	1 (0.2)	47 (8)	1 (0.2)
Gastrointestinal Disorders	267 (42)	29 (4.6)	342 (56)	18 (2.9)
Constipation	77 (12)	0 (0)	130 (21)	1 (0.2)
Diarrhea	74 (12)	5 (0.8)	75 (12)	3 (0.5)
Nausea	74 (12)	3 (0.5)	196 (32)	7 (1.1)
Stomatitis	18 (2.8)	2 (0.3)	33 (5)	0 (0)
Vomiting	51 (8)	3 (0.5)	107 (17)	3 (0.5)
General Disorders & Admin. Site	284 (45)	47 (7)	311 (51)	38 (6)
Chest pain	52 (8)	3 (0.5)	44 (7)	1 (0.2)
Fatigue^	159 (25)	20 (3.1)	209 (35)	24 (3.9)
Malaise	17 (2.7)	1 (0.2)	34 (6)	2 (0.3)
Peripheral edema	31 (5)	7 (1.1)	34 (6)	0 (0)
Pyrexia	65 (10)	2 (0.3)	48 (8)	0 (0)
Hepatobiliary Disorders	33 (5)	14 (2.2)	8 (1.3)	3 (0.5)
Infections and infestations	257 (40)	75 (12)	219 (36)	68 (11)
Bronchitis	34 (5)	7 (1.1)	24 (3.9)	3 (0.5)
Pneumonia	76 (12)	47 (7)	54 (9)	35 (6)
Upper respiratory tract infection	40 (6)	0 (0)	32 (5)	1 (0.2)
Injury, Poisoning & Procedures	38 (6)	5 (0.8)	35 (6)	1 (0.2)
Investigations	236 (37)	41 (6)	255 (42)	92 (15)
Weight decreased	64 (10)	6 (0.9)	45 (7)	1 (0.2)
Metabolism and Nutrition Disorders	207 (33)	47 (7)	217 (35)	8 (1.3)
Decreased appetite	110 (17)	11 (1.7)	131 (21)	9 (1.5)
Musculoskeletal & Connective Tissue	206 (32)	13 (2.0)	240 (39)	8 (1.3)
Back pain	62 (9.7)	2 (0.3)	44 (7)	2 (0.3)

Musculoskeletal pain	41 (6)	0 (0)	27 (4.4)	1 (0.2)
Myalgia	32 (5)	1 (0.2)	70 (11)	0 (0)
Pain in extremity	30 (4.7)	2 (0.3)	34 (6)	1 (0.2)
Neoplasms, benign, malign. unspecified	37 (6)	16 (2.5)	13 (2.1)	4 (0.7)
Nervous System Disorders	129 (20)	20 (3.1)	246 (40)	31 (5)
Dizziness	23 (3.6)	0 (0)	38 (6)	3 (0.5)
Headache	45 (7)	12 (1.9)	51 (8)	18 (2.9)
Neuropathy peripheral	5 (0.8)	0 (0)	53 (9)	5 (0.8)
Peripheral sensory neuropathy	4 (0.6)	0 (0)	43 (7)	6 (1.0)
Psychiatric disorders	68 (11)	6 (0.9)	75 (12)	2 (0.4)
Insomnia	33 (5)	1 (0.2)	44 (7)	0 (0)
Renal and Urinary Disorders	47 (7)	6 (0.9)	46 (8)	8 (1.1)
Respiratory, Thoracic and Mediastinal	324 (51)	86 (14)	221 (36)	45 (7)
Cough	99 (16)	1 (0.2)	65 (11)	2 (0.3)
Dyspnea	105 (17)	13 (2.0)	70 (11)	5 (0.8)
Hemoptysis	48 (8)	7 (1.1)	22 (3.6)	3 (0.5)
Pneumonitis	47 (7)	20 (3.2)	1 (0.2)	0 (0)
Skin and Subc. Tissue Disorders	188 (30)	13 (2.0)	224 (36)	12 (2.0)
Alopecia	3 (0.5)	0 (0)	138 (22)	7 (1.1)
Pruritus	62 (10)	3 (0.5)	18 (2.9)	0 (0)
Rash*	94 (15)	8 (1.3)	49 (8)	1 (0.2)
Vascular Disorder	73 (12)	22 (3.5)	52 (9)	10 (1.6)
Hypertension	27 (6)	12 (1.9)	14 (2.3)	4 (0.7)

^ *Includes: fatigue and asthenia*
** Includes: rash, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular*

Laboratory Findings

Laboratory alterations from baseline throughout the study, graded per NCI CTCAE v. 4.03, are summarized in Tables 36, 37 and 38.

Routine 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 trial and when medically necessary.

Table 36 summarizes the hematologic changes from baseline in patients enrolled in KEYNOTE-042 who received at least one dose of study drug.

Table 36 Hematologic Abnormalities Changes from Baseline

Laboratory Abnormalities	Pembrolizumab N=636 (%)			Chemotherapy N=615 (%)		
	N^	All Grades	Grade 3-4	N^	All Grades	Grade 3-4
Anemia	610	263 (43)	27 (4.4)	597	472 (79)	114 (19)
White blood cell decreased	610	49 (8)	7 (1.1)	600	274 (46)	78 (13)
Lymphocyte count decreased	603	180 (30)	44 (7)	597	244 (41)	76 (13)
Neutrophil count decreased	603	44 (7)	18 (3)	601	236 (39)	109 (18)
Platelet count decreased	607	73 (12)	10 (1.6)	599	252 (42)	56 (9)

Source: P042V01MK3475 CSR, adapted from Merck's table.

As expected based on the mechanism of action and known safety profile of chemotherapeutic agents, patients enrolled in the chemotherapy arm in KEYNOTE-042 experienced a higher incidence of myelosuppression (all grades and grade 3-4) compared to patients enrolled in the pembrolizumab arm.

Table 37 summarizes renal function and serum electrolyte changes from baseline in KEYNOTE-042.

Table 37 Renal and Electrolyte Abnormalities Changes from Baseline

Laboratory Abnormalities	Pembrolizumab N=636 (%)			Chemotherapy N=615 (%)		
	N^	All Grades	Grade 3-4	N^	All Grades	Grade 3-4
Increased creatinine	609	94 (15)	7 (1.1)	595	101 (17)	2 (0.3)
Hypocalcemia	602	153 (25)	15 (2.5)	589	110 (19)	4 (0.7)
Hypercalcemia	602	98 (16)	17 (2.8)	589	69 (12)	7 (1.2)
Hypokalemia	607	73 (12)	16 (2.6)	590	69 (12)	16 (2.7)
Hyperkalemia	607	140 (23)	18 (3.0)	590	118 (20)	13 (2.2)
Hyponatremia	608	186 (31)	53 (9)	593	190 (32)	50 (8)
Hypomagnesemia	596	70 (12)	2 (0.3)	586	162 (28)	3 (0.5)
Hypermagnesemia	596	42 (7)	3 (0.5)	586	28 (4.8)	3 (0.5)
Hypophosphatemia	598	119 (20)	28 (4.7)	585	98 (17)	25 (4.3)

^ *Number of subjects with at least one baseline and post-baseline laboratory measurement used as the denominator in percentage calculation.*
Source: P042V01MK3475 CSR, adapted from Merck's table

In general, the incidence of serum creatinine and electrolyte alterations in KEYNOTE-042 were similar between the two treatment arms, with the exception of hypomagnesemia, which occurred at a higher frequency in the chemotherapy arm (28%) compared to the pembrolizumab arm (12%).

Liver function changes from baseline in KEYNOTE-042 are summarized in Table 38, adapted from Merck's table.

Table 38 Liver Function Abnormalities Changes from Baseline

Laboratory Abnormalities	Pembrolizumab N=636 (%)			Chemotherapy N=615 (%)		
	N^	All Grades	Grade 3-4	N^	All Grades	Grade 3-4
Alanine aminotransferase increased	607	200 (33)	29 (4.8)	201	201 (34)	17 (2.9)
Albumin decreased	600	200 (33)	13 (2.2)	588	172 (29)	6 (1.0)
Alkaline phosphatase increased	602	174 (29)	14 (2.3)	592	171 (29)	2 (0.3)
Aspartate aminotransferase increased	609	191 (31)	22 (3.6)	593	191 (32)	10 (1.7)
Bilirubin increased	608	79 (13)	8 (1.3)	592	46 (8)	2 (0.3)

^ *Number of patients with at least one baseline and post-baseline laboratory measurement used as the denominator in percentage calculation.*
Source: P042V01MK3475 CSR, adapted from Merck's table

Although the overall incidence of all grades liver function abnormalities is similar between the two treatment arms, Grade 3-4 abnormalities are slightly higher in the pembrolizumab arm compared to the chemotherapy arm.

Other treatment-emergent laboratory abnormalities occurring in ≥20% of patients in KEYNOTE-042 were hyperglycemia (all grades/Grade 3-4 52%/4.7% in the pembrolizumab arm and 51%/5% in the chemotherapy arm) and increased prothrombin INR (21%/2.0% in the pembrolizumab arm and 15%/2.9% in the chemotherapy arm.

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-042. 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 and throughout the study, as clinically warranted. Abnormalities in ECGs were reported as AEs. AEs with potential ECG abnormalities occurring in ≥1% of patients in either treatment arm are listed in Table 39.

Table 39 Cardiac Disorder Adverse Events with Potential ECG Abnormalities

MedDRA SOC/PT	Pembrolizumab N=636 (%)		Chemotherapy N=615 (%)	
	All Grades	Grade 3-5	All Grades	Grade 3-5
Patients with an AE	610 (96)	318 (50)	606 (99)	351 (58)
Cardiac Disorder SOC	50 (8)	28 (5.4)	41 (7)	13 (2.2)
Atrial fibrillation	8 (1.3)	2 (0.3)	2 (0.3)	0 (0.0)
Pericardial effusion	9 (1.4)	6 (1.0)	2 (0.3)	1 (0.2)
Tachycardia	5 (0.8)	0 (0)	10 (1.6)	0 (0)

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.

7.2.5. 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 the AEOSI definition as per Merck.

Immune-related Adverse Events

Table 40 summarizes the incidence of AEOSI observed in KEYNOTE-042 by NCI CTCAE v 4.03 toxicity grade. AEOSI were reported in 28% of patients in the pembrolizumab arm and 7% in the chemotherapy arm. The most common immune-related AEs were hypothyroidism (12%), pneumonitis (8%) and hyperthyroidism (6%). Immune-related AEs were severe (Grade 3 or 4) in 50 of 177 (8%) of patients in the pembrolizumab arm. The most common Grade 3 or 4 AEOSI was pneumonitis (3.3%).

Table 40 Incidence of AEOSI* in KEYNOTE-042

AEOSI	Pembrolizumab N=636 (%)		Chemotherapy N=615 (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Patients with ≥ 1 AEOSI	177 (28)	50 (8)	44 (7)	9 (1.4)
Endocrinopathies				
Hypothyroidism	77 (12)	1 (0.2)	9 (1.5)	0 (0.0)
Hyperthyroidism	39 (6)	1 (0.2)	4 (0.7)	0 (0.0)
Thyroiditis	10 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Adrenal insufficiency	4 (0.6)	2 (0.4)	1 (0.2)	0 (0.0)
Hypophysitis	3 (0.5)	3 (0.5)	0 (0.0)	0 (0.0)
Pneumonitis	53 (8.3)	21 (3.3)	3 (0.5)	1 (0.2)
Hepatitis	9 (1.4)	7 (1.2)	0 (0.0)	0 (0.0)
Colitis	7 (1.1)	4 (0.6)	2 (0.3)	1 (0.2)
Nephritis	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
Myocarditis	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Pancreatitis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Severe skin reactions*	15 (2.4)	11 (1.7)	2 (0.3)	1 (0.2)
Infusion related reaction	10 (1.6)	1 (0.2)	26 (4.2)	6 (1.0)

- Source BLA125514/S-47: ADaM datasets adsl.xpt and ae.xpt

- Includes all AEs observed up to 30 days of last study dose and serious AEs up to 90 days of last dose

* *Refer to Appendix, Section 18.3*

A brief narrative of selected AEOSI are summarize below.

Deaths associated with pneumonitis

In KEYNOTE-042, death attributed to or associated with pembrolizumab-induced pneumonitis occurred in three patients, as summarized below:

- Patient ID (b) (6) was a 62 year old white male with stage IV adenocarcinoma of the lung and history of diabetes mellitus and COPD, hospitalized on study day 16 following one cycle of pembrolizumab 200 mg IV with dyspnea and hypoxemia. CT scan showed ground glass appearance, bilateral bronchoalveolar consolidation. Pneumonitis was confirmed by bronchoscopy with a subsequent BLA culture positive for candida. The patient was treated with methylprednisolone, enoxaparin and ceftriaxone, fluconazole and O2 by nasal canula. Pembrolizumab was discontinued due to the SAE. The patient was discharged on day 26 but readmitted three additional times in the following weeks due to progressive worsening of pneumonitis. The patient died on study day 51. Death was attributed to pneumonitis.
- Patient ID (b) (6) was a 46 year old white male with stage IV squamous cell carcinoma of the lung and prior history of pulmonary embolism and dyspnea, hospitalized on study day 2 after one dose of pembrolizumab 200 mg IV with dyspnea and productive cough. The patient was initially diagnosed with respiratory tract infection (grade 3). On study day 5 a CT scan showed signs of pneumonitis, alveolitis

and hepatization. The patient was started on enoxaparin, vancomycin and methylprednisolone and dexamethasone. On study day 10 due to progressive respiratory failure, the patient was placed on mechanical ventilation but died as a result of the respiratory failure. An autopsy was not performed. The cause of death was reported to be respiratory failure due to drug-related SAE.

- Patient ID (b) (6) was a 45 year old white male with stage IV adenocarcinoma of the lung and prior medical history of pneumonia, nasopharyngitis, dyspnea and pleural effusion, hospitalized on study day 27 with worsening dyspnea and hypoxemia. A CT scan showed diffuse nodular lesions, subsegmental emboli and ground glass appearance of the right lung. A BLA culture was positive for Klebsiella bacteria. The patient was treated with antibiotics and dexamethasone but progressed with respiratory failure and died. The cause of death was grade 5 pneumonitis and Klebsiella pneumonia.

Reviewer's comment: Merck reported only one death (patient ID (b) (6) due to pneumonitis in KEYNOTE-042. In the opinion of the clinical reviewer, pneumonitis associated with pembrolizumab contributed to the death of two additional patients (ID (b) (6) and ID (b) (6).

Myocarditis

Grade 3 myocarditis was reported in an 85 year old Hispanic male (ID (b) (6) with stage IV adenocarcinoma of the lung following 26 doses of pembrolizumab 200 mg Q3W. On study day 557 the patient was hospitalized with acute cardiac dysfunction. An echocardiogram showed diffuse left ventricle hypokinesia with an ejection fraction of 35%, and ECG showed decreased amplitude of the QRS complex for which myocarditis was the suspected cause. The patient was treated with prednisone, beta blocker, diuretics, anti-arrhythmics and ACE inhibitor. Myocarditis was reported as resolved with sequelae (grade 1 cardiac failure) on study day 611. Pembrolizumab was permanently discontinued.

The incidences of AEOSI observed in the KEYNOTE-042 trial were compare to the KEYNOTE-024 trial, the pembrolizumab monotherapy RSD and the pembrolizumab cumulative safety dataset, as shown in Table 41.

The overall incidence of AEOSI (all grade and grade 3-5) observed in KEYNOTE-042 was similar to what was observed in KEYNOTE-024, but higher than what is reported in the pembrolizumab monotherapy Reference Safety Database. The most notable difference is the increased incidence of pneumonitis in both KEYNOTE-042 (8.3%) and KEYNOTE-024 (7.8%) compared to the Reference Safety data base (3.4%).

Table 41 Incidence of AEOSI in KEYNOTE-042, KEYNOTE-024 and Applicant's Safety Datasets

AOSI	KEYNOTE-042 Pembrolizumab N=636 (%)		KEYNOTE-024 Pembrolizumab N= 154 (%)		Pembrolizumab Monotherapy RSD* N=2799 (%)		Cumulative Running Safety Dataset N=5246 (%)	
	All Grade	Grade 3-5	All Grade	Grade 3-5	All Grade	Grade 3-5	All Grade	Grade 3-5
Patients with one or more AEs	177 (27.8)	51 (8.0)	45 (29.2)	20 (13.0)	594 (21.2)	142 (5.1)	1188 (22.6)	313 (6.0)
Hypothyroidism	77 (12.1)	3 (0.5)	16 (10.3)	1 (0.1)	237 (8.5)	3 (0.1)	503 (9.6)	8 (0.2)
Pneumonitis	53 (8.3)	22 (3.5)	12 (7.8)	5 (0.6)	94 (3.4)	36 (1.3)	211 (4.0)	81 (1.5)
Hyperthyroidism	39 (6.1)	1 (0.2)	11 (7.1)	0 (0.0)	96 (3.4)	4 (0.1)	200 (3.8)	5 (0.1)
Severe skin react	15 (2.4)	11 (1.7)	6 (3.9)	6 (0.7)	38 (1.4)	29 (1.0)	79 (1.5)	62 (1.2)
Thyroiditis	10 (1.6)	0 (0.0)	4 (2.6)	0 (0.0)	16 (0.6)	0 (0.0)	46 (0.9)	2 (< 0.1)
Infusion reaction	10 (1.6)	1 (0.2)	8 (5.2)	1 (0.1)	71 (2.5)	7 (0.2)	124 (2.4)	10 (0.2)
Hepatitis	9 (1.4)	7 (1.1)	1 (0.1)	1 (0.1)	19 (0.7)	14 (0.5)	36 (0.7)	28 (0.6)
Colitis	7 (1.1)	4 (0.6)	6 (3.9)	3 (0.4)	48 (1.7)^	33 (1.2)	95 (1.8)	59 (1.2)
Adrenal insuf	4 (0.6)	2 (0.3)	0 (0.0)	0 (0.0)	22 (0.8)	10 (0.3)	38 (0.7)	19 (0.4)
Hypophysitis	3 (0.5)	3 (0.5)	1 (0.1)	1 (0.1)	17 (0.6)	9 (0.3)	24 (0.5)	16 (0.3)
Nephritis	3 (0.5)	1 (0.2)	1 (0.1)	1 (0.1)	9 (0.3)	1 (< 0.1)	13 (0.2)	8 (0.2)
Myocarditis	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	5 (0.1)
Pancreatitis	1 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	9 (0.3)	6 (0.2)	15 (0.3)	9 (0.2)
Encephalitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	1 (<0.1)	2 (< 0.1)	2 (< 0.1)
Guillain-Barre Syn	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	3 (0.1)	2 (< 0.1)
Myasthenia Syn	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	1 (<0.1)	2 (< 0.1)	1 (<0.1)
Myositis	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	11 (0.4)	1 (<0.1)	23 (0.4)	4 (0.1)
Sarcoidosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	3 (0.1)	0 (0.0)
Type 1 DM	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	6 (0.2)	2 (0.1)	13 (0.2)	5 (0.1)
Uveitis	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	14 (0.5)	1 (<0.1)	20 (0.4)	3 (0.1)

Source: adapted from Merck's table, BLA125514/S-47, Summary of Clinical Safety

** RSD = pembrolizumab monotherapy Reference Safety Database*

^ Based on Merck's errata in BLA125514/S-47, Summary of Clinical Safety

Reviewer's comment: Pneumonitis occurred at a higher incidence in clinical trials of patients with previously untreated NSCLC (KEYNOTE-042 and KEYNOTE-024) compared to the pembrolizumab monotherapy RSD. This difference can be partly attributed to the differences in population, as patients with NSCLC have characteristics (e.g. smoking history) and underlying comorbid conditions (COPD, cardiovascular disease), that might predispose the population to drug-induced pulmonary toxicity. The clinical reviewer recommends that the increased incidence of pneumonitis observed in KEYNOTE-042 and KEYNOTE-024 be included in the KEYTRUDA Prescribing Information.

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

Patient Reported Outcome (PRO) questionnaires were not planned or administered in KEYNOTE-042.

7.2.7. Safety Analyses by Demographic Subgroups

Age

In KEYNOTE-042, 44% (555/1251) of patients who received at least one dose of study drug were age 65 years or older. Table 42 presents an overview of AEs by age group < 65 years and ≥ 65 years of age.

Table 42 Overview of Adverse Events by Age Group

	Pembrolizumab N=636 (%)		Chemotherapy N=615 (%)	
Years of age	< 65	≥ 65	< 65	≥ 65
N	358	278	338	277
N with any AE	343 (96)	267 (96)	335 (99)	271 (98)
Grade 3-5 AEs	167 (47)	151 (54)	179 (53)	172 (62)
Serious AE	141 (39)	118 (42)	92 (27)	95 (34)
Died due to a drug-related AE	7 (2.0)	6 (2.2)	8 (2.4)	6 (2.2)
Discontinued due to an AE	58 (16)	64 (23)	35 (10)	54 (20)
Discontinued due to a SAE	49 (14)	53 (19)	25 (7)	32 (12)

Source: BLA125514/S-47: ISS ADaM-adsl.xpt; adae.xpt

Overall, in both treatment arms, the proportion of patients age 65 or older who experienced grade 3-5 AEs and serious AEs or discontinued study due to an AE was higher than patients age 65 or younger. Death attributed to a drug-related AE was similar between patients who were age 65 or younger and those who were 65 or older in both treatment arms.

Gender

In KEYNOTE-042, 29% (364/1251) of patients were female. Table 43 summarizes the incidence of AEs by gender in KEYNOTE-042.

Table 43 Overview of Adverse Events by Gender

	Pembrolizumab N=636 (%)		Chemotherapy N=615 (%)	
Gender	Male	Female	Male	Female
N	449	187	438	177
N with any AE	428 (95)	182 (97)	432 (99)	174 (98)
Grade 3-5 AEs	213 (47)	105 (56)	247 (56)	104 (59)
Serious AE	180 (40)	79 (42)	139 (32)	48 (27)
Died due to a drug-related AE	8 (1.8)	5 (2.7)	10 (2.3)	4 (2.3)
Discontinued due to an AE	90 (20)	32 (17)	55 (15)	23 (13)
Discontinued due to a SAE	74 (17)	28 (15)	44 (10)	13 (7)

Source: BLA125514/S-47: ISS ADaM-adsl.xpt; adae.xpt

The incidence of grade 3-4 AEs was higher in females compared to males treated with pembrolizumab. No other substantial differences were noted in the overall incidence of AEs between male and female patients enrolled in KEYNOTE-042 in either treatment arm.

7.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies or clinical trials were included in this application.

7.2.9. Additional Safety Explorations

Safety Analysis by PDL-1 TPS Cutoff

The overall incidence of AEs in patients with tumors with PDL-1 TPS 1-49% was compared with the incidence of AEs in patients with TPS ≥50% and the ITT population (TPS ≥ 1%). Results are summarized in Table 44.

As noted in section 7.2.4, in KEYNOTE-042, more patients in the pembrolizumab arm experienced a serious AE (41% vs. 30%), died due to an AE (11% vs. 8%) or discontinued pembrolizumab due to an AE (19.2% vs. 14.5%) and serious AE (16.0% vs. 9.3%) when compared to the chemotherapy arm.

The incidence of Grade 3-5 AEs, serious AEs and AEs leading to study drug discontinuation were, in general, similar between the subgroups of patients with TPS 1-49% and TPS ≥ 50%. In the pembrolizumab arm, the proportion of patients in the TPS 1-49% subgroup who died due to an AE was higher compared to the TPS 1-49% subgroup in the chemotherapy arm (14% vs. 9%) and higher than pembrolizumab-treated patients in the TPS ≥ 50% subgroup (8%).

Table 44 Adverse Events by TPS 1-49% and TPS ≥ 50%

PDL-1 TPS expression	≥ 1%		1-49%		≥ 50%	
	Pembro N=636 (%)	Chemo N=615 (%)	Pembro N=329 (%)	Chemo N=327 (%)	Pembro N=291 (%)	Chemo N=289 (%)
No. of patients with ≥ 1 AE*^	610 (96)	606 (99)	325 (99)	324 (99)	289 (99)	285 (99)
Grade 3-5	318 (50)	351 (57)	121 (37)	189 (58)	114 (49)	171 (59)
Serious AEs	259 (41)	187 (30)	139 (42)	107 (33)	125 (43)	93 (33)
Patients died due to AE	69 (11)	48 (8)	45 (14)	28 (9)	24 (8)	20 (7)
D/C study drug(s) due to an AE	122 (19)	89 (15)	60 (18)	49 (15)	45 (15)	43 (15)

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"

Reviewer's comment: In KEYNOTE-042, the incidence of serious AEs, AEs leading to death and AEs leading to drug discontinuation was higher in the pembrolizumab arm compared to the chemotherapy arm. The incidence of AEs was in general, similar between the subgroups of PDL-1 TPS 1-49% and TPS ≥ 50%. There was a higher incidence of deaths due to an AE in pembrolizumab-treated patients in the TPS 1-49% subgroup; however, due to the small number, the significance of this finding is unclear (refer to clinical review of deaths/cause of deaths in the previous sections).

CDTL comment: The difference in death attributed to AE observed between subgroups defined by level of tumor PD-L1 expression should be interpreted with caution, as there may be differences between these subgroups which could contribute to the observed difference (e.g., differences in baseline characteristics and in co-morbid conditions).

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

No applicable for this supplement. Merck was granted a waiver from the requirement to conduct pediatric studies under PREA based on the low incidence of NSCLC in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdoses were reported with pembrolizumab in KEYNOTE-042, 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.

7.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Pembrolizumab was first granted marketing authorization in the US on September 4, 2014, for the treatment of patients with unresectable or metastatic melanoma. The current approved indications for pembrolizumab in the U.S. are listed in section 2.3.

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 64,097 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 is well-established. FDA will continue to monitor pembrolizumab safety in the postmarketing setting.

7.2.11. Integrated Assessment of Safety

Pooling of safety data was not conducted by the reviewer in this application.

SUMMARY AND CONCLUSIONS

This application relies primarily on the results of KEYNOTE-042, a randomized, multicenter, global, active-controlled trial conducted in patients with previously untreated advanced or metastatic NSCLC, whose tumors expressed PD-L1 TPS ≥1% as determined by an immunohistochemistry (IHC) assay using the PD-L1 IHC 22C3 pharmDx Kit. The efficacy results from the pre-specified second interim analysis (IA2) and the safety data from 1274 patients enrolled in the trial are intended to support a labeling expansion for pembrolizumab to include patients with previously untreated, locally advanced or metastatic NSCLC whose tumor express PD-L1 with a TPS ≥1% with no EGFR or ALK genomic tumor aberrations and fulfill PMC # 3127-2 from BLA 125514/S-12.

The results of KEYNOTE-042 demonstrate a statistically significant improvement in OS for pembrolizumab compared to platinum-based chemotherapy in the overall study population of patients with NSCLC tumors that express TPS ≥1% [HR 0.81 (95% CI: 0.71, 0.93); p = 0.0018]; the estimated median OS is 16.7 months in patients treated with pembrolizumab and 12.1 months in patients treated with platinum-based chemotherapy. The difference in OS, favoring pembrolizumab, is also statistically significant in the pre-specified subgroups of TPS ≥20% [HR 0.77 (95% CI: 0.64, 0.92); p = 0.0020] and TPS ≥ 50% [HR 0.69 (95% CI: 0.56, 0.85); p = 0.0003]. In the TPS ≥50% subgroup, the estimated median OS is 20.0 months with pembrolizumab and 12.2 months with chemotherapy. The estimated median OS of 12.1 months in the chemotherapy arm of KEYNOTE-042 is similar to that observed in other clinical studies of platinum-based chemotherapy in this patient population. In the TPS ≥50% subgroup, the estimated median PFS was marginally higher in the pembrolizumab arm (7.1 months) compared to the chemotherapy arm (6.4 months), but this difference was not statistically significant. As the result of the pre-specified sequential testing procedure for the secondary endpoints, PFS in the TPS ≥20% subgroup and the ITT population (TPS ≥1%) and ORR were not evaluated for statistical significance. The estimated median PFS was marginally lower in the pembrolizumab arm compared to the chemotherapy arm in the TPS ≥20% subgroup and the ITT population (TPS ≥1%). The ORR was slightly higher in the pembrolizumab arm compared to the chemotherapy arm for the TPS ≥50% and TPS ≥20% subgroups but was similar between arms for the ITT population (TPS ≥1%).

Exploratory analyses were conducted in the subgroup of patients with PD-L1 TPS 1-49%, a predefined subgroup and stratification factor for randomization in KEYNOTE-042. The estimated median OS was 13.4 months (95% CI 10.7, 18.2) in the pembrolizumab arm and 12.1 months (95% CI 11.0, 14.0) in the chemotherapy arm. The estimated median PFS was 4.2 months (95% CI 4.1, 5.2) in the pembrolizumab arm versus 6.8 months (95% CI 6.3, 8.1) in chemotherapy arms [HR 1.32 (95% CI 1.11, 1.56)]. The ORR in the pembrolizumab arm was

16.6% (95% CI 12.8, 21) and 21.7% (95% CI 17.4, 26.5) in the chemotherapy arm.

In KEYNOTE-042, in patients treated with pembrolizumab there was a higher incidence of serious AEs (41% versus 30%), AEs leading to discontinuation of study drug (19% versus 15%) and AEs resulting in death (11% versus 7.5%) than in patients treated with chemotherapy. Serious AEs that occurred at a ≥ 1 % higher frequency in the pembrolizumab arm compared to the chemotherapy arm were: pneumonitis (4.5% vs. 0.4%), pneumonia (8.1% vs. 6.3%), pleural effusion (2.2% vs. 0.8%), death/sudden death (1.8% vs. 0.8%), and dyspnea (1.3 % vs. 0.3%). Death due to an unknown cause/sudden death was reported in 11 patients receiving pembrolizumab. The most common grade 3-5 AEs (≥ 2%) in the pembrolizumab arm were pneumonia, pneumonitis, fatigue/asthenia and dyspnea. Immune-mediated AEs occurred in 28% of the patients treated with pembrolizumab and included hypothyroidism, pneumonitis, hyperthyroidism, severe skin reactions, thyroiditis, hepatitis, colitis, adrenal insufficiency, hypophysitis, myocarditis, pancreatitis, rash, hepatitis, nephritis. Pneumonitis (8.3%) and grade 3 or higher pneumonitis (4.5%) was the most common immune-related AE and occurred at a higher frequency than what has been reported in the pembrolizumab monotherapy safety database (3.4%).

7.3. Statistical Issues

No statistical issues were encountered while performing the primary analysis based on Merck's submission.

Merck submitted data and results from the interim analysis-2 (IA2). Based on the prespecified decision rule, the results of the study have crossed the efficacy statistical boundaries. A statistically significant improvement in OS in the overall ITT population of patients with NSCLC TPS ≥1% has been demonstrated. Non-proportional hazard rates in OS were observed in the overall ITT population and all subgroups, and the HR and estimated medians are not optimal to capture the treatment effect. PFS in the subgroup of NSCLC TPS ≥50% was not significant, and therefore PFS in other TPS subgroups was not evaluated for statistical significance and ORR was analyzed descriptively. The exploratory analyses in the TPS 1-49% subgroup are not conclusive and no inference can be drawn.

While exploratory analyses in Sections- 7.1.2 and 7.1.3 suggest some uncertainty regarding the benefit in the TPS 1-49% subgroup, the statistical team has concluded that further prospectively designed studies and analyses in this subgroup of patients is necessary to draw any conclusions.

7.4. Conclusions and Recommendations

The results of KEYNOTE-042 demonstrate a statistically significant and clinically meaningful (4.6-month difference in estimated median OS) improvement in OS for pembrolizumab compared to chemotherapy in patients with advanced NSCLC whose tumors express PD-L1 (TPS ≥1%).

The overall safety profile of pembrolizumab reported in KEYNOTE-042 was, in general, consistent with the known safety profile based on the pembrolizumab monotherapy Reference Safety Database, with the exception of immune-related pneumonitis, which was reported at a higher frequency in KEYNOTE-042 (8.3% versus 3.4%). A higher incidence of pneumonitis was also noted in KEYNOTE-024 relative to the pembrolizumab monotherapy Reference Safety Database (7.8% versus 3.4%). In KEYNOTE-042, in patients treated with pembrolizumab there was a slightly higher incidence of serious AEs, AEs leading to death and AEs leading to study drug discontinuation than in patients treated with platinum-based chemotherapy. An increased number of deaths due to unknown cause or sudden death was also reported in the pembrolizumab arm. Although underlying malignancy, co-morbid conditions and other confounding factors might have all contributed to the increased number of deaths due to AEs, with the lack of additional information (e.g., autopsy reports), a causal association to pembrolizumab cannot be completely ruled out. The review team recommends that the adverse reactions of death leading to treatment discontinuation of pembrolizumab observed in KEYNOTE-042 be included in the KEYTRUDA Prescribing Information. FDA will continue to closely monitor adverse event reports associated with pembrolizumab in ongoing trials and in the postmarketing setting.

The risk:benefit assessment for the population of patients with previously untreated, advanced or metastatic NSCLC with tumor PD-L1 TPS ≥50% is favorable, given the clinically meaningful improvement in median OS of 7.8 months observed in patients treated with pembrolizumab compared to patients treated with chemotherapy [HR 0.69 (95% CI: 0.56, 0.85); p = 0.0003]. Although not statistically significant, both the PFS and ORR in the subgroup of patients with NSCLC TPS ≥50% were slightly higher in the pembrolizumab arm compared to the chemotherapy arm. The results of KEYNOTE-042 further support the benefit of pembrolizumab for the first-line treatment of patients with metastatic NSCLC with PDL-1 TPS ≥50%, as previously demonstrated in the KEYNOTE-024 study.

The results of exploratory analyses in the TPS 1-49% subgroup raise uncertainty regarding the benefit of pembrolizumab in the TPS 1-49% subgroup and suggest the results in the ITT population (TPS ≥1%) may be driven by the treatment effect in the TPS ≥50% subgroup. The interpretation of these results, however, is complicated by the exploratory nature of these analyses and the observation of non-proportional hazard rates; therefore, it is not possible to draw definitive conclusions based upon the results of these exploratory analyses. The comparator in KEYNOTE-042 is an active control, and there does not appear to be a detrimental effect on overall survival in the subpopulation of patients with NSCLC TPS 1-49%. Therefore, based upon the results of analyses in the overall study population (TPS ≥1%), the review team recommends regular approval of pembrolizumab for the following indication:

Pembrolizumab is indicated 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 core (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

Results of the exploratory analysis of OS in the TPS 1-49% subgroup will be included in product labeling to provide transparency and inform prescribers.

This submission fulfills PMC 3127-2 from BLA 125514/S12: Submit the final report and efficacy datasets for KEYNOTE-042, entitled: "A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer".

Sirisha Mushti, Ph.D.	Lisa Rodriguez, Ph.D.
Primary Statistical Reviewer	Statistical Team Leader
Lee Pai-Scherf, M.D.	Erin Larkins, M.D.
Primary Clinical Reviewer	Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The Office of Oncology Drug Products (OHOP) and the Oncology Center of Excellence (OCE) did not recommend referral of 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 profile of pembrolizumab is well established in patients with NSCLC. The clinical review team expressed concerns regarding the differences in the magnitude of the treatment effect in OS between the subgroup of patients with NSCLC PD-L1 ≥50% and the subgroup with PD-L1 TPS 1-49%, which suggests the treatment effect observed in the ITT population of patients with NSCLC PD-L1 TPS ≥ 1% may be largely driven by the results in the PD-L1 TPS ≥ 50% subgroup as well as the similar differences in magnitude (PFS) and magnitude/direction (ORR) for supportive endpoints. However, given that these were exploratory analyses and the lack of a statistically significant interaction test for PD-L1 expression and survival, based on the recommendation of the statistical review team and Office Director, this supplement was not referred to the Oncologic Drugs Advisory Committee.

9 Pediatrics

NSCLC is a rare disease in the pediatric population. According to the World Health Organization, GLOBOCAN 2018[1], the estimated lung cancer incidence in the pediatric population aged 0 to 15 is 0.0 in the United States and worldwide.

Merck was granted 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 NSCLC in the pediatric population because it would be highly impractical or impossible given the small number of pediatric patients with this disease.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling negotiations on Merck's proposed Prescribing Information for BLA125514/S-47 are ongoing at the time of this review. The review team's proposed changes (high-level) are summarized in Table 44.

Table 45 Summary of Significant Proposed Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
Indication and Usage	Section 1.2, Indication statement revised to clearly reflect the population studied, i.e. "KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with ~~locally advanced~~ stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC whose tumors express PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test"	
Dosage and Administration Dosage Modification for Adverse Events	No change	
Dosage forms and Strengths	No change	
Contraindications	No change	
Warnings and Precautions	Section 5.1 text revised to better describe the incidence of pneumonitis in NSCLC patients with NSCLC who received KEYTRUDA as a single agent as first-line therapy for advanced disease, including data on corticosteroid use, prior history of radiation, frequency of treatment discontinuation due to pneumonitis and resolution.	
Adverse Reactions	• Text updated to total number of patients from KEYNOTE-042 and 024 • Information concerning KEYTRUDA discontinuation due to adverse reactions revised to add "death	

	due to unknown cause or sudden death (1.6%)" as cause of KEYTRUDA discontinuation • Added incidence of most frequent (≥2%) serious adverse reactions • Adverse reactions table revised to combine the incidence of fatigue and asthenia under one adverse reaction. • FDA disagree with (b) (4) (b) (4) [redacted] • Wording and formatting revised throughout for consistency and clarity	
Use in Specific Populations	No changes	
Description	No changes	
Pharmacodynamics	No changes	
Pharmacokinetics	No changes	
Nonclinical Toxicology	No changes	
Clinical Studies	• Added KEYNOTE-042 protocol specified main efficacy outcome measures, i.e., OS in the subgroup of patients with NSCLC TPS ≥50%, NSCLC TPS ≥20%, and the overall population with NSCLC TPS ≥1%" • KEYNOTE-042 Efficacy Results table revised to: - Add OS, PFS and ORR of patients with NSCLC TPS ≥50% • Duration of Response: revised to provide percentages with duration ≥ 12 months and ≥18 months based on observed durations. Median durations of response deleted, given that only 26% of the responders in the pembrolizumab arm have an observed duration of ≥ 18 months. • Added text to describe the result of efficacy outcomes in the subgroup of patients with NSCLC PD-L1 TPS ≥ 20% • Added text to describe the results of pre-specified exploratory	

	subgroup analysis for patients with NSCLC PD-L1 TPS 1-49% • Wording and formatting revised throughout for consistency and clarity	
Additional changes	• Throughout the label, "nab-paclitaxel" changed to paclitaxel protein-bound to be consistent with non-proprietary name found in ABRAXANE labeling; furthermore, nab is proprietary term • Wording and formatting revised throughout for consistency and clarity	

11 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team does not recommend that a risk evaluation and mitigation strategy (REMS) be required to ensure safe and effective use of pembrolizumab for the indicated population given the well-established safety profile of pembrolizumab 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 the safe and effective use of pembrolizumab, including monitoring for immune-mediated adverse events, are made in labeling and a patient medication guide.

12 Postmarketing Requirements and Commitment

No postmarketing commitment was requested by FDA for this application and no postmarketing requirements were identified under 21 CFR 601 or under the provisions of FDAAA..

During the March 6, 2017 Type C Meeting (section 3.2, Summary of Presubmission Regulatory Activity), FDA had requested that Merck, at the time of the sBLA submission, submit a proposal for a PMC to submit the final result of the China extension study, to better characterize pembrolizumab's benefit. In accordance with FDA's 2017 request, Merck submitted the following proposal:

> Submit the final report and efficacy and safety datasets for the China-specific extension study for KEYNOTE-042 entitled: "A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MKL-3475) versus Platinum based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (KEYNOTE-042)".
>
> Agreed upon timeline for submission:
> Final Report Submission: October 2019.

During the sBLA review, the review team concluded that the PMC was no longer necessary given that additional safety and activity data has become available to support the overall risk:benefit assessment of pembrolizumab since the initial request in 2017.

13 Division Director (OB)

Rajeshwari Sridhara, Ph.D.

APPEARS THIS WAY ON ORIGINAL

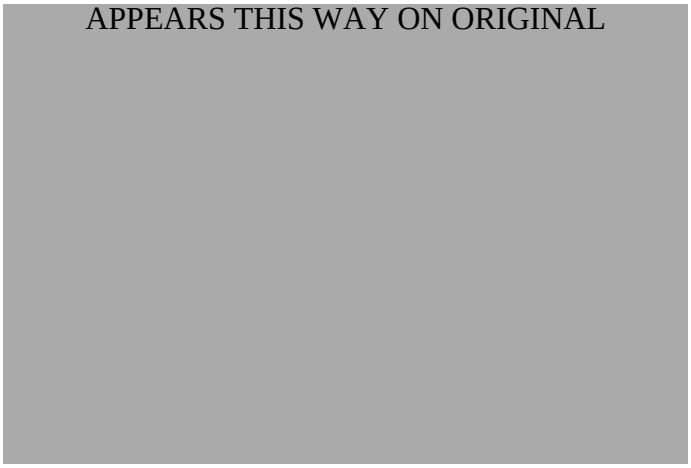
14 Division Director (Clinical)

I concur with the recommendations of the review team that this application be approved with the agreed-upon labeling based upon demonstration of a statistically significant and clinically important improvement in overall survival for patients receiving pembrolizumab as a single agent as compared to a platinum-based chemotherapy regimen in the overall population of PD-L1 expressing for the first-line, systemic treatment of stage III and metastatic NSCLC, with no evidence of an EGFR or ALK gene alteration. The observed effect on survival outweighs the risks of immune-mediate adverse reactions and infusion-related reactions as well as the increase in serious adverse events and sudden or otherwise unexplained deaths which occurred more frequently in the pembrolizumab arm. These risks are acceptable in the indication population whose 5-year survival is estimated to be approximately 5%.

As noted throughout the review, the major concern with this application was whether the treatment effect on overall survival was driven by a subgroup, specifically, the subgroup with PD-L1 strongly expressing (TPS ≥50%) NSCLC. The role of PD-L1 expression on tumor as a critical component of the mechanism of action of anti-PD-(L)1 antibodies, which specifically block the interaction of this ligand and the PD-1 receptor, is undisputed. However, the data regarding the predictive role of PD-L1 expression for efficacy outcomes with anti-PD-(L)1 antibodies is less clear. There was no prespecified hypothesis to be tested in the subgroup with NSCLC TPS 1-49%, which accounts for approximately half of the indicated population; thus all analyses and all cross-study comparisons are considered exploratory. Additionally, a formal interaction test for treatment by PD-L1 subgroup was not significant at a two-sided alpha of 0.05. For all of these reasons, I concur that the application should be approved for the entire study population.

However, these exploratory analyses, which show a difference in the magnitude of the treatment effects on survival in these two subgroups (TPS 1-49% vs. TPS ≥50%), which are greater than in any other subgroups of similar size evaluated (HR 0.92 vs. 0.69) other than current vs. former smokers (0.96 vs. 0.71); the result of the interaction test for treatment by TPS subgroup based on 50% cutoff which was not significant at a 5% significance level showed a relatively persuasive finding (p-value=0.0702); and the cross-study comparisons showed similar results regarding the differences in magnitude in treatment effects based on PD-L1 status observed in both KEYNOTE-042 and KEYNOTE-010, including the results favoring chemotherapy for PFS (HR 1.32 [KN-042]; HR 1.04 [KN-010]) and ORR (17% vs. 22% [KN-042]; 10% vs. 10.5% [KN-010]) among patients with TPS 1-49% NSCLC are concerning. Considering these data, the review team and clinical review division (DOP2) will continue to closely monitor this potential predictive effect of the level of PD-L1 expression and tumor outcomes in NSCLC as the totality of evidence continues to accumulate with pembrolizumab and with other antibodies directed against PD-1 or PD-L1 and with pembrolizumab across other potentially related tumor types (e.g., squamous cell carcinoma of the head and neck).

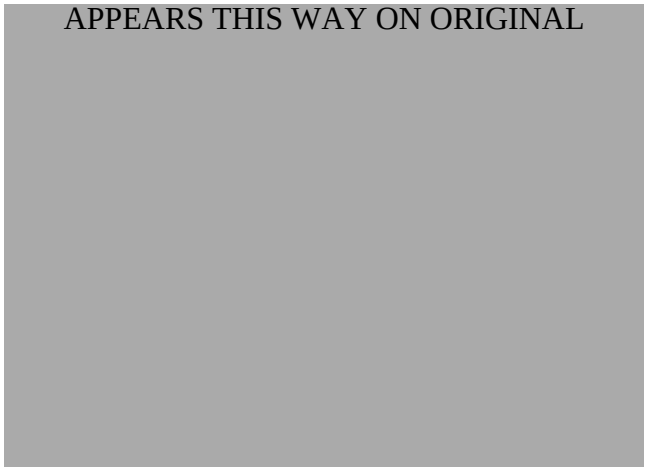
Patricia Keegan, M.D.


APPEARS THIS WAY ON ORIGINAL

15 Office Director (or designated signatory authority)

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

Patricia Keegan, M.D.



16 Appendices

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16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): KEYNOTE-042

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Merck)
Total number of investigators identified: 1476 (investigators and sub-investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in S Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Merck)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Merck)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Merck)

16.3. List of AEOSI Preferred Terms Used by the Applicant for Study KEYNOTE-042

AEOSI Preferred Terms, Version 13.0 (06-Nov-2017) based on MedDRA v. 20.1

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organizing pneumonia	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, necrotising colitis, Colitis erosive, Autoimmune colitis	Yes
Hepatitis	Hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	Yes
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	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in	Yes

Severe Skin Reactions Including Stevens- Johnson	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash,	Yes Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis	Yes
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated necrotising myopathy, Rhabdomyolysis, Myopathy, Dermatomyositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness,	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes

Source: Merck's table. BLA125514/S-047. CSR P042V01MK3475, Table 14.3-27

16.4. Baseline Characteristics for **TPS≥50%** and **TPS≥20%**

Table 46: Baseline demographic characteristics for TPS **≥50%** and TPS **≥20%** subgroups

	TPS **≥50%**		TPS **≥20%**	
	Pembrolizumab N=299	Chemotherapy N=300	Pembrolizumab N=413	Chemotherapy N=405
Sex				
Male	205 (69%)	210 (70%)	283 (69%)	285 (70%)
Female	94 (31%)	90 (30%)	130 (31%)	120 (30%)
Age				
Mean years (SD)	62 (9.8)	63(9.6)	62 (101)	63(9.4)
Median (years)	63	64	63	64
Min, max (years)	25 - 89	36-90	25 - 89	33-90
Age Group				
< 65 years	167 (56%)	161 (54%)	228 (55%)	212 (52%)
≥ 65 years	132 (44%)	139 (46%)	185 (45%)	193 (48%)
Race				
White	188 (63%)	189 (63%)	251 (61%)	259 (64%)
Black or African American	0 (0%)	5 (2%)	2 (<1%)	7 (2%)
Asian	94 (31%)	95 (32%)	130 (31%)	122 (30%)
American Indian or Alaska Native	4 (1%)	3 (1%)	9 (2%)	3 (1%)
Other	13 (4%)	7 (2%)	21 (5%)	13 (3%)
Ethnicity				
Hispanic or Latino	46 (15%)	57 (19%)	70 (17%)	76 (19%)
Not Hispanic or Latino	249 (83%)	238 (79%)	338 (82%)	323 (80%)
Not Reported	4 (1%)	5 (2%)	5 (1%)	6 (1%)
Region				
East Asia	92 (31%)	94 (31%)	128 (31%)	121 (30%)
Europe	71 (24%)	66 (22%)	96 (23%)	95 (23%)
Latin America	53 (18%)	63 (21%)	78 (19%)	82 (20%)
Other	83 (28%)	77 (26%)	111 (27%)	107 (26%)

Table 47: Baseline disease characteristics for TPS **≥50%** and TPS **≥20%** subgroups

		TPS **≥50%**		TPS **≥20%**	
		Pembrolizumab N=299	Chemotherapy N=300	Pembrolizumab N=413	Chemotherapy N=405
Tumor Stage	Stage IV	272 (91%)	265 (88%)	371 (90%)	354 (87%)
	Stage IIIA	5 (2%)	2 (1%)	5 (1%)	6 (1%)
	Stage IIIB	22 (7%)	33 (11%)	37 (9%)	45 (11%)
Histology	Non-Squamous	192 (64%)	186 (62%)	265 (64%)	249 (61%)
	Squamous	107 (36%)	114 (38%)	148 (36%)	156 (39%)
ECOG PS	0	96 (32%)	91 (30%)	122 (30%)	131 (32%)
	1	203 (68%)	209 (70%)	291 (70%)	274 (68%)
Smoking History	Current Smoker	57 (19%)	59 (20%)	75 (18%)	85 (21%)
	Former Smoker	178 (60%)	174 (58%)	243 (59%)	230 (57%)
	Never Smoker	64 (21%)	67 (22%)	95 (23%)	90 (22%)
Brain Metastasis	No	280 (94%)	285 (95%)	390 (94%)	383 (95%)
	Yes	19 (6%)	15 (5%)	23 (6%)	22 (5%)
Choice of Chemotherapy	Paclitaxel	140 (47%)	140 (47%)	199 (48%)	197 (49%)
	Pemetrexed	159 (53%)	160 (53%)	214 (52%)	208 (51%)

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Memorandum
Division of Oncology Drug Products 2
Office of Hematology and Oncology Products

Supplemental BLA	125514/S-047
Submission dates	July 11, 2018 and November 30, 2018
Submission Type	Efficacy Supplement
Priority or Standard	Priority
Proposed Trade Name	KEYTRUDA
Established Name	Pembrolizumab
Dosage Form and Strength	For injection: 50 mg 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
Route of Administration	Intravenous
Proposed Indication	KEYTRUDA is a program death receptor-1 (PD-1)-blocking antibody indicated for first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD L1 [Tumor Proportion Score (TPS) $\geq$ 1%], as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations
Associated INDs	IND 110080 and IND 116833
Regulatory Project Manager	Sharon Sickafuse, MS
Clinical Reviewer	Lee Pai-Scherf, MD
Cross Discipline Team Leader	Erin Larkins, MD

The clinical review of safety and efficacy is complete and has being added to the BLA Multidisciplinary Review and Evaluation.

1

The clinical review team recommends regular approval for pembrolizumab for first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD L1 [Tumor Proportion Score (TPS) $\geq$ 1%], as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

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.

The recommendation for approval is based on the favorable benefit-risk assessment from a pre-specified interim analysis from KEYNOTE-042 study that demonstrated a statistically significant and clinically meaningful improvement in OS for pembrolizumab monotherapy when compared with

chemotherapy in previously untreated patients with advanced or metastatic NSCLC whose tumors express PD-L1 with TPS ≥1% with no *EGFR* or *ALK* genomic tumor aberrations.

This submission fulfills Postmarketing Commitment 3127-2 under BLA125514/S-012 to:
"Submit the final report and efficacy datasets for Keynote-042, entitled: "A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer."

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ERIN A LARKINS
03/17/2019 10:08:11 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s047

OTHER REVIEW(S)

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

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

Memorandum

Date: March 29, 2019

To: Sharon Sickafuse
Regulatory Health Project Manger
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for Keytruda® (pembrolizumab) for injection

BLA: 125514/Supplement-047

Office of Prescription Drug Promotion (OPDP) has reviewed the proposed product labeling (PI) and Medication Guide (MG) for Keytruda® (pembrolizumab) for injection (Keytruda) as requested by Division of Oncology Products (DOP2) in the consult dated July 17, 2018.

OPDP's review of the proposed PI and MG is based on a proposed draft PI and draft MG sent by electronic mail on March 15, 2018 to OPDP (Nazia Fatima) from DOP2 (Sharon Sickafuse). OPDP's comments on the proposed draft PI are attached. 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 Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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

PATIENT LABELING REVIEW

Date:	March 22, 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)** Nazia Fatima, PharmD, MBA, RAC 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-047
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On July 11, 2018, Merck Sharp & Dohne Corp. submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved Biologics License Application (BLA) 125514/S-047 for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection. With this supplement, the Applicant seeks to further expand the population for pembrolizumab, as a single agent for the first-line treatment of patients with metastatic NSCLC whose turmors express PD-L1 with a TPS ≥1% based on interim analysis 2 (IA2) of study KEYNOTE-042.

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 July 17, 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 March 6, 2019, and received by DMPP and OPDP on March 6, 2019.
- Draft KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection Prescribing Information (PI) received on July 11, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on March 15, 2019.
- Approved KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection labeling dated February 15, 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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